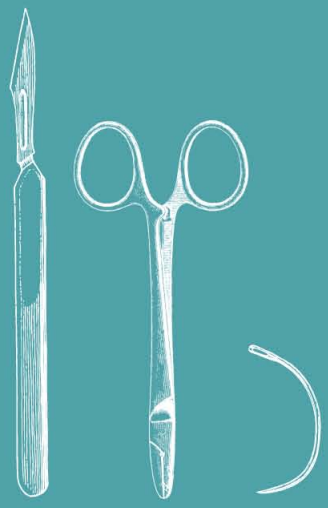
mesh in abdominal wall hernia

new insights



Ruth Posthuma - Kaufmann

Mesh in abdominal wall hernia:

new insights

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MESH IN ABDOMINAL WALL HERNIA: NEW INSIGHTS

MESH BIJ BUIKWANDHERNIA: NIEUWE INZICHTEN

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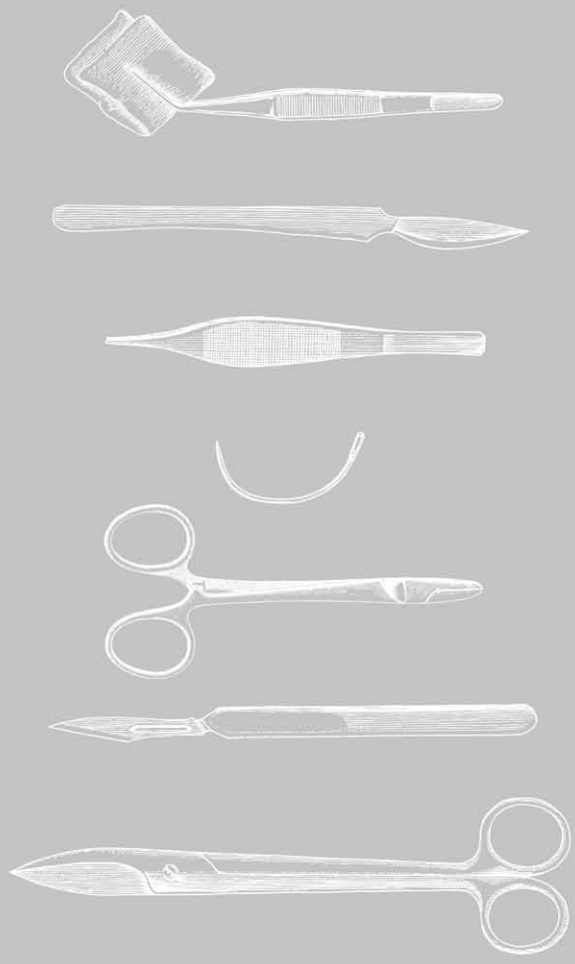

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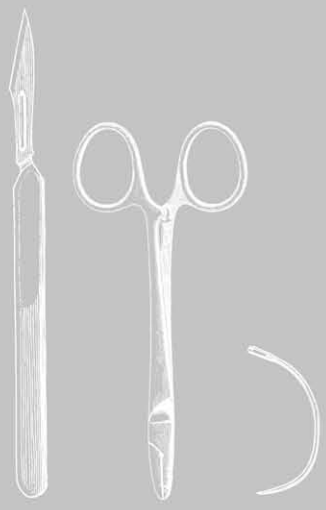
Introduction and outline of thesis



"MESH IN ABDOMINAL WALL HERNIA: NEW INSIGHTS"

Abdominal wall hernia is one of the earliest diseases described in ancient literature. The first description of abdominal wall hernia dates back to the Ebers papyrus (1552 BC): a swelling that comes out during coughing [1]. Later, the Phoenicians (900 BC) and the ancient Greeks (400 BC) described abdominal wall hernia and its surgical treatment. Until the end of the 18th century (inguinal) hernia surgery consisted of ligation and section of the sac including removal of the testicle [2]. From the 18th century, hernia surgery was improved by a better description of the anatomy of the inguinal canal.

In 1700, the French surgeon Alexis Littre described an omphalomesenteric duct that was trapped in a hernia [3]. In 1756, the Scottish anatomist and surgeon John Hunter reported with help of his older brother and anatomist William Hunter the details of the embryological origin of the indirect inguinal hernia [4]. In 1785, the German surgeon August Gottlieb Richter described an incarcerated yet non-obstructing hernia [5]. And in 1846, the British surgeon Thomas Pridgin Teale reported the first prevascular femoral hernia [6].

Other eponyms in inguinal hernia relate to anatomical landmarks described by the Dutch surgeon Anton Nuck (canal; 1650-1692), the French surgeon Jean Louis Petit (hernia; in 1783), the Dutch physician and anatomist Petrus Camper (fascia; in 1801), the English surgeon and anatomist Sir Astley Paston Cooper (ligament; in 1804), the Italian anatomist and surgeon Antonio Scarpa (fascia; in 1814), the German physician, surgeon, and anatomist Franz Kaspar Hesselbach (triangle; in 1814), the French surgeon Jules Germain Cloquet (hernia; in 1817), the French surgeon Stanislas Laugier (hernia; in 1833), and the French surgeon Joseph Casimir Grynfeltt (hernia; in 1866) [5, 6]. Sir Astley Cooper was the first to define important structures such as the pectineal ligament and cremasteric muscles [7]. Since the 18th century developments in abdominal wall surgery happened quickly regarding not only the type of operations but also the indications for hernia repair.

Anatomy

The abdominal cavity is located between the diaphragm and the pelvic floor. Within the abdominal cavity lay various organs, like the liver, small bowels, colon, preperitoneal fat, and omentum. The boundaries of the abdominal cavity are formed by the abdominal wall. The anterior part of the abdominal wall is proximally defined by the xyphoid process and the costal margins and distally by the iliac crests and the pubic bone. The abdominal wall consists of skin, subcutaneous fat, various muscle layers, nerves, blood vessels and connective tissue. From the outside in are these muscles layers: the rectus

abdominis muscle, the external oblique muscle, the internal oblique muscle and the transversus abdominis muscle. Between the two rectus abdominis muscles lays the linea alba (also called "white line" or "midline"). The linea alba is a three-layered collagen structure, reflecting the insertions of the three lateral muscles of the abdominal wall. The linea alba is barely vascularized causing possible difficulties healing after an operation. As the French anatomist Henri Fruchaud (1894-1960) already reported, all regions within the abdominal wall where aponeurosis and fascia are lacking the support of muscles are prone to hernia development [8]. These areas are the hiatus of the diaphragm, the umbilicus, inguinal, femoral and lumbar regions and badly healed incisions.

Abdominal wall hernia

The integrity or function of the abdominal wall can be compromised due to various reasons. This can happen at birth (congenital problem), during life (acquired problem), or after surgery (iatrogenic problem). This impairment of the abdominal wall can lead to an abdominal wall hernia. Abdominal wall hernia is a collective term for a variety of hernias in the abdominal wall. The word "hernia" is known in both Greek and Latin. In Greek it means "bud" or "sprout"; in Latin "tear" or "rupture". An abdominal wall hernia or herniation is a defect in the abdominal wall with an intermittent or continuous protrusion of the abdominal wall with or without intra-abdominal content. A hernia can be asymptomatic, but can also lead to complaints like pain, discomfort, cosmetic complaints, core instability (in case of very large hernia), and incarceration of the hernia. The latter is an indication for an emergency operation. In this thesis, three types of hernias will be discussed.

Umbilical hernia

Umbilical hernia is defined as a midline abdominal wall defect from 3 cm above to 3 cm below the umbilicus [9]. This type of hernia can be congenital or acquired. It is a common diagnosis in both children and adults [10, 11]. Of all abdominal wall hernias, approximately 10 percent are defined as umbilical hernia [12], and the prevalence of umbilical hernia in the adult population is 2 percent [13]. Each year, approximately 4500 umbilical hernias are repaired in the Netherlands. Surgical repair is recommended for most symptomatic or clinically apparent umbilical hernias. Umbilical hernia repair can be achieved by suture repair or use of mesh (surgical prosthesis to reinforce the abdominal wall). Suture repair caused high recurrence rates of up to 54.5 percent [14]. The use of mesh was proven to be beneficial in incisional and inguinal hernia repair, and mesh repair has therefore become the gold standard repair for these types of hernia [15-18]. Mesh repair in umbilical hernia was associated with low recurrence rates of up to 1 percent of large umbilical hernias in two randomized controlled trials of mesh versus suture repair and in a long-term follow-up, retrospective study [19-21].

Inguinal hernia

The inguinal hernia or groin hernia is located in one or both groins. This type of hernia can be congenital or acquired. Inguinal hernia repair is the most frequently performed operation in general surgery worldwide. The incidence is 6 to 12 percent in adult males. The incidence is increasing with age reaching 22.8 percent in people aged 60 to 74 years [22]. Men are affected more often than females. There are many different techniques to operate inguinal hernias. Ways to classify inguinal hernia operations are based on material (sutured versus mesh repair), approach (open versus endoscopic versus robotic), and anatomical plane (anterior versus posterior approach). Open anterior hernia repair according to the Lichtenstein technique and endoscopic inguinal hernia techniques are recommended as the best evidence-based options for the repair of a symptomatic primary unilateral inguinal hernia (given that the surgeon is sufficiently experienced in the specific procedure) [23]. The recurrence rates for both techniques have been reduced to less than the rate of chronic postoperative inguinal pain (CPIP). Therefore, CPIP and its consequences for the quality of life are the challenges of modern inguinal hernia surgery [24].

Incisional hernia

Incisional hernia is a defect of the fascia of the abdominal wall, that occurs after abdominal surgery. It is defined as "any abdominal wall gap with or without a bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging" [25]. The incidence of incisional hernia ranges from 11 to 20 percent [26, 27] and up to 35 percent in "high-risk patient groups" [28-35]. High-risk patient groups are patients with obesity and/or an abdominal aneurysm. Nowadays, incisional hernias are most often reinforced with mesh material [15]. The use of mesh significantly decreases the 10-year recurrence rates [17]. Ways to classify incisional hernia operations are based on material (sutured versus mesh repair), approach (open versus laparoscopic versus robotic), and anatomical position of the mesh (onlay, inlay, sublay/retromuscular, retrorectus, or intraperitoneal position).

Diagnosis

The diagnosis of hernia is mostly a clinical diagnosis: the patient's history combined with a physical examination often lead to the diagnosis. In case of doubt various imaging modalities are available. When imaging is necessary, the first choice is ultrasound in case of a suspected inguinal or umbilical hernia. This technique is also useful for small incisional hernias. For larger incisional hernias a CT scan could be helpful to assess the size of the hernia, but also the "loss of domain" prior to a possible surgical repair [36].

Mesh prosthesis

The first attempts to use a mesh in inguinal hernia repair were done by Phelps [37], Goepel [38], Witzel [39] and Perry [40] using a silver mesh (1894-1904) [41]. Other surgeons used gold, silicon and other materials. They experienced various complications resulting in the quick abandonment of these types of mesh [42]. In 1954, polypropylene was introduced as a mesh material by Nobel Prize winner Giulio Natta together with Karl Ziegler [43]. Polypropylene quickly gained terrain in hernia surgery and became a key part of various hernia repairs according to Lichtenstein [44], Trabucco [45], and in other repairs [46-49]. Nowadays, there are many different meshes available, of which the synthetic non-resorbable meshes are used most often in general practice; polypropylene mesh being the most widely used material [50, 51]. Meshes can be grossly differentiated by their material or materials of origin or their shape (flat, plug, 3D structures). Below, meshes will be discussed according to their material of origin.

Synthetic mesh

Synthetic meshes are made from polymers derived from oil. In 1944, the first meshes of perlon and nylon were implanted. The results however were somehow disappointing; perlon triggered an extreme inflammatory response and nylon tended to lose its strength quickly and to disintegrate. In the following years new synthetic meshes made of polypropylene, polyethylene, polyester and expanded-polytetrafluoroethylene (e-PTFE) were introduced. These polymers have the advantage that they maintain their strength during implantation and that they are relatively cheap. The main disadvantages are a pronounced foreign body response and their susceptibility for infections. Examples of these meshes are Parietene™ (polypropylene) and Omyra® Mesh (condensed polytetrafluoroethylene). These meshes will be investigated in this thesis.

Biological mesh

Biological meshes are made from collagen containing tissues of human or animal origin [52]. These collagen containing tissues originate from intestines, heart valves, or skin. The tissues are processed in various steps to remove cells, cell components and hair (if present) as well as other antigens present in the tissue [53, 54]. After degradation and decellularization of these tissues, a 3D structure of collagen and some protein remnants remains. In this group of meshes, two subtypes can be distinguished: non-cross-linked and cross-linked biological meshes. Although all collagen-containing meshes have some cross-linking within the collagen structures, these meshes are called non-cross-linked meshes. Additional chemical cross-linking of the mesh can be done to increase its strength and to slow down its degradation [53, 55, 56]. After implantation of the mesh starts the degradation of the mesh. There is incorporation of host fibroblasts and collagen replacement occurs. This so-called xenograft remodeling begins within a few

hours after implantation and continues for several months to years. The advantage is that these meshes would be less susceptible to infection. In the presence of infection, the mesh should not get infected. The main disadvantage is their price. Examples of these meshes are Permacol™ (cross-linked porcine acellular dermal matrix), Strattice™ (non-cross-linked porcine acellular dermal matrix) and XCM Biologic® (non-cross-linked porcine acellular dermal matrix). These meshes will be investigated in this thesis.

Resorbable synthetic mesh

Apart from the older synthetic quickly resorbable polyglactin 910 (Vicryl®) mesh, a relatively new category of meshes is represented by the slowly resorbable synthetic meshes. These meshes consist of materials that are fully degradable over time. These meshes are said to have the advantages of biological meshes, but for a much lower price [57]. Examples of these meshes are GORE® BIO-A® Mesh (polyglycolic acid and trimethylene carbonate), TIGR® Matrix Surgical Mesh (copolymers of glycolide, lactide, and trimethylene carbonate), and Phasix™ mesh (poly-4-hydroxybutyrate). None of these meshes will be investigated in this thesis.

Anatomical positions of mesh

Meshes can be placed in various anatomical planes of the abdominal wall (Figure 1). The position of the mesh within the abdominal wall appears to influence outcomes. A recent systematic review found that retromuscular and underlay mesh repair are associated with a lower recurrence rate compared with onlay and interposition mesh repair [58].

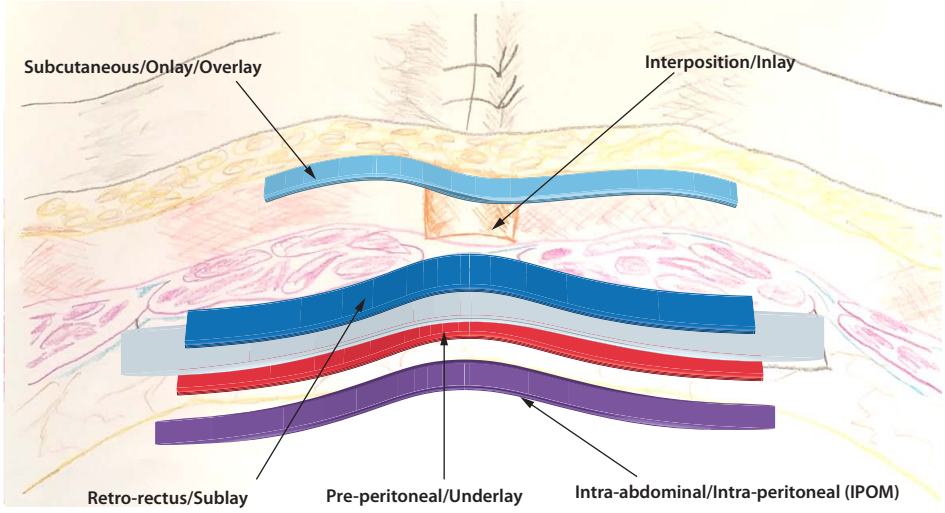


Figure 1. Different positions of the mesh in relation to the abdominal wall layers to repair an abdominal wall hernia by mesh reinforcement

Complications of mesh

The use of mesh in abdominal wall hernia can lead to complications. These complications can be defined as acute and chronic complications. Acute complications are complications shortly after the initial operation: bleeding, seroma, hematoma, and surgical site infection. The chronic complications can be chronic pain after hernia surgery and the occurrence of a complex abdominal wall hernia.

Chronic postoperative inguinal pain

Chronic postoperative inguinal pain (CPIP) can occur after inguinal hernia surgery. Due to different definitions of CPIP the reported incidences of CPIP ranges from 1 to 63 percent [24, 59-64]. Pain directly postoperative is not regarded being CPIP, since that is involving a duration of pain of at least 3 months. CPIP and the consequences for the quality of life are the challenges of modern hernia surgery [24]. This is also urged by the high incidence of CPIP – which is ≈ 10 percent – and because of its socioeconomic effects [23, 24, 65]. The pathophysiology of CPIP is regarded multifactorial due to patient-related and surgery-related risk factors [65-68].

Complex abdominal wall hernia

Complex abdominal wall hernia has different definitions. Following the Ventral Hernia Working Group classification, all patients can be classified into four different categories [69]. These grades range from grade 1 (low risk) until grade 4 (infected/contaminated). The use of synthetic meshes in potentially contaminated (grade 3) or contaminated (grade 4) incisional hernias is not unequivocally supported and may lead to a higher morbidity (i.e. wound healing problems, adhesions and fistula formation) and mortality [51, 70]. As an alternative, a biological mesh might be considered [69].

AIM OF THE THESIS

There are various strategies to investigate meshes. A selection of in vitro, in vivo and clinical testing can be used to assess the characteristics of different meshes. This thesis intends to assess a wide spectrum and therefore meshes will be assessed in both in vivo and in a clinical setting.

The first aim of this thesis was to assess the use of mesh in abdominal wall hernia. The second aim of this thesis was to gain new insights on the use of mesh in both experimental and clinical setting and possible complications of mesh.

OUTLINE OF THE THESIS

The **first part** of this thesis consists of studies about the use of mesh in experimental models.

In **Chapter 2** will be assessed which experimental animal models are available for abdominal wall hernia research. This chapter will give an overview of all available models to select models for further research.

In **Chapter 3** the characteristics of both non-cross-linked and cross-linked biological meshes will be evaluated in a rat model.

In **Chapter 4** various biological meshes will be tested in a peritonitis rat model as most meshes respond differently in presence of an infection [71]. Both non-cross-linked and cross-linked meshes will be assessed to define their characteristics in the presence of intra-peritoneal infection.

In **Chapter 5** a consensus score on adhesions is presented as adhesions are a common complication of mesh in the intra-abdominal cavity. There are many different adhesions scoring systems, that differ in the ways they score adhesions (qualitative versus quantitative scoring of adhesions). This META-consensus score on mesh-tissue adhesions can be helpful to compare future research more easily.

The **second part** of this thesis consists of studies about the clinical use of mesh. These studies will be performed in patients that will undergo a surgical repair of their umbilical hernia.

In **Chapter 6** data will be presented on the repair of small umbilical hernias. The small umbilical hernias of 1–4 cm can be treated with either sutures or mesh. In this randomized controlled trial both treatments for umbilical hernia repair in adults will be compared.

In **Chapter 7** a meta-analysis will be performed using available literature and the data of the previous chapter. In this meta-analysis will be assessed whether treatment of umbilical hernia with mesh or sutures leads to less recurrences.

In **Chapter 8** a systematic review of the literature will be presented regarding the types of anesthesia in umbilical hernia operations. In this review the feasibility of local anesthesia for the surgical treatment of umbilical hernia is assessed.

The **third part** of this thesis consists of studies about possible complications of mesh in patients.

In **Chapter 9** will be assessed whether the use a new self-gripping mesh instead of a sutured mesh will lead to a decrease in chronic postoperative inguinal pain.

In **Chapter 10** an algorithm will be presented with a treatment strategy for the management of patients with chronic postoperative inguinal pain.

In **Chapter 11** data about patients who had to undergo repair of a complex abdominal wall hernia will be presented. All patients were treated with a cross-linked biological mesh.

In **Chapter 12** another group of patients with a complex abdominal wall hernia will be presented. These patients were treated with a non-cross-linked biological mesh.

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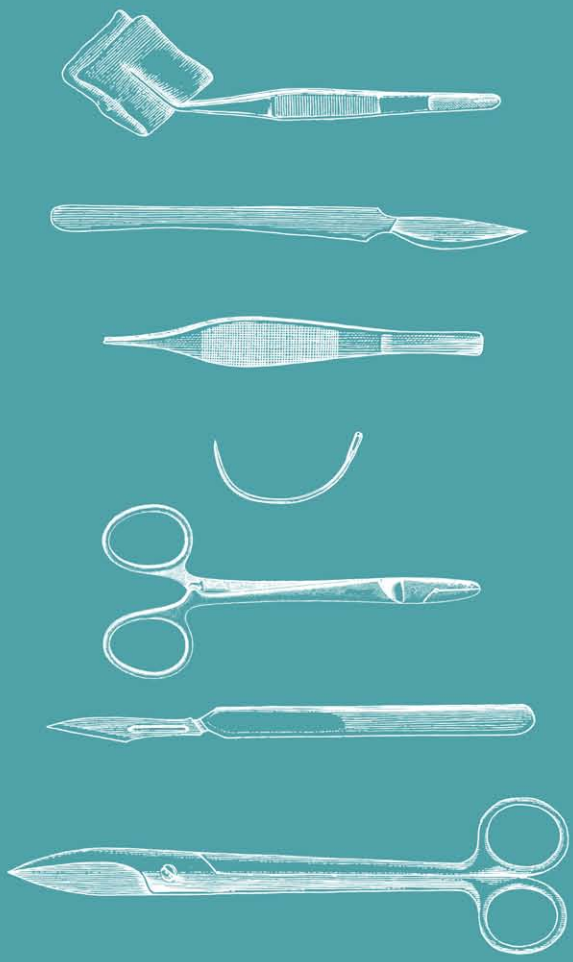
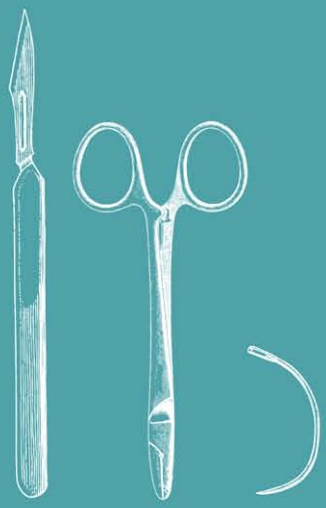
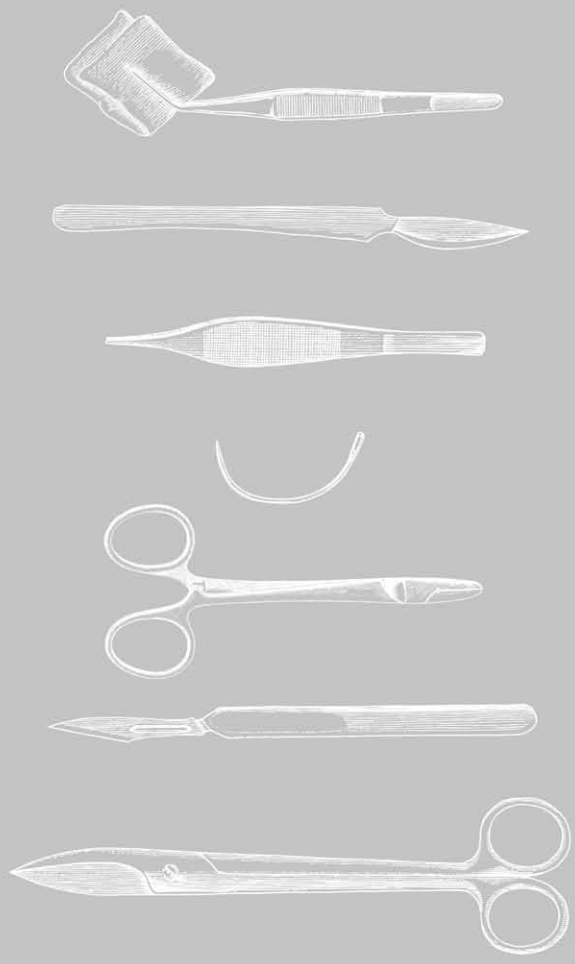


part 1

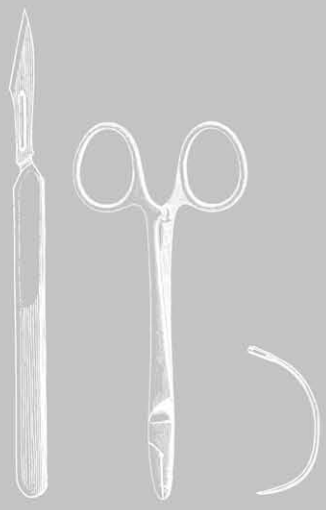
mesh in experimental models





2

Critical overview of all available animal models for abdominal wall hernia research



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R.R.M. Vogels and R. Kaufmann contributed equally to this work.

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ABSTRACT

Introduction

Since the introduction of the first prosthetic mesh for abdominal hernia repair, there has been a search for the "ideal mesh". The use of preclinical or animal models for assessment of necessary characteristics of new and existing meshes is an indispensable part of hernia research. Unfortunately, in our experience there is a lack of consensus among different research groups on which model to use. Therefore, we hypothesized that there is a lack of comparability within published animal research on hernia surgery due to wide range in experimental setup among different research groups.

Methods

A systematic search of the literature was performed to provide a complete overview of all animal models published between 2000 and 2014. Relevant parameters on model characteristics and outcome measurement were scored on a standardized scoring sheet.

Results

Due to the wide range in different animals used, ranging from large animal models like pigs to rodents, we decided to limit the study to 168 articles concerning rat models. Within these rat models, we found wide range of baseline animal characteristics, operation techniques, and outcome measurements. Making reliable comparison of results among these studies is impossible.

Conclusion

There is a lack of comparability among experimental hernia research, limiting the impact of this experimental research. We therefore propose the establishment of guidelines for experimental hernia research by the European Hernia Society (EHS).

INTRODUCTION

Ever since the introduction of the first prosthetic mesh for reinforcement of abdominal hernia repair, there has been a search for the "ideal mesh" [1, 2]. After using meshes of silver and stainless steel for decades, the first "modern" synthetic polypropylene mesh was introduced in the 1950s [1-3]. Today, polypropylene mesh remains the most commonly used mesh worldwide in ventral and inguinal hernia repair [1, 2]. The ideal mesh, however, still has not been developed [1, 2, 4].

The ideal mesh must be tailored to each patient's current needs in the current clinical situation [4, 5]. In order to provide a mesh for most patients, a continuing growth in variety of mesh concepts exists. For instance, meshes of various materials (from prosthetic or biological origin), shapes (flat mesh, plugs, and 3D meshes), heavyweight and low-weight, and with various coatings are available. Along with this is a growing body of data on assessing the feasibility of new meshes with the ultimate goal to improve patient outcomes [6].

Even though clinical research is the best method to really assess the outcome of new mesh concepts, preclinical animal models remain necessary for the assessment of biocompatibility and strength in the long run [7-9]. Especially since several important mesh characteristics, such as inflammation, shrinkage, ingrowth, remodeling, and adhesion formation to the mesh, can only be researched using experimental models, patients cannot be reoperated for evaluation of these key aspects [4]. However, in order to compare studies and to reproduce them, it is important that different research groups use comparable research methods. However, in our search for hernia models in the past, we came across a wide range of different models leading to the hypothesis that there is very little comparability within published animal research on hernia surgery [10, 11]. To support this hypothesis, we hereby present a systematic review of the literature on all available animal models for hernia research between 2000 and 2014.

METHODS

Literature search

A systematic search of the literature was performed using the "Excerpta Medica database" (Embase) and NCBI National Library of Medicine (PubMed). Search strategy was aimed at finding all literature concerning surgical meshes used for abdominal wall hernia in an animal model. Literature search was conducted as follows with aid of an experienced university librarian.

Embase

("surgical equipment"/de OR mesh*:ab,ti OR prothes*:ab,ti OR prosthet*:ab,ti) AND (herni*:ab,ti OR hernioplasty/de OR herniorrhaphy/de OR herniotomy/de OR hernia/de OR "abdominal wall hernia"/exp OR "incisional hernia"/de) AND ["experimental animal"/de OR "animal model"/de OR (vertebrate/exp NOT human/de) OR animal/de OR nonhuman/de OR rodent/exp OR (animal* OR nonhuman* OR rodent* OR rat OR rats OR mice OR mouse OR hamster* OR pigs OR porcine* OR swine* OR goat*)].

PubMed

{mesh*[tw] OR prothes*[tw] OR prosthet*[tw]) AND (herni*[tiab] OR hernia[mesh:noexp] OR Hernia, Abdominal[mesh] OR herniorrhaphy[mesh]) AND ((animals[mesh] NOT humans[mesh]) OR (animal*[tw] OR nonhuman*[tw] OR rodent*[tw] OR rat[tw] OR rats[tw] OR mice[tw] OR mouse[tw] OR hamster*[tw] OR pigs[tw] OR porcine*[tw] OR swine*[tw] OR goat*[tw])}.

Study selection

Two independent researchers screened all titles and abstracts to select animal studies that were eligible for full-text review. Following primary screening, all full-text articles of the remaining studies were screened to identify studies using animal models aimed at mesh research. We included all English, Dutch, and German literature using an animal model to study meshes designed for abdominal wall hernia repair published between January 01, 2000, and January 01, 2014. Clinical trials, abstracts, letters to the editor, or studies not primarily aimed at studying meshes were excluded from further analysis.

Study outcome

All included articles were read, and all relevant parameters concerning the studied animal models used were scored in a standardized scoring sheet. All scored parameters are mentioned in Table 1. First, parameters for the animal model were assessed, including subspecies. Sex, weight, and age of the animals were recorded when mentioned in the article. Also the use of a previously published model was scored; this was defined as a clear reference to a previously published use of the same animal model. Details of the model used were subsequently scored. This included the creation of a hernia defect and size of defect (when applicable), location of the mesh, and size of the implanted mesh. Thereafter, the use and type of control group were scored, and duration of follow-up was recorded. Finally, used outcome parameters were scored (mentioned in Table 1).

Statistics

When applicable, data were tested using the statistical package for the social sciences (SPSS) version 22 for normal distribution using the Kolmogorov–Smirnov test for

Table 1. Scoring system for animal models

Parameter	Outcome
Animal model	Pig Rat Mice Rabbit Guinea Pig Other: specify
Subspecies	Free text
Sex	Male Female Both Unknown/not specified
Validated model	Yes No (no reference to previous research)
Infection model	Yes No Unknown
Defect	Yes, size (cm × cm): No Unknown/not specified
Mesh location	Intraperitoneal Inlay Bridging Subcutaneous Preperitoneal Unknown/not specified
Technique	Laparotomy Laparoscopy Other: specify Unknown
Mesh size	Size of mesh (cm × cm)
Control group	Yes: specify No Unknown/not specified
Follow-up	Duration of follow-up in days (1 month is scored as 30 days)

Outcome parameters		
Mesh ingrowth	Yes	No
Adhesion quality	Yes	No
Adhesion quantity	Yes	No
Mechanical testing/tensiometry	Yes	No
Mesh shrinkage	Yes	No
Histology	Yes	No
Immunohistochemistry	Yes	No

normality. Normally distributed data were presented as mean and standard deviation. Not normally distributed data were presented as median with range. All other data were presented as a percentage.

RESULTS

A total of 315 articles (supplementary data) were included in this study, of which 168 studied rats (53.3 percent), 66 studied rabbits (21.0 percent), and 53 studied pigs (16.8 percent). The remaining studies described use of mice, guinea pigs, primates, dogs, goats, sheep, and hamster models. A representation of the amount of publications per year showed an increase in yearly publications (Figure 1). Due to the variety in animals used, and the even larger variety in different animal models, all further analyses were performed on the 168 articles using a rat model. All other animal types were excluded from further analysis. Results are mentioned in Table 2.

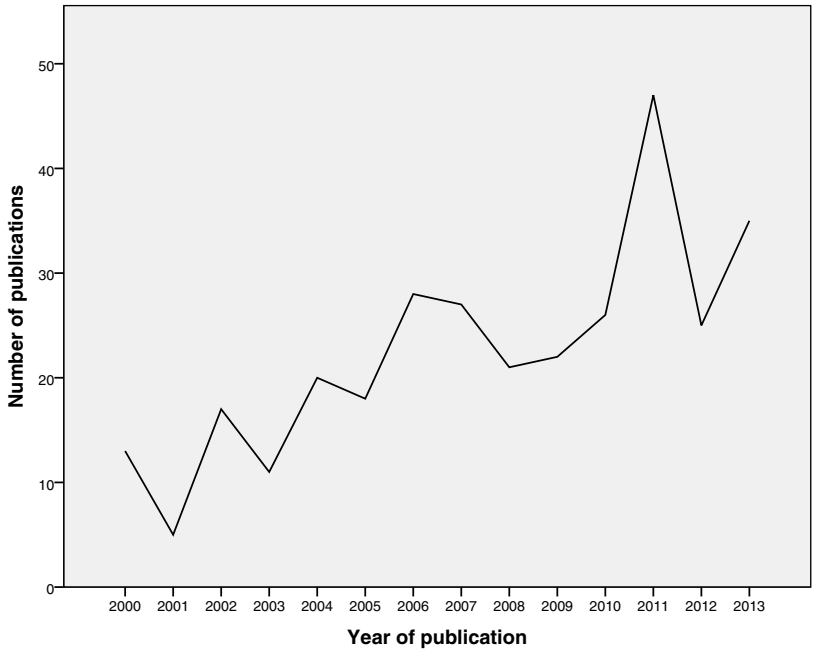

Figure 1. Number of publications per year since 2000

Table 2. Outcome of all scored parameters

Parameter	Outcome	
Animal model (%)[a]	Pig	16.8%
	Rat	53.3%
	Mice	3.5%
	Rabbit	21.0%
	Guinea pig	2.2%
	Other	3.2%
Subspecies (%)	Wistar	46.4%
	Sprague-Dawley	46.4%
	Lewis	4.1%
	Other	1.9%
	Unspecified	1.2%
Sex (%)	Male	66.7%
	Female	16.7%
	Both	1.8%
	Unknown/unspecified	15.4%
Reference to previously used model (%)	Yes	24.2%
	No	75.8%

Table 2. Outcome of all scored parameters (*continued*)

Parameter	Outcome	
Number of meshes/animal (%)	1	85.1%
	2	13.1%
	3	0.6%
	Unspecified	1.2%
Defect (%)	Yes, size (cm^2) mean (range)	72.2%, 4.2 cm^2 (0.5–18.0 cm^2)
	No	27.2%
	Unknown	0.6%
Mesh location (%)	Intraperitoneal	23.8%
	Inlay	11.9%
	Bridging	20.0%
	Subcutaneous	17.9%
	Preperitoneal	5.4%
	Unknown	11.9%
Infection model	Yes	9.5%
	No	90.5%
Mesh size	Size of mesh (cm^2) mean (range)	5.76 cm^2 (0.8–20 cm^2)
	Unspecified (% of articles)	17.3%
Control group	Yes	64.3%
	Polypropylene mesh	22.6%
	Sham	22.6%
	Primary repair	6.6%
	Other	12.5%
	No/not described	35.7%
Antibiotics	Yes	7.1%
	No	92.9%
Analgetics	Yes	15.5%
	No	84.5%
Number of endpoints median (range)	2 time points (1–6 time points), undefined in 1 article	
Follow-up duration median (range)	28 days (6 hours–365 days)	
Outcome parameters used (%)		
Mesh ingrowth		10.1%
Adhesions	Quality	16.1%
	Quantity	10.7%
	Both	24.4%
Mechanical testing/tensiometry		48.2%
Mesh shrinkage		17.3%
Histology		81.0%
Immunohistochemistry		23.2%

[a] For this analysis all animal types were scored, all other parameters only record results for rat studies.

Rat models

A total of 168 articles described the use of a rat model, using a total of 9150 rats in 164 studies, four remaining studies did not define the amount of animals. Median number of animals used per study was 56 (range 10–218) with a median of three groups per study (mean 3.7, mode 2, range 1–20). Most articles described the use of either Sprague-Dawley (78 studies, 46.4 percent) or Wistar (78 studies, 46.4 percent); subspecies was not defined in two studies. Sex of animals was defined in 85.1 percent of studies with 112 (66.7 percent) using male rats, 28 (16.7 percent) female, and 3 (1.8 percent) using both sexes; sex was not defined in the remaining studies (14.9 percent). References, that indicated the use of an established and previously published model, were provided in only 24.2 percent of articles (41 studies). Frequently used models included those published by Alponat and colleagues (12 studies) [12], Peter-Puchner and colleagues (four studies) [13], and Klinge and colleagues (three studies) [14].

Methods

All rats underwent open surgery for mesh implantation, receiving one (85.1 percent), two (13.1 percent), or three (0.6 percent) meshes per animal. Most models included the creation of a true hernia defect model (121 articles, 72.0 percent), one study did not define the use of a defect, and the remainder (46 articles, 27.4 percent) did not create a hernia defect. Defect size varied between 0.5 and 18.0 cm^2 with a mean of 4.2 cm^2 (median 4.0, mode 6.0). Meshes were either placed as bridging within a defect (49 articles, 29.2 percent), intraperitoneal (40 articles, 23.8 percent), subcutaneous (30 articles, 17.9 percent), inlay (20 articles, 11.9 percent), or preperitoneal (nine articles, 5.4 percent). Mesh position was not specified in 11.9 percent of articles (20 studies). Models aimed at mesh infections were only used in 16 publications (9.5 percent).

Meshes were cut to size with a median size of 6 cm^2 (mean 5.76 cm^2, range 0.8–20 cm^2); size of mesh was not defined in 29 articles (17.3 percent). Control groups were defined in 64.3 percent (108 articles). Most articles defined the use of a polypropylene control (including brand named polypropylene, e.g., Parietene™) or sham operated animals (both 38 articles, 22.6 percent). Others included primary/suture repair (11 articles, 6.6 percent). Part of included articles compared mesh coatings instead of different meshes; this leads to uncoated meshes being control group in 17 studies (10.1 percent).

The use of perioperative antibiotics for infection prevention was only mentioned in 7.1 percent of articles (12 studies). Out of these studies, antibiotics used were from the penicillin group, gentamicin, and fluoroquinolone antibiotics (four studies each). If animal models other than rats were added in the analysis, up to 20.6 percent of articles described the use of antibiotics, with cephalosporin-type antibiotics being used most.

Perioperative pain relief using analgesic medication has been mentioned in 15.5 percent of rat models (26 studies, versus 22.8 percent or 72 studies when reviewing all animal models). Within these 26 studies, opioid-type analgesics were used in majority of cases (17 articles, 10.1 percent), sometimes combined with NSAIDs (two articles, 1.2 percent), followed by NSAID (seven articles, 4.2 percent) or local analgesics (five articles, 3.0 percent).

Follow-up

Duration of follow-up was defined in 167 of 168 included articles. The number of endpoints ranged from one to six per article with a median of two time points per article (mean 2.21, mode 1). Duration of follow-up ranged from 6 hours to 365 days, with a median duration of 28 days. Time points that were used most frequently were, respectively, 1 month (including follow-up defined as 4 weeks and 30 days), 3 months (or 90 days), and 1 or 2 weeks.

Outcome parameters

Outcome parameters were scored from all 168 articles. Histological examination of explanted meshes was performed in nearly all articles (81.0 percent, or 136 articles), 39 of these articles (23.2 percent) subsequently added immunohistochemical analysis. Strength of ingrowth was either defined as subjective macroscopic ingrowth (scored in 10.1 percent, 17 articles), or mechanical strength measured by tensiometry (scored in 48.2 percent, 81 articles). Adhesions were scored in 86 articles (51.1 percent), scored as adhesion quality (27 articles, 16.1 percent), adhesion quantity (18 articles, 10.7 percent), or both (41 articles, 24.4 percent). Mesh shrinkage was scored in only 17.3 percent of articles (29 articles). An analysis of the scoring systems used is presented in Table 3.

Table 3. Overview of scoring systems used

	Different scoring systems (number of scoring systems)	Validated scoring system (number of scoring systems/% articles)[a]	(Semi-) quantitative or objective scoring (number of scoring systems/% articles)	New scoring system (% articles)[b]	Unknown or pure descriptive scoring (% of articles)
Ingrowth	12	3 / 5.9	4 / 76.4	5.9	11.8
Adhesion quality	24	19 / 75	16 / 73.5	14.7	7.3
Adhesion quantity	11	5 / 86.4	9 / 94.9	18.6	6.7
Shrinkage	9	3 / 89.6	29 / 100	20.7	0.0
Histology	47	13 / 47.1	7 / 36.8	22.8	30.1
Immunohistochemistry	9	2 / 59.0	3 / 61.5	15.4	20.5

Number indicates the number of different scoring systems involved. The percentage is the percentage of articles involved.

[a] Validated scoring system is defined as either a system with clear reference or an accepted system used in the same manner in multiple articles.

[b] New scoring systems are defined as scoring systems used only in one article.

DISCUSSION

Critical review of the literature revealed a large variety in mesh models; many different models, animal species, meshes, and parameters were assessed in the last decade leading to studies that were difficult to compare among each other.

Identical models including all parameters were not found to be implemented by different centers, in other words all centers apparently use their own specific models. Due to the growing variety in existing and new concepts of meshes, preclinical animal research is necessary to assess biocompatibility and effectiveness of new meshes before implementing them in clinical practice [7-9]. Furthermore, many of the important mesh characteristics are derived from and can only be properly researched using animal models [4]. However, for experimental research to have proper impact, research published by different research groups needs to be comparable and reproducible [3, 15].

In this study, we attempted to provide a systematic overview of all available animal models for mesh research. However, due to the large amount of different animals used we decided to focus on only one species. Although large animal models like pigs are supposed to resemble the human situation most, over 50 percent of all experimental hernia research focused on rat models [7, 16]. Therefore, we decided to limit this overview and only elaborate on rat models. We realize that limitation to one animal group might lead to bias in information leading to a possible underestimation or even overestimation of the problem. This could possibly be solved by using a combination of a small animal model for preliminary testing and immunohistochemistry, which might be followed by testing on a larger animal model, which will better resemble the anatomy of the human abdominal wall.

One of the first issues that needs to be addressed concerns the use of mostly young male rats. Although incisional hernias occur in both male and female patients, with some clinical studies even reporting female sex as an independent risk factor, almost all included experimental studies report the use of male rats only [17, 18]. Furthermore, more than one in every seven authors did not report the sex of the animal in their papers, even though there is an increasing amount of information on the effect of sex on the outcome [19, 20].

Therefore, we believe that in accordance to the ARRIVE guidelines and the recently published NIH policy there should be an effort to report on and also balance sex of animals in experimental hernia repair [20, 21]. Moreover, most studies used rats that were of fairly young age, whereas most patients present with hernias later in life.

The results of our survey lead to the assumption that very few researchers make use of already published articles. Although this might be an underestimation due to the fact that not all researchers reference to previously published articles, there still seems to be a large variety in published models. This could lead to irreproducible results or results that cannot be compared between different publications [10, 11]. This also makes translation to clinical practice extremely difficult [7, 15, 16]. Hence, we think that limiting the range of mesh models to a smaller selection of models and clear referencing to standardized models could lead to increase the impact of future publications and in turn benefit hernia surgery [22-24].

We believe one important factor for the choice of hernia models should be that it closely resembles the human situation and follows the guidelines for hernia repair in humans. One discrepancy between human situation and most hernia models is the "hernia age". Most animal models described use an acute hernia model, where the defect is created in the same procedure as the mesh is placed. In the human situation, hernias take time to mature, possibly altering postoperative results. Perhaps the use of a "mature hernia" model as proposed by Dubay and colleagues in 2006 would better resemble the clinical situation [25]. Furthermore, following the 2014 International Endohernia Society (IEHS) guidelines intraperitoneal onlay meshes (IPOM) with closed defects should be used [26].

Another point of interest is the mesh positioning. Although some mesh positions are considered outdated in the clinical setting, there is no decrease in the use of these models over the years. To further increase the impact of the animal studies on clinical practice, it might be good to translate guidelines for human hernia surgery to preclinical animal models. In particular, the IPOM with mesh augmentation, as is advocated in the recent IEHS guidelines, is only used in less than one-fourth of published studies [26]. Furthermore, since the preclinical studies are mostly aimed at investigating host response to meshes and mesh materials, the use of a standardized control group could improve reproducibility and could help put results in perspective.

Despite official guidelines on laboratory animal welfare in both Europe and the USA requiring the use of analgesics when pain is to be expected, analgesics are only reported in a minority of studies [27, 28]. Since hernia operations can be considered major abdominal surgery, pain is to be expected and use of analgesics and the reporting on their use should be promoted according to international regulations.

Despite the heterogeneity in the included studies, there already seems to be some degree in consensus for some aspects. For instance, most authors seem to agree that the creation of an abdominal wall defect is preferred above primary closure, be it with a

large range in size of defects and meshes used. There also seems to be some degree of consensus for outcome parameters, whereas majority of studies use histological analysis and adhesion scoring as primary outcome. On the other hand, up to one-fifth of these articles seem to introduce new scoring systems to evaluate these outcome measurements instead of using readily available validated methods.

Hence, we believe guidelines for publishing and reporting of experimental research for hernia research need to be put in place. Different aspects of hernia research need to be standardized in order to increase impact of experimental research.

Furthermore, standardization should lead to a reduction in the discrepancy between results in animal research and clinical research, as is often seen in many fields of medicine [23, 29]. Additionally, standardization would make definitive statements on new mesh products easier, as they can easily be compared to results from well-known materials.

Furthermore, the standardization of mesh research should be extended to the industry. The current regulations for approval of a new mesh concept by the FDA require the material only to be "substantially equivalent" to readily available materials, leaving interpretation of this equivalency open to interpretation of the manufacturer [30, 31]. The manufacturer does have to compare the new device to similar devices. However, new guidance documents from the FDA do note that any change to direct or indirect tissue-contacting products should be evaluated using biocompatibility analysis. We believe there should be standardized requirements set by the hernia societies for any new hernia devices introduced on the market.

One of the limitations of this study could be the lack of information on the quality of the animal models, preferably using the ARRIVE guidelines for animal research as proposed by Kilkenny and colleagues in 2010 [21]. However, we believe this does not aid the aim of our study. Furthermore, we believe the quality assessment of hernia research deserves a separate review additionally assessing the implementation of the ARRIVE guidelines within the hernia research.

Therefore, following the consensus for clinical research as published by Muysoms and colleagues, we believe guidelines and recommendations for experimental mesh research need to be put in place or at least start a discussion on the consensus within animal hernia research models [32]. We therefore propose the establishment of an EHS (European Hernia Society) chapter for experimental research.

Authors contributions

R. Vogels was involved in the brainstorm session preliminary to the review process, decision on inclusion and exclusion criteria, literature search and selection of articles, reading of included articles, setting up the database with all parameters included in this review, and writing and proofreading the submitted article. R. Kaufmann was involved in the brainstorm session preliminary to the review process, decision on inclusion and exclusion criteria, literature search and selection of articles, reading of included articles, setting up the database with all parameters included in this review, and writing and proofreading the submitted article. L. van den Hil aided with the database including all article parameters and aided in writing process and proofreading the article. S. van Steensel aided with the database including all article parameters and aided in writing process and proofreading the article. M. Schreinemacher was involved in the preliminary brainstorm session and aided in setting in- and exclusion criteria and relevant scoring parameters. Furthermore, he aided in writing and proofreading process and is involved in setting up an experimental chapter for EHS J. Lange was involved in the preliminary brainstorm session and aided in setting in- and exclusion criteria and relevant scoring parameters. Furthermore, he aided in writing and proofreading process and is involved in setting up an experimental chapter for EHS N. Bouvy was involved in the preliminary brainstorm session and aided in setting in- and exclusion criteria and relevant scoring parameters. Furthermore, he aided in writing and proofreading process and is involved in setting up an experimental chapter for EHS.

Compliance with ethical standards

Conflict of interest

RV, RK, LH, SS, MS, JL, NB declare no conflict of interest.

Statement of human and animal rights

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

No informed consent was necessary for the study.

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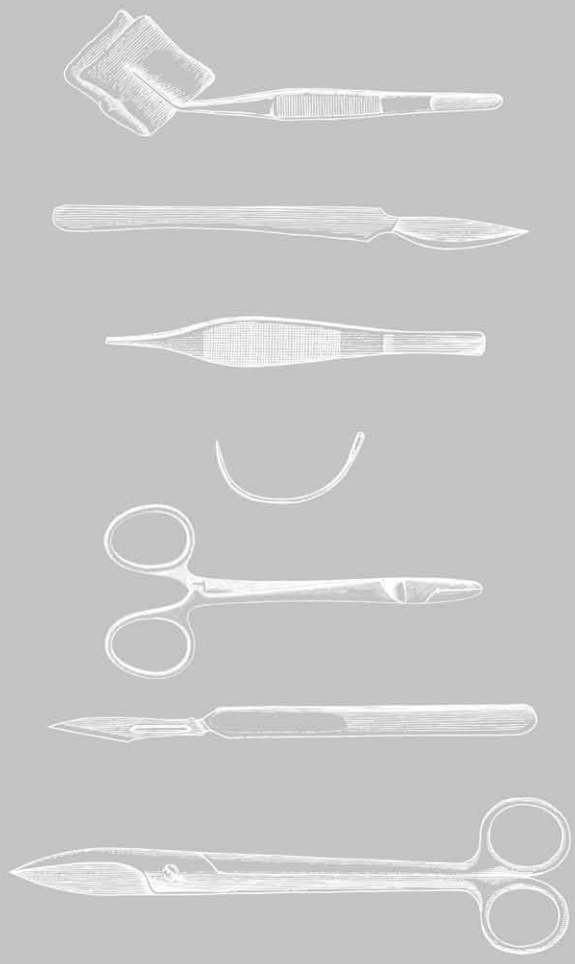
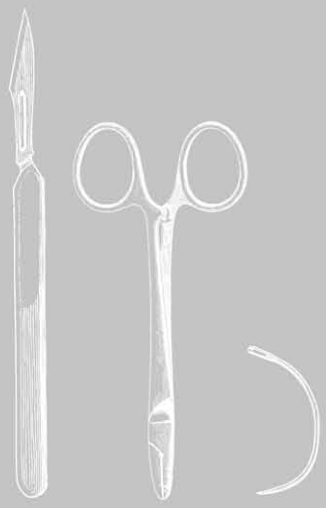


3

Non-cross-linked collagen mesh performs best in a physiologic, non-contaminated rat model



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ABSTRACT

Introduction

In laparoscopic incisional hernia repair, direct contact between the prosthesis and abdominal viscera is inevitable and may lead to adhesions. Despite the large variety of mesh prosthesis, little is known about their in vivo behavior. Biological meshes are considered to have many advantages, but due to their price they're rarely used. A rat model was used to assess biological and conventional synthetic meshes on their in vivo characteristics.

Methods

One-hundred twenty male Wistar rats were randomized into five groups of 24 rats. A mesh was implanted intraperitoneally and fixated with non-resorbable sutures. The following five meshes were implanted: Parietene™ (polypropylene), Permacol™ (cross-linked porcine acellular dermal matrix), Strattice™ (non-cross-linked porcine acellular dermal matrix), XCM Biologic® (non-cross-linked porcine acellular dermal matrix), Omyra® Mesh (condensed polytetrafluoroethylene). The rats were sacrificed after 30, 90, or 180 days. Incorporation, shrinkage, adhesions, abscess formation, and histology were assessed for all meshes.

Results

All animals thrived postoperatively. After 180 days, Permacol™, Parietene™ and Omyra® Mesh had a significantly better incorporation than Strattice™ ($P = 0.001$, $P = 0.019$, and $P = 0.037$ respectively). After 180 days, Strattice™ had significantly fewer adhesions on the surface of the mesh than Parietene™ ($P < 0.001$), Omyra® Mesh ($P = 0.011$), and Permacol™ ($P = 0.027$). After 30 days, Permacol™ had significantly stronger adhesions than Strattice™ ($P = 0.030$). However, this difference was not significant anymore after 180 days. After 180 days, there was significantly less shrinkage in Permacol™ than in Strattice™ ($P = 0.001$) and Omyra® Mesh ($P = 0.050$).

Conclusion

Based on incorporation, adhesions, mesh shrinkage, and histologic parameters Strattice™ performed best in this experimental rat model.

INTRODUCTION

Incisional hernia is a common postoperative complication. Incidences range from 3 to 20 percent in the general population with an increased incidence of up to 39 percent in patients suffering of obesity or aortic aneurysms [1]. Correction of incisional hernias is nowadays most often performed with mesh reinforcement [2]. The use of mesh radically lowered the 10-year recurrence rates after incisional hernia repair [3]. Meshes are produced in a large variety of materials, structures, and shapes, and even composites are available [4]. Conventional synthetic meshes are still used most often in general practice and polypropylene mesh is the most popular product [5].

In laparoscopic incisional hernia repair, direct contact between the mesh prosthesis and the abdominal viscera is inevitable. This may lead to an inflammatory reaction resulting in abdominal adhesion formation. Despite the large variety of available mesh prosthesis, there is only limited knowledge on their in vivo behavior. Synthetic meshes are used for various decades now, however, biological meshes were just recently introduced [6, 7]. Biological meshes are matrices made from collagen containing tissues of human, porcine, bovine, or equine origin. Tissues such as intestines, heart valves, or skin are processed to remove any host debris (cells, cell components, and hairs) as well as various antigens present in the tissue [8, 9]. After decellularization and degradation of these tissues, a 3D structure of collagen and some protein remnants like growth factors remains. After completing this step, additional chemical cross-linking can be done with chemicals like hexamethylene diisocyanate, carbodiimide, glutaraldehyde, or photo-oxidizing agents [10, 11]. Additional cross-linking is performed to increase the strength of the mesh, and to slow down the degradation of the mesh after implantation [8, 12]. During this phase of degradation, there is incorporation of host fibroblasts into the mesh and collagen replacement occurs. This so-called xenograft remodeling begins within a few hours after implantation and takes several months to years.

Biological meshes are said to have many advantages, but are also very expensive [6]. Consequently, these meshes are only rarely used, which leads to studies with heterogeneous populations, mostly short-term follow-up, and little data on long-term results [13-15]. Both biological and conventional synthetic meshes were investigated in a physiologic, non-contaminated rat model in an intraperitoneal position to assess the in vivo characteristics of these prostheses with long-term follow-up. The aim of this study was to compare commonly used biological and synthetic meshes in an intraperitoneal environment on incorporation, shrinkage, adhesion formation, abscess formation, and histology after 30, 90, and 180 days. The working hypothesis for this study is that biological meshes behave better than synthetic meshes in an intraperitoneal position.

METHODS

Animals

One-hundred twenty male Wistar rats were obtained from a licensed breeder of laboratory animals (Harlan Laboratories, Boxmeer, the Netherlands). The rats were bred under specific pathogen-free conditions and kept under standardized laboratory conditions (environmental temperature 20–24°C; relative air humidity of 50–60 percent; and 12-hours light–dark cycles). The rats were housed in pairs in individually ventilated cages. All rats were fed ad libitum with standard rat chow and water. The animals weighed upon arrival in the experimental facility 250–325 grams each. The rats were acclimatized at least for 7 days prior to the start of the experiment. The experimental protocol was approved by the Ethical Committee on Animal Experimentation of the Erasmus University Medical Center, Rotterdam, the Netherlands.

Experimental model

At the start of the experiment, all 120 male Wistar rats were randomly divided into five groups of 24 animals each. Prior to operation, the rats were anesthetized with inhalation anesthesia (mixture of isoflurane (Pharmachemie, Haarlem, the Netherlands) and oxygen) and they received a single dose of buprenorphine analgesia (0.05 mg/kg subcutaneously) (Reckitt Benckiser Healthcare (UK) Limited, Kingston-upon-Thames, United Kingdom). The rats were weighed, their abdomen was shaved, and the skin was disinfected with 70 percent ethanol. The rats were positioned in supine position. The abdominal cavity was opened by a 3-cm midline incision and a sterile mesh of 2.5 × 3.0 cm was inserted. This mesh was placed intraperitoneally and fixated transmuscularly with six non-absorbable nylon sutures (5/0 Ethilon®; Ethicon, Somerville, NJ, USA). The fascia and skin were closed separately with a running absorbable suture of polyglycolic acid (5/0 Safil®; B. Braun, Melsungen, Germany). After mesh implantation, all animals received a single dose of gentamicin (6 mg/kg intramuscularly) and a dose of 5 ml sodium chlorine 0.9 percent subcutaneously. Postoperatively, the rats were placed under a heating lamp to recover from anesthesia in the immediate postoperative phase.

Physiologic rat model

In this rat model, all meshes were placed in a physiologic, non-contaminated intraperitoneal environment to assess their characteristics in the absence of an infection. Contrary to a previous study from this research group in which the same meshes were examined in a contaminated intraperitoneal environment to assess their characteristics in the presence of a fulminant infection [16].

Mesh material

Five different meshes were implanted: polypropylene (Parietene™, Sofradim, Trévoux, France; part of Covidien–Medtronic, New Haven, Connecticut, USA), cross-linked porcine acellular dermal matrix (Permacol™; Sofradim), non-cross-linked porcine acellular dermal matrix (Strattice™; LifeCell Corporation, Branchburg, New Jersey, USA), another non-cross-linked porcine acellular dermal matrix (XCM Biologic®; Kensey Nash Corporation, Exton, Pennsylvania, USA, distributed by DePuy Synthes, Oberdorf, Switzerland), and condensed polytetrafluoroethylene (c-PTFE; Omyra® Mesh, B. Braun). Prior to implantation, all meshes were prepared in a sterile environment to create smaller meshes of 2.5 × 3 cm. All meshes were handled according to the Instructions for Use of their manufacturers.

Postoperative outcomes

Wellness and survival of the animals

Postoperatively, all animals were weighed on a daily base in the first week and thereafter on a weekly base. Based on the weighing results mean weight loss was calculated by subtracting the rat's weight at the start of the experiment and the maximum amount of weight loss during the first 7 days of the experiment. During weighing, the animals were assessed for signs of discomfort. To objectify these signs of discomfort, the rat's behavior was assessed with a 12-point wellness scoring system [17]. Rats reached the humane endpoint if they suffered from at least 20 percent weight loss or a wellness score less than 5 points. All rats that reached the humane endpoint were euthanized. Euthanized or deceased animals underwent a necropsy. The data of euthanized or deceased animals were included for analyses.

Sacrifice

The experimental endpoints were 30 days, 90 days, and 180 days after mesh placement. During sacrifice, a photograph was taken from the inner abdominal wall and the mesh site. Figure 1 shows a photograph taken at time of sacrifice showing inner abdominal wall and mesh site (non-cross-linked biological mesh). The black box in Figure 1 shows a schematic representation of the tissue sampling for histopathology. The following parameters were assessed: incorporation and shrinkage of the mesh, and adhesion formation (coverage, and strength).

Incorporation of the mesh

Incorporation of the mesh was assessed with a slide calliper. The number of millimeters of all sides of the remaining mesh were measured. The standard length and width of the implanted mesh were 30 × 25 mm. Thereafter, the number of millimeters of each side

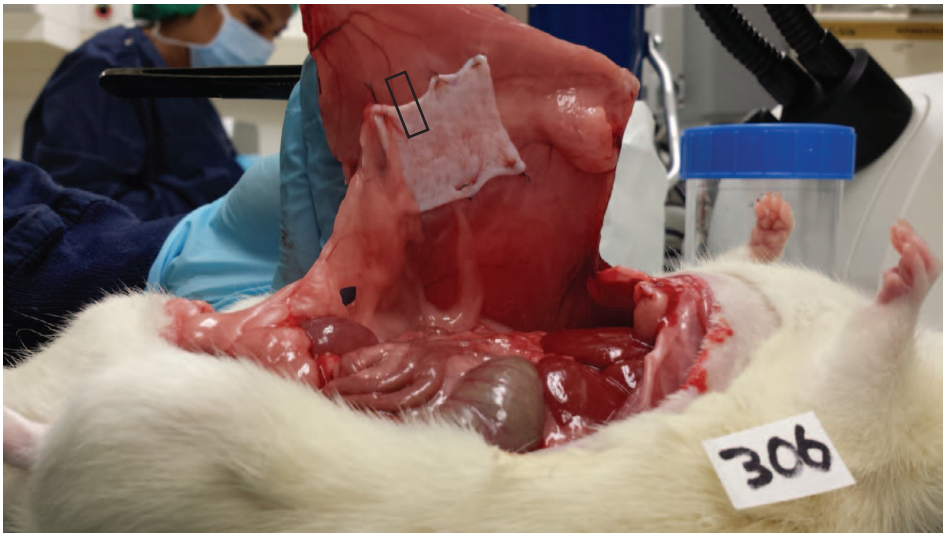

Figure 1. Photograph taken at time of sacrifice showing the inner abdominal wall and mesh site
The depicted mesh is a non-crosslinked biological mesh. The black box is a schematic representation of tissue sampling for histopathology.

of the mesh that showed incorporation were measured. Both measures resulted in a percentage of incorporation. Full incorporation was incorporation of all sides taking any shrinkage of the mesh into account.

Shrinkage of the mesh

Shrinkage of the mesh was assessed by measurement of the surface of mesh that was present during sacrifice. The measurement was performed with a standardized calliper and the mesh surface found during sacrifice was compared with the standardized implant size (7.5 cm^2) and expressed in a percentage of this standardized implant.

Adhesion formation

Adhesion formation was assessed in two ways. Firstly, a qualitative analysis was performed using the Zühlke score [18]. The Zühlke score was used to assess the strength and tenacity of adhesions. The score ranges from 0 (no adhesions) to 4 (very strong adhesions) (Supplementary data, Table S1). Table S1 shows the Zühlke scoring system for adhesions that was used to assess adhesions in this study. Secondly, the quantity of adhesions was assessed and expressed in a percentage of adhesions on the surface of the mesh. Two independent investigators assessed both parameters. Discrepancies were discussed amongst the two investigators and resolved together.

Abscesses

The presence of mesh abscesses was regarded as an expression of an ongoing intra-abdominal infection. The presence of abscesses was assessed with a standardized visual inspection and examination of the abdominal cavity of all rats. If abscesses were present, their size was scored with the Abscess Scoring System [19] (Supplementary data, Table S2). Table S2 shows the abscess scoring system.

Scoring system for the ranking of all meshes

The characteristics that were assessed in this study were incorporation of the mesh, shrinkage of the mesh, adhesion formation, abscess formation, and histologic parameters. To assess the ranking of the meshes, all meshes received a score of 1 (worst performing mesh) to 5 (best performing mesh) for each individual parameter. Adhesions were considered to be the decisive factor, because of the intra-abdominal position of the mesh.

Histologic evaluation

After sacrifice, a full-thickness abdominal wall sample of 1.0 by 0.5 cm was harvested from each rat. This sample was taken from one of the long sides in between the sutures and contained both abdominal wall and mesh (Figure 1). Figure 1 shows a schematic representation of the tissue sampling for histopathology. All samples were fixated in 4 percent formalin and embedded in paraffin. Samples were cut into 4 µmeter thick slices, and stained with either hematoxylin and eosin (HE) or sirius red (SR) according to standard diagnostic procedure.

The histologic evaluation of all slides was performed in a blind fashion by an experienced pathologist (MC-vG). HE slides were analyzed by a scoring system described by Peeters and colleagues [20] (adapted from Jenkins and colleagues [21]). All cells were assessed under the microscope under a 40 × magnification and the number of cells per high-power field (40 × magnification) was counted. No additional stains were performed. SR slides were assessed with the scoring system described by Deeken and Matthews [22]. The histological analysis of the biological meshes focused on the periprosthetic area. The histological analysis of Parietene™ and Omyra® Mesh focused on both the perifilamentary areas and the pores. Both areas were assessed and a grade was given for the overall number of cells per sample. In the SR slides the amount of fibrous encapsulation around each mesh was assessed. The histologic scoring systems can be found in Supplementary data, Table S3, Table S4 and Table S5. Table S3 shows the histologic scoring system for inflammatory cell reaction. Table S4 shows the histologic scoring system for mesh-specific parameters. Table S5 shows the histologic scoring system for collagen deposition.

Statistical analysis

Prior to the start of the experiment, a sample size calculation was performed. The sample size calculation was made regarding an expected decrease in amount of adhesions of 25 to 30 percent. The expected mortality of the mesh model was 10 percent. Aiming for a power of 80 percent and a *P* value of 0.05, the necessary number of animals was 24 per group. All meshes were included in the experiment as equal study groups. None of the study groups served as a control group only.

In this experiment, only the data of incorporation of the mesh showed a normal distribution. All other parameters did not show a normal distribution, thus statistical analyses were performed using non-parametrical Kruskal–Wallis tests for independent samples. If the overall statistical test showed significant differences, pairwise tests were done to determine the groups causing the overall statistical significance.

Baseline characteristics like weight loss were summarized in percentages, continuous variables using means and standard errors of the mean, categorical values were summarized with medians and interquartile ranges. All *P* values were tested with a two-tailed test of significance, a *P* value of < 0.05 was considered statistically significant and all *P* values were adjusted for multiple testing using Dunn's post-test. The statistical analyses were performed using SPSS version 21.0.

RESULTS

Animals

All 120 rats survived the operation and thrived afterwards. None of the rats reached the humane endpoint. The maximum postoperative weight loss varied between 0 to 7 percent among the five groups and was more pronounced in the Parietene™ group ($P = 0.001$), and the Permacol™ group ($P < 0.001$). There were no differences observed in weight change or wellness score among the five groups. Table 1 shows an overview of the experimental groups in this experiment. In this table, the distribution of the animals per study group and per study time point can be found.

Incorporation of the mesh

There was a fluctuating amount of incorporation in all meshes with most often first a decrease in ingrowth at 90 days compared with 30 days, followed by an increase after 180 days compared with 90 days. The amount of incorporation strongly varied between the mesh groups. One-hundred and eighty days after implantation, incorporation was most superior in Permacol™ (62 ± 11 percent), followed by Omyra® Mesh (58 ± 20 per-

Table 1. Overview of the experimental groups in this experiment

	Parietene™	Permacol™	Strattice™	XCM Biologic®	Omyra® Mesh
Mesh material	Polypropylene	Cross-linked collagen of porcine dermis	Non-cross-linked collagen of porcine dermis	Non-cross-linked collagen of porcine dermis	Condensed PTFE
Weight (g/m^2)	78	n.a.	n.a.	n.a.	90
Pore size (mm)	1.0–1.6	n.a.	n.a.	n.a.	2.4
No. of animals	24	24	24	24	24
Postoperative deaths	0	0	0	0	0
No. analyzed					
30 days	8	8	8	7	8
90 days	8	8	8	9	8
180 days	8	8	8	8	8

n.a. = not applicable

cent), Parietene™ (56 ± 9 percent), XCM Biologic® (43 ± 12 percent), and most inferior in Strattice™ (23 ± 13 percent). After 180 days, mesh incorporation was significantly lower in Strattice™ compared with Omyra® Mesh ($P = 0.037$), Parietene™ ($P = 0.019$), and

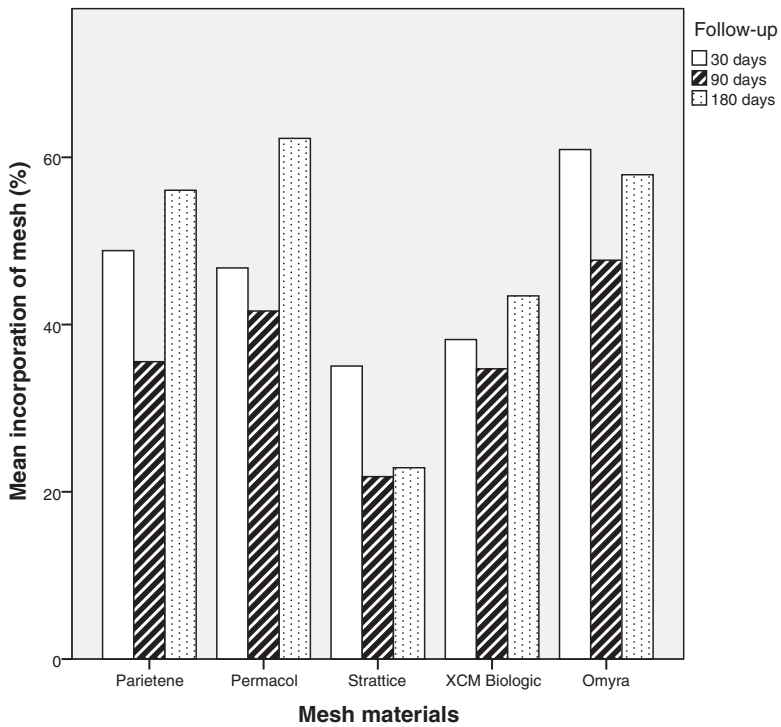

Figure 2. Mean percentage incorporation of each mesh at 30, 90 and 180 days

Permacol™ (P = 0.001) (Figure 2, and Table 2). Figure 2 shows the incorporation of the mesh after 30, 90, and 180 days. The mean incorporation is expressed in percentage. Table 2 shows the results of macroscopic mesh-specific parameters after sacrifice.

Table 2. Results of macroscopic mesh-specific parameters after sacrifice

	n	Incorporation of mesh (%)	Shrinkage of mesh (%)	Adhesions on mesh (%)	Tenacity of adhesions
Parietene™					
30 days	8	49 ± 13	8 (5–13)	83 (78–90)	3 (3–3)
90 days	8	36 ± 12	7 (5–14)	88 (85–93)	3 (3–3)
180 days	8	56 ± 9	9 (5–13)	85 (70–90)	3 (3–3)
Permacol™					
30 days	8	47 ± 18	11 (3–23)	75 (60–85)	4 (3–4) A
90 days	8	42 ± 15	7 (3–11)	75 (70–78)	4 (3–4)
180 days	8	62 ± 11	0 (0–4) B	68 (63–73)	4 (3–4)
Strattice™					
30 days	8	35 ± 14	13 (7–18)	5 (5–10) C	3 (3–3)
90 days	8	22 ± 11	15 (6–18)	5 (5–5) D	3 (3–3)
180 days	8	23 ± 13 E	18 (15–22)	5 (0–5) F	3 (3–3)
XCM Biologic®					
30 days	7	38 ± 6	7 (0–7)	30 (25–55)	3 (3–3)
90 days	9	35 ± 13	12 (8–14)	40 (35–45)	3 (3–3)
180 days	8	43 ± 12	10 (5–16)	35 (28–35)	3 (3–3)
Omyra® Mesh					
30 days	8	61 ± 11	16 (13–17)	53 (45–80)	3 (3–3)
90 days	8	48 ± 21	17 (14–31)	63 (45–85)	3 (3–3)
180 days	8	58 ± 20	13 (8–30)	75 (60–75)	3 (3–4)

Incorporation of mesh values are mean ± SD
All other values are median (IQR).

Significant differences between:

A Permacol™ 30 days and Strattice™ 30 days (P = 0.030)
B Permacol™ 180 days and Omyra® Mesh 180 days (P = 0.050), and Strattice™ 180 days (P = 0.001)
C Strattice™ 30 days and Permacol™ 30 days (P = 0.023), and Parietene™ 30 days (P < 0.001)
D Strattice™ 90 days and Permacol™ 90 days (P = 0.011), and Parietene™ 90 days (P < 0.001)
E Strattice™ 180 days and Omyra® Mesh 180 days (P = 0.037), Parietene™ 180 days (P = 0.019), and Permacol™ 180 days (P = 0.001)
F Strattice™ 180 days and Permacol™ 180 days (P = 0.027), Omyra® Mesh 180 days (P = 0.011), Parietene™ 180 days (P < 0.001)

Shrinkage of the mesh

All meshes shrunk after implantation, however the amount of shrinkage varied strongly: 0 to 18 percent on different time points in different meshes (Figure 3, and Table 2). Figure 3

shows the shrinkage of each mesh after 30, 90, and 180 days. Median shrinkage is expressed in percentage. Table 2 shows the results of macroscopic mesh-specific parameters after sacrifice. After 180 days, shrinkage was most evident in Strattice™ (18 (IQR 15–22) percent), followed by Omyra® Mesh (13 (8–30) percent), XCM Biologic® (10 (5–16) percent), and Parietene™ (9 (5–13) percent). Shrinkage was least prominent in Permacol™ (0 (0–4) percent at 180 days). After 180 days, there was significantly less shrinkage in Permacol™ than in Strattice™ ($P = 0.001$) and Omyra® Mesh ($P = 0.050$).

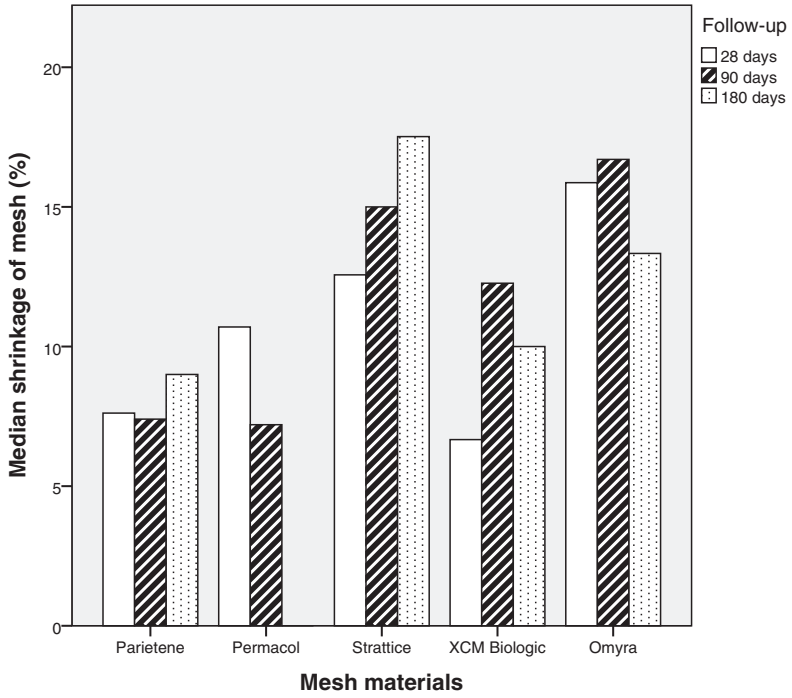

Figure 3. Median shrinkage of each mesh at 30, 90 and 180 days

Adhesions

One-hundred and eighty days after implantation, the percentage adhesions on the mesh surface was highest in Parietene™ (85 (IQR 70–90) percent), followed by Omyra® Mesh (75 (60–75) percent), Permacol™ (68 (63–73) percent), XCM Biologic® (35 (28–35) percent), and lowest in Strattice™ (5 (0–5) percent) (Figure 4). Figure 4 shows the adhesions on each mesh after 30, 90, and 180 days. The median value of adhesions is expressed in percentage. Strattice™ had significantly fewer adhesions on the surface of the mesh than Parietene™ ($P < 0.001$), Omyra® Mesh ($P = 0.011$) and Permacol™ ($P = 0.027$) after 180 days.

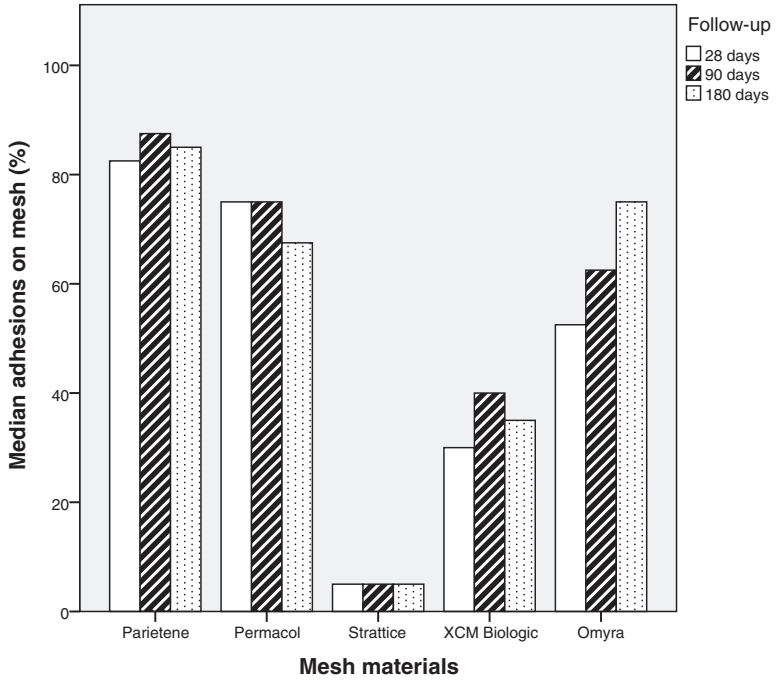

Figure 4. Median percentage of adhesions on each mesh at 30, 90 and 180 days

The tenacity of adhesions, expressed in the Zühlke score, was median 3 in Parietene™, Strattice™, XCM Biologic®, and Omyra® Mesh, and median 4 in Permacol™ at all time points. After 30 days, Permacol™ had significantly stronger adhesions than Strattice™ ($P = 0.03$). However, this difference was not significant anymore after 180 days (Table 2). Table 2 shows the results of macroscopic mesh-specific parameters after sacrifice.

Abscesses

There were no abscesses found on either of the meshes or in the intra-abdominal cavity at all time points.

Histological evaluation

In one of the rats that had Permacol™ implanted, there was no mesh left 180 days after implantation. In all other samples, meshes were still present after sacrifice and histologic evaluation was performed. H&E staining of the samples revealed no significant difference in the total count of inflammatory cells between all meshes. There were however significant differences in the number of eosinophils, macrophages, mononuclear cells, and extracellular matrix deposition between the different mesh groups (Supplementary data, Table S6 and Table S7). Table S6 shows the results of histologic evaluation after sacrifice. The results are presented as median (interquartile ranges). Table S7 shows the results of

mesh-specific parameters after sacrifice. The results are presented as median (interquartile ranges). All histological findings will be discussed individually. Examples of the histological slides can be found in the Supplementary data, Figure S1 to S10. The hematoxylin and eosin slides show samples of 180 days after implantation (10 × magnification). The sirius red slides show samples of 180 days after implantation (5 × magnification).

Parietene™

Parietene™ mesh had a significantly higher number of eosinophils, neutrophils, and macrophages on various time points when compared with Permacol™, Strattice™, and XCM Biologic® (Supplementary data, Table S6). Table S6 shows the results of histologic evaluation after sacrifice. The results are presented as median (interquartile ranges). After 30 days of follow-up, there was a significantly lower number of mononuclear cells in the Parietene™ samples compared with XCM Biologic® ($P = 0.019$). Collagen deposition was higher than in the other meshes, however, there was no significant difference when compared with other meshes.

The mesh-specific histological parameters revealed statistically higher scaffold degradation in the non-cross-linked biological meshes XCM Biologic® ($P = 0.049$) and Strattice™ ($P = 0.018$) when compared with Parietene™ 30 days after implantation. Fibrous encapsulation was significantly lower in Parietene™ than in XCM Biologic® after 90 days ($P = 0.024$). Cellular infiltration, and neovascularization were significantly lower in Parietene™ than in Strattice™ 90 and 180 days after implantation. Extracellular matrix deposition was low to moderate present in all samples and showed no significant differences with other meshes.

Permacol™

Permacol™ contained only very few eosinophils and neutrophils, significantly less than in Parietene™ (at all time points). The number of macrophages and mononuclear cells was low to moderate, but there were no significant differences with other meshes. Collagen deposition was moderate, but significantly lower than in Omyra® Mesh after 180 days.

The mesh-specific histological parameters revealed that fibrous encapsulation was very low and showed no significant differences with other meshes. Scaffold degradation, neovascularization, and extracellular matrix deposition were significantly lower in Permacol™ than in Strattice™ after 90 days. Cellular infiltration was significantly lower than in Strattice™ after both 90 and 180 days.

Strattice™

Strattice™ mesh contained only very few eosinophils and neutrophils, significantly less than in Parietene™ (at all time points). After 180 days, only few macrophages were found in Strattice™, significantly less than in Parietene™ ($P = 0.004$). The number of mononuclear cells and the amount of collagen deposition was quite high, but diminished over time. After 180 days, the amount of collagen deposition was significantly lower than in Omyra® Mesh ($P = 0.003$).

Scaffold degradation was significantly higher in Strattice™ at all time points. Fibrous encapsulation was low and showed no significant differences with other meshes. Cellular infiltration and neovascularization were significantly higher in Strattice™ after 90 and 180 days, when compared with Parietene™, Omyra® Mesh, and Permacol™. Extracellular matrix deposition was significantly higher than in Permacol™ after 180 days ($P = 0.020$).

XCM Biologic®

XCM Biologic® contained only very few eosinophils and neutrophils, significantly less than in Parietene™ after 30 days ($P = 0.001$). After 90 and 180 days, the number of macrophages was significantly lower in XCM Biologic® than in Parietene™ ($P = 0.003$, and $P = 0.010$ respectively). After 30 days of follow-up, there was a significantly higher number of mononuclear cells in the XCM Biologic® samples compared with Parietene™ ($P = 0.019$). After 90 and 180 days, collagen deposition was significantly lower in XCM Biologic®.

After 30 days, scaffold degradation was significantly higher in XCM Biologic® than in Omyra® Mesh ($P = 0.049$). After 90 days, fibrous encapsulation was significantly higher in XCM Biologic® than in Parietene™ and Omyra® Mesh ($P = 0.024$, and $P = 0.024$ respectively). Cellular infiltration, neovascularization, and extracellular matrix deposition were moderate and did not show significant differences when compared with other meshes.

Omyra® Mesh

Omyra® Mesh contained only few eosinophils and neutrophils, but no significant differences were found with other meshes. After 90 days, significantly more macrophages were found in the Omyra® Mesh samples than in the XCM Biologic® samples ($P = 0.003$). Mononuclear cells were present in moderate amounts, there were no significant differences with other meshes. After 90 and 180 days, there was a significantly higher amount of collagen deposition in Omyra® Mesh than in XCM Biologic® ($P = 0.007$, and $P = 0.014$ respectively).

Scaffold degradation was significantly higher in most other meshes at all time points after implantation, when compared with Omyra® Mesh. After 90 days, also fibrous encapsulation was significantly lower in Omyra® Mesh than in XCM Biologic® ($P = 0.024$). After 90 and 180 days, both cellular infiltration and neovascularization were significantly lower in Omyra® Mesh when compared with XCM Biologic®. Extracellular matrix deposition was moderate at all time points and no significant differences were found compared with other meshes.

DISCUSSION

This experimental study in a physiologic, non-contaminated rat model revealed that the use of biological meshes in an intra-abdominal position is feasible. Based on incorporation, adhesions on the surface of the mesh, adhesion strength, mesh shrinkage, and the histologic parameters scaffold degradation, cellular infiltration, neovascularization, and extracellular matrix deposition, Strattice™ performed best in this experimental rat model with intraperitoneal mesh placement.

Ever since the introduction of mesh-assisted abdominal wall hernia repair, there has been a search for the "ideal mesh" [23, 24]. The ideal mesh must be tailored to each patient's needs in the current clinical situation [25]. In case of abdominal wall hernia repair in the intraperitoneal plane, one needs a high incorporation of the mesh, little to no shrinkage of the mesh, few to no adhesions on the mesh, and if adhesions are formed, preferably adhesions of a low tenacity [23-25]. None of the examined meshes in this study showed all the requested characteristics within one product.

In this study, the incorporation of the mesh was best in Permacol™ (62 ± 11 percent) and worst in Strattice™ (23 ± 13 percent) after 180 days. A previous study from this research group with the same mesh materials in a contaminated environment showed similar results for mesh incorporation in Permacol™ and Strattice™ [16]. XCM Biologic®, however, had a much higher incorporation of the mesh in a contaminated environment than in a physiologic, non-contaminated environment (88 (IQR: 72–100) percent versus 43 ± 12 SD percent after 180 days). The other meshes showed a comparable incorporation after 180 days in both the contaminated environment (median (IQR)) and the physiologic, non-contaminated environment (mean ± SD) (Parietene™ 57 (32–87) percent versus 56 ± 9 percent, Permacol™ 62 (58–67) percent versus 62 ± 11 percent, Strattice™ 21 (10–30) percent versus 23 ± 13 percent, and Omyra® Mesh 54 (40–66) percent versus 58 ± 20 percent) [16]. When reviewing the histological parameters of XCM Biologic® in a contaminated environment versus a non-contaminated environment, all the following

parameters scored much higher values in the contaminated environment: the total number of inflammatory cells, macrophages and foreign body giant cells, mononuclear cells, and the amount of collagen deposition. It is possible that a more fulminant inflammatory response led to a better incorporation of XCM Biologic® in a contaminated environment. All other meshes didn't follow this pattern and didn't show an increase in total number of inflammatory cells, macrophages and foreign body giant cells, mononuclear cells, and the amount of collagen deposition. As far as currently known, there is no literature on the head-to-head comparison of mesh incorporation between meshes in a contaminated environment versus a non-contaminated situation.

There was a large variety in shrinkage of the mesh in this study: 0 to 18 percent of shrinkage on various time points. After 180 days, Permacol™ was shrunken significantly less than Strattice™ and Omyra® Mesh (0 percent versus 18 percent and 13 percent respectively). In a previous experimental study of Mulier and colleagues, Strattice™ and Permacol™ were compared alongside. In that study, the surface area of Permacol™ remained stable, but Strattice™ mesh expanded in size 12 months after implantation [26]. This finding might be explained by the growth of the animals; however, it was only found in Strattice™, not in Permacol™. In this current study, no expansion of Strattice™ was found, however, this study only had a maximum of 6 months follow-up. Parietene™ and XCM Biologic® showed a moderate amount of shrinkage (9 percent and 10 percent after 180 days) in this study. This in contrary to a previous study, in which a very high percentage of shrinkage was found in XCM Biologic® (21 (4–36) percent at 30 days, 43 (38–66) percent at 90 days, and 36 (34–51) percent at 180 days) [16]. It is unclear why XCM Biologic® shrunk excessively in the presence of infection and shrunk less in a physiologic, non-contaminated environment. This finding could again be explained by a more fulminant foreign body response in XCM Biologic® in a contaminated environment versus a non-contaminated environment. In the contaminated environment, a higher total number of inflammatory cells, macrophages, foreign body giant cells, mononuclear cells, and a higher amount of collagen deposition was found. Other meshes that were examined in both a contaminated and a physiologic, non-contaminated environment did not show the same pattern of shrinkage neither did they show the same pattern of foreign body response.

All meshes that were investigated in this study formed strong adhesions. The adhesions formed by Permacol™ were significantly stronger compared to Strattice™ after 30 days. The amount of adhesions varied significantly amongst all groups and varied between 5 percent and 88 percent of the surface of the mesh. Strattice™ had significantly the lowest amount of adhesions and Parietene™ had significantly the highest amount of adhesions. The amount of adhesions per mesh are comparable to results from previous

studies from this group [14, 27, 28]. No comparable studies of other research groups were found.

To summarize the findings of this study: when comparing all meshes head-to-head, Permacol™ and Strattice™ showed most often desired characteristics for intraperitoneal mesh placement, but also some characteristics that are less eligible for use in the intra-abdominal cavity. Permacol™ had a better mesh incorporation than Strattice™, less shrinkage than Strattice™, but a much higher adhesion percentage compared with Strattice™. After 30 days, significantly higher adhesion tenacity was observed in Permacol™ compared with Strattice™. Strattice™ however, had less mesh incorporation than Permacol™, higher shrinkage than Permacol™, but a much lower adhesion percentage.

Since adhesions can lead to serious complaints and complications in patients, the surgeon's aim should be to place a mesh that leads to the least possible amount of adhesions, when placed intraperitoneally. This mesh could be suitable for laparoscopic mesh placement in an intraperitoneal onlay mesh (IPOM) technique, or for patient with a giant abdominal wall hernia, in which closure of the fascia is not always possible and in which there could be an eminent risk for direct contact between the mesh and the viscera. Further studies are surgically relevant, because this study only assessed feasibility and in vivo characteristics like incorporation, shrinkage, adhesion formation, and histology. In this study, no analyses were performed regarding the biomechanical properties of the meshes. Properties like tensile strength, ball burst strength, and tear resistance, resemble clinical parameters that are important for the patients' abdominal wall hernia repair [29]. Future investigations could target the assessment of biomechanical characteristics of the meshes, but moreover postoperative assessment of patients that have undergone abdominal wall hernia repair with a biological mesh. This type of mesh seems feasible for different indications in patients, but a careful selection should be done preoperatively, to select the right indication for the right mesh.

The rat model in this study is suitable to assess the behavior of synthetic and biological meshes experimentally in a physiologic, non-contaminated environment. There are however some limitations to this study. Firstly, only the surface of the mesh could be adjusted, proportionally the mesh implants were much thicker in the rats than that they would be in humans. This may lead to a decreased incorporation of the mesh in the abdominal wall. Secondly, in this model all meshes were placed intraperitoneally, whereas in the clinical situation one would be cautious to implant Parietene™ into the abdominal cavity without an anti-adhesive layer. Previous studies showed a more pronounced inflammatory response and adhesion formation after intraperitoneal placement of these meshes compared with extraperitoneal placement [27, 28, 30]. However, closure of the

peritoneum is not always possible in patients with large hernias, and contact between viscera and mesh might still occur. It is therefore important to assess in vivo mesh behavior of synthetic and cross-linked meshes in an intra-abdominal environment. The translation of experimental results to the clinical situation should however be done with caution.

CONCLUSION

Based on incorporation, adhesion surface, adhesion strength, mesh shrinkage, and the histologic parameters scaffold degradation, cellular infiltration, neovascularization, and extracellular matrix deposition, Strattice™ performed best in this experiment in a physiologic, non-contaminated rat model with intraperitoneal mesh placement.

Acknowledgement

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SUPPLEMENTARY DATA

Table S1. Zühlke Scoring System for Adhesions [18]

Score	Definition
0	No adhesions
1	Minimal, filmy adhesions requiring little blunt dissection
2	Moderate adhesions requiring blunt and partly sharp dissection; beginning of vascularization
3	Strong adhesions; lysis possible by sharp dissection only; clear vascularization
4	Very strong adhesions; lysis possible by sharp dissection only; organs attached (damage to organs difficult to prevent)

Table S2. Abscess Scoring System [19]

Score	Definition
0	No abscess present at the site
0.5	One small abscess present at the site
1	Several small abscesses present at the site
2	Medium abscess present at the site
3	Large or several medium abscesses present at the site
4	One very large or several large abscesses present at the site

Table S3. Histologic scoring system for inflammatory cell reaction [20, 21]

	Score			
	0	1	2	3
Inflammatory cell reaction (no. of cells per HPF)	0–50	51–100	101–150	> 150
Eosinophils–neutrophils (no. of cells per HPF)	0	1–5	6–10	> 10
Macrophages–foreign body giant cells (no. of cells per HPF)	0	1–5	6–10	> 10
Mononuclear cells (no. of cells per HPF)	0–10	11–50	51–100	> 100

Number of cells per high-power field (HPF) was determined at 40 × magnification.

Table S4. Histologic scoring system for mesh-specific parameters [20]

	Score		
	0	1	2
Scaffold degradation	– Original scaffold intact, borders clearly demarcated	± Scaffold partially degraded, layers separated by cells, blood vessels, host tissue, etc.	+ Scaffold completely degraded, no evidence of original scaffold
Fibrous encapsulation	+ Extensive encapsulation (50–100%) of periphery)	± Moderate encapsulation (>0–50% of periphery)	– No fibrous encapsulation
Cellular infiltration*	– No cells in contact with scaffold	Periphery Cells infiltrate scaffold, but none reach center	Center Cells penetrate into center of scaffold
Neovascularization	– No blood vessels present	Periphery Vessels infiltrate scaffold but none reach center of scaffold	Center Vessels penetrate into center of scaffold
ECM deposition	– No host ECM deposition	Periphery Host ECM deposited inside scaffold, but not at center	Center Host ECM deposited inside scaffold, including center

*Inflammatory and connective tissue cells. ECM = extracellular matrix.

Table S5. Collagen deposition [22]

Score	Definition
0	No response
1	Minimal/barely detectable
2	Mild/slightly detectable
3	Moderate/easily detectable
4	Marked/very evident

Table S6. Results of histologic evaluation after sacrifice

	n	Inflammatory cells total	Eosinophils–neutrophils	Macrophages–FBGC	Mononuclear cells	Collagen deposition SR
Parietene™						
30 days	8	3 (2–3)	3 (3–3) A	3 (3–3)	1 (1–1) E	3 (3–4)
90 days	8	2 (1–2)	1 (1–3) B	3 (3–3)	1 (1–2)	3 (2–3)
180 days	8	1 (1–1)	1 (1–2) C	3 (3–3) D	1 (1–2)	3 (1–3)
Permacol™						
30 days	8	1 (1–2)	0 (0–0)	1 (1–3)	1 (1–2)	2 (1–2)
90 days	8	0 (0–1)	0 (0–0)	3 (3–3)	1 (1–1)	2 (1–3)
180 days	8	0 (0–1)	0 (0–0)	2 (1–3)	1 (1–1)	1 (0–1)
Strattice™						
30 days	8	2 (1–2)	0 (0–1)	1 (1–2)	3 (2–3)	4 (2–4)
90 days	8	2 (0–3)	0 (0–0)	1 (1–2)	3 (1–3)	3 (2–3)
180 days	8	0 (0–1)	0 (0–0)	1 (1–1)	1 (1–2)	1 (1–2)
XCM Biologic®						
30 days	7	3 (2–3)	0 (0–0)	3 (2–3)	3 (2–3)	3 (2–3)
90 days	9	0 (0–1)	0 (0–0)	1 (1–1) F	1 (1–2)	1 (1–2) G
180 days	8	1 (0–2)	0 (0–0)	1 (0–2)	2 (1–3)	1 (1–2)
Omyra® Mesh						
30 days	8	2 (2–2)	1 (0–1)	3 (3–3)	2 (1–2)	2 (2–3)
90 days	8	1 (1–2)	0 (0–1)	3 (3–3)	1 (1–2)	4 (4–4)
180 days	8	1 (0–1)	0 (0–1)	3 (3–3)	1 (1–1)	4 (4–4) H

Results are presented as median (interquartile ranges). FBGC = foreign body giant cells.

Significant differences between:

A Parietene™ 30 days and Permacol™ 30 days ($P < 0.001$), XCM Biologic® 30 days ($P = 0.001$), and Strattice™ 30 days ($P = 0.033$)

B Parietene™ 90 days and Strattice™ 90 days ($P = 0.004$) and Permacol™ 90 days ($P = 0.023$)

C Parietene™ 180 days and Strattice™ 180 days ($P = 0.010$) and Permacol™ 180 days ($P = 0.018$)

D Parietene™ 180 days and Strattice™ 180 days ($P = 0.004$) and XCM Biologic® 180 days ($P = 0.010$)

E Parietene™ 30 days and XCM Biologic® 30 days ($P = 0.019$)

F XCM Biologic® 90 days and Parietene™ 90 days ($P = 0.003$) and Omyra® Mesh 90 days ($P = 0.003$)

G XCM Biologic® 90 days and Omyra® Mesh 90 days ($P = 0.007$)

H Omyra® Mesh 180 days and Permacol™ 180 days ($P < 0.001$), Strattice™ 180 days ($P = 0.003$), and XCM Biologic® 180 days ($P = 0.014$)

Table S7. Results of mesh-specific parameters after sacrifice

	n	Scaffold degradation	Fibrous encapsulation	Cellular infiltration[X]	Neovascularization	ECM deposition[Y]
Parietene™						
30 days	8	0 (0–0) A	0 (0–1)	1 (1–1)	1 (1–1)	1 (1–1)
90 days	8	0 (0–0)	0 (0–0)	1 (1–1)	1 (1–1)	1 (1–1)
180 days	8	0 (0–0)	0 (0–0)	1 (1–1)	1 (1–1)	1 (1–1)
Permacol™						
30 days	8	1 (1–2)	0 (0–1)	1 (1–1)	1 (1–1)	1 (1–2)
90 days	8	0 (0–0)	0 (0–2)	1 (1–1)	1 (1–1)	1 (0–1) B
180 days	8	1 (0–2)	1 (0–2)	1 (1–1)	1 (1–2)	1 (0–2)
Strattice™						
30 days	8	1 (1–2)	1 (1–1)	2 (2–2)	2 (2–2)	2 (2–2)
90 days	8	2 (1–2) C	1 (1–1)	2 (2–2) D	2 (2–2) E	2 (2–2)
180 days	8	2 (1–2) F	1 (1–1)	2 (2–2) G	2 (2–2) H	2 (0–2)
XCM Biologic®						
30 days	7	2 (1–2)	0 (0–0)	1 (1–1)	1 (1–2)	1 (1–2)
90 days	9	0 (0–1)	1 (1–2) I	2 (1–2)	2 (2–2)	1 (1–2)
180 days	8	1 (0–2)	2 (1–2)	2 (1–2)	2 (1–2)	1 (0–2)
Omyra® Mesh						
30 days	8	0 (0–0) J	0 (0–1)	1 (1–1)	1 (1–1)	1 (1–1)
90 days	8	0 (0–0)	0 (0–0)	1 (1–1)	1 (1–1)	1 (1–1)
180 days	8	0 (0–0)	0 (0–1)	1 (1–1)	1 (1–1)	1 (1–1)

Results are presented as median (interquartile ranges).

[X] Cellular infiltration = inflammatory and connective tissue cells

[Y] ECM = extracellular matrix

Significant differences between:

A Parietene™ 30 days and XCM Biologic® 30 days ($P = 0.049$), and Strattice™ 30 days ($P = 0.018$)

B Permacol™ 90 days and Strattice™ 90 days ($P = 0.020$)

C Strattice™ 90 days and Parietene™ 90 days ($P = 0.003$), Permacol™ 90 days ($P = 0.017$), and Omyra® Mesh 90 days ($P = 0.003$)

D Strattice™ 90 days and Parietene™ 90 days ($P = 0.019$), Omyra® Mesh 90 days ($P = 0.019$), and Permacol™ 90 days ($P = 0.019$)

E Strattice™ 90 days and Parietene™ 90 days ($P = 0.030$), Omyra® Mesh 90 days ($P = 0.030$), and Permacol™ 90 days ($P = 0.030$)

F Strattice™ 180 days and Parietene™ 180 days ($P = 0.008$), and Omyra® Mesh 180 days ($P = 0.008$)

G Strattice™ 180 days and Omyra® Mesh 180 days ($P = 0.002$), Parietene™ 180 days ($P = 0.002$), and Permacol™ 180 days ($P = 0.004$)

H Strattice™ 180 days and Omyra® Mesh 180 days ($P = 0.001$), and Parietene™ 180 days ($P = 0.004$)

I XCM Biologic® 90 days and Parietene™ 90 days ($P = 0.024$), and Omyra® Mesh 90 days ($P = 0.024$)

J Omyra® Mesh 30 days and XCM Biologic® 30 days ($P = 0.049$) and Strattice™ 30 days ($P = 0.018$)

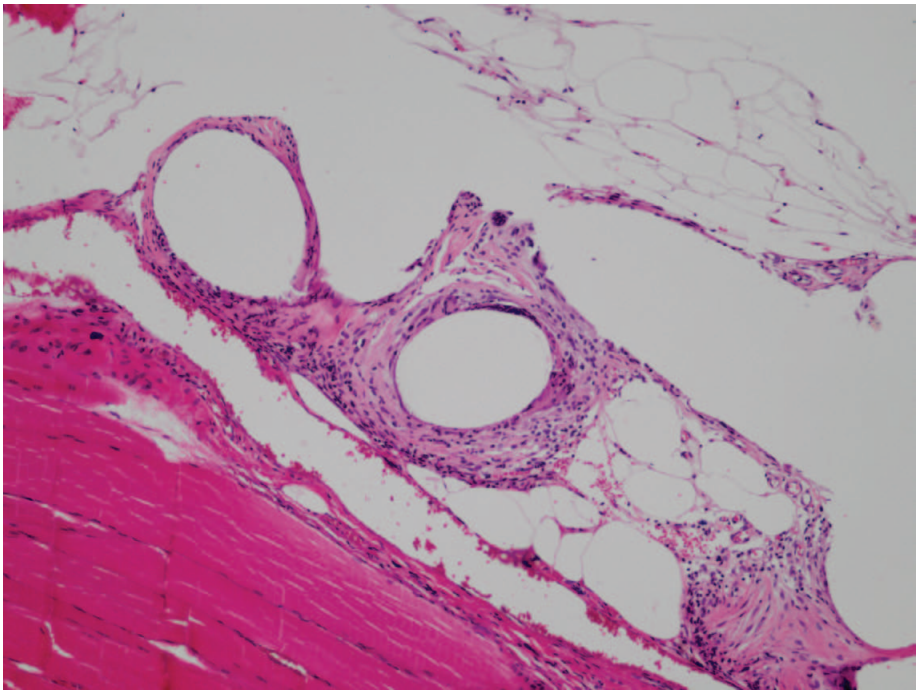


Figure S1. Hematoxylin and eosin staining of Parietene™ (180 days postoperative; 10 × magnification)

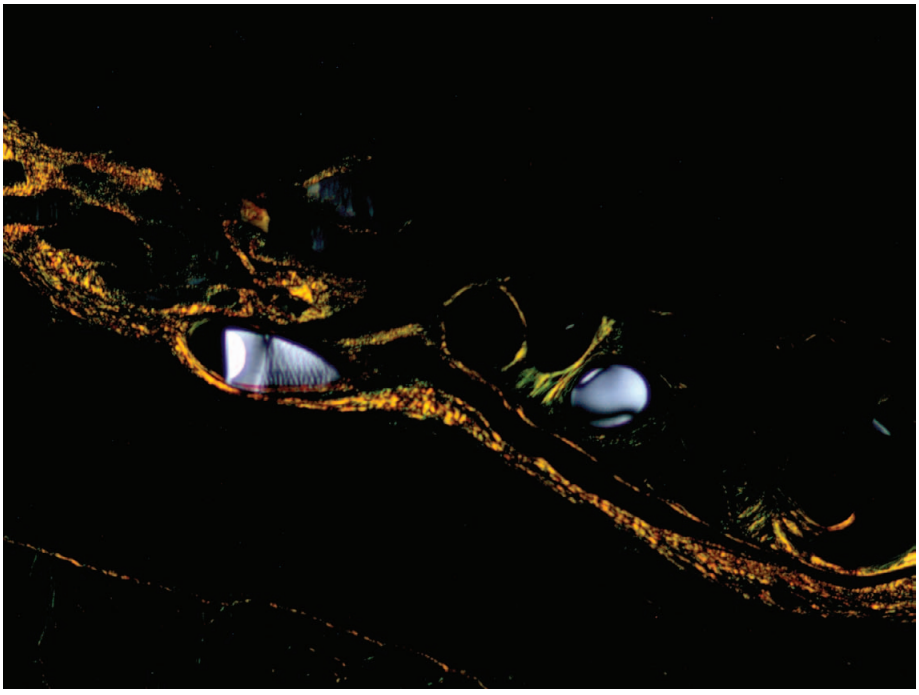


Figure S2. Sirius red staining of Parietene™ (180 days postoperative; 5 × magnification)

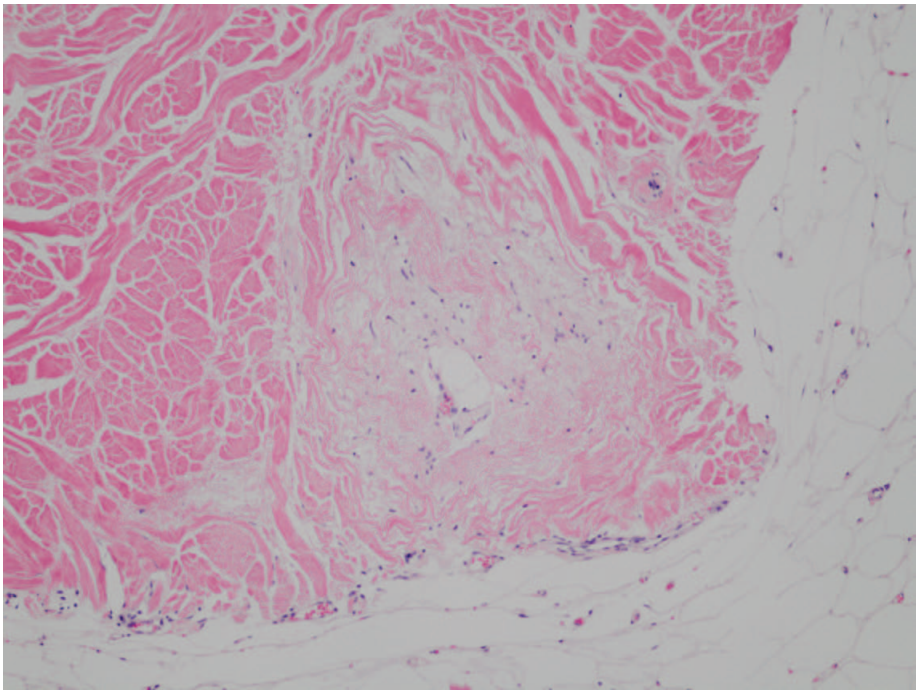


Figure S3. Hematoxylin and eosin staining of Permacol™ (180 days postoperative; 10 × magnification)

Figure S4. Sirius red staining of Permacol™ (180 days postoperative; 5 × magnification)

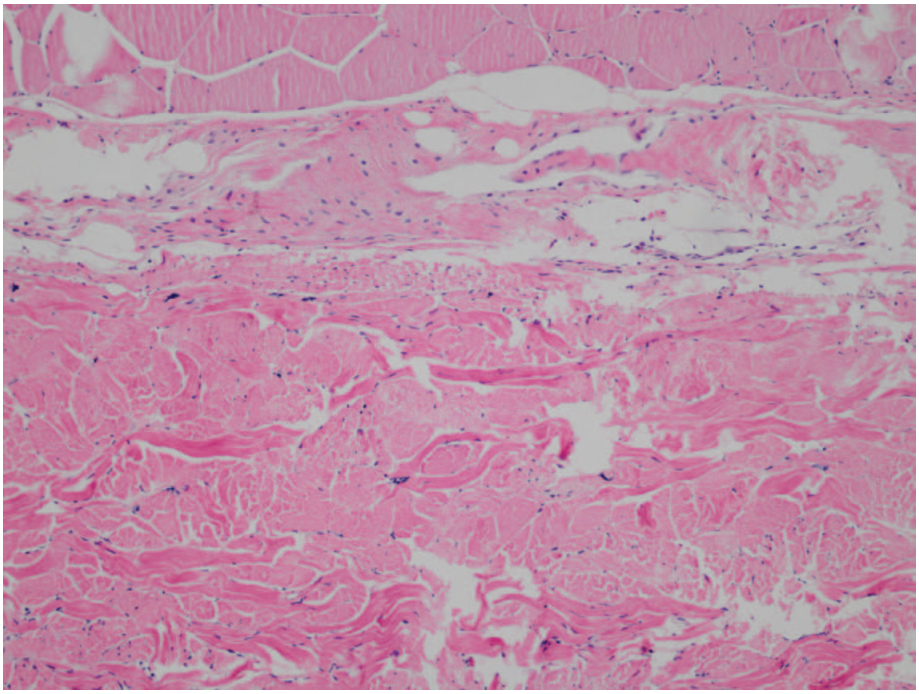


Figure S5. Hematoxylin and eosin staining of Strattice™ (180 days postoperative; 10 × magnification)

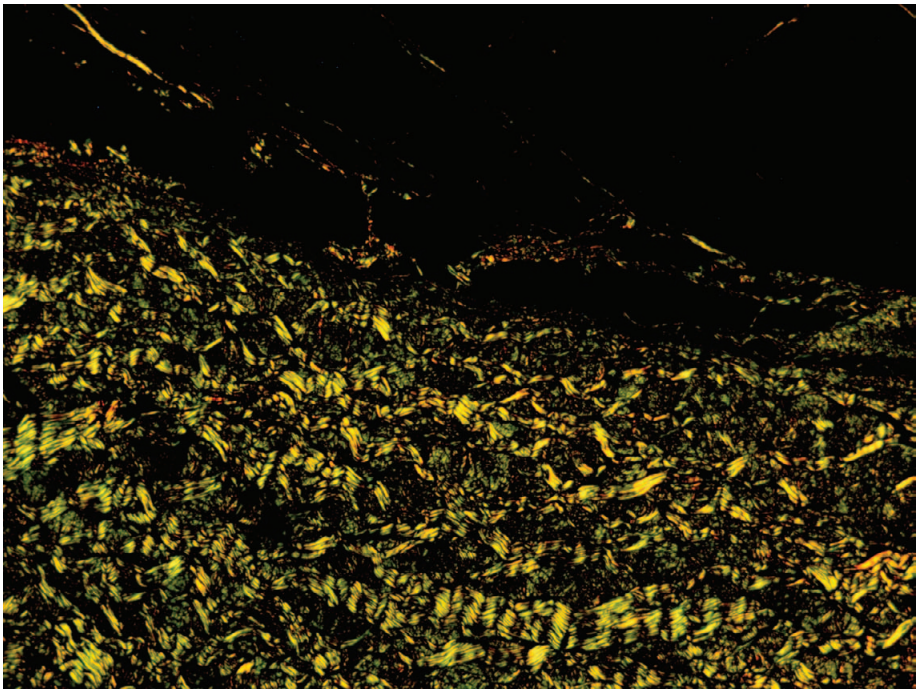


Figure S6. Sirius red staining of Strattice™ (180 days postoperative; 5 × magnification)

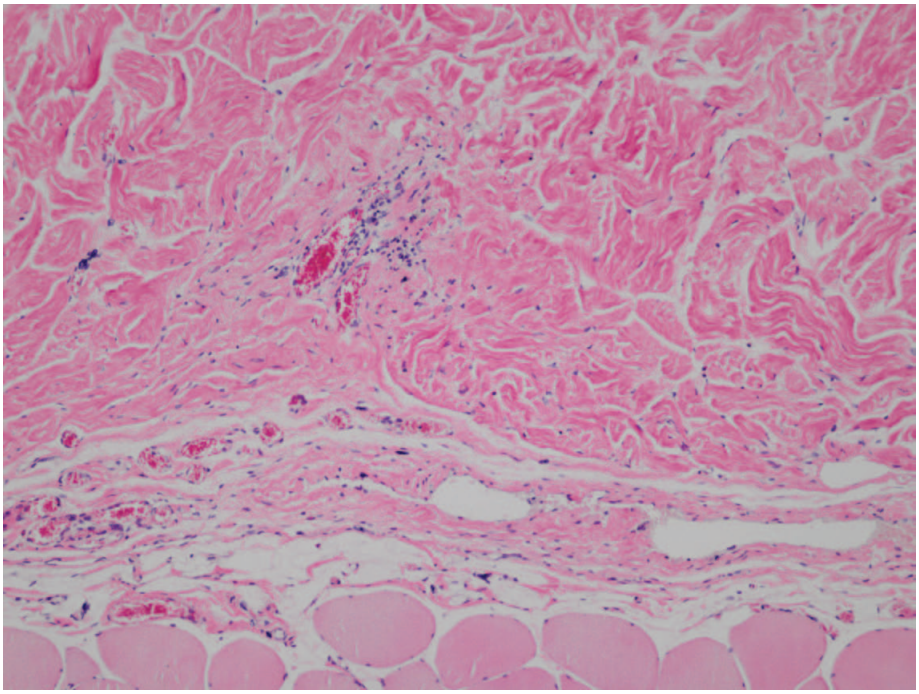


Figure S7. Hematoxylin and eosin staining of XCM Biologic® (180 days postoperative; 10 × magnification)

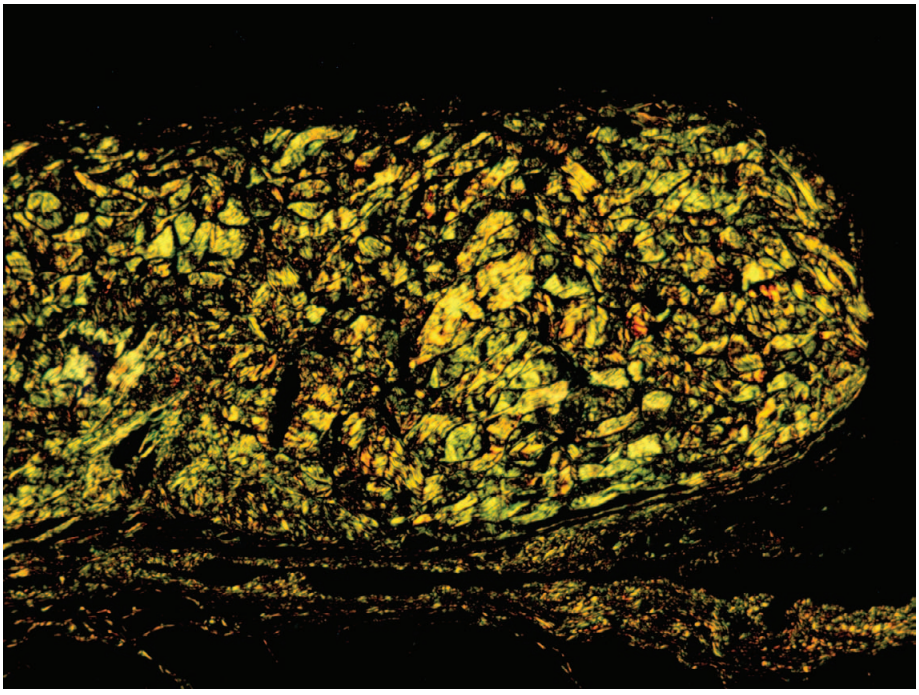


Figure S8. Sirius red staining of XCM Biologic® (180 days postoperative; 5 × magnification)

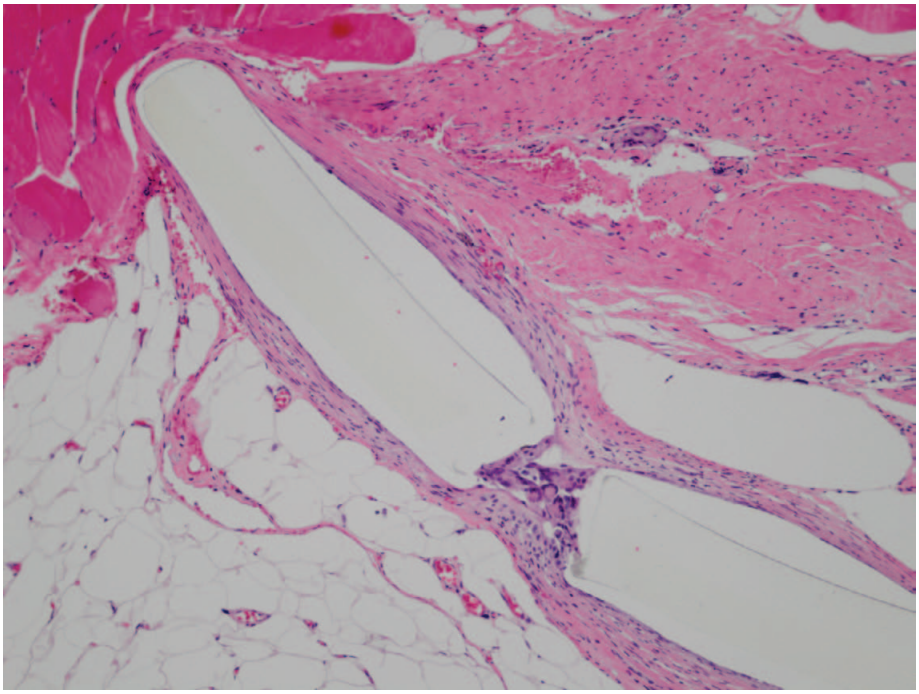


Figure S9. Hematoxylin and eosin staining of Omyra® Mesh (180 days postoperative; 10 × magnification)

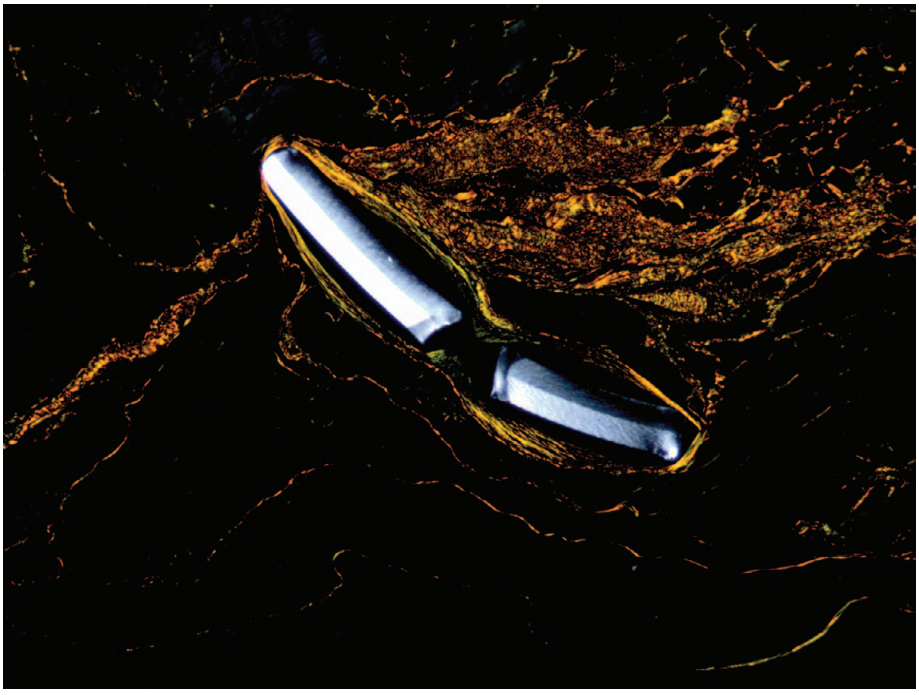
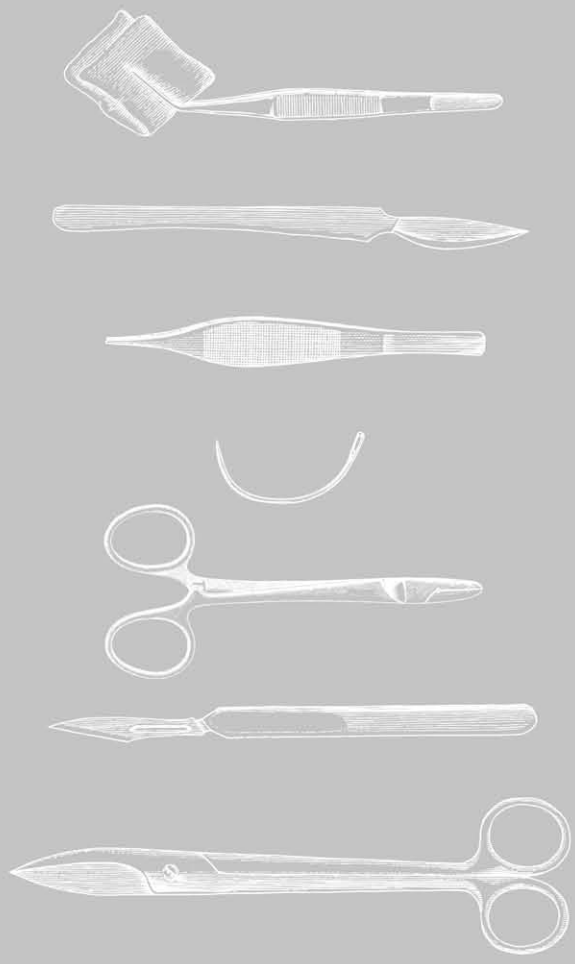
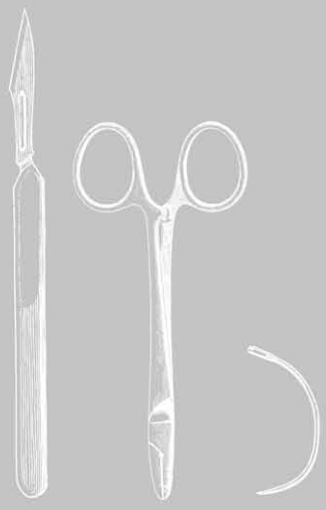


Figure S10. Sirius red staining of Omyra® Mesh (180 days postoperative; 5 × magnification)



4

Characteristics of different mesh types for abdominal wall repair in an experimental model of peritonitis



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ABSTRACT

Introduction

The use of synthetic mesh to repair a potentially contaminated incisional hernia may lead to higher failure rates. A biological mesh might be considered, but little is known about long-term results. Both biological and synthetic meshes were investigated in an experimental model of peritonitis to assess their characteristics in vivo.

Methods

Male Wistar rats were randomized into five groups and peritonitis was induced. A mesh was implanted after 24 hours. Five meshes were investigated: Permacol™ (cross-linked collagen), Strattice™ (non-cross-linked collagen), XCM Biologic® (non-cross-linked collagen), Omyra® Mesh (condensed polytetrafluoroethylene) and Parietene™ (polypropylene). The rats were killed after either 30, 90 or 180 days. Incorporation and shrinkage of the mesh, adhesion coverage, strength of adhesions and histology were analyzed.

Results

Of 135 rats randomized, 18 died from peritonitis. Some 180 days after implantation, both XCM Biologic® and Permacol™ had significantly better incorporation than Strattice™ ($P = 0.003$ and $P = 0.009$ respectively). Strattice™ had significantly fewer adhesions than XCM Biologic® ($P = 0.001$) and Permacol™ ($P = 0.020$). Thirty days after implantation, Permacol™ had significantly stronger adhesions than Strattice™ ($P < 0.001$). Shrinkage was most prominent in XCM Biologic®, but no significant difference was found compared with other meshes. Histological analysis revealed marked differences in foreign body response among all meshes.

Conclusion

This experimental study suggested that XCM Biologic® was superior in terms of incorporation, macroscopic mesh infection, and histological parameters such as collagen deposition and neovascularization. There must be sufficient overlap of mesh during placement, as XCM Biologic® showed a high rate of shrinkage.

Surgical relevance

The use of synthetic mesh to repair a potentially contaminated incisional hernia is not supported unequivocally, and may lead to a higher failure rate. A biological mesh might be considered as an alternative. There are few long-term studies, as these meshes are expensive and rarely used.

This study evaluated the use of biological mesh in a contaminated environment, and investigated whether there is an ideal mesh for this environment. A new non-cross-linked biological mesh (XCM Biologic®) was evaluated in this experiment.

The new non-cross-linked biological mesh XCM Biologic® performed best and may be useful in patients with a potentially contaminated incisional hernia.

INTRODUCTION

Incisional hernia is a common postoperative complication, with an incidence ranging from 11 to 20 percent [1, 2]. Currently, incisional hernias are most often repaired with mesh material [3]. The use of mesh significantly decreases 10-year recurrence rates [4]. There are various mesh types available; polypropylene mesh is the most widely used [5, 6].

The use of synthetic meshes to repair potentially contaminated or contaminated incisional hernias is not supported unequivocally and may lead to complications (wound healing problems, adhesions and fistula formation) and even death [6, 7]. A biological mesh might be considered as an alternative [8]. These meshes are made from collagen-containing tissues of human or animal origin [9]. They are composed of tissue such as intestine, heart valves or skin, and are processed to remove cells, cell components and hair (if present) as well as other antigens present in the tissue [10, 11]. After decellularization and degradation of these tissues, a three-dimensional structure of collagen and some protein remnants remains. Additional chemical cross-linking of the mesh can be done to increase its strength and to slow down its degradation [10, 12, 13]. Degradation takes place after implantation of the mesh. During this phase, there is incorporation of host fibroblasts and collagen replacement occurs. This so-called xenograft remodeling begins within a few hours after implantation and continues for several months to years. Two experimental studies [14, 15] have assessed the efficacy of biological meshes in the short term. There are few long-term studies [16, 17], as these meshes are expensive and rarely used [16, 17].

In this study, both biological and synthetic meshes were investigated in an experimental peritonitis model. They were all compared in several aspects: incorporation, shrinkage, adhesion formation and abscess formation 30, 90 and 180 days after implantation. The aim of this study was to evaluate the feasibility of using a biological mesh in a contaminated environment, and to investigate whether there is an ideal mesh. The working hypothesis for this study was that biological meshes would be better than synthetic mesh in a contaminated field.

METHODS

Some 135 male Wistar rats were obtained from a licensed breeder (Harlan Laboratories, Boxmeer, The Netherlands). They were bred under specific pathogen-free conditions and were kept under standard laboratory conditions. This included a temperature of 20–24°C, a relative humidity of 50–60 percent, and 12-hours light–dark cycles. The rats were housed in pairs in individually ventilated cages, and fed freely with standard rat chow and water throughout the experiment. On arrival, the animals weighed 250–325 grams and were acclimatized for at least 7 days before the experiment. The study protocol was approved by the Ethical Committee on Animal Experimentation of Erasmus University (Rotterdam, The Netherlands).

Peritonitis model

The rats were divided randomly into five groups of 27 animals each before the start of the experiment. All rats were anesthetized with a mixture of isoflurane and oxygen, and received a single preoperative dose of 0.05 mg/kg buprenorphine analgesia subcutaneously. Before operation, all animals were weighed, the abdomen was shaved, and the skin disinfected with 70 percent ethanol. The abdominal cavity was opened via a 3-cm midline incision. To induce peritonitis, the cecum ligation puncture model (CLP) was used [18]. The cecum was ligated just distal to the ileocecal valve (maintaining bowel continuity) and punctured beyond the ligature with an 18-G needle. The fascia and skin were closed separately with a running absorbable suture of polyglycolic acid (5/0 Safil®; B. Braun, Melsungen, Germany). All animals received 5 ml sodium chlorine 0.9 percent and were placed under a heating lamp to recover from anesthesia.

After 24 hours, all rats were again anesthetized with a mixture of isoflurane and oxygen. They received a single dose of buprenorphine (0.05 mg/kg subcutaneously). The skin was disinfected with 70 percent ethanol, the abdomen was reopened, and a bacterial culture swab taken to confirm fecal peritonitis. The necrotic or ischemic part of the cecum was removed. The abdominal cavity was rinsed with 20 ml warmed phosphate buffer and

gentamicin was administered (6 mg/kg intramuscularly). A sterile mesh of 2.5 × 3 cm was implanted intraperitoneally and fixed transmuscularly with six non-absorbable nylon sutures (5/0 Ethilon®; Ethicon, Somerville, New Jersey, USA). The fascia and skin were closed separately with a running absorbable suture of polyglycolic acid (5/0 Safil®). All animals received 5 ml sodium chlorine 0.9 percent and were placed under a heating lamp to recover from anesthesia.

Mesh material

Five different meshes were analyzed in this experiment. Two non-cross-linked collagen matrices of porcine dermis (Strattice™, LifeCell Corporation, Branchburg, New Jersey, USA; XCM Biologic®, Kensey Nash Corporation, Exton, Pennsylvania, USA, distributed by DePuy Synthes, Oberdorf, Switzerland), one cross-linked collagen matrix of porcine dermis (Permacol™; Sofradim, Trévoux, France, part of Covidien–Medtronic, New Haven, Connecticut, USA), one mesh of condensed polytetrafluoroethylene (Omyra® Mesh; B. Braun), and one polypropylene mesh (Parietene™; Sofradim). In a sterile environment, all meshes were cut to 2.5 × 3 cm. Each mesh was handled according to the instructions for use provided by the manufacturer.

Wellness and survival

All animals were weighed on a daily basis in the first week after surgery and weekly thereafter. Maximum weight loss within the first 7 days was expressed as a percentage of the weight at the start of the experiment. Wellness and behavior were assessed using a 12-point wellness scoring system [19]. Animals were killed if they reached the humane endpoint (at least 20 percent weight loss or a wellness score less than 5 points). All animals that died underwent autopsy.

Macroscopic assessment of mesh-specific parameters

Animals were killed 30, 90 or 180 days after mesh placement. They were anesthetized with a mixture of isoflurane and oxygen, the abdomen was shaved, and the skin disinfected with 70 percent ethanol. The abdominal wall was opened via a U-shaped incision in the ventral abdominal wall. A photograph was taken of the inner abdominal wall and mesh site (Figure 1). Incorporation and shrinkage of the mesh, adhesion coverage and strength of adhesions were assessed. All parameters were evaluated by two independent investigators. Discrepancies were discussed and resolved. The rat was killed by cardiac cut.

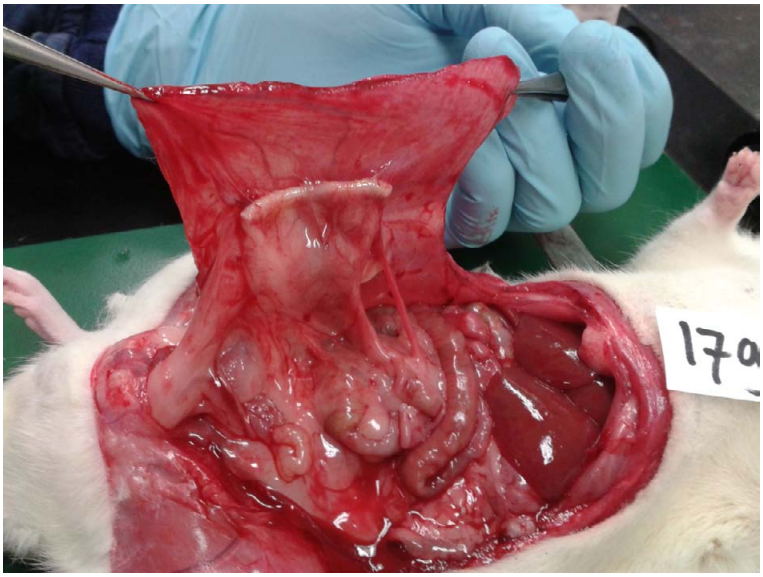

Figure 1. Photograph taken at time of death showing inner abdominal wall and mesh site (cross-linked biological mesh)

Incorporation of mesh

First, the remaining mesh was measured using a calliper and the perimeter calculated. Second, the incorporation of the mesh was assessed by lifting its edges; if the mesh could be lifted from the abdominal wall without adhering tissue, it had not been incorporated. The percentage incorporation was calculated as the length of incorporated mesh as a percentage of the perimeter of remaining mesh. Full incorporation was represented by incorporation of all sides, taking any shrinkage of the mesh into account.

Shrinkage of mesh

Shrinkage of the mesh was assessed by measurement of the surface of the remaining mesh using a calliper. The mesh surface at the time of death was expressed as a percentage of the standard implant size (7.5 cm^2).

Adhesions

Adhesions were evaluated in two ways. First, a qualitative analysis was done to assess strength and tenacity of adhesions using the Zühlke score (Table S1, supporting information) [20]. Second, the quantity of adhesions was assessed and expressed as a percentage of adhesions on the mesh surface.

Abscesses

Abscesses were regarded as an expression of an ongoing intra-abdominal infection. The presence of abscesses was assessed by visual inspection and examination of the abdominal cavity. The size of all abscesses was scored using an abscess scoring system (Table S1, supporting information) [21].

Histological evaluation

Full-thickness abdominal wall samples were harvested from each animal. This sample measured 1.0 × 0.5 cm, was taken from one of the long sides in between the sutures, and contained both abdominal wall and mesh (Figure S1, supporting information). The samples were fixed for 24 hours in 4 percent formalin and subsequently embedded in paraffin. Two 4-µm sections were cut and stained with either hematoxylin and eosin or sirius red, according to standard diagnostic procedure in the pathology department.

All slides were analyzed blind by an experienced pathologist. Hematoxylin and eosin-stained slides were evaluated by means of a scoring system described by Peeters and colleagues [22]. All cells were assessed under the microscope and the number of cells per high-power field (40 × magnification) was counted. No additional stains were performed. Sirius red-stained slides were assessed using an adapted scoring system described by Deeken and Matthews [23]. Histological analysis of the biological meshes focused on the periprosthetic area, whereas analysis of Parietene™ and Omyra® Mesh focused on both the perifilamentary areas and the pores. Both areas were assessed and a grade was given for the overall number of cells per sample. In addition, the extent of fibrous encapsulation around each mesh was assessed. The histological scoring systems used are described in Tables S3–S5 (supporting information).

Statistical analysis

A power calculation was done before the experiment. The calculation was based on an expected difference of 25–30 percent in amount of adhesions between the meshes. The expected mortality of the CLP model was 25 percent. Aiming for a power of 80 percent and $P < 0.050$, the number of animals needed was 27 per group. All meshes were included in the experiment as equal study groups. None of the study groups served as a control group only.

Continuous variables are expressed as median (IQR). As the data did not show a normal distribution for incorporation and shrinkage of the mesh, quantity and tenacity of adhesions, abscess formation and histological scores, statistical analyses were done using non-parametric Kruskal–Wallis tests for independent samples. If the overall test showed significant differences, pairwise tests were carried out to determine which groups

caused these. *P* values were adjusted for multiple testing using Dunn's post-test. $P < 0.050$ was considered statistically significant. All statistical analyses were undertaken in SPSS® version 21.0 (IBM, Armonk, New York, USA).

RESULTS

All 135 rats survived the initial operation to induce peritonitis, but five died within 24 hours after induction of peritonitis and another 13 died in the next 24 hours after implantation of the mesh (overall mortality rate 13.3 percent). There were no significant differences between the groups. None of the rats reached the humane endpoint. Autopsy in all animals showed that the cause of early death was abdominal sepsis secondary to fecal peritonitis. In addition, one rat in the XCM Biologic® group died 14 days after implantation from bowel obstruction caused either by intestinal adhesions or volvulus (adhesion between cecum and mesentery; no adhesions between bowel and mesh). The remaining 117 rats survived and could be analyzed at the intended endpoint. The distribution of the surviving animals per study group is shown in Table 1.

Table 1. Overview of experimental groups

	Parietene™	Permacol™	Strattice™	XCM Biologic®	Omyra® Mesh
Mesh material	Polypropylene	Cross-linked collagen of porcine dermis	Non-cross-linked collagen of porcine dermis	Non-cross-linked collagen of porcine dermis	Condensed PTFE
Weight (g/m^2)	78	n.a.	n.a.	n.a.	90
Pore size (mm)	1.0–1.6	n.a.	n.a.	n.a.	2.4
No. of animals	27	27	27	27	27
Postoperative deaths	3	2	2	3*	9
No. analyzed					
30 days	8	9	9	10	6
90 days	9	8	9	7	6
180 days	7	8	7	7	6

* One rat died from bowel obstruction on day 14; results for this animal were not used for analysis. n.a. = not applicable.

Peritonitis model

The bacterial culture swab on day one confirmed intraperitoneal bacterial contamination with Gram-positive (*Enterococcus*, *Staphylococcus*) and Gram-negative (*Escherichia coli*) microorganisms in all rats. All animals suffered from symptoms of sepsis, including apathetic behavior, piloerection, ocular exudates, abnormal posture, shivering, diarrhea

and weight loss. Mean weight loss varied from 9.0 to 11.2 percent, and was significantly greater in the Omyra® Mesh group than in the XCM Biologic® group ($P = 0.005$) and the Permacol™ group ($P = 0.013$). There were no differences in wellness score among the five groups. The removed part of the cecum was macroscopically ischemic in 89 percent of the animals, necrotic in 4 percent, and both ischemic and necrotic in 7 percent of the animals.

Incorporation of mesh

The percentage incorporation varied greatly between the mesh groups (Table 2 and Figure 2). At 180 days after implantation, it was highest for XCM Biologic® (88 (IQR 72–100) percent), followed by Permacol™ (62 (58–67) percent), Parietene™ (57 (32–87) percent), Omyra® Mesh (54 (40–66) percent) and lowest for Strattice™ (21 (10–30) percent). Both XCM Biologic® and Permacol™ showed significantly better incorporation than Strattice™

Table 2. Results for macroscopic mesh-specific parameters

	n	Incorporation of mesh (%)	Shrinkage of mesh (%)	Adhesions on mesh (%)	Tenacity of adhesions	No. of animals with abscess	Total no. of abscesses	Abscess score (highest)
Parietene™								
30 days	8	52 (40–60)	8 (1–25)	63 (50–75)	3 (3–3)	0	0	n.a.
90 days	9	55 (30–71)	19 (8–29)	58 (48–70)	3 (3–4)	1	2	4
180 days	7	57 (32–87)	14 (5–20)	70 (60–80)	3 (3–3)	0	0	n.a.
Permacol™								
30 days	9	57 (50–60)*	22 (7–26)	70 (55–85)*	3 (3–4)*	0	0	n.a.
90 days	8	47 (43–54)	23 (19–28)	83 (70–93)†	3 (3–4)	1	1	0.5
180 days	8	62 (58–67)‡	20 (17–24)	73 (63–83)‡	3 (3–3)	0	0	n.a.
Strattice™								
30 days	9	16 (12–22)	18 (12–25)	0 (0–5)	0 (0–2)	0	0	n.a.
90 days	9	18 (13–27)	15 (13–20)	0 (0–5)	3 (2–3)	0	0	n.a.
180 days	7	21 (10–30)	13 (5–17)	0 (0–0)	0 (0–3)	0	0	n.a.
XCM™ Biologic								
30 days	10	38 (34–44)	21 (4–36)	25 (5–70)	3 (3–3)	0	0	n.a.
90 days	7	46 (42–75)	43 (38–66)	95 (50–100)†	3 (3–3)	0	0	n.a.
180 days	7	88 (72–100)‡	36 (34–51)	100 (70–100)‡	3 (3–3)	0	0	n.a.
Omyra® Mesh								
30 days	6	59 (43–73)	14 (12–16)	38 (20–55)	3 (3–3)	0	0	n.a.
90 days	6	40 (25–62)	15 (9–20)	48 (30–60)	3 (3–3)	0	0	n.a.
180 days	6	54 (40–66)	27 (3–33)	63 (60–70)	3 (3–3)	0	0	n.a.

Values are median (IQR). n.a. = not applicable. *$P < 0.050$ versus Strattice™ at 30 days, †$P < 0.050$ versus Strattice™ at 90 days, ‡$P < 0.050$ versus Strattice™ at 180 days (Kruskal–Wallis test with Dunn's post-test).

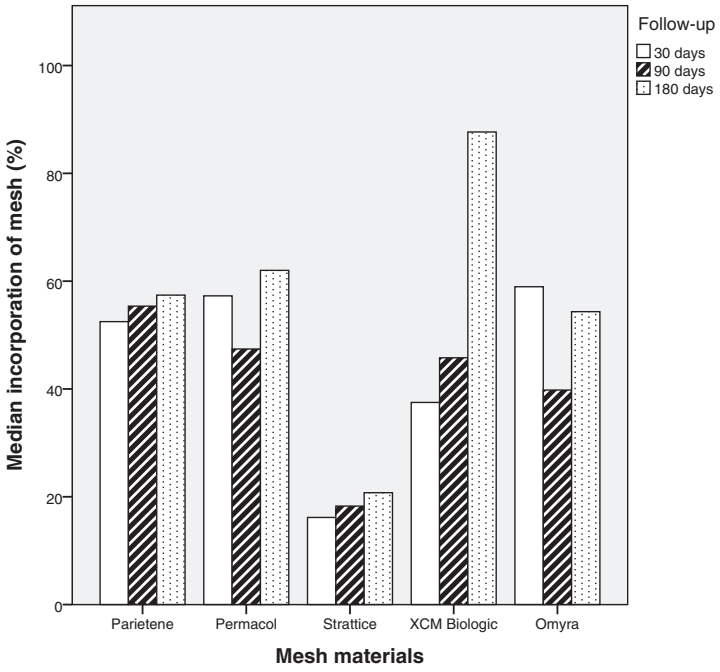

Figure 2. Median percentage of incorporation of each mesh at 30, 90 and 180 days

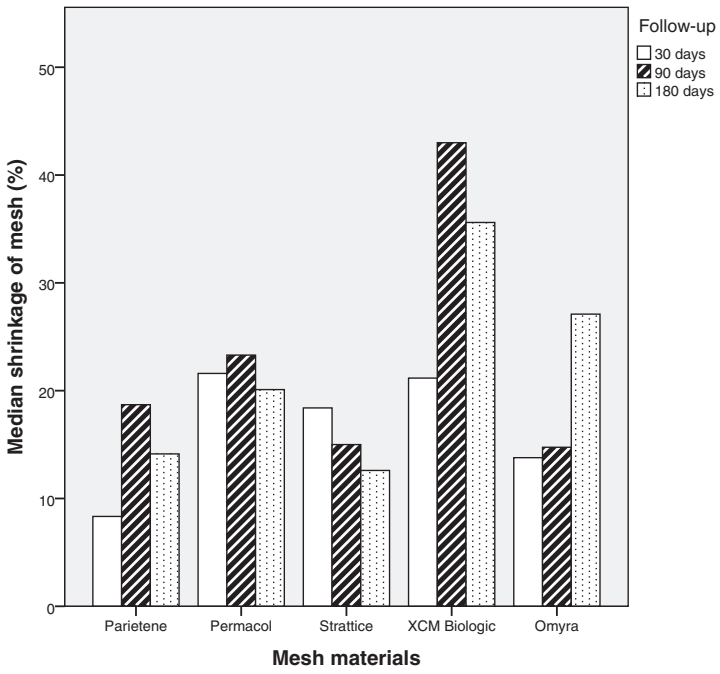

Figure 3. Median shrinkage of each mesh at 30, 90 and 180 days

180 days after implantation ($P = 0.003$ and $P = 0.009$). There were no significant differences in incorporation between the synthetic and biological meshes.

Shrinkage of mesh

All meshes shrank; however, the amount of shrinkage varied widely from 8 to 43 percent at different time points for different meshes (Table 2 and Figure 3). Shrinkage was most evident in XCM Biologic®: 21 (IQR 4–36) percent at 30 days, 43 (38–66) percent at 90 days and 36 (34–51) percent at 180 days. Parietene™ showed the least shrinkage at 30 days after implantation (8 (1–25) percent). Strattice™ and Omyra® Mesh showed the least shrinkage 90 days after implantation (15 (13–20) percent and 15 (9–20) percent respectively). Strattice™ showed the least shrinkage 180 days after implantation (13 (5–17) percent). Although there were considerable differences in shrinkage between the various groups, no significant difference was found.

Adhesions

The percentage of adhesions was relatively high in all mesh groups, except Strattice™ (Table 2). The percentage of adhesions increased over time in the XCM Biologic® and Omyra® Mesh groups. The percentage of adhesions 180 days after implantation was highest in XCM Biologic® (100 (70–100) percent), followed by Permacol™ (73 (63–83) percent), Parietene™ (70 (60–80) percent) and Omyra® Mesh (63 (60–70) percent), and lowest in Strattice™ (0 (0–0) percent). Strattice™ had a significantly lower percentage of adhesions than Permacol™ at all time points ($P = 0.007$, $P = 0.002$ and $P = 0.020$, respectively). The quantity of adhesions in Strattice™ was also significantly lower than in XCM Biologic® 90 and 180 days after implantation ($P = 0.009$ and $P = 0.001$ respectively).

The tenacity of adhesions was strong to very strong at all time points in all mesh groups, except for Strattice™. In the Strattice™ group, there was variation in median tenacity: no adhesions 30 days after implantation, strong adhesions at 90 days, and again no adhesions 180 days after implantation. Permacol™ was the only mesh that had significantly stronger adhesions than Strattice™ 30 days after implantation ($P < 0.001$). All other comparisons between the groups were not significant.

Abscesses

Abscess formation was rare; only two animals developed abscesses (Table 2). Both animals were killed after 90 days: one in the Parietene™ and the other in the Permacol™ group. The animal in the Parietene™ group had a small abscess on the bowel (not in proximity to the cecal ligation site) and a large macroscopic abscess alongside the mesh. The animal in the Permacol™ group had a very small macroscopic abscess alongside the mesh.

Histological evaluation

Four slides from the XCM Biologic® group did not contain mesh material and could not therefore be analyzed. One of these incomplete samples was harvested 30 days after implantation, two samples were harvested 90 days after implantation and the fourth 180 days after implantation.

In general, the hematoxylin and eosin staining revealed no significant differences in the total count of inflammatory cells, mononuclear cells and extracellular matrix deposition between the different mesh groups (Tables S6 and S7, Figures S2–S11, supporting information). The histological findings of all meshes are discussed individually as follows.

Parietene™

Parietene™ mesh had a large number of macrophages, foreign body giant cells, eosinophils and neutrophils at all time points. The number of macrophages and foreign body giant cells was significantly higher after 180 days in Parietene™ than in Strattice™ ($P = 0.022$). Numbers of eosinophils and neutrophils, on the other hand, were significantly higher in Parietene™ mesh than in the non-cross-linked biological mesh at 30 and 90 days. Sirius red staining revealed significantly greater collagen deposition in Parietene™ compared with Strattice™ 30 and 180 days after implantation.

Permacol™

Slides of the Permacol™ meshes showed a moderate amount of macrophages, but only scanty eosinophils and neutrophils. There were no significant differences compared with other mesh groups. There was a significantly greater amount of collagen encapsulation in the Permacol™ group than in the Strattice™ group at 30 days ($P = 0.029$) and 180 days ($P = 0.031$) after implantation.

Evaluation of mesh-specific histological parameters revealed moderate to pronounced scaffold degradation, pronounced fibrous encapsulation, and peripheral cellular infiltration and neovascularization. There were no significant differences between Permacol™ and other mesh groups.

Strattice™

Compared with Parietene™ mesh, Strattice™ had significantly fewer neutrophils and eosinophils 30 and 90 days after implantation, and significantly fewer macrophages 180 days after implantation. In addition, Strattice™ had significantly less collagen encapsulation than Parietene™ and Permacol™ 30 and 180 days after implantation.

Assessment of the mesh-specific histological parameters revealed a significantly increased amount of scaffold degradation in Strattice™ than in Parietene™ and Omyra® Mesh 90 days after implantation.

XCM Biologic®

XCM Biologic® had large numbers of macrophages and foreign body giant cells present 30 and 90 days after implantation (more than 10 cells per high-power field). In contrast, eosinophils and neutrophils were almost absent, and their numbers were therefore significantly lower than in Parietene™ at 90 days ($P = 0.029$). XCM Biologic® had significantly more collagen encapsulation than Strattice™ 30 days after implantation. There were no significant differences at other time points.

Analysis of mesh-specific histological parameters revealed an increased amount of scaffold degradation at all time points compared with other meshes, but this difference was only significant compared with Parietene™ at 30 days after implantation ($P = 0.025$).

Omyra® Mesh

Omyra® Mesh had large numbers of macrophages and foreign body giant cells at all time points (more than 10 cells per high-power field). Thirty days after implantation, there was a large number of eosinophils and neutrophils, but these were absent at 90 and 180 days. At 90 days after implantation, collagen encapsulation was significantly more prominent around the Omyra® Mesh than around Strattice™ ($P = 0.002$).

Assessment of mesh-specific histological parameters revealed the absence of scaffold degradation with an increased amount of fibrous encapsulation at all time points.

DISCUSSION

This experimental study in a peritonitis model revealed that the use of biological mesh is feasible in a contaminated environment. Overall, XCM Biologic® appeared superior in this model; however, adhesions and shrinkage of the mesh were evident.

Regarding the individual meshes, Strattice™ had inferior incorporation, whereas the other meshes incorporated well. This agrees with previous studies [14, 24] using Strattice™ mesh. Even 180 days after implantation, there was little incorporation of this mesh into the abdominal wall. In addition, it was found that collagen deposition was less in Strattice™ than in the other meshes.

Overall, there was a large, but non-significant variation in shrinkage, ranging from 8 to 43 percent at various time points. XCM Biologic® shrank excessively, by 21–43 percent. Structural resistance might be influential with regard to mesh shrinkage. Resistance is a function of the volume of the material used in the mesh. Large-pore, low-weight meshes show less resistance, and thus less shrinkage. No previous studies of XCM Biologic® have assessed shrinkage rates in an experimental model. The other meshes studied shrank between 8 and 27 percent at various time points. This finding highlights the importance of implanting mesh materials with sufficient overlap around a hernia defect.

All meshes, except for Strattice™, formed strong adhesions; those formed by Permacol™ were significantly stronger than those on all other meshes. The tenacity of adhesions is linked to the percentage adhesion on the surface of the mesh.

Although all meshes were assessed in a peritonitis model, active inflammation with abscess formation was found in only two animals at the time of death. Previous studies [14, 24] revealed abscesses in 42–62 percent of animals at the time of death [14, 24]. Both Deerenberg and colleagues [14] and the present study group studied Strattice™, Parietene™ and Omyra® Mesh. In the study of Deerenberg and colleagues [14], these three meshes showed little abscess formation. There were significantly larger numbers of abscesses surrounding the mesh in C-Qur™ (omega-3-fatty acid-coated polypropylene; Atrium, Hudson, New York, USA), and DualMesh® (expanded polytetrafluoroethylene; Gore, Flagstaff, Arizona, USA). Mulder and colleagues [24] reported abscesses on more than 50 percent of Permacol™ meshes. Many abscesses were also found in Surgisis® (non-cross-linked porcine submucosa; Cook Medical, Bloomington, Indiana, USA) and CollaMend™ FM (cross-linked porcine dermis; C.R. Bard (Davol), Warwick, Rhode Island, USA), meshes that were not investigated here. Aside from the mesh materials, another reason for the lack of abscesses could be the fact that the substrain of Wistar rats used in the present study is more resistant to infection.

In this study, the synthetic meshes Parietene™ and Omyra® Mesh and the biological cross-linked mesh Permacol™ incorporated well and had only moderate shrinkage. Although the three meshes are made of different materials, their in vivo response was similar. Interestingly, Permacol™ is the only biological mesh in this study that mimicked the behavior of the synthetic meshes. Permacol™ is of porcine origin and is additionally cross-linked with hexamethylene di-isocyanate [25]. These additional cross-links give a more synthetic-like behavior to the biological mesh compared with the non-cross-linked biological meshes. The foreign body reaction against Permacol™ may therefore be comparable to that of the synthetic meshes, but not to that of the non-cross-linked biological meshes.

Two distinct patterns were identified when the histological mesh-specific parameters were evaluated. First, the synthetic meshes Parietene™ and Omyra® Mesh, and the cross-linked biological mesh Permacol™, showed almost no scaffold degradation, a large amount of fibrous encapsulation, and little or no cellular infiltration, neovascularization and extracellular matrix deposition. Second, the non-cross-linked meshes Strattice™ and XCM Biologic® showed a large amount of scaffold degradation, little to no fibrous encapsulation, and considerable cellular infiltration, neovascularization and extracellular matrix deposition. These two patterns could be explained by the respective mesh materials. If high biocompatibility is desirable, a non-cross-linked biological mesh is optimal. However, slower mesh incorporation and quicker mesh degradation should be taken into account.

There are several limitations to this study that do not allow direct translation to a clinical setting. There are three differences between the human situation and this experimental study. First, there is a difference in the treatment of abdominal sepsis. The rats received a single dose of antibiotics and one abdominal cavity rinse, whereas humans receive long-term intravenous antibiotics and undergo extensive debridement with or without open abdomen treatment. Second, there are differences in the dimension of the mesh. The mesh is proportionally much thicker in rats than in humans, in comparison with the thickness of the abdominal wall. This could lead to decreased incorporation of the mesh in the rat model. Third, all meshes were placed intraperitoneally in this study. This includes non-coated or non-composite synthetic meshes, whereas previous studies [14, 24, 26-28] showed high cellular reactivity and adhesion formation after intraperitoneal placement of these meshes compared with extraperitoneal placement [14, 24, 26-28]. The same applies to the cross-linked mesh Permacol™, which was placed intraperitoneally in the rat model, whereas in humans results of placement in the intraperitoneal plane have been variable [10, 29, 30]. However, closure of the peritoneum is not always possible in patients, and contact between the viscera and mesh could be occurring. Therefore, it is important to assess mesh behavior of synthetic and cross-linked meshes in an intra-abdominal environment in vivo.

In this experimental study, XCM Biologic® appeared superior, in terms of incorporation, macroscopic mesh infection, and histological parameters such as collagen deposition and neovascularization. It is important, however, that there is a sufficient overlap of the mesh during placement, as XCM Biologic® showed a high rate of shrinkage.

Acknowledgements

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SUPPORTING INFORMATION

Table S1. Zühlke scoring system for adhesions [20]

Score	Definition
0	No adhesions
1	Minimal, filmy adhesions requiring little blunt dissection
2	Moderate adhesions requiring blunt and partly sharp dissection; beginning of vascularization
3	Strong adhesions; lysis possible by sharp dissection only; clear vascularization
4	Very strong adhesions; lysis possible by sharp dissection only; organs attached (damage to organs difficult to prevent)

Table S2. Abscess scoring system [21]

Score	Definition
0	No abscess present at the site
0.5	One small abscess present at the site
1	Several small abscesses present at the site
2	Medium abscess present at the site
3	Large or several medium abscesses present at the site
4	One very large or several large abscesses present at the site

Table S3. Histological scoring system for inflammatory cell reaction [22]

	Score			
	0	1	2	3
Inflammatory cell reaction (no. of cells per HPF)	0–50	51–100	101–150	> 150
Eosinophils–neutrophils (no. of cells per HPF)	0	1–5	6–10	> 10
Macrophages–foreign body giant cells (no. of cells per HPF)	0	1–5	6–10	> 10
Mononuclear cells (no. of cells per HPF)	0–10	11–50	51–100	> 100

Number of cells per high-power field (HPF) was determined at 40 × magnification.

Table S4. Histological scoring system for mesh-specific parameters [22]

	Score		
	0	1	2
Scaffold degradation	– Original scaffold intact, borders clearly demarcated	± Scaffold partially degraded, layers separated by cells, blood vessels, host tissue, etc.	+ Scaffold completely degraded, no evidence of original scaffold
Fibrous encapsulation	+ Extensive encapsulation (50–100%) of periphery)	± Moderate encapsulation (>0–50% of periphery)	– No fibrous encapsulation
Cellular infiltration*	– No cells in contact with scaffold	Periphery Cells infiltrate scaffold, but none reach center	Center Cells penetrate into center of scaffold
Neovascularization	– No blood vessels present	Periphery Vessels infiltrate scaffold but none reach center of scaffold	Center Vessels penetrate into center of scaffold
ECM deposition	– No host ECM deposition	Periphery Host ECM deposited inside scaffold, but not at center	Center Host ECM deposited inside scaffold, including center

*Inflammatory and connective tissue cells. ECM = extracellular matrix.

Table S5. Collagen deposition [23]

Score	Definition
0	No response
1	Minimal/barely detectable
2	Mild/slightly detectable
3	Moderate/easily detectable
4	Marked/very evident

Table S6. Results of histological evaluation

	n	Inflammatory cells total	Eosinophils–neutrophils	Macrophages–FBGC	Mononuclear cells	Collagen deposition*
Parietene™						
30 days	8	2 (2–2)	3 (3–3)†	3 (3–3)	2 (1–2)	3 (3–3)†
90 days	9	2 (1–2)	3 (2–3)‡	3 (3–3)	2 (1–2)	3 (2–3)
180 days	7	1 (1–2)	1 (1–3)	3 (3–3)§	1 (1–1)	3 (2–4)§
Permacol™						
30 days	9	1 (1–2)	0 (0–3)	1 (1–2)	2 (1–2)	3 (2–3)†
90 days	8	1 (1–2)	0 (0–2)	2 (2–3)	2 (2–3)	2 (1–3)
180 days	8	1 (1–1)	0 (0–0)	2 (1–3)	1 (1–2)	3 (2–4)§
Strattice™						
30 days	9	1 (0–2)	0 (0–0)	1 (1–3)	1 (1–3)	0 (0–0)
90 days	9	2 (1–3)	0 (0–0)	3 (2–3)	2 (1–3)	0 (0–0)
180 days	7	0 (0–1)	0 (0–0)	1 (0–1)	1 (0–1)	0 (0–0)
XCM Biologic®						
30 days	9	2 (2–3)	0 (0–1)	3 (2–3)	3 (2–3)	3 (2–3)†
90 days	5	3 (2–3)	0 (0–0)¶	3 (1–3)	3 (3–3)	2 (1–2)
180 days	6	1 (1–2)	0 (0–0)	1 (1–1)	3 (1–3)	2 (1–2)
Omyra Mesh®						
30 days	6	2 (2–3)	3 (1–3)	3 (3–3)	3 (2–3)	3 (2–3)
90 days	6	2 (1–2)	0 (0–1)	3 (3–3)	2 (1–2)	3 (3–4)‡
180 days	6	1 (1–1)	0 (0–1)	3 (3–3)	1 (1–2)	3 (2–3)

Values are median (IQR). *Based on sirius red staining. FBGC = foreign body giant cells. †$P < 0.050$ versus Strattice™ at 30 days, ‡$P < 0.050$ versus Strattice™ at 90 days, §$P < 0.050$ versus Strattice™ at 180 days, ¶$P < 0.050$ versus Parietene™ at 90 days (Kruskal–Wallis test with Dunn's post-test).

Table S7. Results for mesh-specific parameters

	n	Scaffold degradation	Fibrous encapsulation	Cellular infiltration*	Neovascularization	ECM deposition
Parietene™						
30 days	8	0 (0–0)	0 (0–0)	1 (1–1)	1 (1–1)	1 (1–1)
90 days	9	0 (0–0)	1 (0–1)	1 (1–1)	1 (1–1)	1 (1–1)
180 days	7	0 (0–0)	1 (0–1)	1 (1–1)	1 (1–1)	1 (1–1)
Permacol™						
30 days	9	1 (1–2)	0 (0–1)	1 (1–1)	1 (1–1)	1 (1–1)
90 days	8	2 (1–2)	0 (0–1)	1 (1–1)	1 (1–1)	1 (1–1)
180 days	8	2 (1–2)	0 (0–1)	1 (1–2)	1 (1–2)	2 (1–2)
Strattice™						
30 days	9	1 (1–2)	2 (1–2)†	1 (1–1)	1 (1–2)	0 (0–2)
90 days	9	2 (2–2)‡	2 (0–2)	2 (2–2)‡	2 (2–2)‡	2 (2–2)
180 days	7	2 (0–2)	2 (2–2)	2 (2–2)	2 (2–2)§	2 (0–2)
XCM Biologic®						
30 days	9	2 (1–2)†	1 (0–1)	1 (1–2)	1 (1–2)	1 (1–2)
90 days	5	2 (1–2)	1 (1–1)	2 (2–2)	2 (2–2)‡	2 (2–2)
180 days	6	1 (1–2)	2 (1–2)	2 (2–2)§	2 (2–2)§	1 (0–1)
Omyra Mesh®						
30 days	6	0 (0–0)	0 (0–0)¶	1 (1–1)	1 (1–1)	1 (1–1)
90 days	6	0 (0–0)#	0 (0–0)	1 (1–1)	1 (1–1)#	1 (1–1)
180 days	6	0 (0–0)	0 (0–0)	1 (1–1)**	1 (1–1)	1 (1–1)

Values are median (IQR). *Inflammatory and connective tissue cells. ECM = extracellular matrix. †$P < 0.050$ versus Parietene™ at 30 days, ‡$P < 0.050$ versus Parietene™ at 90 days, §$P < 0.050$ versus Parietene™ at 180 days, ¶$P < 0.050$ versus Strattice™ at 30 days, #$P < 0.050$ versus Strattice™ at 90 days, **$P < 0.050$ versus XCM™ Biologic at 180 days (Kruskal–Wallis test with Dunn's post-test).

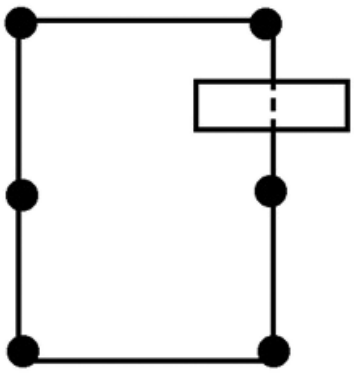


Figure S1. Schematic representation of tissue sampling for histopathology
Drawing depicted in an anteroposterior projection. Full-thickness abdominal wall samples measuring 1.0 × 0.5 cm were taken from one of the long sides in between the sutures, and contained both abdominal wall and mesh.

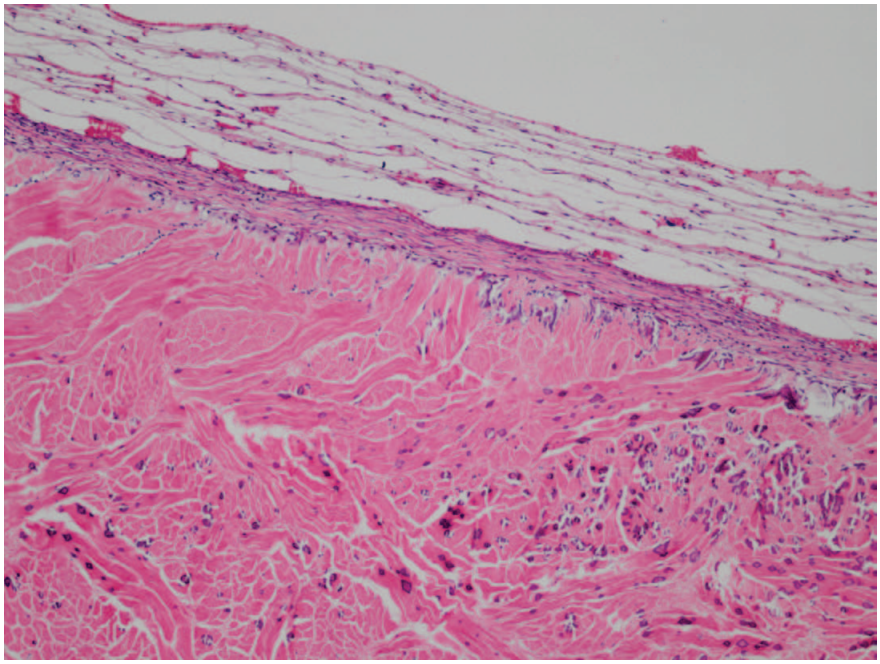


Figure S2. Hematoxylin and eosin staining of cross-linked biological mesh, without abscess (original magnification × 10)

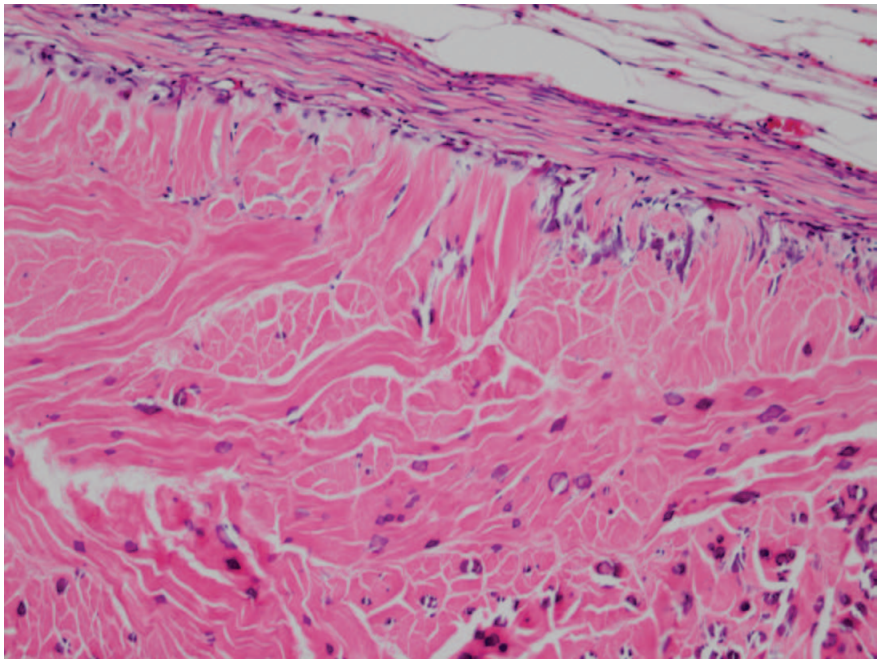


Figure S3. Hematoxylin and eosin staining of cross-linked biological mesh, without abscess (original magnification × 20)

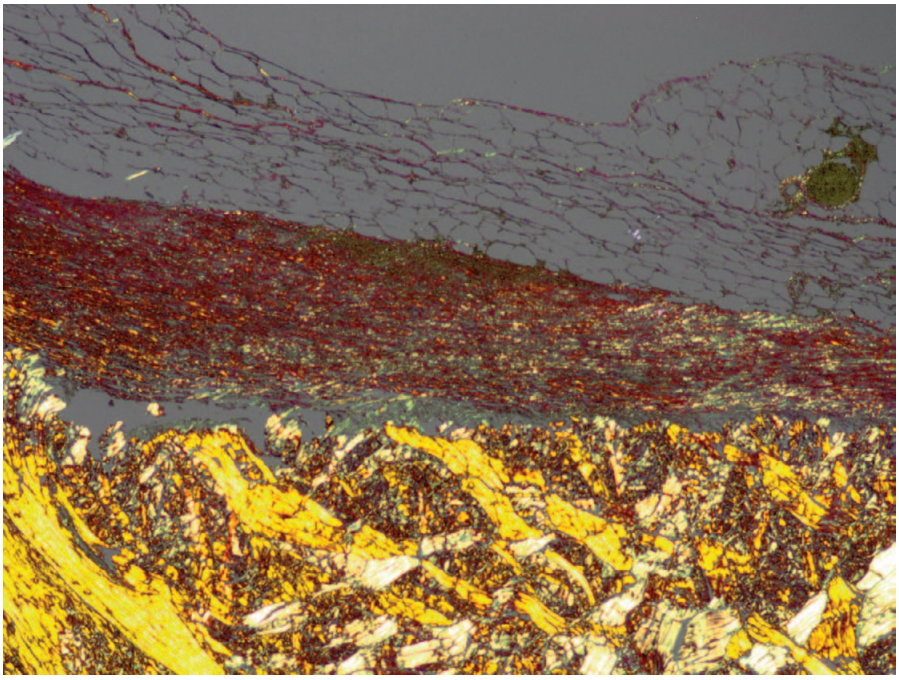


Figure S4. Sirius red staining of cross-linked biological mesh, without abscess (original magnification × 5)

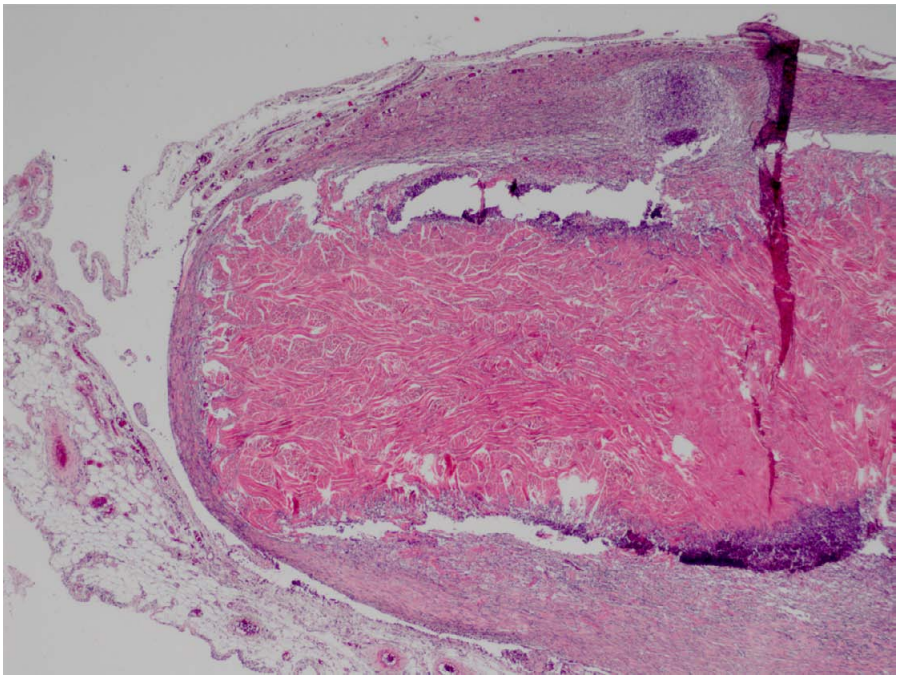


Figure S5. Hematoxylin and eosin staining of cross-linked biological mesh, with abscess (original magnification × 2.5)

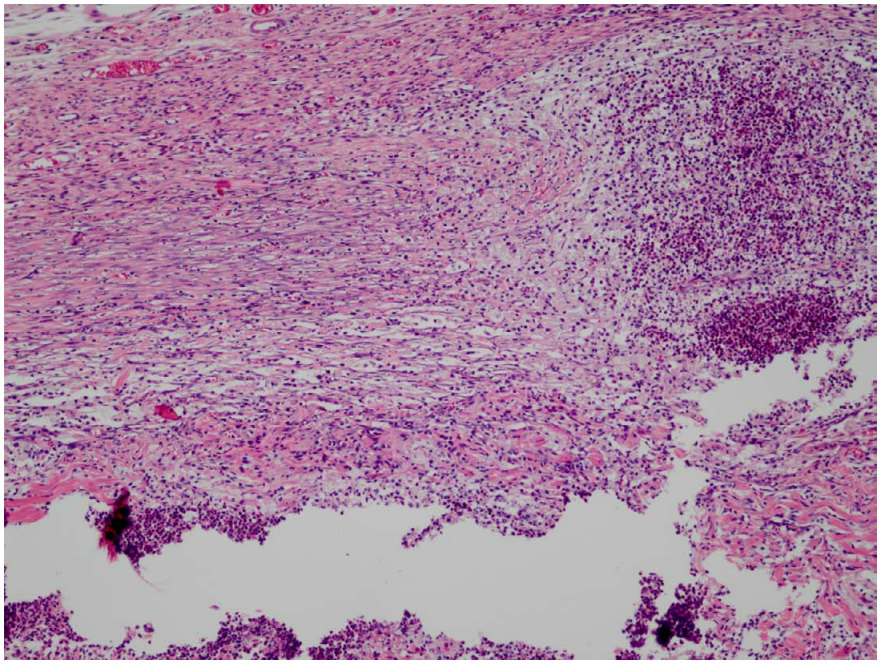


Figure S6. Hematoxylin and eosin staining of cross-linked biological mesh, with abscess (original magnification × 10)

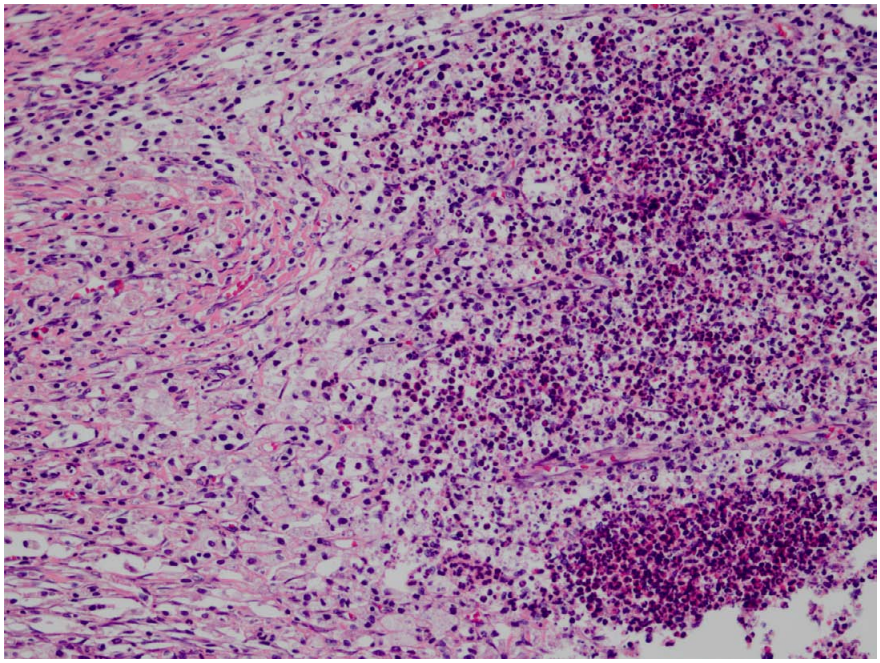


Figure S7. Hematoxylin and eosin staining of cross-linked biological mesh, with abscess (original magnification × 20)

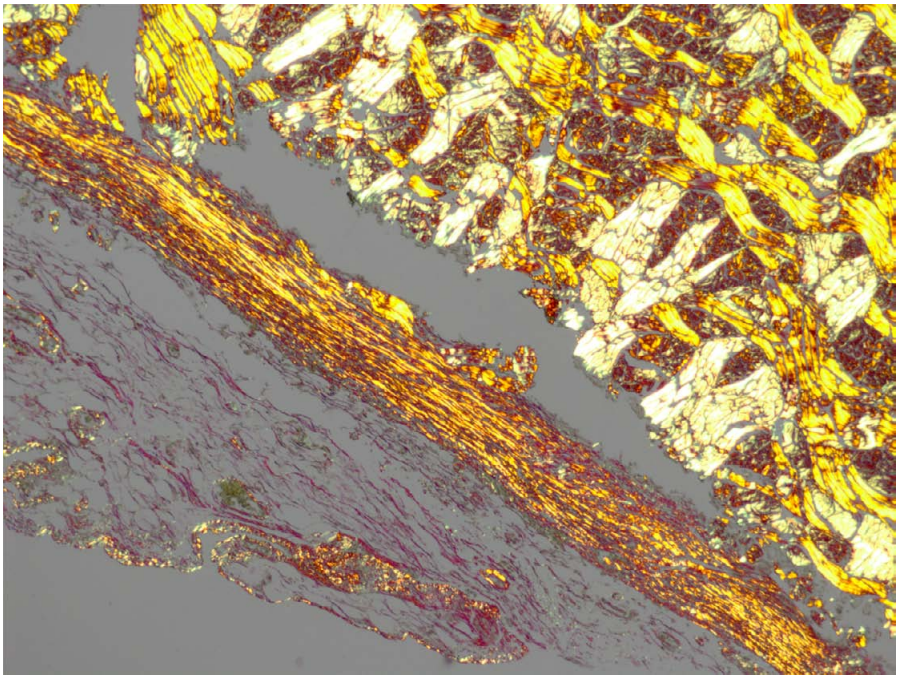


Figure S8. Sirius red staining of cross-linked biological mesh, with abscess (original magnification × 5)

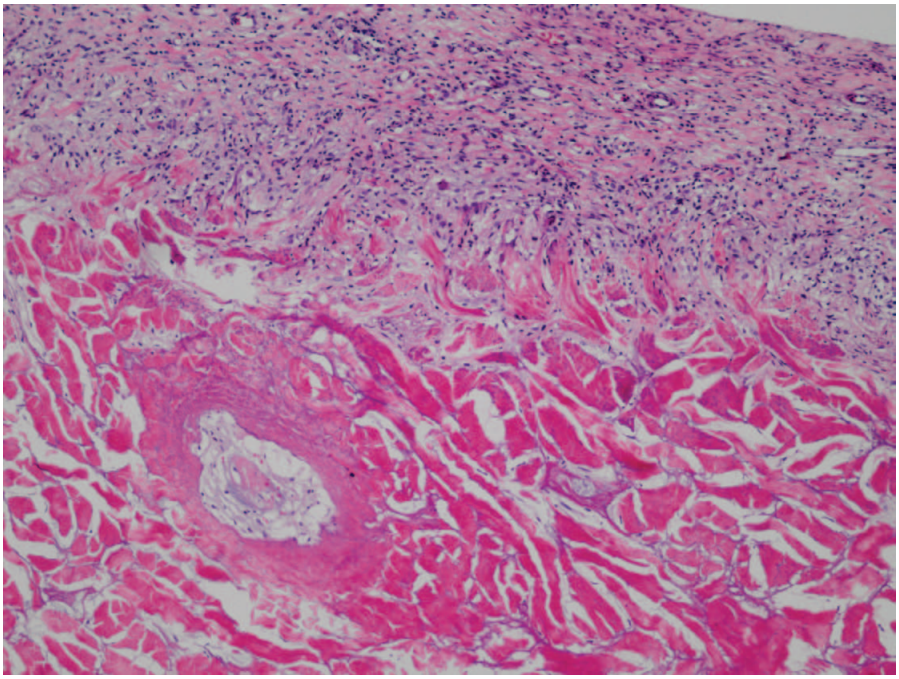


Figure S9. Hematoxylin and eosin staining of non-cross-linked biological mesh (XCM Biologic®), without abscess (original magnification × 10)

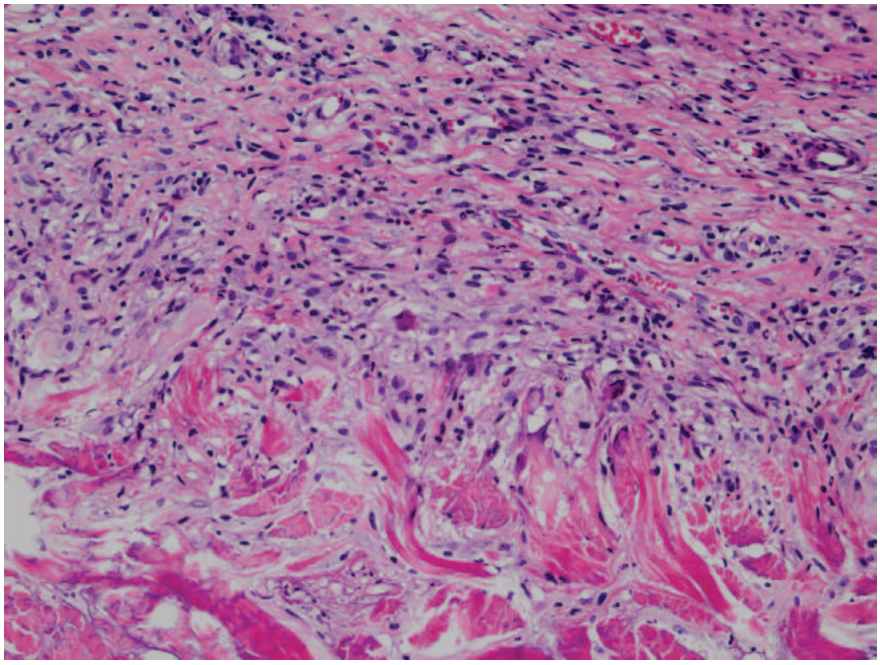


Figure S10. Hematoxylin and eosin staining of non-cross-linked biological mesh (XCM Biologic®), without abscess (original magnification × 20)

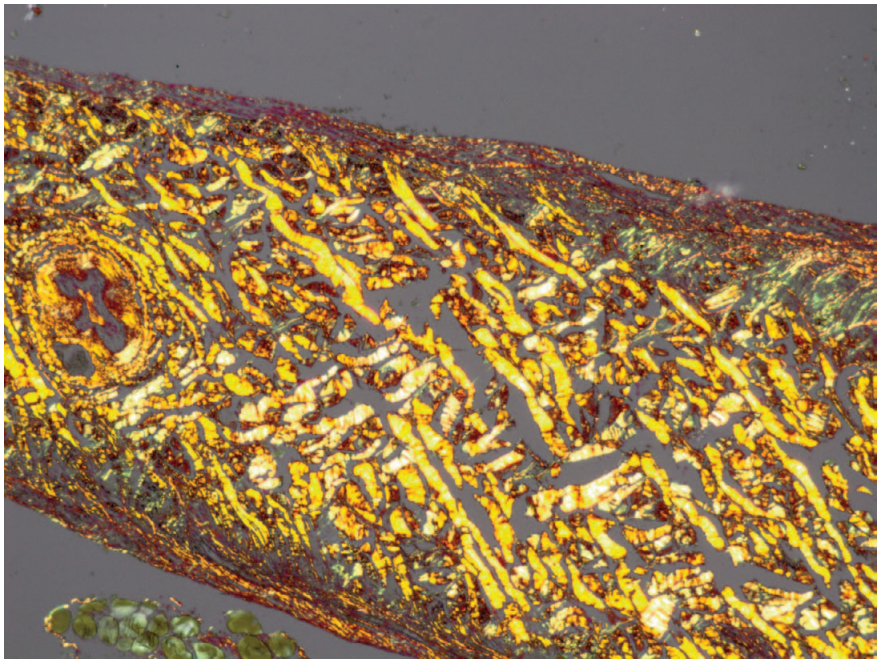
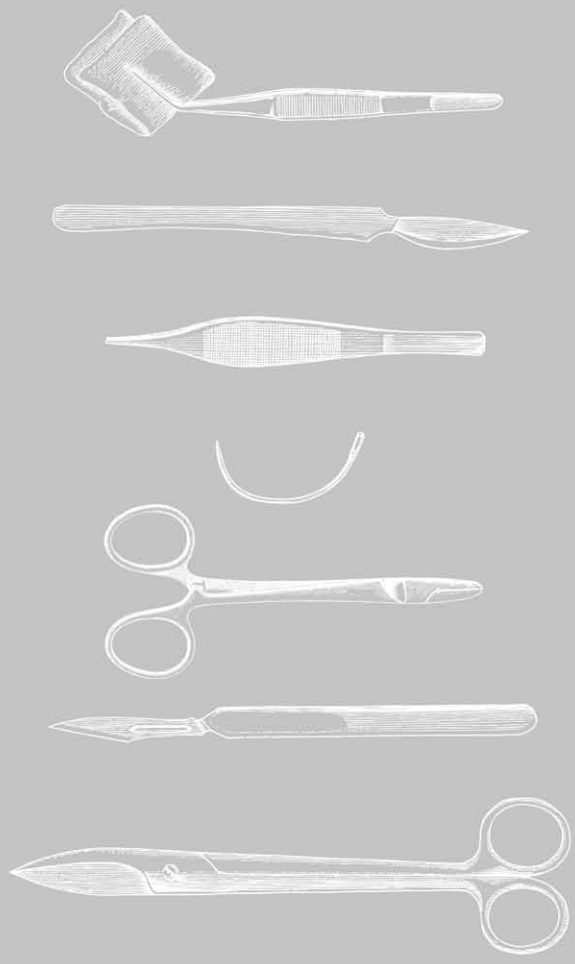
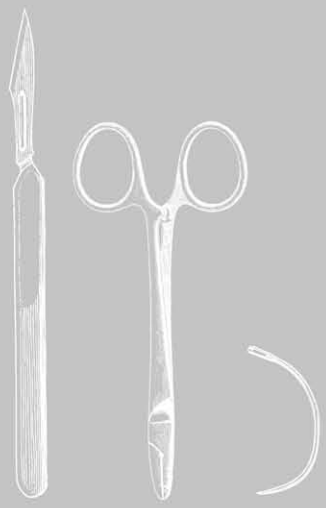


Figure S11. Sirius red staining of non-cross-linked biological mesh (XCM Biologic®), without abscess (original magnification × 5)



5

META-consensus score: an international consensus score on mesh-tissue adhesions



L.C.L. van den Hil, E.H.H. Mommers, J.W.A.M. Bosmans, S. Morales-Conde, V. Gómez-Gil, K. LeBlanc, A. Vanlander, E. Reynvoet, F. Berrevoet, S. Gruber-Blum, E. Altinli, C.R. Deeken, R.H. Fortelny, J.W. Greve, K. Chiers, R. Kaufmann, J.F. Lange, U. Klinge, M. Miserez, A.H. Petter-Puchner, M.H.F. Schreinemacher, N.D. Bouvy

Submitted

ABSTRACT

Introduction

The use of surgical mesh inside the abdominal cavity frequently is associated with adhesion formation, which may lead to clinically significant complications. Currently, there is no consensus on the clinical scoring of postoperative adhesions in the presence of a mesh. The aim of this study is to develop an internationally recognized clinical adhesion score using a modified Delphi method (RAND-UCLA).

Methods

A panel of experts was selected based on previously published literature on adhesion scores and postoperative adhesions. All experts were queried on four items; 1) the general usefulness of adhesion scoring models, 2) preferred design of an adhesion score, 3) appropriateness of macroscopic variables, and 4) appropriateness of microscopy scoring models. This study comprises of two questionnaire-based rounds and one international consensus meeting.

Results

The first round was completed by 82 percent (n = 23) of the panel members, the second round by 18 panel members and ten were able to participate in the final consensus meeting. A total of 140 different items were included in this study. Consensus was reached on 57 percent of the presented items. Mesh surface covered with adhesions, tenacity and thickness of adhesions, and organ involvement were concluded to be a minimal set of variables to be communicated separately in each future study on mesh adhesions.

Conclusion

The META-consensus score presented in this paper can be used to assess and classify mesh-related adhesions and is based on the opinion of 18 international leading experts. We advocate the use of this score in all future research to increase the interstudy comparability and objectivity.

INTRODUCTION

Incisional hernias are a frequent problem after laparotomy, requiring mesh repair in approximately 25 percent of all patients who have undergone a midline laparotomy [1]. Intra-abdominal mesh placement is a well-known inducer of adhesions between intestines and mesh [2]. Approximately 5 to 18 percent of patients showing radiological signs of adhesions will develop complications due to these adhesions [3-5]. Intra-abdominal adhesions are a known cause for serious postoperative complications such as bowel obstruction [6, 7]. To prevent such complications, meshes for intra-abdominal use are either designed with materials that prevent adhesion, such as PTFE, or with conventional polypropylene or polyester coated with anti-adhesive materials. Despite the abundance of anti-adhesive devices, positive clinical results of intra-abdominal mesh placement are scarce [8, 9].

Important factors influencing adhesion formation are mesh material, pore size and the presence of anti-adhesive coatings on the visceral side of the mesh [10]. Aforementioned factors may influence the number of adhesions, though complete adhesion prevention is currently not possible [10, 11]. Before clinical application of anti-adhesive barriers, they are often tested in animal models [12, 13]. However, comparing the efficacy of anti-adhesive devices has become increasingly difficult due to the abundance of various adhesion scores [14, 15]. There are currently over twenty different adhesion scores available. Diamond and colleagues described one of the first scoring systems, which used sub scores for extent, type, and tenacity of adhesions [14]. Up to now there is a lack of consensus on the ideal adhesion scoring method, and interstudy comparability is decreasing due to the increasing diversity in adhesion scores [14-17].

The goal of this study is to use a Delphi method to achieve an international consensus on an adhesion scoring method focusing on mesh-related adhesions amongst an international panel of experts in an attempt to increase consistent outcome reporting in the field of intra-abdominal mesh-related adhesions [18].

METHODS

The Delphi method is an accepted technique to evaluate a topic and to reach consensus on this topic. In short, the Delphi method comprises multiple rounds of questionnaires, which are completed individually by an expert panel. The Delphi method is characterized by anonymity, controlled feedback to the expert panel, and statistical analysis of the results [19]. Anonymity reduces the influence of dominant individuals in the panel,

and it is thought that experts might change their opinion after receiving input of the panel. This study used a modified Delphi method named RAND-UCLA Appropriateness Method (RAM), which is a Delphi score specifically aimed at the medical field [20]. The RAM starts with performing a systematic review, followed by questionnaires, and eventually a face-to-face meeting.

Panel formation

The expert panel was formed based on the results of a systematic literature search on adhesion scoring models. PubMed, MEDLINE and Embase were searched to identify publications. Any author who published at least three full-text publications on adhesion scoring systems or complications due to mesh-related adhesions was invited to participate in the expert panel. After the first invitation, two personalized reminders were sent after one and two weeks. In case authors did not respond to the reminders, they were considered unreachable and were not included in the expert panel.

Questionnaires

Questionnaires were designed and distributed online (SurveyMonkey Inc, Palo Alto, CA). The questionnaires addressed multiple choice questions regarding four main items; 1) general questions regarding the usefulness of adhesion scoring models in both experimental and clinical settings, 2) preferred design of the adhesion score, 3) appropriateness of macroscopic variables, and 4) appropriateness of microscopy scoring models. Panel members could rate these questions on a nine-point Likert scale, ranging from very inappropriate (score 1) to very appropriate (score 9). Participants were encouraged to provide additional remarks in a free text field, such as other important variables or feedback on their answers.

At the end of each round, the results were statistically analyzed and presented during the follow-up round. Participants received a copy of their individual answers separately. Any item on which consensus was reached was not included in the follow-up rounds. Items without consensus were repeated and adjusted if required, according to comments received in the previous round.

Final consensus meeting

The last round of the Delphi method was a face-to-face meeting held during the 38th (2016) International Congress of the European Hernia Society (EHS) in Rotterdam, The Netherlands. During this meeting, any remaining items without consensus were discussed. Any panel member who finished two questionnaire rounds was invited to participate in the meeting.

Each item was presented with a short introduction, and scored on a nine-point Likert scale by each individual participant. A summary of the discussion was sent to the entire panel, followed by two suggestions for a new adhesion scoring model. Panel members were questioned which model had their preference.

Statistical analysis

All data were analyzed using MS Excel 2015 (Microsoft Corporation, Redmond WA). Consensus was reached if the panel rated a topic unanimously as either inappropriate (panel median 1–3) or appropriate (panel median 7–9), without disagreement. Disagreement was tested to identify considerable dispersion between ratings of panel members, using the inter-percentile range adjusted for symmetry, according to the RAND-UCLA Appropriateness Method Manual and as used by Moossdorff and colleagues [20, 21].

RESULTS

Invitations for participation in this mesh-related adhesions Delphi were sent to 57 authors. Thirty-seven authors responded, of which nine declined the invitation and 28 accepted (49 percent acceptance rate). One author declined the invitation though sent another experienced researcher in the field of adhesions to take his place. The first questionnaire was completed by 82 percent (n = 23) of the panel members. From the 23 participants that completed the first questionnaire, 18 (64 percent) participants completed the follow-up questionnaire. Under whom were 12 surgeons, three postdoctoral researchers and nine professors. Ten participants (36 percent) were able to participate in the final meeting. A flow chart with a summary of the study outcomes is shown in Figure 1.

Panel characteristics

All panel members were affiliated to a university and were experienced in performing both animal and clinical research in the field of intra-abdominal mesh-related adhesions. The panel members participated in the Delphi analyses on their own behalf and expertise, no compensation of any kind was provided to the participants. Any personal views of the individual participants did not necessarily reflect the view of their affiliated institutions.

First round

The first questionnaire consisted of 64 items in seven categories, 1) utility of scoring models, 2) adhesion-related complications, 3) macroscopic outcome, 4) scoring scales, 5) composite scores versus subscores, 6) histological assessment, and 7) follow-up. After the first round, consensus was reached on 44/64 items (69 percent) of the presented

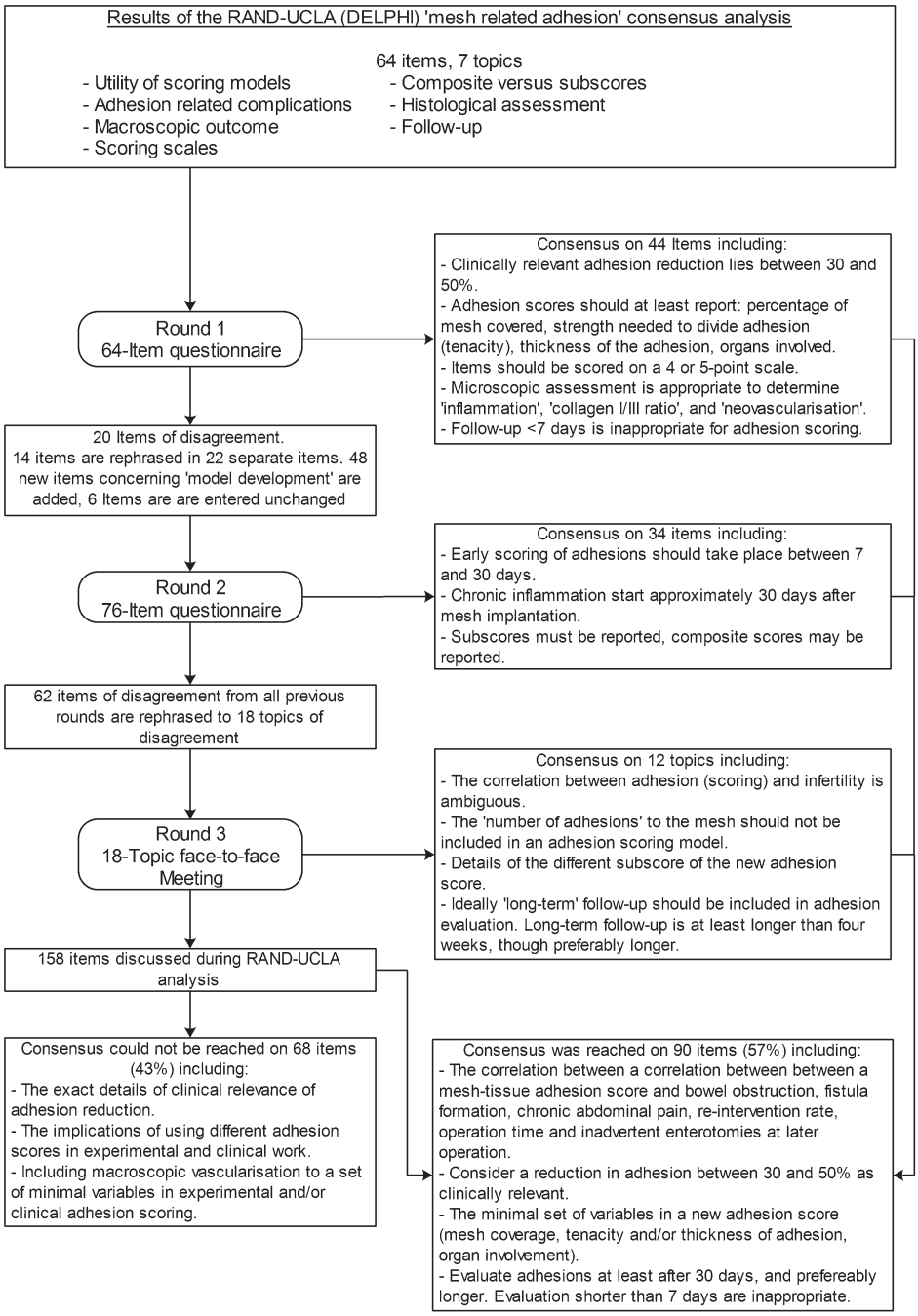


Figure 1. Flow of information through the Delphi analysis
The Delphi analysis consisted of three rounds and resulted in a consensus on 57 percent of the topics discussed. The figure provides a flowchart of information throughout the Delphi analysis, combined with the most important consensus reached in each round.

items. Disagreement existed on the remaining 20 items. Fourteen of these 20 items were rephrased into 22 separate items. Combined with the six unchanged items, 28 remaining items were included in the second questionnaire.

Second round

The second questionnaire consisted of 76 items (28 from the first questionnaire, 48 new items to develop a new adhesion model). Most questions were added to address simplification of a new adhesion scoring model. This model would be discussed during the final face-to-face meeting.

At the end of the second round, consensus was reached on 34/76 items (45 percent) of the presented items. Consensus was achieved on 1/6 of the remaining, unchanged items, 8/22 of the adjusted items and 25/48 of the new items. Including both questionnaire rounds, consensus was reached on 78/140 items (56 percent).

Final meeting

The goal of the meeting was to formulate the final variables that had to be included in a new adhesion scoring model. Furthermore, the most appropriate scoring scales and follow-up times had to be selected. Feedback on the first two rounds was provided to the participants before the final meeting. During the meeting, items on which no consensus was reached (62 questions, regarding 18 topics) were discussed. On 12 topics consensus was reached (66.7 percent).

Consensus-based adhesion scoring model

All panel members consented that mesh-tissue adhesions should be scored systematically in both human and experimental settings, and that a uniform consensus-based scoring method should be used to increase interstudy comparability. According to the panel members, mesh-related adhesion scores had to exist primarily of macroscopic variables. Microscopic variables could also be assessed, but should be presented separately from the macroscopic scores. Items that had to be included in the macroscopic adhesion score were percentage of mesh surface covered with adhesions, strength needed to divide adhesions (tenacity), thickness of adhesions, and organ involvement. The absolute number of adhesions and the macroscopic vascularization were considered inappropriate items for adhesion scoring. Table 1 shows adhesion scores which are currently used often. Presence of inflammatory cells, collagen and neovascularization are important microscopic variables.

Table 1. Most often used adhesion scores

Adhesion score	Year of publication	Advantage	Disadvantage
De Oliveira et al. [23]	1981	Involvement of organs described	Moderate reproducibility
Diamond et al. [14]	1987	Multiple variables implemented	Designed for postoperative adhesions
Zühlke et al. [15]	1990	Grades clearly explained	Multiple variables are combined in one grade of the score
Bellón et al. [22]	1996	Straightforward	Moderate reproducibility
Garrard et al. [24]	1999	Tenacity grades clearly explained	Percentage difficult to assess without use of a computer program

Table 2. META-consensus score

Item		Score
Percentage of mesh surface covered with adhesions	0%	0
	1–25%	1
	26–50%	2
	51–75%	3
	76–100%	4
Tenacity	No adhesions	0
	Loose adhesions easily released by traction only	1
	Adhesions require sharp dissection, no organ/serosal damage	2
	Adhesions require sharp dissection, with unavoidable organ/serosal damage	3
Thickness of adhesions	No adhesions	0
	Single thin, filmy adhesion	1
	Multiple thin, filmy adhesions	2
	Single dense adhesion with or without filmy adhesions	3
	Multiple dense adhesions with or without filmy adhesions	4
Organ involvement	No adhesions	0
	Adhesions between mesh and omentum or a solid organ	1
	Adhesions between mesh and part(s) of the intestinal tract	2
	Adhesions between mesh and part(s) of the intestinal tract with enteric fistulas or bowel erosion	3

The META-consensus score consist of four main items. 1) "Percentage of mesh surface covered with adhesion" can either be scored by automated computer analysis of pictures taken during surgery, or be estimated by the surgeon. 2) "Tenacity" depends on the tools needed for adhesiolysis and relates to the strength of the adhesions. 3) "Thickness of adhesions" is divided in four categories of adhesions. Macroscopically, two types of adhesions can be scored (filmy or dense) the categories are based on either single or multiple adhesions of both types. 4) "Organ involvement" scores the adhered structures and increases in severity with increased adherence to the intestinal tract. The most severe category describes adhesions to the intestinal tract combined with macroscopic damage or interference with an organ such as fistula formation or bowel erosion. When reporting the META-consensus score, each individual score must be reported in order to increase comparability between publications. An overall score can be calculated by adding all individual categories, though the relevance of this sum is unclear.

Preferably, any new scoring system for intra-abdominal mesh-tissue adhesions has to be based on a four-point or five-point scale to allow adequate variation in responses and statistical analyses.

Finally, follow-up times in experimental research have to be a minimum of four weeks after mesh-implantation to evaluate chronic inflammation. Follow-up of clinical studies on mesh-related adhesions have to include a minimal follow-up of 6 months. A new consensus-based adhesion score including the abovementioned recommendations, the META-consensus score, is presented in Table 2.

DISCUSSION

This Delphi analysis consulted eighteen leading experts in the field of adhesion research to create a minimum set of outcome variable and to reach international consensus. Based on this set of variables, a new adhesion score; the META-consensus score was developed according to the RAND-UCLA Appropriateness Method [20].

Consensus was reached on 57 percent of the discussed items. The moderate level of consensus is to be expected in a field that is still developing. Despite the remaining disagreement on several items, this study succeeded in defining a set of minimal outcome parameters. Furthermore, it gives consensus-based recommendations for follow-up and clinical efficacy in mesh-related adhesion research, such as the recommended follow-up for experimental animal studies of at least four weeks.

Due to the abundance of adhesion scores and lack of consensus in relevant outcomes measures, comparability in mesh-related adhesion research is low.

In 2014, an expert group of gynecologists developed several recommendations regarding awareness and counselling concerning adhesions and strategies to prevent adhesions. However, this consensus study did not recommend a specific adhesion score [25].

The META-consensus score is based on four equally important macroscopic variables; mesh surface covered with adhesions, tenacity of adhesions, thickness of the adhesions, and organ involvement. This score can be interpreted as a minimal set of outcome criteria; hence it can be used as a scoring system per se, or be expanded with a larger set of outcome variables, left to the discretion and specific interest of the research question. Including the META-consensus score in all future studies on mesh-related adhesions facilitates comparability between studies across different research groups, different

research models and improve translatability. Nevertheless, all variables of the META-consensus score should be reported separately. A total score can be computed as well, though to compare results between studies accurately.

To maximize interstudy comparability, it is important to use the same score in a similar manner and with comparable follow-up times. Recommended follow-up times are at least four weeks in experimental animal studies and six months in clinical studies to evaluate chronic inflammation. To measure objectively the percentage of the mesh covered with adhesions standardized pictures can be taken and analyzed using a computer program. Another form of objective adhesion measurement consists of using a grid of four quadrants to compute the percentage of mesh coverage.

Subdivisions of tenacity are objectively measurable, although it must be mentioned that it is only appropriate to score adhesions as loose and easily to release bluntly (score 1) if all tissue is easily removed from the mesh. If tissue remains on the mesh, adhesions require sharp dissection and should thus be scored as score 2.

Functional impairment and organ injuries due to adhesions or adhesiolysis should be implemented in a mesh-related adhesion score since these complications are associated with the final quality of outcome. However, functional impairment is difficult to assess in experimental research. Therefore, adhesions between mesh and intestines are used as proxy for functional impairment.

An interesting debate took place regarding thickness of adhesions, since there is some overlap between thickness and percentage of mesh surface covered with adhesions as well as with tenacity of adhesions. The relation between thickness and other variables however is not clear. Furthermore, thickness has been used in several historical scores. Since there was consensus to include all aforementioned items in an adhesion score together with organ involvement, the score as proposed in Table 2, was formulated.

New studies should be designed to assess the relation between the different variables and to validate our new scoring system. A small group of researchers should separately score adhesions using the new score and subsequently the outcomes should be compared. Comparing the sub scores and relate them to the total score will provide us more information about potential overlap between several sub scores.

Next to macroscopic variables, also microscopic variables are of interest in mesh tissue adhesion research. According to this Delphi analysis, presence of inflammatory cells, collagen and neovascularization are important variables. The amount of inflammatory

cells, collagen deposition and neovascularization can provide us information regarding biocompatibility of meshes and adhesion formation [26, 27], and should therefore be assessed in future research. However, our expert panel prefers separate scores for macroscopic and microscopic variables and therefore microscopic items were not included in the new mesh tissue adhesion score.

The META-consensus score was developed by leading authorities in the field of adhesion research. However, not all invited researchers responded to our invitation to participate in this consensus study. Authors who did reply and became panel member are specifically interested in the topic and are convinced that a uniform scoring method is needed. This process may have led to selection bias, though the restricted number of panel members is characteristic of a consensus project. The authors consider the current panel to be convenient to represent researchers who explore mesh-related adhesions.

None of the previously published adhesion scores has been clinically validated, nor has the META-consensus score. It is our hope that with the introduction and subsequent use of a consensus-based measuring tool for mesh-tissue adhesions, our group and others will be able to benefit from all the findings by different research groups. Most importantly, sub scores or even the composite score should be correlated with clinically significant outcomes such as bowel obstruction, pain or female infertility. Although we are aware that even a single, relatively weak adhesion might be the cause of a bowel obstruction needing surgical intervention, we feel that a higher score indicates a higher probability, not a guarantee, that clinical events may arrive. Beyond that, a higher adhesion score is associated with an increased risk of enterotomies in case of surgery [28]. Furthermore, in women which were operated for inflammatory bowel disease, the fertility rate decreases compared to non-operated women, probably due to the presence of adhesions [7].

CONCLUSION

The META-consensus score is the result of a Delphi analysis amongst an international panel of adhesion experts. The score defines a minimum set of outcome parameters and should be measured as objectively as possible. A total score can be calculated, although it is inferior to the presentation of all individual sub scores.

To increase comparability in mesh-related adhesion research, the variables of the META-consensus score should be the minimal requirement of outcome parameters reported.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

Conflicts of interest

SM declares conflicts of interest due to the fact that he was a speaker for several companies. However, this fact did not influence the content of this paper. All other authors declare no conflict of interest.

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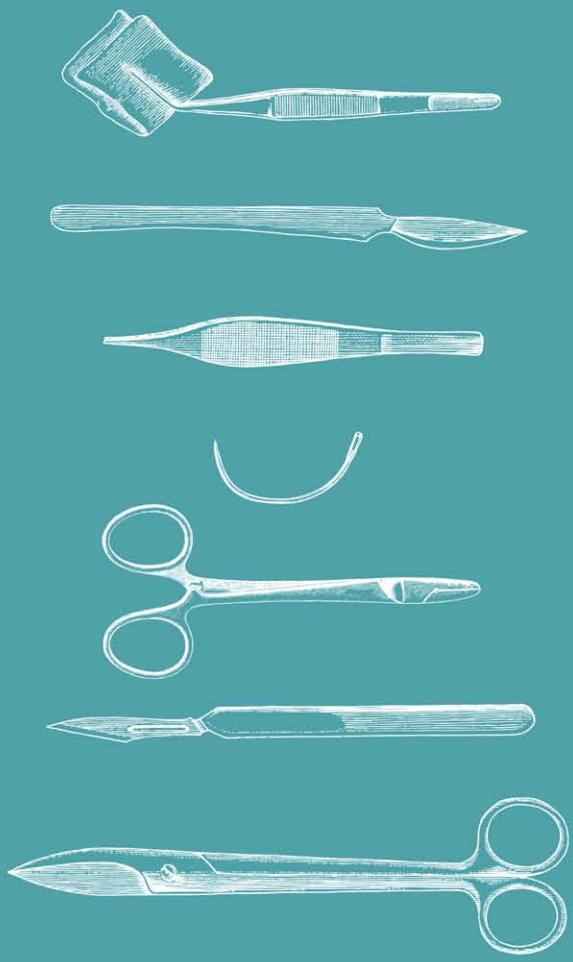
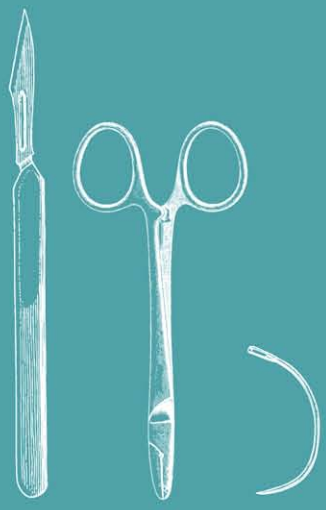
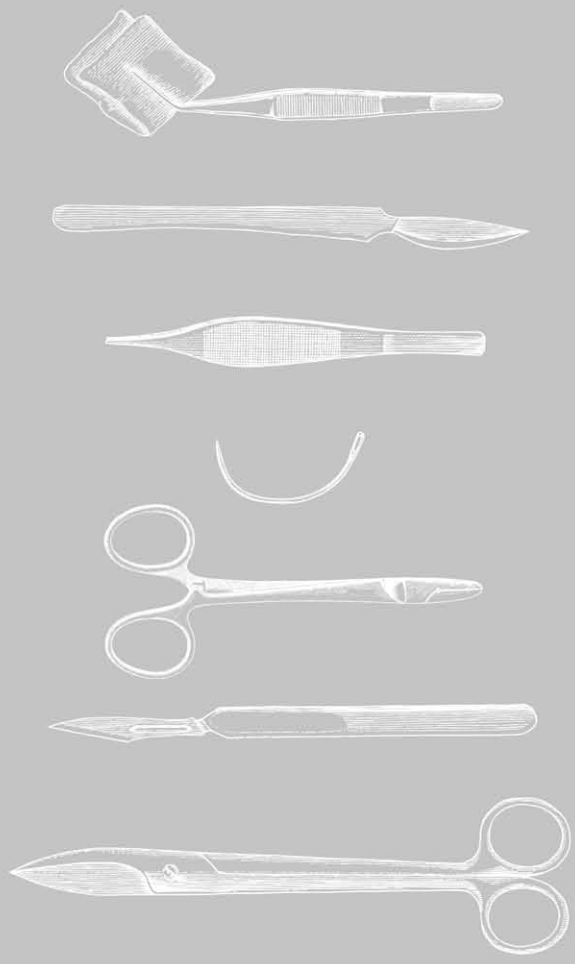


part 2

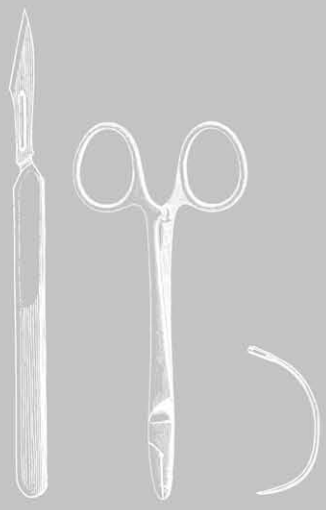
use of mesh





6

Mesh versus suture repair of umbilical hernia in adults: a randomized, double-blind, controlled, multicenter trial



R. Kaufmann, J.A. Halm, H.H. Eker, P.J. Klitsie, J. Nieuwenhuizen, D. van Geldere, M.P. Simons, E. van der Harst, M. van 't Riet, B. van der Holt, G.J. Kleinrensink, J. Jeekel, J.F. Lange

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ABSTRACT

Introduction

Both mesh and suture repair are used for the treatment of umbilical hernias, but for smaller umbilical hernias (diameter 1–4 cm) there is little evidence whether mesh repair would be beneficial. In this study we aimed to investigate whether use of a mesh was better in reducing recurrence compared with suture repair for smaller umbilical hernias.

Methods

We did a randomized, double-blind, controlled multicenter trial in 12 hospitals (nine in the Netherlands, two in Germany, and one in Italy). Eligible participants were adults aged at least 18 years with a primary umbilical hernia of diameter 1–4 cm, and were randomly assigned (1:1) intraoperatively to either suture repair or mesh repair. In the first 3 years of the inclusion period, blocked randomization (of non-specified size) was achieved by an envelope randomization system; after this time computer-generated randomization was introduced. Patients, investigators, and analysts were masked to the allocated treatment, and participants were stratified by hernia size (1–2 cm and >2–4 cm). At study initiation, all surgeons were invited to training sessions to ensure they used the same standardized techniques for suture repair or mesh repair. Patients underwent physical examinations at 2 weeks, and 3, 12, and 24–30 months after the operation. The primary outcome was the rate of recurrences of the umbilical hernia after 24 months assessed in the modified intention-to-treat population by physical examination and, in case of any doubt, abdominal ultrasound. This trial is registered with ClinicalTrials.gov, number NCT00789230.

Results

Between June 21, 2006, and April 16, 2014, we randomly assigned 300 patients, 150 to mesh repair and 150 to suture repair. The median follow-up was 25.1 months (IQR 15.5–33.4). After a maximum follow-up of 30 months, there were fewer recurrences in the mesh group than in the suture group (six [4 percent] in 146 patients versus 17 [12 percent] in 138 patients; 2-year actuarial estimates of recurrence 3.6 percent [95 percent CI 1.4–9.4] versus 11.4 percent (6.8–18.9); $P = 0.01$, hazard ratio 0.31, 95 percent CI 0.12–0.80, corresponding to a number needed to treat of 12.8). The most common postoperative complications were seroma (one [<1 percent] in the suture group versus five [3 percent] in the mesh group), hematoma (two [1 percent] versus three [2 percent]), and wound infection (one [<1 percent] versus three [2 percent]). There were no anesthetic complications or postoperative deaths.

Conclusions

This is the first study showing high level evidence for mesh repair in patients with small

hernias of diameter 1–4 cm. Hence we suggest mesh repair should be used for operations on all patients with an umbilical hernia of this size.

Funding

Department of Surgery, Erasmus University Medical Center, Rotterdam, Netherlands.

RESEARCH IN CONTEXT

Evidence before this study

Umbilical hernia is a common diagnosis in patients. Approximately 10 percent of all abdominal wall hernias are defined as umbilical hernia. In adults, the global prevalence of umbilical hernia is 2 percent. Until now, publications about umbilical hernia included only retrospective cohort studies, prospective observational studies, hernia register analyses, and randomized controlled studies with smaller sample sizes than our study. We searched PubMed, Embase, MEDLINE, Cochrane on Aug 10, 2017, without date or language restrictions, for studies including the terms "hernia, ventral"[mesh] OR "ventral hernia") AND (umbilical AND (surgery OR herniotomy OR herniorrhaphy OR hernioplasty) AND (recurrence OR "chronic pain" OR "surgical site infections" OR "wound infections" OR "seromas" OR "quality of life" OR "cosmesis". Findings from a previous randomized controlled trial with 200 patients by Arroyo and co-workers led them to conclude that the hernia recurrence rate was significantly higher after suture repair (11 percent) compared with mesh repair (1 percent). However, their study had no clear cutoff value for hernia diameter (all hernia diameters were included). Mesh repair was associated with low recurrence rates of up to 1 percent of large umbilical hernia in two randomized controlled trials of mesh versus suture repair and in a long-term follow-up, retrospective study. However, there is no level-1 evidence advocating the use of mesh in smaller umbilical hernias of 1–4 cm diameter.

Added value of this study

In our double-blind, randomized, controlled multicenter trial, we randomly assigned 300 patients with umbilical hernias of 1–4 cm to receive either mesh or suture repair. After a median follow-up of 25 months, there were significantly fewer recurrences in the mesh group than in the suture group. This was the first randomized trial that provided evidence advocating mesh repair in all smaller umbilical hernias with a defect size between 1 and 4 cm.

Implications of all the available evidence

Worldwide, there are still many differences in treatment strategies for umbilical hernia repair between hospitals and even within hospitals between surgeons. The results of this trial combined with previous studies should lead to more uniformity in treatment strategies and enable the development of guidelines for treatment of umbilical hernia. The results support the use of mesh in all patients with an umbilical hernia with a diameter of 1–4 cm.

INTRODUCTION

Umbilical hernia is defined as a midline abdominal wall defect from 3 cm above to 3 cm below the umbilicus [1], and is a common diagnosis in adults, with a global prevalence of 2 percent. Surgical repair is recommended for most symptomatic or clinically apparent umbilical hernias, which can be achieved by suture repair or use of mesh. Disappointingly, high recurrence rates of up to 54.5 percent have been reported with suture repair [2]. The use of mesh was proven to be beneficial in incisional and inguinal hernia repair, and mesh repair has therefore become the gold standard repair for these types of hernia [3-6], associated with low recurrence rates of up to 1 percent of large umbilical hernias in two randomized controlled trials of mesh versus suture repair and in a long-term follow-up, retrospective study [7-9]. However, there is no solid evidence to advocate the use of mesh instead of suture repair in small umbilical hernias (diameter ≤4 cm), and most surgeons would not use mesh repair for many of these small hernias [10]. Both mesh and suture repair are currently used for the treatment of umbilical hernias. We therefore did a study to investigate whether mesh was superior in reducing recurrence of small umbilical hernias (diameter 1–4 cm) compared with suture repair.

METHODS

Study design and participants

We did a randomized, double-blind, controlled, multicenter trial with patients recruited from nine hospitals in the Netherlands, two in Germany, and one in Italy. This trial was approved by the Ethics Board of the Erasmus University Medical Center (Rotterdam, the Netherlands) and all participating hospitals.

Patients were eligible for inclusion if they were aged at least 18 years and had a primary umbilical hernia with a diameter of 1–4 cm. Umbilical hernia was in this study defined according to the European Hernia Society definition (i.e., a primary midline abdominal wall defect from 3 cm above to 3 cm below the umbilicus) [1]. Exclusion criteria were recurrent umbilical hernia, incarcerated umbilical hernia, incisional hernia or epigastric hernia, an American Society of Anesthesiologists (ASA) classification higher than ASA III, or one or more of the following diseases in their medical history: midline laparotomy, laparoscopy with an umbilical entrance port, ascites, peritoneal dialysis, or liver cirrhosis. Patients were recruited from the outpatient clinic of the department of surgery. Patients who visited the outpatient clinic with an umbilical hernia received an information package about our trial. If patients decided to undergo an operation, they were recruited for

the trial as well. All patients who consented to participate were included in this trial, and all patients provided written informed consent.

Randomization and masking

Before the start of the study, a consensus was reached by all participating centers on the methods for umbilical hernia repair. The operation started with a para-umbilical incision and was followed by dissection of the hernia sac. Resection of the hernia sac was avoided. After reduction of the hernia sac, the hernia diameter was measured with a sterile ruler (size expressed in mm). Patients were randomly assigned (1:1) intraoperatively using blocked randomization (block size was not specified in the protocol) to either suture repair or mesh repair. Randomization took place after intraoperative measurement. In the first 3 years of the inclusion period, randomization and trial allocation were achieved by an envelope randomization system. This blinded envelope randomization system was designed by the biostatistician who also did the power calculation for the target sample size of the trial (WCJH). After the first 3 years, computer-generated randomization was introduced. The randomization process was computerized to link the data of the randomization process directly to the database to avoid duplication of work. Patient allocation was organized per hospital and patients were stratified by hernia diameter (1–2 cm and >2–4 cm). Patients, investigators, and data analysts were unaware of the study-group allocation during the entire study. Patients were operated under general anesthesia. Randomization was done perioperatively and patients were only informed about their actual study group after their last follow-up visit (24–30 months postoperatively).

Procedures

At the start of the study, all surgeons were invited to specific trial training sessions, which were organized in the surgical SkillsLab of the coordinating center (Erasmus University Medical Center, Rotterdam, Netherlands) to ensure that all participating surgeons would use the same standardized techniques to close an umbilical hernia. In addition to the training sessions, there was a clear chapter on operation techniques provided in the study protocol to instruct all surgeons and surgeons in training.

Suture repair of the umbilical defect consisted of adaptation of the fascia in the midline by either interrupted or continuous, non-absorbable, monofilament, polypropylene sutures of thickness 0/0 (monofilament Prolene suture). Sutures were placed in a transverse direction. In this study, Mayo reconstruction of the umbilical defect was not permitted [11].

Mesh repair was done with a flat polypropylene mesh (Bard Mesh or Prolene polypropylene mesh) placed in the preperitoneal plane. Fixation of the mesh was achieved using 0/0 individual, non-absorbable, monofilament sutures (monofilament Prolene). The overlap of the mesh had to be at least 3 cm in each direction of the circular mesh [12]. It was not preferred to enlarge the umbilical hernia defect during the repair procedure. If the surgeon had to enlarge the umbilical defect during the operation to place the mesh in the preperitoneal plane, this step was recorded in the operation report. To protect the viscera, it was possible to place the remains of the hernia sac between the viscera and the mesh. The fascia defect was closed over the mesh by sutures when this was possible in a tension-free manner to protect the mesh from contact with the skin. The use of drains was permitted. Closure of the subcutaneous tissue and skin could be achieved using a method chosen by the individual surgeon.

Postoperative analgesics could consist of diclofenac 50 mg three times daily and paracetamol 1000 mg three times daily (or equivalent) administered orally for 6 days after surgery. If there were no complaints of pain, patients could stop using analgesics. A visual analogue scale (VAS) was used to assess postoperative pain.

Outcomes

The primary endpoint was defined as the rate of hernia recurrences after 24 months. All patients were examined preoperatively and at 2 weeks, and 3, 12, and 24–30 months postoperatively. Hernia recurrence was assessed by physical examination and, in case of any doubt, by supplementary abdominal ultrasound. Secondary endpoints were peri-operative VAS scores, postoperative pain measured in the short term (at 2 weeks) and in the long term (at 2 years), and postoperative complications such as wound infection, seroma, and hematoma.

Complications were assessed during all planned visits (2 weeks, 3 months, 12 months, and 24–30 months after the operation) and in-between visits when patients came to the hospital. Quality of life (QOL) was assessed using the MOS SF-36 health survey [13] and the EQ-5D-5L [14] preoperatively and at 12 months postoperatively. The SF-36 includes one multi-item scale that assesses eight health concepts: limitations in physical activities because of health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities because of physical health problems; bodily pain; general mental health; limitations in usual role activities because of emotional problems; vitality; and general health perceptions. The EQ-5D-5L recognizes five dimensions of QOL: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression [13]. A single index is generated for all health states. We also assessed a vertical VAS regarding the patient's own health state on a particular day that

was marked by the patient [15]. All outcomes were transformed into a number between 0 (which indicated the worst possible outcome) and 100 (which indicated the best possible outcome). All data were collected by masked researchers.

Statistical analysis

The target sample size calculation was based on the primary endpoint (rate of hernia recurrences after 24 months). Assuming a decrease of 10 percent (13 percent after suture repair versus 3 percent after mesh repair after 24 months) [7, 8] in the rate of recurrences, 135 patients in each group were required at a two-sided significance level of $\alpha = 0.05$ and a power of 80 percent (by Fisher's exact test). To compensate for an expected 10 percent projected loss to follow-up, 150 patients were recruited per treatment group.

A statistical analysis plan was written before analysis of the data from this clinical trial. All analyses were done according to intention-to-treat principles; i.e., analyzed according to the treatment group that patients were assigned to. The primary analysis concerned the comparison of the time to recurrence during a follow-up period of 24 months between the suture repair group and the mesh repair group. All other analyses (i.e., time to recurrence between the two groups within subgroups, and postoperative pain, postoperative complications, and quality of life) were considered to be exploratory and therefore only served as hypothesis generating. All reported *P* values were two-sided, and were not adjusted for multiple testing (nominal *P* values).

Time to recurrence was estimated by means of the Kaplan-Meier estimator (product-limit estimator), and the variance (and thus the SE) by the Greenwood formula. Actuarial estimates were determined with SEs and 95 percent CIs at appropriate time points, for all patients and per treatment group. The formal test for difference in time to recurrence between the two treatment arms was done with the stratified log-rank test with stratification by the hernia defect size, and a *P* value of less than 0.05 was considered statistically significant. This implied that 20 recurrences had to be reported before the final analysis could be done. Additionally, whether there was an effect modification; i.e., whether the difference in recurrence rate between both study groups depended on the hernia defect size, was investigated by a Cox-regression analysis. Reciprocal Kaplan-Meier curves (starting at 0 percent instead of 100 percent) were generated to illustrate time to recurrence. The study was not powered sufficiently to detect a statistical difference between the hernia size subgroups.

The secondary endpoints were postoperative pain, postoperative complications, and quality of life. Postoperative pain was assessed with VAS pain scores. Postoperative complications were predefined in the study protocol. We scored for postoperative infections,

hematoma, seroma, and other complications. Postoperative infections were defined as surgical site infections (SSI) that occurred within 30 days after the operation. SSIs were divided into three categories, superficial incisional SSI, deep incisional SSI, and organ or space SSI [16]. Hematoma was defined as an accumulation of blood in the wound area, which warranted surgical exploration and intervention. Seroma was defined as accumulation of clear fluid in the surgical field as diagnosed by aspiration of clear fluid. Other complications were scored within the categories skin necrosis, pulmonary complications, cardiovascular complications, and urinary tract complications. Postoperative complication rates were compared using Fisher's exact test. The two QOL scales (SF-36 and EQ-5D-5L) at 12 months after surgery were compared using ANCOVA while allowing for baseline score, age, and sex. The operation times were compared using the Mann-Whitney *U* test. All statistical analyses were done as described in the statistical analysis plan using Stata version 13. No data monitoring committee oversaw this study. The study was registered at ClinicalTrials.gov, number NCT00789230.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between June 21, 2006, and April 16, 2014, we randomly assigned 300 patients to repair treatments during surgery; 150 to suture repair and 150 to mesh repair (Figure 1). There were no anesthetic complications or postoperative deaths. During follow-up, 16 patients were lost to follow-up or decided to terminate trial participation and were excluded from the analysis, leaving 138 in the suture group and 146 in the mesh group eligible for analysis.

Most of the participants were male (Table 1) and the median age was 52 years (range 20–77 years, IQR 44–61). The two groups were well balanced in demographic variables. Occurrence of other risk factors such as malnutrition, cardiovascular disease, steroid use, benign prostate hyperplasia, or other types of hernia in medical history were less frequent and also did not differ between the two groups.

Characteristics of preoperative hernia-related factors were similar in both groups. Outpatient examination revealed that the hernia defect was palpable without Valsalva

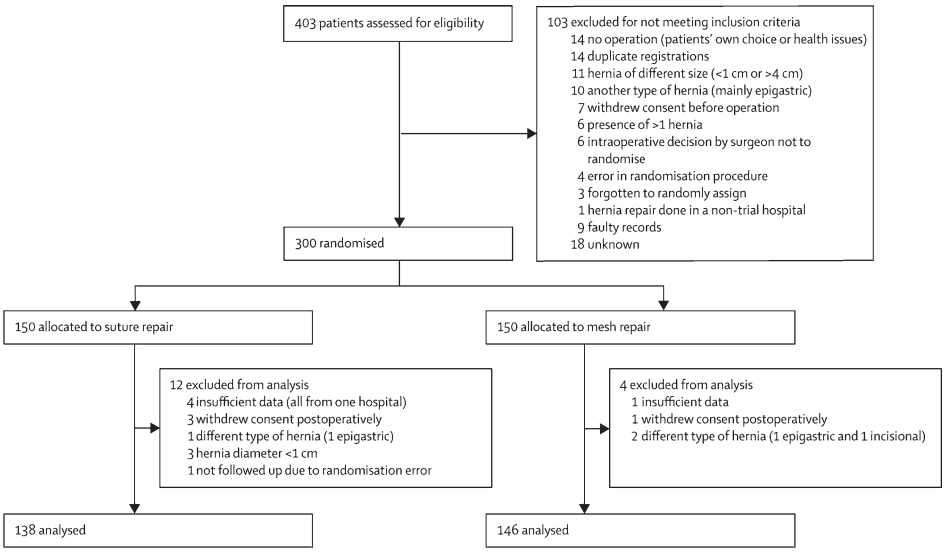

Figure 1. Trial profile
Patients were analyzed in the intention-to-treat population.

Table 1. Baseline characteristics of the intention-to-treat population

	Suture repair (n=138)	Mesh repair (n=146)
Sex		
Male	113 (82%)	122 (84%)
Female	25 (18%)	24 (16%)
Age (years)	52 (43–59; 20–74)	55 (44–63; 25–77)
Height (cm)	179 (172–185; 152–202)	178 (172–185; 150–198)
Weight (kg)	90 (83–99; 57–155)	90 (83–102; 44–170)
BMI (kg/m^2)	28 (25–31; 19–44)	28 (26–31; 19–59)
ASA classification		
I	87 (63%)	80 (55%)
II	47 (34%)	58 (40%)
III	4 (3%	8 (5%)
Hernia diameter (cm)		
1–2 cm	101 (73%)	101 (69%)
>2–4 cm	37 (27%)	45 (31%)
Risk factors		
COPD	15 (11%)	10 (7%)
Diabetes	13 (9%)	13 (9%)
Smoking	23 (18%)	17 (11%)
Operation time (range) min.	33 (25–43; 10–95)	44 (32–57; 20–122)

Data are n (%) or median (IQR; range). BMI = body-mass index. ASA = American Society of Anesthesiologists. COPD = chronic obstructive pulmonary disease.

manoeuvre in 109 patients (79 percent) in the suture repair group and in 120 patients (82 percent) in the mesh group.

Pain was reported by 97 patients (70 percent) in the suture repair group and in 99 patients (68 percent) in the mesh group. Mechanical complaints were present in 33 patients (24 percent) in the suture repair group and in 35 patients (24 percent) in the mesh group. Cosmetic aspects were the reason for hernia repair in 37 patients (27 percent) in the suture repair group and in 37 patients (25 percent) in the mesh group. There were no significant differences in the occurrence of hernia symptoms between the two treatment groups.

The median duration of the operation was longer in the mesh group than in the suture group (Table 1). Patients in both groups were mainly operated under general anesthesia (266 [94 percent]); the other patients were operated under local anesthesia (local infiltration around the umbilicus in rectus sheath) or spinal anesthesia.

Most patients underwent surgery through an incision caudally to the umbilicus; 89 patients (64 percent) in the suture repair group and 87 patients (60 percent) in the mesh group ($P = 0.40$). Crossover of treatment occurred in both groups; four patients (3 percent) in the suture repair group underwent mesh repair and five patients (3 percent) in the mesh group underwent suture repair ($P = 1.00$). The most common reason for crossover to mesh repair in the suture group was comorbidity of the patient (high body-mass index [BMI] and heavy occupational lifting). The most common reason in the mesh group to use a suture repair was the diameter of the hernia defect. Use of drains was more frequent in the mesh group than in the suture group: 13 patients versus one, respectively ($P = 0.002$). Drain production did not exceed 30 mL and all drains were removed on the first postoperative day.

The 284 patients included in the analysis were operated on by 212 different surgeons in training and specialists (in the Netherlands, an individual is either surgeon in training or a specialist surgeon). 217 patients were operated on by two surgeons (a specialist surgeon with a surgeon in training or two surgeons in training) and 53 patients were operated on by one. In 71 cases, patients were operated on by a specialist surgeon with or without assistance of a surgeon in training. In 156 cases, patients were operated on by a surgeon in training, directly supervised by a specialist surgeon. In 43 cases, patients were operated on by a surgeon in training without direct supervision of a specialist surgeon. For 14 patients the data about their surgeon were missing. Most participating surgeons attended the laboratory course about standardization of repair techniques.

The median follow-up was 25.1 months (range 0.0–87.8, IQR 15.5–33.4). Consequently, there were patients who had more than the intended 24 months of follow-up. The presented data, in first instance, were the data after 24 months of follow-up as documented in the study protocol. Additionally, data were gathered on recurrence outcomes after 30 months. From September, 2011, to August, 2012, the trial team was short-staffed, and during this period a short gap of follow-up systematics occurred, rendering a follow-up of 6 months longer than stated in the protocol. With the data after 30 months, a 24-month actuarial estimate of recurrence was calculated. We decided to present the data until 30 months of follow-up, because for several patients the 24-months assessment was done after 24 months postoperatively but before 30 months. We also decided to assess the recurrence rate as a time-to-event endpoint instead of a dichotomous outcome, and censor the follow-up of patients without recurrence at 30 months.

After a maximum follow-up of 30 months, there were fewer recurrences in the mesh group than in the suture group (six [4 percent] in 146 patients versus 17 [12 percent]; 2-year actuarial estimates of recurrence 3.6 percent [95 percent CI 1.4–9.4] versus 11.4 percent [6.8–18.9]; $P = 0.01$, hazard ratio [HR] 0.31, 95 percent CI 0.12–0.80; [Figure 2], corresponding to a number needed to treat [NNT] of 12.8). The difference in recurrences between suture and mesh occurred in both hernia defect size subgroups (1–2 cm and >2–4 cm), although the study was not powered sufficiently to detect a difference.

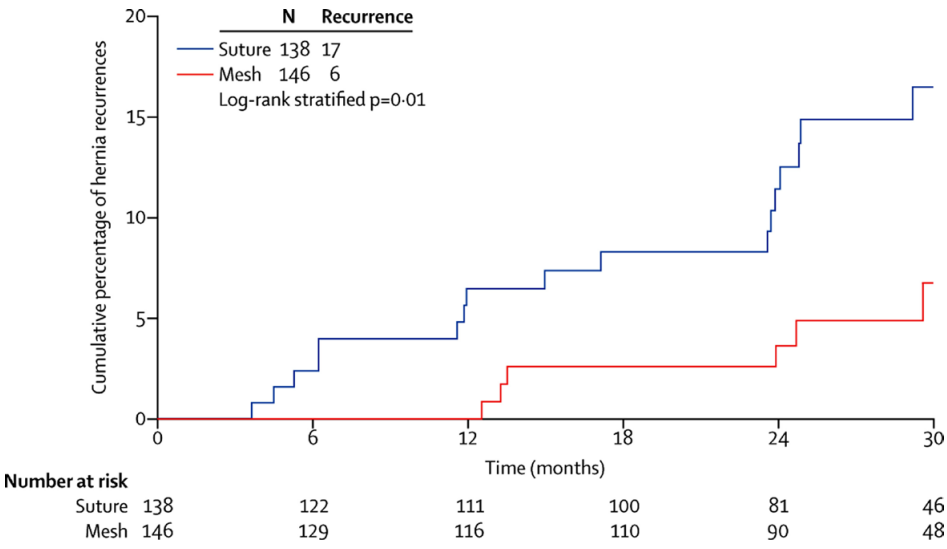

Figure 2. Time to recurrence for mesh versus suture (all hernia diameters, 1–4 cm)
The X-axis shows the time in months until recurrence of an umbilical hernia.

There were 11 recurrences in 202 patients in the subgroup of hernia size 1–2 cm. In this subgroup fewer recurrences occurred in the mesh group than in the suture group (two [2 percent] versus nine [8 percent] in the suture group; HR 0.23, 95 percent CI 0.05–1.07, Figure 3). In the subgroup hernia size of greater than 2 cm to 4 cm, 12 recurrences occurred

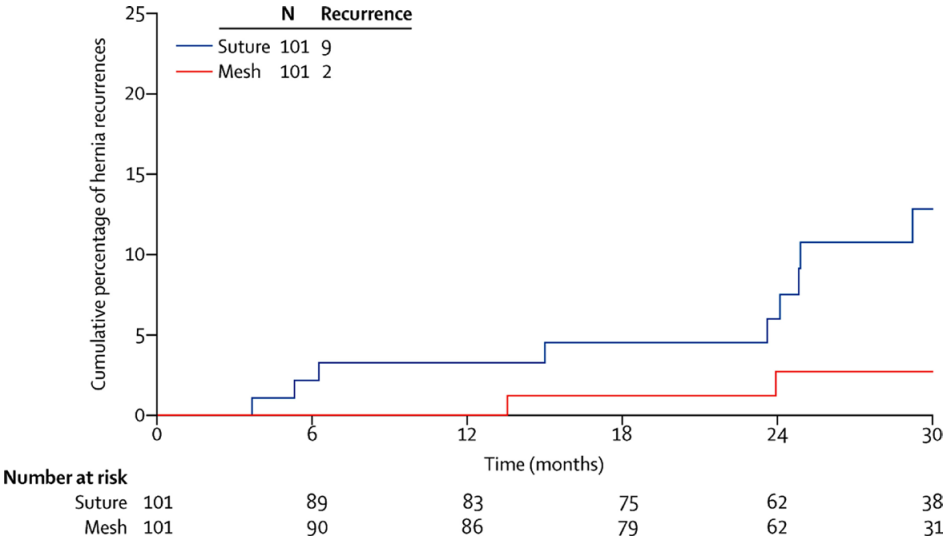

Figure 3. Time to recurrence in mesh versus suture (hernia diameters 1–2 cm)
The X-axis shows the time in months until the recurrence of umbilical hernia.

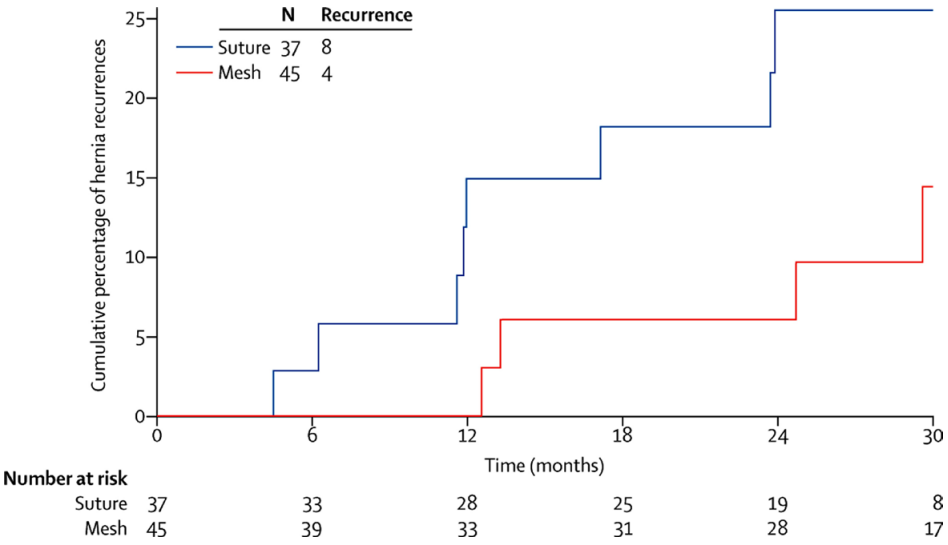

Figure 4. Time to recurrence in mesh versus suture (hernia diameters >2–4 cm)
The X-axis shows the time in months until the recurrence of umbilical hernia.

in 82 patients. In this subgroup, fewer recurrences again occurred in the mesh group than in the suture group (four [9 percent] versus eight [22 percent]; 0.39, 0.12–1.30, Figure 4).

Patients treated by either suture or mesh developed a recurrence after a median 15.0 months (IQR 6.2–24.8) after their surgery. When divided into the different treatment groups, recurrences occurred in the suture group after a median 15.0 months (IQR 6.2–23.9) and in the mesh group after a median 18.7 months (13.3–24.7). Patients treated with sutures developed a recurrence earlier than patients treated with mesh. The onset of recurrences in the suture group started 3.6 months after surgery versus 12.6 months in the mesh group. The shape of the recurrence curves in all diameter subgroups was similar, and BMI did not affect the number of recurrences.

During analysis of all intraoperative data, violations were found in both the mesh and suture materials and in the technique that was used during hernia repair. Additional analysis of the data without violations was done. In this per-protocol analysis, no changes in results were noted compared with the intention-to-treat analysis (appendix).

There were no between-group differences in the incidence of postoperative wound infections (Table 2). No mesh had to be surgically removed because of infection (Table 2). There were no significant differences in perioperative VAS scores (Figure 5). Median VAS scores after surgery were 2.8 in the suture group and 3.8 in the mesh group ($P = 0.13$), and after 4 days, the median VAS score was 1.0 or less in both groups, and similar between the two groups at all time points (P values between 0.54 and 0.82). There was no difference in the amount of postoperative pain between patients in the mesh and suture repair groups at all time points. Two weeks after the operation, 102 patients (74 percent) in the suture repair group and 111 patients (76 percent) in the mesh group were free from pain ($P = 0.57$). At 2 years, 129 patients (93 percent) in the suture repair group and 138 patients (95 percent) in the mesh group were free from pain ($P = 0.45$).

Table 2. Postoperative complications

	Suture repair (n=138)	Mesh repair (n=146)	Number needed to harm
Wound infection	1 (<1%; 17 days)	3 (2%; 21 days, 14–23)	75
Hematoma	2 (1%; 24 days, 13–34)	3 (2%; 13 days, 11–16)	165
Seroma	1 (<1%; 20 days)	5 (3%; 14 days, 7–20)	37
Seroma evacuation	0	1 (<1%; 20 days)	146
Skin necrosis	0	0	..
Pulmonary complications	0	0	..
Cardiovascular complications	0	0	..
Urinary tract complications	0	0	..

Data are n (%) or median time in days (range) to occurrence of complication.

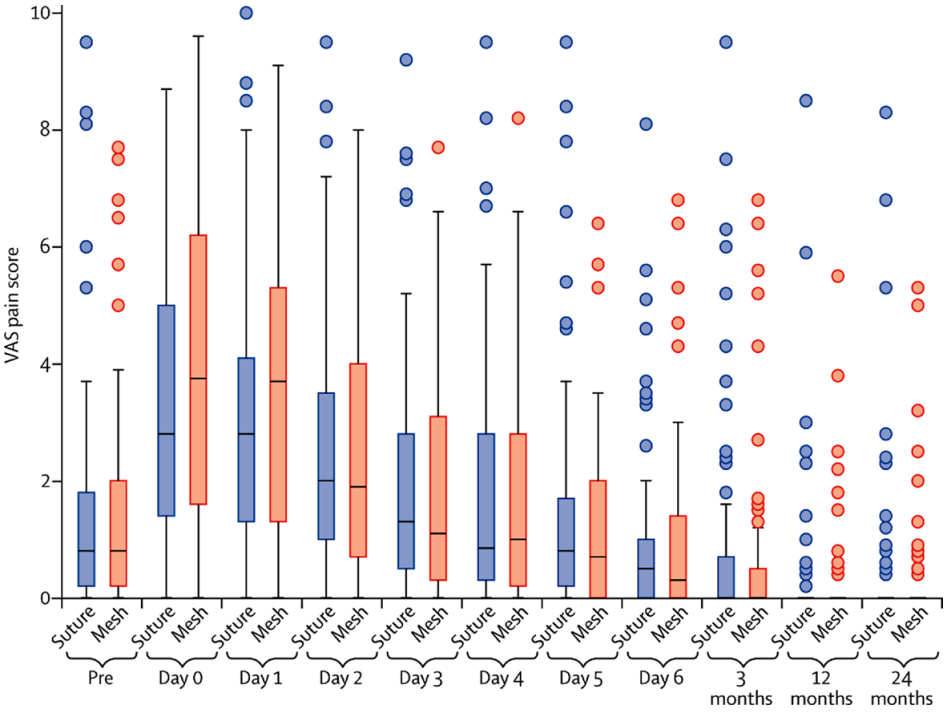

Figure 5. Box-and-whisker plots of VAS pain scores
Each box is drawn from the 25th percentile to the 75th percentile of the visual analogue scale (VAS) scores, and the horizontal bar within the box indicates the median VAS score. Upper error bars go from the 75th percentile of the VAS score to the upper adjacent value as defined by Tukey. Dots indicate VAS scores greater than the upper adjacent value. pre = before surgery. Day 0 = date of surgery.

There were no significant between-group differences in other postoperative complications: seroma ($P = 0.21$) or hematoma ($P = 1.00$). Other postoperative complications such skin necrosis, pulmonary complications, cardiovascular complications, or urinary tract complications did not occur in this study.

SF-36 and EQ-5D-5L data were available at baseline for a maximum of 91 patients in the suture group and 82 patients in the mesh group, and for 73 versus 68 patients at 12 months after operation. For any of the eight health concepts of the SF-36, the single EQ-5D-5L index and the EQ-5D-5L VAS score, there was no significant difference between the two groups at baseline or at 12 months. For example, the median value of the physical function was 95 (IQR 80–100) at baseline and at 12 months, in both the suture and mesh groups. Further examples are in Figure 6, which shows box-and-whisker plots of SF-36 general health, SF-36 bodily pain, EQ-5D-5L VAS and EQ-5D-5L index for both groups before operation and 12 months after operation. 60 suture patients (43 percent) and 51 mesh patients (35 percent) completed the forms at both time points and were included

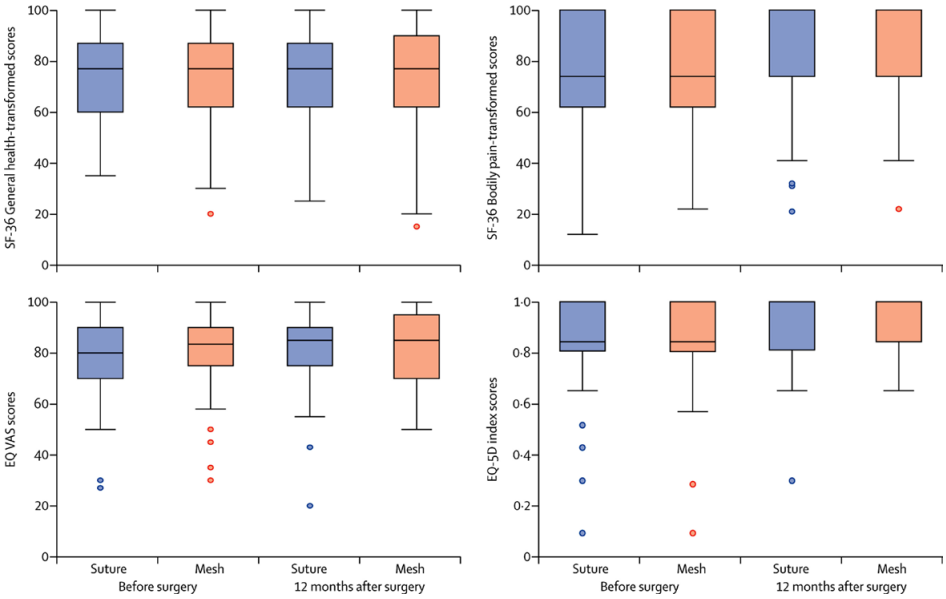

Figure 6. Box-and-whisker plots of SF-36 and EQ-5D-5L
Each box is drawn from the 25th percentile to the 75th percentile of the scores, and the horizontal bar within the box indicates the median score. Lower error bars go from the 25th percentile of the VAS score down to the lower adjacent value as defined by Tukey. Dots indicate scores less than the lower adjacent value. SF-36 = 36-Item Short Form Health Survey. EQ-5D-5L = EuroQol five-dimensional five levels of severity. EQ = EuroQol. VAS = visual analogue scale.

in the ANCOVA analyses. These analyses confirmed that there was no significant effect of treatment on outcome of SF-36 and EQ-5D-5L at 12 months after operation.

DISCUSSION

This study showed that mesh repair for small umbilical hernias (diameter 1–4 cm) significantly reduced the number of recurrences compared with suture repair. There were no between-group differences in pain scores. Since most surgeons would use suture repair for smaller hernias, this is a particularly important finding.

Until now, publications about umbilical hernia were limited to retrospective cohort studies [17-21], prospective observational studies [8, 22, 23], hernia register analyses [24, 25], and randomized controlled studies with smaller sample sizes than this study [7, 9]. In this study, only patients with umbilical hernia were included, whereas other studies included patients with all types of primary ventral hernias [18], para-umbilical hernia [26, 27], or both umbilical and epigastric hernia [28, 29]. None of the other studies clari-

fied the exact definition of the included hernias. The results of the reported treatments in these studies could therefore be affected by the different types of hernias that were included [18, 26-29]. Additionally, recurrences were not reported per type of hernia.

In this study, 4 percent of patients in the mesh repair group had a hernia recurrence after 24–30 months. 70 percent of patients in this study had a hernia of diameter 1–2 cm, but mesh repair was shown to be effective in the entire group of 1–4 cm. Surgeons might hesitate to use a mesh in the repair of smaller hernias [10]. In the studies of Lal and colleagues [26] and Murtaza and colleagues [30], patients were only included in the analysis if their hernia defect was at least 4 cm. In this study, only the hernias less than 1 cm were excluded since mesh placement in these smaller hernias can be difficult and could lead to an artificial increase of the hernia defect to achieve mesh placement. The role of mesh in these very small umbilical hernias of less than 1 cm remains uncertain.

The number of recurrences overall after 24 months in this study was more than twice as high in the suture repair group as in the mesh group, and similar to findings from studies by Arroyo and colleagues [7] (11 percent after interrupted suture repair) and Polat and colleagues [9] (11 percent after Mayo repair). The recurrence rate in this study after suture repair was however higher than shown by Christoffersen and colleagues [24] (5.6 percent after suture repair). The proportion of patients with recurrences after mesh repair was slightly higher in this study (4 percent) when compared with studies by Arroyo and colleagues [7] (1 percent), Polat and colleagues [9] (zero), and Christoffersen and colleagues [24] (2.2 percent). Important differences with these studies were the type of mesh, the technique of mesh placement, the duration of follow-up, the diagnostic methods, the heterogeneous groups, and the study populations that were used (smaller randomized samples [7, 9], and a large, non-randomized cohort population [24]). Arroyo and colleagues [7] used mesh plug repair in hernias with a diameter of less than 3 cm (68 patients) and a standard flat mesh repair in the preperitoneal plane in hernias with a diameter of more than 3 cm (32 patients). Follow-up ranged from 21 to 80 months and it was not specified when recurrences occurred [7]. Polat and colleagues [9] studied two different mesh groups: 17 patients with the Prolene Hernia System (Ethicon, West Somerville, NJ, USA) and 15 patients with a standard flat mesh repair in the onlay technique [9]. However, the mesh groups studied by these investigators were heterogeneous. In the case of Polat and colleagues' study, there were only few patients per mesh group. The study by Christoffersen and colleagues [24] was heterogeneous with respect to suture techniques.

Another important difference between this study and previous studies was that incarcerated umbilical hernia or emergency operations were not included in this study. This was

specifically studied in two other studies by Kulah and colleagues [31] and Abdel-Baki and colleagues [32]. In the randomized study by Abdel-Baki and colleagues [32] the use of mesh in emergency operations did not lead to a significant increase of complications when compared with suture repair in emergency operations (23.8 percent after mesh repair versus 28.6 percent after suture repair). However, the total number of complications was much higher in emergency patients than in the randomized studies about elective umbilical hernia repair [7, 9]. Complications in these studies were defined as wound infection, hematoma, seroma, and other postoperative complications. Recurrences were not taken into account. In this study, 8 percent of patients had complications after mesh repair versus 3 percent of patients after suture repair; Arroyo and colleagues [7] noted 10 percent of patients had complications after mesh repair versus 11 percent after suture repair, and Polat and colleagues [9] showed 15.6 percent had complications after mesh repair versus 16.7 percent after suture repair. Our study was powered for the primary endpoint of the number of recurrences after 24 months and could therefore have been underpowered to address significant differences in postoperative complications.

Most of the patients in this study were operated under general anesthesia (94 percent). This finding was earlier confirmed for treatment of inguinal hernia in the Netherlands [33]. Use of general anesthesia can, however, lead to specific postoperative complications (e.g., pulmonary and cardiovascular complications). However, none of these complications occurred during this study. Operation time between the two study groups in this study differed significantly. This result is similar to findings from Arroyo and colleagues [7], reporting an operation time of 38 minutes in the suture group and 45 minutes in the mesh group. In our study, the operation time in the flat mesh technique was much shorter than in the flat mesh group reported by Polat and colleagues [9]. This could be a result of the more extensive operation procedure studied by Polat and colleagues. Generally, one could assume that the smaller the hernia defect, the more challenging it might be to place a mesh in the sublay position. This in an important issue in the education of residents and the learning curve for every surgeon. In this study, none of the surgeons enlarged the hernia defect to place a mesh in the sublay position. However, all participating surgeons were largely skilled in hernia repair.

Quality-of-life analyses revealed no significant differences between both study groups on the outcome of SF-36 and EQ-5D-5L preoperatively and at 12 months after operation. There were no other studies in small umbilical hernias available with a head-to-head comparison of SF-36 and EQ-5D-5L between mesh and sutures regarding quality of life. A previous study by Malik and colleagues [34] showed a benefit of mesh versus non-mesh repair in ventral abdominal wall hernias (includes epigastric hernia, para-umbilical hernia, umbilical hernia, and incisional hernia). Quality-of-life analysis was done accord-

ing to their report; however, the exact method that was used was unknown. Malik and colleagues concluded that although mesh had a higher complication rate, mesh repair was a better option in ventral hernia repair than non-mesh repair and was safe. Long-term effects of mesh repair were not mentioned in this study.

In another study [35] the long-term effects of intra-abdominal mesh in patients with a ventral hernia were assessed. After 49 months, 16 (12 percent) patients complained of discomfort in the umbilical region, two (2 percent) patients had an infection of the mesh that resulted in removal of the mesh (Ventralex patch), and two (2 percent) required adhesiolysis for obstruction. In our study, the mesh was placed in the preperitoneal plane, which does not lead to direct contact between the mesh and the viscera, therefore causing fewer adhesions.

A limitation of our study was that no records were kept about the number of patients who immediately declined participation, or who were eligible but were not recruited for participation in the study. This could have led to a potential selection bias. A conscious choice in this study was not to include hernia diameters smaller than 1 cm. Therefore it cannot be stated whether mesh repair is beneficial in these hernia defects. Furthermore, the follow-up period might have been too short to assess the difference between mesh and suture repair. Long-term follow-up could reveal that the differences between the two treatment arms are even larger than in our study. However, it has proven to be difficult to keep young patients with mostly ASA I and ASA II motivated for regular follow-up in this study, since patients are most often cured from their hernia after operation. The inclusion rate of patients in our study was slow for a few reasons: patient factors (no interest in returning to the hospital for study visits and questionnaires), hospital factors (research infrastructure in a hospital), and researcher factors (this trial had several coordinators because of staff shortages). This slow inclusion rate led to a longer recruitment time and partly to a longer follow-up (24–30 months of follow-up in some patients instead of the intended 24 months).

An additional flaw to this study might be represented by a few operations (6.3 percent) in which the protocol was violated. However, overall results did not differ, although subgroup analysis for the smallest hernia group was not conclusive.

In conclusion, this study shows a substantial advantage of mesh use in the treatment of small umbilical hernias of 1–4 cm. There were significantly fewer recurrences in the mesh group without an increase in postoperative pain or complications and with similar quality of life at 12 months after operation. There were no significant differences in the incidence of postoperative wound infections, although the incidence in the mesh

group was slightly higher in the mesh group versus the suture group. No mesh had to be surgically removed because of infection. The number needed to harm was 19 patients. Therefore, we advocate using mesh repair in all patients with an umbilical hernia with a diameter of at least 1 cm.

Contributors

RK contributed to acquisition, analysis, and interpretation of data, drafting and revising the manuscript, and final approval of the manuscript. JAH (principal investigator) contributed to conception and design of the study, acquisition of data, drafting and revising the manuscript, and final approval of the manuscript. HHE, PJK, JN, DvG, MPS, EvdH, and Mv'tR contributed to acquisition of data for the work, revising the manuscript, and final approval of the manuscript. BvdH contributed to analysis of data, revising the manuscript, writing the statistical analysis plan, and final approval of the manuscript. GJK, JJ, and JFL (principal investigators) contributed to conception and design of the study, revising the manuscript, and final approval of the manuscript. All authors agreed to be accountable for all aspects of the work.

Declaration of interests

We declare no competing interests.

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SUPPLEMENTARY APPENDIX

HUMP trial – per protocol analysis

In this material per protocol analysis, 121 patients in the suture group and 145 patients in the mesh group were analyzed. The suture group was stratified into 88 patients with a hernia of 1–2 cm and 33 patients with a hernia of >2–4 cm. The mesh group was stratified into 99 patients with a hernia of 1–2 cm and 46 patients with a hernia of >2–4 cm. In this analysis, 70 percent of the patients had a hernia of 1–2 cm. Reasons for exclusion from the suture group were use of absorbable sutures (Vicryl® suture (polyglactin 910)), and/or use of Mayo repair. Reason for exclusion from the mesh group was use of a resorbable mesh (Vicryl® mesh (polyglactin 910)). After a maximum follow-up of 30 months, there were significantly less recurrences in the mesh group; seven recurrences (4.8 percent) versus 13 recurrences (10.7 percent) in the suture group ($P = 0.048$) (Figure S1).

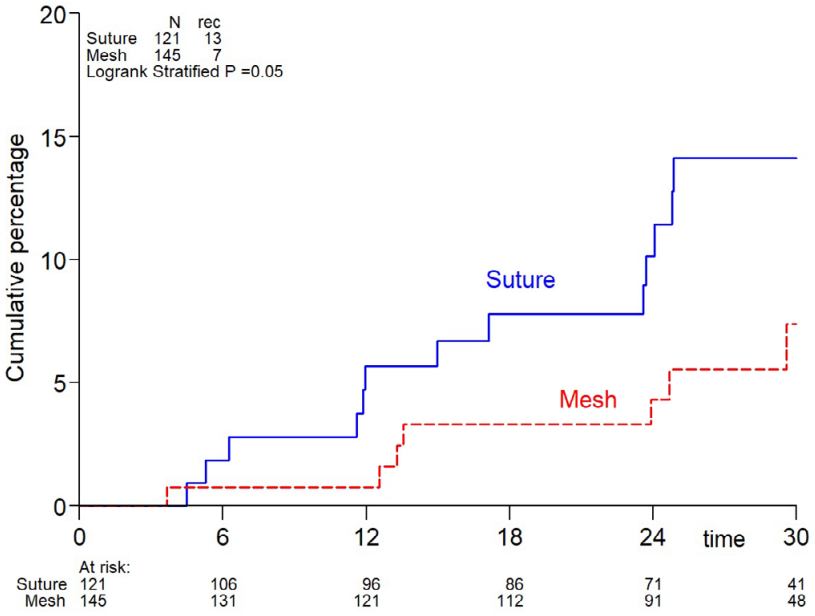
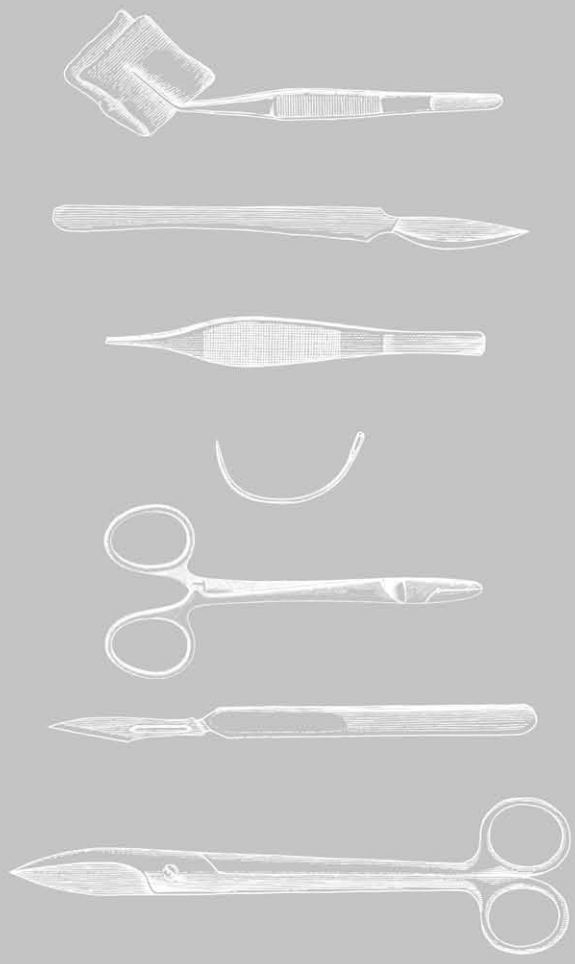


Figure S1. Time to recurrence in mesh versus suture (material per protocol analysis)
On the X-axis, time in months until the occurrence of a recurrence of umbilical hernia can be found. On the Y-axis the cumulative percentage of hernia recurrences is expressed. In this figure both the primary group and the mesh group consist of all hernia diameters (material per protocol analysis).



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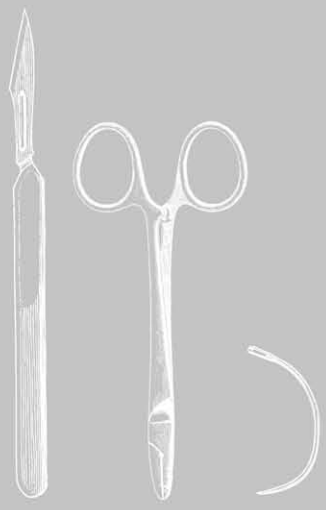
Lower risk of recurrence after mesh repair versus non-mesh sutured repair in open umbilical hernia repair: a systematic review and meta-analysis of randomized controlled trials



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ABSTRACT

Introduction

The use of mesh repair in a small- or middle-sized umbilical hernia remains controversial, and evidence is based on only few and small heterogeneous randomized trials. The primary aim was to assess differences, if any, in recurrence (clinical and reoperation), and the secondary aim was to assess differences in infections, seroma formation, hematomas, chronic pain, cosmetic result, and quality of life.

Method

A systematic review (predefined search strategy) and meta-analyses were conducted based on pre-study strict and well-defined methodology. The literature search was completed on 1 January 2018. The study protocol was registered in PROSPERO.

Results

Five randomized controlled trials were identified (mesh repair, n = 326 versus non-mesh sutured repair, n = 330) and 602 records were excluded. Randomized controlled trials included patients with defect diameters of ≥1 to 4 cm. Mesh repair reduced the risk of recurrence compared with sutured repair with a relative risk of 0.28 (95 percent confidence interval = 0.13–0.58, $I^2 = 0$ percent, number needed to treat = 13 patients). Additional analyses found no differences between the two surgical techniques regarding infection (relative risk = 0.80, 95 percent confidence interval = 0.36–1.79), seroma formation (relative risk = 1.38, 95 percent confidence interval = 0.57–3.32), or hematomas (relative risk = 0.55, 95 percent confidence interval = 0.23–1.30). Lack of sufficient data precluded meta-analysis evaluating risk of seroma formation, hematomas, chronic pain, cosmetic result, and quality of life.

Conclusion

Mesh repair is recommended for umbilical hernia of ≥1 to 4 cm. More evidence is needed for the optimal placement of the mesh (sublay or onlay) and the role of mesh in patients with an umbilical hernia <1 cm.

INTRODUCTION

Open umbilical hernia repair is one of the most commonly performed minor surgical procedures. The incidence is approximately 1500 repairs in Denmark [1] and 175 000 repairs in the United States [2]. In particular, recurrence remains a concern, but also the risk of chronic pain has drawn increasing attention, although it has only been scarcely investigated [3-6]. The controversy concerning the use of mesh in these repairs is not settled despite being a high volume and minor surgical intervention [1].

Two previous systematic reviews compared open umbilical or epigastric hernia repair with or without mesh reinforcement including only one and three randomized controlled trials (RCTs), respectively [7, 8]. Both analyses contained mainly retrospective older cohort studies, a mixture of elective and emergency repairs, and umbilical and epigastric hernia repairs. Included studies did not discriminate between recurrences as primary or secondary outcomes. Moreover, two recent meta-analyses [8, 9] compared a mixture of elective and emergency procedures including a variety of types of ventral hernias (i.e. incisional and primary (umbilical) hernia repair) with or without liver cirrhosis and did not discriminate between recurrence as primary or secondary outcome. Although it is well accepted that reoperation for recurrence severely underestimates clinical recurrence [10], the four previous systematic reviews [7-9, 11] and previous RCTs [12-15] did not discriminate clinical recurrence or reoperation for recurrence. In addition, a large high-quality Dutch RCT (n = 300) was recently published [16] and was not included in the previous meta-analyses. Finally, and perhaps most important, none of the previous systematic reviews and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for meta-analysis conductance [17].

For the above-mentioned reasons, it was regarded important to present an updated systematic review based exclusively on RCT data on strict inclusion criteria including only adult patients undergoing elective open umbilical hernia repair. The primary outcomes of this meta-analysis include exclusively primary outcome results from RCTs. Before study start, it was decided that the primary aim was to assess the difference, if any, in recurrence defined as clinical, reoperation, and combined assessment. Secondary aims were to appraise differences, if any, in surgical site infections, seroma formation, hematomas, chronic pain, cosmetic result, and quality of life (QOL).

METHODS

This systematic review was based on a registered protocol in PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=46845) and results are reported according to the PRISMA guidelines [17].

Search strategy (end of search April 1st 2018)

We searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and Science Citation Index Expanded. We used the Cochrane highly sensitive search strategies for identification of clinical RCTs (Table 1) [18].

The search string was ((“Hernia, Ventral” (Mesh) OR “ventral hernia”) AND (umbilical AND (surgery OR herniotomy OR herniorrhaphy OR hernioplasty)) AND (recurrence OR “chronic pain” OR “surgical site infections” OR “wound infections” OR “seromas” OR “quality of life” OR cosmesis)). In the manual searches, we scanned reference lists of relevant articles and proceedings from meetings. We also wrote to the principal authors of RCTs for information about any ongoing trials and searched the online trial registries, ClinicalTrials.gov (clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trial Registry Platform (www.who.int/ictrp), for ongoing or unpublished trials. Two authors (T.B. and L.L.G.) scrutinized searches, performed additional manual searches, listed potentially eligible RCTs, and collected data. Contrary opinions were resolved through consensus before analyses. All authors read the potentially eligible RCTs and participated in the final selection of RCTs. We described the characteristics of included trials in summary tables and described reasons for exclusion for all excluded trials. Extracted data included study design, type of surgical techniques, number of participants, hernia defect size, length of follow-up, and outcomes as defined above.

Table 1. Characteristics of randomized controlled trials (RCTs) included in the meta-analyses

RCT	Recurrence definition	Defect size (cm)	Follow-up method (and period)	Suture technique	Mesh placement
Kaufmann et al. [16]	Clinical	1–4	Clinical (24 months)	Simple interrupted or continuous	Sublay
Arroyo et al. [13]	Clinical	>3	Clinical (64 months)	Simple interrupted	Sublay
Lal and Ase [14]	Clinical	>4	Clinical (12 months)	Simple interrupted	Onlay
Polat et al. [12]	Reoperation	Not stated	Not stated (24 months)	Simple interrupted	Mesh sandwich or Mayo repair with mesh
Sadiq and Khurshid [15]	Not stated	Not stated	Not stated (6 months)	Mayo repair	Not stated

We included RCTs regardless of their publication status (published manuscript or abstract). Inclusion of studies was limited to the English language. The assessed interventions were elective umbilical hernia repair with either open mesh repair or non-mesh repair. We excluded patients with liver cirrhosis, patients undergoing emergency repairs, other types of ventral hernia repair (i.e. epigastric, Spigelian, parastomal, or incisional hernia repairs), and repairs during concomitant surgery. To secure robustness of recurrence outcomes, we excluded RCTs where recurrence was not the primary outcome as mentioned above [19].

Types of outcome measures

Study outcomes were predefined before the study was conducted. The primary analysis of the meta-analysis was differences, if any, in clinical recurrence, non-clinical assessment (reoperation and unclear defined recurrence), and total recurrence (clinical and not clinically defined). Secondary analyses were also performed on other outcomes such as differences, if any, in surgical site infections, seroma formation, hematomas, chronic pain, cosmetic result, and QOL after mesh repair or sutured repair. We assessed all outcomes at the maximum duration of follow-up.

Bias and quality assessment

Bias control was assessed using the Cochrane domains. Due to the nature of the intervention, we only included an assessment of blinding of outcome assessors [20]. The domains were combined into an overall assessment and graded RCTs as low risk of bias if none of the individual domains were classified as unclear/high risk of bias.

The GRADEpro system [21] was used to evaluate the quality of the combined evidence for outcomes reported in the review, considering the within-study risk of bias (methodological quality), inconsistency, imprecision, indirectness, and publication bias.

Statistical analyses

Meta-analyses were conducted and results reported as relative risks (RR) with 95 percent confidence intervals (CIs). Trial Sequential Analyses were conducted to evaluate the risk of error and futility. For our primary outcome, we calculated the number needed to treat (NNT) based on 1/risk difference. We expressed heterogeneity as I^2 values using the following thresholds: 0 to 40 percent (unimportant), 40 to 60 percent (moderate), 60 to 80 percent (substantial), and >80 percent (considerable). We initially conducted random-effects and fixed-effect meta-analyses. The estimates of the random-effects and fixed-effect meta-analyses were similar for all analyses. We chose to report the random-effects models, which provided the most conservative estimate of the intervention effect. We did not conduct planned subgroup analyses evaluating bias because only one RCT

had a low risk of bias [16]. A Trial Sequential Analysis was performed in the assessment of primary outcome. The required information size was defined as the number of participants needed to detect or reject an intervention's effect based on the relative risk reduction (RRR) and assumed control risk (ACR). We defined evidence as established if the Z-curve crossed the monitoring boundary before reaching the required information size. We performed the analyses with alpha set to 5 percent, power to 80 percent, and model-based diversity. Based on previous evidence [7, 8], we set the RRR to 46 percent and the ACR to 10 percent. We performed the analyses in Review Manager 5 (Nordic Cochrane Centre, Copenhagen, Denmark), STATA (version 14, Philadelphia, USA), and Trial Sequential Analysis (Copenhagen Trial Unit, Copenhagen, Denmark).

RESULTS

The electronic searches revealed 767 potentially eligible references. The manual searches identified additional 13 references (Figure 1). We excluded RCTs evaluating patients with incisional hernias, liver cirrhosis, or emergency surgery, and a total of 602 records were excluded. In total, we included five RCTs (full paper articles published in English

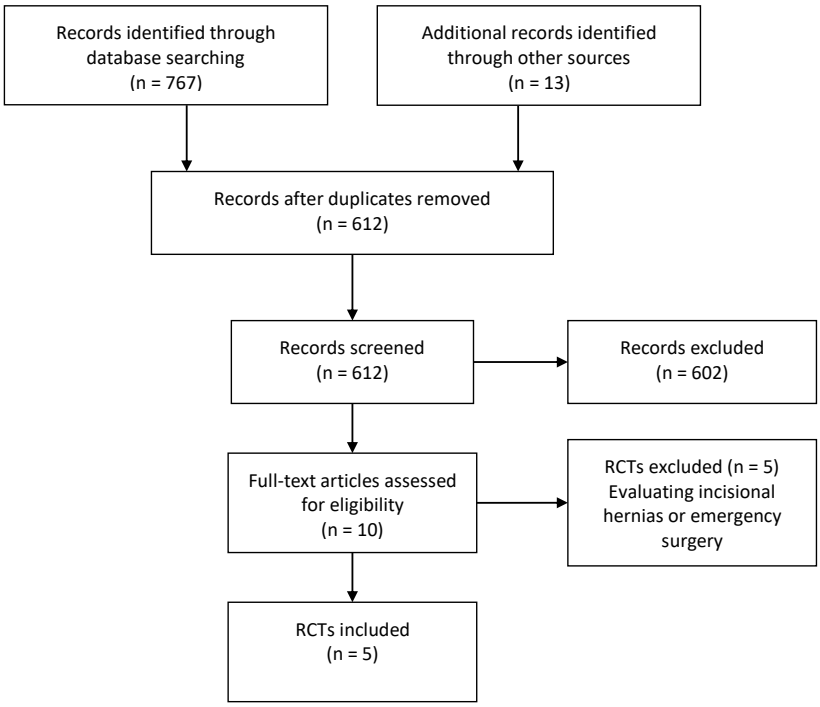

Figure 1. PRISMA flowchart of studies for the analysis

language) in our meta-analyses [12-16]. The RCTs were published between 2001 and 2018, and varied clinically in respect of hernia defect size, follow-up method (clinical or non-clinical assessment (reoperation and unclear defined recurrence)), and total recurrence (clinical and non-clinical assessment), follow-up period, and mesh placement (Table 1). The duration of follow-up varied between 6 and 64 months.

Bias assessment

Two RCTs reported the allocation sequence generation and one the allocation concealment (Table 2). None of the trials employed blinded outcome assessment. Only one of the RCTs had a low risk of bias in the overall assessment [16].

Table 2. Risk of bias in included RCTs

Bias domain	RCT				
	Arroyo et al. [13]	Polat et al. [12]	Lal and Ase [14]	Sadiq and Khurshid [15]	Kaufmann et al. [16]
Allocation sequence generation	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk
Incomplete outcome data	Low risk	Low risk	Low risk	Unclear risk	Low risk
Outcome reporting	Low risk	Low risk	Low risk	Low risk	Low risk
Other bias	Low risk	Low risk	Low risk	High risk	Low risk
Overall bias assessment	High risk	High risk	High risk	High risk	Low risk

Meta-analyses

We were able to gather data on recurrence from all five RCTs [12-16] (Figure 1). In total, 326 patients were randomized to a mesh and 330 to sutured repair. Overall, mesh repair reduced the risk of recurrence with a relative risk (RR) of 0.28 (95 percent CI = 0.13–0.5; $I^2 = 0$ percent; NNT = 13 patients; i.e. for every 13 patients undergoing elective repair for an umbilical hernia, use of mesh repair will prevent one hernia recurrence) (Figure 2).

In a sub-analysis of RCTs using either a clinically well-defined classification of recurrence or an unclear definition of recurrence, there was a significant difference between mesh repair or no mesh repair (RR = 0.24 (95 percent CI = 0.10–0.57) and RR 0.32 (95 percent CI = 0.05–2.03), test for subgroup differences, $P = 0.06$). In Trial Sequential Analysis, the Z-curve crossed the monitoring boundary after inclusion of all RCTs, suggesting that the result of the meta-analysis did not reflect random or systematic error.

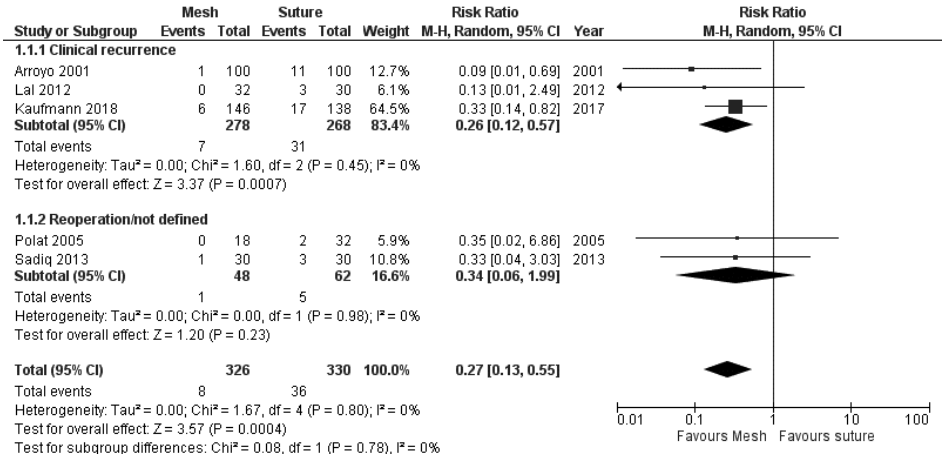

Figure 2. Risk for recurrence

A Forest plot for risk of recurrence in favor of mesh versus suture repair by subtype using clinically assessment or not assessed clinically (reoperation for recurrence or non-defined recurrence) or combined total events. Odds ratios (95 percent CIs) are denoted by black boxes (black lines). The combined OR estimate for all subtypes is represented by a black diamond, where diamond width corresponds to 95 percent CI bounds. Box and diamond heights are inversely proportional to precision of the OR estimate. The *P* value for heterogeneity (P heterogeneity) of odds ratios by subtype is shown.

Table 3. Relative risks of surgical outcomes in randomized controlled trials (RCTs) comparing mesh versus suture

Outcome (events/patients)	RCT	Relative Risk (95% CI)
Wound infection	Arroyo et al. [13]	0.67 (0.11–3.90)
	Kaufmann et al. [16]	2.84 (0.30–26.94)
	Lal and Ase [14]	0.38 (0.08–1.79)
	Polat et al. [12]	0.89 (0.09–9.14)
	Sadiq and Khurshid [15]	1.00 (0.22–4.56)
Total 11/326 versus 14/330		0.80 (0.36–1.79)
Seroma formation	Arroyo et al. [13]	1.20 (0.38–3.81)
	Kaufmann et al. [16]	4.73 (0.56–39.94)
	Lal and Ase [14]	4.70 (0.23–94.01)
	Polat et al. [12]	0.58 (0.02–13.52)
	Sadiq and Khurshid [15]	0.20 (0.01–4.00)
Total 13/326 versus 9/330		1.38 (0.57–3.32)
Hematoma	Arroyo et al. [13]	1.00 (0.06–15.77)
	Kaufmann et al. [16]	1.42 (0.24–8.36)
	Lal and Ase [14]	0.09 (0.00–1.48)
	Polat et al. [12]	1.78 (0.27–11.57)
	Sadiq and Khurshid [15]	0.14 (0.01–2.65)
Total 6/326 versus 13/330		0.55 (0.23–1.30)

RCT = randomized controlled trial. CI = confidence interval.

As shown in Table 3, there were no differences between the two surgical techniques regarding infection (RR = 0.80, 95 percent CI = 0.36–1.79), seroma formation (RR = 1.38, 95 percent CI = 0.57–3.32), or hematomas (RR = 0.55, 95 percent CI = 0.23–1.30).

Only one RCT reported data on acute and chronic pain and QOL [16]. No significant difference was found in postoperative pain between mesh and suture repair during all time points. Two weeks after the operation, 102 patients (74 percent) in the suture repair group and 111 patients (76 percent) in the mesh group were free of pain ($P = 0.57$). After 2 years, 129 patients (93 percent) in the suture repair group and 138 patients (95 percent) in the mesh group were free of pain ($P = 0.45$). QOL was evaluated using the MOS SF-36 health survey [22] and the EQ-5D-5L [23]. There was no significant difference at baseline preoperatively and 12 months after umbilical repair ($P > 0.05$).

DISCUSSION

Based on the updated literature search, five RCTs were identified [12-16]. The current analysis of the data revealed that mesh repair of umbilical hernia protected significantly against recurrence compared with a non-mesh sutured repair. The use of mesh repair did not increase risk of surgical site infection, seroma formation, hematomas, or chronic pain.

RCTs and meta-analyses based exclusively on RCTs with low heterogeneity provide the highest level of evidence for the effects of treatment [24-26]. However, surgical research questions, including hernia surgery, cannot always be answered through RCTs. Registry-based cohort studies tend to reflect the daily clinical practice (high external validity) but can be criticized due to risk of selection bias and possible confounding [27]. In the present systematic review, all included RCT studies reported significantly lower risk of recurrence of umbilical hernia after mesh repair compared with a sutured repair. The findings are in line with the results from a recent regional cohort study reflecting daily surgical life (nationwide hernia databases are prone to provide high external validity opposed to high internal validity from RCTs) [5] by comprising 1313 patients from the Danish Ventral Hernia Database. The study demonstrated that mesh reinforcement for an umbilical hernia significantly lowered the risk of recurrence [5]. On the other hand, a single-center study on 162 patients undergoing sutured repair for epigastric hernias performed by two dedicated surgeons found that a simple suture technique leads to acceptable low clinical recurrence rate of 6 percent [28]. As mentioned above, previous published systematic reviews [7-9, 11] used methodology of problematic quality, including several mainly observational prospective and retrospective studies, emergency

repairs, patients with liver cirrhosis, and a mixture of repairs for epigastric, incisional, and other types of ventral hernias. Furthermore, these meta-analyses included studies that did not clearly define primary outcomes in terms of recurrence. The consequence was therefore probably lack of robust quality and unclear definition of recurrence [19]. Due to the RCTs of moderate or even lower methodology quality [7-9, 11], final conclusions from these meta-analyses are not possible. A high-quality RCT has recently been published and was therefore not included in previous systematic reviews [16]. Kaufmann and colleagues included 300 patients with an umbilical hernia, diameter 1 to 4 cm, and a 24- to 30-month follow-up with clinical examination [16]. The findings from the Kaufmann study were in accordance with an earlier nationwide study with subgroup analyses of hernia defect size in relation to recurrence (>0–1 and >1–2 cm) [5].

Mesh position (onlay, sublay, etc.) has been suggested to be a risk factor for recurrence in incisional hernia repair [29]. Recent evidence supports that anatomic position of mesh affects the risk of recurrence after incisional hernia repair [29], but this has been contradicted by a later long-term follow-up from the same study cohort [30]. A previous nationwide cohort study on umbilical hernia repair (different mesh positioning compared with sutured repair; n = 4786) [31] and RCT data (onlay versus sublay mesh position; n = 80 [32]) reported no significant difference regarding mesh position for risk of recurrence, surgical site infection, and seroma formation in the onlay mesh position [32]. In addition, the onlay mesh repair resulted in significantly shorter operation time [32]. It may therefore be concluded that onlay mesh position for umbilical hernia repair is probably safe, efficient, and associated with comparable low risk of complication and recurrence rates although final conclusion is awaiting more solid data. Also, the necessary mesh overlap is not evidence-based.

In contrast to clinical results after groin hernia repair, chronic pain after umbilical hernia mesh repair has not been an often patient-reported outcome. In the recent RCT by Kaufmann and colleagues [16], 93 percent patients in the suture repair group and 95 percent in the mesh group were free of chronic pain 2 years after repair ($P = 0.45$). These findings were confirmed by the smaller Dalenbäck retrospective single-center study (n = 162) [28]. Two other retrospective studies (n < 232) [3, 4] and one prospective regional study (n = 1313) [5] found that an open umbilical or epigastric hernia repair induces chronic pain in 5 percent of the patients but with no difference between mesh or sutured repair. Christoffersen and colleagues [5] found that recurrence was the only independent risk factor for chronic pain and a previous retrospective study concluded that chronic complaints can, in part, be explained by recurrence [3]. However, the overall lack of chronic pain as the primary outcome makes final conclusions difficult.

QOL has exclusively been reported by Kaufmann and colleagues using the MOS SF-36 health survey [22] and the EQ-5D-5L [23] preoperatively and at 12 months postoperatively. The QOL was without significant difference after umbilical repair [16].

The included RCTs in the present meta-analysis [12-16] found seroma prevalence varying from 0 to 8 percent in the mesh group and 0 to 7 percent in the suture group after varying follow-up period. The inconsistencies of the results are comparable with previous literature and may be explained by the lack of definition and different diagnostic procedures. Thus, final conclusions on seroma formation with or without mesh repair are not possible.

There are several limitations of the present systematic review. Only one RCT of high quality was included [16]. Furthermore, most studies included only few patients, and recurrence outcome was not based on a statistical power analysis with the risk of statistical type I and II errors. Another limitation is that several of the studies have included different surgical techniques in both groups, which may introduce some possible confounders. The literature search was limited to the English language, which may introduce a possible language bias. However, it has previously been shown that this restriction will probably have only limited impact on final conclusions [33]. In addition, the extensive literature search across different databases limited the risk of omitting relevant literature. However, the most important limitation of the present analysis is the lack of high methodologic quality in the majority of the included studies and that studies, except one [16], were probably underpowered and comprised no prior statistical power analysis.

The strength of the present systematic review and meta-analysis is – in contrast to previous systematic reviews and meta-analyses – the coherence to a strict meta-analysis methodology to reduce risk of bias and subsequently an overestimation of intervention effects impeding final conclusions [34]. The present analysis included exclusively patients undergoing elective umbilical hernia repair. A previous study has shown that emergency repair has significantly worse outcome than elective repair with up to 15-fold higher mortality, reoperation, and readmission rates [35]. Therefore, the results on emergency and elective repairs are not comparable.

Future long-term high quality RCTs with a long-term follow-up with recurrence as primary outcome and chronic pain as secondary are awaited before final recommendations can be given on routine use of mesh repair in patients undergoing umbilical for defects ≤1 cm. Until then, and based on convincing data from a large nationwide clinical database study (not included in the present meta-analysis), defects even ≤1 cm may be closed using mesh repair.

In conclusion, mesh repair is probably safe and can be recommended for routine use to reduce the risk of recurrence after a small- and middle-sized umbilical hernia repair. More data are warranted for the optimal placement of mesh (sublay or onlay) and indication for mesh patients with an umbilical hernia defects <1 cm.

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The paper is not based on any previous communications.

Declaration of Conflicting Interests

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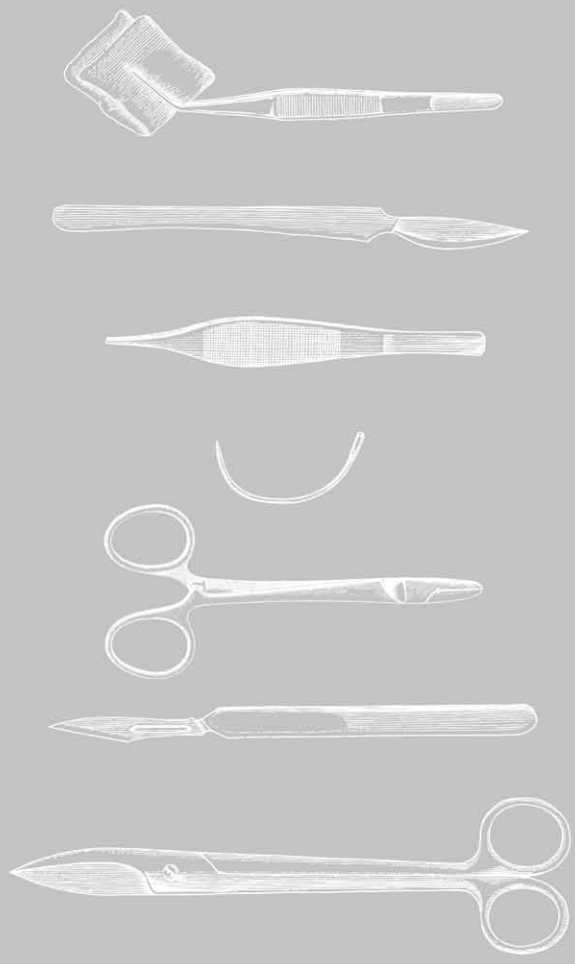

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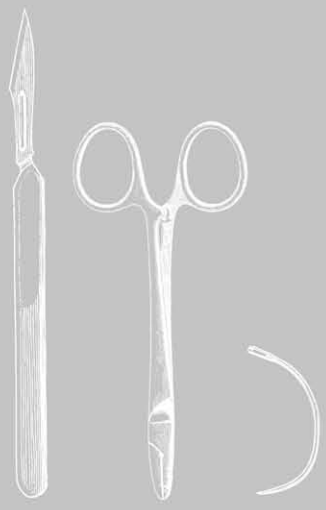
The feasibility of local anesthesia for the surgical treatment of umbilical hernia: a systematic review of the literature



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ABSTRACT

Introduction

Yearly approximately 4500 umbilical hernias are repaired in the Netherlands, mostly under general anesthesia. The use of local anesthesia has shown several advantages in groin hernia surgery. Local anesthesia might be useful in the treatment of umbilical hernia as well. However, convincing evidence is lacking. We have conducted a systematic review on safety, feasibility, and advantages of local anesthesia for umbilical hernia repair.

Methods

A systematic review was conducted according to the PRISMA guidelines. Outcome parameters were duration of surgery, surgical site infection, perioperative and postoperative complications, postoperative pain, hernia recurrence, time before discharge, and patient satisfaction.

Results

The systematic review resulted in nine included articles. Various anesthetic agents were used, varying from short acting to longer acting agents. There was no consensus regarding the injection technique and no conversions to general anesthesia were described. The most common postoperative complication was surgical site infection, with an overall percentage of 3.4 percent. There were no postoperative deaths and no allergic reactions described for local anesthesia. The hernia recurrence rate varied from 2 to 7.4 percent. Almost 90 percent of umbilical hernia patients treated with local anesthesia were discharged within 24 hours, compared with 47 percent of patients treated with general anesthesia. The overall patient satisfaction rate varied from 89 to 97 percent.

Conclusion

Local anesthesia for umbilical hernia seems safe and feasible. However, the advantages of local anesthesia are not sufficiently demonstrated, due to the heterogeneity of included studies. We, therefore, propose a randomized controlled trial comparing general versus local anesthesia for umbilical hernia repair.

INTRODUCTION

Umbilical hernia is a common diagnosis in surgery [1, 2]. Approximately 10 percent of all abdominal wall hernias are defined as umbilical hernia [3], and the prevalence of umbilical hernia in the adult population is 2 percent [4]. The European Hernia Society defines a primary umbilical hernia as a ventral hernia present at birth or developed spontaneously without trauma to the abdominal wall as the cause of the hernia and with its center at the umbilicus [5]. Each year, approximately 4500 umbilical hernias are repaired in the Netherlands and most of these patients are operated under general anesthesia.

Worldwide, ever more patients undergo ambulatory hernia surgery performed under local anesthesia [6]. Local anesthesia in the treatment for groin hernias has been already thoroughly investigated. Studies showed the superiority of local anesthesia for open groin hernia repair compared with general anesthesia or spinal anesthesia [7-13]. However, only 7 percent of Dutch surgeons uses local anesthesia in Lichtenstein repair [13]. This is surprising, since the use of local anesthesia could prevent complications related to general anesthesia. Possible advantages of the use of local anesthesia are less postoperative pain and extended postoperative analgesia, less perioperative and postoperative complications, early mobilization, and therefore a shorter duration of hospital stay. Furthermore, use of local anesthesia could be more cost-effective than general anesthesia or spinal anesthesia, since there is no anesthesiologist needed and only less expensive local anesthetics are used [7, 13-16]. There is a lack of convincing literature on umbilical hernia repaired under local anesthesia [1]. We have conducted a systematic review of the literature on the safety, feasibility, and advantages of local anesthesia for the repair of umbilical hernia.

METHODS

We conducted a systematic review following the PRISMA guidelines [17]. A systematic search was performed in MEDLINE, Embase, Web of Science, Scopus, PubMed Publisher, and the Cochrane Library.

The search strategy was prepared by the biomedical information specialist of the Medical Library (Erasmus University Medical Center, Rotterdam, the Netherlands). A syntax with search terms was designed, which is available at Appendix 1.

The identified records were independently evaluated by two reviewers. All records were screened by title and abstract for eligibility, and the full-text of eligible records

was assessed. Studies were included into the analysis if they met the following inclusion criteria: adult patients with umbilical hernia or paraumbilical hernia, who were operated under local anesthesia with or without a control group operated with another type of anesthesia. Articles had to be written in Dutch, English or German, and randomized controlled trials, cohort studies and case series (with more than five patients) were included. Exclusion criteria were studies investigating local anesthesia for other types of hernia than umbilical hernias, laparoscopic surgery, and animal studies or in vitro experiments.

The following outcome measurements were assessed: postoperative pain, duration of surgery, surgical site infection, perioperative and postoperative complications, hernia recurrence, time before discharge, and patient satisfaction. We also extracted the baseline study characteristics from all included studies: study design, study period, and year of publication. The quality of the studies was assessed on the Level of Evidence scale of the Oxford Centre for Evidence-based Medicine [18].

Both reviewers independently sampled the data in a standardized database. This database was set up in Microsoft Office Excel 2010. The data presented in this review were directly abstracted from the original articles. No statistical analyses were performed.

RESULTS

A total of 1107 articles were identified after the removal of duplicates. After screening of these records 77 articles were found eligible for further assessment. After assessment of the full-text versions of these 77 articles, nine articles were suitable for inclusion in this review. The reasons for exclusion were as follows: anesthesia or umbilical hernia were not well described and not the main subject, research was performed in children or animals, the article contained a case report, there was only an abstract available, or the article was written in another language than Dutch, English or German. The PRISMA flow diagram is shown in Figure 1.

Of the nine included articles, six were prospective cohort studies, and three were retrospective cohort studies. No randomized study comparing local versus general anesthesia was found. All studies contained a Level of Evidence of 2B on the scale of the Oxford Centre for Evidence-based Medicine. Table 1 gives an overview of the articles we included for this review.

In this review, the following outcome parameters will be highlighted: anesthesia technique, postoperative pain, duration of surgery, surgical site infection, perioperative and

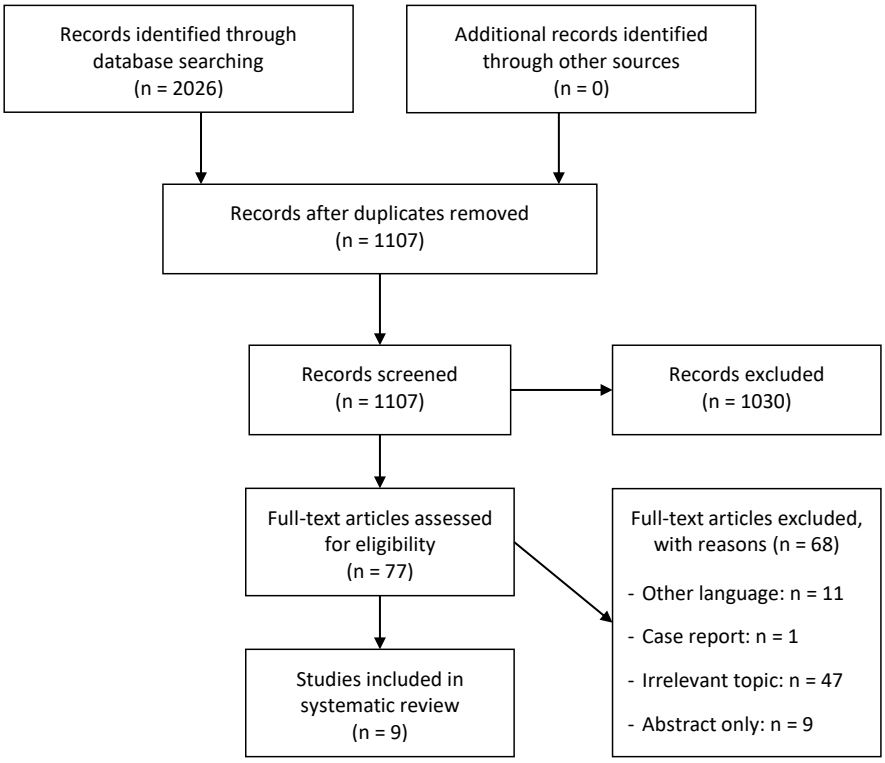

Figure 1. PRISMA flow diagram

postoperative complications, recurrence, time before discharge and patient satisfaction. The anesthesia technique was described to outline if there was any consensus regarding the injection technique and the type of anesthetics.

Surgical technique

There were two studies in which a Mayo repair was performed, with the classical "vest over pants" technique [19, 20]. Bennett and colleagues inserted a polypropylene soft mesh plug if the defect was <2 cm. In case the defect was >2 cm, a preperitoneal pocket was made and a polypropylene soft mesh was placed, with a 2 cm margin [14]. In the study of Kurzer and colleagues a cone polypropylene mesh was used for defects <3 cm, and a flat piece of mesh for defects >3 cm [2]. Garcia and colleagues used 1 cm as a cutoff point for a primary suture, and "large" hernias, as they stated, received a polypropylene mesh [4]. Three articles did not mention which cutoff point they used to determine the use of primary sutures or a mesh, and in one study only umbilical hernia operations with meshes were performed [1, 3, 6, 19]. Dalenbäck and colleagues were the only authors who specified the type of surgical procedure for the type of anesthesia. A total of 162

Table 1. Study characteristics

Author	Study type	Year of publication	Total number of patients	Level of evidence	Type of hernia	Outcome measurements
Acevedo and Léon	Prospective cohort study	2010	2031 (326 umbilical hernia)	2B	Inguinofemoral, epigastric, umbilical, incisional	Perioperative pain, complications
Bennett et al.	Prospective cohort study	2013	63	2B	Paraumbilical	Duration of surgery, patient satisfaction
Dalenbäck et al.	Retrospective cohort study	2013	162	2B	Umbilical	Recurrence, pain, complications
Garcia-Urena et al.	Prospective cohort study	2000	157	2B	Umbilical, epigastric	Complications, time to discharge
Kulacoglu et al.	Prospective cohort study	2012	100	2B	Umbilical	Pain (VAS), time to discharge, complications, recurrences
Kurzer et al.	Prospective cohort study	2004	54	2B	Umbilical	Pain, complications
Menon and Brown	Retrospective cohort study	2003	32	2B	Umbilical	Duration of surgery, complications, recurrence
Sinha and Keith	Retrospective cohort study	2004	34	2B	Umbilical	Duration of surgery, time to discharge, complications, recurrences
Stabilini et al.	Prospective cohort study	2009	69	2B	Umbilical, epigastric	Time to discharge, recurrence, complications

patients underwent an umbilical hernia operation. Of the patients operated with a suture repair, 59 percent were operated under local anesthesia and 41 percent under general anesthesia. Of the patients receiving a mesh repair, 18 percent were operated under local anesthesia and 82 percent under general anesthesia.

Anesthesia technique

There are various anesthesia techniques assessed in the studies. Only Acevedo and Léon described the use of local anesthesia without addition of a sedative [6]. Four other studies combined the use of local anesthesia with sedatives and another four studies used local anesthesia (without sedatives) or general anesthesia for their patient groups [1-4, 14, 19-21]. None of the authors randomized between local anesthesia and general anesthesia. Table 2 shows the various types of anesthesia (local anesthesia or general anesthesia, local anesthesia with or without sedatives) and the different types of anesthetic drugs that were used. The anesthetic drugs varied from the short acting lidocaine

Table 2. Anesthesia techniques: the different types of anesthesia used and types of local anesthetics

Author	LA	LA + sedation	LA or GA
Acevedo and Léon	Lidocaine 0.5%	n.a.	n.a.
Bennett et al.	n.a.	n.a.	GA: not described LA: xylocaine 2%, bupivacaine 0.5%
Dalenback et al.	n.a.	n.a.	GA: not described LA: not described
Garcia et al.	n.a.	Lidocaine 1% + midazolam	n.a.
Kulacoglu et al.	n.a.	Lidocaine, bupivacaine 0.5% + midazolam and fentanyl	n.a.
Kurzer et al.	n.a.	Bupivacaine 0.25% + midazolam	n.a.
Menon and Brown	n.a.	Xylocaine 1% + bupivacaine 0.5% + midazolam	n.a.
Sinha and Keith	n.a.	n.a.	GA: not described LA: xylocaine 1%
Stabilini et al.	n.a.	n.a.	GA: not described LA: mepivacaine

LA = local anesthesia. LA + sedation = local anesthesia combined with sedation. LA or GA = local anesthesia or general anesthesia. n.a. = not applicable.

and xylocaine to the longer acting agent bupivacaine. Bennett and colleagues were the only authors who described the injection technique, which was a field block technique: infiltration of the skin and rectus sheath around the umbilicus [14]. Kulacoglu and colleagues studied patients with umbilical hernia treated with local anesthesia. They stated there were no conversions to general anesthesia; all patients tolerated local anesthesia and there were no intraoperative anesthesia-related complications [1].

Postoperative pain

One study made use of the Visual Analogue Scale (VAS) as a measurement scale to define "postoperative pain". The authors included patients with different types of hernia and concluded that 79 percent of lean patients (BMI < 30) had a VAS of < 3, compared with 71.9 percent of the obese patients (BMI ≥ 30). This difference was statistically significant ($P = 0.007$). In this study, no distinction was made between VAS scores per hernia type. It was neither described what VAS score patients had who were operated under local anesthesia [6].

Two other studies used terminology like "mild, moderate or severe" and "no severe postoperative pain" to report pain [1, 2]. The authors did not mention which questionnaire or measurement scale was used for these statements.

Duration of surgery

Six authors investigated the duration of surgery, which ranged from 24 to 78 minutes [1, 4, 6, 14, 20, 21]. Table 3 shows that Bennett and colleagues were the only authors making a distinction between local anesthesia and general anesthesia for this outcome parameter. This study showed that the use of local anesthesia for paraumbilical hernia could lead to a shorter duration of surgery than the use of general anesthesia (*P* value < 0.0003). However, patients with a lower BMI were more frequently operated under local anesthesia. When BMI was categorized to see if there was any difference between patients with a BMI less or more than 25, and less or more than 30 (obese), there was no difference found in the length of the procedure [14]. Kulacoglu and colleagues and Menon and Brown all included patients with umbilical hernia treated with local anesthesia alone. Kulacoglu and colleagues showed that the mean operative time was 69 minutes (range 25–150 minutes), but in the patient group of Menon and Brown, the duration of surgery was significantly shorter with a mean operative time of 30 minutes (range 22–40 minutes) [1, 20].

Table 3. Duration of surgery

Author	N	Hernia type	Anesthesia	Duration of surgery, mean (min)
Acevedo and Léon	2031	Inguinofemoral, epigastric, umbilical, incisional	LA	Lean 62 (± 8.6) min Obese 78 (± 11.7) min, *P* < 0.001
Bennett et al.	63	Paraumbilical	LA + GA	LA 24 (17.5–30) GA 35 (27–45), *P* < 0.0003
Garcia et al.	157	Umbilical, epigastric	LA	49.7
Kulacoglu et al.	100	Umbilical	LA	69 (25–150)
Menon and Brown	32	Umbilical	LA	30 (22–40)
Sinha and Keith	34	Umbilical	LA + GA	50 (40–108)

LA = local anesthesia. LA + GA = local anesthesia and general anesthesia.

Surgical Site Infection

Surgical site infection (SSI) is a common postoperative complication and one of the most commonly described outcome parameters. The overall percentage of SSI was 3.4 percent (15/431), and ranged from 1 to 12.9 percent [1, 2, 4, 19, 20]. Three studies described that SSI responded well to conservative wound care or oral antibiotics, and no further treatment was required. Two remaining studies did not describe the treatment for SSI. Besides Acevedo and Léon, none of the authors described in which patient group SSI occurred [1, 2, 4, 19, 20]. Acevedo and Léon noted that there was a significantly higher rate of SSI in obese patients (BMI > 30) than in non-obese patients, respectively 2.1 percent and 0.7 percent (*P* < 0.023). None of the articles specified the SSI rate per hernia or anesthesia type, nor was it described if SSIs were more frequently seen in patients treated with a mesh.

Other postoperative complications

The most frequent postoperative complications were seromas, with a range of 3 to 8.9 percent, and an overall percentage of 4.8 percent. All seromas either resolved spontaneously or were successfully treated with drainage [1, 3, 4, 21]. The second most frequent postoperative complication were hematomas (1 percent) [1, 3, 4]. There was one patient who suffered from postoperative bleeding and one other patient who suffered from intestinal obstruction. Both patients needed emergency surgery to resolve these complications [19]. Postoperatively, there were two patients suffering from allergic skin changes due to a plaster allergy [1]. Finally, there was one 86-year old patient operated under general anesthesia, who experienced episodes of confusion and dizziness postoperatively. Therefore, a prolonged hospital stay of 12 days was needed [21]. In total, three patients passed away after surgery, respectively due to the following causes: liver cirrhosis, cerebral infarction and chronic renal failure. All causes were not related to the operation [3]. No perioperative complications were described. None of the articles made a comparison between type of anesthesia.

Recurrence

Seven studies described hernia recurrence rate as an outcome measurement [1-4, 19-21]. In three of these studies, no recurrences occurred [1, 2, 20]. The mean follow-up in these studies was 17 months (5–41), 43 months (28–67), and 70 months (27–142). The remaining four articles measured a recurrence rate ranging from 2 to 7.4 percent [3, 4, 19, 21]. These four studies did not mention which patients presented with a recurrence. Dalenbäck and colleagues were the only authors who included umbilical hernia patients alone. They made a distinction in recurrence rates between patients operated under general anesthesia and patients operated under local anesthesia. The authors found two recurrences (out of 144 patients) in the general anesthesia group and five recurrences (out of 144 patients) in the local anesthesia group. No statistical comparison was made between these two groups [19]. The studies did not describe how the recurrence was diagnosed: with physical examination only or with the addition of radiological examination.

Duration of postoperative stay

The mean duration of postoperative stay at the hospital varied from 2 hours to almost 2 days [1, 3, 4, 20, 21]. Table 4 gives an overview of the mean time before discharge. Kulacoglu and colleagues showed that patients with umbilical hernia, operated under local anesthesia, stayed 122 ± 58 minutes in hospital before discharge [1]. Sinha and Keith described that 89 percent of the patients in the local anesthesia group were discharged in less than 24 hours, compared with 47 percent of the patients in the general anesthesia group [21]. The other articles did not specify the duration of stay for the type

Table 4. Time to discharge

Author	Type of anesthesia	Type of hernia	Time to discharge (mean)
Garcia et al.	LA	Umbilical, epigastric	7.2 hours
Kulacoglu et al.	LA	Umbilical	122 min ± 58 min (45–420)
Menon and Brown	LA	Umbilical	Same day, discharge before 20:00 p.m.
Sinha and Keith	GA or LA	Paraumbilical	LA: 89% discharged < 24 hours GA: 47% discharged < 24 hours
Stabilini et al.	GA or LA	Umbilical, epigastric	1.8 days (3 hours to 15 days)

LA = local anesthesia. GA = general anesthesia.

of anesthesia or type of hernia. The longest mean duration of stay was 1.8 days (range 3 hours to 15 days) and was required due to severe associated diseases of the patients, emergency surgery for hernia strangulation and wound hematoma [3].

Patient satisfaction

Five studies reported on patient satisfaction, which was reported to be good in 89 to 97 percent of patients. Different methods of measuring this outcome parameter were used. Acevedo and Léon defined patient satisfaction as good, if the VAS for patient satisfaction was >7 points on a 10 points scale, in combination with a positive answer to the question "would you recommend this kind of surgery to others?". This was measured at the 1 week control [6]. Sinha and Keith stated that 97 percent of their patient population was satisfied, according to the definition of Reitter [21]. The remaining three authors did not describe which questionnaire was used to define and measure patient satisfaction [1, 14, 19]. Two authors specified the patient satisfaction with regard to the body mass index of the patient [6, 14]. None of the articles specified the patient satisfaction per hernia type or anesthesia type [1, 19, 21].

DISCUSSION

The data from this systematic review reveal that the use of local anesthesia in umbilical hernia repair led to a shorter duration of postoperative stay, and that repair of a paraumbilical hernia performed under local anesthesia leads to a shorter duration of surgery. The use of local anesthesia did not lead to perioperative complications, serious postoperative complications, allergic responses or anesthesia-related deaths.

Umbilical hernia is a common surgical problem [1, 2]. At this moment, data on umbilical hernia surgery under local anesthesia are only scarcely available. In contrast, groin hernias operated under local anesthesia are very well described in literature, and several

studies have been performed [7, 10-13, 15, 22]. All these studies show the advantages of local anesthesia: less postoperative and general anesthesia-related complications, a shorter duration of surgery, less overnight admissions, less postoperative pain and no deaths. Van Veen and colleagues showed that significantly more urinary retentions occurred in patients undergoing Lichtenstein hernia repair under spinal anesthesia [13]. Furthermore, the conversion rate to general anesthesia was lower for patients operated under local anesthesia (2 percent) than patients operated under spinal anesthesia (10 percent) [15]. Nordin and colleagues also showed that local anesthesia has significant cost advantages compared to spinal anesthesia and general anesthesia [15]. We therefore performed a review of literature to investigate the safety and feasibility of the use of local anesthesia for umbilical hernia and to explore if there are any advantages to the use of local anesthesia for umbilical hernia.

We have performed a literature search and found no randomized controlled trials or other significant papers giving solid evidence for the use of local anesthesia as being superior in the treatment of umbilical hernias. Only a few small prospective or retrospective cohort studies were included in this review. The studies we included do not solely include umbilical hernias, and when the studies did include solely umbilical hernias, the authors did not describe their local anesthesia treatment well.

If we take a closer look at the included studies, a very high heterogeneity can be noticed. First of all; there is no consensus regarding the local anesthetic drug, and the technique to induce local anesthesia. The used local anesthetic drug varies from shorter acting lidocaine to the longer acting ropivacaine. The technique to inject is not discussed in most of the articles, one article mentioning the "field block" as a way to induce local anesthesia. Some authors diluted their anesthetic with another type of anesthetic, others diluted it with saline or adrenaline. Amid and colleagues described a simple step-by-step infiltration technique for inguinal hernia, which is adapted and followed in most of the studies using local anesthesia for inguinal hernia [7, 10, 13, 15, 23]. Furthermore, Amid and colleagues used a solution which consisted of 1 percent lidocaine, 1 percent bupivacaine and epinephrine, which is used by other authors as well [7, 15]. In local anesthesia of umbilical hernia, a standardized protocol is missing and should, therefore, be set up.

Pain is an important outcome measurement. However, not all studies describe perioperative or postoperative pain as an outcome measurement, and not all authors who do describe postoperative pain use the Visual Analog Scale (VAS) to measure pain. Several studies regarding inguinal hernia have shown that postoperative pain in patients treated with local anesthesia is (significantly) lower compared to general anesthesia or

spinal anesthesia [7, 15], but this outcome measurement is, despite of its importance, not thoroughly investigated for umbilical hernia. Due to this inconsistency, comparison of the studies is impossible.

Another essential outcome measurement is represented by postoperative complications. Surgical site infections and seromas are the most common complications. In the underlying studies, these complications either resolved spontaneously, were treated with drainage or antibiotics, and had no serious consequences for the patient. It is not clear if complications occurred more frequently among patients treated with local anesthesia, since the authors did not describe which patient developed a postoperative complication. There were no perioperative complications, nor any allergies against local anesthetics, or deaths described.

The hernia recurrence rate varied from 2 to 7.4 percent, with a higher percentage for patients who were treated with primary sutures. This is comparable with the available literature, which describes a recurrence rate of approximately 2 percent for mesh repair, rising up to 8 percent for suture repair [24, 25]. However, recently the cohort study of Christoffersen and colleagues showed that the total cumulated recurrence rate after primary repair was 10 percent for mesh repair and 21 percent for sutured repair after 55 months of follow-up ($P = 0.001$) [26], which is a surprisingly high percentage. Dalenbäck and colleagues showed that the recurrence rate among umbilical hernia patients operated under local anesthesia was higher (5/144) than in patients operated under general anesthesia (2/144) [19]. However, since there was no statistical comparison made, no conclusions can be drawn.

The duration of surgery varied from 24 to 78 minutes and was for all studies, with one exception, not specified per type of hernia or type of anesthesia. Bennett and colleagues were the only authors who did specify the outcomes per anesthesia type and showed that patients with a paraumbilical hernia operated under local anesthesia had a shorter duration of surgery than patients operated under general anesthesia [14]. However, when BMI was categorized (more or less than BMI 25, and more or less than a BMI of 30), there were no differences found for duration of surgery. It can be concluded that BMI was a confounding factor, and patients who were operated under local anesthesia had more frequently a lower BMI.

Almost 90 percent of the patients operated with local anesthesia were discharged within 24 hours. This percentage rate is almost twice as high as patients operated under general anesthesia: 47 percent was discharged within 24 hours. This is comparable with the available literature for groin hernias. Studies show a significantly shorter in hospital

stay as well, and significantly less postoperative overnight admissions [7, 15]. There is no study comparing the difference in discharge time for local anesthesia and general anesthesia in umbilical hernia patients.

In our opinion, patients that would be eligible to undergo umbilical hernia repair under local anesthesia are cooperative patients with a low to normal BMI without certain mental disorders or physical disabilities and with a primary, up to maximally 4–5 cm large, non-recurrent umbilical hernia that will undergo repair in an elective setting. In case of end-stage cardiac and/or pulmonary disease local anesthesia must be considered as the preferred option.

This review has some limitations. Heterogeneity is the main disadvantage of this study. There is no consensus regarding the injection technique or the anesthetic drug that should be used. Postoperative pain, an essential outcome parameter, is not thoroughly described, and no standardized questionnaires were used to measure this outcome parameter. Furthermore, it is not clear if the complications and recurrences described in the included articles, occurred in the patient group we aimed to investigate. Finally, we cannot conclude if patients with umbilical hernia treated with local anesthesia have a shorter duration of operation and a shorter duration of stay, since no comparison is made with a control group. Based on our findings, we cannot state that local anesthesia for umbilical hernia patients has any advantages.

CONCLUSION

Local anesthesia for umbilical hernia patients seems safe and feasible. However, the advantages of local anesthesia are not sufficiently demonstrated in the currently available literature. Almost every outcome parameter is not specified for the patient group we aimed to investigate: patients with umbilical hernia treated with local anesthesia. We still do not know if local anesthesia for umbilical hernia gives excellent results, so we cannot implement it in daily practice. Therefore, we propose to initiate a randomized controlled trial, comparing local anesthesia with general anesthesia for patients with umbilical hernia. This could reveal if local anesthesia has any advantages.

Acknowledgements

We would like to thank Wichor M. Bramer for his assistance in the literature search.

Compliance with ethical standards

Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose. AJ declares no conflict of interest. RK declares no conflict of interest. FM declares no conflict of interest. JJ declares no conflict of interest. JL declares no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and animal rights

This article does not contain any studies with animals performed by any of the authors.

Informed consent

For this type of study formal consent is not required.

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APPENDIX 1

Literature search strategy

PubMed Publisher: 15

In PubMed the following search strategy was performed: ((((umbilic*[tiab] OR "abdominal wall"[tiab] OR ventral[tiab]) AND (herni*[tiab] OR defect*[tiab])) OR exomphal*[tiab])) AND ((((local[tiab] OR topical[tiab] OR region*[tiab] OR infiltrat*[tiab] OR conduct*[tiab] OR block*[tiab]) AND (anesthe*[tiab] OR anaesthe*[tiab])) OR ((ambula*[tiab] OR day[tiab] OR daycare[tiab] OR outpatient*[tiab] OR "short stay"[tiab]) AND (surg*[tiab] OR setting*[tiab] OR operati*[tiab] OR procedure*[tiab] OR treat*[tiab] OR therap*[tiab] OR repair*[tiab] OR hernioplast*[tiab] OR herniorrhaph*[tiab])) OR "day case"[tiab])) AND publisher[sb].

Embase: 507

In Embase the following search strategy was performed: ('umbilical hernia'/de OR 'abdominal wall hernia'/de OR (umbilicus/de AND (hernioplasty/de OR herniorrhaphy/de)) OR (((umbilic* OR 'abdominal wall' OR ventral) NEAR/6 (herni* OR defect*)) OR exomphal*):ab,ti) AND ('local anesthetic agent'/exp OR 'local anesthesia'/exp OR 'ambulatory surgery'/de OR 'outpatient department'/de OR outpatient/de OR 'ambulatory care'/de OR 'anesthetic needle'/de OR (((local OR topical OR region* OR infiltrat* OR conduct* OR block*) NEAR/3 (anesthe* OR anaesthe*)) OR ((ambula* OR day OR daycare OR outpatient* OR 'short stay') NEAR/3 (surg* OR setting* OR operati* OR procedure* OR treat* OR therap* OR repair* OR hernioplast* OR herniorrhaph*)) OR 'day case'):ab,ti).

MEDLINE: 36

In MEDLINE the following search strategy was performed: ("Hernia, Umbilical"/OR "Hernia, Ventral"/OR (umbilicus/AND (herniorrhaphy/)) OR (((umbilic* OR "abdominal wall" OR ventral) ADJ6 (herni* OR defect*)) OR exomphal*).ab,ti.) AND ("Anesthesia, Local"/OR "Anesthetics, Local"/OR "Ambulatory Surgical Procedures"/OR "outpatients"/OR "Ambulatory Care"/OR (((local OR topical OR region* OR infiltrat* OR conduct* OR block*) ADJ3 (anesthe* OR anaesthe*)) OR ((ambula* OR day OR daycare OR outpatient* OR "short stay") ADJ3 (surg* OR setting* OR operati* OR procedure* OR treat* OR therap* OR repair* OR hernioplast* OR herniorrhaph*)) OR "day case").ab,ti.).

Cochrane: 6

In Cochrane the following search strategy was performed: ((((umbilic* OR 'abdominal wall' OR ventral) NEAR/6 (herni* OR defect*)) OR exomphal*):ab,ti) AND ((((local OR topical OR region* OR infiltrat* OR conduct* OR block*) NEAR/3 (anesthe* OR anaesthe*)) OR

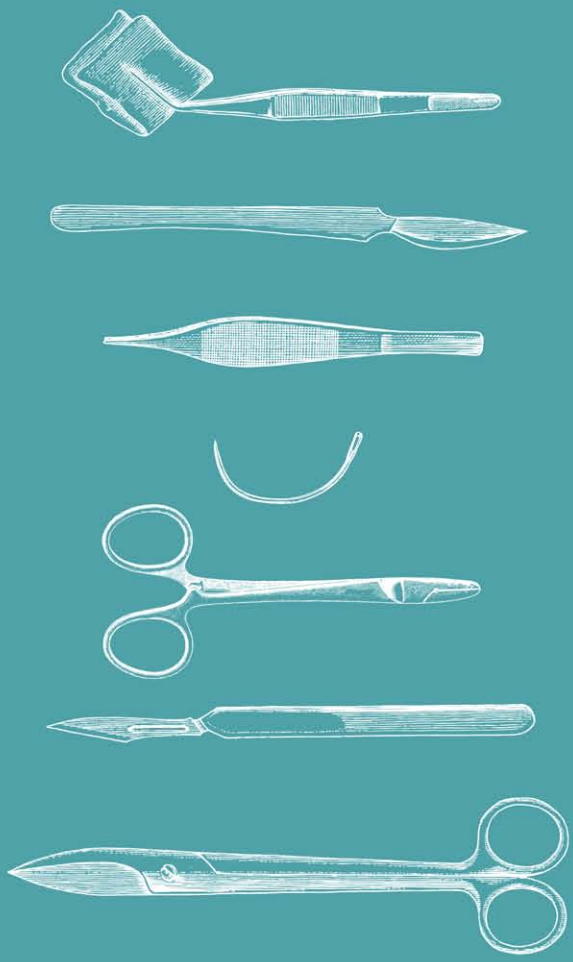
((ambula* OR day OR daycare OR outpatient* OR 'short stay') NEAR/3 (surg* OR setting* OR operati* OR procedure* OR treat* OR therap* OR repair* OR hernioplast* OR herniorrhaph*)) OR 'day case'):ab,ti).

Web of Science: 152

In Web of Science the following search strategy was performed: TS = (((((umbilic* OR "abdominal wall" OR ventral) NEAR/6 (herni* OR defect*)) OR exomphal*)) AND ((((local OR topical OR region* OR infiltrat* OR conduct* OR block*) NEAR/3 (anesthe* OR anaesthe*)) OR ((ambula* OR day OR daycare OR outpatient* OR "short stay") NEAR/3 (surg* OR setting* OR operati* OR procedure* OR treat* OR therap* OR repair* OR hernioplast* OR herniorrhaph*)) OR "day case"))).

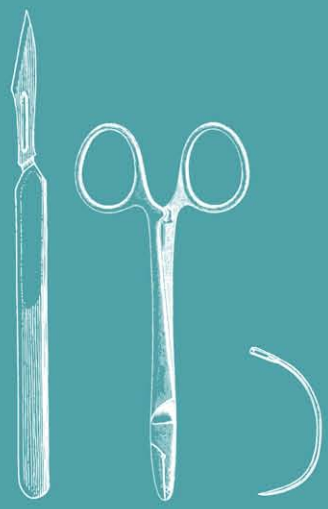
Scopus: 230

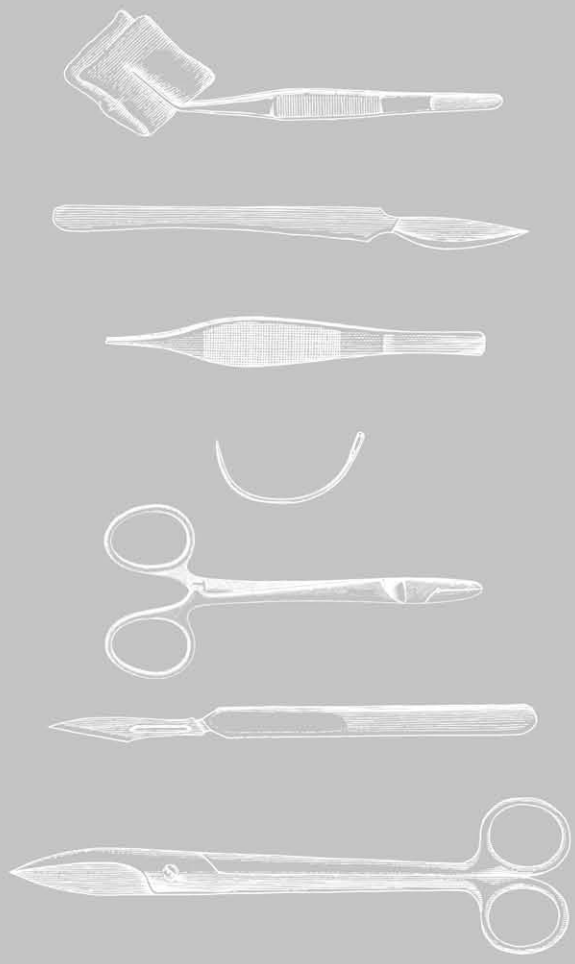
In Scopus the following search strategy was performed: TITLE-ABS-KEY(((((umbilic* OR "abdominal wall" OR ventral) W/6 (herni* OR defect*)) OR exomphal*)) AND ((((local OR topical OR region* OR infiltrat* OR conduct* OR block*) W/3 (anesthe* OR anaesthe*)) OR ((ambula* OR day OR daycare OR outpatient* OR "short stay") W/3 (surg* OR setting* OR operati* OR procedure* OR treat* OR therap* OR repair* OR hernioplast* OR herniorrhaph*)) OR "day case"))).



part 3

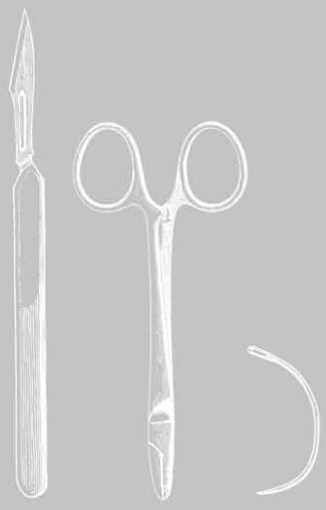
complications of mesh





9

Comparison of self-gripping mesh and sutured mesh in open inguinal hernia repair: a meta-analysis of long-term results



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Surgery 2018 Feb;163(2):351-360

ABSTRACT

Introduction

Complications after inguinal hernioplasty pose a significant burden on individual patients and society because of high numbers of repair procedures. Recently, the long-term results of a self-gripping ProGrip™ mesh for open inguinal hernia repair have become available. The aim of this meta-analyses was to compare these long-term results with the results of a Lichtenstein hernioplasty with a sutured mesh focusing on chronic pain, recurrence rate, foreign body sensation, and operation duration.

Methods

A systematic review of the literature was undertaken to identify randomized controlled trials comparing open inguinal hernia repair with a self-gripping ProGrip™ mesh and a conventional Lichtenstein hernioplasty.

Results

In the present meta-analysis, the outcomes of ten randomized controlled trials enrolling 2541 patients were pooled. The mean follow-up was 24 months (range 6–72 months). There was no significant difference in the incidence of chronic pain (odds ratio = 0.93; 95 percent confidence interval, 0.74–1.18), recurrence (odds ratio = 1.34; 95 percent confidence interval, 0.82–2.19), or foreign body sensation (odds ratio = 0.82; 95 percent confidence interval, 0.65–1.03), between the self-gripping mesh and sutured mesh group at all follow-up time points. The mean operating time was significantly shorter (odds ratio = −7.58; 95 percent confidence interval, −9.58 to −5.58) in the self-gripping mesh group.

Conclusions

The self-gripping mesh has comparable results with a sutured mesh regarding the incidence of chronic postoperative inguinal pain, recurrence and foreign body sensation. However, long-term results still are based on relatively small patient numbers and outcomes measures are heterogenic. The main advantage of the self-gripping mesh is the consistently significantly reduced operation time.

INTRODUCTION

Open hernia repair according to Lichtenstein and endoscopic inguinal hernia techniques still are recommended as the best evidence-based options for the repair of a symptomatic primary unilateral inguinal hernia, providing the surgeon is sufficiently experienced in the specific procedure [1]. Factors popularizing the Lichtenstein technique compared with the endoscopic techniques are its easiness to perform, lower rate of serious complications, and the possibility to perform the operation under local anesthesia [2-4]. Because the recurrence rate for both techniques has been reduced to less than the rate of chronic postoperative inguinal pain (CPIP), CPIP and its consequences for the quality of life (QOL) are the challenges of modern hernia surgery [5]. This is also urged by the high incidence of CPIP – which is ≈ 10 percent – and because of its socioeconomic effects [1, 5, 6]. The pathophysiology of CPIP is regarded multifactorial due to patient-related and surgery-related risk factors [6-9]. Among the surgical risk factors are the type of mesh and its fixation technique [5, 10, 11]. Several meta-analyses have shown that lightweight meshes are associated with less CPIP and less foreign body feeling because of a reduced inflammatory response and a less intense foreign body reaction, although the incidence of severe CPIP is not significantly lower [12-14]. It is thought that fixation of meshes with traumatic devices such as sutures or tacks can cause entrapment and injury of muscles and nerve fibers [15, 16]. Numerous studies therefore aimed to reduce the need for fixating materials in tension-free hernia repair. Results of meta-analysis examining glue fixation of mesh are heterogeneous [17-20]. Another atraumatic way of mesh fixation may be found in the self-gripping ProGrip™ mesh (Medtronic, Dublin, Ireland). This component semiresorbable macroporous knit made of monofilament polypropylene (Parietene™ ProGrip™) or polyester (Parietex™ ProGrip™) incorporates a one-sided coating of resorbable micro-hooks providing atraumatic anchorage of the mesh in the underlying tissue bed. The self-gripping mesh is supposed to reduce CPIP because of atraumatic mesh fixation and the use of low-weight monofilament mesh, thereby reducing the material-dependent inflammatory reaction. Several randomized controlled trials have compared the Lichtenstein repair using this self-gripping mesh with the Lichtenstein repair using a conventionally sutured mesh, and long-term results of these studies have become available. Because former meta-analyses are based on short-term results, a new meta-analysis was performed to investigate differences in the occurrence of CPIP and recurrence rate between a sutured mesh and a self-gripping mesh in the long term [21-24].

METHODS

The systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [25]. All trials published up to January 2017 comparing self-gripping mesh and conventional sutured mesh for the Lichtenstein procedure were identified. The literature search was performed in the following databases: Embase, MEDLINE Ovid, CINAHL EBSCOhost, Cochrane, Web of Science, Scopus, and Google Scholar. The search strategy was designed by a biomedical information specialist of the Medical Library (Erasmus University Medical Center, Rotterdam, the Netherlands). A syntax with search terms was prepared; both the syntax and the search strategy are available in Appendix 1.

All identified records were transferred into an EndNote database (EndNote X7.7.1, Thomson Reuters, New-York). Two identical duplicate versions of this database were evaluated individually by two independent reviewers (M.M. and R.K.). First, all records were screened by title and abstract for eligibility. After this step, both independent libraries were combined and compared via an EndNote comparing strategy [26]. Then all full-text articles were assessed for eligibility. Any discrepancies were discussed between the two reviewers and the senior author (J.F.L.).

Studies were included in the meta-analysis if they met all the following inclusion criteria: randomized controlled trials enrolling adult patients with a unilateral or bilateral primary inguinal hernia; hernia repair according to Lichtenstein comparing either a self-gripping polypropylene or polyester mesh (respectively, Parietene™ ProGrip™ and Parietex™ ProGrip™ mesh, Medtronic) with a conventional mesh being sutured; CPIP among the primary or secondary outcomes. Articles had to be written in Dutch, English, or German. Interim analyses were excluded if an article with longer follow-up was available.

The following outcomes were extracted from the included trial: CPIP, foreign body sensation (FBS), and recurrence of hernia. The methodologic quality of the included studies was assessed according to criteria specified by the Cochrane handbook for Systematic Reviews of Interventions Version 5.0.1 and the guidelines of Jadad and colleagues [27] and Higgins and colleagues [28]. In addition, all trials were scored on the availability of a baseline pain score, a validated assessment tool for CPIP, a definition of the outcome parameter CPIP, data on extra sutures placed in the self-gripping mesh group and perioperative nerve handling. Both reviewers independently sampled the data of all articles into a standardized database. This database was set up in Review Manager (RevMan, version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A random check was performed by the senior author (J.F.L.).

Data analysis

A random effects model was used to calculate a pooled mean of the data, taking into account both the variance between studies and study populations and the variance within a study [29]. For continuous data, the mean difference with a 95 percent confidence interval (CI) was calculated; for dichotomous data, the effect measures odds ratio (OR) and risk ratio (RR) with 95 percent CI were calculated to evaluate the statistical difference between outcomes. Because RevMan 5.3 excludes trials with zero events when calculating an OR or RR, a risk difference (RD) also was calculated in which zero event trials were included. Outcomes were displayed in forest plots. Statistical heterogeneity was assessed by calculating the test statistic Cochran's Q. The consistency of study effects was tested using I^2 statistic [30]. I^2 values of 0 to 25 percent was assigned as low, 25 to 50 percent moderate, and 75 to 100 percent as high. In addition, the overall effect was provided for each total or subtotal. Analyses were performed using RevMan 5.3.

Outcomes not presented as mean (SD) but as mean (range, 95 percent CI, interquartile range or nothing at all) were not included in the combined analyses.

RESULTS

In total, 464 articles were identified after the removal of duplicates. After screening of these records, 42 articles were found eligible for full-text assessment. After assessment of the full-text versions, nine articles were suitable for inclusion in this meta-analysis. Another article was identified though a monthly mail summarizing recently published articles [31]. During the writing of the meta-analyses the long-term results of two already included studies were published and included in the meta-analyses [32, 33]. A PRISMA flowchart of the literature search is shown in Figure 1.

The included ten randomized controlled trials enrolled 2541 patients (n = 1216 self-gripping mesh group, n = 1245 sutured mesh group). The duration of follow-up ranged from 6 to 72 months. Study characteristics are shown in Tables 1 and 2.

Methodologic quality of included studies

The quality assessment of the study methods according to the Cochrane guidelines is given in Table 3, including a Jadad Score. Three of the ten included studies scored <4 points. The quality of two trials was poor (2 points) due the absence of an adequate randomization technique or no information about it, absence of blinding, no power calculations, and no baseline score [34, 42]. The quality of one trial was moderate (3 points) due to the absence of blinding and baseline scoring [40]. The study reported by

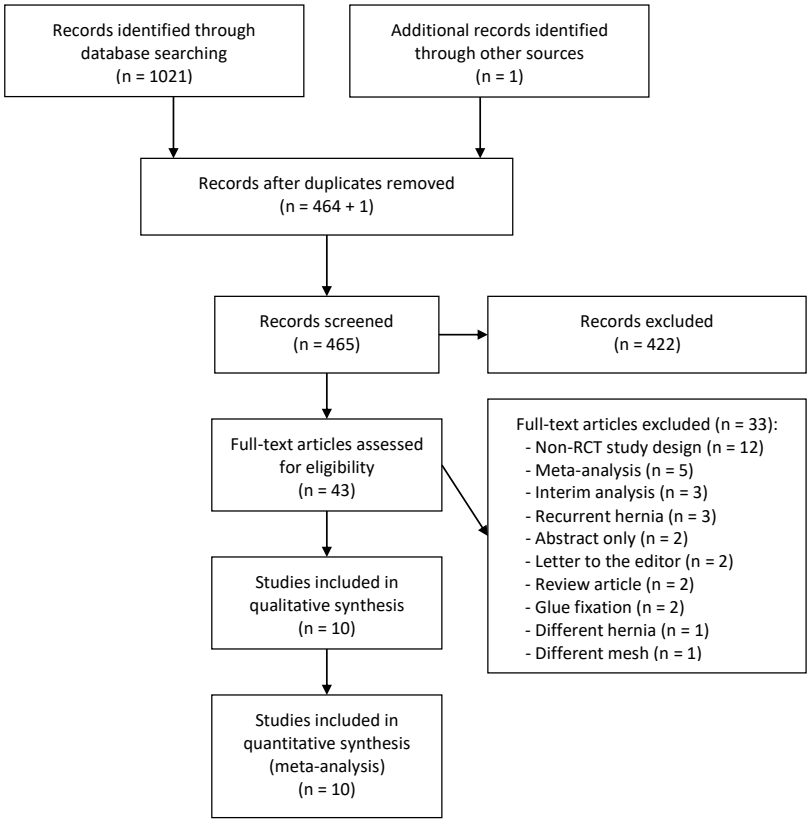

Figure 1. PRISMA flow diagram

Fan and colleagues scored 5 points, although it was not powered for the outcome CPIP and did not provide a definition nor an assessment method of CPIP [31].

Four studies did not perform a baseline pain score although preoperative pain is a well-known risk factor for CPIP [31, 34, 35, 40]. Four studies only performed a quantitative assessment of CPIP and no qualitative assessment with some kind of QOL score [34, 39, 40, 42].

Some trials compared different types of meshes in the two study groups instead of only changing the method of mesh fixation (polypropylene and polyester, and heavyweight and low-weight) [31, 33, 34, 40].

CPIP definition

Other than Fan and colleagues [31] and Esteban and colleagues [35], all authors provided a definition of the primary or secondary outcome parameter CPIP. Three studies referred

Table 1. Characteristics of included studies

First Author Year of publication	Study design	Sample size	Type of meshes	FU (months)	Validated Assesment Tool(s)	CPIP definition	Outcomes	Baseline score	Power analysis
Chatzimavroudis 2014 [34]	RCT	25 25	Parietene™ ProGrip™ HW Polypropylene	3, 12, 24	VAS	IASP	1, 3, 4, 5, 6	No	No
Esteban 2014 [35]	RCT	45 45	Parietene™ ProGrip™ LW polypropylene (Microval1)	12	VAS	NG	1, 3, 6	No	No
Fan 2017 [31]	RCT	22 23	Parietex™ ProGrip™ Polypropylene	1/4, 1, 3, 12, 24, 72	NG	NG	1, 2, 3, 4, 5, 6	No	Yes, but powered for operation time
Jorgensen 2013 [36]	RCT	163 171	Parietene™ ProGrip™ Parietene™ Light	1, 12	VAS, SF-12	VAS >30 at 12 months	1, 3, 4, 6	Yes	Yes
Molegraaf 2017 [37]	RCT	166 164	Parietex™ ProGrip™ Parietex™ Light	1/2, 3, 12, 24	VAS, SF-36, VRS	IASP	1, 2, 3, 4, 6	Yes	Yes
Nikkolo 2014 [38]	RCT	70 75	Parietex™ ProGrip™ Optilene® LP	1/2, 1, 6, 36	SF-36, VAS	Pain during different activities >6 months	1, 2, 4, 5	Yes	Yes
Pierides 2012 [39]	RCT	198 196	Parietene™ ProGrip™ Parietene™ Light	1/2, 12	First 2 weeks VAS	IASP	1, 2, 3, 5, 6	Yes	Yes
Porrero* 2015 [40]	RCT	89 89	Parietene™ ProGrip™ HW Polypropylene	1/4, 12	VAS	VAS ≥4 >3 months	1, 3, 4, 5, 6	No	Yes
Sanders 2014 [41]	RCT	270 287	Parietex™ ProGrip™ Parietene™ Light	1/4, 1, 3, 12	VAS 150, SPS, AAS	VAS 45/150 persisting ≥ 3 months	1, 3, 4, 5, 6	Yes	Yes
Zwaans 2018 [33]	RCT	168 170	Parietene™ ProGrip™ HW Polypropylene	12, 36	VRS, VAS 150	Pain on VRS after 1 year	1, 2, 3, 4, 6	Yes	Yes

Outcome parameters: 1: CPIP; 2: foreign body sensation; 3: recurrence; 4: operation time; 5: acute pain; 6: wound complications (seroma, hematoma, infection).
FU = follow-up; CPIP = chronic postoperative inguinal pain; RCT = randomized controlled trial; HW = heavyweight; LW = lightweight; NG=not given; IASP = International Association for the Study of Pain; VAS = Visual Analog Scale; SPS = Surgical Pain Scale; SF-12 = Short-Form 12; SF-36 = Short-Form 36; AAS = Activity Assessment Scale; VRS = Verbal Rating Scale.
*Bilateral hernia

Table 2. Characteristics of included studies

First Author Year of publication	Type of anesthesia ProGrip versus Sutured mesh	Operation team	Extra stitch	Nerve handling
Chatzimavroudis 2014 [34]	GA	Experienced surgeons	Chastan†	Nerves were identified and preserved
Esteban 2014 [35]	SA	Experienced surgeons	No	Nerves were preserved, but not systematically search
Fan 2017 [31]	17 versus 19 SA 5 versus 4 GA	Experienced surgeons or supervised advanced surgical trainees; $P > 0.05$*	No	Nerves were protected
Jorgensen 2013 [36]	22 versus 16 LA 2 versus 4 SA 77 versus 81 GA	Experienced surgeons	No	Attention was paid to identification and preservation of nerves. Any nerve division was recorded
Molegraaf 2017 [37]	123 versus 119 SA 41 versus 47 GA	Experienced surgeons or supervised surgical trainees; $P > 0.05$*	Chastan†	According to Wijsmuller et al.‡; nerve divisions were recorded
Nikkolo 2014 [38]	1 versus 0 LA 7 versus 11 SA 93 versus 89 GA	Experienced surgeons or supervised surgical trainees; $P > 0.05$*	No	All nerves in the inguinal canal were identified and preserved when possible
Pierides 2012 [39]	63 versus 61 LA + IV sed 34 versus 34 SA 3 versus 5 GA	Experienced surgeons	–	All nerves in the inguinal canal were identified and preserved when possible
Porrero 2015 [40]	RA	Experienced surgeons	No	All nerves in the inguinal canal were identified and preserved when possible
Sanders 2014 [41]	17 versus 20 LA + IV sed 17 versus 16 SA 66 versus 65 GA	Experienced surgeons	Chastan†	According to Wijsmuller et al.‡; nerve divisions were recorded
Zwaans 2018 [33]	133 versus 139 SA 49 versus 42 GA	Experienced surgeons or supervised surgical trainees; $P > 0.05$*	No	All nerves in the inguinal canal were identified and preserved when possible; nerve divisions were recorded

GA = general anesthesia. SA = spinal anesthesia. LA = local anesthesia. IV sed = intravenous sedation. RA = regional anesthesia.

* No significant difference in experience level per study group.

† Chastan: one suture (2-0 polypropylene suture, Prolene®, Ethicon, Johnson & Johnson, New Brunswick, New Jersey) is allowed to be placed superficially to the pubic tubercle to prevent mesh dislocation [44].

‡ Wijsmuller et al.: identify and preserve all three inguinal nerves during open inguinal hernia repair to reduce the risk of chronic groin pain; perform elective resection of a suspected injured nerve [10].

Table 3. Risk of bias

First Author Year of publication	Randomization technique (selection bias)	Allocation concealment	Blinding (performance bias)	Lost to or incomplete FU ProGrip mesh Sutured mesh	Baseline comparable	Jadad scores
Chatzimavroudis 2014 [34]	NG	Sealed envelope	Not blind	0/25 0/25	No baseline score	2
Esteban 2014 [35]	Self-written	Drawing a paper out of a bag	NG	6/45 5/45	No baseline score	2
Fan 2017 [31]	Computer generated	Computer display during operation	Double blind	13/58	No baseline score	5
Jorgensen 2013 [36]	Computer generated	Sealed envelopes	Double blind	4/163 4/171	Yes	5
Molegraaf 2017 [37]	Computer generated	Online message during the operation	Double blind	18/166 16/164	Yes	5
Nikkolo 2014 [38]	Computer generated	Sealed envelopes	Single blind	1/70 2/75	Yes	4
Pierides 2012 [39]	Shuffled envelopes	Sealed envelopes	Double blind	40/198 30/196	Yes	4
Porrero 2015 [40]	Computer generated	Computer-generated list	Not blind	0/89 0/89	No baseline score	3
Sanders 2014 [41]	Computer generated	Sealed envelopes	Single blind	26/270 31/287	Yes	4
Zwaans 2018 [33]	Computer generated	Sealed envelopes	Double blind	14/168 14/170	Yes	5

NG = not given; FU = follow-up

to the definition provided by the International Association for the Study of Pain, which states that "chronic pain is any pain that persists beyond the normal tissue healing time usually taken to be 3 months" [34, 37, 39, 43]. Three other studies used a threshold of a minimal Visual Analog Scale score of ≥30/100 [36], 40/100 [40], or 45/150 [41] after which discomfort was regarded to be pain. Three authors used a time frame of 6 [32] or 12 [33, 36] months.

Meshes

In the study group, patients were treated with either a polypropylene self-gripping mesh (Parietene™ ProGrip™ mesh, 64 percent) or a polyester self-gripping mesh (Parietex™ ProGrip™ mesh, 36 percent). In the control group, different meshes were used (i.e., heavyweight polypropylene [31, 33, 34, 40], low-weight polypropylene [35], Parietene™ Light [36, 39, 41], Parietex™ Light [37], or Optilene® LP [32]). Five studies assessed meshes of the same material, construction, and weight in both the study group and the control

group except for the additional polylactic acid micro-hooks on the study group mesh [35-37, 39].

Chronic pain

CPIP was assessed in all trials and nine of them reported the incidence of chronic pain according to the definition used in their study protocol [31-37, 39, 40]. Incidence rates were analyzed separately for the different moments of follow-up (3, 6–12, 24, 36, and 72 months). Heterogeneity between the trials was very unlikely ($P = .87$, $Q/df < 1$, I^2 0 percent). At all follow-up time points, there was no significant difference in the incidence of CPIP between the self-gripping mesh and sutured mesh group (3 months OR = 0.89, 95 percent confidence interval [CI], 0.48–1.64; 6–12 months OR = 1.00; 95 percent CI, 0.75–1.34; 24 months OR = 1.00; 95 percent CI, 0.39–2.61; 36–72 months OR = 0.77; 95 percent CI, 0.38–1.58). The forest plot is shown in Figure 2A. A subgroup analyses (Figure 2B) accounting for mesh weight and including only studies that used a lightweight mesh in both the study and control group also showed no difference in CPIP rates between the self-gripping mesh and sutured mesh (OR = 0.89; 95 percent CI, 0.68–1.16) [32, 36, 37, 39, 42].

All studies except that of Fan and colleagues [31] presented an assessment of the intensity of chronic pain, but different assessment methods were used. Although all had a visual analog scale score among it, both a 0 to 100 mm and a 0 to 150 mm scale were used. Also, outcomes were presented in different ways hindering a combined analysis. However, none of the studies reported a significant difference in pain intensity scores for CPIP between the two kinds of meshes.

A combined analysis of the quantitative assessment of CPIP, reflecting the influence of CPIP on daily life, was not possible because the four studies that used this kind of measure (SF-12, SF-36, Activity Assessment Scale (AAS)) did not provide full outcomes [36-38, 41]. The separate studies did not find significant differences in the QOL scores between the two meshes, except for Pierides and colleagues who found significantly improved social functioning with the self-gripping mesh [39].

Foreign body sensation

Five studies reported the rate of FBS. There was no heterogeneity among the trials ($P = .86$, $Q/df < 1$ and I^2 0 percent). None of the studies reported a significant difference between groups for the rate of FBS, although the combined analyses showed a trend toward less FBS in the self-gripping mesh group (Figure 3). A subgroup analyses (not shown) corrected for mesh weight also did not reach significance. Incidences were declining during follow-up except among the study population of Zwaans and colleagues who reported a higher incidence after 3 years compared with 1 year postoperatively [33].

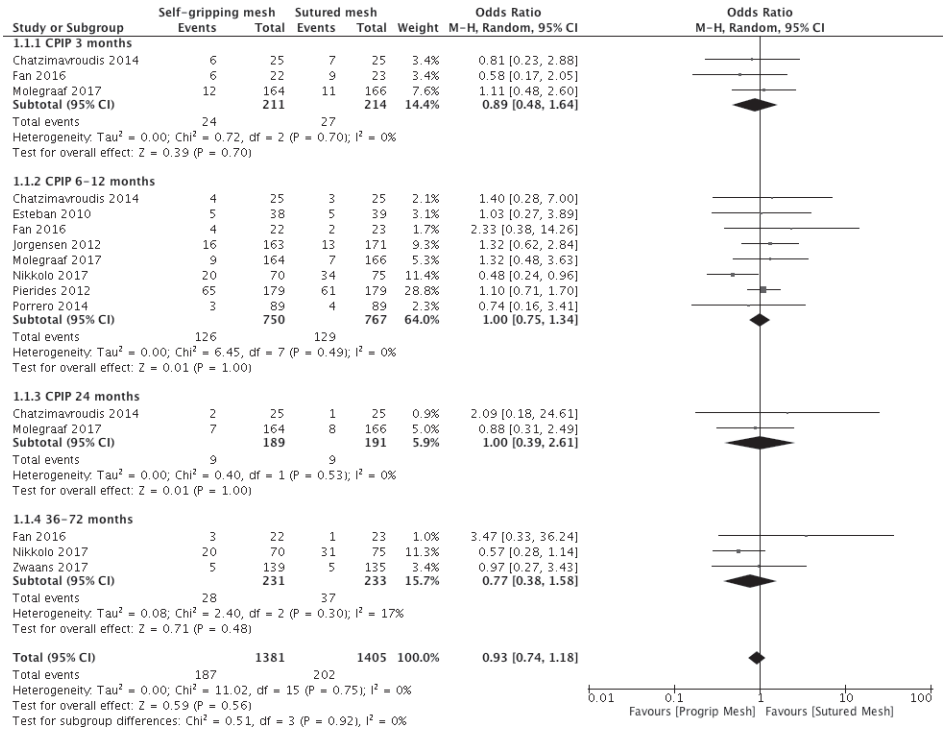

Figure 2A. Incidence of CPIP

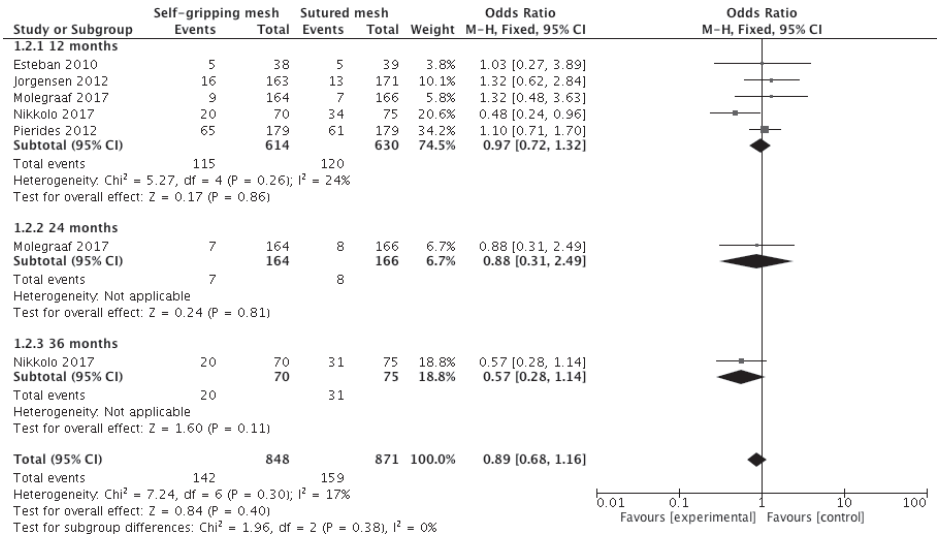

Figure 2B. Incidence of CPIP for lightweight meshes

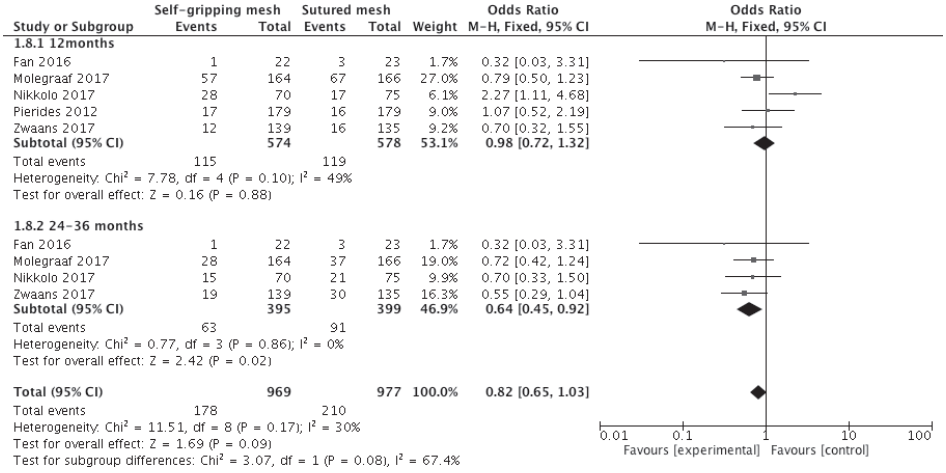

Figure 3. Foreign body sensation

Recurrence

All trials reported recurrence rates after 12 months of follow-up. Two studies also provided recurrence rates after 24 months [34, 37], two after 36 months [32, 33], and one after 72 months [31]. There was no heterogeneity among the trials ($P = .41$, Q/df < 1 and I^2 4 percent). The difference in recurrence rate between the self-gripping mesh group

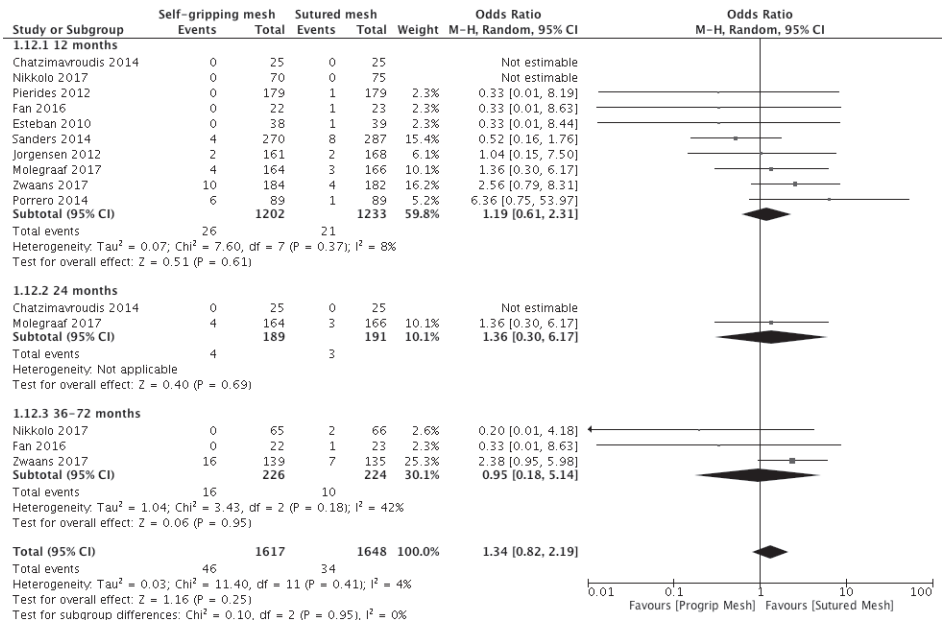

Figure 4. Recurrence rate

and the sutured mesh group was not significant at 12 months (OR = 1.19, 95 percent CI, 0.61–2.31), 24 months (OR = 1.06, 95 percent CI, 0.27–4.17), or 36 months (OR = 0.95, 95 percent CI, 0.18–5.14). A RD analysis showed the same results (12 months: RD = 0.00, 95 percent CI, –0.01 to 0.01; 24 months: RD = 0.00, 95 percent CI, –0.03 to 0.03; Figure 4).

Extra stitch in the self-gripping mesh group

In seven of the ten studies in this meta-analyses, no extra sutures were placed in the self-gripping mesh group [31-33, 35, 36, 39, 40]. The three studies that allowed an extra stitch according to the instructions of Chastan did not perform a subgroup analysis [34, 37, 41, 44].

Nerve handling and paresthesia

Except for Esteban and colleagues [35], all trials tried to identify and preserve the inguinal nerves; four reported the actual rates of nerve identification and resection [33, 36, 37, 41]. The techniques of nerve division of a suspected injured nerve were not clear from the study methods, and numbers were not always recorded (Table 2). Five studies investigated postoperative numbness in the groin region [32, 33, 36, 37, 39]. They found no significant difference in numbness between the two mesh fixation methods and reported comparable rates of nerve resection for the two study groups. Sanders and colleagues performed a subgroup analysis on the impact of nerve resection and mesh fixation method on CPIP and found that when the iliohypogastric nerve was preserved, postoperative pain was significantly lower in the self-gripping mesh group than the sutured mesh group at all follow-up points from discharge to 1 year postoperatively. There was no significant difference between the groups when the iliohypogastric nerve was resected [41]. Zwaans and colleagues reported no relation between hypesthesia or hyperesthesia and previous neurectomy [33].

Operation duration

Five studies reported mean operating time with SD and could contribute to the combined analyses (Figure 5). The mean operating time was significantly shorter in the

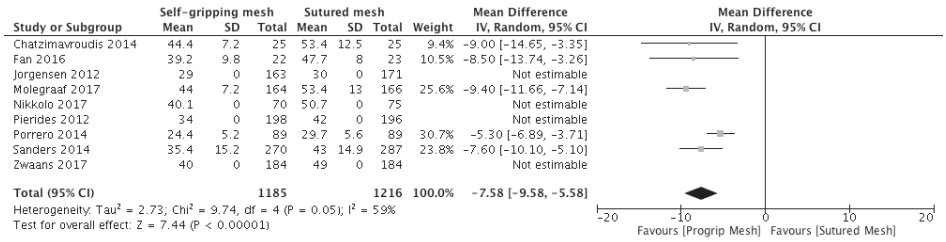

Figure 5. Operation duration

self-gripping mesh group than in the sutured mesh group (mean difference −7.58; 95 percent CI, −9.58 to −5.58). There was a high heterogeneity direction of effect, and the effect size was high and significant (Z = 7.44; $P < .00001$). The trials that could not contribute to the combined calculation confirmed this significant reduction in operating time for the self-gripping mesh. The mean reduction in operation time ranged from 1 to 10 minutes (17 percent) [36, 37].

DISCUSSION

Chronic pain and recurrence are the main complications of inguinal hernia surgery and need to be studied during long-term follow-up. Recently, four large trials published their long-term results comparing the self-gripping mesh with a sutured mesh for open inguinal hernia repair; therefore, a new meta-analysis was performed, focusing on these long-term results [31, 33, 37, 41]. In line with the individual studies, the meta-analysis showed no significant benefits regarding the incidence of CPIP, FBS, and recurrence rate. The main advantage of the self-gripping mesh thus lies in its efficiency, thereby significantly reducing operative times. Previous meta-analyses reported similar outcomes, but the inclusion of studies with short-term follow-up, low inclusion rates, or no randomization limits their conclusions [21-23, 45]. The negative results should be interpreted through patient-related and surgery-related factors as well as methodologic factors.

Before looking at the pathophysiologic factors of CPIP, there are methodologic issues to address when a study fails to reach its primary outcome [46]. First, is there an indication of benefit using a self-gripping mesh? It was hypothesized that a self-gripping lightweight mesh would lower the incidence of CPIP because of avoidance of traumatic suture fixation and reduction in the amount of foreign body reaction because of its material reduced structure. Although this hypothesis is reasonable because of the expected reduction of neuropathic and nociceptive pain stimuli, it is too simplistic. Only the fixation method and material weight of the mesh are changed, but not, for example, the surgical approach, which still needs dissection in a neuralgic plane. Therefore, some will wonder why an open anterior approach should be performed at all, because laparoscopic techniques have shown faster recovery times and a lower chronic pain risk [47, 48]. This disregards the obligation that surgeons have to tailor treatments based on expertise, local/national resources, and patient-related or hernia-related factors. For high-risk inguinal hernia patients with extensive comorbidities or patients with pelvic scarring, an open mesh repair (under local anesthesia) still is the preferred technique as is the case for recurrent inguinal hernia after laparoscopic repair according to the 2016 world guidelines for groin hernia management.

A second contributor in failure to meet the primary outcome may be that studies were underpowered because half of the studies enrolled <100 patients. This meta-analysis should address the limitations of the study size of individual RCTs; however, not all RCTs could contribute to the combined analyses because of differences in outcome measures. The combined analysis for the between-group difference in incidence of CPIP after 6 to 12 months was based on the response of 750 patients in the self-gripping mesh group and 767 patients in the sutured mesh group. After 36 months, these numbers were 231 and 233 per group, respectively, for the incidence and recurrence of CPIP. Hence, the long-term conclusions about CPIP and recurrence rate still are based on relatively low patient numbers, which lowers the strength of the results.

Other questions to be asked are whether the trials had deficiencies in their treatment regimen, the studied population, and the trial conduct. The latter is a focus of concern for two studies because they had an inadequate randomization technique, no blinding, no power calculations, and no baseline score [34, 35]. In addition, two other studies did not measure a baseline pain score, although preoperative pain is a well-known risk factor for CPIP [31, 40]. Thereafter, four studies did not perform a qualitative assessment of CPIP to evaluate the influence of CPIP on daily life and well-being [34, 35, 39, 40].

Meta-analysis should be conducted when a group of studies is sufficiently homogeneous in terms of subjects involved, interventions, and outcomes to minimize performance and measuring bias so to provide a meaningful summary. This was the reason for including only RCTs that compared the two meshes for a Lichtenstein hernia repair in adult patients with a primary hernia. Recurrent hernias were excluded because this is a risk factor for the development of CPIP. Although the inclusion criteria were strict, there was still heterogeneity among the trials in this meta-analysis, caused by clinical and methodologic variation. First, the hernia repairs were performed by different surgeons with different levels of experience (trainees, general surgeons, hernia specialists). It is known that there is a substantial disparity between the state-of-the-art Lichtenstein repair and its application in general practice, especially with respect to steps that are suggested to play a role in the origin of chronic groin pain [49]. Other clinical variations that could modify the intervention effect were different types of anesthesia (spinal, general, regional), use of different meshes in the conventional Lichtenstein group (both heavyweight and lightweight), differences in the method of nerve handling, timing of follow-up, and whether an extra stitch was allowed for the self-gripping mesh. However, this clinical heterogeneity reflects daily practice and will therefore be of less influence on the generalizability of the results. Methodologic variation was caused by the variable definitions and assessment methods for CPIP and the unstandardized way of presenting outcomes. Thus, comparisons could be made for between-group differences in CPIP

rates, but not for incidence rates of CPIP overall or special subgroups. This methodologic heterogeneity is a common problem in hernia research and hinders comparison of outcomes to draw firm conclusion [50-52].

Regarding surgical factors, there are several discussions specific to self-gripping mesh. First, there is discussion on the influence of the extra stitch in the self-gripping mesh group; this stitch is placed near the neuralgic pubic tubercle to prevent a medial recurrence. The RCTs in this meta-analysis did not perform subgroup analyses on whether the stitch induced more CPIP. However, a recent evaluation of the Herniamed register did not find a correlation. The same applies to recurrence rates [53]. From this, it may be concluded that although it seems to have no influence on CPIP rates, avoidance of the single stitch could be recommended in this neuralgic place, especially in the case of small or medium size hernias. A second consideration is the influence of the additional polylactic acid micro-hooks. It is possible that the presence of micro-hooks and their disintegration exaggerates the foreign body reaction, leading to inflammatory damage to surrounding nerves. This was not seen in experimental models, and human studies are not available [54]. However, because CPIP and FBS rates are not increased for the microgrip-added meshes, the inflammatory reaction to these micro-hooks seems be of less influence. Because the foreign body reaction decreased over time, however, there may be a relation with the resorption of the micro-hooks, which are completely resorbed at 12 months postoperatively. Zwaans and colleagues [33] were the only group to report increased FBS during follow-up, especially for their group sutured with heavyweight mesh. Thereafter, a possible augmented inflammatory reaction may be counterbalanced by the lightweight nature of the self-gripping mesh, because lightweight meshes are known to induce less fibrosis and hence less FBS. This brings us to the third factor of discussion, the influence of the lightweight macroporous structure of the ProGrip™ mesh. This was supposed to augment the pain-reducing effect of the atraumatic fixation, but they together failed to do so.

Nerve injury during dissection or mesh placement and fixation (or afterward by the inflammatory reaction), is regarded to be one of the major causative factors for CPIP; therefore, nerve handling is important to report [55]. Almost all studies reported trying to identify and protect the nerves and to resect nerves that were accidentally damaged or in the way of mesh placement, but only four studies reported identification and resection rates [33, 36, 37, 41]. These were comparable for the self-gripping and sutured mesh groups and do not seem to influence the between-group results. Sanders and colleagues and Zwaans and colleagues performed subanalyses of the effect of neurectomy and found no significant influence of neurectomy on the rates of CPIP or an altered sensation in the groin [33, 41].

Finally, patient-related risk factors need to be addressed. Known risk factors for the development of CPIP are moderate to severe preoperative pain >1 month, psychologic vulnerability, female sex, younger age, and genetic predisposition. They often are underestimated compared with surgical factors, but there is increasing awareness of the individual variance in foreign body reaction and sensory disturbances that may or may not lead to CPIP. Hence, these patient-related risk factors need to be considered in the indication for surgery, which in the future can be facilitated with tests like genotyping and quantitative sensory testing [9, 55-57].

In this meta-analysis we did not address acute postoperative pain because we wanted to report the long-term results of self-gripping mesh. However, acute postoperative pain is one of the strongest and most consistent risk factors for CPIP, urging an approach of so-called "preventive or pre-emptive analgesia" by the use of preoperative local anesthesia [58-60].

Several conclusions can be made. First, self-gripping mesh has results comparable to sutured mesh regarding the incidence of CPIP and recurrence. Second, the self-gripping mesh does not resolve CPIP; however, conclusions on long-term results still are based on relatively small patient numbers. Third, there is high heterogeneity in CPIP definition, assessment, and presentation of outcomes, making it hard to compare incidence rates. There must be a call for a more uniform methodology. Finally, the main advantage of the self-gripping mesh is its efficiency, with consistently significantly reduced operation times. To date, no cost-effectiveness study has been performed, but when the reduction time ≤17 percent is translated into better utilization of operating theatre resources and manpower, the higher price of the mesh could be amply compensated.

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SUPPLEMENTARY DATA: APPENDIX 1

Search strategy

Inguinal hernia open self-adhesive versus sutured mesh

Embase	262	258
MEDLINE ovid	163	18
Web of science	157	56
Scopus	292	83
Cochrane	43	1
CINAHL EBSCOhost	5	0
Google scholar	100	48
Total	**1021**	**464**

Embase: 262

('inguinal hernia'/exp OR hernia/de OR 'herniorrhaphy'/de OR hernioplasty/de OR (((inguinal* OR groin*) NEAR/6 herni*) OR (hernia* NEAR/6 (repair* OR surg* OR operat*)) OR herniorrhap* OR hernioplas* OR herniaplas* OR lichtenstein* OR (liechtenstein* NEAR/3 (procedure* OR operat* OR surg* OR method* OR technique*))):ab,ti) AND ('adhesive agent'/de OR (adhesive* OR selfadhesive* OR Self-grip* OR progrip OR sutureless* OR suture-less*):ab,ti) AND ('suture'/exp OR 'suturing method'/de OR (sutur* OR tacking):ab,ti)

MEDLINE Ovid: 163

("Hernia, Inguinal"/ OR hernia/ OR "Herniorrhaphy"/ OR (((inguinal* OR groin*) ADJ6 herni*) OR (hernia* ADJ6 (repair* OR surg* OR operat*)) OR herniorrhap* OR hernioplas* OR herniaplas* OR lichtenstein* OR (liechtenstein* ADJ3 (procedure* OR operat* OR surg* OR method* OR technique*))).ab,ti.) AND ("Adhesives"/ OR (adhesive* OR selfadhesive* OR Self-grip* OR progrip OR sutureless* OR suture-less*).ab,ti.) AND ("Sutures"/ OR "Suture Techniques"/ OR (sutur* OR tacking).ab,ti.)

CINAHL EBSCOhost: 5

(MH "Hernia, Inguinal" OR MH hernia OR MH "Herniorrhaphy" OR TI (((inguinal* OR groin*) N5 herni*) OR (hernia* N5 (repair* OR surg* OR operat*)) OR herniorrhap* OR hernioplas* OR herniaplas* OR lichtenstein* OR (liechtenstein* N2 (procedure* OR operat* OR surg* OR method* OR technique*))) OR AB (((inguinal* OR groin*) N5 herni*) OR (hernia* N5 (repair* OR surg* OR operat*)) OR herniorrhap* OR hernioplas* OR herniaplas* OR lichtenstein* OR (liechtenstein* N2 (procedure* OR operat* OR surg* OR method* OR technique*)))) AND (MH "Adhesives" OR TI (adhesive* OR selfadhesive* OR Self-grip* OR

progrip OR sutureless* OR suture-less*) OR AB (adhesive* OR selfadhesive* OR Self-grip* OR progrip OR sutureless* OR suture-less*)) AND (MH "Sutures" OR MH "Suture Techniques" OR TI (sutur* OR tacking) OR AB (sutur* OR tacking))

Cochrane: 43

((((inguinal* OR groin*) NEAR/6 herni*) OR (hernia* NEAR/6 (repair* OR surg* OR operat*)) OR herniorrhap* OR hernioplas* OR herniaplas* OR lichtenstein* OR (liechtenstein* NEAR/3 (procedure* OR operat* OR surg* OR method* OR technique*))):ab,ti) AND ((adhesive* OR selfadhesive* OR Self-grip* OR progrip OR sutureless* OR suture-less*):ab,ti) AND ((sutur* OR tacking):ab,ti)

Web of science: 157

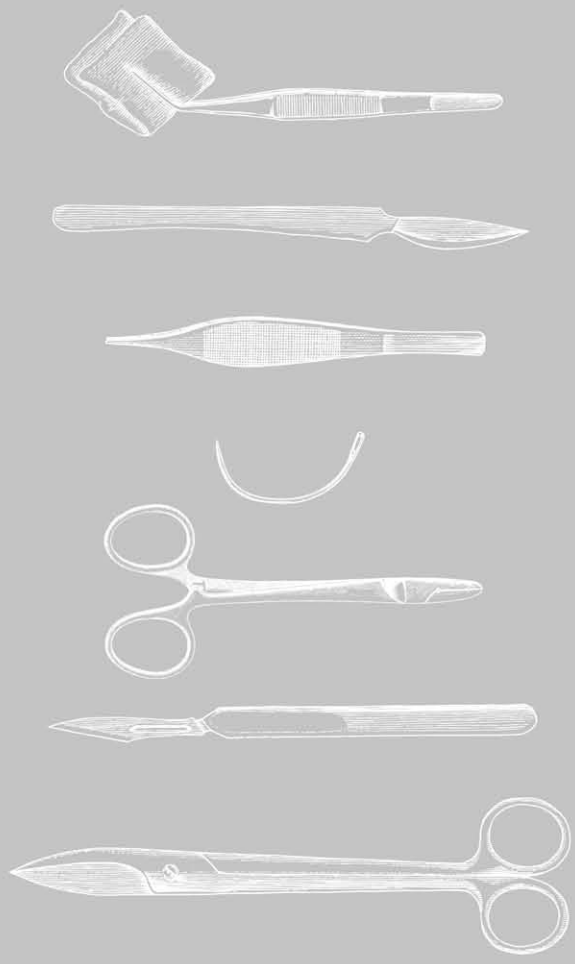
TS=(((((inguinal* OR groin*) NEAR/5 herni*) OR (hernia* NEAR/5 (repair* OR surg* OR operat*)) OR herniorrhap* OR hernioplas* OR herniaplas* OR lichtenstein* OR (liechtenstein* NEAR/2 (procedure* OR operat* OR surg* OR method* OR technique*)))) AND ((adhesive* OR selfadhesive* OR Self-grip* OR progrip OR sutureless* OR suture-less*)) AND ((sutur* OR tacking)))

Scopus: 292

TITLE-ABS-KEY(((((inguinal* OR groin*) W/5 herni*) OR (hernia* W/5 (repair* OR surg* OR operat*)) OR herniorrhap* OR hernioplas* OR herniaplas* OR lichtenstein* OR (liechtenstein* W/2 (procedure* OR operat* OR surg* OR method* OR technique*)))) AND ((adhesive* OR selfadhesive* OR Self-grip* OR progrip OR sutureless* OR suture-less*)) AND ((sutur* OR tacking)))

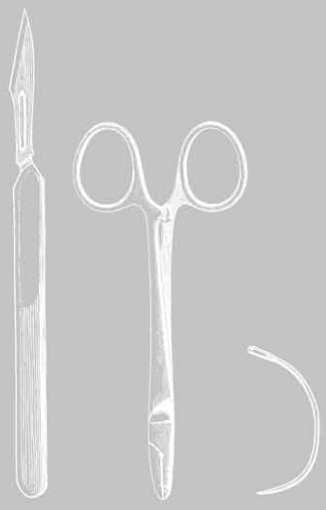
Google scholar: 100

"inguinal|groin hernia"|"hernia repair|surgery|operation"|herniorrhapy|hernioplasty|herniaplasty|"lichtenstein procedure|operation|surgery|method|technique" selfadhesive|"self adhesive"|"Self grip|gripping"|progrip|sutureless|"suture less" suture|sutures



10

An international consensus algorithm for management of chronic postoperative inguinal pain



J.F.M. Lange, R. Kaufmann, A.R. Wijsmuller,
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Hernia 2015 Feb;19(1):33-43

ABSTRACT

Introduction

Tension-free mesh repair of inguinal hernia has led to uniformly low recurrence rates. Morbidity associated with this operation is mainly related to chronic pain. No consensus guidelines exist for the management of this condition. The goal of this study is to design an expert-based algorithm for diagnostic and therapeutic management of chronic inguinal postoperative pain (CPIP).

Methods

A group of surgeons considered experts on inguinal hernia surgery was solicited to develop the algorithm. Consensus regarding each step of an algorithm proposed by the authors was sought by means of the Delphi method leading to a revised expert-based algorithm.

Results

With the input of 28 international experts, an algorithm for a stepwise approach for management of CPIP was created. Twenty-six participants accepted the final algorithm as a consensus model. One participant could not agree with the final concept. One expert did not respond during the final phase.

Conclusion

There is a need for guidelines with regard to management of CPIP. This algorithm can serve as a guide with regard to the diagnosis, management, and treatment of these patients and improve clinical outcomes. If an expectative phase of a few months has passed without any amelioration of CPIP, a multidisciplinary approach is indicated and a pain management team should be consulted. Pharmacologic, behavioral, and interventional modalities including nerve blocks are essential. If conservative measures fail and surgery is considered, triple neurectomy, correction for recurrence with or without neurectomy, and meshoma removal if indicated should be performed. Surgeons less experienced with remedial operations for CPIP should not hesitate to refer their patients to dedicated hernia surgeons.

INTRODUCTION

With the success of tension-free mesh-based inguinal repair, the incidence of chronic postoperative inguinal pain (CPIP) has surpassed that of recurrence after open and laparoscopic herniorrhaphy. Due to different definitions of CPIP the reported incidences of CPIP ranges from 1 to 63 percent [1-7]. Significant CPIP affects daily life of 5 to 10 percent of patients [8, 9]. Quality of life has become the most relevant outcome of inguinal hernia repair. Considering the high prevalence of CPIP, a systematic approach is needed for optimal management.

In 2008, two international consensus conferences led by widely published and lectured panelists formally defined CPIP as new or different quality of pain (if pain existed prior to hernia repair) arising as a direct consequence of a nerve lesion or a disease affecting the somatosensory system after inguinal hernia repair [10]. Common sources of CPIP were considered to include hernia recurrence, nociceptive problems (tissue inflammation, foreign material, meshoma) and neuropathic causes (direct nerve injury or perineural scarring). There is no discrete distinction between neuropathic and nociceptive pain, and the diagnosis is further complicated by excitatory coupling between sympathetic and afferent nociceptive nerve fibers, neuroplasticity, deafferentation hyperalgesia, and pain centralization, in addition to economic, social, genetic, and patient-related factors. Patients with neuropathic pain classically demonstrate hypo- or hyperesthesia, allodynia, and paresthesia. While the majority of these patients can be managed with pharmacologic, interventional, and behavioral measures, operative management is sometimes necessary. Complicating the management of this challenging patient population, there is no universally agreed consensus upon pathophysiology or treatment for CPIP. In 1999, Heise and Starling proposed the new syndrome of mesh-related inguinodynia [11]. It is, however, important to recognize that the problem of CPIP preceded mesh-based repairs and, in their report, CPIP after tissue-based repairs was far more common. Although ultrastructural histologic changes of neural tissue in contact with mesh material have been clinically and experimentally described, the presence of a mesh, per se, is not causative [12-14]. In 2004, Amid described potential risk factors for developing acute pain after open mesh repair: taut fixation of the mesh instead of fixation with some laxity, peri-ostial sutures, and herniotomy instead of repositioning of the hernia sac [15].

In CPIP, neuropathic pain predominates over nociceptive or visceral pain. Amid emphasized the role of iatrogenic damage to one or more of the three inguinal nerves from direct damage due to direct contact of mesh with nerves, unrecognized nerve injury, or nerve entrapment from suture or mesh fixation as the primary cause of neuropathy. The central causative role of the three inguinal nerves in CPIP is supported by the favorable

results of therapeutic neurectomy [16-18]. Structural changes of the mesh as it contracts and fibroses may lead to nociceptive pain or nerve entrapment by wrinkling of the mesh, representing a so-called meshoma [19]. Mesh excision has reduced CPIP in patients in which a meshoma was identified based on clinical and radiographic examination.

There are several options for the treatment of CPIP often dictated by the expertise of the specialist caring for a patient. Conservative treatment modalities include non-steroidal anti-inflammatory agents, neuropathic medications, opioids, topical anesthetics, behavioral therapy, and physical therapy. Non-surgical interventional treatment includes local nerve blocks, steroid injections, cryotherapy, alcohol or phenol injection, transcutaneous nerve stimulators, and neurolysis [20]. These methods may serve both diagnostic and therapeutic roles and can aid in the identification and localization of the involved nerves. Operative management is reserved for cases refractory to conservative measures and consists of variations of groin exploration, mesh removal, and neurectomy [11, 14, 21].

Despite numerous publications addressing treatment of CPIP, no consensus guidelines regarding its management currently exist. Considering the high prevalence of CPIP, the magnitude of the problem is too great to depend solely upon dedicated hernia surgeons for management. Most hernia repairs are performed by general surgeons and the initial management of CPIP is done by a general surgeon or primary care physician. Many patients can be treated without reoperation and early intervention will help to prevent centralization of pain. The goal of this project was to develop a consensus algorithm with a stepwise approach to patients with CPIP, summarizing best-available practices based on the expertise of international specialists managing this condition.

METHODS

The objective of this study was the development of a consensus algorithm based on the opinion of an international group of surgeons considered experts on inguinal hernia surgery. Experts invited to participate in this study were:

1. Surgeons with one or more publications on surgical aspects regarding CPIP.
2. Chairman of study sessions on CPIP in major international hernia congresses in 2010, 2011 and 2012 (EHS Istanbul, RICH Rotterdam, AHS New York).
3. Surgeons identified as experts by peers in the first two groups.

An initial algorithm proposed by the authors was presented to this group for commentary. All inputs were implemented into a revised version of the algorithm. This second algorithm was the focus of discussion and debate during an expert meeting on CPIP during the 2012 combined congress of the American (AHS) and European (EHS) Hernia Societies in New York leading to a revised third version.

In the subsequent stage of the study, consensus regarding each step of the algorithm was sought based on the Delphi method in which anonymous and ongoing responses from the predefined group of surgeons led to a decision that is representative of this "collective intelligence" [22]. All consultants were asked to anonymously respond to each step of the algorithm. Steps that did not have 100 percent agreement were submitted back as a multiple choice survey in which all responses of the expert group were incorporated as possible answers. It was agreed that the answer with the most votes would be the consensus response for that respective step. The final version distilled from this process was sent to all experts for review. Three response options were possible:

1. Total agreement
2. Partial agreement but approval of the flowchart for practical use
3. Disagreement and rejection

RESULTS

Forty-seven experts were identified and invited to participate in this study. Of these 47 experts, 28 responded and agreed to participate. From these 28 consultants, 15 participants provided additional comments and feedback on the initially proposed algorithm. Responses were collected and analyzed, with identification of common and conflicting viewpoints summarized in a second iteration.

The second version did not differ significantly with regard to the basic structure of the algorithm. The algorithm starts with the two categories of patients who require medical attention: patients with pain immediately after inguinal hernia surgery (acute pain) and patients who develop pain later in their course. This second group is subdivided in two categories: patients who complain in the early postoperative phase and those who have persistent pain or develop pain after some months. Acute, excruciating pain is considered an indication for early re-exploration. If postoperative pain develops later in the course of recovery or if symptoms of pain persist beyond the normal postoperative recovery period, an expectative phase of 3 months is indicated. During this time, analgesics and conservative measures are recommended.

If pain persists after 3 months, recurrence should be excluded based on physical examination. In cases of clinical recurrence, operative correction is indicated, with or without triple neurectomy depending on the type of pain (neuropathic or nociceptive). If physical examination does not demonstrate recurrence, ultrasonography is recommended as the initial diagnostic procedure of choice to exclude occult recurrence or meshoma. If ultrasonography is unrevealing, cross-sectional imaging with MRI might detect potential recurrence, meshoma, or other pathologies.

If recurrence is identified and associated with pain, open anterior repair is recommended in conjunction with triple neurectomy if accompanied by neuropathic pain. If the initial hernia operation was an anterior repair (Lichtenstein, Shouldice, Bassini, McVay), laparoscopic surgery is not the primary recommended modality because placement of mesh in the preperitoneal space may lead to additional neuropathy of the preperitoneal nerves (main trunk of the genitofemoral nerve and the preperitoneal segment of its genital branch). This is contrary to the recommendations for simple recurrence without neuropathic pain which would favor a laparoscopic remedial operation. If laparoscopic repair of recurrence fails to address the pain, it would not be possible to differentiate whether the source of pain is from neuropathy of nerves in front or behind the transversalis fascia. If the initial hernia operation was a posterior repair (TEP, TAPP, PHS, TIPP, and other preperitoneal repairs), anterior repair is recommended with open "extended" triple neurectomy including the genitofemoral nerve trunk if needed. Laparoscopic repair for recurrence may be performed but neuropathic pain if present must be addressed with retroperitoneal triple neurectomy proximal to the site of neuropathy.

If no anatomical pathology is identified, the surgeon should refer the patient to a pain management team familiar with CPIP. In addition to pharmacologic and behavioral treatment, interventions play a major role in the diagnosis and treatment of CPIP. Nerve blocks of the ilioinguinal, iliohypogastric, and genital nerves are of significant importance as they serve both a diagnostic and therapeutic role. If conservative or interventional modalities are unsuccessful or not durable, surgical intervention should be offered. If the original operation involves mesh in the preperitoneal space from open or laparoscopic repair, open extended triple neurectomy to resect the genitofemoral trunk or laparoscopic retroperitoneal triple neurectomy is indicated [18].

With the second iteration, all participating experts were independently surveyed. Consensus was reached on 19 of the 28 steps in this algorithm. There were divergent responses on nine of the 28 steps. The authors defined nine multiple choice questions based on the submitted responses. Participants of the expert panel agreed that the majority response would be selected in the algorithm.

MULTIPLE CHOICE QUESTIONS ABOUT ALGORITHM ON CPIP

1. **When a patient presents with postoperative pain after inguinal hernia surgery without any signs of overt pathology like recurrence, abscess, hematoma etc., how long do we want to stay expectative after operation?**
   A) 0–3 months
   B) 3–6 months
   C) 6–9 months
   D) 9–12 months

2. **What should we do during the expectative phase?**
   A) Only watchful waiting, possibly with "basic analgesics"
   B) Already try to treat with specific analgesics such as Neurontin or Lyrica
   C) Already consult pain team
   D) Already consult neurologist

3. **How to differentiate between neuropathic and nociceptive pain?**
   A) The surgeon can differentiate this based on his physical examination and experience
   B) The surgeon should use the McGill-pain questionnaire
   C) The surgeon should use the CRPS-score
   D) Differentiation should be done by a dedicated anesthesiologist
   E) Differentiation should be done by a neurologist
   F) There is no need to differentiate between nociceptive and neuropathic pain; pain=pain and differentiation has no implication for the algorithm

4. **To evaluate if the patient has a recurrence**
   A) Physical examination is enough and as reliable as imaging
   B) Ultrasonography is the first choice of imaging, like in the current algorithm
   C) Ultrasonography should be bypassed by MRI directly
   D) Herniography is as good as ultrasonography as a first choice of imaging

5. **When recurrence is diagnosed as the cause of pain (no obvious consensus 52 versus 48%)**
   A) Repair is sufficient
   B) Repair should always be accompanied by triple neurectomy
   C) Repair should be accompanied by triple neurectomy only if there is neuropathic pain

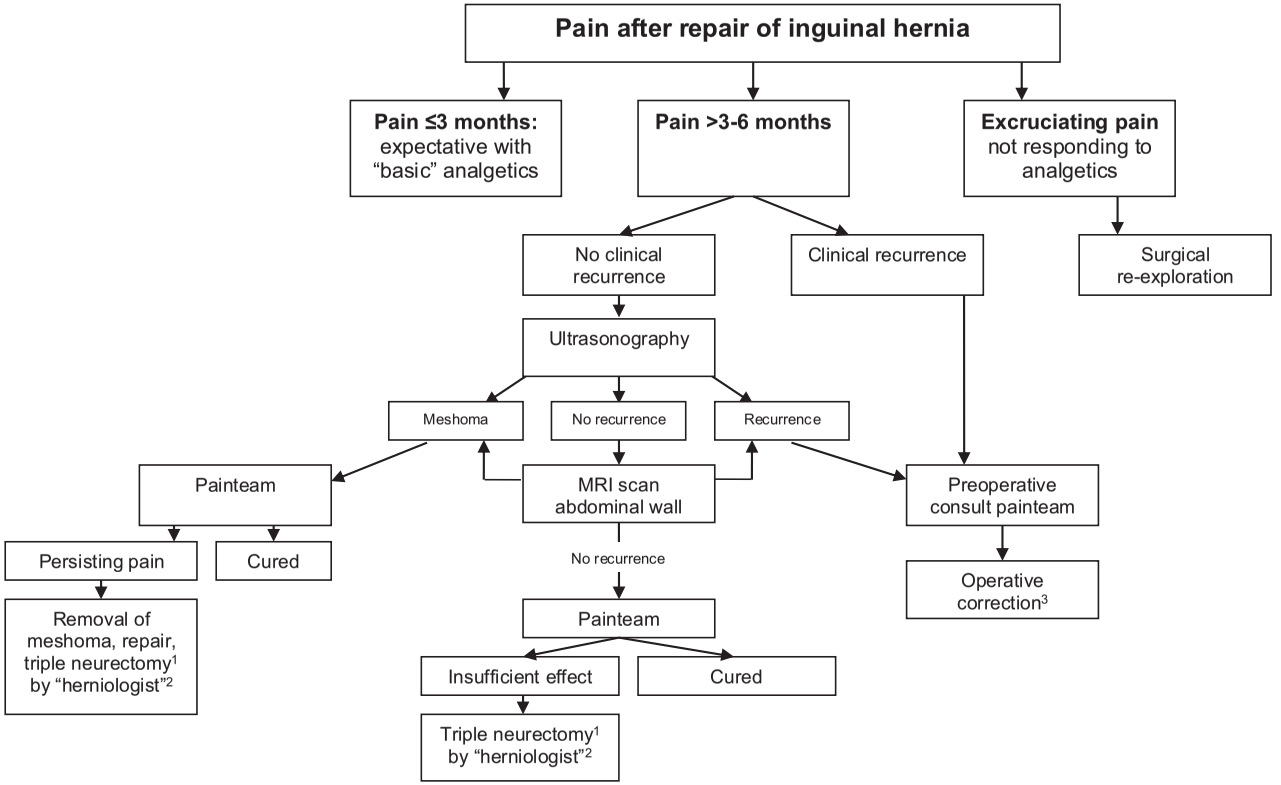
6. **When re-operation is indicated in case of postoperative pain**
   A) The pain team should be consulted for elaborate peri-operative pain management in case of pain due to recurrence
   B) The pain team should be consulted for elaborate peri-operative pain management in case of neuropathic pain
   C) The pain team should be consulted for elaborate peri-operative pain management in case of meshoma
   D) The pain team should be consulted for elaborate peri-operative pain management in all cases
   E) The pain team is already involved because re-operation should be recommended by the pain team

7. **When a meshoma is diagnosed with ultrasonography**
   A) You do not have to verify this by MRI as ultrasonography is sufficient to diagnose meshoma
   B) MRI should always be performed to verify this

8. **Re-operation in case of pain should**
   A) Always be performed by an expert/herniologist
   B) Can be performed by a general surgeon
   C) Can be performed by a general surgeon only in case of recurrence (without neuropathic pain)

9. **Local infiltration in diagnostic or therapeutic setting**
   A) Should be performed by the pain team
   B) Should be performed by the surgeon

Figure 1. Most-voted answers are underlined



1 Including proximal genitofemoral nerve-neurectomy in case of chronic pain after open or laparoscopic preperitoneal mesh technique
2 Open or endoscopic procedure
3 In case of neuropathic pain anterior correction in combination with triple neurectomy is optional

Figure 2. International consensus algorithm for management of chronic postoperative inguinal pain

Twenty-one of the original 28 experts participated in the Delphi method stage of algorithm development. The nine questions with divergent opinions are listed in Figure 1 with the majority answer underlined. For eight out of nine questions, there was an answer with a vast majority. Question No. 5 had equal responses for answer A and C and the responses were integrated to represent both opinions. The majority responses of the 23 remaining experts led to the final iteration of the algorithm (Figure 2). Of the 28 participating experts, 26 accepted the consensus algorithm: 12 totally agreed with the algorithm, 14 agreed despite a few minor details with overall approval of the algorithm. One expert could not agree with the final concept. One expert did not respond during the final phase.

DISCUSSION

Recurrence has become a lesser issue in modern inguinal hernia surgery owing to the success of tension-free mesh-based repairs. Correspondingly, quality of life and the avoidance of CPIP are considered primary outcomes of elective inguinal herniorrhaphy. The high incidence of CPIP has become a significant factor in the consideration of a "watchful waiting" approach for elderly and asymptomatic inguinal hernia patients. CPIP has increasingly been identified as an important outcome of clinical trials and its prevention and management have become prominent topics in inguinal hernia research.

The International Association for the Study of Pain (IASP) broadly classifies postherniorrhaphy inguinodynia into nociceptive and neuropathic pain [23]. Nociceptive pain is caused by activation of nociceptors by nociceptive molecules. It is caused by tissue injury or inflammatory reaction. Neuropathic pain is caused by direct nerve injury. It is characterized by inguinodynia with radiation to the scrotum/femoral triangle, paresthesia, allodynia, hyperpathia, hyperalgesia, hyperesthesia, hypoesthesia, and positive Tinel's sign. There is no precise demarcation between nociceptive and neuropathic pain, and the complexity of diagnosis is increased by social, genetic, patient, and psychological factors.

In-depth groin neuroanatomy knowledge is of paramount importance to prevent and treat postherniorrhaphy chronic pain. Knowledge of the original operative technique and detailed evaluation of the original operative report help to determine the likely etiologies of pain and the nerves at risk. The diagnosis is very much dependent on a detailed history and physical examination. Physical exam findings are dependent on the neuroanatomic course of the three inguinal nerves, their respective dermatomes, and the presences of mesh or recurrence. Tools including pre-operative dermatomal map-

ping [18], quantitative sensory testing, imaging, and diagnostic interventions (nerve blocks) help to characterize the etiology and direct treatment.

Treatment of the patient with CPIP remains a challenge and several different therapeutic strategies have been proposed. Conservative treatment with pharmacologic, topical, behavioral, and expectant measures is advocated in all patients. Interventional techniques including nerve infiltration, blockade, neuromodulation, and ablative techniques have all been used in the management of CPIP. Results of selective or triple neurectomy of one or more of the three inguinal nerves and resection of meshoma have been published with practical efficacy [15, 19]. Despite this volume of information, no consensus on the management of CPIP has been published and high-level evidence on the management of CPIP is lacking. Triple neurectomy described by Amid in 1995 is currently an accepted surgical treatment for neuropathic pain refractory to conservative measures [10].

While some surgeons have had success with selective neurectomy, triple neurectomy is generally recommended due to neuroanatomic and technical considerations. There is significant cross-innervation between the inguinal nerves and reoperating in the scarred field becomes increasingly more difficult and morbid for subsequent remedial operations. Extensive study of the anatomical variation of these nerves from the retroperitoneum to its terminal branches in the inguinal canal demonstrates significant variation in the number, location, and cross-innervation of these three nerves. In addition, visual identification of the nerve at the time of reoperation cannot adequately exclude injury. Electron micrography of grossly normal nerves resected at the time of triple neurectomy often demonstrates ultrastructural nerve damage. It is often challenging to identify nerves in the scarred field. Reoperation, especially with concurrent mesh removal, carries the added risk of recurrence, vascular injury, testicular compromise, and visceral injury. Best-available evidence suggests that triple neurectomy has higher efficacy than selective neurectomy.

Open or endoscopic methods are available to perform triple neurectomy depending on the type of prior repair, the presence of recurrence or meshoma, and if orchialgia is present. Open triple neurectomy involves re-exploration through the prior operative field and is indicated when recurrence or meshoma is present or for treatment of patients that originally underwent anterior repair without preperitoneal placement of mesh. The ilioinguinal nerve is identified lateral to the internal ring, between the ring and the anterior superior iliac spine. The iliohypogastric nerve is identified within the anatomical cleavage between the external and internal oblique aponeurosis. The nerve is then traced proximally within the fibers of the internal oblique muscle to a point lateral to the field of the original hernia repair. Failure to do so may leave the injured intramus-

cular segment of the nerve behind. The inguinal segment of the genital branch of the genitofemoral nerve can be identified adjacent to the external spermatic vein between the cord and the inguinal ligament and traced proximal to the internal ring where it is severed. Alternatively, the nerve may be visualized within the internal ring through the lateral crus of the ring. Standard triple neurectomy does not address neuropathy of the preperitoneal nerves (main trunk of genitofemoral nerve and preperitoneal segment of its genital branch) after open or laparoscopic preperitoneal repair. In these cases, an "extended" triple neurectomy may be performed dividing the floor of the inguinal canal to access the genitofemoral trunk in the retroperitoneum directly over the psoas muscle.

Nerves should be resected proximal to the field of original hernia repair. Although there are no specific data available, ligation of the cut ends of the nerves to avoid sprouting and neuroma formation and intramuscular insertion of the proximal cut end to keep the nerve stump away from scarring within the operative field are recommended [10]. Neurolysis, which does not address ultrastructural changes of nerve fibers, is not recommended. Simple removal of entrapping sutures or fixating devices while leaving the injured nerves behind is not recommended and does not address irreversible damage to the nerve.

Endoscopic retroperitoneal triple neurectomy allows for access proximal to all potential sites of peripheral neuropathy overcoming many of the limitations of open triple neurectomy after laparoscopic or open preperitoneal repair [18, 24, 25]. Prior preperitoneal laparoscopic or open procedures may damage or entrap the nerve in the preperitoneal position making proximal access to the three nerves a challenge. Endoscopic access to these three nerves in the retroperitoneum allows for definitive identification of the ilioinguinal and iliohypogastric nerves at the L1 nerve root overlying the quadratus lumborum muscle and the genital and femoral branches of the genitofemoral nerve exiting from the psoas muscle. The operative technique is safe and proximal to the field of scarring from all prior inguinal hernia repairs. Complications including deafferentation hypersensitivity are a significant concern. In addition to numbness in the groin region and flank, patients undergoing proximal neurectomy may develop bulging of the lateral abdominal wall because of the additional loss of motor function of the iliohypogastric and ilioinguinal nerve (innervation of transversus abdominis muscle). In the absence of recurrence or meshoma, endoscopic management may be the preferred technique for definitive operative management of CPIP. Selection of appropriate patients is most important and management is best deferred to experienced hernia specialists.

The consensus recommendation is that re-operation for CPIP should be performed only by experienced surgeons [10].

CPIP caused by recurrence is a less common etiology in these predominantly neuropathic pain syndromes. However, it still represents a cause of CPIP largely to be excluded by physical examination and imaging. This contrasts with neuropathic pain, for which there are no reliable tests and can be considered a diagnosis *per exclusionem*. Ultrasound is recommended as the first diagnostic test for recurrence (and meshoma) because of costs and facility. It becomes more complicated if there is a possible combined origin for pain: recurrence and neuropathic pain. In case of the combination of recurrence and neuropathic pain it is important to consider the prior technique of hernia repair and the location of the mesh as this will dictate the ideal approach for neurectomy and the subsequent repair (Figure 3). In case of initial anterior repair, anterior to the transversalis fascia (i.e., Lichtenstein procedure, Shouldice, tissue repairs), a standard open triple neurectomy including resection of the intramuscular segment of the iliohypogastric nerve should be performed [26]. Laparoscopic repair of the recurrence can potentially lead to neuropathy of the preperitoneal nerves (main trunk of genitofemoral nerve and preperitoneal segment of its genital branch) and when combined with open triple neurectomy, it would not be possible to differentiate between neuropathy of nerves in front and behind the transversalis fascia as source of pain after this second operation. An alternative is to perform an endoscopic hernia repair and an endoscopic triple neurectomy. In case of recurrence and neuropathic pain after preperitoneal mesh repair (i.e., TEP, TIPP, TAPP), the recurrence should be corrected with an anterior technique (preferable Lichtenstein procedure) to avoid the prior scarred field. However, a triple neurectomy via this approach would not be useful as the potential damaged nerves are located behind the transversalis fascia. As a result the anterior correction should ideally be combined with an endoscopic triple neurectomy in the "untouched" plane proximal to the preperitoneal mesh. A remedial laparoscopic operation is an alternative approach with proximal neurectomy if indicated.

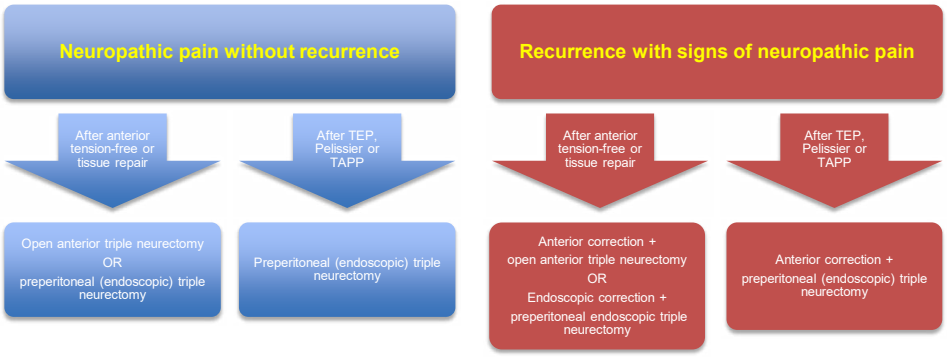


Figure 3. Management of chronic postoperative inguinal pain with and without recurrence

Partial or complete mesh removal is indicated in case of meshoma pain refractory to conservative management. Meshoma as a pathologic entity can present in different gradations from mass-like density to more subtle effects of mesh wrinkling or fibrosis. While meshoma will require surgical intervention if persistent and severe, occasionally patients whose overall pain levels improve can be managed without re-exploration and removal. If the pain team is able to decrease the pain with pharmacologic, behavioral, and interventional treatment, this would be preferable. The greatest morbidity in these reoperative surgeries is from removal of the mesh given its apposition to vital structures with the potential for bleeding, testicular loss, visceral injury, and creation of a new hernia. Any potential to spare a patient from surgery is advisable.

Systematic triple neurectomy instead of removal of meshoma only or removal of the nerves entrapped by meshoma only, is recommended because of neuroanatomic and technical considerations [24]. From a neuroanatomic perspective, there is significant cross-innervation of the nerves within the inguinal canal and within the preperitoneal space. Any neuropathic pain cannot be isolated to one specific nerve and if neurectomy is performed, all potentially damaged nerves within an operative field should be taken. From a technical perspective, the reoperative surgery to remove the mesh will likely damage the nerves within the operative field and neurectomy was advised by the panel.

Chronic testicular pain (orchialgia) has been left out of the scope of this algorithm, focusing primarily on inguinal pain. In most cases of orchialgia, the etiology is neuroanatomically and causatively distinct from CPIP. Accordingly, triple neurectomy is typically ineffective for this indication. The management of orchialgia after inguinal herniorrhaphy remains challenging and it is important to note that it can arise after all variants of inguinal repair [18, 24, 27]. Resection of the paravasal fibers or spermatic cord denervation might be an option for patients with neuropathic testicular pain but must be performed proximal to the level of pathology. Orchiectomy remains an option, but should only be reserved for refractory cases with evidence of nociceptive pain and parenchymal testicular compromise [28].

This current study was designed to create a working algorithm using the Delphian method integrating the existing cumulative knowledge on the clinical management of CPIP. This method is predicated on the concept of "collective intelligence" of a focused group and is designed to prevent bias through anonymity and regular feedback. By ensuring these factors, personal bias is minimized and free expression of opinions is encouraged without influence from authority or personality. Open critique is fostered allowing for admission of errors and revision of the working construct. The process continues through thesis and antithesis, until synthesis and consensus are reached. Bias

within the group is minimized through this method. The limitation of this process is that some notable and respected authorities in the field did not participate. That being said, the product of 26 authorities on CPIP represents the most comprehensive and inclusive effort to create a consensus algorithm to date.

The flowchart produced is the first consensus version of a fluid algorithm based upon best-available evidence and opinion to date. As it is opinion-based by nature, it should not be considered as a strict guideline. Rather, it should serve as a practical tool for surgeons and clinicians treating the complex problem of CPIP. The algorithm can help direct appropriate management based upon the standard practice of an international group of surgeons considered expert on inguinal hernia surgery. It will also serve as a standard for further research representing the starting point for a developing dynamic algorithm.

In conclusion: with the frequency of inguinal hernia correction as one of the most performed operations worldwide and the high incidence of CPIP, there is need for guidelines with regard to management of CPIP. This algorithm will hopefully serve as a guide to the management of these patients and help to improve clinical outcomes. If an expectative phase of a few months has passed without any amelioration of CPIP, a multidisciplinary approach is indicated and a pain management team should be consulted. If conservative measures fail and surgery is considered, triple neurectomy or correction for recurrence with or without neurectomy should be performed. Surgeons less experienced with remedial operations for CPIP should not hesitate to refer their patients to dedicated hernia surgeons.

Conflict of interest

None

Acknowledgement to the board of international experts who gave consensus

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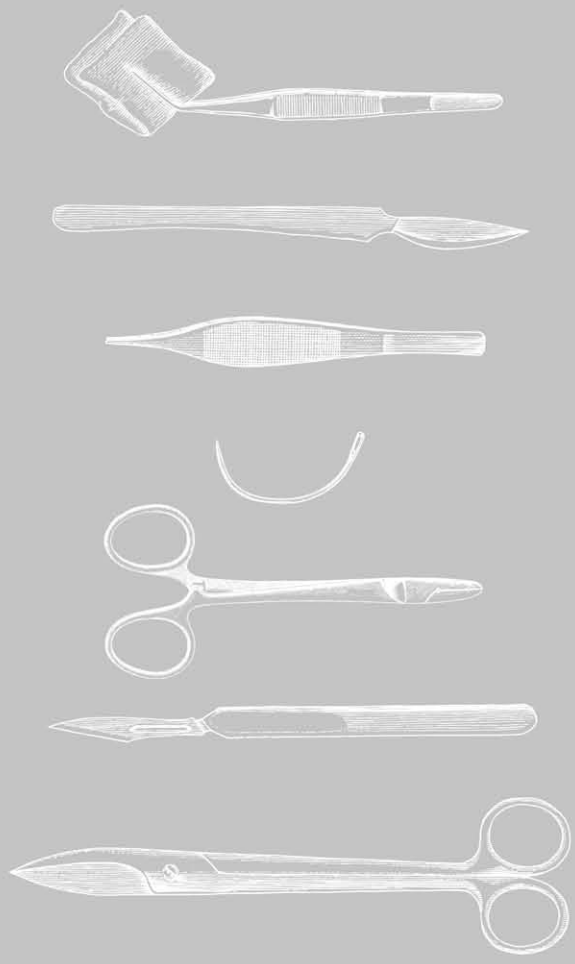
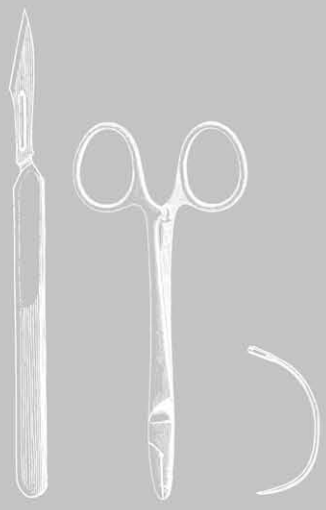


11

Repair of complex abdominal wall hernias with a cross-linked porcine acellular matrix: cross-sectional results of the Dutch cohort study



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Submitted

ABSTRACT

Introduction

The use of synthetic mesh in potentially contaminated and contaminated incisional hernias may lead to a higher morbidity and mortality. Biological meshes may provide a solution, but since these meshes are rarely used, little is known about long-term results. The aim of this cohort study was to evaluate the long-term clinical efficacy and patient satisfaction following Permacol™ in complex abdominal wall hernia repair (CAWHR) patients in a cross-sectional fashion.

Methods

All patients were operated for CAWHR with Permacol™ in the Netherlands between 2009 and 2012. Patients were interviewed, underwent abdominal examination, and completed quality-of-life questionnaires. ClinicalTrials.gov Identifier: NCT02166112.

Results

Seventy-seven patients were seen in the outpatient clinic. Their hernias were classified as potentially contaminated in 25 patients (32.5 percent) and infected in 52 patients (67.5 percent). The mean follow-up was 22.2 ± 12.6 SD months. The most frequent post-operative complication was wound infection (n = 21; 27.3 percent), meshes had to be removed in five patients (6.5 percent). By the time of their visit to the outpatient clinic, 22 patients (28.6 percent) had a recurrence of whom ten (13 percent) had undergone reoperation. Thirty-nine patients (50.6 percent) had bulging of the abdominal wall. Quality-of-life analyses revealed that patients graded their health status with a mean 6.8 (± 1.8 SD) out of 10 points.

Conclusion

Bulging and recurrence are frequently observed in patients treated with Permacol™ for CAWHR. Considering both recurrence and bulging as undesirable outcomes of treatment, a total of 46 patients (59.7 percent) had an unfavorable outcome. Infection rates were high, but comparable with similar patient cohorts. Quality-of-life analyses revealed that patients were satisfied with their general health, but scored significantly lower on most quality-of-life modalities of the Short Form-36 questionnaire.

INTRODUCTION

As a rule nowadays incisional hernia is repaired with a mesh-assisted technique [1]. In potentially contaminated and infected incisional hernias, the use of conventional synthetic mesh is controversial and may be dangerous: infected meshes are invalidating to the patient and may eventually be life-threatening.

Contamination can be caused by the presence of stoma, enterocutaneous fistula, bowel leakage, reanastomosis procedure, and burst abdomen, or may be present after the removal of an infected mesh. The grade of contamination is an important factor in the treatment of incisional hernia. Therefore, the Ventral Hernia Working Group (VHWG) developed a hernia grading system to classify the different grades of contamination and its treatment complexity in abdominal wall hernia repair (grade 1: low risk to grade 4: infected) [2].

The so-called complex abdominal wall hernia repair (CAWHR) is a surgical challenge. Patients often have multiple comorbidities and risk factors increasing the risk for postoperative complications and hernia recurrence. Patients who need CAWHR often undergo a strictly planned, staged repair of their hernia defect [3]. At first, the aim is to achieve a reduction of bacterial load in the operation field by surgically debriding the operative area, temporary placing of conventional meshes and/or use of vacuum-assisted therapy (VAC) or skin grafts to cover any granulating open abdominal defect. These surgical techniques are mostly combined with antibiotic treatment. Thereafter, definitive repair of the remaining hernia is planned. This staged repair is time consuming, uncomfortable for the patient, and is associated with higher healthcare costs and a decrease in quality of life.

Therefore a single-stage hernia repair would be a better alternative. In single-stage hernia repair the surgeon has to cope with the presence of contamination. In this situation biological meshes may provide a solution. These meshes, made of collagen of either human or animal origin, are associated with a lower infection risk and might increase the strength of primary repair [4]. However, little known is about long-term results, since these meshes are expensive and rarely used [5].

Permacol™ is a mesh prosthesis consisting of type I collagen, derived from porcine dermis. The porcine dermis is processed to remove hair, cells, cell components, as well as other antigens present in the tissue [6]. After decellularization and degradation of the porcine dermal tissue, a 3D structure of collagen remains. Thereafter, the collagen fibers are chemically cross-linked with hexamethylene diisocyanate to increase the strength

of the mesh and to slow-down the degradation of the mesh [3, 6]. During degradation, ingrowth of host fibroblasts and collagen replacement can take place. This so-called xenograft remodeling begins directly after implantation and takes several months to years. In this article Permacol™ is referred to as cross-linked porcine acellular dermal matrix (X-PADM).

The aim of this study was to evaluate the indication for the use of cross-linked porcine acellular dermal matrix and to assess the results of CAWHR in potentially contaminated and infected abdominal wall hernia (VHWG classification grade 3 and 4 [2]). We also assessed patient satisfaction following Permacol™ (X-PADM) repair.

METHODS

Patients

Patients were eligible for inclusion if they had been operated in the Netherlands between 2009 and 2012, with X-PADM for the indication CAWHR. CAWHR was defined as a repair for a potentially contaminated to infected hernia, which is grade 3 to grade 4 according to the system developed by the VHWG [2]. Data of patients who had passed away within a year after X-PADM implantation were also analyzed.

Study design

A list with anonymized operation dates was disclosed to the research group by the company (Covidien, Mansfield MA, USA). This list comprehended a registry of all X-PADM prostheses that were sold to hospitals in the Netherlands within the time-span of 2009 to 2012. This list contained only patients with grade 3 and grade 4 hernia according to the VHWG [2]. Additional information to match the operation dates with patient records was gathered from all hospitals, that had used X-PADM in the past to treat complicated abdominal wall defects. Patient records were identified via contact with the operating surgeons. They identified their own patients from the list of anonymized operation dates.

All living patients received written information on the study and an invitation to participate. If consent was received, we invited them to the outpatient clinic. During this visit, patients were interviewed to collect baseline parameters and their medical and abdominal operations history. Baseline parameters were defined as age, gender, BMI, length of follow-up, smoking history, and occupational heavy lifting. Medical history was focused on medical conditions like COPD/chronic coughing, steroid use, malignancy, diabetes, general abdominal operations and specific abdominal wall operations.

All patient underwent physical examination. Quality-of-life parameters were assessed with the following three questionnaires: EuroQol (EQ-5D-5L), Short Form-36 (SF-36) and Body Image Questionnaire (BIQ). The operating surgeons were interviewed on the indication for the use of X-PADM. The STROCSS statement was followed [7].

Outcomes

The primary endpoints were recurrence of abdominal wall hernia and bulging of the abdominal wall after X-PADM implantation. Both incisional hernia and recurrence were defined as any abdominal wall gap with or without bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging [8]. Bulging was defined as a substantial increase in abdominal circumference, not explicable by weight gain, in the absence of a palpable or objectifiable fascia defect, and observed by either the patient or the doctor [9-11]. All patients were diagnosed by clinical examination.

Secondary outcomes included postoperative complications, i.e. occurrence of wound infection, mesh infection, intra-abdominal abscess, skin abscess, seroma, hematoma, necrotic abdominal wall, fistulas, and burst abdomen. Also mesh explantations, additional abdominal operations, visits to the outpatient clinic, and quality-of-life parameters were recorded. The results of SF-36 were compared with the results of an incisional hernia population [12] and with the general Dutch population [13]. Patient files of deceased patients were also analyzed.

Ethical approval

This cohort study was ethically approved by the Ethics Board of the Erasmus University Medical Center in Rotterdam, the Netherlands. After ethical approval in the Erasmus University Medical Center, ethical approval from all ethical comities in all participating hospitals was achieved. The study was also registered at ClinicalTrials.gov with Identifier NCT02166112.

Statistical analysis

Continuous variables using means and standard deviations and categorical values with frequencies and percentages were all summarized. Correlations were assessed with Spearman's correlation coefficient and were tested with a two-tailed test of significance. All statistical analyses were performed using SPSS version 21.0.

RESULTS

Patients characteristics

A total of 118 patients met the inclusion criteria, of whom 22 were deceased, 11 did not consent to participate in the study, and eight were lost to follow-up (Figure 1). Seventy-seven patients (65.3 percent) were seen at the outpatient clinic (47 male (61 percent), 30 female (39 percent), mean age: 60 years). The ventral hernias were classified as potentially contaminated hernia in 25 patients (32.5 percent; VHWG classification grade 3) and infected hernia in 52 patients (67.5 percent; VHWG classification grade 4) [2]. The mean follow-up was 22.2 ± 12.6 months (Table 1).

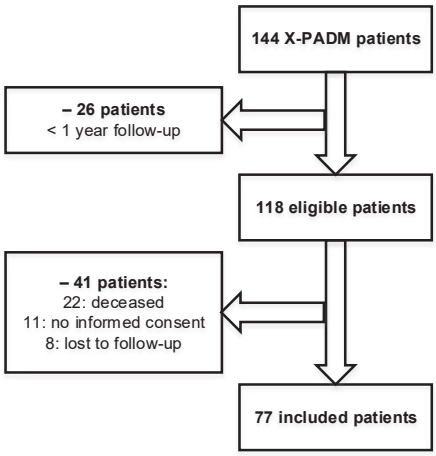

Figure 1. Flow chart of included patients

Table 1. Baseline criteria

Mean follow-up (SD)	22.2 months (± 12.6)
Gender: male versus female	47 (61%) versus 30 (39%)
Age (SD)	60 year (± 11.4)
Body Mass Index (SD)	28.7 kg/m^2 (± 6.8)
Ventral Hernia Working Group Grade 3	25 (32.5%)
Ventral Hernia Working Group Grade 4	52 (67.5%)
Operations before X-PADM repair	4.8 (range 0–30)
Smoking	40 (57.1%)
Occupational heavy lifting	30 (46.2%)
COPD/chronic coughing	26 (37.7%)
Steroid use	24 (31.2%)
Malignancy	22 (31.4%)
Diabetes	17 (23.9%)

SD = standard deviation. COPD = chronic obstructive pulmonary disease. X-PADM = cross-linked porcine acellular dermal matrix.

In this cohort the three main risk factors for the development of a complex abdominal wall hernia were smoking (n = 40; 57.1 percent), occupational heavy lifting (n = 30; 46.2 percent), and COPD/chronic coughing (n = 26; 37.7 percent). Other risk factors were steroid use (n = 24; 31.2 percent), malignancy (n = 22; 31.4 percent), diabetes (n = 17; 23.9 percent), and a relatively high BMI (28.7 ± 6.8 kg/m^2). History of burst abdomen was significantly correlated with bulging and both length and hernia in history were significantly correlated with recurrence (Table 2). Other risk factor or patient characteristics were not significantly correlated to either bulging or recurrence.

Table 2. Correlations between clinical outcome and risk factors

	Bulging	Recurrence
Length	0.289	0.034*
BMI	0.390	0.414
Hernia in history	0.273	0.007**
History of SSI	0.191	0.082
History of burst abdomen	0.023*	0.445
History of open abdomen treatment	0.101	0.031*

* $P < 0.05$ ** $P < 0.01$ BMI = body-mass index. SSI = surgical site infection.

The main reason for the use of X-PADM was potential contamination in the presence of a stoma (n = 38; 52.1 percent). Other indications for X-PADM use were enterocutaneous fistulas (n = 25; 34.2 percent), intra-abdominal abscess (n = 23; 31.9 percent), wound infection (n = 21; 27.3 percent), mesh infection (n = 18; 25.0 percent), open abdomen (n = 17; 23.6 percent), or anastomotic leakage (n = 10; 13.9 percent). Some patients had more than one of the previous mentioned indications. Therefore, the total number of indications exceeded the total number of patients.

In most cases the surface area of the actual defect was not defined in the patient's file. Therefore the derived factor "mesh surface" (from the patient's file) was recorded. The most frequently used mesh size was 20 cm by 30 cm (600 cm^2) as used in 22 patients (71.2 percent). Other sizes were 15 cm by 20 cm (300 cm^2) in 12 patients (22.7 percent), 20 cm by 40 cm (800 cm^2) in eight patients (12.1 percent), and 18 cm by 28 cm (504 cm^2) in seven patients (10.6 percent), respectively.

The meshes were placed in different anatomical planes: sublay in 31 patients (40.3 percent), intraperitoneal onlay mesh (IPOM) in 20 patients (26.0 percent), onlay in eight patients (10.4 percent), inlay in three patients (3.9 percent), and in 15 patients (19.5 percent) it remained unclear in which anatomical plane the mesh was placed. Component

separation was performed in 26 patients. There were also 26 patients in which the fascia defect could not be closed tension-free. In these cases mesh bridging was performed.

Postoperative outcomes

Postoperative complications occurred in 30 patients (39 percent). The most frequent complication after X-PADM implantation was wound infection (n = 21; 27.3 percent). In five patients (6.5 percent) the mesh had to be removed due to mesh infection. The remaining 16 patients (20.8 percent) with wound infection could be treated conservatively by either use of antibiotics and/or the use of vacuum-assisted therapy. The incidence of wound infection was significantly correlated with a previous episode of mesh infection in the history of the patient, prior to the operation (not being the indication of the operation). Less frequent complications were enterocutaneous fistula (n = 4; 5.2 percent), skin necrosis (n = 3; 3.9 percent), and fascia dehiscence (n = 2; 2.6 percent). Although a high mortality in this series was observed, there was no evidence for mesh-related mortality. The group of deceased patients will be discussed separately.

Long term outcomes

Twenty-nine patients had no recurrence or bulging (37.7 percent). Twenty-two patients (28.6 percent) had a recurrence of abdominal wall hernia, of whom ten (13 percent) had undergone reoperation. Thirty-nine patients (50.6 percent) had bulging of the abdominal wall. A total of 15 patients suffered from both bulging and a recurrence (19.5 percent). Considering both recurrence and bulging as undesirable outcomes of treatment, a total of 46 patients (59.7 percent) had an unfavorable outcome.

No correlation has been found between hernia recurrence and/or abdominal bulging and the anatomical plane in which the mesh was placed. Also bridging the hernia with mesh and VHWG classification [2] were not significantly associated with recurrence and/or bulging. The results of physical examination were plotted in a Kaplan-Meier analysis (Figure 2).

Quality-of-life parameters

Thirty-two patients (42 percent) were satisfied with the cosmetic result. Patients rated their scars with a mean of 6.0 ± 2.4 out of 10 points (10 being the best cosmetic outcome). Patients graded their general health at the moment of their visit to the outpatient clinic with a mean of 6.8 ± 1.8 out of 10 points (10 is the best health status).

When patients compared their postoperative general health status during their visit to the outpatient clinic with their health status a year before, it was graded "much better" in 20 patients (27.4 percent), and "somewhat better" in 13 patients (17.8 percent), which

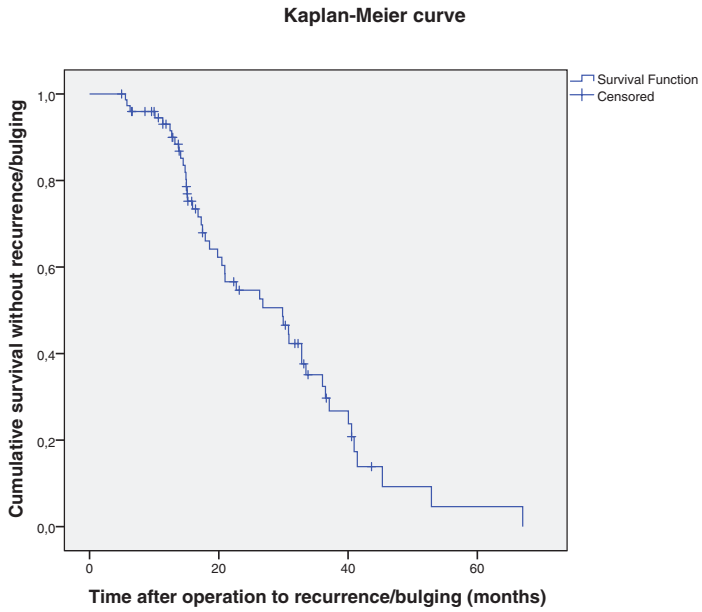

Figure 2. Kaplan-Meier survival analysis
Cumulative survival of patients without recurrence or bulging versus time of operation until recurrence or bulging (expressed in months).

is an improvement in 45.2 percent of cases. In 26 patients (35.6 percent), the general health status was graded "about the same as one year ago". In 14 patients a worsening occurred: in nine patients (12.3 percent) a small deterioration and in five patients (6.8 percent) a severe deterioration. In four patients, data were missing regarding the comparison between the current health status and the health status before.

Analysis of SF-36 questionnaires revealed that patients who had undergone CAWHR with X-PADM had a significantly lower score on six out of eight quality-of-life modalities, when compared with an incisional hernia population (VHWG classification grade 1 and 2) [2]. The only two modalities that were not significantly different were the "mental health" status and "vitality" of both groups (Table 3A). When this cohort was compared to the general Dutch population, patients who had been treated for a complex abdominal wall hernia had a significantly lower score on seven out of eight quality-of-life modalities. The only modality that was not significantly different was the "mental health" status of both groups (Table 3B).

Deceased patients

The group of deceased patients consisted of 22 patients (18.6 percent of total cohort): 12 males (54.5 percent) and ten females (45.5 percent). The mean age at decease was 67.8 ±

Table 3A. Quality-of-life analysis assessed with Short Form-36
The results of this cohort were compared with an incisional hernia population (Rickert, 2012) [9]. This incisional hernia population consists mainly of VHWG classification grade 1–2 patients.

Modality	X-PADM patient population Mean ± SD	Incisional hernia population Mean ± SD	Difference with incisional hernia population
Physical functioning	54.4 ± 28.7	80.2 ± 23.7	Significantly lower
Role physical	43.9 ± 44.3	69.6 ± 32.4	Significantly lower
Bodily Pain	54.4 ± 30.0	80.6 ± 20.6	Significantly lower
General health	49.0 ± 25.7	72.1 ± 19.5	Significantly lower
Vitality	57.5 ± 23.3	63.9 ± 17.0	Not significant
Social Functioning	67.3 ± 29.1	85.2 ± 20.4	Significantly lower
Role emotional	62.5 ± 46.1	78.2 ± 26.2	Significantly lower
Mental Health	75.9 ± 19.8	69.8 ± 13.7	Not significant

Table 3B. Quality-of-life analysis assessed with Short Form-36
The results of this cohort were compared with the Dutch validation sample of the SF-36 (Aaronson, 1998) [10]. This group consists of a random selection of the general Dutch population.

Modality	X-PADM patient population Mean ± SD	General Dutch population Mean ± SD	Difference with general Dutch population
Physical functioning	54.4 ± 28.7	76.8 ± 22.6	Significantly lower
Role physical	43.9 ± 44.3	70.8 ± 39.1	Significantly lower
Bodily Pain	54.4 ± 30.0	70.8 ± 24.2	Significantly lower
General health	49.0 ± 25.7	65.0 ± 19.7	Significantly lower
Vitality	57.5 ± 23.3	69.0 ± 18.9	Significantly lower
Social Functioning	67.3 ± 29.1	82.7 ± 22.5	Significantly lower
Role emotional	62.5 ± 46.1	82.4 ± 32.3	Significantly lower
Mental Health	75.9 ± 19.8	75.6 ± 17.8	Not significant

11.8 years and the postoperative survival after X-PADM was 124.6 ± 159.5 days. Only two of the deceased patients (9.1 percent) survived more than one year after CAWHR. Causes for decease were formally unknown due to no autopsy in 15 patients (68.2 percent), abdominal sepsis/septic shock in three patients (13.6 percent), general clinical deterioration in two patients (9.1 percent), respiratory insufficiency in one patient (4.5 percent), and cardiac arrest in one patient (4.5 percent). Mortality seemed not associated with the mesh; all patients passed away due to a deterioration in general health caused by the underlying disease (abdominal sepsis in the majority of the cases). Fifteen patients (68.2 percent) passed away during admission in hospital, three patients (13.6 percent) deceased at home or in a nursing home, and in four patients (18.2 percent) it remained unknown where they passed away.

DISCUSSION

Taking into account the complexity of potentially contaminated or infected ventral hernias, this Dutch cohort study demonstrates that repair of this category of abdominal wall hernia with X-PADM leads to disappointing results. There was bulging and recurrence in 59.7 percent of patients and infection rates were high. Quality-of-life analyses revealed that patients were satisfied with their general health, but scored significantly lower on most quality-of-life modalities of the Short Form-36 questionnaire.

Study approach

Since treatment of complex abdominal wall hernia with a biological mesh is relatively new, there are only a few studies comparable to ours with respect to characteristics and methodology. The RICH study, in which the results of Strattice™ mesh (Acelity™, non-cross-linked porcine acellular dermal matrix) were analyzed, seems to have the most similarities in methodological approach [14]. Also a recently published study of Nockolds and colleagues has a comparable methodological approach but had different inclusion criteria, leading to a quite heterogeneous patient group [15]. Most other studies differ with regard to the following characteristics: they were either single-center studies [15, 16], presented retrospective data [17, 18], involved small patient samples [15, 19] analyzed heterogeneous patient groups (i.e. different types of hernias, repairs or meshes in one study [15, 20]), used different surgical techniques, had a different follow-up period (9.1 months in Diaz and colleagues [17] to 24.0 months in Itani and colleagues [14]), applied the Ventral Hernia Working Group grading system less stringently [21, 22], had a different patient population, and/or analyzed a different biological mesh prosthesis [14, 17, 18]. The current study is a multicenter cohort study, with a carefully selected patient group. In this patient group were cross-sectional data collected and was quality of life assessed.This is an important but rarely studied item in CAWHR research. To our knowledge, other studies with quality-of-life assessment in this specific patient group have not been published yet. Therefore, the current study gives a more complete impression of the efficacy of X-PADM in the treatment of potentially contaminated and infected ventral hernia (VHWG classification grade 3 to 4) [2].

After completion of this study, two new classifications for complex abdominal wall hernia were proposed. In this study, the VHWG classification was used to classify the severity of the complex abdominal wall hernias [2]. Later in 2012 the modified VHWG classification was proposed [23]. The modified VHWG classification was divided into grade 1 to 3 (grade 1: low risk, grade 2: co-morbid, grade 3A: clean-contaminated, grade 3B: contaminated, and grade 3C: dirty) instead of grade 1 to 4 in the VHWG classification [2]. The aim of Kanters and colleagues was to propose a new classification to improve

the accuracy of predicting surgical site occurrences after complex abdominal wall hernia repair [23]. Reclassifying this patient cohort could lead to a shift of patients from VHWG classification grade 3 and 4 into modified VHWG classification grade 3B of grade 3C. Another classification for complex abdominal wall hernia was proposed by Slater and colleagues [24]. This new classification takes more different factors into account. This new classification is – compared with the VHWG classification [2] – extended with the categories "size and location" (of hernia) and "clinical scenario" (of patient). Another difference, is the subdivision of the group complex abdominal wall hernia into the severity classes "minor", "moderate" and "major". In this new classification, most of our patients would be scored as "complex abdominal wall hernia, severity grade major". This could lead to a shift of patients from VHWG classification grade 3 into the group of complex abdominal wall hernia, severity major [24].

Patient group

In this study, we enrolled patients belonging to a very difficult treatment group. All patients had a potentially contaminated or infected ventral hernia i.e. grade 3 to 4 hernia according to the VHWG classification [2]. Moreover, two-third of this cohort consisted of patients with an infected hernia (VHWG classification grade 4). In addition to a complex abdominal wall hernia, most patients suffered from multiple comorbidities and risk factors which increased the risk of postoperative complications such as wound infection and hernia recurrence.

Risk factors seen in the underlying cohort study included smoking, preoperative wound infection, and COPD. Other risk factors mentioned in literature are age, pre-existent disease (obesity, diabetes, hypertension, American Society of Anesthesiologists (ASA) score >3), operation setting (emergency presentation and operation, duration of operation, fistula at the time of operation, defect size >30 cm^2), and hospital stay over 14 days [25, 26]. In other studies these risk factors were associated with more postoperative wound infections [25, 26]. In this study the incidence of postoperative wound infection was significantly correlated with a previous episode of mesh infection. This episode of mesh infection was defined as an episode some time before the operation with X-PADM, not representing the actual indication for this operation. To our knowledge, this finding was not reported in other studies. A hypothesis could be that there is some ongoing state of infection, there might be a spill of encapsulated bacterial material during the operation, or that patients have a poor immune response to invasion of bacteria. However, the exact mechanism is unclear. We did not find this correlation with postoperative wound infection for other patient characteristics and risk factors.

A history of burst abdomen was significantly correlated with bulging. Burst abdomen can lead to loss of domain of the abdominal wall. To achieve a tension-free closure of the abdominal wall, surgeons use in some patients the technique of component separation [27]. Thereafter, a relative weakness of the abdominal wall can occur, due to separation of different components in the abdominal wall. This could lead to an increasing risk for bulging. Progressive bulging might be the result of failure of the mesh implant due to elongation [28].

Both length of the patient and other abdominal wall hernias in history were significantly correlated with recurrence. The correlation with the length of the patient could be a coincidence. Since we found no other studies reporting this correlation, we can only hypothesize what the cause can be. One could consider a longer abdominal wall and therefore a larger force on a mesh prosthesis when implanted in a longer/larger abdominal wall. About one-fifth of these patients had a hernia in their history (not being the indication for X-PADM placement). Since we investigated CAWHR, many patients had a hernia in history or a hernia as indication for X-PADM placement. Therefore this correlation is not a "true" correlation. Other risk factor or patient characteristics were not significantly correlated to either bulging or recurrence.

Long-term postoperative results

The hernia recurrence rate found in this study (28.6 percent) was similar to that seen in the RICH study. This study evaluated patients treated with Strattice™ mesh for contaminated incisional hernia two years after their operation and had a recurrence rate of 28 percent. Rosen and colleagues had a much higher recurrence rate of over 50 percent after three years of follow-up [16]. This high recurrence rate could possibly be explained by the use of a different mesh (non-cross-linked biological mesh) and a longer follow-up. Only ten out of 77 patients in this study underwent reoperation to treat hernia recurrence, which is relatively low in comparison with other studies published in literature [16, 17]. Despite the relatively low rate of hernia recurrence in this study, a high rate of abdominal wall bulging was observed in more than half of all patients. This finding was also seen in other studies, but these studies displayed a lower percentage of bulging than the present study [29, 30]. An explanation for this difference could be that larger hernia defects were included in this study in which patients also had a higher VHWG classification.

The high rate of abdominal wall bulging could also be secondary to an intense inflammatory response to X-PADM without (or with insufficient) xenograft remodeling. The inflammatory response on X-PADM in experimental animal models is ranging from mild/low [31] to moderate [32]. Due to the variety in animal species, it is difficult to extrapo-

late these results to the human situation. There is a recent publication available with X-PADMs that were explanted from humans [33]. In this study, the authors examined seven explanted X-PADMs and analyzed these histologically. Their conclusion was that the explants lacked identifiable biologic behavior; i.e. absence of xenograft remodeling and a large variety in histological response. However, these conclusions are based on only seven X-PADM explants.

In another attempt to acquire data for the human situation, Grotenhuis and colleagues [34] performed an in vitro study in which was shown that X-PADM in a human macrophage culture model led to mild local inflammation. The latter study implies that local inflammation in X-PADM might not be the explanation for the large amount of patients suffering from bulging. However, evidence is not strong yet and partly contradictory.

Operation techniques and plane of mesh placement

It is generally assumed, that complete fascial closure is the preferred method in CAWHR, and that the bridging technique increases the risk for recurrence and bulging. In spite of these assumptions, we found no significant association between hernia recurrence and/or abdominal bulging and the anatomical plane in which the mesh was placed. Also bridging was not significantly associated with recurrence and/or bulging. These results are confirmed by studies of Iacco and colleagues [3] and Sbitany and colleagues [35]. However, Lupinacci and colleagues did find a significant association between bridging and recurrence in a smaller group of patients [21].

Postoperative complications

Since two-third of the patients in this cohort had an infected hernia, one could expect that there would be a higher incidence of postoperative wound infections than in other studies in literature [14, 17, 18]. Against our expectation, we found less surgical site infections (27.3 percent) than the RICH study [14] (35 percent) and the study by Diaz and colleagues [17] (33 percent infections). The infection rates as observed are similar to those found by Helton and colleagues [18] (23 percent). This is an interesting finding, because the other studies mainly included patients with VHWG classification grade 2 to 3. Therefore, the results in this study with mainly VHWG classification grade 4 patients are still high, though comparable with other studies.

Although 21 patients in this study suffered from wound infection, many of these infections could be treated conservatively. The mesh removal rate following a wound infection was 6.5 percent in the current study, a rate similar to that seen in the study of Diaz and colleagues [17] but lower than that found by Helton and colleagues [18] and Rosen and colleagues [16]. Rosen and colleagues investigated a large group of CAWHR

patients and found a wound complication rate of 47.7 percent. Despite this high number of wound complications, Rosen and colleagues found no long-term infectious complications related to the biological mesh [16].

Recent studies about X-PADM by Giordano and colleagues [36] and Doussot and colleagues [37] concluded that X-PADM is safe and effective for complex abdominal wall hernia. Giordano and colleagues assessed a group of 109 patients and found that the recurrence rates after one year and two years were 9.2 and 18.3 percent, respectively, and were higher in cases without fascial closure. Doussot and colleagues assessed the short-term and long-term outcomes of a group of 250 patients undergoing abdominal wall hernia repair with X-PADM [37]. They found a one-year, two-years and three-years recurrence-free survival of 90 percent, 74 percent and 57 percent, respectively. They concluded that single-stage abdominal wall hernia repair is feasible using X-PADM. However, mortality and complication rates are high due to patients' comorbidities and the degree of contamination of the operative field. An important disclaimer is that given the observed recurrence rate, the benefit of biological meshes remains to be ascertained.

Sainfort and colleagues assessed the literature regarding all available biological abdominal wall implants [38]. They concluded that in the current state of knowledge, there are no high-level evidence data on the therapeutic contribution of biological meshes that allow prioritization of the various biological meshes according to their characteristics or their different manufacturing processes. Tripolli and colleagues also assessed the available literature regarding five biological meshes (Permacol™, Strattice™, Surgisis®, Tutomesh™, and XenMatrix™) [39]. They found 11 studies of a poor methodological quality. A significantly lower rate of recurrence at 12 months was found for Permacol™ compared with Strattice™. They concluded that the different types of meshes showed a marked statistical variability in the clinical outcomes.

Financial implications

Biological meshes are expensive and therefore rarely used [5]. In this study no cost analysis was performed. A previous study by Byrge and colleagues compared head-to-head the costs of using Permacol™ and Strattice™ meshes in a similar patient group. The costs of the mesh were significantly higher for Strattice™ (median cost $8940) compared to Permacol™ (median costs $1600). The use of Permacol™ resulted in a savings of $181,320 with similar clinical outcomes when compared with Strattice™ [40]. Another alternative could be found in the use of biosynthetic meshes (i.e. slowly resorbable synthetic meshes like Phasix™ Mesh (poly-4-hydroxybutyrate), GORE® BIO-A® Mesh (poly(glycolide:trimethylene carbonate) copolymer), and TIGR® Matrix Surgical mesh (fast-resorbing fiber: copolymer of glycolide, lactide, and trimethylene carbonate (40

percent of weight) and a slow resorbing fiber: copolymer of lactide, and trimethylene carbonate (60 percent of weight))). In a recent consensus review by Köckerling and colleagues all available literature about these meshes was assessed, but they concluded that there is a lack of studies comparing the use of biological or biosynthetic versus synthetic meshes in complex abdominal wall hernia [41].

Mortality

A mortality of 22 patients (18.6 percent) was observed in this cohort. Reported mortality in other studies varied between 2.4 percent [35] and 15–22 percent [3]. Reported mortality rates strongly depended on the inclusion criteria in these studies compared with the current study. Mortality is not only depending on the design of the study (retrospective, cross-sectional, or prospective analyses), but also on the inclusion criteria (type of abdominal wall hernia, VHWG classification, analysis of living patients only). The design of this study and its results are comparable to the study of Iacco and colleagues [3]. We possibly found a relatively high mortality due to high number of VHWG classification grade 3 to 4 patients in this initial cohort.

Limitations

The outcome of this study may have been influenced by the small numbers, the heterogeneity, and the high mortality in this study. There is also another methodological limitation: the current study was designed as a cohort study assessing cross-sectional data (partly retrospective, partly prospective). A well-performed full prospective trial would improve our knowledge on biological meshes even more. We also have to take into account that there might be a difference in clinical outcomes between cross-linked and non-cross-linked collagen matrices. Since convincing evidence is lacking and no head-to-head studies were performed, the impact of cross-linking on the outcome cannot be judged. Further studies on this topic are required.

Conclusion

Our results of repair of potentially contaminated and infected complex abdominal wall hernias with Permacol™ show that bulging and recurrence are frequently observed (59.7 percent of patients). Infection rates were high (27.3 percent), but comparable with similar patient cohorts. Quality-of-life analyses revealed that patients were satisfied with their general health, but scored significantly lower on most quality-of-life modalities of the Short Form-36 questionnaire. Until now no ideal mesh has been identified for complex abdominal wall hernia repair. Therefore future studies are required.

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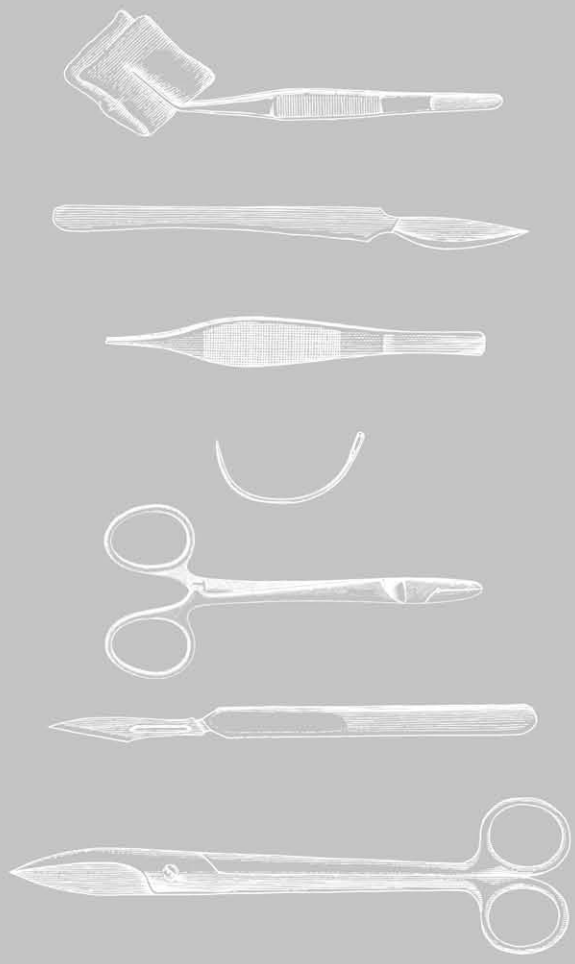

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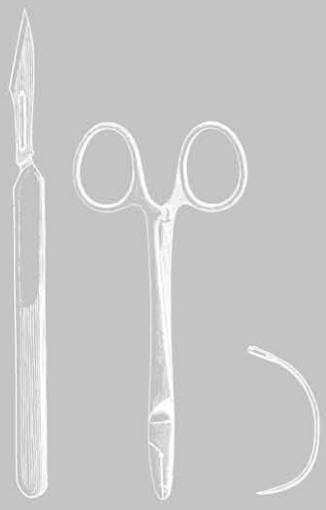
Non-cross-linked biological mesh in complex abdominal wall hernia: a cohort study



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Submitted

ABSTRACT

Introduction

Complex abdominal wall hernia repair (CAWHR) is a surgically challenging procedure. As a rule a mesh prosthesis is indicated, but use of conventional synthetic mesh in a contaminated area may be controversial. Biological meshes may provide a solution, but since these meshes are expensive and rarely used, little is known about long-term results. The aim of our study was to evaluate clinical efficacy and patient satisfaction following Strattice™ (PADM) placement.

Methods

In this cohort study, all patients operated for CAWHR with PADM in three large community hospitals in Germany (both academic and peripheral centers) were included. Patients underwent abdominal examination to assess hernia recurrence and bulging, an abdominal wall ultrasound was performed, and patients completed quality-of-life questionnaires to assess patient satisfaction. ClinicalTrials.gov Identifier: NCT02168231.

Results

Twenty-seven patients have been assessed for long-term follow-up (14 male, mean age 67.5 years, mean follow-up 42.4 months). With regard to the surgical intervention, the most frequently used mesh size was 400 cm^2 and the most frequent postoperative complication was wound infection (39.1 percent). PADM did not have to be removed. Four patients had passed away after surgery (range 5–904 days). By the time of outpatient clinic visit, six out of 23 patients (26.1 percent) had a recurrence of hernia, of whom one patient had undergone reoperation. Another five patients (21.7 percent) had bulging of the abdominal wall. Quality-of-life analyses revealed that patients judged their scar with a median 3.5 out of 10 points (0 is best) and judged their restrictions during daily activities with a median of 0 out of 10.0 (0 means no restriction).

Conclusion

These results show that despite a high rate of postoperative wound infection no biological mesh had to be removed. Both the recurrence rate and the amount of bulging after long-term follow-up are high (failure rate of 47.8 percent). The reported quality of life is good after repair of these complex hernias.

Keywords: Complex abdominal wall hernia, non-cross-linked biological mesh, long-term results

INTRODUCTION

Incisional hernia is a common complication after abdominal surgery. Incidences range from 3 to 20 percent in the general population [1-7] with an increased incidence of 26 percent up to 39 percent in patients suffering of obesity or aortic aneurysms [5, 7-19]. Currently, incisional hernias are most often reinforced with mesh material [20, 21]. The use of mesh radically lowered the 10-year recurrence rates after incisional hernia repair [21]. There are various mesh prosthesis available (conventional synthetic meshes, biological meshes, and since recently also biosynthetic meshes (i.e. slowly resorbable synthetic meshes)) [22-24]. Conventional synthetic meshes are still used most often in general practice and polypropylene mesh is the most popular product [25].

There are various reasons, like mesh infections, enterocutaneous fistulas, burst abdomen, and anastomotic leakage, that could turn an uncomplicated ventral hernia repair into a complex abdominal wall hernia repair (CAWHR) [26].

The grade of contamination is an important factor in the treatment of incisional hernia. To classify the amount of contamination, the Ventral Hernia Working Group (VHWG) developed a hernia grading system to classify the different grades of contamination and its treatment complexity in abdominal wall hernia repair (grade 1: low risk to grade 4: infected) [27]. In potentially contaminated and infected incisional hernia the use of conventional synthetic mesh is controversial and might lead to a higher morbidity and even mortality. Patients often have multiple comorbidities and risk factors that increase the risk for postoperative complications and hernia recurrence. To prevent such situation as much as possible, further attempts were done to classify complex abdominal wall hernia to develop a treatment strategy for CAWHR [28].

Patients who need CAWHR often undergo a strictly planned, staged repair of their hernia defect [29]. Part of a different treatment strategy for CAWHR is the use of biological mesh instead of synthetic mesh in a one-stage procedure. Biological mesh is however only seldom used, since costs per prosthesis are high and little is known about long-term results. In this study, the use of Strattice™ mesh was evaluated. Strattice™ is a decellularized, intact, non-cross-linked porcine acellular dermal matrix, derived from porcine dermis [30]. The study is initiated after a nationwide German questionnaire of the ROKI Group [31]. The aim of this study was to evaluate clinical efficacy and patient satisfaction following Strattice™ placement in patients treated for CAWHR in three academic and peripheral hospitals in Germany. In this study, Strattice™ is referred to as non-cross-linked porcine acellular dermal matrix (PADM).

METHODS

Study design

A cohort study was performed in three large community hospitals in Germany (both academic and peripheral centers). Patients were identified retrospectively and were invited to an outpatient clinic appointment. Ethical approval for this study was obtained from the Ethics Board of the Johann Wolfgang Goethe University in Frankfurt, Germany. After ethical approval from the Johann Wolfgang Goethe University Frankfurt, ethical approval was obtained from all local ethical comities in the participating hospitals.

Patients

Patients were eligible for inclusion in the cohort if they had been operated with PADM for the indication CAWHR in one of the participating centers in Germany. CAWHR was defined as the repair for a potentially contaminated to infected hernia, which is grade 3 to grade 4 according to the system developed by the VHWG [27]. Patients had to provide written informed consent to participate in the study.

Procedure

Patients were identified by the surgeons of the participating centers. The surgeons contacted all their patients and gave them – if they were interested – additional information about participation in the study. After written informed consent was obtained, patients were invited to an appointment in the outpatient clinic.

Patients were interviewed to collect baseline parameters, and to assess their medical history. Baseline parameters were defined as age, gender, BMI, length of follow-up, smoking history, and occupational heavy lifting. The assessment of their medical history focused on medical conditions like COPD/chronic coughing, steroid use, malignancy, diabetes, general abdominal operations, and specific abdominal wall operations.

All patients underwent abdominal examination to assess the presence of a hernia recurrence or bulging of the abdominal wall. Patients underwent an abdominal wall ultrasound in case of doubt. Patients completed quality-of-life questionnaires to assess patient satisfaction. The EuraHS quality-of-life questionnaires were used to assess patients' quality of life [32, 33]. The STROBE statement was followed [34].

The data acquired in this study were registered in the standardized Case Record Forms of the Incisional ventral hernia route in the EuraHS Database (http://www.eurahs.eu). These Case Record Forms were registered in a private group and were only accessible to the members of this study group.

Outcomes

The primary outcome for this study was recurrence of hernia and/or bulging of the abdominal wall after PADM repair. Both incisional hernia and the recurrence of incisional hernia were defined as any abdominal wall gap with or without bulge in the area of a postoperative scar perceptible or palpable by clinical examination or medical imaging [35]. Bulging of the abdominal wall was defined as a substantial increase in abdominal circumference, not explicable by weight gain, in the absence of a palpable or objectifiable fascia defect, and observed by either the patient or the doctor [36-38]. All patients were diagnosed by clinical examination. In case of doubt abdominal wall medical imaging (i.e. ultrasound and/or CT scan) was performed to confirm or reject the diagnosis.

Secondary outcomes in this study included postoperative complications, i.e. wound infection, mesh infection, intra-abdominal abscess, skin abscess, seroma, hematoma, necrotic abdominal wall, fistulas, and burst abdomen. The occurrence of mesh explantation was also recorded, just like additional abdominal operations, and quality-of-life parameters. Complications were classified according to Dindo and Clavien [39].

Statistical analysis

Continuous variables were summarized by using means and ranges, categorical values were summarized with frequencies and percentages. Quality-of-life questionnaires were summarized with medians and ranges. The database was made in Microsoft Excel version 2016 (MSO 16.0.11029.20045). There was no data safety committee overseeing the study. The study was registered in ClinicalTrials.gov under Identifier NCT02168231.

Role of the funding source

Funding to execute this study, was obtained from LifeCell Corporation, a KCI company, Branchburg, NJ, USA. The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data of the study and had final responsibility for the decision to submit for publication.

RESULTS

Patients characteristics

A total of 27 patients met the inclusion criteria, of whom four were deceased. These four patients had passed away after surgery after 5, 22, 50, and 904 days respectively. Twenty-three patients have been assessed for long-term follow-up (14 male (61 percent), mean age 67.5 years, mean follow-up 42.4 months) (Table 1).

Table 1. Baseline criteria

Mean follow-up	42.4 months
Gender: male versus female	14 (61%) versus 9 (39%)
Age	67.5 years (48–90)
Arterial hypertension	9 (39.1%)
Cardiac disease	6 (26.1%)
Diabetes mellitus type II	8 (34.8%)
Malignant disease	2 (8.7%)
Pulmonary disease (COPD/asthma)	3 (13%)
Renal disease	5 (21.7%)
Other: peritonitis, fistula, cachexia, hypothyroidism, portal vein thrombosis	8 (34.8%)
No comorbidities	5 (21.7%)
Smoking (daily/occasional smoking)	6 (26.1%)
Ex-smoker	7 (30.4%)

Data are n (%) or mean (range). COPD = chronic obstructive pulmonary disease.

Perioperative information

The risk factor seen most often was a personal history of previous abdominal wall hernia operation (Table 2).

The estimated diameter of the hernia was median 18.25 cm (range 10–30 cm). The median defect size of the hernia was 357 cm^2 (range 100–900 cm^2). The operation was elective in 16 patients, and an emergency procedure in five patients. In two patients was unknown whether it was an elective or an emergency procedure.

The hernia was located most often in the midline in the areas M2, M3, M4, and M5. Only three patients had undergone a previous hernia repair. These patients had undergone a median number of two previous hernia repairs (range 1–3 operations). All patients were operated under general anesthesia. Most patients received a single dose of antibiotics preoperatively (n = 11). In none of the patients, preoperative botulinum toxin or progressive preoperative pneumoperitoneum was used.

Table 2. Risk factors for complex abdominal wall hernia

Abdominal aortic aneurysm	1 (4.3%)
Anticoagulation therapy	2 (8.7%)
Chronic use of cortisone	1 (4.3%)
No other risk factors	7 (30.4%)
Personal history of previous abdominal wall hernia operation	9 (39.1%)

The wound classification was median class III (contaminated). In ten patients, a part of the bowel had to be removed during operation. The abdomen was closed with a combined component separation and mesh placement in 15 patients. In eight patients mesh repair sufficed. All patients received a Strattice™ mesh. The most frequently used mesh size was 400 cm^2. The mesh was fixated with transfascial sutures and the entire hernia defect could be closed in all patients. There were no intraoperative surgical complications. The median length of stay after operation was 15 days (range 7–124 days).

Postoperative outcomes

The most frequent postoperative complication was wound infection (39.1 percent). In six patients it was a superficial wound infection. PADM did not have to be removed. Other intrahospital complications were a bleeding complication in one patient and in four patients there were general complications (acute renal failure, pleural effusion, peritonitis, primary wound treatment with vacuum-assisted closure therapy system). In five patients there were no intrahospital complications. The classification of the complications according to Dindo and Clavien was median grade IIIb (intervention under general anesthesia) [39].

Long term outcomes

By the time of outpatient clinic visit, six out of 23 patients (26.1 percent) had a recurrence of hernia, of whom one patient had undergone reoperation. All recurrences were found at the original hernia site. Another five patients (21.7 percent) had an asymptomatic bulging of the abdominal wall. Fourteen patients were evaluated by clinical examination combined with medical imaging, seven patients were evaluated with clinical examination, and in two patients it was unknown whether clinical examination was used with or without medical imaging. Patients with a recurrence or bulging often wore an abdominal binder.

Quality-of-life parameters

Patients reported a good quality of life on the EuraHS quality-of-life questionnaires (Table 3). Patients had no pain in rest or during activities and the worst pain they had felt in the last week was no pain. Patients had no restriction in their daily activities. They experienced only minor limitations in their activities outside the house. Patients that were capable of doing sports or heavy labor experienced limited restrictions. However, in the latter two situations there were six and seven patients respectively that could not perform these activities.

Table 3. Quality-of-life parameters
Outcomes measured with the EuraHS quality-of-life scale [32, 33] after complex abdominal wall hernia repair with PADM. Scores are expressed as median scores (range).

Pain at the side of the hernia 0 = no pain, 10 = worst pain imaginable	
Pain in rest (lying down)	0 – no pain (range 0–6)
Pain during activities (walking, biking, sports)	0 – no pain (range 0–8)
Pain felt during the last week	0 – no pain (range 0–10)
Restrictions of activities because of pain or discomfort at the site of the hernia 0 = no restriction, 10 = completely restricted, X = The patient does not perform this activity	
Restriction from daily activities (inside the house)	0 – no restrictions (range 0–10)
Restriction outside the house (walking, biking, driving)	1.5 (range 0–10; 2 times X)
Restriction during sports	1 (range 0–7; 6 times X)
Restriction during heavy labor	2 (range 0–9; 7 times X)
Cosmetic discomfort 0 = very beautiful, 10 = extremely ugly	
Shape of your abdomen	4 (range 0–10)
Site of the hernia	3.5 (range 0–10)

DISCUSSION

These results show that despite a high rate of postoperative wound infection no biological mesh had to be removed. Both the recurrence rate and the amount of bulging after long-term follow-up are significant (failure rate of 47.8 percent). The reported quality of life is good after repair of these complex hernias.

The use of biological mesh in complex abdominal wall hernia is relatively new. There are not that many studies comparable to ours regarding methodology and characteristics. The RICH study, in which the results of Strattice™ mesh (Acelity™, non-cross-linked porcine acellular dermal matrix) were analyzed, seems to have the most similarities in methodological approach [30]. Itani and colleagues found a recurrence rate of 28 percent after two years [30]. This is comparable to the outcome of this study (26.1 percent). In the study of Maxwell and colleagues a much lower recurrence rate of 11.2 percent was found after median 20.9 months [40]. Patients received an additional CT scan to confirm recurrence. Patients with bulging were excluded from the study. This could lead to certain bias, since bulging is also an unfavorable outcome. In a study by Rosen and colleagues a much higher recurrence rate of over 50 percent was found after three years of follow-up. In Rosen's study, the following meshes were assessed: Strattice™ (same mesh; non-cross-linked porcine acellular dermal matrix), Alloderm™ (non-cross-linked human dermal matrix), Biodesign® (porcine small intestinal submucosa sheet),

XenMatrix™ (non-cross-linked porcine acellular dermal matrix), and GORE® BIO-A® Mesh (biosynthetic web scaffold made of 67 percent polyglycolic acid (PGA): 33 percent trimethylene carbonate) [41]. This high recurrence rate could possibly be explained by a longer follow-up. Another difference is the use of a number of different meshes, which could also lead to a higher recurrence rate. Moreover, Itani and colleagues did not assess the amount of bulging in their study [30]. In this study, a bulging rate of 21.7 percent was found. This bulging rate is lower compared with data of a previous study from our study group (bulging rate 50.6 percent; unpublished data form the Permacol Dutch cohort study) [42]. This difference could be explained by the difference in material; cross-linked versus non-cross-linked porcine acellular dermal matrix.

The patients that were enrolled in this study were operated in three hospitals in Germany. Each hospital had at least one surgeon dedicated to abdominal wall surgery. These surgeons treated their patients with PADM. The surgeons also united themselves in the ROKI group to assess their results of PADM repair [31]. Aside from the multicenter character of the study, another important asset was the assessment of quality-of-life parameters. This is only rarely studied in complex abdominal wall hernia repair. These patients suffer not only from a complex abdominal wall hernia but also of multiple comorbidities and risk factors that increase the risk of postoperative complications. A previous study of Roth and colleagues published about quality-of-life parameters in this specific patient group [43]. In this study, they used the Short form-12 health survey [44] and found an improvement of the quality-of-life indicators after 12 months compared with the baseline. This improvement however was not significant. In the current study no comparison was made with the preoperative situation, since these data were not prospectively obtained.

The most frequent postoperative complication in this study was wound infection (39.1 percent). This percentage is slightly lower than in a recent study of Roth and colleagues [43]. Roth and colleagues found 43 percent wound infections after acellular dermal matrix placement (FlexHD® and Strattice™). The median follow-up was one year. The wound infection percentage in our study however was somewhat higher than previous studies by Itani and colleagues [30] (35 percent), Diaz and colleagues [45] (33 percent), Maxwell and colleagues [40] (26.2 percent), Helton and colleagues [46] (23 percent) and Cheng and colleagues [47] (5 percent). All studies [30, 40, 45-47] contained – in percent – a large group of patients that had a hernia classified as clean or clean-contaminated [27]. This could have led to a lower postoperative infection rate. In this study, PADM did not have to be removed representing a better result than found in the studies of Diaz and colleagues [45] (five mesh removals; 6.7 percent) and Helton and colleagues [46] (five mesh removals; 9.8 percent).

There is contrasting evidence available regarding biological meshes and their characteristics. A recent review by Sainfort and colleagues assessed the literature about biological abdominal wall matrices [48]. They concluded that there were no high-level evidence data on biological meshes that allowed prioritization of the various biological meshes according to their characteristics or their different manufacturing processes. A more recent study by Tripolli and colleagues assessed the literature on Permacol™, Strattice™, Surgisis®, Tutomesh™, and XenMatrix™ [49]. Eleven studies of a poor methodological quality were assessed and included in the review. They concluded that there was a striking statistical variability in the outcomes of all meshes. The only significant finding in their study was that cross-linked meshes had a significantly lower recurrence rate at 12 months than non-cross-linked meshes [49].

Incisional hernia repair is associated with overall financial losses [50]. Especially biological meshes are expensive and rarely used [51]. In the current study no cost analysis was performed. In a study of Huntington and colleagues a cost-analysis was performed comparing AlloDerm®, AlloMax™, FlexHD®, Strattice™, and XenMatrix™ [52]. In that study, Strattice™ was the second most expensive mesh (mesh charge per patients US$ 31,875 ± 17,960 and total costs hospital stay per patient US$ 140,394 ± 80,709). The mesh charges and total costs of hospital stay per patient seem higher in the United States than they are in the Netherlands, however these data are illustrative for the current ratios. In another study by Byrge and colleagues., a head-to-head comparison was performed between Permacol™ and Strattice™ meshes in a similar patient group. The costs of the mesh were significantly higher for Strattice™ (median cost $8940) compared with Permacol™ (median costs $1600). The use of Permacol™ resulted in a savings of $181,320 with similar clinical outcomes when compared with Strattice™ [53].

The field of complex abdominal wall hernia is in ongoing development. Therefore, alternatives for the use of biological mesh are explored. These alternatives could be found in the use of biosynthetic meshes. Meshes like Phasix™ Mesh, GORE® BIO-A® Mesh, and TIGR® Matrix Surgical mesh are made of slowly resorbable synthetic fibers. Köckerling and colleagues wrote recently a consensus review about mesh use in complex abdominal wall hernia [54]. They assessed all available literature, but concluded that there is lack of studies comparing the use of biological or biosynthetic meshes versus synthetic meshes in complex abdominal wall hernia. Therefore the routine use of biological and biosynthetic meshes could not be recommended. In a study by Buell and colleagues a cost analysis was performed in which the use of Strattice™ was compared with the use of Phasix™ Mesh [55]. Strattice™ was found to be significantly more expensive than Phasix™ Mesh (total costs per patient: US$ 48,793.43 versus US$ 39,223.35). It was a retrospective study with limited patient numbers (42 patients received Strattice™ and

31 patients received Phasix™ Mesh) and the financial follow-up was only 90 days. It is worth exploring this comparison in a prospective study with a longer follow-up since long-term complications like hernia recurrence, bulging, and fistula occur mostly after 90 days follow-up.

Limitations

The mesh in this study (PADM) is not used on a large scale and therefore there is only a limited amount of patients that can be assessed. As only patients with potentially contaminated and contaminated incisional hernia were evaluated, there was only a relative small number of patients to include in this study. Although there were more hospitals that work with PADM, not all surgeons seemed that keen to share their data. Another limitation is the design of the study (a cross-sectional cohort study). Data were partly retrospective and partly prospectively collected. This could have led to a bias.

CONCLUSION

The data of this study show that despite a high rate of postoperative wound infection no biological mesh had to be removed. There was a high failure rate of 47.8 percent due to recurrences and bulging. However, patients reported a good quality of life after repair of these complex hernias.

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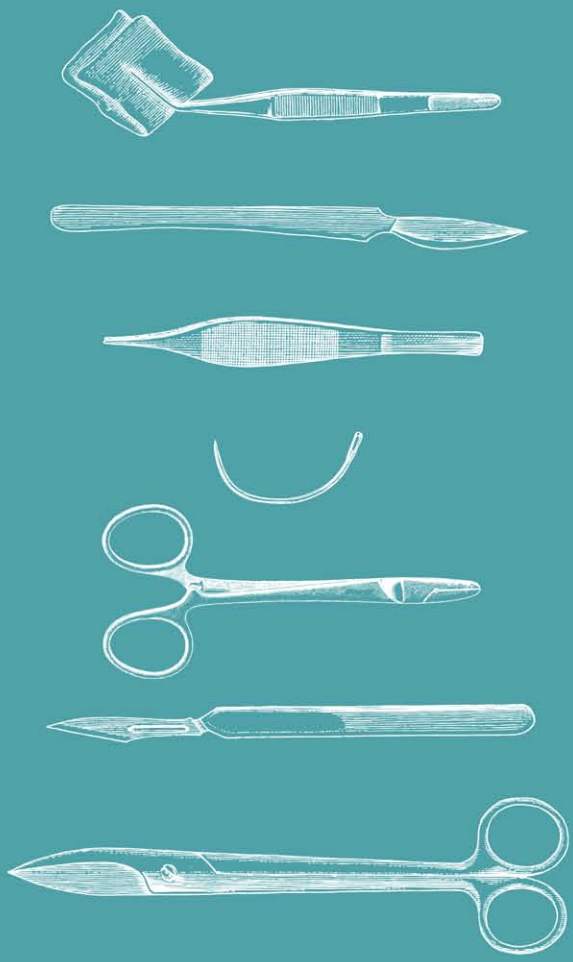
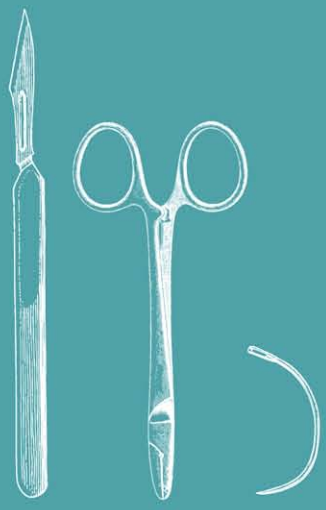
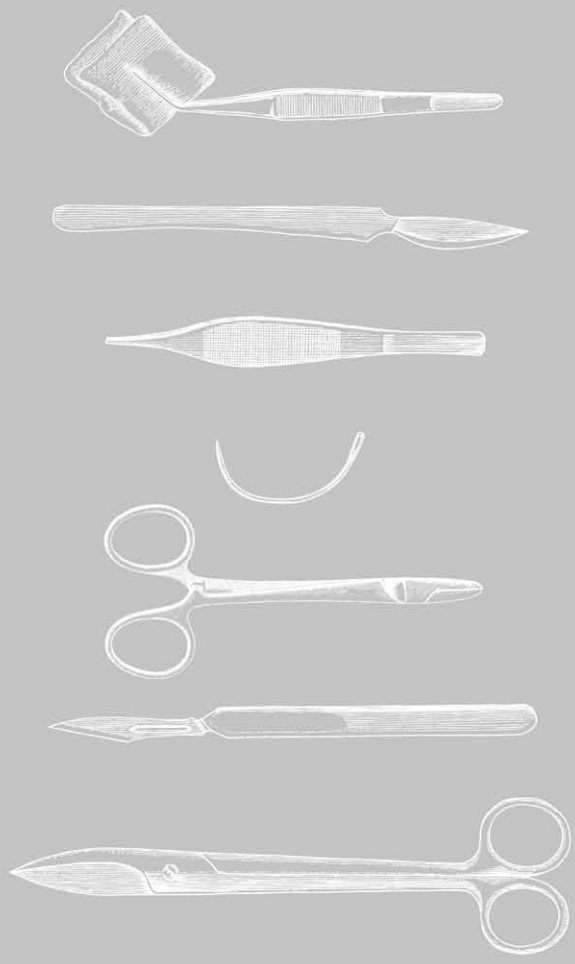


part 4

summary, general discussion and future perspectives





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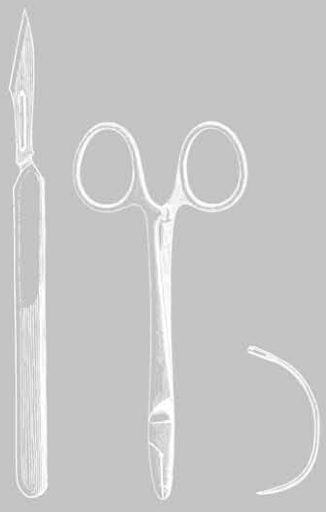
Summary



In **Chapter 1** the subject of the thesis is introduced: different types of repair of abdominal wall hernias. In this thesis, abdominal wall hernias include umbilical, inguinal, incisional, and complex abdominal wall hernias. There are mainly two techniques to repair hernias: by suture repair, only successful in small hernias, and by mesh repair. Suture repair can be executed with various suture materials and in various techniques (interrupted sutures or continuous sutures). Mesh repair can also be executed with various mesh materials (synthetic mesh, biological mesh, or resorbable synthetic mesh). These meshes can be placed in different anatomical planes (onlay, inlay, sublay, and intra-abdominally). Both suture and mesh techniques can be executed in an open or laparoscopic fashion.

PART 1. MESH IN EXPERIMENTAL MODELS

The **first part** of this thesis consists of studies about the use of mesh in experimental models.

Chapter 2 reports the results of a systematic review of the literature on experimental animal models for abdominal wall hernia research. In this chapter, a complete overview of all animal models published between 2000 and 2014 is provided. It was decided to limit the study to 168 articles concerning rat models. It was concluded that there is a lack of comparability among experimental hernia research, limiting the impact of this experimental research. Consequently the establishment of guidelines for experimental hernia research by the European Hernia Society is proposed.

In **Chapter 3** data of a randomized animal study are presented, in which five meshes were assessed: Parietene™ (polypropylene), Permacol™ (cross-linked porcine acellular dermal matrix), Strattice™ (non-cross-linked porcine acellular dermal matrix), XCM Biologic® (non-cross-linked porcine acellular dermal matrix), and Omyra® Mesh (condensed polytetrafluoroethylene). The meshes were implanted into the abdominal wall of healthy rats. The rats were sacrificed after 30, 90, or 180 days. Incorporation, shrinkage, adhesions, abscess formation, and histology were assessed for all meshes. It was concluded that based on incorporation, adhesions, mesh shrinkage, and histologic parameters Strattice™ performed best in this experimental rat model.

Most meshes respond differently in presence of an infection. In **Chapter 4** both biological and synthetic meshes were evaluated in an experimental model of peritonitis to define their characteristics in vivo. Five meshes were investigated: Parietene™ (polypropylene), Permacol™ (cross-linked porcine acellular dermal matrix), Strattice™ (non-cross-linked porcine acellular dermal matrix), XCM Biologic® (non-cross-linked porcine acellular

dermal matrix), and Omyra® Mesh (condensed polytetrafluoroethylene). The rats were killed after either 30, 90 or 180 days. Incorporation and shrinkage of the mesh, adhesion coverage, strength of adhesions, and histology were analyzed. This experimental study suggested that XCM Biologic® was superior in terms of incorporation, macroscopic mesh infection, and histological parameters such as collagen deposition and neovascularization. There must be sufficient overlap of mesh during placement, as XCM Biologic® showed a high rate of shrinkage.

Adhesions are a common complication of mesh in the intra-abdominal cavity. The presence of adhesions can be evaluated by many different adhesions scoring systems (qualitative versus quantitative scoring of adhesions). In **Chapter 5** a consensus score on mesh-tissue adhesions is presented. This adhesion score is designed by a panel of international expert using a modified Delphi method (RAND-UCLA). This study comprises of two questionnaire-based rounds and one international consensus meeting. The META-consensus score presented in this paper can be used to assess and classify mesh-related adhesions and is based on the opinion of 18 international leading experts. The use of this score is advocated in all future research to increase the interstudy comparability and objectivity.

PART 2. USE OF MESH

The **second part** of this thesis consists of studies about the use of mesh in patients. These studies are performed in patients that underwent a surgical repair of their umbilical hernias.

In **Chapter 6** the data of a randomized controlled trial are presented in which patients with small umbilical hernias were assessed. Small umbilical hernias of 1–4 cm can be repaired with either sutures or mesh. In this randomized controlled trial were both treatments compared in umbilical hernia repair in adults. Eligible participants were adults aged at least 18 years with a primary umbilical hernia of diameter 1–4 cm. Patients were randomly assigned (1:1) intraoperatively to either suture repair or mesh repair. Patients underwent physical examinations at 2 weeks, and 3, 12, and 24–30 months after the operation. The primary outcome was the rate of recurrences of the umbilical hernia after 24 months. The median follow-up was 25.1 months. After a maximum follow-up of 30 months, there were significantly fewer recurrences in the mesh group than in the suture group. It was concluded that this is the first study showing high level evidence for mesh repair in patients with small umbilical hernias of diameter 1–4 cm. Hence it is suggested that mesh repair should be used for operations on all patients with an umbilical hernia of this size.

In **Chapter 7** data of a meta-analysis are presented in which it was assessed whether treatment of umbilical hernias with either mesh or sutures leads to less recurrences. The primary aim was to assess differences in the risk of recurrence (clinical and reoperation) and secondarily differences in infections, seroma formation, hematomas, chronic pain, cosmetic result, and quality of life. A systematic review with meta-analyses was conducted. Five randomized controlled trials were identified (mesh repair n = 326 versus non-mesh sutured repair n = 330) and 602 records were excluded. The randomized controlled trials included patients with defect diameters of ≥1–4 cm. Mesh repair reduced the risk of recurrence compared with sutured repair with a relative risk (RR) of 0.28. It was concluded that mesh repair is recommended for umbilical hernia of ≥1 cm up to 4 cm. More evidence is needed for the optimal placement of the mesh (sublay or onlay) and to assess the role of mesh in patients with an umbilical hernia <1 cm.

In **Chapter 8** the data of a systematic review of the literature are presented. Umbilical hernia is often treated under general anesthesia. However, in this review the feasibility of local anesthesia is assessed for the surgical treatment of umbilical hernia. Outcome parameters were duration of surgery, surgical site infection, perioperative and postoperative complications, postoperative pain, hernia recurrence, time before discharge, and patient satisfaction. The systematic review resulted in nine included articles. There is a large variation in anesthetic agents and there is no consensus about injection techniques. No conversions to general anesthesia were described. Local anesthesia for umbilical hernia seems safe and feasible. However, the advantages of local anesthesia are not sufficiently demonstrated, due to the heterogeneity of included studies. Therefore a randomized controlled trial is proposed comparing general versus local anesthesia for umbilical hernia repair.

PART 3. COMPLICATIONS OF MESH

The **third part** of this thesis consists of studies about possible complications of mesh in patients.

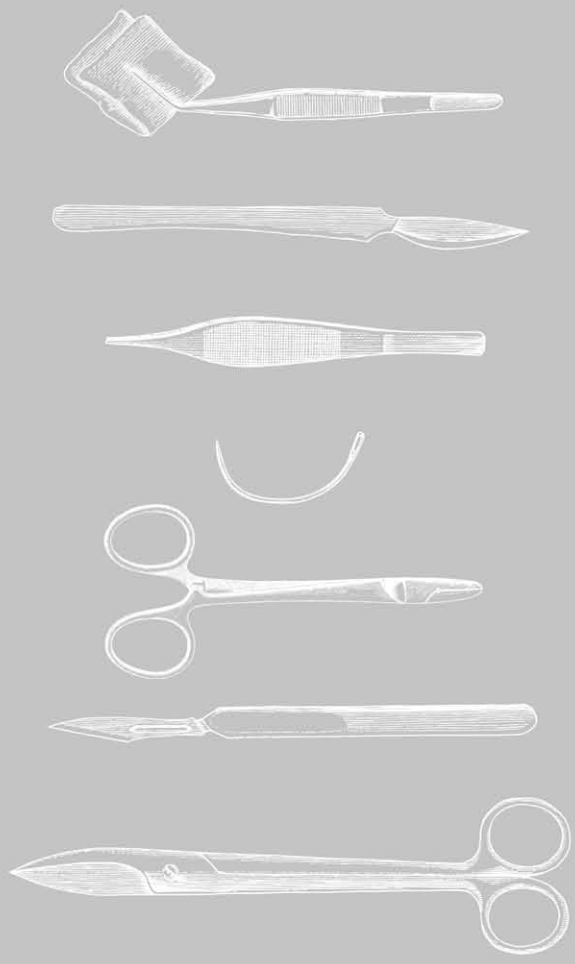
Chronic postoperative inguinal pain is a common complication after mesh-assisted inguinal hernia repair. In **Chapter 9** it was assessed in a meta-analysis whether the use of a new self-gripping mesh instead of a sutured mesh leads to a decrease in chronic postoperative inguinal pain. In the present meta-analysis, the outcomes of ten randomized controlled trials enrolling 2541 patients were pooled. The mean follow-up was 24 months. There was no significant difference in the incidence of chronic pain, recurrence, or foreign body sensation, between the self-gripping mesh and sutured mesh group at

all follow-up time points. The mean operating time however was significantly shorter in the self-gripping mesh group. It was concluded that the self-gripping mesh has comparable results with a sutured mesh regarding the incidence of chronic postoperative inguinal pain, recurrence and foreign body sensation. However, long-term results are still based on relatively small patient numbers and outcomes measures are heterogenic. The main advantage of the self-gripping mesh is the consistently significantly reduced operation time.

In **Chapter 10** an algorithm is presented with a treatment strategy for the management of patients with chronic postoperative inguinal pain. The goal of this study was to design an expert-based algorithm for diagnostic and therapeutic management of chronic inguinal postoperative pain. A group of surgeons considered experts on inguinal hernia surgery was solicited to develop the algorithm. Consensus regarding each step of an algorithm proposed by the authors was sought by means of the Delphi method leading to a revised expert-based algorithm. With the input of 28 international experts, an algorithm was created for a stepwise approach for the management of chronic postoperative inguinal pain. Twenty-six participants accepted the final algorithm as a consensus model. It was concluded that there is a need for guidelines with regard to management of chronic postoperative inguinal pain. This algorithm can serve as a guide with regard to the diagnosis, management, and treatment of these patients, and can improve clinical outcomes. If an expectative phase of a few months has passed without any amelioration of chronic postoperative inguinal pain, a multidisciplinary approach is indicated and a pain management team should be consulted.

In **Chapter 11** data are presented about patients that had to undergo a complex abdominal wall hernia repair. All patients were treated with a cross-linked biological mesh (Permacol™). A total of 77 patients was assessed in the outpatient clinic. The mean follow-up was 22.2 ± 12.6 months. The most frequent postoperative complication was wound infection (n = 21; 27.3 percent), meshes had to be removed in five patients (6.5 percent). By the time of their visit to the outpatient clinic, 22 patients (28.6 percent) had a recurrence of whom ten (13 percent) had undergone reoperation. Thirty-nine patients (50.6 percent) had bulging of the abdominal wall. It was concluded that bulging and/or recurrence were frequently observed in patients treated with a cross-linked biological mesh for complex abdominal wall hernia repair. Considering both recurrence and bulging as undesirable outcomes of treatment, a total of 46 patients (59.7 percent) had an unfavorable outcome. Infection rates were high, but comparable with similar patient cohorts. Quality-of-life analyses revealed that patients were satisfied with their general health.

In **Chapter 12** another group of patients with a complex abdominal wall hernia is presented. These patients underwent a hernia repair and were treated with a non-cross-linked biological mesh (Strattice™). Twenty-seven patients have been assessed for long-term follow-up (14 male, mean age 67.5 years, mean follow-up 42.4 months). With regard to the surgical intervention, the most frequently used mesh size was 400 cm^2 and the most frequent postoperative complication was wound infection (39.1 percent). The non-cross-linked biological mesh did not have to be removed. Four patients had passed away after surgery (range 5–904 days). By the time of outpatient clinic visit, six out of 23 patients (26.1 percent) had a recurrence of hernia, of whom one patient had undergone reoperation. Another five patients (21.7 percent) had bulging of the abdominal wall. Quality-of-life analyses revealed that patients judged their scar with a median 3.5 out of 10 points (0 is best) and judged their restrictions during daily activities with a median of 0 out of 10.0 (0 means no restriction). It was concluded that despite a high rate of postoperative wound infection no biological mesh had to be removed. Both the recurrence rate and the amount of bulging after long-term follow-up are high (failure rate of 47.8 percent). The reported quality of life is good after repair of these complex hernias.



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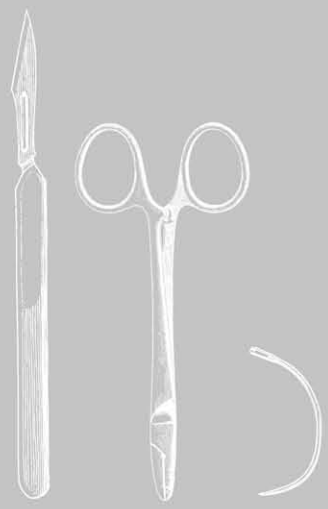
General discussion



Abdominal wall hernia is a frequently occurring disease. In this thesis, umbilical, inguinal and incisional hernia, and different aspects of their respective treatment strategies are discussed. The most common treatment of an abdominal wall hernia is operation with mesh [1-6]. The use of mesh has become a major component in hernia operations. There are various meshes available; however the "ideal mesh" has not been developed yet [7-9].

PART I: MESH IN EXPERIMENTAL MODELS

In the preclinical phase, meshes are investigated in experimental models, both in vitro and in vivo. In this thesis, only results of in vivo studies were presented. Preclinical mesh assessment is necessary to assess the biocompatibility and effectiveness of new meshes before using them in patients [10-12]. **Chapter 2** of this thesis was about the best experimental model for mesh testing in vivo [13]. An in-dept literature assessment showed that there is a large variety in experimental models and that the quality of experimental mesh studies strongly varies. This has also been acknowledged by the United Kingdom-based scientific organization National Centre for the Replacement Refinement & Reduction of Animals in Research. They designed the ARRIVE guidelines to stimulate profound scientific reports about experimental animal studies [14]. To improve the quality of experimental hernia research, guidelines should be designed to improve publishing and reporting of these studies.

The introduction of mesh in incisional hernia repair has drastically lowered the 10-year recurrence rates [3]. Currently, there are many different meshes available; meshes differ in material of origin, structure, shape, weight, and even composites are available [15]. The most often used products are conventional synthetic meshes and polypropylene is the most popular material, as it is biocompatible, strong and cheap [16]. In specific situations, the choice for a synthetic mesh is less favorable. In those often contaminated situations a biological mesh could provide a solution [17, 18]. Since these meshes are expensive, they are only rarely used. Therefore is only little known about these biological meshes compared with the synthetic meshes. Most studies have short-term follow-up and heterogeneous populations [19-21]. We investigated commonly used biological and synthetic meshes in an intraperitoneal environment on incorporation, shrinkage, adhesion formation, abscess formation, and histology after 30, 90, and 180 days. Two different experimental animal studies were performed: (1) the meshes were examined in a physiologic, non-contaminated rat model with intraperitoneal mesh placement (**Chapter 3**), and (2) the meshes were examined in a peritonitis rat model with intraperitoneal mesh placement (**Chapter 4**) [22]. The performance of the meshes differed in the presence or absence of an infection. In the absence of infection, Strattice™ performed

best. However, in the presence of infection, XCM Biologic® was superior. Both meshes are non-cross-linked porcine acellular dermal matrices. Strattice™ and XCM Biologic® performed best in the two experiment, taking into account incorporation, mesh shrinkage, adhesion surface, and adhesion strength. Intra-abdominal adhesions can lead to serious complications, therefore the surgeon has an important role in the prevention of adhesion formation.

Placement of a mesh in the intra-abdominal cavity is a well-known inducer of adhesions between the intestines and mesh [23]. The presence of adhesions is a known cause of serious postoperative complications such as bowel obstructions [24, 25]. If intra-abdominal adhesions occur in the presence of a mesh, there is no consensus yet on the clinical scoring of these adhesions. The META consensus score was designed based on the opinion of 18 international leading experts and deduced by a Delphi method (**Chapter 5**). The score consist of four main items: "percentage of mesh surface covered with adhesions", "tenacity", "thickness of adhesions", and "organ involvement". All parameters consist of macroscopic items. However, also macroscopic items could be of great interest. The quantity of inflammatory cells, the amount of collagen deposition, and neovascularization can provide valuable information regarding the foreign body response on a mesh and the adhesions formation [25, 26]. Microscopic parameters should therefore be assessed in future research. The new scoring system was designed to improve comparability between different studies about adhesions. The score is based on the consensus between 18 experts in adhesion research. These experts represent a large group of experts from the hernia community. Since it is a consensus score, there will always be researchers that cannot fully agree with the rationale behind this new scoring system. In comparison with existing adhesion scoring systems, the META consensus score is more enhanced. In this new scoring system, the best items of five adhesion scoring systems were integrated to one scoring system. The META consensus score is based on previous studies from De Oliveira and colleagues [26], Diamond and colleagues [27], Zühlke and colleagues [28], Bellón and colleagues [29], and Garrard and colleagues [30]. The META consensus score has not been validated yet, nor have other adhesion scoring systems. The META consensus score was designed to improve interstudy comparability. We therefore recommend to use the META consensus score in all new studies on adhesions; not only to maximize the interstudy comparability, but also to validate the new scoring system.

PART II: USE OF MESH

The use of mesh in patients is legally only allowed, when meshes pass various tests in the preclinical phase. In this part of the thesis, the use of meshes in umbilical hernia patients was assessed. In a previous study by Schumacher and colleagues about umbilical hernia repair high recurrence rates of up to 54.5 percent have been reported in the suture repair group [31]. Previous data about large umbilical hernias suggest low recurrence rates of up to 1 percent after mesh repair [4, 32, 33]. For the smaller umbilical hernias (diameter ≤4 cm) there is no solid evidence that the use of mesh instead of suture repair leads to better results. Therefore, most surgeons would not use mesh repair for many of these small hernias [34].

The data from the HUMP trial showed that there were significantly more recurrences of umbilical hernia after suture repair compared with mesh repair (**Chapter 6**) [35]. These data are similar to previous findings by Arroyo and colleagues [32] (11 percent after interrupted suture repair) and Polat and colleagues [33] (11 percent recurrence after Mayo repair). The recurrence rates were however slightly higher than in the study of Christoffersen and colleagues [36] (5.6 percent after suture repair). The amount of postoperative complications found in our study was fairly low: 8 percent of patients had complications after mesh repair versus 3 percent of patients after suture repair. In literature the complication rates vary: a previous study of Arroyo and colleagues [32] found complications in 10 percent of patients after mesh repair versus 11 percent after suture repair, and Polat and colleagues [33] found that 15.6 percent of patients had complications after mesh repair versus 16.7 percent after suture repair. Quality-of-life analyses revealed no significant differences between both study groups on the outcome of SF-36 and EQ-5D-5L preoperatively and at 12 months after operation. Thus was concluded that this is the first study showing high level evidence for mesh repair in patients with small umbilical hernias of diameter 1–4 cm. Evidence for the use of mesh in umbilical hernia repair was previously limited to retrospective cohort studies [37-41], prospective observational studies [4, 42, 43], hernia register analyses [36, 44], and randomized controlled studies [32, 33] with smaller sample sizes than this study [35]. We suggest mesh repair should be used for operations on all patients with an umbilical hernia of 1–4 cm.

The data of the previous chapter were used in a new meta-analysis (**Chapter 7**) [45]. In this meta-analysis the data of the following studies were included: Arroyo and colleagues [32], Polat and colleagues [33], Lal and Ase [46], Sadiq and Khurshid [47], and Kaufmann and colleagues [35]. Meta-analysis of these data revealed that mesh repair of umbilical hernia significantly lowered the amount of recurrences compared with suture repair. There was no increase found in the risk of surgical site infection, seroma forma-

tion, hematomas, or chronic pain after mesh repair. Even though this meta-analysis was based on only randomized controlled trials, there were differences found in the quality of the included studies. There was only one randomized controlled trial identified that had a high quality [35]. The amount of patients in each study varied strongly (range 50–300 patients per study), and most studies did not report in their paper whether they were based on a statistical power calculation prior to the start of the study. Therefore, studies could have been underpowered. Another issue that has not been addressed in the included studies, is how to handle the smallest umbilical hernias (<1 cm). A new, high-quality randomized controlled trial with long-term follow-up could address the risk for recurrence and the incidence of chronic postoperative pain after repair of umbilical hernias smaller than 1 cm. We concluded that mesh repair is probably safe and can be recommended for routine use to reduce the risk of recurrence after a small- and middle-sized umbilical hernia repair [45]. In the future, more data are necessary to determine the optimal placement of mesh (sublay or onlay) and to assess whether there is an indication for mesh in patients with an umbilical hernia defect <1 cm.

In the Netherlands, approximately 4500 umbilical hernias are repaired every year. Most of these umbilical hernia operations are performed under general anesthesia. Another option is an operation under local anesthesia. This technique has been thoroughly investigated for inguinal hernias. However, only a minority of 7 percent of Dutch surgeons uses local anesthesia in Lichtenstein repair [48]. The use of local anesthesia however could prevent complications related to general anesthesia and could lead to a shorter duration of stay in the hospital. There is a lack of convincing literature on umbilical hernia repair under local anesthesia [49]. A systematic review was performed on the safety, feasibility, and advantages of local anesthesia for the repair of umbilical hernia (**Chapter 8**) [50]. The data showed that the use of local anesthesia in umbilical hernia repair led to a shorter length of postoperative stay, and that repair of a paraumbilical hernia performed under local anesthesia led to a shorter duration of surgery [50]. The use of local anesthesia did not lead to perioperative complications, serious postoperative complications, allergic responses or anesthesia-related deaths. The difficulty in this systematic review was the heterogeneity of the included studies. There was no consensus regarding the local anesthetic drug, nor about the technique to achieve local anesthesia. A standardized protocol is missing and should be designed to achieve a better implementation of the use of local anesthesia in umbilical hernia repair. Also the design of the trials on this topic should be adjusted. Pain is an important outcome parameter. However, not all studies in this systematic review described pain as an outcome and various pain measurement scales were used. We could not conclude from the available data if patients operated because of an umbilical hernia had a shorter duration of stay if they were operated under local anesthesia. Based on the current findings, it was

concluded that local anesthesia for umbilical hernia seems safe and feasible. Though due to heterogeneity in the included studies, the advantages of local anesthesia are not sufficiently demonstrated. Further studies are necessary to investigate whether there is an advantage of the use of local anesthesia compared with general anesthesia for umbilical hernia repair.

PART III: COMPLICATIONS OF MESH

The use of mesh in abdominal wall hernia has not only advantages, but also leads to complications in certain situations. Complications after inguinal hernia repair pose a significant burden on individual patients and society due to the high numbers of repair procedures worldwide. A well-known complication is chronic postoperative inguinal pain. A possible solution to lower the incidence of chronic postoperative inguinal pain could be the use of a self-gripping mesh (ProGrip™ mesh) instead of a sutured mesh. A meta-analysis of recent long-term results was undertaken (**Chapter 9**) [51]. The aim of this study was to compare these long-term results with the results of a Lichtenstein herniorrhaphy with a sutured mesh. The analyses were focusing on chronic pain, recurrence rate, foreign body sensation, and operation duration. From this meta-analysis, the following conclusions were drawn: the use of self-gripping mesh has results comparable to sutured mesh regarding the incidence of recurrence and chronic postoperative inguinal pain. The use of a self-gripping mesh does not resolve chronic postoperative inguinal pain; however, conclusions on long-term results are still based on relatively small patient numbers. A complicating factor was the large heterogeneity in the included studies: there were vast differences in the definition of chronic postoperative inguinal pain, the assessment of patients, and the presentation of outcomes, making it hard to compare incidence rates. We therefore plead for a more uniform methodology of studies, to improve the interstudy comparability. Consistently, the main advantage of using a self-gripping mesh is its efficiency (consistently significantly reduced operation times compared with the sutured mesh).

Since the introduction of tension-free mesh repair of inguinal hernias, the recurrence rates dropped to uniformly low recurrence rates. The main complication is chronic postoperative inguinal pain. No consensus guidelines existed for the management of this condition. The goal of this study was to design an algorithm for the diagnostic and therapeutic management of chronic postoperative inguinal pain based on expert opinion and deduced by Delphi method (**Chapter 10**) [52]. With the input of 28 international experts, an algorithm for a stepwise approach for management of chronic postoperative inguinal pain was created. The main outcome was that after an expectative phase of a

few months has passed without any decrease of the pain, one should choose a multidisciplinary approach and consult a pain management team. The treatment should include pharmacologic, behavioral, and interventional modalities, including nerve blocks [52]. If surgery is considered, a triple neurectomy, correction for recurrence with or without neurectomy, and meshoma removal – if indicated – should be performed. If surgeons are not that experienced with remedial operations in case of chronic postoperative inguinal pain, they are encouraged to refer their patients to dedicated hernia surgeons [53].

When treating patients with a complex abdominal wall hernia, the use of synthetic mesh in potentially contaminated and contaminated incisional hernias may lead to a higher morbidity and mortality after such operations. Use of biological meshes may provide a solution. However, due to their price they are only scarcely used and therefore only little data are known. A cohort of patients underwent complex abdominal wall hernia repair with a cross-linked porcine acellular dermal matrix (Permacol™) (**Chapter 11**). It was found that recurrence and bulging are frequently observed and 59.7 percent of the patients had an unfavorable outcome. Infection rates were high, but comparable with similar patient cohorts. Quality-of-life analyses revealed that patients were satisfied with their general health, but scored significantly lower on most quality-of-life modalities of the Short Form-36 questionnaire. This study enrolled patients belonging to a very difficult treatment group. All patients had a potentially contaminated or infected ventral hernia i.e. grade 3 to 4 hernia according to the Ventral Hernia Working Group classification [54]. Most patients suffered from multiple comorbidities and risk factors which increased the risk of postoperative complications such as wound infection and hernia recurrence. The recurrence rate in our study (28.6 percent) was similar to that seen in the RICH study [55]. In another study of Rosen and colleagues a much higher recurrence rate of over 50 percent was found after three years of follow-up [56]. In our study, only ten out of 77 patients underwent reoperation to treat hernia recurrence. This is relatively low in comparison with other studies published in literature [56, 57]. Given the patient population, there was a relatively low recurrence rate in our study. However, a high rate of abdominal wall bulging was observed. This finding was also seen in other studies, but these studies displayed a lower percentage of bulging than the present study [58, 59]. An explanation for this difference could be that larger hernia defects were included in our study in which patients also had a higher Ventral Hernia Working Group classification. In our study, 21 patients had a wound infection, but many of these infections could be treated conservatively. The mesh removal rate following a wound infection was 6.5 percent in the current study, a rate similar to that seen in the study of Diaz and colleagues [57], but much lower than that seen by Helton and colleagues [60] and Rosen and colleagues [56]. Until date, no ideal mesh has been identified for complex abdominal wall hernia repair. Therefore future studies are required. It is nevertheless of

paramount importance that both the patient and the surgeon have realistic expectations of the treatment with cross-linked porcine acellular dermal matrix.

Another alternative could be the use of non-cross-linked porcine acellular dermal matrix. This is another type of biological matrix, which is also only rarely used because of its costs [61-64]. A cohort of patients undergoing a complex abdominal wall hernia repair was treated with a non-cross-linked porcine acellular dermal matrix (Strattice™) (**Chapter 12**). Twenty-seven patients have been assessed for long-term follow-up (14 male, mean age 67.5 years, mean follow-up 42.4 months). Four patients had passed away after surgery (range: 5–904 days). The most observed postoperative complication was wound infection (39.1 percent). No meshes needed to be removed. Six out of 23 patients (26.1 percent) had a recurrence of hernia, of whom one patient had undergone reoperation. Another five patients (21.7 percent) had bulging of the abdominal wall. Quality-of-life analyses revealed that patients judged their scar with a median 3.5 out of 10 points (0 is best) and judged their restrictions during daily activities with a median of 0 out of 10.0 (0 means no restriction). These results show that despite a high rate of postoperative wound infection no biological mesh had to be removed. Both the recurrence rate and the amount of bulging after long-term follow-up are significant (failure rate of 47.8 percent). The reported quality of life is good after repair of these complex hernias. This study has a similar recurrence rate as the RICH study by Itani and colleagues [55]. In the RICH study, a recurrence rate of 28 percent was found after two years of follow-up [55]. The recurrence percentage in this study is 26.1 percent, the follow-up in this study is however much longer (42.4 months versus 24.0 months [55]). In another study of Maxwell and colleagues a much lower recurrence rate of 11.2 percent was found after median 20.9 months follow-up [65]. Maxwell and colleagues had both a lower recurrence rate, but also a shorter follow-up than our study. The patients in Maxwell's study received an additional CT scan to confirm recurrence. Patients with bulging on the CT scan were excluded from the study. Excluding this subgroup could lead to certain bias, since bulging is also an unfavorable outcome. In a study by Rosen and colleagues a much higher recurrence rate of over 50 percent was found after three years of follow-up. In Rosen's study, the following meshes were assessed: Strattice™, Alloderm™, Biodesign®, XenMatrix™, and GORE® BIO-A® Mesh [56]. The high recurrence rate could be explained by the use of different meshes. The follow-up is shorter than in this current study. In this study, the most observed postoperative complication was wound infection (39.1 percent). This percentage is slightly lower than in a study by Roth and colleagues [66] (43 percent). The median follow-up was one year. The wound infection percentage in our study however was somewhat higher compared with other studies (Itani and colleagues [55] (35 percent), Diaz and colleagues [57] (33 percent), Maxwell and colleagues [65] (26.2 percent), Helton and colleagues [60] (23 percent) and Cheng and colleagues [67]

(5 percent)). All studies [55, 57, 60, 65, 67] included hernias that were classified as clean or clean contaminated according to the Ventral Hernia Working Group classification [54]. This could have led to a lower postoperative infection rate. In this study, the mesh did not have to be removed representing a better result than found in the studies of Diaz and colleagues [57] (five mesh removals; 6.7 percent) and Helton and colleagues [60] (five mesh removals; 9.8 percent). Alternatives for the use of biological mesh are explored. These alternatives could be found in the use of biosynthetic meshes (like Phasix™ Mesh, GORE® BIO-A® Mesh, and TIGR® Matrix Surgical mesh). However, Köckerling and colleagues wrote recently a consensus review about mesh use in complex abdominal wall hernia concluding that there is lack of studies comparing the use of biological or biosynthetic meshes versus synthetic meshes in complex abdominal wall hernia Therefore the routine use of biological and biosynthetic meshes could not be recommended [68].

CONCLUSION

Regarding all evidence, it can be concluded that abdominal wall hernia surgery is a diverse field of surgery. Although there are many different preclinical and clinical studies available; one still has to assess the value of all these data. Therefore the more complex abdominal wall hernia surgery should be executed by dedicated hernia surgeons. These surgeons will be more familiar with the varieties in "hernia disease", the anatomical possibilities, and materials (meshes, fixation techniques). The choice when which mesh with which fixation technique (suture, staple, glue) will be applied is a decision based on a large variety of research, but should still be a tailormade approach for each patient. Still more research needs to be performed to assess the most suitable mesh for complex abdominal wall hernia management.

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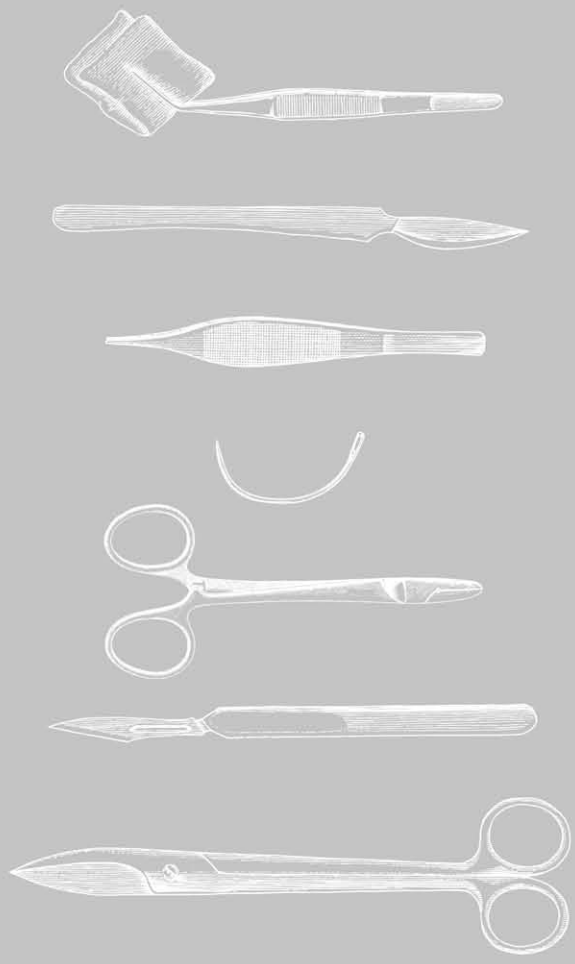

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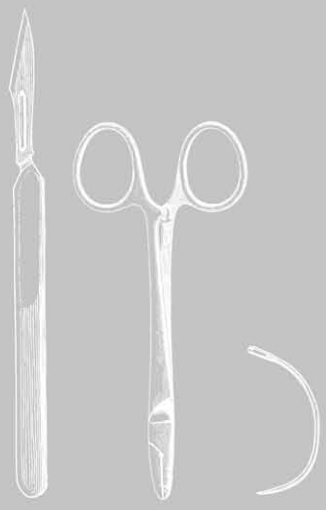
Future perspectives



The future of abdominal wall hernia research lies within reach and there are various things that can brighten this future.

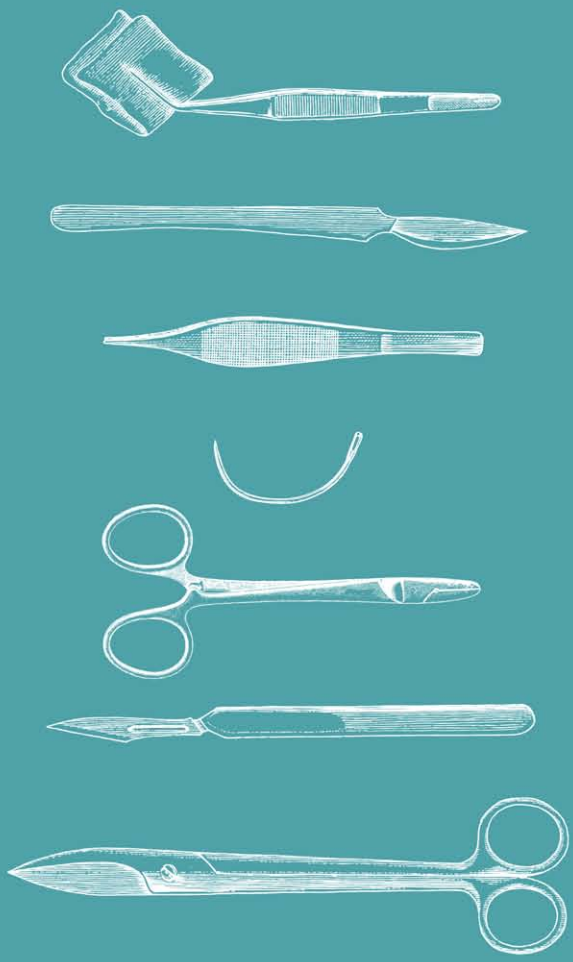
Most important is the attitude towards abdominal wall hernia repair. For years it has been a disease that surgeons treated as "part of their jobs", now it is evolving towards a new and exciting research field with many opportunities. These opportunities lie within research, but also in collaboration between various fields.

Research was traditionally performed within universities, however mesh products were assessed premarket as well by mesh manufacturers. Results of the latter are only rarely published. Collaboration in hernia research gives responsibility to the mesh industry, the researchers, and the healthcare professionals. It can lead to more transparency. It would be a great development if mesh manufacturers could only market their products with approved data. These data should be gathered by independently working researchers that should be working without sponsoring by individual mesh manufacturers. In this respect the role of international scientific societies like the European, American and Asian Pacific Hernia Societies are considered pivotal.

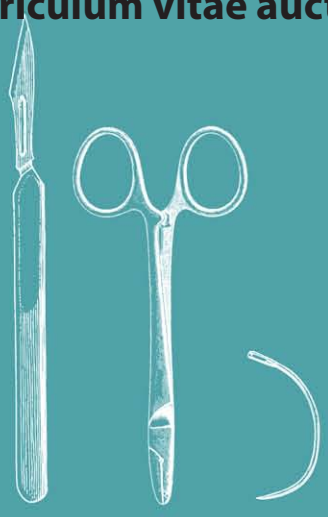
Collaboration could not only lead to better and fairer sharing of results, but in case of premarket studies, it can also lead to a decrease in animal studies. In this respect have simulation models of the abdominal wall – as recently developed by our research group – already proven to be of help. This all goes well with the adagio reduction, replacement and refinement. This adagio is used in the design of animal studies to decrease the number of animals that are used within a study.

Another way of collaboration is through social media. In December 2012, a Facebook group for hernia enthusiasts was established. This International Hernia Collaboration has grown ever since to an online community of to date almost 7000 members. On this Facebook site surgeons can share their cases via short videos or ask for advice from their fellow hernia colleagues in a difficult case.

Finally, researchers and hernia surgeons must wonder what is the most important outcome of abdominal wall hernia surgery. What is the true hernia parameter? Is it the percentage of recurrences (easily quantified) or is it the regained quality of life of an individual patient? And lies the solution in the use of mesh? Patients and patient-reported outcomes have to be involved in research. Generous striving for new collaborations!



appendices



NEDERLANDSE SAMENVATTING

Hoofdstuk 1 beschrijft het onderwerp van dit proefschrift: verschillende typen operaties van buikwandbreuken. In dit proefschrift omvat de term buikwandbreuken navelbreuken, liesbreuken, littekenbreuken en complexe buikwandbreuken. Er zijn grosso modo twee technieken om buikwandbreuken te behandelen: door deze te hechten (alleen succesvol bij kleine buikwandbreuken) of door een mesh (mat) te plaatsen. Een operatie met behulp van hechtingen alleen kan worden uitgevoerd met verschillende hechtmaterialen en verschillende technieken (staande hechtingen of doorlopende hechtingen). Herstel door middel van mesh kan worden uitgevoerd met verschillende soorten meshes (synthetische mesh, biologische mesh of resorbeerbare synthetische mesh). De meshes kunnen worden geplaatst in verschillende anatomische vlakken (onlay, inlay, sublay en intra-abdominaal). Zowel herstel door middel van hechtingen als met een mesh kan uitgevoerd worden door gebruik te maken van een open of een laparoscopische techniek.

DEEL 1. MESH IN EXPERIMENTELE MODELLEN

Het **eerste deel** van dit proefschrift omvat studies over het gebruik van mesh in experimentele diermodellen.

In **Hoofdstuk 2** worden de resultaten besproken van een systematische review van de literatuur over het gebruik van experimentele diermodellen bij onderzoek naar buikwandbreuken. In dit hoofdstuk wordt een compleet overzicht gegeven van alle diermodellen die gepubliceerd zijn tussen 2000 en 2014. Er werd besloten de zoektermen te limiteren op ratten, waarbij gekeken werd naar 168 artikelen over ratmodellen. Daarbij werd geconcludeerd dat er een gebrek aan vergelijkbaarheid is bij experimentele studies over buikwandbreuken, waardoor de impact van dit onderzoek afneemt. Er wordt voorgesteld om richtlijnen voor experimentele studies over buikwandbreuken op te stellen via de European Hernia Society om de vergelijkbaarheid tussen experimentele studies te verbeteren.

In **Hoofdstuk 3** worden de data van een gerandomiseerde dierenstudie besproken. In deze studie zijn vijf meshes onderzocht: Parietene™ (polypropyleen), Permacol™ (gecrosslinkte matrix van acellulair collageen van varkenshuid), Strattice™ (niet-gecrosslinkte matrix van acellulair collageen van varkenshuid), XCM Biologic® (niet-gecrosslinkte matrix van acellulair collageen van varkenshuid) en Omyra® Mesh (gecondenseerd polytetrafluoroethyleen). De meshes werden geïmplanteerd in de buikwand

van gezonde ratten. De ratten werden geofferd na 30, 90 of 180 dagen. Er werd bij alle meshes gekeken naar ingroei, krimp, adhesievorming, abcesvorming en histologische parameters. Strattice™ presteerde het best in dit experimentele ratmodel.

In **Hoofdstuk 4** werd gekeken naar de in vivo eigenschappen van zowel biologische als synthetische meshes in een peritonitis ratmodel, aangezien de meeste meshes anders reageren in de aanwezigheid van een infectie. Er werden vijf meshes onderzocht: Parietene™ (polypropyleen), Permacol™ (gecrosslinkte matrix van acellulair collageen van varkenshuid), Strattice™ (nietgecrosslinkte matrix van acellulair collageen van varkenshuid), XCM Biologic® (nietgecrosslinkte matrix van acellulair collageen van varkenshuid), Omyra® Mesh (gecondenseerd polytetrafluoroethyleen). De ratten werden geofferd na 30, 90 of 180 dagen. Er werd gekeken naar de ingroei en krimp van de mesh, het percentage adhesies op de mesh, de sterkte van deze adhesies en de histologische eigenschappen van de mesh. Deze experimentele studie suggereert dat XCM Biologic® het beste presteerde op basis van ingroei van de mesh, (de afwezigheid van) macroscopische mesh infectie en histologische parameters zoals collageen depositie en neovascularisatie. Er moet wel voldoende overlap van de mesh zijn gedurende plaatsing, daar XCM Biologic® een grote hoeveelheid krimp heeft laten zien.

Adhesies zijn een vaak voorkomende complicatie van mesh in de intra-abdominale ruimte. Er zijn verschillende adhesiescoringssystemen beschikbaar (kwalitatieve versus kwantitatieve scoringsmethoden van adhesies), maar er is nog geen consensus over hoe adhesies gescoord moeten worden in de aanwezigheid van een mesh.

In **Hoofdstuk 5** is een nieuwe consensus score gepresenteerd, waarmee adhesies tussen de mesh en de intra-abdominale weefsels geclassificeerd kunnen worden. Deze adhesiescore is ontwikkeld door een panel van internationale experts door gebruik te maken van een gemodificeerde Delphi methode (RAND-UCLA). Deze studie omvatte twee rondes gebaseerd op vragenlijsten en één internationale consensus bijeenkomst. De META-consensus score die in dit hoofdstuk gepresenteerd wordt kan worden gebruikt om adhesies in aanwezigheid van een mesh te onderzoeken en te classificeren en is gebaseerd op de mening van 18 internationale vooraanstaande experts. Er wordt gepleit om deze score in toekomstige studies te gebruiken om de vergelijkbaarheid tussen studies en de objectiviteit te vergroten.

DEEL 2. HET GEBRUIK VAN MESH

Het **tweede deel** van dit proefschrift bevat studies over het gebruik van mesh bij patiënten. Deze studies zijn uitgevoerd met patiënten die operatief herstel van een navelbreuk ondergingen.

In **Hoofdstuk 6** worden de data gepresenteerd van een gerandomiseerde en gecontroleerde studie waarin patiënten met kleine navelbreuken worden onderzocht. Deze kleine navelbreuken van 1 tot 4 cm kunnen zowel met hechtingen als met een mesh geopereerd worden. In deze gerandomiseerde en gecontroleerde studie worden beide behandelingen vergeleken bij navelbreukherstel bij volwassenen. Patiënten waren geschikt voor inclusie in de studie als zij 18 jaar of ouder waren en een primaire navelbreuk hadden met een diameter van 1 tot 4 cm. Patiënten werden intra-operatief gerandomiseerd in een verhouding van 1:1 naar ofwel hechtingen ofwel mesh. Patiënten ondergingen lichamelijk onderzoek 2 weken, 3 maanden, 12 maanden en 24 tot 30 maanden na de operatie. De primaire uitkomst was het aantal recidieven navelbreuk na 24 maanden. De mediane follow-up was 25,1 maanden. Na een maximale follow-up van 30 maanden werden er significant minder recidieven gezien in de mesh groep dan in de hechtingen groep. Er werd geconcludeerd dat dit de eerste studie is, waarin bewijs van hoge kwaliteit geleverd wordt voor mesh-herstel bij patiënten met kleine navelbreuken met een diameter van 1 tot 4 cm. Daarom wordt gesuggereerd dat mesh-herstel gebruikt zou moeten worden bij alle patiënten met een navelbreuk van die diameter.

In **Hoofdstuk 7** worden de data gepresenteerd van een meta-analyse, waarin werd onderzocht of de behandeling van navelbreuken ofwel met mesh ofwel met hechtingen tot minder recidieven leidt. Het primaire doel was om verschillen te onderzoeken in het risico op recidief (klinisch of heroperatie). Het secundaire doel was om de verschillen te onderzoeken in infecties, seroomvorming, hematomen, chronische pijn, cosmetische resultaten en kwaliteit van leven. Er werd een systematische review met meta-analyse uitgevoerd, waarbij vijf gerandomiseerde en gecontroleerde studies geïdentificeerd (herstel met behulp van mesh n = 326 versus herstel met hechtingen n = 330) en 602 records geëxcludeerd werden. De gerandomiseerde en gecontroleerde studies hebben patiënten geïncludeerd met navelbreuken met een diameter van ≥1 tot 4 cm. Mesh-herstel liet het risico op recidief afnemen ten opzichte van herstel met hechtingen met een relatief risico van 0,28. Er werd geconcludeerd dat herstel door middel van mesh aangeraden wordt voor navelbreuken van ≥1 tot 4 cm. Er is meer onderzoek nodig naar de optimale positie van de mesh (sublay of onlay) en de rol van mesh bij patiënten met een navelbreuk van <1 cm.

In **Hoofdstuk 8** worden data gepresenteerd van een systematische review van de literatuur aangaande de haalbaarheid van navelbreuk-herstel onder lokale anesthesie. Uitkomsten waren operatieduur, het ontstaan van wondinfecties, perioperatieve en postoperatieve complicaties, postoperatieve pijn, recidief navelbreuk, opnameduur en patiënttevredenheid. In dit systematische review konden negen studies geïncludeerd worden. Er was een grote variatie in de geneesmiddelen die gebruikt werden voor lokale anesthesie en er bleek geen consensus over de te gebruiken injectietechnieken. Er werden geen conversies naar algehele anesthesie beschreven. Lokale anesthesie voor navelbreukherstel lijkt veilig en haalbaar. Niettemin, de voordelen van lokale anesthesie zijn niet voldoende aangetoond door heterogeniteit van de geïncludeerde studies. Daarom wordt voorgesteld om een gerandomiseerde en gecontroleerde studie uit te voeren waarin algehele en lokale anesthesie voor navelbreukherstel wordt vergeleken.

DEEL 3. COMPLICATIES VAN MESH

In het **derde deel** van dit proefschrift worden studies naar de mogelijke complicaties van mesh in patiënten gepresenteerd.

In **Hoofdstuk 9** werd in een meta-analyse onderzocht of het gebruik van een nieuwe zelf-fixerende mesh leidt tot een afname van chronische postoperatieve inguinale pijn ten opzichte van een met hechtingen gefixeerde mesh, aangezien chronische postoperatieve inguinale (lies)pijn een bekende complicatie na liesbreukherstel met mesh is. In de huidige meta-analyse werden de data van tien gerandomiseerde en gecontroleerde studies samengevoegd (2541 patiënten). De gemiddelde follow-up was 24 maanden. Er waren geen significante verschillen in het optreden van chronische pijn, recidief of "vreemd lichaam gevoel" tussen de zelf-fixerende en de met hechtingen gefixeerde mesh op alle follow-up momenten. Niettemin was de gemiddelde operatieduur significant korter bij de groep met de zelf-fixerende mesh. Er werd geconcludeerd dat de zelf-fixerende mesh vergelijkbare resultaten had als de met hechtingen gefixeerde mesh voor de incidentie van chronische postoperatieve inguinale pijn, recidief en "vreemd lichaam gevoel". Echter, langetermijnresultaten zijn gebaseerd op relatief kleine patiëntgroepen en uitkomstmaten zijn heterogeen. Het voornaamste voordeel van de zelf-fixerende mesh is de consequent significant verlaagde operatieduur.

In **Hoofdstuk 10** wordt een algoritme gepresenteerd met een behandelingsstrategie voor het behandelen van patiënten met chronische postoperatieve inguinale pijn. Het doel van deze studie was om samen met experts een algoritme te ontwikkelen voor de diagnostische en therapeutische aanpak van chronische postoperatieve inguinale pijn.

Een groep chirurgen, die expert geacht werd op het gebied van liesbreukchirurgie, werd uitgenodigd om mee te werken aan de ontwikkeling van dit algoritme. Er werd een algoritme voorgesteld door de auteurs, waarna consensus gevraagd werd voor elke stap in dit algoritme door middel van de Delphi methode. De antwoorden werden gebruikt om een gereviseerd, expert-gebaseerd algoritme te maken. Met de bijdrages van 28 internationale experts, werd een algoritme opgesteld voor de stapsgewijze aanpak van chronische postoperatieve inguinale pijn. Door 26 deelnemers werd het definitieve algoritme geaccepteerd als consensus model. Er werd geconcludeerd dat het nodig is dat richtlijnen voor de aanpak van chronische postoperatieve inguinale pijn geformuleerd worden. Dit algoritme kan fungeren als een leidraad voor de diagnose, het beleid en de behandeling van deze patiënten en kan bijdragen aan een verbetering van het klinisch resultaat. Als een expectatieve fase van enkele maanden achter de rug is, waarin de chronische postoperatieve inguinale pijn niet verbeterd is, dient er gekozen te worden voor een multidisciplinaire aanpak en zou een chronisch pijnteam geconsulteerd moeten worden.

In **Hoofdstuk 11** worden data gepresenteerd van patiënten die herstel van een complexe buikwandbreuk hebben ondergaan. Alle patiënten werden behandeld met een gecrosslinkte biologische mesh (Permacol™). In totaal werden 77 patiënten gezien op de polikliniek. De gemiddelde follow-up was 22,2 ± 12,6 maanden (SD). De meest voorkomende postoperatieve complicatie was wondinfectie (n = 21; 27,3 percent), bij 5 patiënten (6,5 percent) moesten de meshes verwijderd worden. Tijdens het polikliniekbezoek bleken 22 patiënten (28,6 percent) een recidief van de buikwandbreuk te hebben gehad, waarbij 10 patiënten (13 percent) een heroperatie hadden ondergaan. Ook hadden 39 patiënten (50,6 percent) bulging van de buikwand. Er werd geconcludeerd dat bulging en/of recidief vaak voorkwamen bij patiënten die behandeld waren met een gecrosslinkte biologische mesh voor de indicatie complexe buikwandbreuk. In ogenschouw nemende dat zowel recidief als bulging onwenselijke uitkomsten zijn, had een totaal aantal van 46 patiënten (59,7 percent) een ongunstige uitkomst. Infectiepercentages waren hoog, maar vergelijkbaar met soortgelijke patiëntencohorten. Uit de kwaliteit van leven-vragenlijsten bleek dat patiënten tevreden waren met hun algemene gezondheid.

In **Hoofdstuk 12** werden data van een andere patiëntengroep met complexe buikwandbreuken gepresenteerd. Deze patiënten hadden een herstel ondergaan met behulp van een niet-gecrosslinkte biologische mesh (Strattice™). Er werden 27 patiënten onderzocht voor de langetermijnresultaten (14 mannen, gemiddelde leeftijd 67,5 jaar, gemiddelde follow-up 42,4 maanden). Wat betreft de chirurgische interventie was de meest gekozen afmeting van de mesh 400 cm^2 en de meest voorkomende postoperatieve complicatie

was wondinfectie (39,1 percent). De niet-gecrosslinkte biologische mesh hoefde niet verwijderd te worden. Vier patiënten zijn postoperatief overleden (range: 5–904 dagen). Tijdens het polikliniekbezoek hadden 6 van de 23 patiënten (26,1 percent) een recidief complexe buikwandbreuk, waarbij 1 patiënt een heroperatie had ondergaan. Nog eens 5 patiënten (21,7 percent) hadden bulging van de buikwand. Uit de kwaliteit van leven-vragenlijsten bleek dat patiënten hun litteken gemiddeld een cijfer 3,5 uit 10 punten gaven (0 was het best) en zij beoordeelden hun restrictie tijdens dagelijkse activiteiten met gemiddeld 0 uit 10 punten (0 betekent geen restrictie). Er werd geconcludeerd dat ondanks een hoog percentage postoperatieve wondinfecties, geen van de meshes verwijderd hoefde te worden. Zowel recidief als bulging komen vaak voor in de lange termijn follow-up (faalpercentage 47.8 percent). De gerapporteerde kwaliteit van leven is goed na herstel van deze complexe buikwandbreuken.

LIST OF ABBREVATIONS

Abbreviation	Meaning
AAS	Activity assessment scale
ACR	Assumed control risk
AHS	American Hernia Society
ANCOVA	Analysis of covariance (statistical method)
ARRIVE	Animal research: reporting of in vivo experiments (reporting guideline)
ASA	American Society of Anesthesiologists
BC	Before Christ
BIQ	Body image questionnaire
BMI	Body-mass index
CAWHR	Complex abdominal wall hernia repair
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CLP	Cecum ligation puncture (experimental model)
COPD	Chronic obstructive pulmonary disease
CPIP	Chronic postoperative inguinal pain
CT scan	Computerized Tomography scan (imaging technique)
ECM	Extracellular matrix
EHS	European Hernia Society
Embase	Excerpta Medica database
e-PTFE	Expanded-polytetrafluoroethylene
EQ	EuroQol
EQ-5D-5L	EuroQol five dimensions five level version (quality-of-life questionnaire)
EuraHS	European registry of abdominal wall hernias
FBGC	Foreign body giant cells
FBS	Foreign body sensation
FDA	Food and Drug Administration (agency of United States Department of Health and Human Services)
FU	Follow-up
GA	General anesthesia
HE	Hematoxylin and eosin (staining)
HPF	High-power field
HR	Hazard Ratio
HW	Heavyweight (qualification of mesh weight)
IASP	International Association for the Study of Pain
IEHS	International Endohernia Society
IPOM	Intraperitoneal onlay mesh
IQR	Interquartile range
IV	Intravenous

Abbreviation	Meaning
LA	Local anesthesia
LA + sedation	Local anesthesia combined with sedation
LW	Lightweight (qualification of mesh weight)
MOS SF-36	Short Form-36 (quality-of-life questionnaire)
MS	Microsoft
n	Number
n.a.	Not applicable
NG	Not given
No.	Number
NIH	National Institutes of Health (agency of United States Department of Health and Human Services)
NNH	Number needed to harm
NNT	Number needed to treat
OR	Odds ratio
PADM	Non-cross-linked porcine acellular dermal matrix
PHS	Prolene® Hernia System (polypropylene mesh)
PRISMA	Preferred reporting items for systematic reviews and meta-analysis (reporting guideline)
PROSPERO	International database of prospectively registered systematic reviews in health
PTFE	Polytetrafluoroethylene
PubMed	NCBI National Library of Medicine
QOL	Quality of life
RA	Regional anesthesia
RAM	RAND-UCLA Appropriateness Method (research technique)
RAND-UCLA	Modified Delphi method (research technique)
RCT	Randomized controlled trial
RD	Risk difference
RR	Relative risk or risk ratio
RRR	Relative risk reduction
SA	Spinal anesthesia
SD	Standard deviation
SE	Standard error
SF-12	Short Form-12 (quality-of-life questionnaire)
SF-36	Short Form-36 (quality-of-life questionnaire)
SPS	Surgical Pain Scale
SPSS	Statistical package for the social sciences
SR	Sirius red (staining)
SSI	Surgical site infection
STATA	Statistical software package
STROBE	Strengthening the reporting of observational studies in epidemiology (reporting guideline)
STROCCS	Strengthening the reporting of cohort studies in surgery (reporting guideline)

Abbreviation	Meaning
TAPP	Transabdominal preperitoneal (hernia repair)
TEP	Totally extraperitoneal (hernia repair)
TIPP	Transinguinal preperitoneal (hernia repair)
VAC	Vacuum-assisted therapy
VAS	Visual analogue scale
VHWG	Ventral Hernia Working Group
VRS	Verbal Rating Scale
WHO	World Health Organization
X-PADM	Cross-linked porcine acellular dermal matrix
µm	Micrometer (10^{-6} meter)
18-G	18-Gauge (needle size, i.e. 1.2 mm)
3D	Three dimensional

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A

Zeer geachte leden van de promotiecommissie, veel dank dat u op 29 maart deel wilt uitmaken van de corona. Ik kijk er naar uit om met u van gedachten te wisselen.

Beste coauteurs, veel dank voor de mooie samenwerkingen. Ik kijk uit naar nieuwe, gezamenlijke projecten! Dear co-authors, many thanks for the beautiful collaborations. I'm looking forward to new, joint projects!

Een speciaal woord van dank gaat ook uit naar Marian Clahsen-van Groningen. Veel dank voor de gezellige pathologie-sessies. Je wist me te winnen voor een onbekend terrein. Top!

Beste Annelies, je weet niet alleen professor Lange in goede banen te leiden, maar je wist ook de eindfase van mijn promotie soepel te laten verlopen. Veel dank voor je hulp en begeleiding tijdens de laatste loodjes van dit traject.

Het hebben van een goede datamanager maakt het leven als arts-onderzoeker een stuk eenvoudiger. Daarom Anneke van Duuren, veel dank voor je jarenlange inzet en het minutieus bijhouden van de HUMP database. Mede dankzij jouw hulp staat er nu een prachtige publicatie.

Beste oud-collega's van het Erasmus MC, zowel in de Z-flat als in "de kelder", dank voor alle koffie, verjaardagstaartjes, (Schmidt)lunches, borrels, diners, skireizen en andere memorabele momenten. Ik heb een heerlijke tijd gehad! Het ga jullie goed.

"Eens een REPAIR'der, altijd een REPAIR'der." Wat een prachtige club! Pas achteraf realiseer ik me welke kansen ik bij de mooiste onderzoeksgroep van het Erasmus MC gekregen heb. Kansen die niet alleen gecreëerd worden door de professoren, maar zeker ook door de samenwerkingen met collega-onderzoekers. Eva, Irene, Simone, Konstantinos, Zhouqiao, Sandra, Joost, An, Barry, Lucas, Marijke, Leonard, Yağmur, Heijdo, Michael, Daniël, Cloë en alle voorgangers/opvolgers, het was een genoegen om met jullie te werken. De wekelijkse REPAIR-vergadering met het "uurtje cultuur(tje)" leerde me welke jazz-giganten ons nu weer ontvallen waren en welke tentoonstellingen en films ik kon bezoeken. Ook op wetenschappelijk gebied leverde het vaak waardevolle nieuwe inzichten op. Veel dank voor alle mooie momenten zowel bij het doen van onderzoek als tijdens de momenten van ontspanning.

Beste oud-collega's van het Maasstad. Onder leiding van drs. Rene Klaassen maakte ik bij jullie na mijn onderzoekstijd de eerste stappen in de kliniek. Hard werken en er samen voor gaan. Dank voor jullie geduld en begeleiding!

Beste oud-collega's uit het Albert Schweitzer Ziekenhuis. Onder leiding van dr. Peter Plaisier – dé dokter – mocht ik verder kennismaken met de chirurgie. Ik heb een geweldige tijd gehad met jullie. Veel dank voor alle vrijdagen in Lambarene, goede koffie, mooie feestjes, hamertje tik, een briljant skiweekend en de rondleiding op Curaçao. Lieve Yvonne, Joanny en Sjanie, veel dank voor verse koffie en mooie verhalen.

Beste collega's uit Tergooi, onder de bezielende leiding van dr. Nanette van Geloven. Jullie zijn mijn nieuwe thuis geworden. Ik voel me enorm welkom bij jullie en geniet van karaoke, koffiemomenten en samen lunchen. Veel dank voor jullie steun en interesse in de laatste fase van dit proefschrift!

Lieve Bassie, vriend in den verre. Wat ontzettend tof dat jij de cover van mijn boek hebt willen ontwerpen! Van "utter despair" naar "radiant flair" kent slechts een dunne scheidslijn. Vanaf nu hebben we hopelijk meer tijd voor ook de ontspannende dingen in het leven.

Lieve vrienden en vriendinnen, dit boek is de reden dat ik soms feestjes moest skippen of later kwam op onze afspraken. Ik ben heel blij met jullie interesse, steun en begrip! "Ik ben bezig met de afronding", is nu "de afronding is gepland" geworden. Voor jullie ligt het bewijs. 😉 Vanaf nu wordt het tijd om het leven te vieren.

Lieve Hanna, born without a zip on her mouth. Wat heerlijk om af en toe te mogen "venten"! Gelukkig kunnen we ook (in stilte) ontspannen samen. Heel veel succes in Nkhoma!

Lieve Lidwien, sinds 2005 mijn "partner in medical crimes", van uren keten tijdens college of tijdens het zoveelste practicum, naar wonen en afspreken in de Randstad. Echt top! Ik ben blij dat we dat anno 2019 nog steeds doen.

Lieve Jaarclub Admiratio, lieve Catherine, Fabienne, Maud en Nienke, wat hebben we een heerlijke tijd gehad in Maastricht. Eindeloze jaarclubavonden en feesten op de kroeg. Inmiddels is iedereen uitgevlogen, maar spreken we elkaar gelukkig nog wel geregeld. Ik hoop jullie snel weer te zien!

Weledelzeergeleerde dr. Lucieer, lieve Suus, eerst kende ik je alleen als "zusje van". In 2011 kruisten onze paden elkaar weer in het Erasmus MC. Beiden deden we onderzoek bij professor Lange. Jij vanuit de onderwijskant, ik vanuit de chirurgie. Nu mag ook ik mijn proefschrift verdedigen. Veel dank dat je me wegwijs wilde maken in de statistiek en mijn manuscript wilde helpen reviseren. Nu wordt het snel tijd voor die borrel.

Lieve Frederieke, als twee brugklassers kwamen we elkaar voor het eerste tegen en sindsdien zijn we niet gestopt met kletsen. Nu 20 jaar later kunnen we nog steeds onbedaarlijk hard lachen om alle mooie dingen in het leven. Wat heerlijk om je zo gelukkig te zien met Lot!

Lieve Lijn, sinds de middelbare school zijn we onafscheidelijk. Zelfs meermaals emigreren krijgt onze band niet stuk. Ik geniet van alle verhalen over je avonturen in Australië, maar ik verheug me enorm op jullie terugkeer naar Nederland. Ik kan niet wachten om weer ouderwets te komen theeleuten!

Weledelzeergeleerde dr. Molegraaf, lieve Marijke, mede-REPAIR'der, een jaar geleden stond jij te schitteren achter het katheder en mocht ik aan jouw zijde staan. Ik voel me zeer vereerd dat je nu ook bij mijn verdediging mijn paranimf wilt zijn. Ik hoop op een mooie toekomst voor jou en Wouter in Zwolle!

Weledelzeergeleerde dr. Halm, lieve Jens, oud-buiksluiter, wat geweldig dat ook jij mijn paranimf wilt zijn. Ruim 12 jaar geleden pionierde jij al met de stelling "Herstel van een navelbreuk dient met een kunststof mat verricht te worden". Het onderzoek dat hieruit volgde kreeg afgelopen jaar een climax. Wat hebben we een te gekke tijd achter de rug. Met de HUMP trial op zak had ik de beste weddenschap ooit gewonnen: én The Lancet, én een krat champagne..! 😉 Lieve Purdey, Amélie en Juliette, wat fijn dat ik Jens even mag 'lenen' voor deze bijzondere dag. Op naar veel mooie momenten samen!

Liebe Oma, vielen lieben Dank für dein Interesse an meinen Studien. Es ist letztendlich fertig! Ich hoffe das du noch lange gesund bleibst. Ich komme dich bald wieder besuchen. Alles Liebe!

Lieve oma Henny, opa Dick, opa Horst-Arthur en oma en opa Posthuma, ik had gehoopt deze dag nog samen met jullie te mogen beleven. Dank voor jullie steun en liefde!

Zeer geachte hooggeleerde emeritus professor Kaufmann, lieve papa. We hebben veel meegemaakt de afgelopen jaren. Heel veel dank voor je onvoorwaardelijke steun en liefde! Die beloofde gezamenlijke publicatie gaat er hopelijk ook nog komen. Binnenkort wordt het eerst tijd voor die veelbesproken reis naar Japan.

Lieve Dia, het allermooiste cadeau was jouw aanwezigheid bij mijn verdediging geweest. Helaas mocht het niet zo zijn. Onze tijd samen was een cadeau van onschatbare waarde. Ik mis je!

Zeer geachte weledelgeleerde drs. Posthuma, lieve Victor, geen woorden kunnen beschrijven hoe dankbaar ik je ben voor je onvoorwaardelijke liefde en steun tijdens dit soms bizarre traject! Je humor, adviezen en frisse kijk op de wereld hebben me enorm geholpen. Hoe heftig zo'n traject kan zijn kun je binnenkort zelf ervaren, want "jouw tijd komt nog wel". Ik vind het echt superstoer dat je nu zelf begonnen bent aan een promotietraject! Hopelijk doe je dat niet alleen om mij terug te pakken voor de afgelopen jaren. 😉 Ik ben ontzettend trots op jou en kijk uit naar een mooie toekomst samen! Ik hou zielsveel van jou!

Ruth

PhD PORTFOLIO

Name PhD fellow: Ruth Kaufmann
Erasmus MC Department: Surgery

PhD period: December 2011 – February 2015
Promotor(s): Prof. dr. J.F. Lange
Supervisors: Prof. dr. J. Jeekel

1. PhD training

Courses	**Year**	**ECTS**
- BROK ("Basiscursus Regelgeving Klinisch Onderzoek")	2012	1.5
- Systematic literature retrieval	2012	1
- Laboratory animal science ("Artikel 9")	2012	4.5
- Biostatistics for clinicians (NIHES)	2012	2
- "Omgaan met groepen"	2012	0.5
- CPO mini course	2013	0.5
- Biomedical English Writing and Communication	2013	4

Presentations		
- Rotterdam Interactive Congress on Hernia 2.0, Rotterdam, the Netherlands. *Invited speaker*	2019	1
- Najaarsdag, Hilversum, the Netherlands. *Oral presentation*	2018	1
- American College of Surgeons, Boston, USA. *Invited speaker*	2018	1
- Chirurgendagen, Veldhoven, the Netherlands. *Invited speaker*	2018	1
- American Hernia Society, Miami, USA. *Poster presentation*	2018	1
- European Hernia Society, Vienna, Austria. *Oral presentation*	2017	1
- European Hernia Society, Rotterdam, the Netherlands. *Invited speaker*	2016	1
- American Hernia Society, Washington, USA. *Oral (1×) & poster (2×)*	2016	3
- Wetenschapsdag Erasmus MC, Rotterdam, the Netherlands. *Oral presentation*	2015	1
- Najaarsdag, Hilversum, the Netherlands. *Oral presentation*	2015	1
- World Conference on Abdominal Wall Hernia, Milan, Italy. *Oral (1×) & poster (2×)*	2015	3
- Wetenschapsdag Erasmus MC, Rotterdam, the Netherlands. *Oral presentation*	2014	1
- Rotterdam Interactive Congress on Hernia, Rotterdam, the Netherlands. *Invited speaker*	2014	1
- Najaarsdag, Utrecht, the Netherlands. *Oral & poster presentation*	2014	1
- Stichting Experimenteel Onderzoek Heelkundige Specialismen, Groningen, the Netherlands. *Poster presentation (2×)*	2014	2
- European Hernia Society, Edinburgh, United Kingdom. *Oral presentation*	2014	1
- Chirurgendagen, Veldhoven, the Netherlands. *Oral presentation*	2014	1
- American Hernia Society, Las Vegas, USA. *Poster presentation*	2014	1
- Stichting Experimenteel Onderzoek Heelkundige Specialismen, Maastricht, the Netherlands. *Poster presentation (3×)*	2013	3
- Najaarsdag, Den Bosch, the Netherlands. *Oral presentation*	2013	1

- OK dagen, Veldhoven, the Netherlands. *Invited speaker*	2013	1
- International Surgical Week, Helsinki, Finland. *Oral presentation*	2013	1
- European Society for Surgical Research, Istanbul, Turkey. *Oral presentation (2×)*	2013	2
- Chirurgendagen, Veldhoven, the Netherlands. *Poster presentation*	2013	1
- European Hernia Society, Gdansk, Poland. *Oral presentation*	2013	1
- Association of Surgeons of Great Britain and Ireland, Glasgow, United Kingdom. *Poster presentation*	2013	1
- Wetenschapsdag Erasmus MC, Rotterdam, the Netherlands. *Oral presentation*	2012	1
- European Society for Surgical Research, Lille, France. *Oral presentation*	2012	1
- Chirurgendagen, Veldhoven, the Netherlands. *Oral presentation*	2012	1

Attended conferences

- Chirurgendagen, Veldhoven, the Netherlands	2017	1
- Chirurgendagen, Veldhoven, the Netherlands	2016	1
- Acelity™ Make Better Summit, Madrid, the Netherlands	2015	1
- Acelity™ Advanced Educational Forum – Complex Abdominal Wall Hernia, Amsterdam, the Netherlands	2015	1
- Rotterdam Interactive Congress on Hernia, Rotterdam, the Netherlands	2012	1

Research grants

- DSM Medical, Exton, USA (€ 4.600,–)	2014
- LifeCell, New Jersey, USA (€ 91.375,–)	2013
- Stichting Coolsingel, Rotterdam, the Netherlands (€ 20.000,–)	2012
- Stichting Coolsingel, Rotterdam, the Netherlands (€ 44.000,–)	2012

Other

- Journal club	2012-2015	2
- REPAIR research meeting	2011-2015	2
- Organiser "Rotterdam International Congress on Hernia" (congress in Rotterdam, the Netherlands)	2013-2014	3

2. Teaching	Year	ECTS
Lecturing		
- College "Dokter, ik ben zo moe" (1st year medical students)	2013	1
Supervising practicals and tutoring		
- Supervising first aid exams medical students	2012-2014	1
- Tutor to 1st year medical students	2012-2014	3
- "Kennismaking met de Beroepspraktijk" (1st year medical students)	2013-2014	2
Supervising Master's theses		
- Kevin Wiese	2012	2
- Vivian Zwart	2012	2
Total		**74**

CURRICULUM VITAE AUCTORIS

Ruth Posthuma-Kaufmann werd geboren op 15 februari 1987 in Kamp-Lintfort te Duitsland. Ze verhuisde in december 1992 naar Nederland. In 2005 behaalde zij haar Gymnasiumdiploma en werd ingeloot voor de studie Geneeskunde aan de Universiteit van Maastricht. Tijdens haar studie deed Ruth een keuze-coschap Traumatologie in Paarl, Zuid-Afrika (onder supervisie van prof. dr. P.R.G. Brink). Haar oudste coschap deed ze op de afdeling Intensive Care in Maastricht (prof. dr. W.N.K.A. van Mook en dr. D.C.J.J. Bergmans). Eind 2011 begon Ruth als arts-onderzoeker bij de REPAIR onderzoeksgroep (prof. dr. J.F. Lange, prof. dr. J. Jeekel, prof. dr. G.J. Kleinrensink en dr. A.G. Menon), waar zij meewerkte aan verschillende onderzoeken in zowel de kliniek als in het laboratorium. Vanaf maart 2015 was Ruth naast haar promotieonderzoek achtereenvolgens werkzaam als ANIOS (arts-assistent niet in opleiding tot specialist) op de afdelingen chirurgie van het Maasstad Ziekenhuis te Rotterdam (drs. R.A. Klaassen), het Albert Schweitzer Ziekenhuis te Dordrecht (dr. P.W. Plaisier) en het Tergooi te Hilversum (dr. A.A.W. van Geloven). Het onderzoek dat Ruth in de afgelopen jaren verrichtte heeft geresulteerd in dit proefschrift.

Ruth Posthuma-Kaufmann was born on February 15th 1987 in Kamp-Lintfort in Germany. She moved to the Netherlands in December 1992. In 2005, she obtained her Gymnasium degree and started her study in Medicine at the Maastricht University. During her study she enrolled in an elective rotation Trauma surgery in Paarl, South Africa (supervised by prof. dr. P.R.G. Brink). She did her last year's rotation in the Intensive Care department of the Maastricht University Medical Center in Maastricht (prof. dr. W.N.K.A. van Mook and dr. D.C.J.J. Bergmans). At the end of 2011, Ruth started working as a research fellow in the REPAIR research group (prof. dr. J.F. Lange, prof. dr. J. Jeekel, prof. dr. G.J. Kleinrensink, and dr. A.G. Menon), where she collaborated in both clinical and experimental research. Since March 2015 is Ruth concurrently working on her research and working as a resident not in training in the surgical departments of the Maasstad Hospital (drs. R.A. Klaassen), the Albert Schweitzer Hospital in Dordrecht (dr. P.W. Plaisier) and the Tergooi Hospital in Hilversum (dr. A.A.W. van Geloven). The research that Ruth conducted in the past years resulted in this thesis.

Always laugh when you can.
It is cheap medicine.

(Lord Byron)