NEW INSIGHTS

IN INCISONAL AND VENTRAL HERNIA SURGERY

An Jairam

COLOFON

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Anuradha Jairam
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Promotor:	Prof. dr. J.F. Lange
Overige leden:	Prof. dr. C.H.J. van Eijck Prof. dr. S.E.R. Hovius Prof. dr. N.D. Bouvy
Copromotor:	Prof. dr. J. Jeekel

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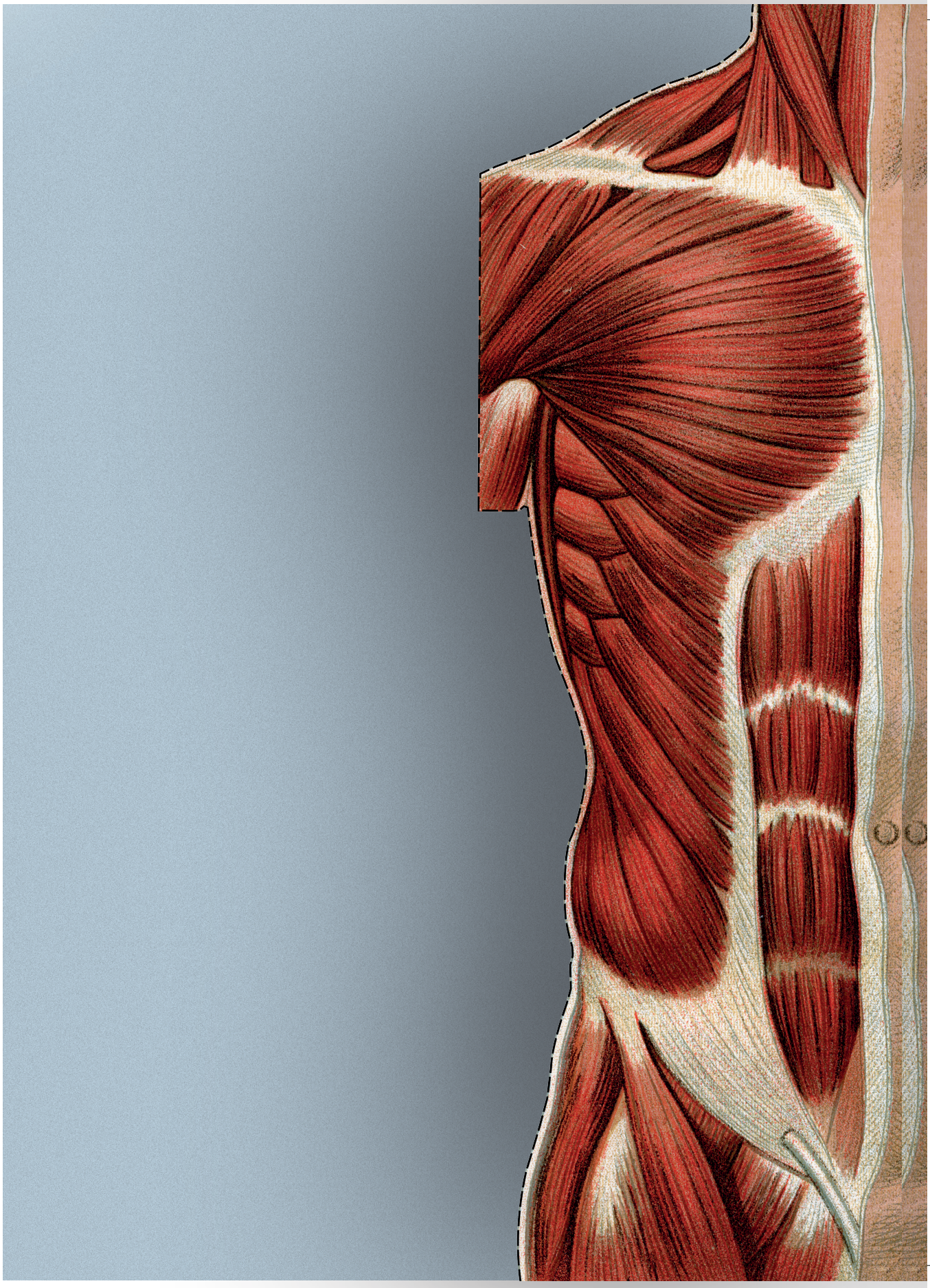

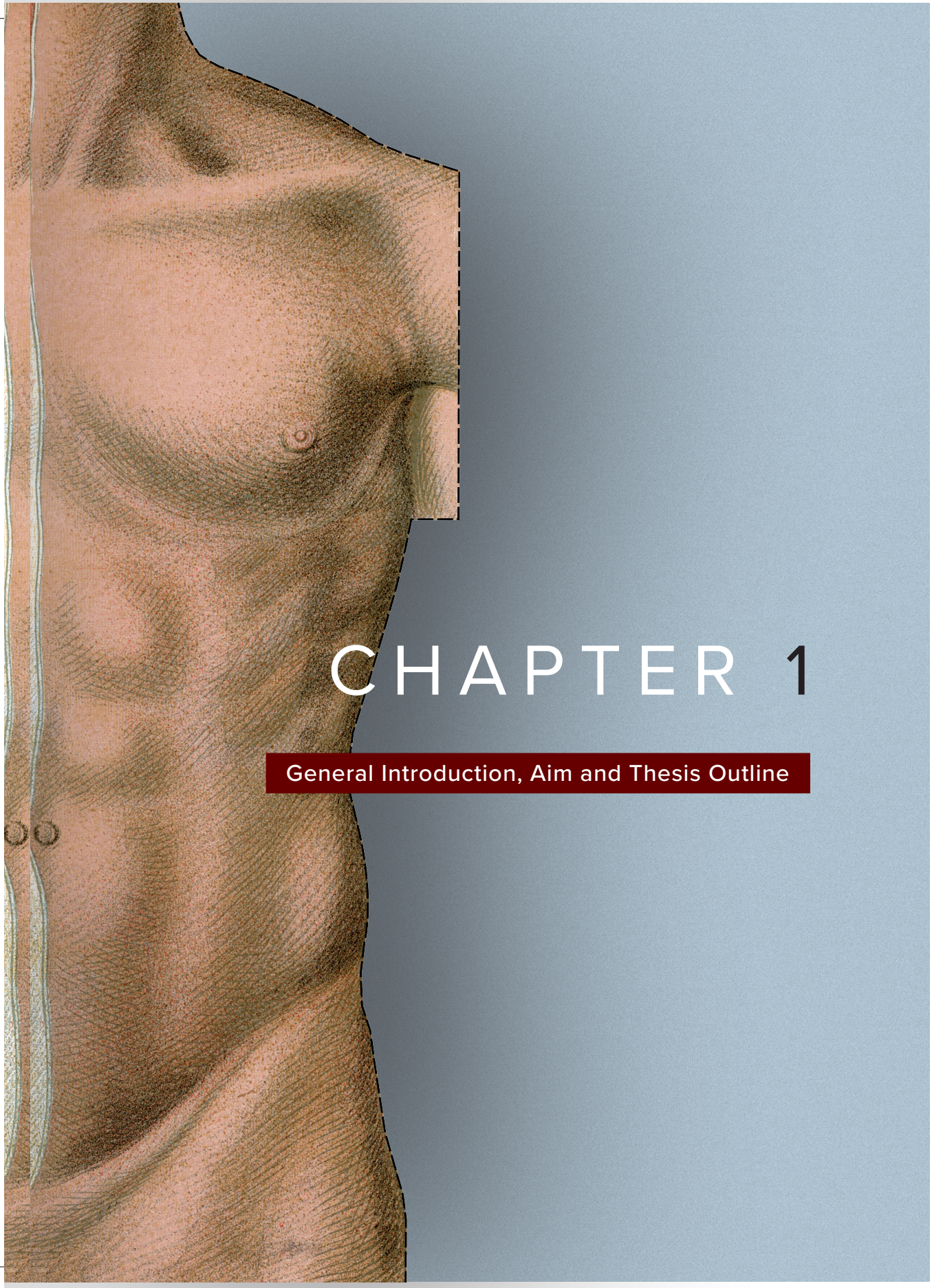

CHAPTER 1

General Introduction, Aim and Thesis Outline

INTRODUCTION

Ventral Hernia

History

Ever since human kind is able to stand in a vertical position, abdominal wall hernias exist. The abdominal wall was first described in 1500 BC by the Ebers Papyrus, which was found by Professor George Ebers in a tomb in Thebes. Incisional hernias were not mentioned, however, epigastric hernias were described. In the passage that was found, it is suggested that reduction of the hernia takes place when the patient lies down. The importance of closure of the abdominal wall is first described centuries later (first century AD), by Aulus Cornelius Celsus. Surgical closure was named 'gastrorrhaphy', which literally means 'suturing of the abdomen'. A layered closure of the abdominal wall was described to prevent incisional hernia (IH). The abdominal wall was more in detail described by Galen, a Roman of Greek origin and one of the most important physicians of the Greek-Roman period. Galen was most probably aware of the risk of IHs, since he described how to prevent it: by paramedian incisions. The work of Galen form the basis of modern surgery (1).

Anatomy

The abdominal wall is defined by several landmarks: cranially by the xiphoid process of the sternum, craniolaterally by the costal margins, inferolaterally by the inguinal ligaments and caudally by the iliac crests and pubic bone of the pelvis in the midline. The abdominal wall muscles ensure essential movements such as respiration, urination, defecation, coughing and giving birth. In addition, the abdominal wall muscles stabilize the trunk for walking upright. The abdominal wall exists of a layered structure, with nine layers in total: skin, subcuteanous tissue, superficial fascia (of Scarpa), external oblique muscle, internal oblique muscle, transversus abdominis muscle, fascia transversalis, preperitoneal adipose and areolar tissue and peritoneum. The internal oblique muscle, external oblique muscle and transversus abdominis muscle are positioned laterally to the abdominal rectus muscle. The linea alba is the preferred location to access the abdominal cavity. This structure, which literally means 'white line', is an avascular fibrous structure composed of collagen and elastin. It derives from the xiphoid process, extending to the pubis symphysis. The linea alba is the most important structure, since restoration of it remains the goal of abdominal wall reconstruction. It manifests a highly complex structure, consisting of three layers of collagen fibers in the same direction compared to the three lateral abdominal wall muscles. Closure can be achieved by approximating the paired rectus muscles back to the midline. The superior and inferior epigastric arteries are responsible for blood supply to the rectus muscles, originating

from the internal thoracic artery and external iliac artery. The epigastric arteries are situated between the abdominal rectus muscle and the posterior rectus fascia. The intercostal nerves innervate the rectus muscles.

Definition and classification

Incisional hernia 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'* (2). Primary abdominal wall hernias, or IHs, can be classified in midline and lateral abdominal wall hernias. Borders of a midline hernia are: the xyphoid (cranial), the pubic bone (caudal) and the lateral margin of the rectal sheath (lateral). Epigastric and umbilical hernias can be considered midline hernias. The borders of a lateral hernia are as follows: the costal margin (cranial) and the inguinal region (caudal). Spigelian and lumbar hernias are lateral hernias. An umbilical hernia is defined as *'a midline abdominal wall defect from three centimetres above up to three centimetres below the umbilicus'*. The size of the hernia is described by the length and width of the hernia (3).

Incisional Hernia

Incidence, prevalence and risk factors

Incisional hernia is the most frequent postoperative complication after abdominal surgery. Approximately 20% of patients undergoing midline laparotomy will develop IH. This can increase to more than 35% in 'high-risk groups' (4-12). High-risk groups are defined as patients with an aneurysm of the abdominal aorta (AAA) and obese patients. It is suggested that AAA patients suffer from an underlying connective tissue disorder. A dysregulation of collagen type I/III ratio has an important role in the pathogenesis of distension of the aorta. In the abdominal wall fascia of patients with IH, a reduced type I/III collagen ratio is observed. Patients with a BMI of more or equal than 27 kg/m^2 have more than 30% chance of developing IH after midline laparotomy (13). These patients have a higher intra-abdominal pressure, which can cause a high tension on abdominal sutures and can thus lead to IH. Besides a high intra-abdominal pressure, there is another factor that can contribute to the development of IH. Obesity is associated with impaired wound healing, due to decreased vascularity of the tissue. This leads to a hypoxic wound, with an impaired synthesis of mature collagen, which results into weaker tissue with poor wound healing. Other risk factors for IH include surgical site infection, smoking, malignancy, diabetes, pulmonary disease, steroid use, malnutrition and collagen disorders like Ehlers Danlos and Marfan diseases (14-18).

Diagnostic tools

IH is a complication, which should be prevented. However, so far this is not possible. Diagnostics and adequate follow up of IH may be underestimated, but are crucial. Approximately 80% to 95% of all IHs occur within three years after initial surgery. Thus, adequate, reliable long-term follow up is essential in providing high-quality care after midline laparotomies. There are several methods of follow up, such as physical examination and radiological examination (ultrasound, CT-scan). Until now, IH is a clinical diagnosis, which can be made by physical examination alone. Radiological examination (i.e., ultrasound or computed tomography) is being applied in case there is uncertainty regarding diagnosis. Earlier performed studies have shown that the sensitivity of physical examination is 77%, compared with computed tomography (CT) (19). Another study by Den Hartog et al. showed that the sensitivity of ultrasound, compared with CT, was 70.8%, the specificity being 100%, the positive predictive value 100% and the negative predictive value 69.6% (20).

Routinely scheduled outpatient visits to monitor or diagnose IH are time consuming, costly and demand devotion of both patient and doctor. Furthermore, it is not always necessary to conduct a three year follow up after abdominal surgery and patients will not attend a physician if symptoms are absent. Another method of follow-up might be the use of questionnaires (21). However, there is little evidence on their reliability. Currently, there is no validated questionnaire that can be used as a diagnostic tool.

Treatment and prevention

Incisional hernia often causes morbidity, such as pain (in patients with symptomatic IH). Furthermore, it can have a negative effect on patients' quality of life and body image (22-24). Worst-case scenario, it can lead to obstruction or strangulation of the bowel, with possible mortality as a result. Therefore, IH repair is a frequently performed surgical procedure. Studies have shown that mesh reinforcement has a 10-year cumulative recurrence rate of 23%, compared to 63% for primary suture repair (25, 26). The use of mesh in ventral hernia repair is therefore a well-accepted and frequently performed technique. However, the ideal location of mesh placement is still a topic of discussion. Mesh repair can be achieved by placing the mesh intraperitoneally (IPOM), onlay, sublay (retromuscular) or inlay. Currently, there is no level 1-evidence that favours one of these techniques. Focus should be on prevention of IH, specifically in high-risk groups. Nowadays conventional laparotomy can frequently be avoided by performing laparoscopy or horizontal incisions (27). However, this is not always possible. No golden standard is described in literature to prevent IH in patients undergoing midline laparotomy. Prevention can be achieved by mesh reinforcement (either onlay or sublay) in patients, undergoing midline laparotomy. Patients with a high BMI and

patients with AAA might benefit most from prevention. Several prospective studies and randomized controlled trials have already been conducted, investigating how IH can be prevented (8, 10, 28-30), and which surgical technique should be applied in order to lower the incidence of IH. Until recently, there was no level 1-evidence available. The European Hernia Society guidelines on the closure of abdominal wall incisions made a recommendation in 2015. The Guidelines Development Group stated that prophylactic mesh augmentation for an elective midline laparotomy in a high-risk patient is suggested, in order to reduce the IH incidence. However, the evidence was weak and the authors therefore stated as well that larger trials would be needed to make a strong recommendation (2).

The use of meshes

As stated earlier, use of mesh is proven to be beneficial in ventral hernia repair and has become standard practice. The 10-year cumulative recurrence rate of mesh repair of IH has been proven to be 23% (25). This percentage rate is 1% for umbilical hernia repair (31, 32). One of the most important questions that still remain unanswered is: which mesh is the 'ideal' mesh? This search is still ongoing, and will not be answered in this thesis. Currently, there are a wide variety of synthetic, biological and biosynthetic, resorbable/non-resorbable meshes on the market. Several factors determine which mesh is perfect for each specific patient: type of hernia, patient risk factors, type of surgery (clean or contaminated setting) and the indication (prevention or treatment). The most commonly used mesh in ventral hernia repair (in a clean setting) is the non-resorbable synthetic mesh, mostly polypropylene and polyester. These meshes are biocompatible, strong, and inexpensive. However, if placed in contact with abdominal viscera, complications of adhesion formation, small bowel obstruction, pain and enterocutaneous fistulas can occur (33-36). Furthermore, synthetic meshes cannot be easily used in contaminated settings. In these cases, biological meshes should be considered as an alternative. These meshes are made of collagen, containing tissues of human or (most often) animal origin (37). Biological meshes can be divided in cross-linked en non cross-linked meshes. Crosslinking is a chemical process that can be performed to increase the strength and to slow down degradation of the mesh. Biological meshes are gradually vascularized and remodelled in the host tissue by degradation of the extracellular matrix. The use of biological meshes has led to a reduction of foreign body and chronic inflammatory response in a contaminated field, since they are more infection resistant than synthetic materials (38-40). Unfortunately, high evidence in long-term data of clinical outcome and complications is lacking. Another disadvantage is the fact that biological meshes are expensive (37).

An alternative for abdominal wall repair and soft tissue reinforcement might be the use of slowly resorbable synthetic mesh ('biosynthetic' mesh). This mesh aims to combine advantages of both synthetic (no degradation shortly after implantation) and biological (remodelling aspects) meshes. It is also less expensive than a biological mesh. Many studies regarding biosynthetic meshes report that there is 'optimal tissue remodelling'. However, the definition of this is unclear, not standardized, and furthermore, there is not enough evidence yet that these meshes provide sufficient strength on long-term (41).

Umbilical Hernia

Approximately 10% of all abdominal wall hernias are umbilical hernias. According to the European Hernia Society, an umbilical hernia (UH) is defined as a midline abdominal wall defect from three centimetres above up to three centimetres below the umbilicus. It can either be present at birth, or it can develop spontaneously throughout life, for example by increased intra-abdominal pressure. The prevalence in the adult population is 2%. Each year, approximately 4500 umbilical hernias are repaired in the Netherlands. Surgical repair of umbilical hernia can be performed by either suture or mesh repair. High recurrence rates are reported for suture repair, especially with hernia orifices larger than four centimetres. The recurrence rate for mesh repair is very low, with a percentage of up to one percent (31) (32). At this moment, level-1 evidence is lacking regarding the umbilical hernia size that should be treated with a mesh. The HUMP trial aims to investigate whether mesh repair is superior compared to suture repair in reducing the recurrence rate for smaller umbilical hernias (1-4 centimetres). As expected, the results of the HUMP trial will be published this year.

Most of the UHs are repaired under general anesthesia. Nowadays it is becoming more common to operate patients with inguinal and UHs under local anesthesia. Many studies, investigating local anesthesia for inguinal hernia repair, have been conducted until now. It has been shown that local anesthesia is superior for open inguinal hernia repair, compared to general or spinal anesthesia (42). Local anesthesia can have several advantages, such as less postoperative pain, less micturition problems and early mobilisation of patients, which can lead to a shorter duration of hospital stay. Until now, there is a lack of evidence regarding local anesthesia for the repair of umbilical hernia. A systematic review could not sufficiently show the advantages of local anesthesia, due to the heterogeneity amongst included studies. A prospective cohort study, using Ropivacaine as a local agent and Remifentanil as a sedative, showed that the use of local anesthesia is safe and feasible in umbilical hernia repair.

OUTLINE OF THIS THESIS

The first aim of this thesis is the *prevention of incisional hernia*. The second aim focuses on *new tools, techniques and meshes in ventral hernia surgery*.

Part I: Prevention of incisional hernia

Chapter 2 presents the European Hernia Society Guidelines on the closure of abdominal wall incisions. In this study, a recommendation is made regarding prophylactic mesh augmentation in elective midline laparotomies in high-risk patients.

In **Chapter 3**, the short-term results of the PRIMA trial are presented. This is a randomized controlled trial, investigating the efficacy of mesh reinforcement in high-risk patients undergoing midline laparotomy, in order to reduce the incidence of incisional hernia. The short-term results focus only on the complications in the first month.

Chapter 4 presents the long-term results of the PRIMA trial. In this chapter, it is investigated whether mesh reinforcement is able to prevent incisional hernia in high-risk patients undergoing midline laparotomy.

Chapter 5 presents a meta-analysis of studies describing the results of primary suture versus mesh reinforcement after midline laparotomy. In this meta-analysis it is investigated whether mesh reinforcement reduces the incidence of incisional hernia.

Chapter 6 presents a meta-analysis of studies describing the results of primary suture versus mesh reinforcement after midline laparotomy, using a biological or (slow) resorbable synthetic mesh.

Part II: New tools, techniques and meshes in ventral hernia surgery

Chapter 7 presents the PROMID pilot study. In this pilot study, the reliability of a questionnaire, to assist in diagnosing incisional hernia, is being determined.

Chapter 8 is a review, in which an overview is given of the characteristics of slowly resorbable synthetic meshes, for the treatment and prevention of abdominal wall hernias.

Chapter 9 presents the protocol of a prospective cohort study, in which 85 patients with a Ventral Hernia Working Group (VHWG) Grade 3 hernia will be treated with Phasix™ mesh (a slowly resorbable synthetic mesh).

Chapter 10 presents the in-vivo characteristics of both synthetic and biological meshes in a validated peritonitis rat model.

Chapter 11 presents a review on the feasibility of local anesthesia for the surgical treatment of umbilical hernia.

Chapter 12 presents a pilot study, in which the safety and feasibility of local anesthesia in the treatment of umbilical hernia is being investigated.

In **Chapter 13** the findings of this thesis will be discussed. Furthermore, recommendation for the future will be provided.

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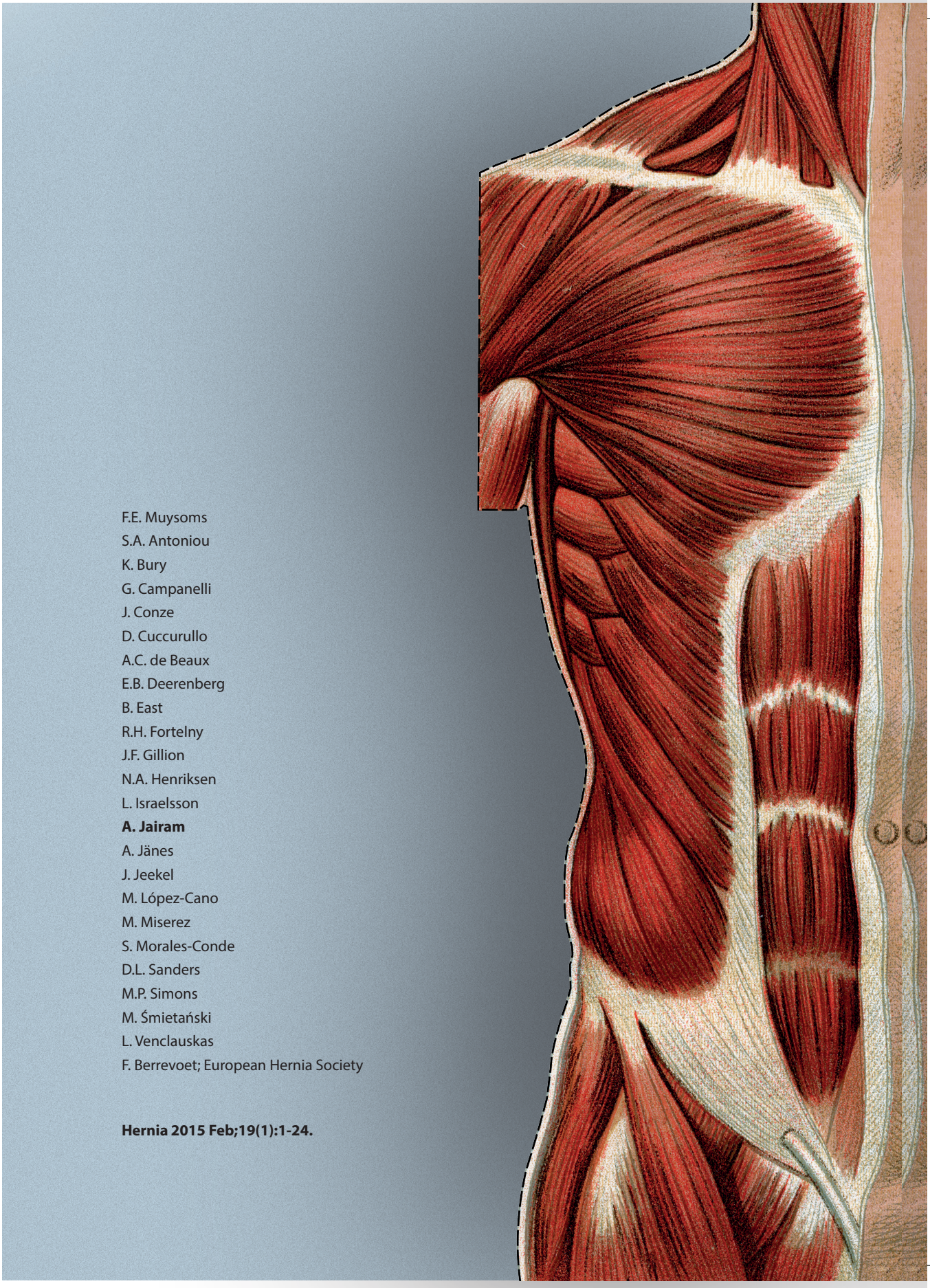
PART 1

Prevention of Incisional Hernia



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K. Bury
G. Campanelli
J. Conze
D. Cuccurullo
A.C. de Beaux
E.B. Deerenberg
B. East
R.H. Fortelny
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D.L. Sanders
M.P. Simons
M. Śmietański
L. Venclauskas
F. Berrevoet; European Hernia Society

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CHAPTER 2

European Hernia Society Guidelines on Closure of Abdominal Wall Incisions

ABSTRACT

Background: The material and the surgical technique used to close an abdominal wall incision are important determinants of the risk of developing an incisional hernia. Optimizing closure of abdominal wall incisions holds a potential to prevent patients suffering from incisional hernias and for important costs savings in health care.

Methods: The European Hernia Society formed a Guidelines Development Group to provide guidelines for all surgical specialists who perform abdominal incisions in adult patients on the materials and methods used to close the abdominal wall. The guidelines were developed using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) and methodological guidance was taken from SIGN (Scottish Intercollegiate Guidelines Network). The literature search included publications up to April 2014. The guidelines were written using the AGREE II instrument. An update of these guidelines is planned for 2017.

Results: For many of the Key Questions that were studied no high quality data was detected. Therefore, some strong recommendations could be made but, for many Key Questions only weak recommendations or no recommendations could be made due to lack of sufficient evidence.

Recommendations: To decrease the incidence of incisional hernias it is strongly recommended to utilise a non-midline approach to a laparotomy whenever possible. For elective midline incisions, it is strongly recommended to perform a continuous suturing technique and to avoid the use of rapidly absorbable sutures. It is suggested using a slowly absorbable monofilament suture in a single layer aponeurotic closure technique without separate closure of the peritoneum. A small bites technique with a suture to wound length (SL/WL) ratio at least 4/1 is the current preferred method of fascial closure. Currently, no recommendations can be given on the optimal technique to close emergency laparotomy incisions. Prophylactic mesh augmentation appears effective and safe and can be suggested in high-risk patients. For laparoscopic surgery it is suggested using the smallest trocar size adequate for the procedure and closure of the fascial defect if trocars larger or equal to 10 mm are used. For single incision laparoscopic surgery we suggest meticulous closure of the fascial incision to avoid an increased risk of incisional hernias.

INTRODUCTION

Background

Incisional hernias are a frequent complication of abdominal wall incisions, but a wide range of incisional hernia rates are reported (1-6). The weighted mean incisional hernia rate at 23.8 months was 12.8 % in a systematic review and meta-regression study(7), but incidence rates up to 69 % have been reported in high-risk patients with prospective long-term follow-up(8). The reported incidence is determined by several factors: the patient population studied, the type of abdominal wall incision, the length of follow-up and the method of incisional hernia diagnosis. Risk factors for incisional hernias include postoperative surgical site infection, obesity and abdominal aortic aneurysm(9-11). Nevertheless, it seems that the suture material and the surgical technique used to close an abdominal wall incision, are the most important determinants of the risk of developing an incisional hernia(4, 12). The development of an incisional hernia has an important impact on the patients' quality of life and body image(13). Furthermore, the repair of incisional hernias still has a high failure rate with long term recurrence rates above 30%, even when mesh repair is performed(14-16). Optimising the surgical technique to close abdominal wall incisions using evidence based principles, holds a potential to prevent patients suffering from incisional hernias and the potential sequelae of incisional hernia repairs(17). The mean direct and indirect costs for the repair of an average incisional hernia in an average patient in France in 2011 was € 7,089(18). Thus, reducing the incisional hernia rate by optimising the closure of abdominal wall incisions holds a great potential for costs savings in the use of health care facilities and in reducing postoperative disability.

The European Hernia Society (EHS) originated from the "Groupe de la recherche de la paroi abdominal" (GREPA), which was founded in 1979 with the aim: "The promotion of abdominal wall surgery, the study of anatomic, physiologic and therapeutic problems related to the pathology of the abdominal wall, the creation of associated groups which will promote research and teaching in this field, and the development of interdisciplinary relations". During the autumn board meeting of the EHS in September 2013 in Italy it was decided to extend our mission to actively promote the prevention of incisional hernias by the Sperlonga statement: "Maybe we should first learn and teach how to prevent incisional hernias, rather than how to treat them?"

Objective

The objective is to provide guidelines for all surgical specialists who perform abdominal incisions in adult patients on the optimal materials and methods used to close the abdominal wall. The goal is to decrease the occurrence of both burst abdomen and incisional hernia. The guidelines refer to patients undergoing any kind of abdominal wall incision, including visceral surgery, gynaecological surgery, aortic vascular surgery, urological surgery or orthopaedic surgery. Both open and laparoscopic surgeries are included in these guidelines.

METHODS

As EHS secretary of Quality, Filip Muysoms, under the auspices of the European Hernia Society board, proposed the Guidelines Development Group. The project was presented to the EHS board and accepted during the board meeting in Sperlonga, Italy, on September 28th 2013. The members of the Guidelines Development Group were chosen to recruit key opinion leaders and researchers on the subject from Europe. A geographical distribution across European countries was attempted and some younger surgeons having performed research on the subject were included in the Guidelines Development Group. Many of the members have contributed previously in producing guidelines on a national and international level. The Guidelines Development Group included abdominal wall surgeons, upper gastro-intestinal surgeons, hepato-biliary surgeons, colorectal surgeons and a vascular surgeon.

During a Kick Off meeting of the Guidelines Development Group in the Bonham Hotel in Edinburgh on October 28th 2013, the members attended a seminar on the methodological aspect of developing guidelines by Robin T Harbour, the Lead Methodologist of the Scottish Intercollegiate Guidelines Network (SIGN)(19). The AGREE II instrument was used from the start of the project to guide our methodology and structure of producing the guidelines(20). AGREE II gives as definition for the Quality of a guideline: "The confidence that the potential biases of guideline development have been addressed adequately and that the recommendations are both internally and externally valid, and are feasible for practice." During this first meeting Key Questions were formulated and translated into 24 patients-intervention-comparison-outcome (PICO) formats. For each Key Question at least three Guidelines Development Group members were assigned as investigators and specific search terms were formulated.

On November 11th 2013, a meeting in Glasgow at the SIGN headquarters was held with the steering committee of the Guidelines Development Group to discuss the search strategy. A clinical librarian working for SIGN performed the primary literature research for all Key Questions. This involved a search for systematic reviews and/or meta-analyses on the Key Questions in Medline, Embase, NIHR CRD, NICE and The Cochrane library. The PRISMA flow diagram is shown in Figure1. The Guidelines Development Group members evaluated the systematic reviews for their relevance to the Key Questions and a qualitative assessment was done using the SIGN checklist No 1 for systematic reviews and meta-analyses(19). Only systematic reviews of High Quality were used as basis for the guidelines development. A second search (no filters) on the Key Questions was performed for relevant RCT's published after the end of the search performed for the systematic reviews involved. If no High Quality systematic review was identified for a Key Question, the working group members performed a separate systematic review using the PRISMA statement methodology(21). To avoid lengthening of this guidelines manuscript, the results of these systematic reviews will be submitted as a separate manuscript on behalf of "The Bonham Group", which are the members of the Guidelines Development Group. The members working together on a Key Question provided a Summary of Findings table from the results of the literature search, which were presented and discussed during the second group meeting.

The second Guidelines Development Group meeting was held in Edinburgh on April 25th 2014. For evaluation of evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used(22). For each Key Question, a level of evidence was proposed using the GRADE approach and four levels of quality of the body of evidence were used: high, moderate, low, very low (Table 1). Based on the research evidence, the clinical experience and patient values the Guidelines Development Group formulated a recommendation for each Key Question. In the GRADE approach only three levels of recommendation are used: strong recommendation, weak recommendation and no recommendation.

The results of the guidelines proposed by the Guidelines Development Group were presented during the 36th Annual International Congress of the European Hernia Society in Edinburgh on May 31st 2014. The manuscript was subsequently written by the first author in a uniform manner for all Key Questions and send for review and agreement by all co-authors. Prior to submission, the manuscript of the guidelines was externally reviewed by experts and evaluated using the AGREE II instrument.

Table 1. Using the GRADE approach to guideline development(22) the Quality of the body of evidence is rated (high/moderate/low/very low) and the recommendations are graded as strong or weak

Grading the Quality of the body of evidence for each Key Questions using the GRADE approach			
Underlying methodology	**Quality rating**	**Symbols**	**Definitions**
Randomized trials; or double-upgraded observational studies.	High	■■■■	Further research is very unlikely to change our confidence in the estimate of effect
Downgraded randomized trials; or upgraded observational studies.	Moderate	■■■□	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Double-downgraded randomized trials; or observational studies.	Low	■■□□	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Triple-downgraded randomized trials; or downgraded observational studies; or case series/case reports.	Very low	■□□□	Any estimate of effect is very uncertain.
Grading of recommendations using the GRADE approach			
Strong recommendation	Based on the available evidence, if clinicians are very certain that benefits do, or do not, outweigh risks and burdens they will make a strong recommendation.		
Weak recommendation	Based on the available evidence, if clinicians believe that benefits and risks and burdens are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks, they must offer a weak recommendation.		
No recommendation	If based on the literature research no evidence could be found, no recommendation can be made.		

RESULTS

The results of the searches are shown in the PRISMA flow diagram in Figure 1. From the 97 records detected by the SIGN process, 69 records were excluded based on the title and abstract as not being relevant to the guidelines. The remaining 28 systematic reviews(4, 23-49) were assessed by full text for their relevance to the Key Questions and if retained were assessed qualitatively using the SIGN checklist No 1(19). Additional searches on PubMed and by checking the references of all manuscripts were performed by the members of the Guidelines Development Group assigned to each Key Question. Relevant studies published up until April 2014 were included to provide the Summary of Evidence tables.

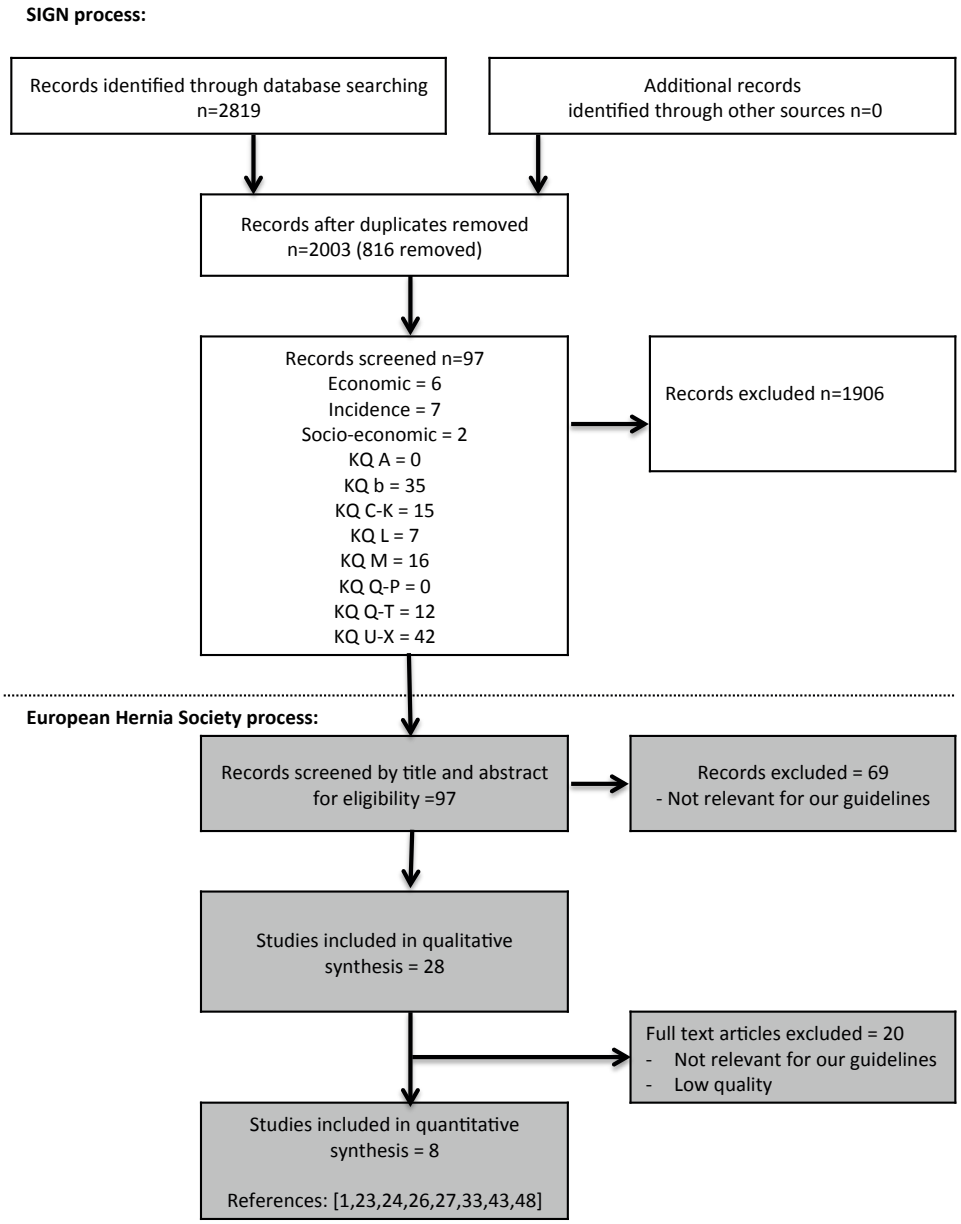


Figure 1. PRISMA flow diagram for the search for systematic reviews and/or meta-analyses performed by Scottish Intercollegiate Guidelines Network (SIGN) for the Guidelines Development Group of the European Hernia Society guidelines on the closure of abdominal wall incisions. The search was performed in November 2013 and included searches in Medline, Embase, NIHR CRD, NICE and The Cochrane library

Which diagnostic modality is the most suitable to detect incisional hernias?

No systematic reviews on diagnostic modalities for incisional hernias were found. Fifteen records were included in the qualitative analysis(1-3, 6, 50-60). Only four studies were retained as High Quality and are listed in the Summary of Findings table (Table 2) (3, 50, 51, 60).

The quality of most studies investigating the diagnostic accuracy of imaging techniques was low to very low. Only some provided a sensitivity analysis. Because no studies compared different diagnostic modalities in a similar methodology and with similar study arms, no pooling of data was useful or possible. In general, most studies show that medical imaging will increase the rate of detection of incisional hernias compared to physical examination. In an everyday clinical setting this is usually not important, because most asymptomatic hernias do not require treatment and their diagnosis is thus not necessary.

CT scan is reliable and reproducible, whereas ultrasound is more operator-dependant. However, CT scan will induce a radiation load to the patients and ultrasound is more accessible in most health care settings. A good standardisation and dynamic evaluation by ultrasound of the abdominal wall is needed, as described by Beck et al.(51) as the dynamic abdominal sonography for hernia (DASH) technique.

The difference in accuracy between physical examination and imaging technique is most important in the context of comparative studies evaluating incisional hernia rate. Next to the method of incisional hernia diagnosis the length of follow-up is important. Fink et al.(5) reported in a follow-up study of two prospective trials an increase from 12.6 % at 12 months to 22.4 % at 36 months ($p < 0.001$) and concluded that follow-up for 3 years should be mandatory in any study evaluating the rate of postoperative incisional hernia after midline laparotomy.

Statement	It is recommended that prospective studies with incisional hernia as a primary outcome integrate medical imaging, either dynamic ultrasound or CT-scan, in the follow-up.	■■□□	strong

Statement	It is recommended that studies with incisional hernia as a primary outcome include follow-up of at least 24 months (and preferably 36 months).	■■□□	strong

Table 2. Summary of Findings table for Key Question A: which diagnostic modality is the most suitable to detect incisional hernias?

Bibliographic citation	Study type	SIGN assessment	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measure
Baucom et al. Journal of the American College of Surgeons 2013; 218(3):363-6.	prospective cohort study	High Quality ++	181	patients seen at a general surgery department who had a prior abdominal operation and an available CT scan within six months before the visit	Physical examination by a surgeon	CT scan reviewed by surgeon	not available	Physical examination had a low sensitivity (77%) and negative predictive value (77%). It fails to detect 23% of hernias and in 32% of the patients with a BMI ≥ 30 kg/m^2.
General comments: Adequate designed study to compare physical examination to CT scan diagnosis of incisional hernias. CT scan was used a "gold standard" for the sensitivity analysis.								
Beck et al. Journal of the American College of Surgeons 2013;216(3):447-53	prospective cohort study	High Quality ++	181	patients seen at a general surgery department who had a prior abdominal operation and an available CT scan within six months before the visit	dynamic abdominal ultrasound by surgeon	CT scan reviewed by surgeon	not available	Dynamic Ultrasound has a high sensitivity (98%) and specificity (88%). It has a positive predictive value of 91 % and negative predictive value of 97%. It is a good alternative to CT scan diagnosis.
General comments: Paper from the same group as Baucom et al. Concerns the same patient population. Adequate designed study to compare dynamic ultrasound to CT scan diagnosis of incisional hernias. CT scan was used a "gold standard" for the sensitivity analysis.								
den Hartog et al. Hernia 2009;13(1):45-8	prospective cohort study	High Quality ++	40	patients that had aortic surgery by midline incision at least 12 months before	Ultrasound by radiologist	CT scan (by 2 independent radiologists.	mean 3.4 years	Incisional hernia prevalence was 60.0% with CT scan and 42.5% with ultrasound. The sensitivity of US was 70.8% and the specificity 100%. Us has a positive predictive value of 100% and a negative predictive value of 69.6%. CT scan diagnosis of the incisional hernias has a good intra- and inter -observer reliability.
General comments: Adequate designed study to compare ultrasound to CT scan diagnosis of incisional hernias. No comparison to physical examination. Limited number of patients. CT scan was used as "gold standard" for the sensitivity analysis.								
Schreinemacher et al. Arch Surg. 2011;146:94-9	retrospective cohort study with prospective examination	High Quality ++	111	patients that have a closure of a temporary stoma (42% ileostomies and 58% colostomies).	Ultrasound of the abdominal wall by surgeon	Physical examination by surgeon	median 35 months	Incisional hernia prevalence was 32.4% with ultrasound evaluation. Physical examination had a sensitivity of 58.3% and a specificity of 97.3%. The positive predictive value was 91.3% and the negative predictive value was 83%.
General comments: Both examinations were performed by the same person. Ultrasound was used a "gold standard" for the sensitivity analysis.								

Does the type of abdominal wall incision influence the incidence of incisional hernias or burst abdomen?

Laparotomy incisions can be classified as midline, transverse, oblique or paramedian incisions(61). Six systematic reviews have compared midline laparotomies to alternative incisions(26, 27, 31, 36, 38, 61), but only two were considered High Quality (26, 27). A recent systematic review by Bickenback et al.(26) compared midline, transverse (including oblique) and paramedian incisions. This review included all relevant studies from previous reviews and no additional RCT's were detected that were published after this review. The literature search of this systematic review(26) identified studies published until 2009 and 24 RCT's directly comparing different laparotomy incisions were included in the analysis. The incisional hernia rates after non-midline incisions were significantly lower compared to the incisional hernia rates after midline incisions, for both transverse incisions (RR = 1.77; 95 % CI:1.09–2.87) and paramedian incisions (RR = 3.41; 95 % CI: 1.02–11.45)(26). However, data on burst abdomen (deep wound dehiscence or fascial dehiscence) were not significantly different between the different incisions types.

A Cochrane review by Brown et al.(27) published in 2005 and updated in 2011, compared transverse versus midline incisions, but excluded studies comparing paramedian incisions. A decreased incisional hernia rate after transverse incisions was reported compared to midline incisions (OR = 0.49; 95 % CI: 0.30–0.79).

Both reviews concluded that non-midline incisions significantly reduced the risk of incisional hernia compared to midline incisions, but did not influence the risk of burst abdomen. Interestingly, the Cochrane conclusions were more moderate, due to methodological and clinical heterogeneity of the studies and the risk of potential bias.

Statement	Non-midline incisions are recommended where possible	■■■□	strong

What is the optimal technique to close a laparotomy incision?

Ten systematic reviews on the techniques and/or the materials to close abdominal wall incisions were identified (4, 32, 34, 37, 38, 42, 43, 48, 62, 63). The data from the different systematic reviews are very incoherent and conclusions are often completely contradictory. The overall quality of most systematic reviews is low and therefore, several should be rejected as evidence to create guidelines. A major problem to identify the evidence from the literature is the fact that most prospective studies compared

several variables between the study arms. Moreover, the populations studied are often very different: midline only or including other incisions, emergency or elective surgery, and different operative indications.

The current guidelines on techniques and materials are based on the systematic reviews by Diener et al.(4) and van't Riet et al.(48) which were evaluated as High Quality. Both systematic reviews included only studies involving midline laparotomies and the review by Diener et al. was the only one to distinguish between elective or emergency surgery. The systematic review by Sajid et al.(43) was used for the question on suture materials and a recent Cochrane review by Gurusamy et al.(62) was used for the question on peritoneal closure.

Using separate PICO's the shortcoming of many study designs to deliver clear answers becomes obvious. Another shortcoming in most studies on closure of laparotomies is the failure to monitor the technical details of the suturing technique, like the SL/WL ratio and the stitch size. As demonstrated by Israelsson(64) this might be an important confounding factor in studies comparing different suture materials. An updated systematic review taking into account the mentioned shortcomings of individual studies might be performed, but for these guidelines the conclusions are based on the data from the currently available systematic reviews. The protocol for an ongoing Cochrane review(65) was published in 2006 but the final data have not yet been published.

Statement	It is recommended that prospective randomized studies on the suture material to close abdominal wall incisions use the same suturing technique in both study groups.	strong

Statement	It is recommended that prospective randomized studies assessing the technique to close abdominal wall incisions use the same suture material in both study groups.	strong

Continuous suturing versus interrupted sutures

Both meta-analyses concluded that continuous suturing for closure of midline laparotomies was beneficial compared to interrupted closure (4, 48). Diener et al.(4) found a significant lower incisional hernia rate for continuous suturing (OR 0.59: p = 0.001) in elective surgery. Most of the included studies were at high risk of bias because the interrupted study arm used rapidly absorbable multifilament sutures and the continuous arm used either non-absorbable or slowly absorbable monofilament

sutures. van't Riet et al.(48) included studies involving emergency laparotomies and did not find any difference in incisional hernia rate between interrupted and continuous suturing. Continuous suturing was recommended because it was significantly faster.

Statement	Continuous suturing for closure of midline abdominal wall incisions in elective surgery is recommended	■■□□	strong

Closure versus non-closure of the peritoneum

The Cochrane review by Gurusamy et al.(62) concluded that there was no short-term or long-term benefit in peritoneal closure. Five studies were included but were heterogeneous in type of incision (midline and non-midline) and included both elective and emergency laparotomies. In all studies the peritoneum was closed as a separate layer in the study arm with peritoneal closure.

Statement	Closure of the peritoneum as a separate layer during closure of laparotomy incisions is NOT recommended	■■□□	weak

Mass closure versus single layer closure

The search for the most appropriate layers to be sutured when closing a laparotomy is hampered by the lack of good definitions on what constitutes a mass closure, layered closure or single layer closure. No clinical studies directly comparing different closure methods were found.

For future research the Guidelines Development Group proposes the following definitions:

- *mass closure*: the incision is closed with a suture bite including all layers of the abdominal wall except the skin.
- *layered closure*: the incision is closed with more than one separate layer of fascial closure
- *single layer aponeurotic closure*: the incision is closed by suturing only the abdominal fascia in one layer.

Statement	For closure of midline abdominal wall incisions in elective surgery, a single layer aponeurotic closure is suggested	■□□□	weak

Suture length to wound length ratio (SL/WL)

The beneficial effect of a high SL/WL ratio on reducing the incidence of incisional hernias has been recognised for a long time(66), but evidence from clinical prospective studies remains scarce and most of the work addressing the topic comes from the Clinic of Sundsvall in Sweden(64, 67, 68). A RCT, performed in Sundsvall, demonstrated the importance of the SL/WL ratio in reducing incisional hernia rate. The critical value was determined to be at a ratio of 4/1(64). Although a SL/WL ratio ≥4 is often mentioned in the protocol of prospective studies, many fail to document that the SL/WL ratio was recorded for the individual study patients.

Statement	A suture to wound length ratio (SL/WL) of at least 4/1 for continuous closure of midline abdominal wall incisions in elective surgery is suggested.	■■□□	weak

Statement	It is recommended that all prospective studies on the closure of laparotomy incisions will document the suture to wound length ratio (SL/WL) in all patients, as well as the number of stitches.		strong

Small bites versus large bites

Millbourn et al.(69) demonstrated that closure of a midline laparotomy with a "small bites" technique resulted in significant less incisional hernias (5.6% *vs* 18.0 %; p< 0.001) and less surgical site infections (SSIs) (5.2% *vs* 10.2%; p= 0.02). In the small bite technique the laparotomy wound is closed with a single layer aponeurotic suturing technique taking bites of fascia of 5 - 8 mm and placing stitches every 5 mm.

Statement	The "small bites technique" for continuous closure of midline incisions is suggested.	■■■□	weak

What is the optimal suture material to close a laparotomy incision?

Despite significant heterogeneity and confounders in most SRs identified, a study by Sajid et al.(43) focused solely on the suture material. Table 3 defines the suture materials used in the included studies.

Rapidly absorbable suture versus non-absorbable or slowly absorbable sutures

Diener et al. (4) reported a significantly lower incisional hernia rate with slowly absorbable sutures (OR 0.65: p= 0.009) in elective surgery. Subgroup analysis performed by van 't Riet et al.(48) comparing only continuous suturing studies, detected only one

RCT by Wissing et al.(70) using continuous suturing in both study arms. This study, which included 21% of emergency operations, showed significantly more incisional hernias with rapidly absorbable sutures compared to non-absorbable sutures (p= 0.001) and compared to slowly absorbable sutures (p = 0.009).

Statement	The use of rapidly absorbable suture material for closure of midline abdominal wall incisions in elective surgery is NOT recommended.	■■■□	strong

Table 3. List of the most commonly used suture materials to close abdominal wall incisions and their characteristics

Suture	Producer	Material	Absorbable	Absorption time	Filaments	Antibiotics impragnated
Prolene	Ethicon	Polypropylene	Non		Mono	No
Surgipro	Covidien	Polypropylene	Non		Mono	No
Ethilon	Ethicon	Nylon	Non		Mono	No
Monosof	Covidien	Nylon	Non		Mono	No
Ethibond	Ethicon	Polyethylene	Non		Multi	No
Mersilene	Ethicon	Polyester	Non		Multi	No
Surgilon	Covidien	Nylon	Non		Multi	No
Maxon	Covidien	Polyglyconate	Slowly	180 days	Mono	No
PDS	Ethicon	Polydioxanone	Slowly	183–238 days	Mono	No
PDS plus	Ethicon	Polydioxanone + triclosan	Slowly	183–238 days	Mono	Yes
Monoplus	B Braun	Polydioxanone	Slowly	180–201 days	Mono	No
Monomax	B Braun	Poly-4-hydroxybutyrate	Slowly	390–1080 days	Mono	No
Vicryl	Ethicon	Polyglactin	Rapidly	56–70 days	Multi	No
Vicryl plus	Ethicon	Polyglactin + triclosan	Rapidly	56–70 days	Multi	Yes
Polysorb	Covidien	Polyglycolic acid	Rapidly	60–90 days	Multi	No
Dexon	Covidien	Polygglycolic acid	Rapidly	60–90 days	Multi	No

Non-absorbable versus slowly absorbable sutures

No difference in incisional hernia rate for continuous suturing of midline incisions with slowly absorbable versus non-absorbable sutures (p= 0.75) was identified(48). However, an increased incidence of prolonged wound pain (p< 0.005) and suture sinus formation (p= 0.02) with non-absorbable sutures was reported(48). Another MA (which included non-midline incisions) identified no difference in incisional hernia rate between slowly-

absorbable polydioxanone and non-absorbable sutures (OR 1.10: p= 0.43)(43). Once again, non-absorbable sutures had a significant higher risk of suture sinus formation (OR 0.49: p= 0.01)(43).

Statement	Using slowly-absorbable suture material instead of non-absorbable sutures for continuous closure of midline abdominal wall incisions in elective surgery is suggested.	■■□□	weak

Monofilament versus multifilament sutures

Monofilament sutures are believed to be associated with a lower SSI rate than multifilament sutures(12). However, none of the SRs commented on this issue specifically. If the previous recommendation to use slowly absorbable sutures for closure of elective midline laparotomies is followed, this question becomes superfluous because the slowly absorbable sutures are all monofilament sutures.

Statement	We suggest using monofilament suture material for continuous closure of midline abdominal wall incisions in elective surgery.	■□□□	weak

Concerning the size of the suture, no studies comparing directly the size of the sutures used to close abdominal wall incisions were identified during our searches. For the "small bites" technique, Isrealsson et al(12) suggest to use a suture size USP 2/0 (USP = United States Pharmacopeia).

Statement	No recommendation on the size of the sutures for closure of abdominal wall incisions can be given due to lack of data.	■□□□	no

Sutures impregnated with antibiotics

Sutures coated with Triclosan as an antimicrobial agent have been introduced to decrease the rate of surgical site infection in surgery. A recent meta-analysis has demonstrated a significant beneficial effect in the prevention of surgical site infection after all kinds of surgery(71). Surgical site infection is a risk factor for subsequent development of incisional hernias and therefore the use of antibiotics impregnated sutures to close laparotomies might be beneficial in the prevention of incisional hernias. Recently Diener et al.(72) published a large RCT on 1,224 patients undergoing an elective midline laparotomy comparing polydioxanone sutures with versus without triclosan impregnation. No reduction in the incidence of surgical site infection was reported (OR

0.91: CI 0.66–1.25; p = 0.39). Four other RCT's have compared sutures with or without triclosan in laparotomy closure, either with polyglactin sutures (Vicryl)(73, 74) or with polydioxanone (PDS)(75, 76). A meta-analysis on all five studies performed by Diener et al. showed a significant decrease in surgical site infection (OR 0.67: CI 0.47–0.98). No data on incisional hernias are available from these studies.

Statement	Monofilament sutures impregnated with antibiotics for closure of elective midline incisions is NOT advised, because of insufficient data on their efficiency on prevention of surgical site infections and the lack of data on incisional hernias or burst abdomen.	■■■□	weak

Limitations of the statements in these guidelines on suture technique and suture materials

The statements are limited by the quality of the data on which they are based. In total, 61 RCT's have been identified that compared suture materials or techniques to close laparotomy incisions. Many studies have more than one variable between study arms and therefore analysing them in meta-analyses is difficult. Moreover, many studies have flaws in the methodology increasing the risk of bias. We would like to encourage researchers that plan studies on abdominal wall closure to improve the methodology of their study protocol. Preferably study arms are only different in the variable under investigation, either a suture technique or a suture material. Moreover we recommend documenting the technical details such as SL/WL ratio, the number of stitches used in the patients and to provide a follow up of at least 24 months.

Although some of the systematic reviews detected included non-midline incisions(43) or emergency operations(48), these guidelines are currently limited to elective midline laparotomies. For emergency operations and non-midline incisions there is currently not enough data available.

Statement	No recommendation on suture material or suturing technique for use in emergency surgery can be given due to lack of sufficient data.	■□□□	no

Statement	No recommendation on suture material or suturing technique for use in non-midline incisions can be given due to lack of sufficient data	■□□□	no

Suture needles and retention sutures

Blunt tip versus sharp needles

Only one SR assessing the type of needle used to close the abdominal wall(23) and one RCT comparing blunt needles with sharp needles were identified. The RCT reported no difference in SSI rate between blunt and sharp needles(77).

Statement	No recommendation on the type or the size of needle to close a laparotomy can be given due to lack of data.	■□□□	no

Is there a place for retention sutures when closing a laparotomy?

No SR on the use of retention sutures was found. Eight records were screened by full text(78-85). Three RCTs on the prevention of burst abdomen by using either retention sutures or a reinforced tension line suture in patients with increased risk for wound dehiscence and burst abdomen were identified(78, 81, 85). Follow up was too short to evaluate incisional hernia rate. The Summary of Evidence is listed in Table 4. Two studies showed favourable results(78, 81), but one study reported a high number of adverse events when using retention sutures(85).

Statement	No recommendation on the use of retention sutures in patients with multiple risk factors for burst abdomen can be given due to insufficient data.	■■□□	no

Postoperative care

Postoperative management and instructions for patients are not supported by high quality prospective data, but rely mostly on surgeons' habits, tradition and common beliefs (86-88). Long term follow up studies are needed to research the impact on the occurrence of incisional hernias of prescribing abdominal binders or restricting postoperative activity. The additional searches did not reveal any relevant study on long term outcome. Some studies on the short term benefits of abdominal binders were found.

Table 4. Summary of Findings table for Key Question M: is there a place for retention sutures when closing a laparotomy?

Bibliographic citation	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measure
Khorgami et al. J Surg Res. 2013;180:238-43.	RCT	300	Patients undergoing midline laparotomy with ≥ 2 risk factors of a list of defined risk factors for burst abdomen	extra retention sutures Nylon 1 (every 10 cm and with 5 cm bites of skin) kept for 3-4 weeks	continuous loop size 1 nylon suture (1 cm from the edge /1 cm intervals)	median 5 months	Wound dehiscence was 4.1% (6/147) in the intervention group and 13.5% (20/148) in the control group (p = 0.007). "We showed that prophylactic retention sutures could reduce wound dehiscence in midline laparotomy in high-risk patients with multiple risk factors without imposing remarkable postoperative complications. "
Agrawal Trop Gastroenterol. 2009;30:237-40.	RCT	190	Emergency midline laparotomy	reinforced tension line suture	continuous suture		Burst abdomen was 0.0% (0/90) in the intervention group and 13.0% (13/100) in the control group (p = 0.0026). "Closure of midline incision by RTL reduces the incidence of burst abdomen."
Rink et al Eur J Surg. 2000;166:932-7.	RCT	95 (92 midline)	Patients needing major abdominal surgery with infective or malignant intra-abdominal diseases. + at least one risk factor	extra retention sutures with sutures retention bridge for 12 days	interrupted Vicryl 1 sutures	12 days	"Retention sutures used to close abdominal wounds cause inconvenience, pain, and specific morbidity."

Subcutaneous drains in laparotomy incisions

Prophylactic routine placement of subcutaneous drains after laparotomy is occasionally used to decrease wound complications: infection, hematoma, seroma or wound dehiscence(88). However, there are several disadvantages to the routine use of subcutaneous drains. Namely, they cause patient discomfort and pain at removal, they hinder early mobilisation and demand additional nursing care. Therefore their use should be driven by a proven benefit.

One systematic review(89) and several RCTs (90-98) on the use of subcutaneous drains in abdominal surgery were found. They cover a wide range of operative indications: liver surgery, colorectal surgery, cholecystectomy, gynaecological surgery, caesarean section, and gastric bypass surgery. With few exceptions, most studies did not show a benefit for the use of subcutaneous drains. However, none of these studies had incisional hernias or burst abdomen as primary or secondary endpoint.

Statement	The routine placement of a subcutaneous drain during closure of abdominal wall incisions is NOT recommended.	■■■□	strong

Postoperative binders

One systematic review on the use of abdominal binders was found(86). The review included four RCT's (99-102) and a national survey by questionnaire on the use of abdominal binders in French surgical practice(86). One additional recent RCT was identified(103). The French survey reported that postoperative support of the wound with an abdominal binder is common practice after major laparotomies in many surgical departments (94% use them in some patients). It is expected to reduce postoperative pain and to improve early mobilisation of the patients. Moreover 83% of users expect a benefit in the prevention of abdominal wall dehiscence(86). No significant improvement for the short term benefits was found by the small RCTs from the review(98, 99, 101, 102). The additional study by Clay et al.(100) found a significant lower VAS (Visual Analogue Scale) score for pain at the fifth postoperative day and no adverse effect on postoperative lung function. No studies were found that had burst abdomen or incisional hernias as a primary or secondary endpoints.

Statement	No recommendation can be given on the use of postoperative abdominal binders due to lack of data on their effect on incisional hernias or burst abdomen rates.	■□□□	no

Postoperative restriction of activity

No prospective studies were found on the restriction of physical activity after abdominal incisions. Nevertheless, it is advocated by some surgeons in order to decrease the risk of incisional hernias, but there is no consensus on the level or the duration of the restriction(87). Postoperative restriction might have an adverse impact on the return to normal activity and delay the return to work.

Statement	No recommendation can be given on routine restriction of activity after abdominal surgery due to lack of data on the effect on incisional hernias or burst abdomen rates.	■□□□	no

Prophylactic mesh augmentation

Three systematic reviews on the topic were found(24, 39, 104).

1. Nachappian et al.(39) did not assess of the quality of the individual studies and included non published data. Therefore this review did not qualify for inclusion in this guideline.
2. The systematic review by Bhangu et al.(24) is of High Quality and offers a good and extensive evaluation of the quality of the individual studies included. However, the quality of the non RCTs was usually low and these studies were not be used as evidence for these guidelines.
3. Timmermans et al.(104) published a good meta-analysis on five RCT's using polypropylene mesh, including a RCT published in 2013 by Abo-Ryia et al.(105).

One additional RCT published after the review by Timmermans et al.(106) was identified. In this RCT, one hundred and sixty patients were included. This is the first trial on non-selected elective midline laparotomies (with a majority of oncological patients). All the other trials have only included patients deemed at high risk for incisional hernias. In this RCT by Caro-Tarrago et al. the mesh augmentation was performed with a light weight polypropylene mesh in the onlay position. A significant reduction in incisional hernias at 12 months was observed clinically and with CT scan in favour of prophylactic mesh, 1.5 vs 35.9 % ($p < 0.0001$). A significantly higher number of postoperative seroma was detected in the mesh group, 11.3 vs 28.8 % ($p < 0.01$). No major complications related to the mesh augmentation were reported.

The details of the six published RCT's using polypropylene mesh including 506 patients are listed in Table 5(105-110). Using Review Manager 5.2 software a new meta-analysis was performed. The data for this meta-analysis were extracted from the Timmermans et

al. meta-analysis and the additional RCT(104, 106). A meta-analysis on the outcomes of incisional hernia, seroma and SSI was performed. The pooled analyses data are shown in a Forrest plot for each outcome in Figure 2. Prophylactic mesh augmentation is effective in the prevention of incisional hernias (RR 0.17: CI 0.08–0.37). An increased incidence of postoperative seroma is identified, but the majority of these are from the single study by Caro-Tarrago et al.(106) where the mesh was placed in an onlay position, with a weight of 45.9 % on the cumulative Risk Ratio for seroma (RR = 1.71; 95 %CI: 1.06–2.76) (Figure 2c).

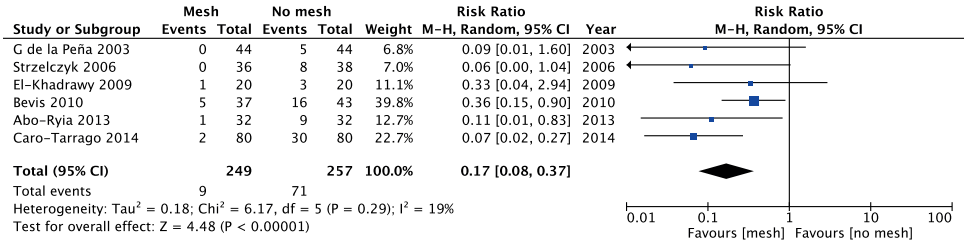
Although the data are favourable and consistent for prophylactic mesh augmentation, the Guidelines Development Group decided that larger trials are needed to make a strong recommendation to perform prophylactic mesh augmentation for all patients within certain risk groups.

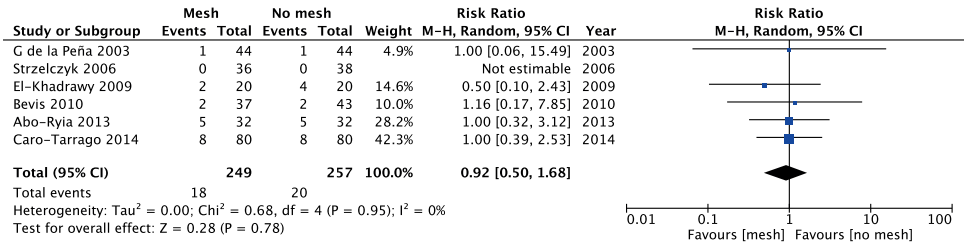
Statement	Prophylactic mesh augmentation for an elective midline laparotomy in a high-risk patient in order to reduce the risk of incisional hernia is suggested.	■■■□	Weak

Which mesh type, which mesh position and which type of mesh fixation?

No comparative studies are published between different mesh type, mesh position or method of mesh fixation. Pans et al.(111) found no significant protective effect on incisional hernia rate by intra-peritoneal augmentation with a polyglactin mesh (Vicryl; Ethicon) on incisional hernia rate in a RCT on obesity surgery (n = 288). Llaguna et al.(112) placed a biological mesh (Alloderm; LifeCell) in a retro-muscular position in bariatric patients. In this non-randomised comparative study (n = 106 of which 44 with mesh) a significantly lower incisional hernia rate was observed in the mesh group, 2.3 vs 17.7 % (p = 0.014). All other studies published used a polypropylene mesh, most often a small pore/heavy weight mesh: Prolene; Ethicon(107), Premilene; B. Braun(109), no name mentioned(105, 108, 110). Only Caro-Tarrago et al.(106) used a large pore/light weight mesh: Biomesh Light P8; Cousin Biotech.

There is a large variation between the studies on the mesh position for the prophylactic mesh augmentation. Onlay, retro-muscular and pre-peritoneal mesh positioning was performed in two studies each. No studies on the use of intra-peritoneal augmentation with a non absorbable synthetic mesh are reported. Only one study on the use of intra-peritoneal augmentation with an absorbable synthetic mesh is reported(111).





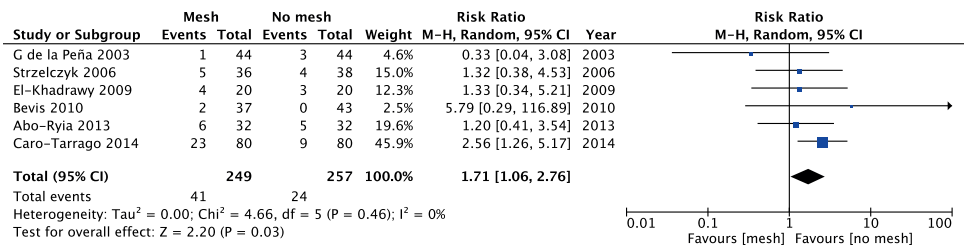


Figure 2. Forrest plots of a meta-analysis performed by the Guidelines Development Group on prophylactic mesh augmentation with polypropylene mesh after laparotomy. Analysis on the outcomes of incisional hernia, seroma and surgical site infection was performed.
A: Incisional hernia
B: Wound infection
C: Seroma

Table 5. List of the randomized clinical trials and their characteristics on prophylactic mesh augmentation using a polypropylene mesh

								Incisional hernias			Effect size
RCT	**publ. date**	**LoE**	**SIGN**	**n**	**population**	**mesh position**	**FU months**	**diagnosis incisional hernia**	**NO Mesh**	**Mesh**	**Risk Ratio (95% CI)**
Gutiérrez (109)	2003	2b	+	88	High risk patients	onlay	36	clinical + selective CT scan	5/44	0/44	0.09 (0.01-1.60)
Strelczyk (110)	2006	1b	++	74	Obesity surgery	retro-muscular	28	clinical + ultrasound in all	8/38	0/36	0.06 (0.00-1.04)
El-Kadrawy (108)	2009	2b	+	40	High risk patients	pre-peritoneal	36	clinical	3/20	1/20	0.33 (0.04-2.94)
Bevis (107)	2010	1b	++	80	AAA	retro-muscular	25.4	clinical+ selective ultrasound	16/43	5/37	0.36 (0.15-0.90)
Abo-Ryia (105)	2013	2b	+	64	Obesity surgery	pre-peritoneal	48	clinical + selective ultrasound	9/32	1/32	0.11 (0.01-0.83)
Caro-Tarrago (106)	2014	1b	++	160	midline laparotomies	onlay	12	clinical + CT scan in all	30/80	2/80	0.07 (0.02-0.27)
Overall				506					71/257	9/249	0.17 (0.08 - 0.37)

The mesh was in all studies fixed with sutures to the fascia except for the study of Pans et al.(111) which used no fixation. No studies on mesh augmentation with glue or a self-fixating mesh are reported.

Statement	No recommendation on the optimal mesh position for prophylactic mesh augmentation can be given due to lack of data.	■□□□	no
Statement	No recommendation on the optimal method of mesh fixation for prophylactic mesh augmentation can be given due to lack of data.	■□□□	no
Statement	No recommendation on the type of mesh for prophylactic mesh augmentation can be given due to lack of data.	■□□□	no

Trocar wounds for laparoscopic surgery and single port surgery

Trocar size and trocar type

The first search for systematic reviews resulted in 5 records(33, 40, 41, 46, 49) and 25 additional records were screened by full text(113-136). Several studies comment on the incidence of trocar-site hernia for various trocar sizes. However the quality of many studies is insufficient and challenge the validity of results. Shortcomings of the individual studies include retrospective study design, short or unclear length of follow up and inappropriate or no information on diagnostic methods to detect incisional hernias. Most importantly, available data derive from studies in which the same patient serves as case and control; i.e. the incidence of trocar-site hernia is measured for different sizes of trocars inserted at different abdominal sites in the same patient. This may impose significant bias, related to the strength of the abdominal wall and the wound repair mechanisms at varying sites of the abdominal wall, in particular the linea alba to other parts of the abdominal wall.

Helgstrand et al.(33) performed a systematic review on the incidence of trocar-site hernia. Although they found a risk reduction after sutured closure and a lower hernia rate for 5-mm versus larger diameter trocars, no meta-analysis was undertaken. The poor quality and design of the majority of the included reports preclude further in-depth evaluation for supporting evidence. No RCT's have investigated the incidence of trocar-site hernia after insertion of blunt versus bladed trocars and no RCT's or case-control studies have investigated the incidence of trocar-site hernia with reference to trocar size or diameter. Available data derive from univariate and multivariate analyses of cohort studies, which have investigated the effect of potential risk factors for trocar-

site hernia. Obesity, age above 60 years diabetes, long duration of surgery, and the need for fascia enlargement for specimen extraction were identified as risk factors for the development of trocar-site hernia(120, 136).

Statement	For laparoscopic procedures, using the smallest trocar size adequate for the procedure is suggested.	■■□□	Weak

Statement	For laparoscopic procedures, suturing the fascial defect, if trocars larger than or equal to 10 mm have been used, in the presence of established risk factors for incisional hernia formation is suggested.	■□□□	weak

Closure of trocar incisions

There are no good quality comparative studies investigating different suture materials or techniques for closure of trocar fascia defects. Armananzas et al.(113) reported in a recently published RCT a benefit for prophylactic intraperitoneal placement of a ventral patch at the umbilical site in high-risk patients to reduce the incidence of trocar-site hernia from 18.5% to 4.4% (OR 10.1: CI 2.15-47.6; p< 0.001). Larger sample-sized studies with a good risk-benefit assessment and longer follow-up are needed to confirm and support a stronger recommendation.

Statement	For laparoscopic procedures a mesh-augmented closure may be applied in patients at high risk for trocar-site hernia.	■■■□	weak

Single incision laparoscopic surgery and incisional hernia

The incidence of trocar-site hernia after single port surgery has been mostly investigated as a secondary outcome measure in the setting of RCTs and 3 High Quality MAs were found(137-139). Two MAs of RCTs have found no difference in the incidence of trocar-site hernia between single port and multiple port surgery, although a trend in favour of multiple port surgery was demonstrated(137, 139). The most recent MA included 19 RCTs involving 676 patients and found a higher incidence of trocar site hernia following single port surgery(138).

Statement	Emerging evidence suggests an increased incidence of trocar-site hernia for single-incision surgery as compared to conventional surgery; therefore meticulous closure of the incised fascia in single-port surgery is recommended.	■■■□	weak

DISCUSSION

Limitations

Not many strong recommendations could be made due to lack of sufficient evidence on many of the PICO questions. It is somewhat confusing to notice that the first strong recommendation in these guidelines is to avoid midline laparotomies in favour of alternative incisions and that all other recommendations are only valid for elective midline incisions. Indeed most research is focused on midline laparotomies. A midline laparotomy is still the favoured approach for most surgeons. It allows quick entrance to the abdominal cavity and extension of the incision is easy if this is required for the operation. Nevertheless, the linea alba is probably the most vulnerable and least vascularized part of the abdominal wall. Some refer to incisional hernias as "a midline crisis". Optimising closure of abdominal wall incisions would appear to hold a large potential in reducing the incidence of incisional hernias and the subsequent need for incisional hernia repair. This has obvious benefits for the individual patient relating to an improved quality of life, avoidance of secondary operations and at a macro-economical level a significant reduction in costs for health care resources. It is not easy to see the impact of each recommendation separately. Therefore, implementation of the optimised abdominal wall closure is probably best done by teaching all involved specialists a standardised technique described as the "Principles" of abdominal wall closure(17). This incorporates all recommendations, although the Guidelines Development Group is aware that the level of evidence for the different aspects is sometimes low to very low. David Sackett, a pioneer in evidence-based medicine wrote: "…any external guideline must be integrated with individual clinical expertise in deciding whether and how it matches the patient's clinical state, predicament, and preferences, and thus whether it should be applied"(140).

Discussions

For most Key Questions on the technique and material to close abdominal wall incisions, the grading of the Quality of Evidence and the choice of recommendation was straightforward. For several recommendations, while the quality of evidence was low, there was good consensus between the members of the Guidelines Development Group on the formulated statements. For prophylactic mesh augmentation there was disagreement on the strength of recommendation (weak or strong). For this reason, an additional meta-analysis was performed (Figure 2). Although the effect size in favour of mesh augmentation is large and consistent over the studies, the Guidelines Development Group felt that larger trials are needed to support a strong recommendation for prophylactic mesh augmentation in high-risk patients. Indeed, the number of patients

in the reported studies for each risk group separately (e.g. abdominal aortic aneurysm, obesity surgery, oncological surgery) seems too low to recommend prophylactic mesh augmentation in all these patient groups. Nevertheless, we are aware that several large RCT's are on-going and this grade of recommendation might be changed in the light of future publications.

No recommendations could be made on non-midline incisions due to insufficient evidence. Nevertheless, it seems reasonable to promote similar material (slowly absorbable suture) and techniques (continuous aponeurotic closure with small bites and SL/WL >4/1) for closure of non-midline incisions.

No recommendations could be made on the type or the size of the needle used to close abdominal incisions. No studies comparing the size of the sutures were identified in our searches.

No recommendation could be made for emergency surgery, which is often a contaminated procedure. The Guidelines Development Group consider that the use of retention sutures or of reinforced tension line sutures, should be prospectively studied in patients at high risk for development of burst abdomen. A risk model and score for burst abdomen has been developed by van Ramshorst et al.(141) and could be used as basis for including patients in these studies.

No recommendations could be made on the postoperative care after laparotomies. Long-term follow-up studies are needed to assess the impact on the occurrence of incisional hernias of prescribing abdominal binders or restricting or indeed encouraging early postoperative activity.

Applicability

To adopt the guidelines and "evidence based principles" for abdominal wall closure, surgeons must be convinced that these are valid recommendations with a large impact on the outcome for the patients. These guidelines are an attempt to create awareness amongst surgeons about these principles. Adaptation can be done by systematic quality control of the suturing technique as described by van Ramshorst et al.(142). The EuraHS, European registry for abdominal wall hernias, has developed an online platform for registration and outcome measurement of abdominal wall surgery(140). An additional route in the database on the closure of abdominal wall incisions and for prophylactic mesh augmentation will be provided from 2015 onwards. It is hoped that such a registry database will facilitate the data collection for prospective studies.

Validity of the guidelines

Prior to submission of the manuscript the guidelines were evaluated and scored using the AGREE II instrument. Several large multi-centre studies on the closure of abdominal wall incisions are currently on-going. High Quality data on the use of the "small bites" technique in midline incisions, on the closure of laparotomies in emergency and on prophylactic mesh augmentation will be published in the coming years. The Guidelines Development Group has decided to update these guidelines in 2017 and present the results during the 39th Annual Congress of the European Hernia Society in Vienna in May 2017.

CONCLUSIONS

To decrease the incidence of incisional hernias it is recommended to utilize a non-midline approach to a laparotomy whenever possible. For elective midline incisions, it is strongly recommended to perform a continuous suturing technique and to avoid the use of rapidly absorbable sutures. It is suggested that the use of a slowly absorbable monofilament suture in a single layer aponeurotic closure technique without separate closure of the peritoneum and using a small bites technique with a SL/WL ratio at least 4/1 is the current recommended method of fascial closure. Currently, no recommendations can be given on the optimal technique to close emergency laparotomy incisions. Prophylactic mesh augmentation appears effective and safe and can be suggested in high-risk patients like, aortic aneurysm surgery and obese patients.

OTHER INFORMATION

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Conflict of interest

The authors report no conflict of interest in relation to this manuscript.

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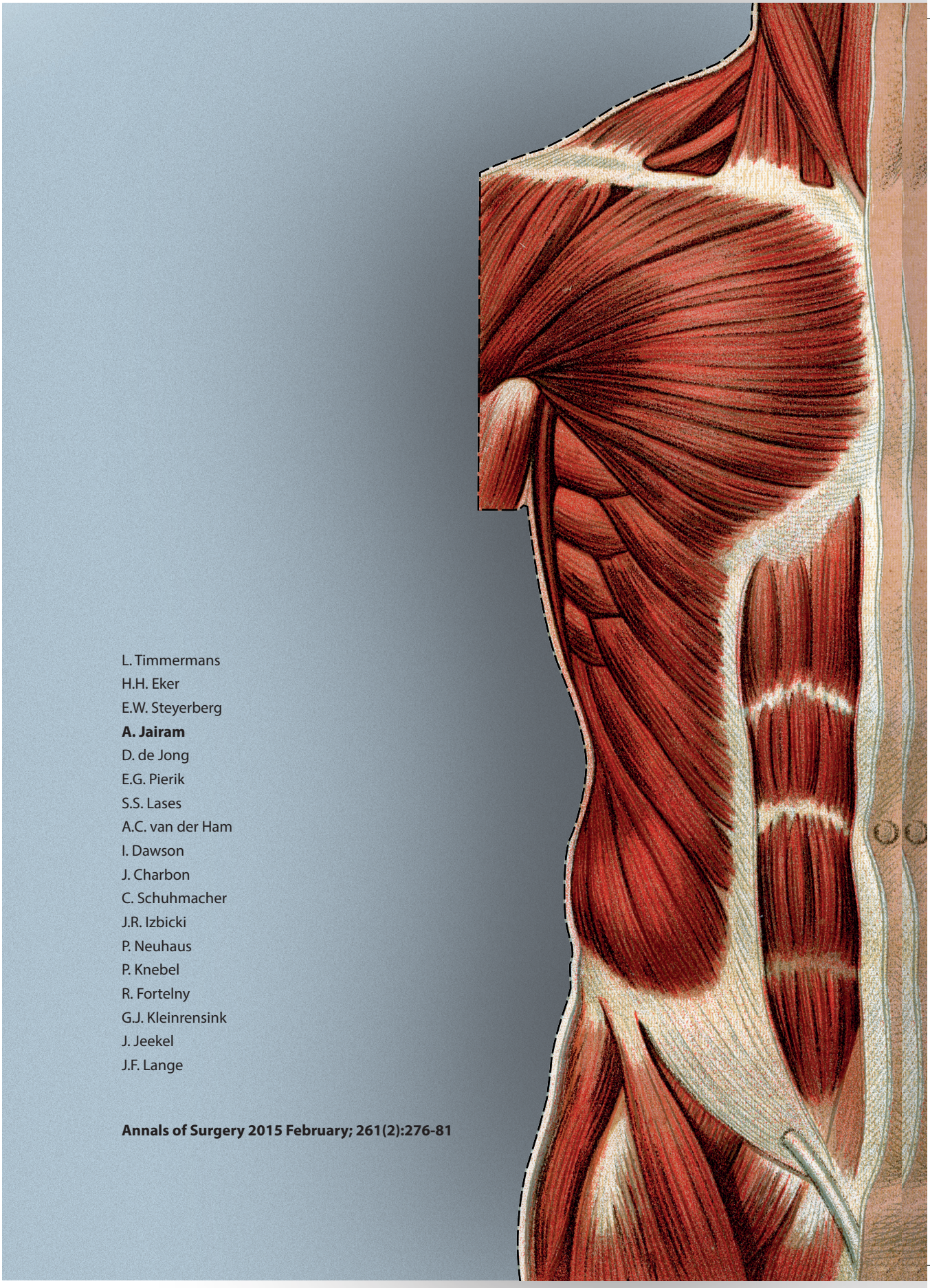

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I. Dawson
J. Charbon
C. Schuhmacher
J.R. Izbicki
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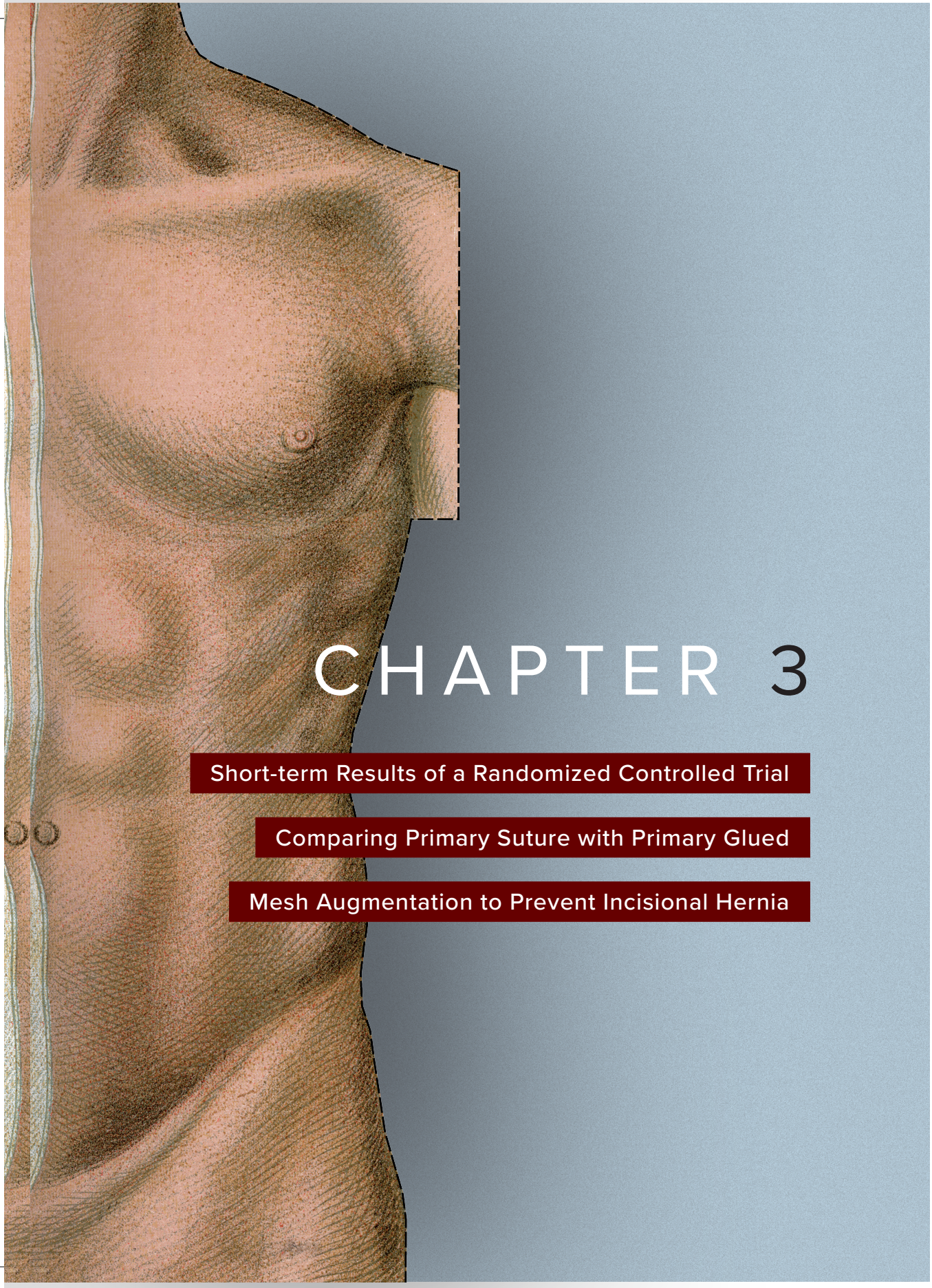

CHAPTER 3

Short-term Results of a Randomized Controlled Trial Comparing Primary Suture with Primary Glued Mesh Augmentation to Prevent Incisional Hernia

ABSTRACT

Background: Incisional hernia (IH) is one of the most frequent postoperative complications after abdominal surgery. Patients with an abdominal aortic aneurysm (AAA) and patients with a BMI of 27 or higher have a risk of more than 30% to develop an IH. Primary mesh augmentation (PMA) is a method in which the abdominal wall is strengthened to reduce IH incidence. This study focussed on the short-term results of the PRIMA trial, a multicentre double blind randomized controlled trial (RCT).

Methods: The RCT was conducted in 11 hospitals in the Netherlands, Germany and Austria. Between 2009 and 2012 patients were included if they were either operated via midline laparotomy for an AAA or if they had a BMI of 27 or higher. Patients were randomly assigned to either receive primary suture (PS), onlay glued mesh augmentation (OMA), or sublay glued mesh augmentation (SMA).

Results: A total of 498 patients were selected of which 18 patients were excluded preoperatively, leaving 480 randomized patients. Outcomes represent results after 1 month follow-up. During analysis statistically significant ($p = 0.002$) more seromas were detected after OMA (n = 34, 18.1%) compared to PS (n = 5, 4.7%) and SMA (n = 13, 7%). No differences were discovered in any of the other outcomes such as postoperative surgical site infection, hematoma, reintervention or readmission. Multivariable analysis revealed an increase in seroma formation after OMA with an odds ratio (OR) of 4.5 ($p = 0.003$) compared to PS and an OR of 2.9 ($p = 0.003$) compared to SMA.

Conclusion: Based on these short-term results, PMA is a save procedure with only an increase in seroma formation after OMA , but without an increased risk of surgical site infection (SSI).

INTRODUCTION

Incisional hernia (IH) is one of the most frequent postoperative complications after abdominal surgery. IH incidence ranges between 11% and 20% in the general population (1-3). However, risk factors for the development of IH, such as abdominal aortic aneurysm (AAA) and obesity, can increase the incidence of IH up to 35% (4-8). In AAA patients the connective tissue, especially the ratio between mature and immature collagen, is thought to be compromised(9, 10). The formation of collagen of insufficient strength plays an important role in the development of the distension of the aorta. But this loss of balance is also thought to be of key importance in the formation of IH after laparotomy (11, 12). In patients with obesity it is thought that the increase in intra-abdominal pressure induces stress on the suture line which promotes IH formation (7, 13).

IH can cause morbidity such as pain, reduced quality of life and poor body image, and in some cases can become incarcerated and even lead to mortality (3, 14). In the United States around 500.000 IH are surgically repaired annually (15). IH repair with mesh reinforcement has shown to produce lower recurrence rates compared with primary closure (16). However, recurrence rates for mesh repair are still unacceptably high, with a 10 year cumulative incidence rate of 32% (15). Considering the high incidence of IH, the unsatisfactory results of IH repair and the high impact on quality of life, research should be focusing on prevention rather than on treatment. In 2009 the PRIMA trial (**PRI**mary**M**esh Closure of **A**bdominal Midline Wounds), an international multicenter randomized controlled trial (RCT), was initiated to investigate primary mesh augmentation (PMA) as means to reduce IH incidence. This paper will focus on the short-term results (postoperatively up to 1 month) such as fascial dehiscence, surgical site infection (SSI), seroma, hematoma and mesh infection, of this RCT. We hypothesize that PMA does not increase postoperative complications compared to primary suture (PS).

METHODS

Study design

The PRIMA trial is a multicenter randomized controlled trial, which included patients between 2009 and 2012 in 11 hospitals in the Netherlands, Germany and Austria and follow-up is currently being conducted. This trial was initially approved by the local Ethics Board in the Erasmus University Medical Center in Rotterdam and was later extended to all participating centers. The primary endpoint of this study was IH incidence after 2

years, and secondary endpoints were postoperative complications, postoperative pain, cost-effectiveness and quality of life. This study was registered in the clinicaltrials.gov database and was assigned ID number: NCT00761475.

Patient population and randomization

Patients were eligible for inclusion in case of: 1. midline laparotomy, 2. presence of an AAA and / or body mass index (BMI) equal to or higher than 27. Exclusion criteria were: 1. Age < 18 years, 2. Inclusion in other trials with interference of the primary endpoint, 3. Life expectancy less than 24 months (as estimated by the treating physician), 4. Pregnant women, 5. Immune suppression therapy within 2 weeks before surgery, 6. Bovine allergy, 7. presence of IH. After obtaining informed consent patients were included into the trial via the TOP system (Trial Online Process; see http://www.primatrial.nl), where data were securely stored. Patients were randomized into 3 groups also via the TOP system by means of the minimization method and stratified by centre and operation indication. Randomization was performed during the operation, securing optimal allocation concealment (17). Patients could be randomized for either primary suture (PS), onlay mesh augmentation (OMA) or sublay mesh augmentation (SMA).

The following data were prospectively gathered and collected: *Pre-operative data* (sex, age, length, weight, BMI, current smoking status, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), American Society of Anesthesiologists score (ASA), previous midline incision, other hernia) *intra-operative data* (type of operation, antibiotics used, length of incision, subcutis suture, wound drain, operation time, blood loss, intestinal lesion, bleeding, mesh placement not possible) and *postoperative* data (up until 1 month)(intensive care admission, ventilation, blood transfusion, admission days, SSI (CDC definitions of SSI), seroma (a collection of serous fluid in a dead space, which can either be in situ or leaking through a wound), hematoma, fascial dehiscence, mesh removal, ileus, reinterventions, readmissions, death). The doctors who performed the surgery did not perform the follow-up, as this could lead to bias. Patients and the research personnel that performed the follow-up-were kept unaware to which group patients were randomized, reducing possible bias.

Surgical Procedures

1. PS

PS consisted out of a running slowly absorbable suture *(*MonoPlus*, USP 1 ,Needle HRT48, 150 cm loop, B.Braun Surgical Spain, Rubi, Spain)* of the linea alba. A suture length to wound length (SL:WL) ratio of 4:1 was routinely applied in all centers, however the ratio was not measured in order to reproduce real world surgery.

2. OMA

OMA consisted of creating an anterior plane (between anterior rectus fascia and subcutis) and closing the midline with a running slowly absorbable suture (MonoPlus) (4:1 ratio recommended). A polypropylene light weight mesh *(Optilene Mesh LP 6 x 35 cm, B. Braun Aesculap AG, Tuttlingen, Germany)* was cut to fit the dissected space and placed on the anterior rectus fascia with an overlap of 3 cm at each side. The mesh was then fixed with fibrin sealant (Tissucol DUO 500 2,0ml; Baxter Healthcare, Deerfield, IL, USA). The edges of the mesh were primarily glued, followed by center. The glued mesh was smoothed with the back of a forceps to get a good fixation of the mesh on the entire surface. In case of an incision larger than 22cm, it was advised to use two vials of fibrin sealant.

3. SMA

SMA consisted of creating a posterior plane (between posterior rectus fascia and rectus muscle, and below the arcuate line between the peritoneum and rectus muscle). After dissection, the posterior plane (fascia and peritoneum) was closed with running slowly absorbable suture (MonoPlus) (4:1 ratio recommended). A polypropylene light weight mesh was cut to fit the dissected space and placed on the posterior plane with an overlap of 3 cm at each side.. The mesh was then fixed with fibrin sealant (Tissucol DUO 500 2,0ml; Baxter Healthcare, Deerfield, IL, USA). The edges of the mesh were primarily glued, followed by center. The glued mesh was smoothed with the back of a forceps to get a good fixation of the mesh on the entire surface. In case of an incision larger than 22cm, it was advised to use two vials of fibrin sealant. Afterwards, closure of the midline/ lineaalba was established with running slowly absorbable suture (MonoPlus) (4:1 ratio recommended).

Statistical analysis

The sample size calculation was partially based on the data provided by the INSECT trial (18). In this study it was discovered that patients with a BMI over 27 have 20% chance of developing an IH within one year after the initial operation. Considering that only 50% of incisional hernia will be clinically evident in the first 12 months, the total incidence is likely to be above 30% after 2 years (2). In addition, patients were also eligible for inclusion if an AAA was diagnosed, as AAA patients also have an IH incidence of over 30%.

For the PRIMA trial, an IH rate of 30% for PS group was expected and of 10% for both PMA groups. The 3 comparisons lead to a pair-wise comparison of alpha = 0.017 (0.05/3) according to Bonferroni's correction for multiple testing. A superiority model for the comparison between PS vs OMA, and PS vs SMA was used with a power of 90%. A

non-inferiority model for the comparison of OMA versus SMA was used, with the non-inferiority margin set at 10%, with a power of 80%. Allowing for some dropouts, 100 patients were included in the control group and 180 patients in each experimental group. A total number of 460 patients were needed to detect a significant difference in IH incidence. During the course of the trial it was discovered that a larger number then initially anticipated dropped out of the study and thus 20 additional patients were included in agreement with the local Medical Ethics committee (19).

The one-way ANOVA, the Kruskal-Wallis test and the Pearson Chi-Square test were used for statistical analysis of demographic data, perioperative and postoperative data. Univariate and multivariate logistical regression analyses were conducted to predict Odds Ratios (OR) of potential risk factors. Risk factors discovered in this study or known in the literature will be added to the multivariate logistic regression analyses. The primary analysis was performed on an intention-to-treat principle (patients remained in their assigned group even if for instance during the procedure placement of the mesh was not possible). All statistical calculations were done using IBM SPSS© 17 Software (SPSS, Chicago, Illinois, USA). In accordance with Bonferroni´s correction for multiple testing, significance was assumed at $P < 0.017$.

RESULTS

Between March 2009 and December 2012, a total of 498 patients were selected for inclusion (Figure 1). Eighteen patients were not randomized due to withdrawal of informed consent, no midline incision used for access to the abdominal cavity, or a presence of an incisional hernia discovered during the operation. Of the 480 patients, 107 patients were randomized for PS, 188 patients were randomized for OMA, and 185 patients were randomized for SMA (Figure 1). Mesh augmentation was not applied in 18 cases (9.6%) in the OMA group, and 27 cases (14.6%) in the SMA group.

Patient characteristics

The majority of patients was male (60.8%) and the mean age of the included patients was 64.5 years (SD 11.2). No differences were found between groups in preoperative data. The majority of patients were operated for either a vascular operation (33.1%) or lower gastro-intestinal (GI) operation (33.8%). The median duration of the operation was 200 (IQR 150-253) minutes. Statistically ($p<0.001$) more patients received additional subcutaneous suturing in the OMA group (n = 70, 37.2%) compared to PS (n = 18, 16.8%) and SMA (n=34, 18.4%). No other differences were found in intraoperative and postoperative data (Table1).

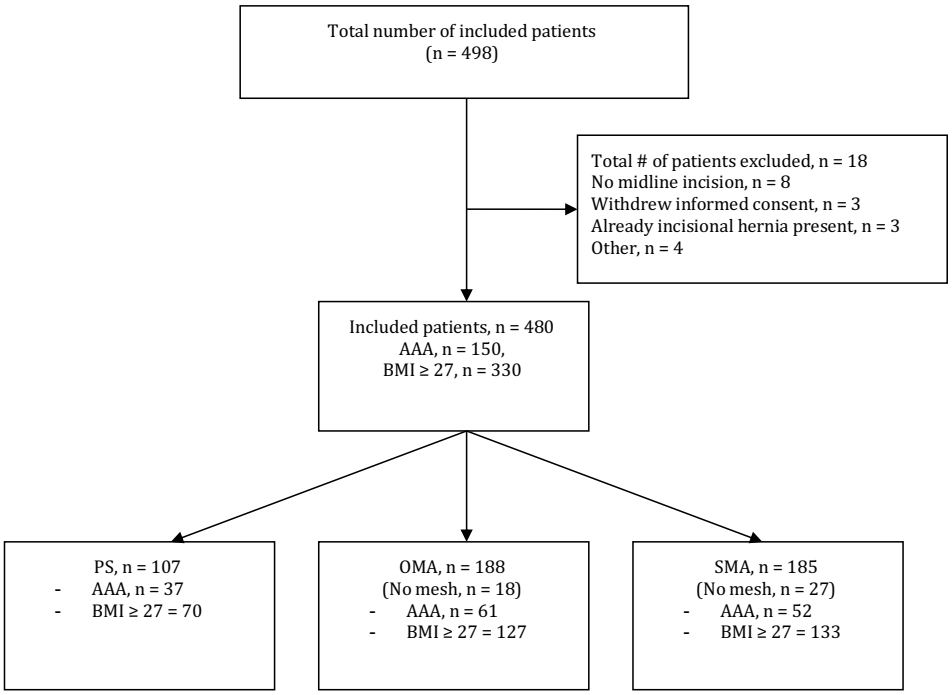

Figure 1. Study flow diagram

Outcome parameters

All outcomes are presented in Table 2. For all outcomes an intention-to-treat analysis was used. A per protocol analysis was also conducted but did not alter results and thus is not presented here. A total of 68 SSI (14.2%) were diagnosed postoperatively. According to CDC classifications SSIs were divided in to superficial infections (n =27, 5.6%), deep infections (n = 22, 4.6%) and intra-abdominal infections (n = 19, 3.9%). After stratifying for inclusion criteria, significantly ($p = 0.006$) more superficial SSIs were detected if a patient was included due to BMI ≥ 27 (n = 25, 7.6%) compared to patients included for an AAA (n = 2, 1.3%). Stratification with regards to type of operation (vascular, upper GI, lower GI, HPB, gynaecology or urology) was not possible due to low number of SSI making statistics unreliable. No significant differences were observed between intervention groups with regards to SSI.

A total of 52 seromas were observed postoperatively. Significantly ($p = 0.002$) more seromas were diagnosed after OMA (n = 34, 18.1%) compared to PS (n = 5, 4.7%) and SMA (n = 13, 7%). No significant difference was observed between PS and SMA.

Table 1. Patient characteristics

	General	PS	OMA	SMA	p-value
Total	480	107	188	185	
Preoperative					
Male, no (%)	292 (60.8)	68 (63.5)	116 (61.7)	108 (58.4)	NS
Age, mean (SD)	64.5 (11.2)*	65.2 (10.5)*	64.2 (12.3)*	64.4 (10.4)	NS
Length, mean (SD)	171.6 (9.6)	170.8 (9.5)	171.6 (10.2)	172.1 (9)	NS
Weight, mean (SD)	90.1 (17.1)	86.9 (15.5)	90.7 (18.2)	91.3 (16.1)	NS
BMI, mean (SD)	30.6 (5.3)*	29.8 (4.4)*	30.8 (5.9)*	30.8 (5.2)	NS
Smoking, no (%)	102 (21.3)	17 (15.9)	41 (21.8)	44 (23.8)	NS
DM, no (%)	94 (19.6)	19 (17.8)	36 (19.1)	39 (21.1)	NS
COPD, no (%)	52 (10.8)	9 (8.4)	24 (12.8)	19 (10.3)	NS
ASA, no (%)					NS
I	44 (9.2)	10 (9.3)	21 (11.2)	13 (7.0)	
II	234 (48.8)	55 (51.4)	90 (47.9)	89 (48.1)	
III	150 (31.3)	35 (32.7)	54 (28.7)	61 (33.0)	
IV	6 (1.3)	1 (0.9)	3 (1.6)	2 (1.1)	
unspecified	46	6	20	20	
Previous midline incision, no (%)	21 (4.4)	3 (2.8)	10 (5.3)	8 (4.3)	NS
Other hernia, no (%)	50 (10.4)	13 (12.1)	19 (10.1)	18 (9.7)	NS
Intraoperative					
Type operation, no (%)					NS
- Vascular	159 (33.1)	39 (36.4)	64 (34)	56 (30.3)	
- Upper GI	65 (13.5)	18 (16.8)	22 (11.7)	25 (13.5)	
- Lower GI	162 (33.8)	29 (27.1)	67 (35.6)	66 (35.7)	
- HPB	21 (4.4)	3 (2.8)	8 (4.3)	10 (5.4)	
- Gynaecology	66 (13.8)	15 (14)	24 (12.8)	27 (14.6)	
- Urology	7 (1.5)	3 (2.8)	3 (1.6)	1 (0.5)	

	General	PS	OMA	SMA	p-value
Antibiotics, no (%)	431 (89.8)	94 (87.9)	167 (88.8)	170 (91.9)	NS
Length incision, mean (SD)	24.8 (9.6)	23.6 (10.5)	24.9 (9.3)	25.2 (9.5)	NS
Suture subcutis, no (%)	122 (25.4)	18 (16.8)	70 (37.2)	34 (18.4)	<0.001
Wound drain, no (%)	23 (4.8)	3 (2.8)	14 (7.4%)	6 (3.2%)	NS
Blood loss, mean (IQR)	700 (300-1500)**	750 (300-1700)**	600 (300-1300)**	615 (300-1400)**	NS
Intraoperative complications , no (%)					
- intestinal lesion	9 (1.9)	2 (1.9)	1 (0.5)	6 (3.2)	NS
- bleeding	28 (5.8)	6 (5.6)	10 (5.3)	12 (6.5)	NS
- no mesh placement	45 (12.1)	-	18 (9.6)	27 (14.6)	NS***
Duration operation, mean (IQR)	200 (150-253)	180 (145-240)	200 (150-260)	212 (155-255)	NS
Postoperative					
Intensive care, no (%)	245 (51)	59 (55.1)	93 (49.5)	93 (50.3)	NS
Ventilation, no (%)	74 (15.4)	20 (18.7)	29 (15.4)	25 (13.5)	NS
Blood transfusion, no (%)	63 (13.1)	16 (15)	21 (11.2)	26 (14.1)	NS
Admission days, mean (IQR)	10 (7-16)	10 (7-15)	11 (7-17)	10 (7-15)	NS

*Values are represented as mean and standard deviation
**Values represent the median and interquartile ranges.
***Only OMA and SMA groups are used for comparison
*** p-values are two-sided. For dichotomous variables Chi-square test was performed, for continuous variables the one-way ANOVA was use, in case of non-parametric continuous variables the Kruskal-Wallis test was used.
ASA indicates American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GI, gastrointestinal; IQR, interquartile range; SD, standard deviation.

A total of 21 hematomas were observed postoperatively that required a reintervention. Of all hematomas, only 1 (0.9%) was observed in the PS group, 11 (5.9%) in the OMA group and 9 (4.9%) in the SMA group. No significant differences were observed between groups.

A total of 16 fascial dehiscences were observed postoperatively. Of all fascial dehiscences, 1 (0.9%) was observed in the PS group, 6 in the OMA group (3.2%), and 9 (4.9%) in the SMA group. No differences were observed between groups.

A total of 6 (1.6%) meshes got infected postoperatively and required reintervention. In 3 cases the mesh was removed completely. In 3 other cases the surgeons opted to perform only a partial mesh removal as only a part of the mesh was infected. In total 10 meshes were completely removed, 4 were partially removed, and 2 meshes were removed and reimplanted during the same operation. Besides before mentioned mesh infection, meshes were (partially) removed during reoperation for anastomotic leakage, intra-abdominal bleeding and fascial dehiscence. No differences were observed between groups.

A total of 26 (5.4%) postoperative ileus cases were observed. Of all ileus cases, 3 (2.8%) were observed in the PS group, 12 (6.4%) in the OMA group, and 11 (5.9%) in the SMA group. No differences were observed between groups. With regards to postoperative reinterventions, readmissions or death within one month postoperatively, no differences were observed between groups. None of the deaths were related to dissection of the posterior or anterior plane, or the mesh or glue.

Multivariable analysis

Seroma was the only outcome which was significantly increased. It was opted to perform a multivariable analysis to ascertain the OR of seroma after OMA. We adjusted for a number of factors (BMI, subcutaneous suture, wound drain, deep SSI) which could be of influence on seroma formation. After correction, seroma formation in OMA had an OR of 4.5 ($p = 0.003$) compared with PS, and an OR of 2.9 ($p = 0.003$) compared with SMA.

Table 2. Postoperative outcomes

			OMA		SMA		
	General	**PS**	**ITT**	**PP**	**ITT**	**PP**	**p-value**
Total	480	107	188	170	185	158	
SSI (%)							
- superficial	27 (5.6)	4 (3.7)	14 (7.4)	13 (7.6)	9 (4.9)	8 (5.1)	NS
- deep	22 (4.6)	2 (1.9)	13 (6.9)	12 (7.1)	7 (3.8)	6 (3.8)	NS
- intra-abdominal	19 (3.9)	8 (7.5)	8 (4.3)	7 (4.1)	3 (1.6)	3 (1.9)	*NS*
Seroma (%)	52 (10.8)	5 (4.7)	34 (18.1)	32 (18.8)	13 (7)	13 (8.2)	*0.002**,0 *.002***
Hematoma (%)	21 (4.4)	1 (0.9)	11 (5.9)	11 (6.5)	9 (4.9)	9 (5.7)	NS
Fascial dehiscence (%)	16 (3.3)	1 (0.9)	6 (3.2)	6 (3.5)	9 (4.9)	5 (3.2)	NS
Mesh infection	6 (1.6)	-	5 (2.7)	4 (2.4%)	1 (0.5)	1 (0.6)	NS
Mesh removal (%)*							
- complete	13 (3.5)	-	8 (4.3)	6 (3.5)	5 (2.7)	3 (1.9)	NS
- partial	4 (1.1)	-	3 (1.6)	3 (1.8)	1 (0.5)	1 (0.6)	NS
- reimplanted	7 (1.9)	-	2 (1.1)	3 (1.8)	5 (2.7)	3 (1.9)	NS
Ileus (%)	26 (5.4)	3 (2.8)	12 (6.4)	10 (5.9)	11 (5.9)	10 (6.3)	NS
Reintervention (%)	77 (16)	12 (11.2)	33 (17.6)	27 (15.9)	32 (17.3)	25 (15.8)	NS
Readmission (%)	76 (15.8)	12 (11.2)	37 (19.7)	31 (18.2)	27 (14.6)	22 (13.9)	NS
Death (%)	18 (3.8)	4 (3.7)	7 (3.7)	6 (3.5	7 (3.8)	5 (3.2)	NS

* Only OMA and SMA groups are used for comparison
Chi-square test was performed with two-sided p-values
P-values are based on the following comparisons: *PS vs OMA (ITT), **OMA vs SMA (ITT)
ITT indicates intention-to-treat analysis; PP, per protocol analysis

Table 3. Multivariable analysis

	PS vs OMA				PS vs SMA				OMA vs SMA			
	ITT		PP		ITT		PP		ITT		PP	
Seroma	OR	p	OR	p	OR	p-value	OR	p	OR	p	OR	P
Multivariable*	4.3	*0.004*	4.7	0.002	1.5	0.425	1.8	0.265	2.9	*0.002*	2.6	*0.007*

Values are presented as Odds Ratios. Missing values were adjusted by multiple imputation method.
* = adjusted for age, BMI, subcutaneous suture, wound drain, deep SSI
ITT indicates intention-to-treat-analysis; PP, per protocol analysis

DISCUSSION

This RCT shows that apart from a significant increase in seroma formation, no differences were observed for other short-term complications after PMA. OMA increased the odds of developing seroma compared to PS and SMA. This increase in seroma and the use of prosthetic material did not significantly increase the rate of SSI, mesh infections or admission period.

Short term results

Although these results are not the primary outcomes of this RCT, and power calculations were not based on these parameters, they are highly relevant. Previously other RCTs and even meta-analyses focussing on IH prevention by means of PMA have been published (20-23). However, as pointed out in the most recent meta-analysis, the quality of the RCT's was generally low and short term results, such as hematoma, fascial dehiscence, mesh infection and mesh removal, were often not described (24). This study is the first RCT that carefully documented all short-term results and discovered that solely seroma was significantly increased after OMA. In most cases seroma was defined as a minor complication and no intervention was necessary. However, seroma can become infected but no increase in SSI was detected in this study. The anterior subcutaneous space created by dissection during OMA is prone for seroma formation and should be minimized if possible. In this trial an attempt was made to reduce this space by implementing fibrin glue. Mesh glue fixation is not new and has been in use in inguinal hernia repair and laparoscopic IH repair for some time (25). These studies have shown that the effectiveness dependent on the mesh/glue combination used, as not all meshes adhere well to all glues (26). However, the clinical use of glue for PMA has not yet been documented and studies comparing mesh suture fixation with mesh glue fixation are not available. Surgeons did like the quickness and technique of fixation of the mesh with fibrin glue. A recent meta-analysis focussing on seroma formation preventing by means of glue after breast surgery concluded that although data is scarce and not of high quality, currently no reduction could be observed (27). In another study by Lau et al. that focussed on inguinal hernia repair it was suggested that the timing of glue application is also important(28). Once polymerization of the sealant has occurred before ventral layer closure, the dissected space will not have been reduced. In the study protocol, standard suturing of the subcutis was not implemented, neither was wound drainage. These are techniques which may reduce the incidence of seroma formation (29). For instance, none of the patients with a wound drain acquired a seroma. Future research regarding onlay or OMA should focus on reducing seroma formation.

PMA

This is the first trial which compares PS with OMA and SMA. Although in hernia surgery the sublay technique is assumed to be superior compared to the onlay technique with regards to IH recurrence, evidence is scarce In addition, prevention of IH is quite different compared to reducing recurrence. In this study the anatomical natural structure of the abdominal wall was still *intact* and it was not very difficult to acquire a tensionless closure. Furthermore, it was opted to only use 3cm overlap on both sides, even though in hernia surgery 5cm is now recommended. We opted for a smaller overlap as the evidence for the 5cm overlap in hernia surgery is still insufficient, and further dissection of the wound could induce more morbidity and might thus not be necessary. Furthermore, prevention of IH is quite different from reducing recurrence, due to the fact that there is no fascia defect and the mesh is positioned on a closed midline.

A goal of our study group is to prevent IH from occurring in general, not only in the surgical field but also in other specialities, such as gynaecology and urology. However, some of the participants were not familiar with hernia techniques at the beginning of this trial but were required to perform both PMA techniques nonetheless. The learning curve might influence the results and could be bias. However, doctors inexperienced with the techniques were supervised by the study coordinator during the initial procedures, and both techniques were easily adapted by all doctors. Most of the doctors that were not familiar with hernia surgery preferred the OMA technique. A big advantage of OMA is that it is far easier to explain and perform and the dissection doesn´t take as long as SMA. In this study we did not measure the time of the closure process, but the time for the entire operation. It is evident that additional dissection will increase operating time, and the results resemble our own experiences. In general, dissection and closure in OMA took 15-20 minutes and in SMA took about 25-30 minutes. As in all studies, a number of patients did not receive the randomized treatment as was described in the study protocol. These cases did stay in their original randomization group as in accordance with the intention-to-treat principle. The reason for not applying OMA or SMA varied and include extensive blood loss, contaminated abdomen with an increased risk of SSI, fascia of insufficient strength to apply augmentation and time constraints.

Conclusion

Based on the short term results of this trial, OMA increased the amount of seroma but did not increase SSI or mesh infection. The true effectiveness of OMA will have to be evaluated during the long term results of this trial. During that time we will also be able to evaluate IH incidence, fistula formation, chronic pain, quality of life and cost-effectiveness.

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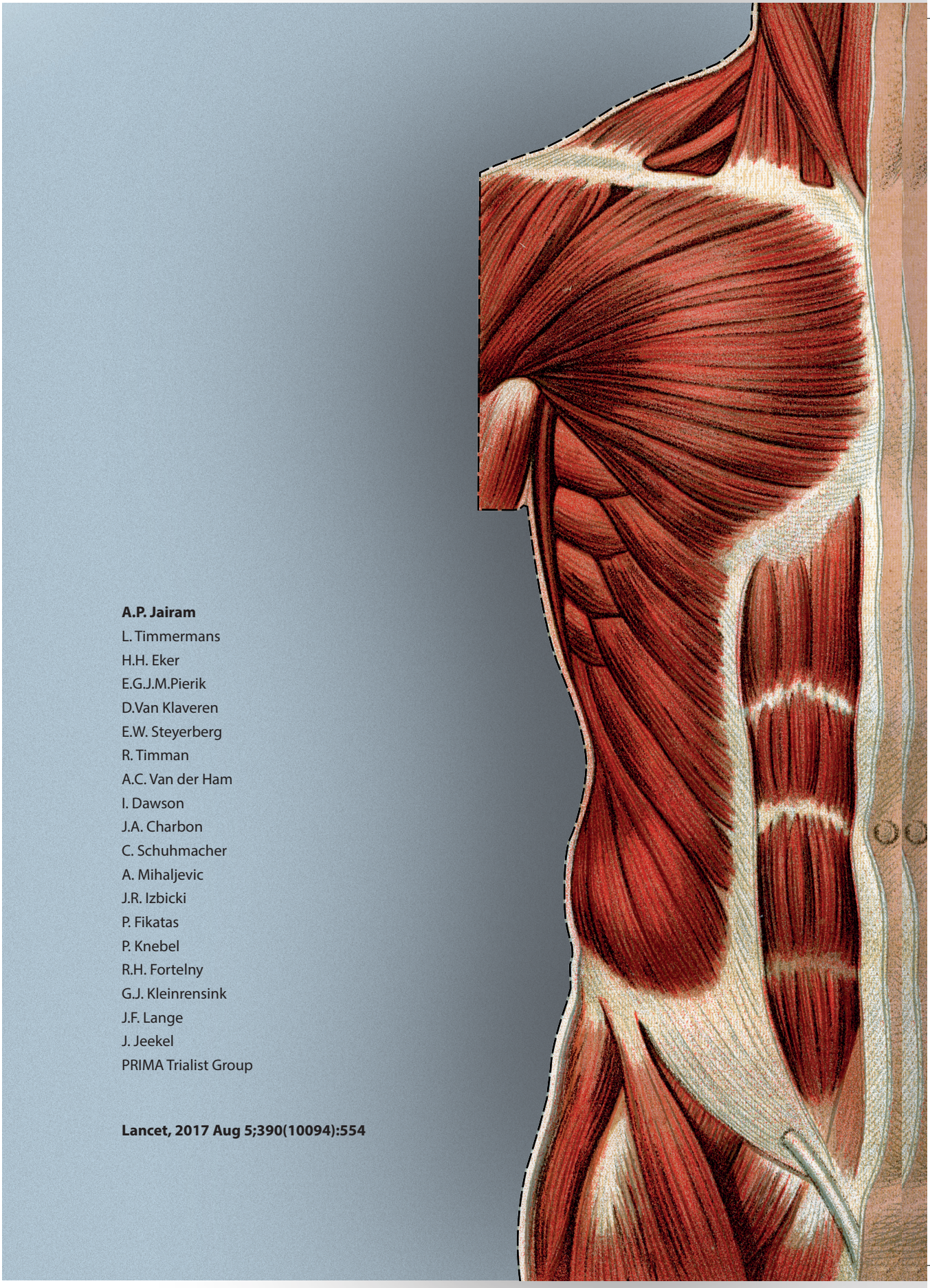

A.P. Jairam
L. Timmermans
H.H. Eker
E.G.J.M.Pierik
D.Van Klaveren
E.W. Steyerberg
R. Timman
A.C. Van der Ham
I. Dawson
J.A. Charbon
C. Schuhmacher
A. Mihaljevic
J.R. Izbicki
P. Fikatas
P. Knebel
R.H. Fortelny
G.J. Kleinrensink
J.F. Lange
J. Jeekel
PRIMA Trialist Group

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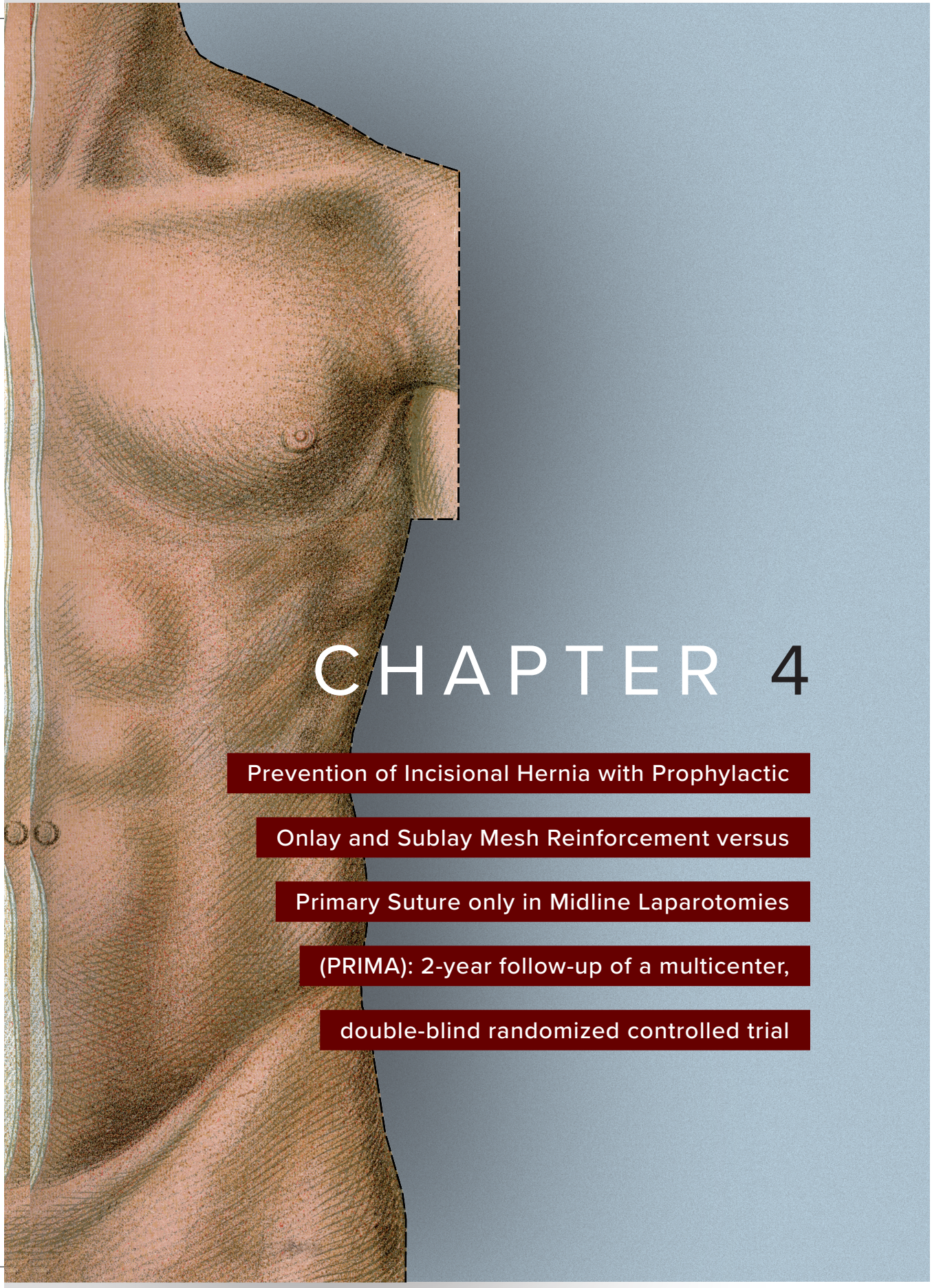

CHAPTER 4

Prevention of Incisional Hernia with Prophylactic Onlay and Sublay Mesh Reinforcement versus Primary Suture only in Midline Laparotomies (PRIMA): 2-year follow-up of a multicenter, double-blind randomized controlled trial

ABSTRACT

Background Incisional hernia is a frequent long-term complication after abdominal surgery, with a prevalence greater than 30% in high-risk groups. The aim of the PRIMA trial was to evaluate the effectiveness of mesh reinforcement in high-risk patients, to prevent incisional hernia.

Methods We did a multicentre, double-blind, randomised controlled trial at 11 hospitals in Austria, Germany, and the Netherlands. We included patients aged 18 years or older who were undergoing elective midline laparotomy and had either an abdominal aortic aneurysm or a body-mass index (BMI) of 27 kg/m2 or higher. We randomly assigned participants using a computer-generated randomisation sequence to one of three treatment groups: primary suture; onlay mesh reinforcement; or sublay mesh reinforcement. The primary endpoint was incidence of incisional hernia during 2 years of follow-up, analysed by intention to treat. Adjusted odds ratios (ORs) were estimated by logistic regression. This trial is registered at ClinicalTrials.gov, number NCT00761475.

Findings Between March, 2009, and December, 2012, 498 patients were enrolled to the study, of whom 18 were excluded before randomisation. Therefore, we included 480 patients in the primary analysis: 107 were assigned primary suture only, 188 were allocated onlay mesh reinforcement, and 185 were assigned sublay mesh reinforcement. 92 patients were identified with an incisional hernia, 33 (30%) who were allocated primary suture only, 25 (13%) who were assigned onlay mesh reinforcement, and 34 (18%) who were assigned sublay mesh reinforcement (onlay mesh reinforcement *vs* primary suture, OR 0·37, 95% CI 0·20–0·69; p=0·0016; sublay mesh reinforcement *vs* primary suture, 0·55, 0·30–1·00; p=0·05). Seromas were more frequent in patients allocated onlay mesh reinforcement (34 of 188) than in those assigned primary suture (five of 107; p=0·002) or sublay mesh reinforcement (13 of 185; p=0·002). The incidence of wound infection did not differ between treatment groups (14 of 107 primary suture; 25 of 188 onlay mesh reinforcement; and 19 of 185 sublay mesh reinforcement).

Interpretation A significant reduction in incidence of incisional hernia was achieved with onlay mesh reinforcement compared with sublay mesh reinforcement and primary suture only. Onlay mesh reinforcement has the potential to become the standard treatment for high-risk patients undergoing midline laparotomy.

INTRODUCTION

Incisional hernia is one of the most frequent long-term complications after abdominal surgery, with an incidence of 5–20% in the general patient population. However, in high-risk patients, the incidence of incisional hernia can increase to more than 30% (1-3). Obese individuals (ie, those with a body-mass index [BMI] ≥30 kg/m^2) and people with Abdominal Aortic Aneurysm (AAA) are especially high-risk groups. Patients with abdominal aortic aneurysm are at risk because of an underlying connective tissue disorder, caused partly by dysregulation of collagen type 1 and 3; this impairment probably has an important role in the pathogenesis of distension of the aorta and in formation of incisional hernia in patients after median laparotomy (4). Individuals with obesity or a BMI equal to or higher than 27 kg/m have a more than 30% chance of developing incisional hernia after median laparotomy (5). This group of patients are believed to have a higher intra-abdominal pressure, which can cause higher tension on abdominal wall sutures. However, this pressure might not be the only contributing factor: obesity is also associated with wound-healing complications due to decreased vascularity of adipose tissue, leading to local hypoxia. In hypoxic wounds, the synthesis of mature collagen is impaired, resulting in weaker tissue and a deficiency in the overall healing process. In wound healing, other known risk factors play an important part—eg, malignant disease, parastomal hernia, wound infection, and smoking (6-10).

Incisional hernia can cause morbidity (eg, pain) and can have a negative effect on patients' quality of life and body image (11-13). Furthermore, there is a risk of obstruction and strangulation of the bowel with perforation and possible mortality as a result. For these reasons, repair of incisional hernia is a surgical procedure that is done frequently. However, even though repair with mesh reinforcement has lower risk of recurrence compared with primary suture, the cumulative 10-year incidence is 32%, which is still too high (14, 15). Use of laparoscopic techniques has not yielded better results with respect to recurrence of incisional hernia (16-18). Incisional hernia not only has a large effect in medicine but also has a great socioeconomic effect. Therefore, prevention of incisional hernia is of paramount importance: it will lead to reduction of disease and is, thus, cost-effective.

Many studies have evaluated different types of incision, suture materials, and closure techniques to reduce the incidence of incisional hernia (19-21). Horizontal incisions and laparoscopy, or endovascular aneurysm repair (EVAR), in patients with abdominal aortic aneurysm are well-known surgical techniques that minimise the risk of incisional hernia. In each patient undergoing surgery, the best available technique should be considered. However, for several individuals, conventional laparotomy is unavoidable. Until now,

no adequate method or gold standard to prevent incisional hernia has been reported for people undergoing midline laparotomy. Patients at particular high risk of incisional hernia, including those with abdominal aortic aneurysm and high BMI, might benefit most from prevention (22-25). In 1995, Pans and colleagues did a prospective study to compare patients undergoing surgery for morbid obesity with or without intraperitoneal polyglactin mesh. No difference in incidence of incisional hernia was noted between the two groups (26). Several randomised and non-randomised prospective studies have been done to investigate how incisional hernia can be prevented. Currently, no level 1 evidence is available. The quality of published randomised studies is low and there is no consensus about the mesh position in the abdominal wall that should be used (27, 28).

We initiated the PRIMA trial (PRImary Mesh closure of Abdominal midline wounds) in 2009 with the aim to investigate prophylactic mesh reinforcement in high-risk groups (ie, patients with abdominal aortic aneurysm or a BMI ≥27 kg/m^2) (29, 30). We also aimed to assess which mesh position in the abdominal wall should be used to prevent incisional hernia. The primary aim of the PRIMA trial was to study the effectiveness of prophylactic mesh reinforcement to prevent incisional hernia.

METHODS

Study design and patients

The PRIMA trial is an international, multicentre, double-blind, randomised controlled trial. The study methods and initial (short-term) results of the PRIMA trial have been described previously (29), and the trial protocol has been published elsewhere (30). The medical ethics committee of the Erasmus University Medical Centre in Rotterdam approved the trial; we also obtained approval from the local ethics committees of the participating hospitals.

We selected patients from 11 hospitals in Austria, Germany, and the Netherlands. We included adults aged 18 years or older who underwent elective midline laparotomy and had either an abdominal aortic aneurysm or a BMI equal to or higher than 27 kg/m^2. We excluded individuals who underwent an emergency procedure, had incisional hernia in the medical history, were included in other trials, or had a life expectancy less than 24 months. Furthermore, we excluded pregnant women, those who received immune suppression therapy within 2 weeks before surgery, and people with bovine allergy. All participants gave written informed consent.

Initially, we included patients with a BMI of 30 kg/m^2 or greater. However, 9 months after the start of the study, Seiler and colleagues (5) on the INSECT trial showed that patients with a BMI of 27 kg/m^2 or greater have a 20% chance of developing an incisional hernia within 1 year after the initial operation. Therefore, we reduced the BMI threshold of 30 kg/m^2 to 27 kg/m^2. The medical ethics committee of the Erasmus University Medical Centre approved this amendment.

Randomisation and masking

After obtaining informed consent we registered patients via the trial's online process system, in which data were stored securely, and every patient received a unique trial code. We randomly allocated participants at the end of the elective midline laparotomy procedure, before closing the abdomen, securing optimum allocation concealment. We used a computer-generated randomisation sequence to allocate patients to one of three groups: closure of the abdomen with primary sutures; closure with onlay mesh reinforcement; or closure with sublay mesh reinforcement. We stratified randomisation by centre and operation indication.

Trial researchers who followed up participants were unaware of the procedure until the endpoint of the trial. To avoid bias, the surgeons who did the laparotomy and closure did not follow-up patients. The safety monitoring board had access to all data.

Procedures

The trial researcher attended the first operation of each surgeon, urologist, or gynaecologist to give instructions if needed. The operating (vascular or gastrointestinal) surgeon, urologist, or gynaecologist closed the abdomen, not a specialised abdominal wall surgeon. We assessed whether a learning curve occurred by comparing early versus later procedures per surgeon.

For the primary suture procedure, the midline fascia was closed with running, slowly absorbable sutures (MonoPlus, suture size USP 1, needle HRT 48, 150 cm loop; B Braun Surgical SA, Rubi, Spain), preferably with a loop technique. We advised a suture length-to-wound length ratio of 4:1 in all centres, which we did not measure. Subcutaneous tissue and skin were closed with sutures preferred by the surgeon.

For onlay mesh reinforcement, the midline fascia was closed with running, slowly absorbable sutures (MonoPlus), with a recommended suture length-to-wound length ratio of 4:1. An anterior plane with a width of about 8 cm was created between the anterior rectus fascia and the subcutis. A lightweight polypropylene mesh (Optilene mesh LP, 6 × 35 cm; B Braun Surgical SA) was used and placed on the anterior rectus

fascia with an overlap of 3 cm. The mesh size was made particularly for the PRIMA trial by cutting an Optilene mesh LP to size. In case of an incision longer than 35 cm, two meshes were tied to each other to obtain an overlap of 3 cm. After the mesh was fitted in the dissected space it was fixed with 4·0 mL of fibrin sealant (Tisseel; Baxter Healthcare, Deerfield, IL, USA), which was done by glueing the edges and the centre of the mesh to the tissue and fixing it with the back of a pair of forceps on the entire surface. The subcutaneous tissue and skin were closed with sutures preferred by the surgeon.

For sublay mesh reinforcement, a posterior plane was created between both the posterior rectus sheath and the rectus muscle, and caudally to the arcuate line between the peritoneum and rectus muscle. The posterior plane (fascia and peritoneum) was closed with running, slowly absorbable sutures (MonoPlus), with a recommended suture length-to-wound length ratio of 4:1. A lightweight polypropylene mesh (Optilene) was used and placed on the posterior rectus fascia, with an overlap of 3 cm. Mesh adjustments were made as described for onlay placement, and the mesh was fixed as described for onlay mesh reinforcement. The subcutaneous tissue and skin were closed with sutures preferred by the surgeon.

Outcomes

The primary endpoint of the PRIMA study was the presence of incisional hernia during 2 years of follow-up. We defined incisional hernia as any abdominal wall gap with or without bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging, as determined by the European Hernia Society (28). We measured this outcome variable by inviting patients for follow-up at the outpatient clinic of the 11 hospitals 1 year and 2 years after the operation. During the visit at the outpatient clinic, we undertook a physical examination of the abdomen. Furthermore, a radiological examination (ultrasound or CT) was done by an independent radiologist, 6 months and 2 years after surgery; the radiologist was not aware of the specific closure procedure. If disagreement was noted between the observations of the doctor who did the clinical examination and the radiologist who undertook the radiological examination, we deemed the outcome of the radiological examination decisive.

Secondary endpoints were postoperative complications (assessed clinically), quality of life (self-reported), and postoperative pain (self-reported). Short-term postoperative complications (up to 1 month) have been described elsewhere (29). Here, we report long-term postoperative complications (up to 2 years). The surgeon and trial researcher gathered data for postoperative complications— ie, intensive-care admission, ventilation, blood transfusion, admission days, surgical site infection, seroma, haematoma, fascial dehiscence, mesh removal, ileus, re-interventions, re-

admissions, and death. We obtained data for short-term and long-term outcomes at outpatient clinic visits at 1 month, 1 year, and 2 years after surgery. We defined surgical-site infection according to guidelines proposed by Mangram (31). The trial researcher and surgeon also obtained preoperative data for sex, age, height, weight, BMI, current smoking status, diabetes mellitus, chronic obstructive pulmonary disease (COPD), American Society of Anaesthesiologists (ASA) score, previous midline incision, and other hernia; and intraoperative data for type of operation, use of antibiotics, length of incision, subcutis suture, wound drain, operation time, blood loss, intestinal lesion, bleeding, and whether mesh placement was not possible. Intraoperative outcomes have been reported elsewhere (29). We sent questionnaires to patients at fixed timepoints (preoperatively, 1 month after surgery, and at 3 months, 6 months, 1 year, and 2 years after surgery) to gather data for quality of life (measured with the 36-item short form health survey [SF-36] and EuroQol five dimensions [EQ-5D]) and postoperative pain (measured on a visual analogue scale).

Statistical analysis

We made three comparisons, leading to a pairwise comparison at an alpha of 0·017 (0·05/3) according to Bonferroni's correction for multiple testing. We based the sample size calculation on the results of the INSECT trial (5), which suggested that patients with a BMI of 27 kg/m^2 or higher have a 20% risk of developing incisional hernia within the first year after initial surgery. After taking into account that only 50% of patients with incisional hernia will be detectable in the first year after surgery, the total risk will be more than 30% after 2 years. Patients with abdominal aortic aneurysm were included also, since they have a high risk of developing incisional hernia.

We assumed the risk of incisional hernia after 2 years was 30% for primary suture and 10% for both onlay and sublay mesh reinforcement. Primary suture versus onlay or sublay mesh reinforcement was a superiority comparison with a power of 90%, whereas onlay versus sublay mesh reinforcement was an equivalence comparison with a power of 80%. We accounted for 10% dropouts. In total, we needed 100 patients in the primary suture group and 180 patients each in the primary mesh reinforcement groups; thus, 460 patients were needed to detect a significant difference in incidence of incisional hernia. However, during the trial, more dropouts occurred than initially expected and, therefore, we aimed to recruit an additional 20 patients.

For the comparison of both experimental groups (onlay and sublay mesh reinforcement) with the control group (primary suture), we analysed incisional hernia as a binary outcome. We used mixed-effects logistic regression with two group levels to account for clustering of patients in hospitals and according to operation type. We did not

apply a time-to-event analysis as stated in the protocol, since patients were seen at the outpatient clinic at specific timepoints (1 year and 2 years after surgery) and, therefore, the exact time to event (incisional hernia) was unclear. However, as a sensitivity analysis, we checked if a mixed-effects Cox regression analysis led to different results. We adjusted outcomes for the following covariates: age, sex, smoking, BMI, abdominal aortic aneurysm, COPD, cardiovascular diseases, ASA classification, and steroids. We analysed data according to the intention-to-treat principle. In addition to intention-to-treat analyses, we also did a per-protocol analysis of the primary outcome for the comparison of onlay versus sublay mesh reinforcement.30 We assessed quality of life and pain by the intention-to-treat principle.

For the comparison of the two experimental groups (onlay and sublay mesh reinforcement), we calculated a two-sided 98·3% CI for the difference in the probability of incisional hernia. Thus, we used an equivalence test for the comparison of onlay versus sublay mesh reinforcement instead of a non-inferiority test of onlay versus sublay mesh reinforcement (which was incorrectly suggested in the protocol), since we postulated that both techniques would have a similar risk of incisional hernia. We defined equivalence between the two experimental groups as the absolute difference in the probability of incisional hernia being below an equivalence margin of 10%. A rejection of the null hypothesis of non-equivalence, the 98·3% CI of the absolute difference in the probability of incisional hernia is fully between -10% and 10%, is evidence in favour of equivalence. If the evidence in favour of equivalence is not strong enough, non-equivalence cannot be ruled out.

We did not account for dropouts in our analyses: we calculated numbers and percentages for all included patients (in that specific treatment group). Therefore, we assessed not only the baseline characteristics of all participants but also those of remaining participants, since differential loss to follow-up could bias comparisons between treatment groups (32). To analyse the effect of potential differences in baseline characteristics on the comparisons between treatment groups, we repeated the mixed-effect regression analysis with adjustment for baseline characteristics.

We analysed quality of life with multilevel regression models. We judged incisional hernia a time-varying covariate, indicating whether the incisional hernia had taken place in the period preceding follow-up. We determined the covariance structures with the deviance test on the restricted maximum likelihood function. For the difference in quality-of-life measurements between treatment groups, we entered dummy variables indicating onlay or sublay mesh reinforcement as covariates, with primary suture as the reference group. We estimated contrasts at 24 months. We analysed postoperative pain

with linear logistic regression. We used mixed modelling for the quality-of-life analysis to handle data efficiently with missing and unbalanced timepoints (33). We did the statistical analysis with IBM SPSS version 20.0 and R version 3.1.0. This trial is registered at ClinicalTrials.gov, number NCT00761475.

Role of the funding source

The funders 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 March, 2009, and December, 2012, 498 patients were enrolled to the study (figure). 18 individuals were excluded because they either withdrew informed consent (n=3), did not have midline incision (n=8), had already presented with incisional hernia (n=3), or for other reasons (n=4). Of the 480 included patients, 150 (31%) patients had an abdominal aortic aneurysm and 330 (69%) individuals had a BMI of 27 kg/m^2 or greater. At randomisation, 107 patients were assigned closure by primary suture, 188 were allocated closure by onlay mesh reinforcement, and 185 were assigned closure by sublay mesh reinforcement. Primary mesh reinforcement was not done in 18 (10%) patients assigned onlay mesh reinforcement and in 27 (15%) allocated sublay mesh reinforcement (figure 1). Baseline characteristics were similar between groups (table 1).

Median follow-up was 23 months (IQR 12–25), and 376 (78%) of 480 patients completed follow-up. 104 patients were lost to follow-up during the study, 21 who were assigned closure by primary suture, 45 allocated onlay mesh reinforcement, and 38 assigned sublay mesh reinforcement. The main reasons for loss to follow-up were death and patient's decision to withdraw from the study. Baseline characteristics of remaining participants are shown in the appendix.

Besides the physical examinations at 1 year and 2 years, 283 (59%) of 480 patients also underwent radiological examinations at 6 months and 2 years, 60 in the primary suture group, 115 in the onlay mesh reinforcement group, and 108 in the sublay mesh reinforcement group. Of the 376 patients who completed follow-up, 265 (70%) underwent radiological examination, 58 in the primary suture group, 105 in the onlay mesh reinforcement group, and 102 in the sublay mesh reinforcement group.

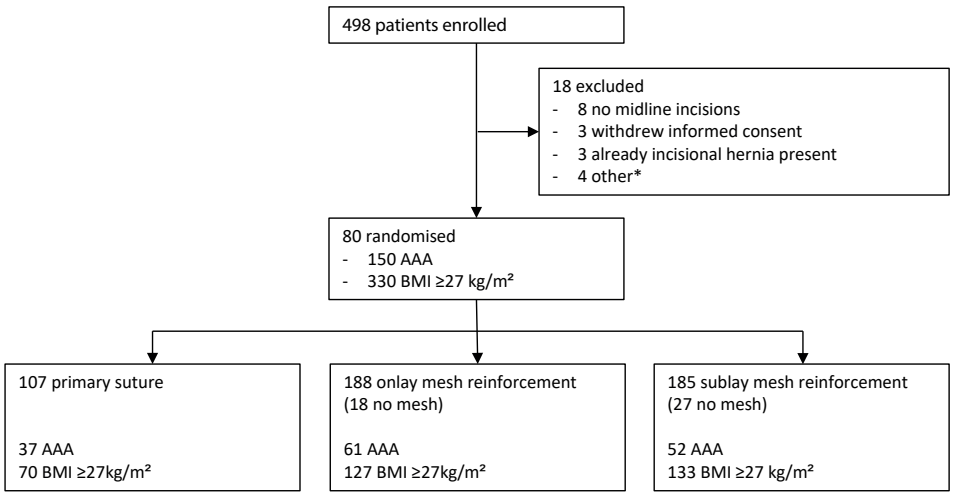

Figure 1. Trial profile

AAA= abdominal aortic aneurysm. BMI=body-mass index. *Surgeon's decision (n=1), laparoscopy done rather than laparotomy (n=1), and no operation done (n=2)

92 (19%) of 480 patients developed incisional hernia during the 2 years of follow-up, 33 (31%) of 107 in the primary suture group, 25 (13%) of 188 in the onlay mesh reinforcement group, and 34 (18%) of 185 in the sublay mesh reinforcement group. The incidence of incisional hernia differed significantly between onlay mesh reinforcement and primary suture (OR 0·37, 95% CI 0·20-0·69; p=0·0016), but did not differ for the comparisons of sublay mesh reinforcement versus primary suture (0·55, 0·30-1·00; p=0·05) or onlay versus sublay mesh reinforcement (1·39, 0·73-2·65; p=0·31; table 2). The 98·3% CI for the difference in probability of incisional hernia between sublay and onlay mesh reinforcement was -6·8 to 15·2. This confidence interval included the equivalence margin of 10%; therefore, non-equivalence of the experimental treatments cannot be ruled out. The sensitivity analysis using mixed-effects Cox regression led to very similar results, and adjustment for covariates did not had any effect on these findings either.

Among the subgroup of 150 patients with abdominal aortic aneurysm, incisional hernia occurred in 36 (24%), 16 who were assigned closure by primary suture, ten allocated onlay mesh reinforcement, and ten assigned sublay mesh reinforcement. Among the subgroup of 330 patients with a BMI of 27 kg/m^2 or higher, incisional hernia occurred in 54 (16%), 16 who were allocated closure by primary suture, 15 assigned onlay mesh reinforcement, and 23 allocated sublay mesh reinforcement. Subgroup analysis showed that treatment effects were consistent in both subgroups (table 2).

Table 1. Baseline characteristics

	Total	PS	OMR	SMR
Total	480	107	188	185
Male, no (%)	292 (60.8)	68 (63.5)	116 (61.7)	108 (58.4)
Age, mean (SD)	64.5 (11.2)*	65.2 (10.5)*	64.2 (12.3)*	64.4 (10.4)
BMI, mean (SD)	30.6 (5.3)*	29.8 (4.4)*	30.8 (5.9)*	30.8 (5.2)
Smoking, no (%)	102 (21.3)	17 (15.9)	41 (21.8)	44 (23.8)
Diabetes mellitus, no (%)	94 (19.6)	19 (17.8)	36 (19.1)	39 (21.1)
COPD, no (%)	52 (10.8)	9 (8.4)	24 (12.8)	19 (10.3)
ASA, no (%)				
I	44 (9.2)	10 (9.3)	21 (11.2)	13 (7.0)
II	234 (48.8)	55 (51.4)	90 (47.9)	89 (48.1)
III	150 (31.3)	35 (32.7)	54 (28.7)	61 (33.0)
IV	6 (1.3)	1 (0.9)	3 (1.6)	2 (1.1)
Unspecified	46	6	20	20
Previous midline incision, no (%)	21 (4.4)	3 (2.8)	10 (5.3)	8 (4.3)
Other hernia, no (%)	50 (10.4)	13 (12.1)	19 (10.1)	18 (9.7)
Type operation, no (%)				
Vascular	159 (33.1)	39 (36.4)	64 (34)	56 (30.3)
Upper GI	65 (13.5)	18 (16.8)	22 (11.7)	25 (13.5)
Lower GI	162 (33.8)	29 (27.1)	67 (35.6)	66 (35.7)
HPB	21 (4.4)	3 (2.8)	8 (4.3)	10 (5.4)
Gynecology	66 (13.8)	15 (14)	24 (12.8)	27 (14.6)
Urology	7 (1.5)	3 (2.8)	3 (1.6)	1 (0.5)

BMI= body mass index, COPD=chronic obstructive pulmonary disease, ASA=American Society of Anesthesiologists, GI=gastrointestinal, HPB=hepatobiliary and pancreatic, SD=standard deviation

Almost a quarter of patients had a postoperative complication after 2 years of follow-up. Seromas were seen most frequently in individuals assigned onlay mesh reinforcement at 1-month follow-up; however, this outcome had no further adverse outcomes for the patient ie, the frequency of surgical-site infections, re-interventions, or re-admissions with onlay mesh reinforcement was not different when compared with primary suture or sublay mesh reinforcement. With respect to long-term complications at 2-year follow-up, there were three pulmonary infections (two with onlay mesh reinforcement, one with sublay mesh reinforcement), one urinary infection (with primary suture), one seroma (with sublay mesh reinforcement), one deep surgical site infection with an abscess (with primary suture), seven re-interventions (four with onlay mesh reinforcement, three with sublay mesh reinforcement), and six re-admissions (two with primary suture, one with onlay mesh reinforcement, three with sublay mesh reinforcement). The risk of re-intervention (p=0·343) and re-admission (p=0·508) did not differ between groups.

None of the re-interventions or re-admissions was related to the mesh used or the fibrin sealant. 73 (15%) of 480 patients died, 15 (14%) of 107 assigned primary suture, 34 (18%) of 188 allocated onlay mesh reinforcement, and 24 (13%) of 185 assigned sublay mesh reinforcement. The most common cause of death was malignant disease or tumour progression. None of the deaths was related to development of an (incarcerated) incisional hernia, the mesh used, or the fibrin sealant.

Table 2. Incidence of incisional hernia in all patients with 2-year follow-up and by subgroups

	Incidence (%)	Odds ratio (95% CI)	P value
All patients with follow-up to 2 years (n=480)			
Primary mesh reinforcement vs primary suture*	59/373 (16%) *vs* 33/107 (30%)	0·45 (0·27–0·77)	0·003
Onlay mesh reinforcement vs primary suture*	25/188 (13%) *vs* 33/107 (30%)	0·37 (0·20–0·69)	0·0016
Sublay mesh reinforcement vs primary suture*	34/185(18%) *vs* 33/107 (30%)	0·55 (0·30–1·00)	0·05
Onlay mesh reinforcement vs sublay mesh reinforcement**	25/188 (13%) *vs* 34/185 (18%)	1·39 (0·73–2·65)	0·31
Abdominal aortic aneurysm (n=150)			
Primary mesh reinforcement vs primary suture*	20/113 (17%) *vs* 16/37 (43%)	0·29 (0·12–0·67)	0·004
Onlay mesh reinforcement vs primary suture*	10/61 (16%) *vs* 16/37 (43%)	0·27 (0·10–0·71)	0·008
Sublay mesh reinforcement vs primary suture*	10/52 (19%) *vs* 16/37 (43%)	0·36 (0·13–0·93)	0·03
Onlay mesh reinforcement vs sublay mesh reinforcement**	10/61 (16%) *vs* 10/52 (19%)	1·04 (0·32–3·39)	0·95
BMI ≥ 27kg/m (n=330)			
Primary mesh reinforcement vs primary suture*	38/260 (15%) *vs* 16/70 (23%)	0·58 (0·29–1·19)	0·14
Onlay mesh reinforcement vs primary suture*	15/127 (12%) *vs* 16/70 (23%)	0·47 (0·21–1·06)	0·07
Sublay mesh reinforcement vs primary suture	23/133 (17%) *vs* 16/70 (23%)	0·72 (0·32–1·60)	0·42
Onlay mesh reinforcement vs sublay mesh reinforcement**	15/127 (12%) *vs* 23/133 (17%)	1·62 (0·73–3·63)	0·24

* Intention-to-treat analysis** Per-protocol analysis

At baseline, 245 (51%) of 480 patients completed SF-36 and 342 (71%) of 480 submitted the EQ-5D questionnaire. After 2 years of follow-up, 188 and 333 patients, respectively, completed these questionnaires. No differences were recorded between the three treatment groups in SF-36 domains or the mental component summary score and physical component summary score (table 3). Moreover, no differences were noted between treatment groups with respect to EQ-5D scores and postoperative pain (measured with the visual analogue scale). Further analysis of the quality-of-life measures for patients with and without an incisional hernia showed no differences in scores on the SF-36 or EQ-5D questionnaires (table 4). However, patients with an incisional hernia had a higher score on the visual analogue scale for postoperative pain (mean estimate 1·94 [SE 0·39]) compared with patients who did not develop an incisional hernia (0·96 [0·15]; p=0·01).

DISCUSSION

The findings of the PRIMA trial show that onlay mesh reinforcement significantly reduced the incidence of incisional hernia after midline laparotomy in patients at high risk for incisional hernia (ie, those with abdominal aortic aneurysm or a BMI ≥27 kg/m^2). Sublay mesh reinforcement did not have a significant effect on the incidence of incisional hernia compared with primary suture. Although the absolute difference in incidence of incisional hernia between onlay and sublay mesh reinforcement was less than the equivalence margin of 10%, the 98·3% CI for the difference did not provide strong evidence in favour of equivalence.

Postoperative complications were analysed after 1 month (short-term) (29) and after 2 years. With respect to the short-term complications, only seromas were more frequently seen in patients allocated onlay mesh reinforcement, compared with those assigned primary suture and sublay mesh reinforcement. However, this increased incidence did not have any adverse outcomes for the patient, because the frequency of surgical-site infections, mesh infections, re-interventions, or re-admissions did not differ between treatment groups. No other differences in short-term postoperative complications were seen between the groups and no further postoperative complications were recorded after follow-up of 2 years. Furthermore, 15% of the included population died. Most deaths were due to malignant disease and no death was associated with either the fibrin sealant or the mesh used. Therefore, use of primary mesh reinforcement to reduce the incidence of incisional hernia is a safe procedure.

Table 3. Quality-of-life scores

	Primary suture (n=107)		Onlay mesh reinforcement (n=188)			Sublay mesh reinforcement (n=185)		
	baseline Mean (SE)	24 months Mean (SE)	baseline Mean (SE)	24 months Mean (SE)	p-value*	baseline Mean (SE)	24 months Mean (SE)	p-value**
Pain	69·03 (3·12)	80·38 (3·43)	69·16 (2·31)	78·90 (2·60)	0·73	68·95 (2·18)	78·90 (2·53)	0·73
Physical functioning	69·55 (3·25)	66·61 (3·63)	60·74 (2·43)	64·00 (2·69)	0·56	60·40 (2·29)	64·78 (2·65)	0·68
Physical health	52·42 (5·19)	65·79 (5·75)	47·66 (3·82)	65·13 (4·36)	0·93	36·31 (3·60)	61·81 (4·29)	0·58
Emotional problems	74·36 (4·84)	83·92 (5·36)	72·82 (3·59)	77·34 (4·11)	0·33	63·30 (3·39)	69·97 (4·00)	0·04
Energy / fatigue	62·30 (2·64)	61·10 (2·90)	58·20 (1·98)	62·60 (2·20)	0·68	51·70 (1·86)	60·40 (2·14)	0·85
Emotional well-being	74·90 (2·16)	79·60 (2·34)	74·00 (1·63)	76·30 (1·79)	0·26	69·00 (1·53)	74·80 (1·74)	0·10
Social functioning	79·00 (3·02)	82·10 (3·40)	70·70 (2·28)	79·20 (2·54)	0·50	65·30 (2·13)	78·40 (2·49)	0·38
General health	62·90 (2·40)	58·10 (2·61)	57·60 (1·81)	57·50 (1·99)	0·84	57·50 (1·71)	57·20 (1·94)	0·77
Mental component	49·20 (1·32)	52·20 (1·42)	48·80 (0·97)	50·20 (1·09)	0·27	45·10 (0·91)	48·90 (1·08)	0·06
Physical component	43·80 (1·31)	44·90 (1·42)	42·00 (0·97)	45·40 (1·08)	0·76	41·70 (0·91)	45·10 (1·07)	0·90
EQ-5D	0·81 (0·02)	0·93 (0·02)	0·82 (0·019)	0·90 (0·01)	0·33	0·77 (0·02)	0·91 (0·02)	0·63
Postoperative pain	1·12 (0·25)	1·27 (0·31)	1·16 (0·19)	0·71 (0·25)	0·17	1·04 (0·20)	1·06 (0·26)	0·61

Data are mean (SE). SF-36 scores range from 0 to 100. EQ-5D scores range from -0.329 to 1.000. EQ-5D=EuroQol five dimensions. SF-36=36-item short form health survey. *Difference at 24 months between primary suture and onlay mesh reinforcement. ** Difference at 24 months between primary suture and sublay mesh reinforcement. *** Measured on a visual analogue scale (range 0-10)

Table 4. Quality-of-life scores for patients with and without incisional hernia

	No incisional hernia (n=388)	Incisional hernia (n=92)	p-value
Pain	79·49 (1·68)	77·79 (3·15)	0·60
Physical functioning	65·89 (1·72)	58·98 (3·14)	0·03
Physical health	64·84 (2·85)	58·34 (5·57)	0·26
Emotional problems	75·93 (2·67)	75·35 (5·25)	0·92
Energy / fatigue	61·97 (1·42)	58·17 (2·57)	0·14
Emotional well-being	76·24 (1·15)	77·08 (2·03)	0·67
Social functioning	79·70 (1·67)	78·23 (3·18)	0·65
General health	57·54 (1·27)	57·07 (2·23)	0·83
Mental component score	49·96 (0·71)	51·04 (1·34)	0·42
Physical component score	45·44 (0·70)	43·47 (1·35)	0·14
EQ-5D	0·91 (0·01)	0·91 (0·02)	
Postoperative pain *	0·96 (0·15)	1·94 (0·39)	0·01

Data are mean (SE). SF-36 scores range from 0 to 100. EQ-5D scores range from -0.329 to 1.000. EQ-5D=EuroQol five dimensions. SF-36=36-item short form health survey. *Measured on a visual analogue scale (range 0-10).

Incisional hernia is one of the most common complications after abdominal wall surgery. In high-risk groups, the frequency of incisional hernia is 30–40%. Incisional hernia can create a social burden for the patient and a financial burden for public health. Furthermore, it can lead to worse quality of life. In the PRIMA trial, we noted that patients with incisional hernia had a higher pain score compared with those without an incisional hernia. Thus, prevention is of paramount importance. Until now, several trials have been done to investigate whether primary mesh reinforcement can reduce the incidence of incisional hernia. Most study findings showed that use of prophylactic mesh in patients with abdominal aortic aneurysm reduced the risk of incisional hernia to almost zero. For example, in a study by Muysoms and colleagues (PRIMAAT trial) (34), in which patients with abdominal aortic aneurysm were included, the cumulative incidence of incisional hernia was 28% in the non-mesh group compared with 0% in the mesh group, after follow-up of 2 years. Our data also provide strong evidence that use of prophylactic mesh in patients with abdominal aortic aneurysm—and in those with a high BMI (≥27 kg/m^2)— significantly reduces the incidence of incisional hernia (30% incidence with primary suture vs. 13% with onlay mesh reinforcement and 18% with sublay mesh reinforcement).

The reasons for the discrepancy in incidence between our study and other studies, including the PRIMAAT trial, could be explained by several factors. First, radiological examination was done in 59% of patients in our study, which is a more accurate procedure to diagnose hernia. In most other studies, radiological examination was not done (1, 34, 35), and incisional hernia was diagnosed clinically in the PRIMAAT trial (34).

Second, follow-up of patients in our trial was for 2 years, whereas follow-up in other studies (1, 36, 37) was usually shorter. A higher incidence of incisional hernia is typically seen with a longer duration of follow-up (2, 35). In a study by Fink and colleagues (2), the incidence of incisional hernia was 12·6% in the first year, which increased significantly to 22·4% at 3 years after midline laparotomy, representing a relative increase of 60%. Thus, length of follow-up seems to affect the incidence of incisional hernia after midline laparotomy.

Third, different clinician specialties played a part in our study, not solely an abdominal closing team, as was the case in the PRIMAAT trial (34) In the PRIMA trial, we included not only surgical patients but also those from the departments of urology and gynaecology. Thus, general surgeons and those from these different specialties operated on patients. This difference is exceptional because—as far as we know—no other study has included this variety of surgical specialties, patients, and surgical indications. Even though several specialists participated in the PRIMA trial, it is unlikely that this variety might have affected the results, considering the few gynaecological and urological patients.

Finally, we included different groups of high-risk patients in our trial, not only those with abdominal aortic aneurysm but also individuals with a BMI of 27 kg/m^2 or higher. Published work is contradictory with respect to primary mesh reinforcement in obese patients. For example, findings of a randomised controlled trial in obese individuals (BMI ≥40 kg/m^2) did not show significant results (35); however, this trial used an absorbable mesh. Findings of several other trials of a non-absorbable mesh did show a significant effect of prophylactic mesh placement in patients with morbid obesity (BMI ≥45 kg/m^2) (23, 24). In another trial (25), a non-crosslinked biological mesh was placed in patients with a BMI greater than 40 kg/m^2 (or BMI >35 kg/m^2 with weight-related comorbidity), which did not reduce the incidence of incisional hernia substantially.

Participation of surgeons from different specialties might have led to a learning curve in our trial, but this possibility is also a strong advantage of the PRIMA trial: the results of our study are applicable to every patient undergoing midline laparotomy, operated on by different types of specialists. It is remarkable that placement of a mesh in an onlay position led to our significant results, because the sublay technique has always

been assumed superior (38). Placement of a mesh in an onlay position is a less complex surgical technique, which might have contributed to our results. The participation of different specialties might also have been a contributing factor to our findings: urologists and gynaecologists were not familiar with both onlay and sublay mesh reinforcement. However, sublay mesh reinforcement in particular is a complex technique. This factor makes onlay placement of a mesh with glue even more interesting, particularly because the onlay position did not lead to complications that had any adverse outcomes for patients.

In the PRIMA trial, we included patients not only with abdominal aortic aneurysm but also with a BMI of 27 kg/m^2 or higher. The possibility exists that these different risk factors affect each other in a synergistic way, which might lead to biased results. Therefore, we analysed mean BMI in both subgroups; this variable was similar among the three treatment groups of both subgroups, and the distribution was not skewed. Median BMI in the abdominal aortic aneurysm subgroup was lower than 27 kg/m^2 (26·6, IQR 24·3-29·3), whereas in the high BMI subgroup it was higher than this value (median 30·9, IQR 28·7-34·1). Thus, abdominal aortic aneurysm and BMI act as independent risk factors, and our results are not biased.

Findings of previous studies have shown that the combination of mesh and sealant we used in our study is effective (39, 40). As noted by us previously (29), use of fibrin sealant in clinical practice, in combination with prophylactic mesh reinforcement, has not been investigated before. In our trial, no great complications or adverse events can be attributed with certainty to the sealant or the mesh. Application of the sealant aimed to reduce the anterior subcutaneous dissected space during onlay mesh reinforcement, which is prone to formation of seromas. Our results for postoperative complications did not confirm this expectation. This outcome can be explained by the timing of the application of the sealant, which is essential. There will be no reduction of the dissected space if polymerisation occurs before the ventral layer is closed (41). Furthermore, other techniques that could diminish seroma formation were not applied, such as placement of a wound drain and suturing of the subcutaneous tissue plane. Even though the expectation of fewer seromas could not be confirmed during this trial, the incidence of seroma without glue is unknown in these particular groups of patients.

We applied Bonferroni correction for multiple testing (α=0·017) in our analysis. Opinions on multiple-testing correction for multiarm trials are conflicting (42), because controlling the overall probability of a false-positive treatment effect comes at the price of rejecting

prematurely potentially effective treatments. In our study, the Bonferroni correction affected the interpretation of the difference between sublay mesh reinforcement versus primary suture (borderline significance vs non-significant).

We did not take into account the dropout rate in our statistical analysis. If the frequency of dropouts is equal in each arm of a trial, odds ratios should not be affected, assuming that the treatment effect in patients with complete follow-up and in those who dropped out is equal. In our trial, this assumption was plausible: the frequency of dropouts was very similar in the three treatment groups, so dropout of patients probably does not bias the odds ratios. Furthermore, we assessed whether differences in baseline characteristics between treatment groups were similar in remaining participants (appendix), which was the case. To correct for imbalance between the three treatment groups, an adjusted analysis for covariates was done, which led to a similar treatment effect.

One of the main limitations of the PRIMA study is the fact that not all included patients underwent radiological examination: 59% had radiological examination, and 70% of all individuals who completed follow-up underwent imaging. This procedure might have led to underestimation of the number of patients with incisional hernia, because radiological examination is more sensitive than physical examination alone. Therefore, we assessed incidence of incisional hernia in two subgroups: in individuals who underwent radiological examination (additional to physical examination); and in patients who did not receive radiological examination (data available on request). This analysis showed consistent treatment effects in both subgroups. Even though our study was not powered on these (small) subgroups, we believe our results are generalisable in daily practice. The fact that only 59% of participants had radiological assessment makes our study more comparable with daily practice but limits confidence of the study to some extent.

The PRIMA trial provides level one evidence for the prevention of incisional hernia after midline laparotomy in patients at risk for incisional hernia. Closure of laparotomy with onlay mesh reinforcement has the potential to become the standard treatment in high-risk groups, which will reduce the socioeconomic burden of incisional hernia. The results of the PRIMA trial also offer future perspectives. The next step will be a trial in which onlay mesh reinforcement is combined with the small bites suture technique to lower the incidence of incisional hernia even further, because the small bite technique has been shown to be superior in closing midline laparotomy.

Contributors

APJ and LT contributed to data collection, data interpretation, data analysis, and writing of the report. JFL and HJJ contributed to study design, data collection, data interpretation, and writing of the report. DvK, EWS, and RT contributed to data analysis, data interpretation, and writing of the report. G-JK contributed to data interpretation and writing of the report. HHE contributed to study design and reviewed the report. REGJMP, ACvdH, ID, JAC, CS, AM, JRI, PF, PK, and RHF contributed to data collection and reviewed the report.

Other members of the PRIMA Trialist Group

Jeroen Nieuwenhuizen, Wim C J Hop, Pim C W Burger, Hence J Verhagen, Pieter J Klitsie, Michiel van de Berg, Markus Golling.

Declaration of interests

We declare no competing interests.

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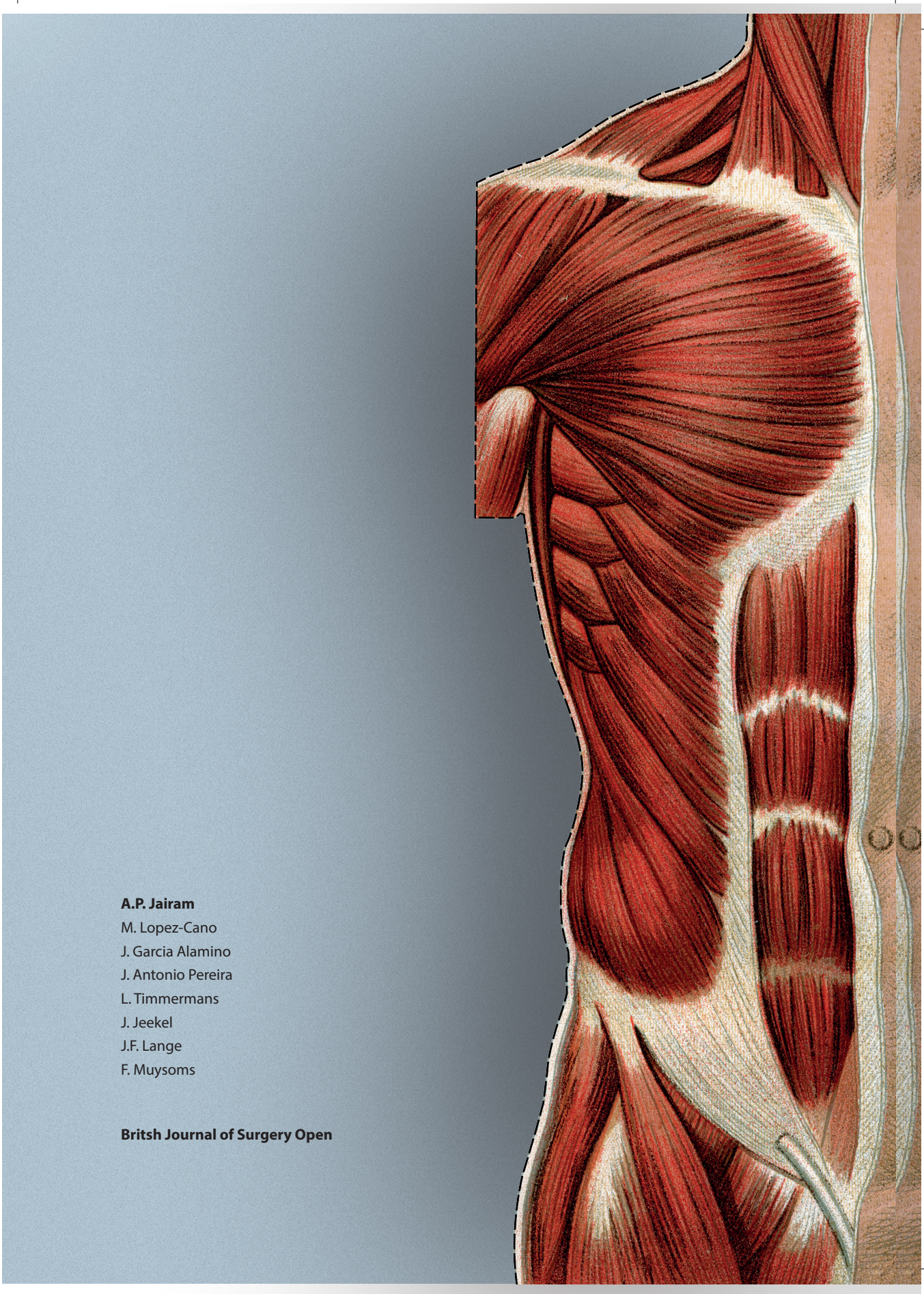

A.P. Jairam
M. Lopez-Cano
J. Garcia Alamino
J. Antonio Pereira
L. Timmermans
J. Jeekel
J.F. Lange
F. Muysoms

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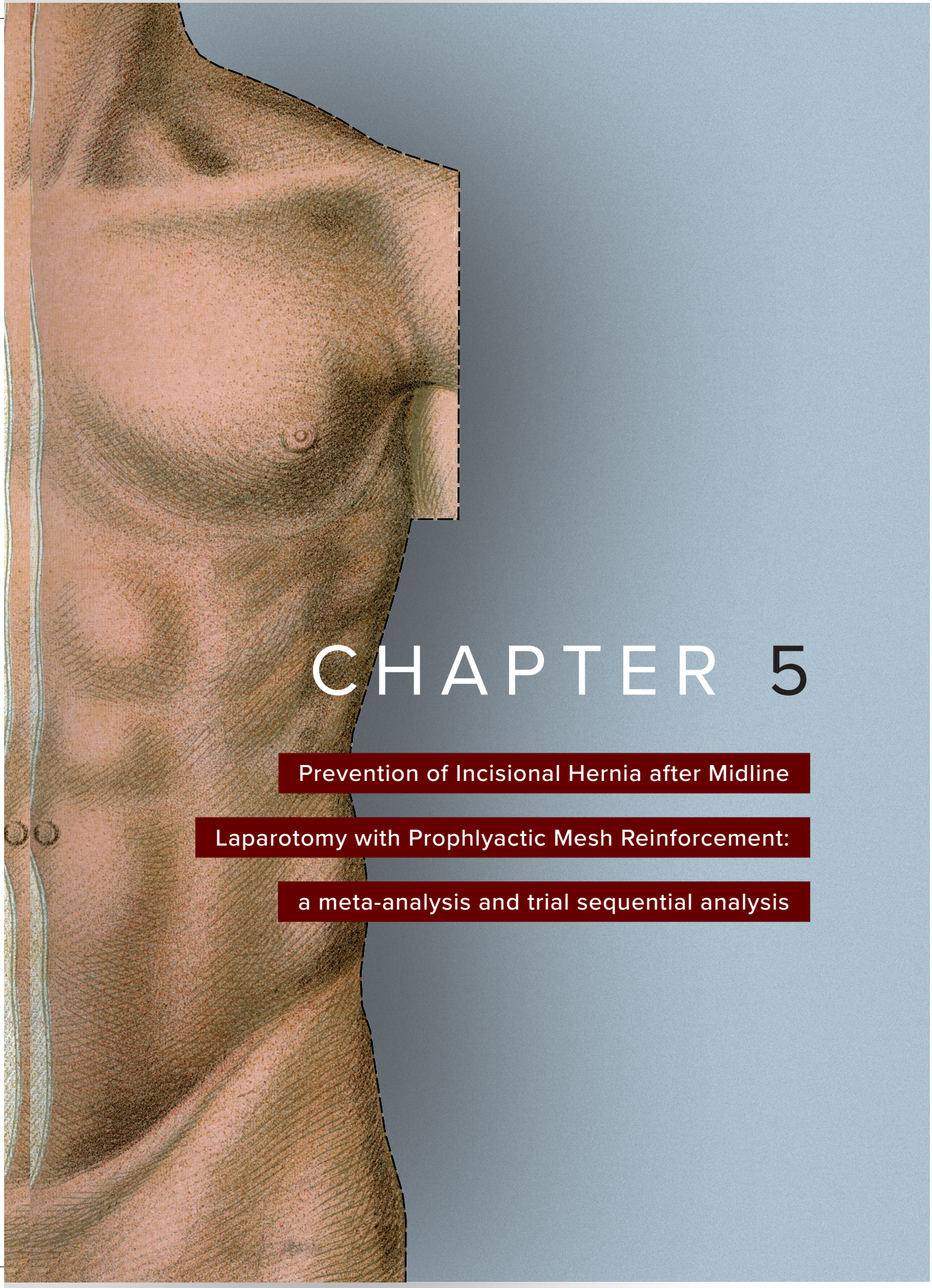


CHAPTER 5

Prevention of Incisional Hernia after Midline Laparotomy with Prophlyactic Mesh Reinforcement: a meta-analysis and trial sequential analysis

ABSTRACT

Introduction: Incisional hernia is a frequent complication after abdominal surgery. The aim is to assess the efficacy of prophylactic mesh reinforcement after midline laparotomy, in order to reduce the incisional hernia incidence.

Method: A meta-analysis was conducted, following the PRISMA guidelines. Primary outcome was the incidence of incisional hernia after a follow-up of at least 12 months. Secondary outcomes were postoperative complications. Only randomised controlled trials were included. A random-effects model was used for the meta-analysis and trial sequential analysis was conducted.

Results: Twelve randomized controlled trials were included, encompassing 1815 patients. The incisional hernia incidence was significantly lower after prophylactic mesh reinforcement compared with sutured closure (RR 0.35, 95%CI 0.21-0.57, p<0.0001). Both onlay (RR 0.26, 95%CI 0.11-0.67, p= 0.005) and retromuscular (RR 0.28 95%CI 0.10-0.82, p= 0.02) mesh reinforcement lead to a significant reduction of the incisional hernia. The occurrence of seromas was higher in patients who underwent onlay mesh reinforcement (RR 2.23, 95%CI 1.10-4.52, p=0.03). Prophylactic mesh reinforcement does not result in an increased rate of surgical site infections.

Conclusion: Prophylactic mesh reinforcement of a midline laparotomy leads to a significant reduction of incisional hernia in high-risk patients for both onlay and retromuscular mesh reinforcement. Onlay PMR was associated with a lager size of effect than retromuscular PMR. Onlay mesh was associated with significant postoperative morbidity, in form of seroma. Further research is needed to define the discriminating patient risk factors when prophylactic mesh reinforcement has to be recommended.

INTRODUCTION

Incisional hernia (IH) is one of the most frequent complications after abdominal surgery, with incidences ranging from 11% to 20% in a general surgical population (1-4). The incidence of IH can increase up to 40% in high-risk groups, such as patients with an Abdominal Aortic Aneurysm (AAA) or morbid obesity (5-12). An IH can be asymptomatic, but it can also lead to serious and potentially fatal complications, such as incarceration and strangulation of bowel. Furthermore, IH has a high impact on patients' quality of life and body image (13, 14). Moreover, IH treatment represent a financial burden on our healthcare system (15).

The current treatment of IH is mesh repair, which has led to a lower recurrence rate compared with the primary suture (PS) technique (16). However, the recurrence rate is still high even when a mesh is used. In a Danish nationwide registry study, a cumulative recurrence rate after IH repair at 3 years follow-up is reported to be 37% (17). Currently, there is no definitive solution for the high recurrence rates and complications related to recurrences of IH. It can be concluded that prevention is of paramount importance (18). In the past few years, several studies regarding prevention of IH with prophylactic mesh reinforcement (PMR) have been conducted. Most randomized controlled trials (RCTs) included a limited number of patients. Different surgical techniques of PMR, including mesh placement in onlay, retromuscular or intraperitoneal position, have been studied. The European Hernia Society guidelines on the closure of abdominal wall incisions made a recommendation in 2015 (19). The Guidelines Development Group stated that PMR to reduce the IH incidence after elective midline laparotomy in a high-risk patient is suggested with a weak recommendation. They also stated that larger trials were needed to make a strong recommendation.

Since the publication of the European Hernia Society guidelines on the closure of abdominal wall incisions, three meta-analyses (20, 21, 22) together with the long-term data of the largest multicentre RCT on IH prevention after midline laparotomy comparing PMR with PS (PRIMA trial) (23) have been published. However, in one of these meta-analyses, RCTs and observational studies were mixed (20). In the meta-analysis of Wang et al., some studies on non-midline incisions were added (21) and in all three meta-analysis (20,21,22), long-term data from the PRIMA trial were not included.

This meta-analysis includes only RCTs and long-term data from the recently published PRIMA trial (23). Moreover, we performed a Trial Sequential Analysis (TSA) to evaluate the strength of the current evidence on PMR after midline laparotomies.

The aim of this meta-analysis is to assess the safety and efficacy of PMR in order to reduce the IH incidence after elective midline laparotomy. Furthermore, the efficacy of both onlay and retromuscular PMR were compared with PS.

METHODS

Protocol and registration

A meta-analysis was conducted and reported following the PRISMA guidelines (24). This meta-analysis was registered prospectively at the Prospero database at the 5th of November 2015 (CRD42015027079) with the acronym MARIA review. Our meta-analysis was finalized after the publication of the final results of the PRIMA trial on June 19th 2017.

Information sources and search terms

A systematic computerized literature search was performed until the first of January 2017, using 12 databases: EMBASE, Medline, Web-of-Science, SCOPUS, Cochrane, CINAHL, Pubmed publisher, Lilacs, Scielo, ScienceDirect, Proquest and Google scholar. The Biomedical Information Specialist of the Medical Library (Erasmus University Medical Center, Rotterdam, the Netherlands) prepared the search strategy. The syntax with search terms is shown in Appendix 1.

Study selection data extraction and quality assessment

Three reviewers (A.J., M.L.C and F.M.) independently screened all records by title and abstract for eligibility. After this first screening, the full text of records was assessed. Only eligible RCTs were included. The methodological quality of RCTs was assessed with SIGN checklists (Scottish Intercollegiate Guidelines Network). Risk of bias assessment was done using the Cochrane Collaboration's tools, in which the following aspects are assessed: random sequence generation, allocation concealment, blinding of patients, personnel or outcome assessors, incomplete outcome data and selective reporting (25). Assessment of both methodological quality and risk of bias was performed by three independent reviewers. Studies were assessed as either low risk of or high risk of bias.

RCTs were included if they met the following inclusion criteria: patients aged ≥ 18 years, undergoing midline laparotomy, for all types of indications, with all types of meshes and all types of mesh positions. Primary outcome was the incidence of IH. Secondary outcomes were postoperative complications: seroma, surgical site infection (SSI), hematoma and burst abdomen. Follow-up was determined to be at least 12 months. No language restrictions were used.

All required data were extracted and collected in a standardized manner by at least two authors independently (A.J. and M.L.C.). Any divergences during the data extraction phase were resolved through discussion and by consulting a third investigator (F.M.). A Summary of Findings table (SoF table) was created, in which the following information was collected: study characteristics (title, year of publication, study design, number of included patients), indication for midline laparotomy, description of intervention and description of the compared intervention ('control group'), type of mesh that was used, mesh placement, length of follow up and outcome measurements. In case a manuscript included data for different mesh positions, the data for these different mesh positions was described separately per group in the SOE table. For duplicate data reported by the same author(s), the article with the longest follow-up period was selected.

Statistical analysis

A meta-analysis, pooling the results of the retrieved studies, was performed. A sensitivity analysis as conducted to reduce the risk of possible bias of primary and secondary outcomes was conducted. Meta-analyses that combine other subgroups (mesh position) were also performed. A random effects model was used and presented as risk ratios (RR) with 95% confidence intervals (CI). Effects were considered statistically significant if the 95% CI of the overall effect estimate did not overlap. The I^2 statistic was used to assess heterogeneity. Groups with zero events were adjusted with a constant continuity adjustment of 0.5 in each arm (as per the default adjustment in the software used). Publication bias was assessed by a funnel plot. Analyses were performed using Review Manager software (RevMan version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark). Two sided p-values of <0.05 were considered statistically significant.

Conducting a meta-analysis can lead to type I errors (false positives) or overestimation of treatment effects due to systematic errors (bias) and random errors (play of change). In order to avoid this, Trial Sequential Analysis (TSA) was applied. TSA can provide a required information size (RIS). The RIS is the required number of patients that needs to be included in the meta-analysis to provide firm evidence (26,27). Control Event Rate (CER) and Relative Risk Reduction (RRR) were calculated. CER is the proportion participants in the control group that have the outcome. RRR can be interpreted as the reduction of the relative risk of the specified outcome in the treatment group, compared with the control group. Trial Sequential Analysis (TSA) was planned for all retrieved studies and for the group of studies with low risk of bias. TSA was performed using the TSA software v0.9 (www.uct.dk/tsa/index.html).

RESULTS

Study characteristics

Figure 1 shows the PRISMA flow diagram. A total of 1497 records were identified after removal of the duplicates. After screening of title and abstract, 39 articles were found relevant for full text assessment. After full text assessment, 29 articles were excluded; leaving 13 RCTs that fulfilled the inclusion criteria, for the qualitative and quantitative assessment (5-11, 23, 28-32). The study of Timmermans et al. (32) was excluded, since only the short-term results (postoperative complications in the first month) were discussed. The article with the longest follow-up (long-term results, with the primary endpoint IH), was selected (23). Thus, 12 RCTs were analyzed. Six studies were considered low risk of bias (7, 8, 11, 23, 29, 31) and six studies were considered high risk of bias (5, 6, 9, 10, 28, 30). Table 1 captures the risk of bias assessment.

The 12 included RCTs comprised 1815 patients in total. Study and patient characteristics are presented in the SoF table (Table 2). Inclusion criteria for PMR of the midline laparotomy in the individual RCTs were either the presence of an AAA (8, 10, 11, 23), morbid obesity (5, 7, 9, 30), colorectal cancer surgery (31) or a mixture of operative indications (6, 28, 29). Most studies placed a polypropylene mesh in an onlay (6,10,23,29,31) or retromuscular position (7,8,11,23). Two studies used biological meshes (10, 30) and one study used a rapid absorbable intra-peritoneal mesh (5).

Outcome measurements

Primary outcome is the incidence of IH after a follow-up of at least 12 months. Twelve RCTs were included in the overall quantitative analysis for the primary outcome and publication bias was thus evaluated (33). This meta-analysis showed a significant reduction of IH in patients with PMR compared with PS patients (RR 0.35, 95%CI 0.21-0.57, I=69%, p<0.0001) (Figure 2). The funnel plot is slightly asymmetric, indicating a possible publication bias of studies that favour mesh prophylaxis (Figure 3). Analysis of the primary outcome for the low risk of bias studies (6 RCTs) showed that the occurrence of IH is significantly less (RR 0.23, 95%CI 0.10-0.52, I=71%, p= 0.0004) in the PMR group compared with the PS group (Figure 2). Both onlay and retromuscular PMR lead to a significant reduction of the IH incidence compared with PS, with respectively a RR of 0.26 (95%CI 0.11-0.67, I=72%, p=0.005) and a RR of 0.28 (95%CI 0.10-0.82, I=66%, p=0.02) (Figure 4).

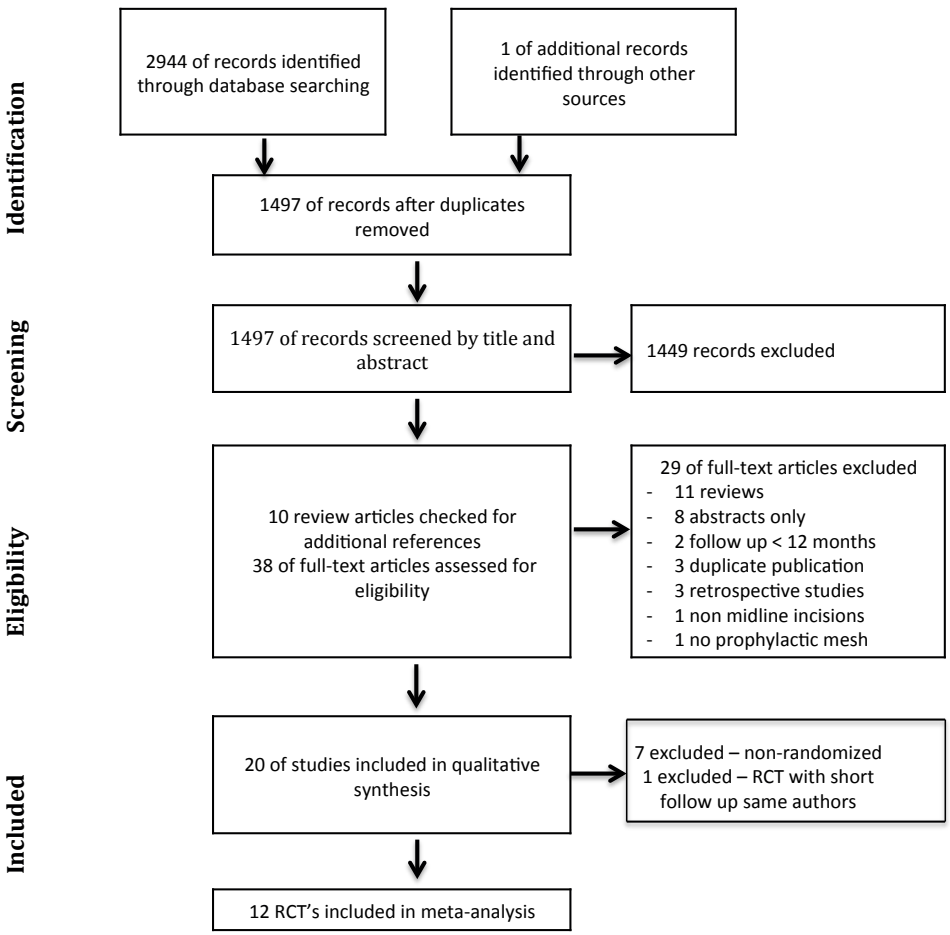


Figure 1. PRISMA flow diagram of a systematic review and meta-analysis on the prevention of incisional hernia with prophylactic mesh reinforcement.

Table 1. Risk of bias assessment on the prevention of incisional hernia with prophylactic mesh reinforcement in midline laparotomies

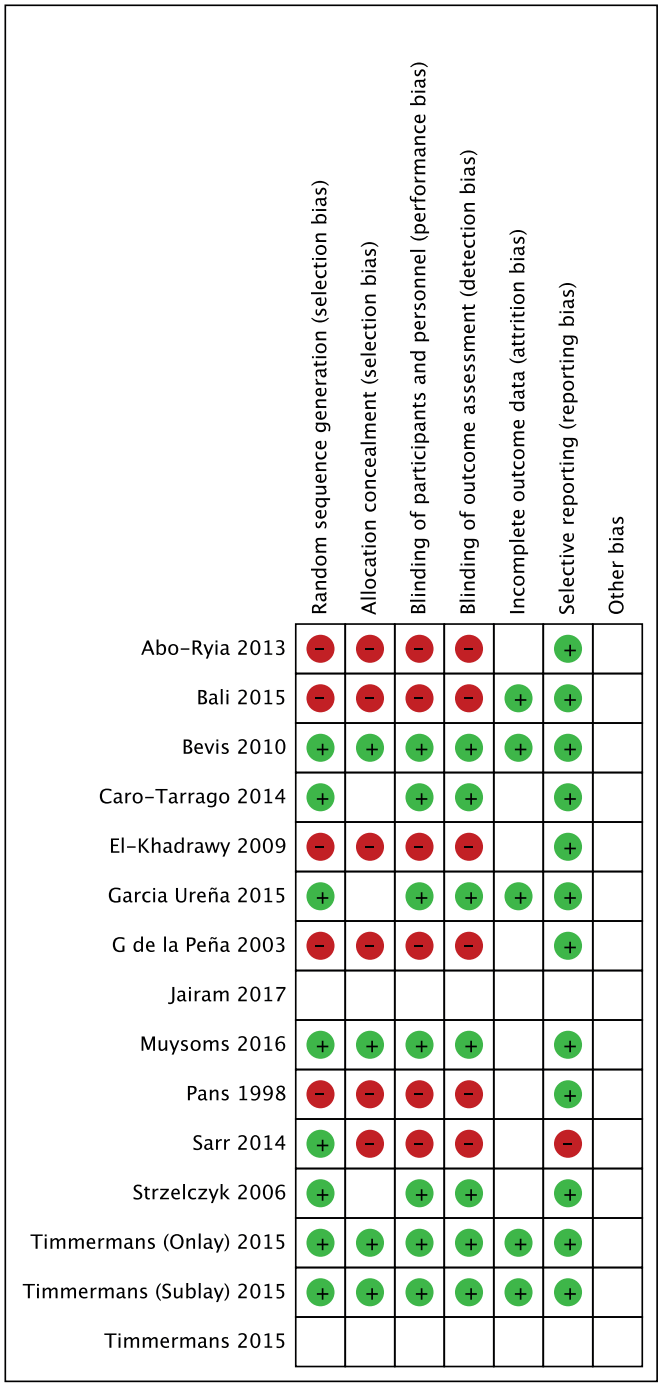


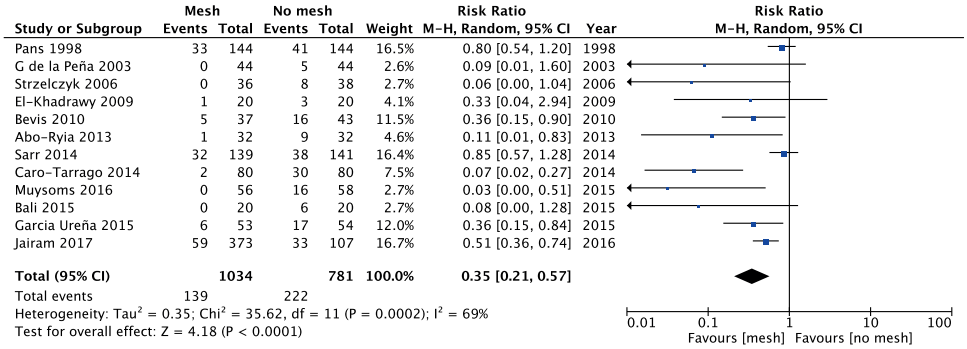
Table 2. Summary of findings table of the included studies on the prevention of incisional hernia with prophylactic mesh reinforcement in midline laparotomies

Author Year of publication	N	Indication midline laparotomy	Type of mesh	Mesh position	Follow up (months)	Outcome measurements	IH Diagnostic (clinical/radiologic)
Pans 1998 (5)	288	Morbid Obesity	Polyglactin	Intra-peritoneal	29.8	IH, postoperative morbidity	Unreported
G. de la Peña 2003 (6)	88	Cancer colon, rectum, gastric cancer, cholelithiasis, diverticulosis, crohn's disease, pancreatic cystoadenoma, gastric ulcer, cancer of small intestine	Polypropylene	Onlay	36	IH, Hematoma, seroma, infection, pain	Clinical. If notconclusive CT
Strzelczyk 2006 (7)	74	Gastric bypass surgery	Polypropylene	Retromuscular	28	IH, wound leakage, bleeding, other surgical complications	Clinical plus US
El-Khadrawy 2009 (28)	40	High risk	Polypropylene	Preperitoneal	36.7	IH, seroma SSI, wound disruption, chronic wound pain, cardiac, pulmonary problems, DVT, ascitis	Clinical
Bevis 2010 (8)	80	AAA	Polypropylene	Retromuscular	Mesh 30.2 No mesh 19.6	IH, wound infection, hernia operation	Clinical, if doubt US
Abo-Ryia 2013 (9)	64	Open bariatric surgery	Polypropylene	Preperitoneal	Mesh 48 No mesh 49	Safety and efficacy of preperitoneal prosthetic enforcement, seroma, infection, partial dehiscense	Clinical, US in suspected cases
Caro-Tarrago 2014 (29)	160	Colorectal and general surgery	Polypropylene	Onlay	Mesh 14.8 No mesh 12.5	IH, all adverse events, postoperative complications	Clinical and CT
Sarr 2014 (30)	280	Open RYGB	Biologic	Intraperitoneal	24	IH, wound infection, wound dehiscence, wound sinus tract, wound erythema, seroma	Clinical, phone call, primary care physician
Bali 2015 (10)	40	Open AAA	Biologic	Onlay	36	IH, duration surgery, postoperative complications, reoperation rate	Clinical and CT
Garcia-Ureña 2015 (31)	107	Colorectal surgery	Polypropylene	Onlay	24	IH, incidence of local complications: SSI, seroma, evisceration, mesh rejection Systemic complications	Clinical and CT

Table 2. (Continued)

Author Year of publication	N	Indication midline laparotomy	Type of mesh	Mesh position	Follow up (months)	Outcome measurements	IH Diagnostic (clinical/radiologic)
Muysoms 2016 (11)	114	AAA and ASA<4	Partially absorbable Polypropylene	Retromuscular	24	IH Postoperative complications SSI Duration Surgery	Clinical and if available US or CT
Jairam 2017 (23)	480	Open AAA surgery or midline laparotomy in patients with BMI>27	Polypropylene	Onlay (188 patients) Retromuscular (185 patients)	24	IH, Postoperative complications Quality of life Cost-effectiveness	Clinical and US or CT

(a)



(b)

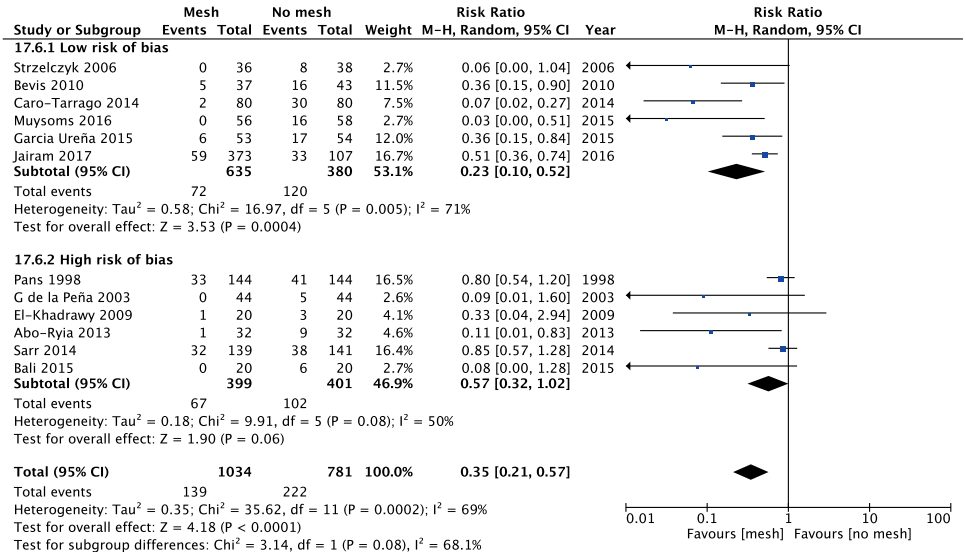


Figure 2. Forest plots on the incidence of incisional hernias comparing prophylactic mesh reinforcement of a midline laparotomy with primary sutures:
a) overall data from all 12 included studies
b) separate data for studies with low risk of bias and studies with a high risk of bias

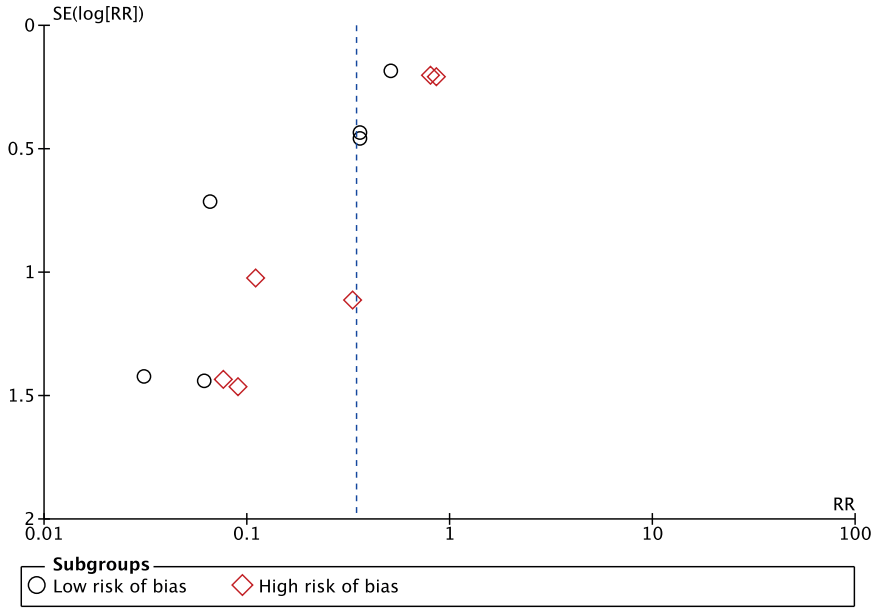
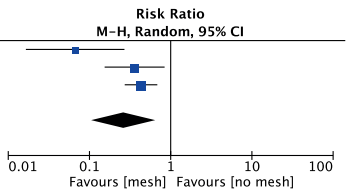


Figure 3. Funnel plot

(a)

Study or Subgroup	Mesh Events	Total	No mesh Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Caro-Tarrago 2014	2	80	30	80	22.9%	0.07 [0.02, 0.27]	2014
Garcia Ureña 2015	6	53	17	54	34.2%	0.36 [0.15, 0.84]	2015
Jairam 2017	25	188	33	107	42.9%	0.43 [0.27, 0.68]	2016
Total (95% CI)		**321**		**241**	**100.0%**	**0.26 [0.11, 0.67]**	
Total events	33		80				

Heterogeneity: Tau² = 0.46; Chi² = 7.16, df = 2 (P = 0.03); I² = 72%
Test for overall effect: Z = 2.82 (P = 0.005)



(b)

Study or Subgroup	Mesh Events	Total	No mesh Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Strzelczyk 2006	0	36	8	38	10.9%	0.06 [0.00, 1.04]	2006
Bevis 2010	5	37	16	43	34.8%	0.36 [0.15, 0.90]	2010
Muysoms 2016	0	56	16	58	11.0%	0.03 [0.00, 0.51]	2015
Jairam 2017	34	185	33	107	43.4%	0.60 [0.39, 0.90]	2016
Total (95% CI)		**314**		**246**	**100.0%**	**0.28 [0.10, 0.82]**	
Total events	39		73				

Heterogeneity: Tau² = 0.63; Chi² = 8.94, df = 3 (P = 0.03); I² = 66%
Test for overall effect: Z = 2.33 (P = 0.02)

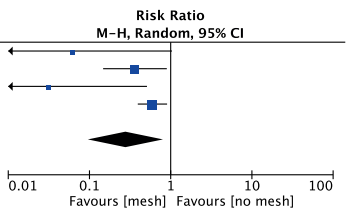


Figure 4. Forest plots on the incidence of incisional hernias comparing prophylactic mesh reinforcement of a midline laparotomy with primary sutures:
a) data from studies using onlay mesh reinforcement
b) data for studies using retromuscular mesh reinforcement

TSA calculation (for the primary outcome) was performed for all 12 included studies. The Control Event Rate (CER) proportion is 28%, the Relative Risk Reduction (RRR) is 65% and a constant continuity adjustment was set at 0.5 events per group. The accrued information size (n=1815) is 273,3% of the estimated RIS (n=664). This means that firm evidence is available. In the group of low risk of bias studies (6 RCTs), the CER proportion is 31% and RRR is 77%. The accrued information size (n=1015) is 283,5% of the estimated RIS (n=358) (Figure 5).

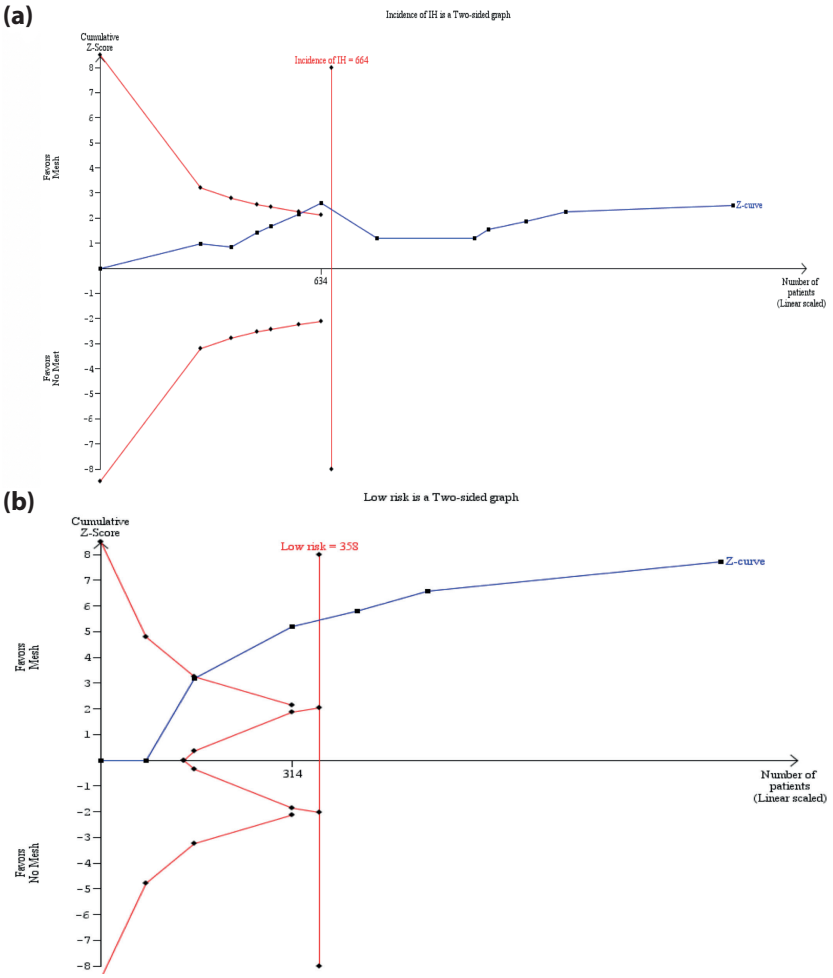
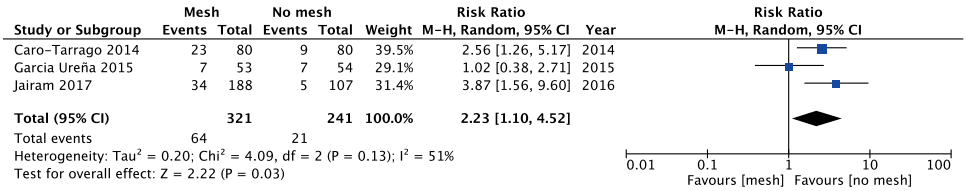


Figure 5. Trial Sequential Analysis curve for the incidence of IH comparing prophylactic mesh reinforcement of a midline laparotomy with primary sutures:
a) overall data from all 12 included studies
b) data from studies with low risk of bias

Secondary outcomes were analysed for the low risk of bias studies only (6 RCTs). Patients with an onlay PMR had a higher risk of developing seroma (RR 2.23, 95%CI 1.10-4.52, I=51%, p=0.03) compared with patients who underwent PS. This finding is statistically significant. This is not applicable for the comparison of retromuscular PMR with PS: patients who underwent retromuscular PMR did not have a higher chance of developing seroma compared with patients who underwent PS (RR 1.67, 95%CI 0.81-3.47, I=0%, p=0.17) (Figure 6). The occurrence of SSI was not significantly higher in onlay PMR compared with PS (RR 0.82, 95%CI 0.55-1.23, I=0%, p=0.33) or in patients who underwent retromuscular PMR compared to PS (RR 0.85, 95%CI 0.50-1.45, I=0%, p=0.55) (Figure 7). The incidence of hematoma and burst abdomen was not analysed because of insufficient data.

(a)



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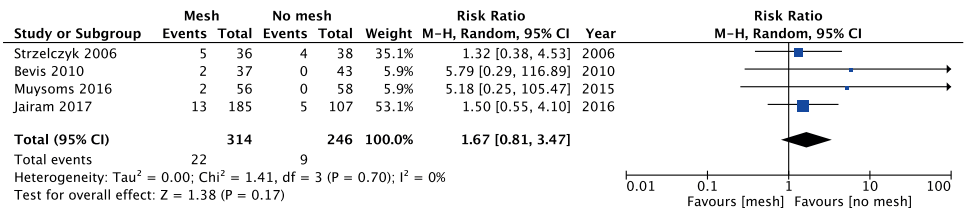
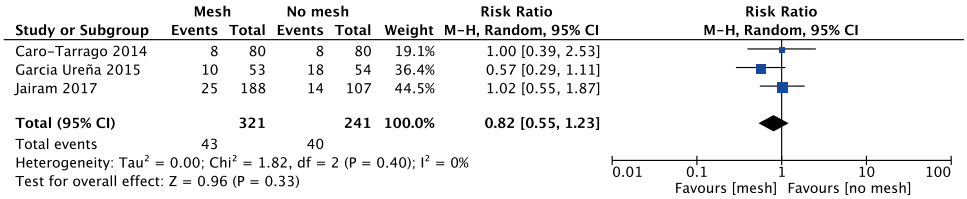


Figure 6. Forest plots for postoperative seroma comparing prophylactic mesh reinforcement of a midline laparotomy with primary sutures:
a) data from studies using onlay mesh reinforcement
b) data for studies using retromuscular mesh reinforcement

(a)



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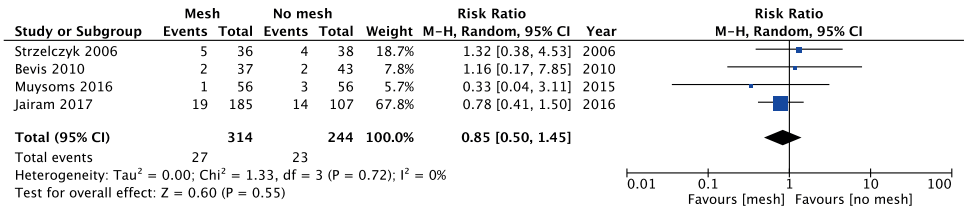

Figure 7. Forest plots for surgical site infection comparing prophylactic mesh reinforcement of a midline laparotomy with primary sutures:
a) data from studies using onlay mesh reinforcement
b) data for studies using retromuscular mesh reinforcement

DISCUSSION

Key results

This meta-analysis shows that the use of PMR in patients undergoing midline laparotomy leads to a significantly lower occurrence of IH, compared with PS closure (RR 0.35, 95%CI 0.21-0.57, p<0.0001). TSA shows that this evidence is firm with an accrued information size of 273% of the estimated required information size and an IH reduction of 65%. Significant effect was shown both for *onlay PMR* (RR 0.26, 95%CI 0.11-0.67, p=0.005) and for *retromuscular PMR* (RR 0.28, 95%CI 0.10-0.82, p=0.02). Moreover, this meta-analysis shows that PMR is safe with no increase in surgical site infections. Only an increased risk of seroma formation for *onlay PMR* (RR 2.23, 95%CI 1.10-4.52, p=0.03) was found.

Limitations

A substantial statistical heterogeneity among studies regarding the primary outcome is seen (I^2=71%). This probably reflects the variability on surgical technique and methodological approach across studies, even though they are *a priori* the same type of study (i.e. RCTs).

Although the technique of PMR in the treatment arm of the RCTs is most often well described, there is much less information on the control group with PS. Often the protocol describes the use of a suture to wound length ratio (SL/WL) of more than 4/1, but the data on the SL/WL ratio is only recorded and reported in a few studies (11), so the adherence to the optimal PS technique is unclear in most studies. Moreover, the short stitch technique, which is currently known as the best-evidenced technique with the lowest incidence of IH (3), was not used in any of the RCTs in this meta-analysis. Therefore, one could argue that the treatment effect of PMR is increased because of a suboptimal suturing technique in the control groups.

Of the 12 RCTs included in this meta-analysis, 50% were considered to have a high risk of bias. However, due to the use of sensitivity analysis, the treatment effect is maintained and shows even a larger treatment effect when only studies with a low risk of bias are analyzed (RR 0.23, 95%CI 0.10-0.52, P= 0.0004).

Only RCTs with a minimum follow-up of 12 months were included. All studies except one (29) had a follow-up of at least 24 months. Nevertheless, this is still too short to evaluate the long-term efficacy or potential late adverse effects of PMR.

In most studies physical examination was used to detect the number of patients during follow-up. Some studies added selective or systematic medical imaging for the evaluation of IH, either ultrasound or CT scan. Added imaging is expected to increase the number of patients with IH by detection of subclinical IHs and this might overestimate the importance of PMR to provide a clinical benefit for the patients.

Interpretation

It should be taken into account that the results of this meta-analysis are applicable to a certain patient group, who are operated under certain circumstances, using a specific surgical technique and a specific type of mesh. Most of the 12 included studies used a polypropylene mesh in either an onlay or a retromuscular mesh position. Two studies used a biological mesh (10, 30) and one study an absorbable synthetic mesh (5). Two of these studies did not show PMR to be effective and all 3 were considered at high risk of bias. Considering the mesh position, all studies with a low risk of bias had either an onlay or a retromuscular mesh position for PMR. Moreover, all included trials were done in an elective surgery setting. Thus, there is no evidence on how PMR behaves in emergency situations. Therefore, the results of this meta-analysis on PMR can only be considered valid for synthetic non-absorbable mesh in either an onlay or a retromuscular mesh

position. No evidence is available to support the use PMR with a biological or a synthetic absorbable mesh. Also, no evidence is available to support the use of an intra-peritoneal mesh position in PMR.

Another remarkable point was the slightly asymmetric funnel plot for IH, indicating possible publication bias towards studies that favour PMR. An overestimation of the underlying beneficial effect of the intervention due to selective publication of studies might be the reason for this finding.

As stated earlier, most studies included only patients who are considered as 'high-risk to develop an IH'. It is difficult to identify the individual risk factors that could be applied to select patients to benefit from PMR. The guidelines on the closure of abdominal wall incisions of the European Hernia Society stated that the evidence is weak for the use of PMR in patients at high risk for IH development (19). Such a guideline can only be implemented if the guidelines development group also describes the exact criteria that would select those patients considered at high risk. From this perspective, the study performed by Fischer et al. is quite interesting (18). They stratified patients in four IH risk groups (Low, Moderate, High, Extreme), based on characteristics of the patient and the surgical procedure. Selection of patients to perform PMR should be based on evidence. From this meta-analysis it seems clear that patients undergoing AAA repair and patients undergoing bariatric surgery through a midline incision will benefit from PMR. However, midline incisions have become rare, since most AAA patients are now treated with endovascular procedures and bariatric surgery is performed by laparoscopic access. Selection, based on patients' characteristics, needs cut off values. It can be questioned what the cut-off BMI value needs to be in order to advice PMR. The PRIMA trial used BMI ≥ 27kg/m2 as an inclusion criterion for PMR (23). Further research is needed to identify the maximum BMI cut-off point, which can increase the risk to develop IH. Data from large clinically oriented prospective registries (34) might be helpful to explore those risk factors that would lead to an increased IH risk. Those data are currently not available.

PMR can be considered safe in elective laparotomies. The only adverse event detected in this meta-analysis was an increased rate of seroma formation after onlay PMR. This finding is related to the subcutaneous dissection needed for onlay PMR. Even though the occurrence of seromas was higher in the onlay PMR group, there were not an increased number of surgical site infections. There was not enough data available to analyse the number of other adverse events, such as hematoma's or burst abdomen.

One of the main strengths of this meta-analysis is the fact that RCTs with low risk of bias were analysed separately, to overcome bias affecting meta-analysis (35). Furthermore, data of the most recently published RCTs were included (23). TSA shows firm evidence in favour of PMR in midline laparotomy for high-risk patients (i.e. morbid obese patients and AAA patients). This statement is not only applicable in the overall group, but in the low risk of bias studies as well. With TSA, it is suggested that no further trials would be needed to address the effects of PMR. However, conducting RCTs in other patient populations with another level of risk would be helpful to evaluate the effectiveness of a PMR.

Laparotomies are performed by a variety of surgical specialties, such as vascular surgeons, colorectal surgeons, gynaecologists and urologists. Many of those surgeons have little experience in treating abdominal wall hernias with meshes, especially in retromuscular mesh placement. This meta-analysis shows that an onlay PMR is also effective, is definitely easier to perform and probably more acceptable by these surgeons.

CONCLUSION

This meta-analysis provides level-1 evidence in favour of closure of midline laparotomies with prophylactic mesh reinforcement in high-risk patients. Thus, in high-risk groups (AAA patients and patients with morbid obesity), it should become standard treatment. Onlay PMR leads to a significantly lower incidence of IH with a larger size of the effect than retromuscular PMR. Seromas occurred more frequently in the onlay mesh reinforcement group, however, there were not more surgical site infections seen in this group.

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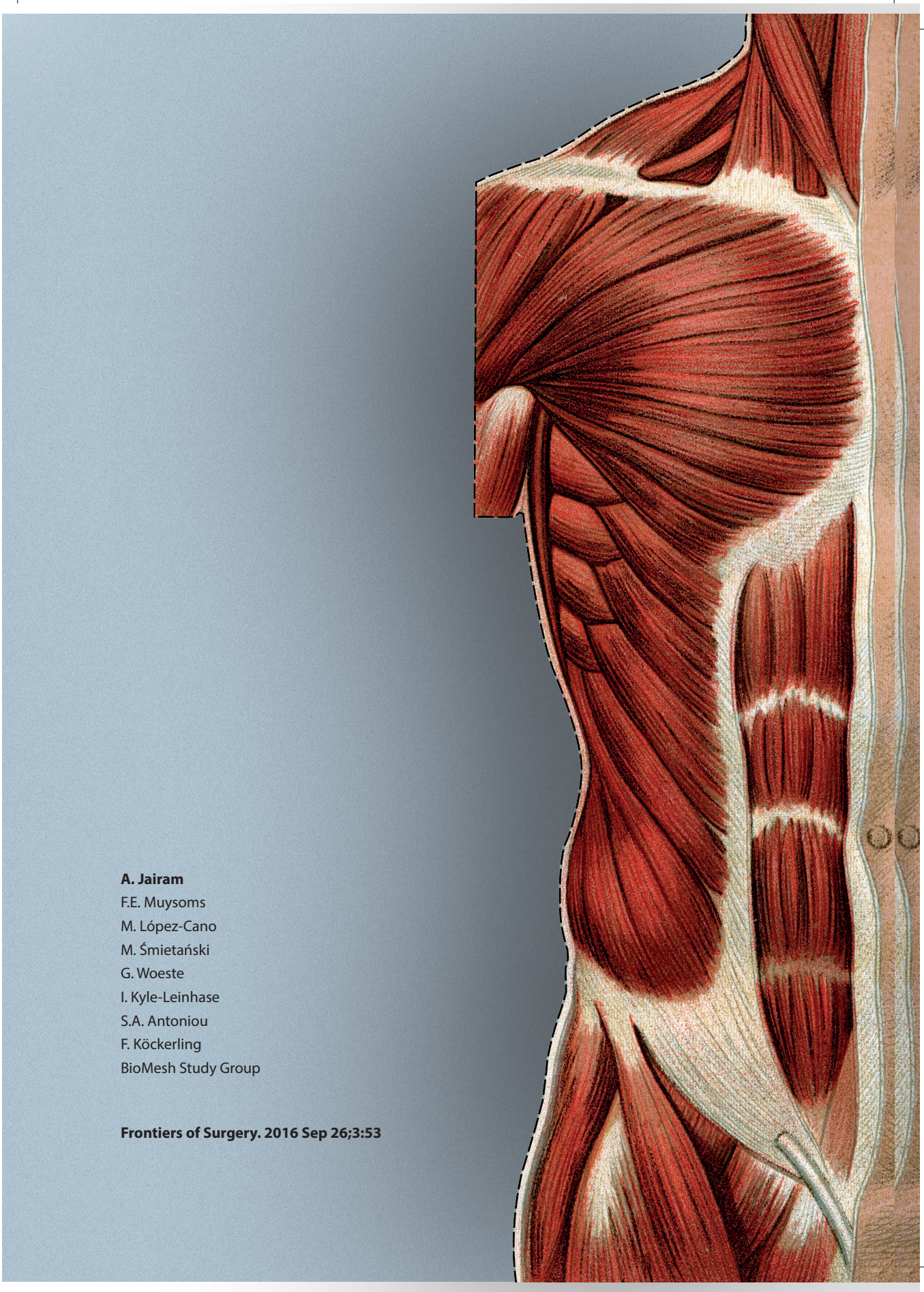

A. Jairam
F.E. Muysoms
M. López-Cano
M. Śmietański
G. Woeste
I. Kyle-Leinhase
S.A. Antoniou
F. Köckerling
BioMesh Study Group

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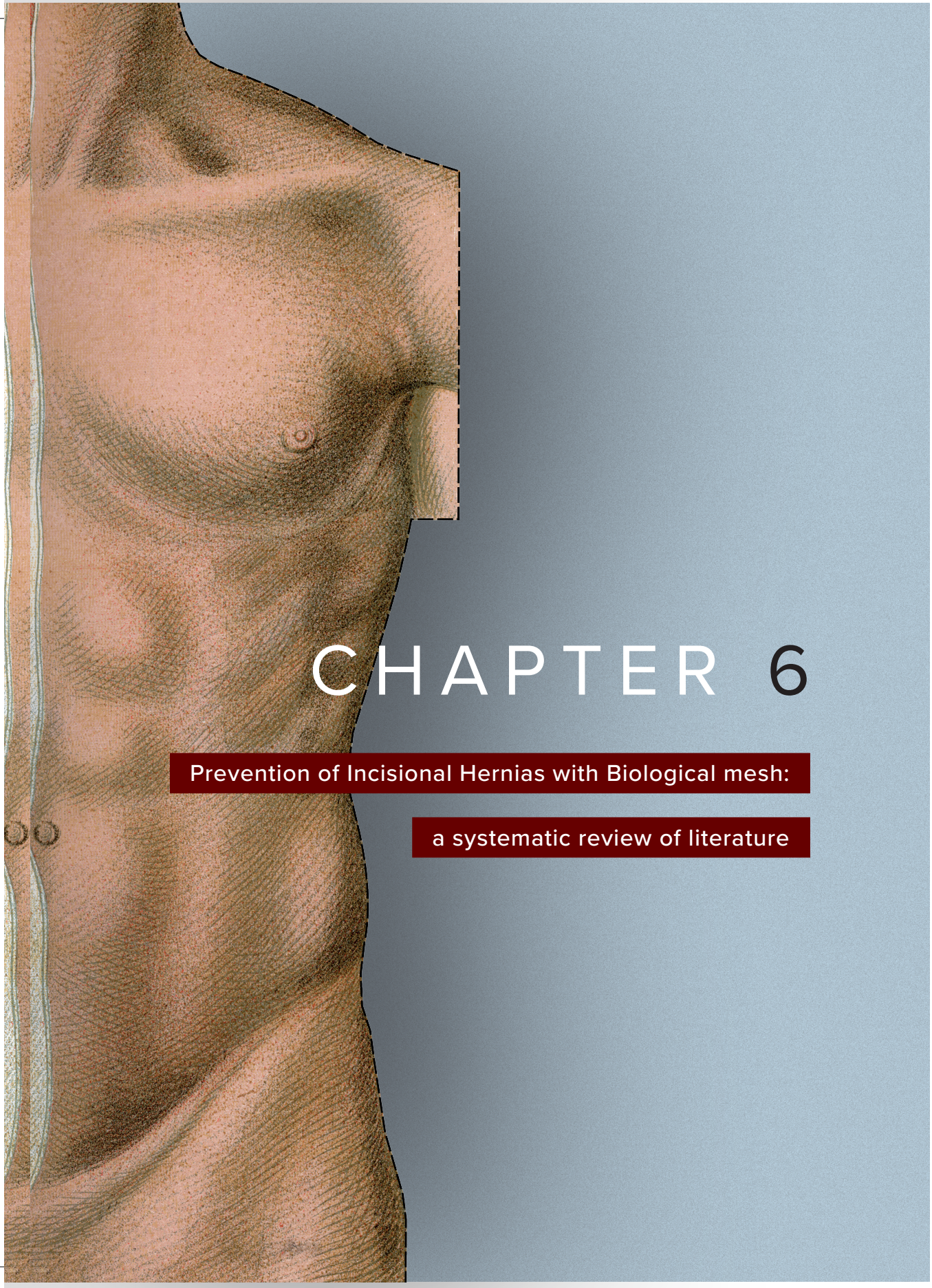


CHAPTER 6

Prevention of Incisional Hernias with Biological mesh:

a systematic review of literature

ABSTRACT

Background: Prophylactic mesh augmented reinforcement (MAR) during closure of abdominal wall incisions has been proposed in patients with increased risk for development of incisional hernias (IHs). As part of the BioMesh consensus project a systematic literature review has been performed to detect those studies where MAR was performed with a non-permanent absorbable mesh (biological or biosynthetic).

Methods: A computerized search was performed within 12 databases (Embase, Medline, Web-of-Science, Scopus, Cochrane, Cinahl, Pubmed publisher, Lilacs, Scielo, ScienceDirect, ProQuest, Google scholar) with appropriate search terms. Qualitative evaluation was performed using the MINORS score for cohort studies and the JADAD score for randomized clinical trials (RCTs).

Results: For midline laparotomy incisions and stoma reversal wounds, two RCTs, two case control studies and two case series were identified. The studies were very heterogeneous in terms of mesh configuration (cross linked *versus* non-cross linked), mesh position (intraperitoneal *versus* retro-muscular *versus* onlay), surgical indication (gastric bypass *versus* aortic aneurysm), outcome results (effective *versus* non effective). After qualitative assessment, we have to conclude that the level of evidence on the efficacy and safety of biological meshes for prevention of IHs is *very low*. No comparative studies were found comparing biological mesh with synthetic non-absorbable meshes for the prevention of IHs.

Conclusion: There is no evidence supporting the use of non-permanent absorbable mesh (biological or biosynthetic) for prevention of IHs when closing a laparotomy in high-risk patients or in stoma reversal wounds. There is no evidence that a non-permanent absorbable mesh should be preferred to synthetic non-absorbable mesh, both in clean or clean-contaminated surgery.

INTRODUCTION

Prophylactic mesh-augmented reinforcement during closure of abdominal wall incisions has been proposed in patients with increased risk for development of incisional hernias (IH). Several randomized clinical trials (RCTs) have been published on the use of prophylactic mesh in patients undergoing aortic aneurysm surgery (1-4), obesity surgery (3,5-7), stoma creation (8-14), in colorectal cancer patients (15-16) or other high-risk patients (17-18). The recently published guidelines of the European Hernia Society have provided the following *weak* recommendation: *"Prophylactic mesh augmentation for an elective midline laparotomy in high-risk patients in order to reduce the risk of incisional hernias is suggested."* Due to the lack of sufficient data, no recommendations on the type of mesh, the optimal mesh position or the optimal mesh fixation technique could be made (19). Although prophylactic mesh-augmented reinforcement has been performed safely in clean-contaminated setting, one concern is the potential short- or long-term harm by implantation of a permanent mesh (20). Application of a non-permanent absorbable for prophylactic mesh-augmented reinforcement might therefore hold some benefit if these meshes will be as effective as permanent meshes.

A systematic literature review has been performed to detect those studies where prophylactic mesh-augmented reinforcement was performed with a non-permanent absorbable biological or biosynthetic mesh and provide guidance for future research on the use of biological or biosynthetic meshes.

METHODS

Protocol

The systematic search was part of the BioMesh consensus project. This project, initiated by Ferdinand Köckerling, gathered surgical expertise in a working group to provide a summary on the use of non-permanent absorbable biological or biosynthetic meshes in different indications. During a consensus meeting in Berlin on January 27, 2016, the working group decided in consensus on the statements and conclusions derived from the level of evidence for each indication. This manuscript reports on the review of the use of non-permanent absorbable biological or biosynthetic meshes for the prevention of IHs.

Eligibility criteria

Inclusion criteria: because of the paucity of available studies on prophylactic mesh-augmented reinforcement with biological or biosynthetic mesh for the prevention of IHs, no limitation to the study design, length of follow-up, or number of included patients was used.

Exclusion criteria: prevention of parastomal hernias were excluded because this was part of a separate search within the BioMesh study group (21).

Information sources

A computerized search was performed within 12 databases (Embase, Medline, Web-of-Science, Scopus, Cochrane, Cinahl, Pubmed publisher, Lilacs, Scielo, ScienceDirect, ProQuest, Google scholar) on June 25, 2015.

Search

The biomedical librarian of the Erasmus University Medical Centre, Rotterdam, The Netherlands, performed the search and the search strategy is provided in Section 'Addendum 1' in Appendix.

Study selection

From the search, only the studies reporting on the use of a non-permanent absorbable biological or biosynthetic mesh were retained. Studies written in English, Dutch, French and Spanish were considered.

Data collection process

Two authors (Filip Etienne Muysoms and An Jairam) independently screened all records retrieved upon application of the search strategy by title and abstract. The full text of all retained records was screened for eligibility. The references of all review articles found were cross-checked for additional eligible records.

Data items

The following data were extracted by two authors independently and cross-checked: type of study, number of patients included patient characteristics, indication for surgery, type of biological mesh, position of the mesh, method of mesh fixation, length of follow-up and outcome measures (hernias, seroma, wound infections, burst abdomen). Primary outcome was IH incidence, and secondary outcomes were postoperative seroma, wound infection, and burst abdomen.

Quality assessment of individual studies

Qualitative evaluation was performed using the MINORS score for non-randomized studies and the JADAD score for RCTs. Additionally, the quality of evidence across the RCTs was done using the GRADE Pro software.

Statistical Analysis

A meta-analysis of the outcome from the RCTs detected was performed for relevant outcomes: IH, seroma, wound infections and burst abdomen. Meta-analysis was performed using the Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2013). Our outcomes were expressed as risk ratios (RRs) with 95% confidence intervals (CIs) to estimate the pooled effect size and p-value. All tests were two-sided.

RESULTS

Study selection

The PRISMA flow diagram of our search is illustrated in Figure 1. Six studies were retained after the screening and sift for eligibility. Four studies included patients with *midline laparotomy* (2,7,22,23) and two studies investigated the prevention of incisional hernias after *stoma reversal* (24,25).

Study characteristics

Midline laparotomy

Our literature review revealed four studies where a biological mesh was used to prevent IHs in high-risk patients. Details of the study characteristics and quality assessment (MINORS score, Jadad score) are shown in the summary of evidence table (Table 1). A small cohort study on eight patients that underwent a midline laparotomy for cyto-reductive surgery and hyperthermic intra-peritoneal chemotherapy (HIPEC) described short-term outcome, using an intra-peritoneal biological mesh (22). In a prospective non-randomized case-control study, obese patients operated for a gastric bypass through a midline laparotomy were either treated with an intra-peritoneal biological mesh (n=59) or primary suture closure (n=75). A significant reduction in the number of IHs by prophylactic mesh was reported (2.3% (90%CI: 2.31-6.86) versus 17.7% (90%CI: 7.92-27.52), p=0.014) (25). In a RCT in obese patients undergoing a gastric bypass operation through a midline laparotomy, patients were randomized between an intraperitoneal biological mesh (n=185) and primary suture closure (n=195).

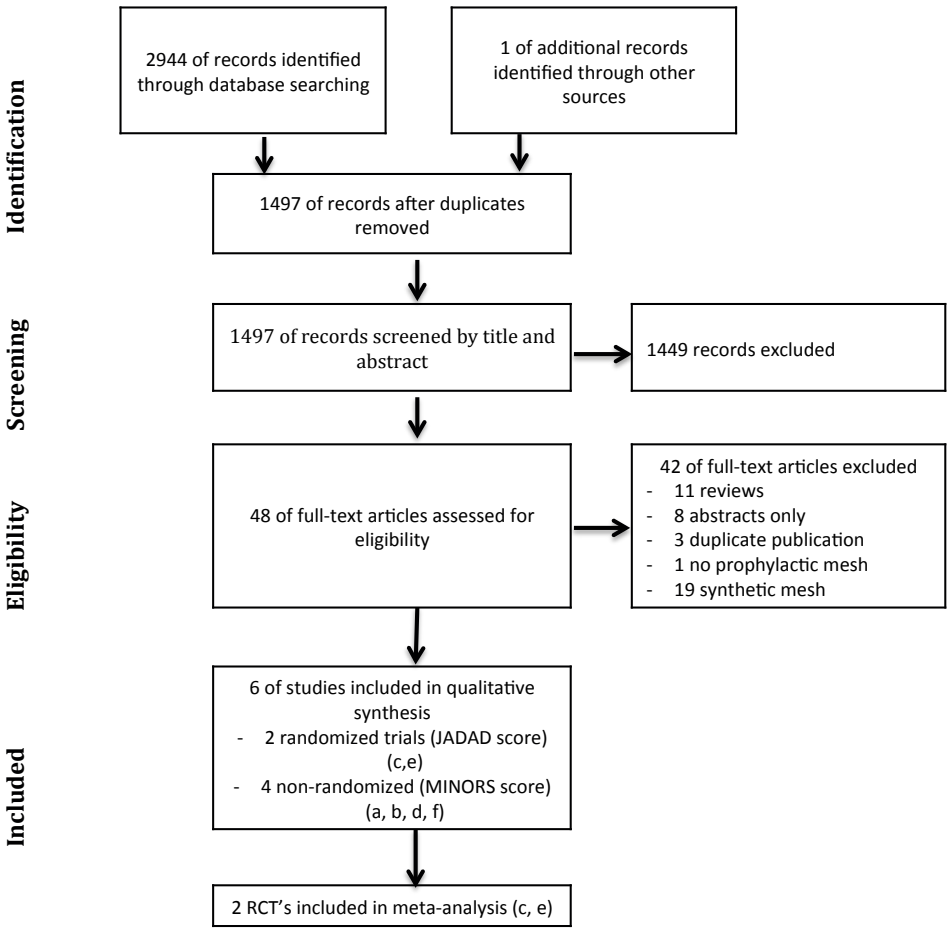


Figure 1. PRISMA flow diagram of a systematic review on the use of biological mesh for prevention of incisional hernias.

References: [a] Boutros 2010, [b] Llaguna 2011, [c] Sarr 2014, [d] Bhangu 2014, [e] Bali 2015, [f] Maggiore 2015.

Table 1. Summary of Evidence table of a systematic review on the use of biological mesh for prevention of incisional hernias after midline laparotomy

Bibliographic citation [reference]	Study type	Quality assessment	N (Mesh/ No mesh)	Patient characteristics	Intervention	Comparison	Length of follow-up (months)	Outcome measure
Boutros 2010 World J Surg Oncol 8:72	Non comparative case series	MINORS score 5/16	8 / -	Midline laparotomy for cytoreductive surgery and HIPEC in peritoneal carcinoma patients.	Intra-peritoneal Surgisis 20x20cm fixed with PDS sutures	-	mean 6.3	7 patients had no abdominal wall morbidity. 1 patient had an incisional hernia and entero-cutaneous fistula following re-laparotomy 2 weeks after the primary operation
General comments: Very low MINORS score of this case series. Follow up inadequate to make conclusion about incisional hernia rate. **Funding:** no direct funding; speakers fee from Cook. **Study registration**: no								
Llaguna 2011 World J Surg 35: 1651-1655	Prospective case control study	MINORS score 19/24	134 (59/75)	Patients undergoing gastric bypass surgery with midline laparotomy	Intra-peritoneal Alloderm 16 cm long and 6 cm wide, fixed with PDS sutures	Sutured with PDS no 1, running suture	mean 17.3	Incisional hernia mesh: 1/44 (2%) no mesh: 11/62 (18%) *P*= 0.014 (OR 0.06)
General comments: Prospective single surgeon non-randomized study, with adequate follow-up. Statistical significant differences on the number of patients with some confounding factors were seen: prior abdominal surgery, postoperative BMI. **Funding:** not mentioned. **Study registration**: no								
Sarr 2014 Surgery 156: 902-909	RCT	JADAD score 2/5	402 (185/ 195)	Patients undergoing gastric bypass surgery with midline laparotomy	Intra-peritoneal Surgisis 8cm wide fixed with PDS sutures	Suture non absorbable and absorbable, running suture	24	Incisional hernia mesh: 32/185 (17.3%) no mesh: 38/195 (19.5%) *P*= 0.60 Wound infections: 11.9% vs 3.6% (p<0.003) Wound seroma: 4.9% vs 0.5% (p<0.01)
General comments: Open label RCT with adequate sample calculation and power. Showed no difference in incisional hernia rate. The number of clinically relevant wound infections and wound seroma was significant higher in the Mesh group. **Funding:** Industry-funded study (Cook Biotech, Inc, West Lafayette, IN, USA). **Study registration**: www.ClinicalTrials.gov NCT00274625								
Bali 2015 Hernia 19: 267-271	RCT	JADAD score 1/5	40 (20/20)	Elective midline laparotomy for AAA repair	Onlay Periguard 8 cm wide fixed with non-absorable sutures	Sutured with PDS no 1, running suture	36	Incisional hernia mesh: 0/20 (0%) no mesh: 6/20 (32%) Estimate freedom of incisional hernia was significantly higher for the mesh group (*p*<0.008)
General comments: Small open label RCT, no sample size calculation. Prophylactic mesh was effective and safe. **Funding:** not mentioned. **Study registration**: no								

This adequately powered RCT, did not show any benefit for prophylactic mesh concerning the risk for IH at 24 months (17.3% versus 19.5%, *p*=0.60), but did show a significant higher number of wound infections and wound seroma in the mesh group (7). In a RCT of aortic aneurysm patients, midline laparotomy closure with an onlay biologic mesh (n=20) was compared to primary suture closure (n=20). The study was not powered with a sample size calculation, but the follow up was adequate in length (36 months) and methodology (systematic CT scan evaluation). A highly significant protective effect of the mesh was shown, with no hernias in the mesh group and 32% in the non-mesh group (cumulative freedom of incisional hernia at 36 months was 100% versus 74.4%, *p*<0.008) (2).

Stoma reversal wound

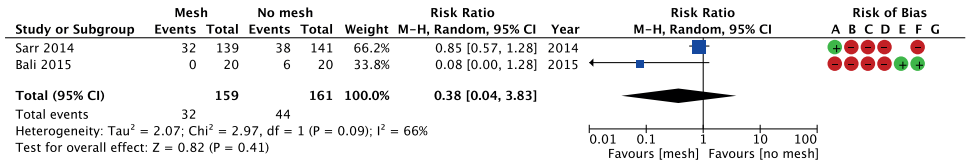
Our literature review revealed two studies in which a biological mesh was used to prevent incisional hernias after reversal of a temporary ileostomy. Details of the studies are shown in the summary of evidence table (Table 2). In a pilot study with a limited patient population (n=7) the feasibility of an intraperitoneal prophylactic mesh was investigated in terms of safety in the short term (27). The second report was a matched case-control study of 30 patients that received a retro-muscular prophylactic biological mesh, compared to 64 matched patients with suture closure of the stoma wound. At 1-year follow-up with CT scan, the number of patients with IH was significantly lower for the mesh group (*p* = 0.043) (25).

Meta-analysis

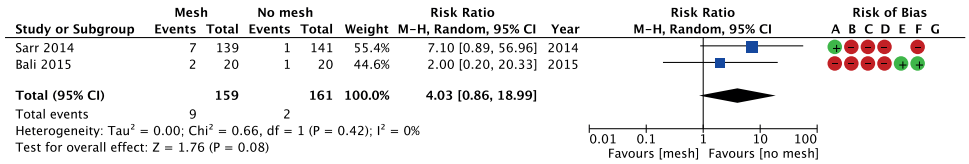
The pooled analysis for the outcome IH showed no statistical differences between groups (RR 0.38, 95%CI 0.04-3.83; p=0.41). The forest plots of the meta-analysis of the two RCTs on prevention of midline laparotomy IHs and the secondary outcomes are shown in Figure 2.

Table 2. Summary of Evidence table of a systematic review on the use of biological mesh for prevention of incisional hernias after stoma reversal.

Bibliographic citation [reference]	Study type	Quality assessment	N (Mesh/ No mesh)	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measure
Bhangu 2014 Tech Coloproctol 18:305-308	Non comparative case series	MINORS score 4/16	7 / -	Patients with a temporary ileostomy needing stoma closure.	Intra-peritoneal Strattice 3cm overlap fixed with PDS sutures	-	30 days	One superficial wound infection. No early hernias.
General comments: Very low MINORS score of this case series. Follow up inadequate to make conclusion about incisional hernia rate. This study is a pilot study on the safety of the technique, before starting a large RCT. **Funding:** Industry funded study. **Study registration**: part of the ROCCS study: ClinicalTrials.gov NCT02238964								
Maggiori 2015 Surgery 158:1651-1657	Matched case control study	MINORS score 15/ 24	94 (30/64)	Closure of a diverting ileostomy following rectal cancer resection.	Retro-muscular Meccellis mesh 10x10 cm , fixed with Prolene sutures	2 layer continuous suture of anterior and posterior fascia with Vicryl 1	1 year	Radiological incisional hernia rate mesh: 1/30 (3%) no mesh: 12/64 (19%) *P*= 0.043
General comments: Significant reduction of the number of incisional hernias at the stoma wound diagnosed with CT scan. No difference in morbidity. **Funding:** Industry funded study. **Study registration**: no								



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias



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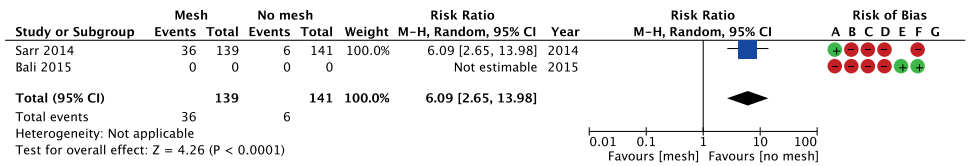

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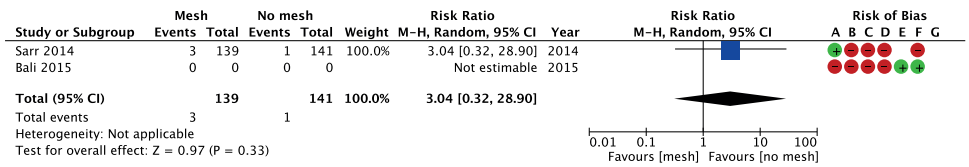

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Figure 2. Forest plots and Risk of bias assessment of randomized studies on the prevention of incisional hernias by biological mesh reinforcement.
a) Incisional hernia
b) Seroma
c) Wound infection
d) Burst abdomen

DISCUSSION

Midline laparotomy

Overall, the *Level of Evidence* on the efficacy of biological mesh to prevent IHs is *very low*. Moreover, the study with the highest level of evidence and lowest risk of bias, did not show any advantage in reducing IHs by prophylactic intraperitoneal biological mesh in patients undergoing a midline laparotomy for performing gastric bypass surgery (7). On the contrary, it did show a higher number of wound complications after the use of the prophylactic mesh. Another study regarding gastric bypass patients did show a benefit, but this study was non-randomized and had a high risk of bias (25).

For aortic aneurysm patients, only one RCT is available, which showed a high efficacy with 3 years follow-up. However, this study was poorly powered, non-blinded, and scored low in the Jadad scale (2). Moreover, no information on sources of funding and protocol registration was provided, and therefore, the risk of bias cannot be assessed.

The currently available evidence is not strong enough to make any statements regarding the optimal mesh position (intra-peritoneal, retro-muscular or onlay) in case a prophylactic biological mesh is used. Also the different meshes used in the studies (non cross-linked human origin; non cross-linked porcine small intestinal submucosa; cross-linked bovine pericardium) might have an important impact on the outcome.

On the contrary, the Level of Evidence on the efficacy of prophylactic synthetic non-absorbable mesh (all polypropylene) in high-risk patients currently is high, with 8 published RCTs encompassing 727 patients with a follow-up of at least 12 months (1,4-6,15-18). Moreover the safety of prophylactic retro-muscular or onlay meshes in clean or clean contaminated surgery, is shown in 9 published RCTs encompassing 1207 patients (1,3-6,15-18).

No comparative studies were found comparing biological mesh with synthetic non-absorbable meshes for the prevention of incisional hernias. There is a study on-going at the Vall d'Hebron Hospital, Universidad Autónoma de Barcelona on prevention of incisional hernias from midline laparotomies using an absorbable synthetic mesh (Bio-A, WL Gore & Ass, US), PREBIOUS trial (ClinicalTrials.gov NCT02208557).

4.2. Stoma reversal wound

Overall the *Level of Evidence* on the efficacy of biological mesh to prevent incisional hernias of stoma reversal wounds is *very low*. Currently, the only study providing evidence is a matched case-control study, showing a lower incisional hernia rate at 1-year. This study is a pilot study for an RCT that is planned in France, the MEMBO trial (ClinicalTrials.gov NCT02576184) (27). The small pilot study by Banghu et al. is part of a large project, the ROCSS study, which is a properly powered multi-centre RCT from the University of Birmingham (ClinicalTrials.gov NCT02238964 & controlled-trials.com ISRCTN46330337) (26). This study compares the technique described in the pilot study with sutured closure of the stoma wound and has now included 790 patients and the follow-up is ongoing. Furthermore, a study from the Vall d'Hebron Hospital (Universidad Autónoma de Barcelona), ILEOCLOSE study, (ClinicalTrials.gov NCT02226887) will investigate in a RCT the application of prophylactic mesh reinforcement of closure of temporary diverting ileostomy with an absorbable synthetic mesh (Bio A) in 120 patients.

4.3. CONCLUSIONS

So far, there is no solid evidence on the effectiveness of prophylactic non-permanent absorbable biological or biosynthetic mesh for closure of midline laparotomies or reinforcement of a stoma reversal site . There is no evidence that in this setting a non-permanent absorbable biological or biosynthetic mesh should be preferred to synthetic non-absorbable mesh, both in clean or clean-contaminated surgery.

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Publication statement

This manuscript was written in accordance with the PRISMA statement: The Prisma statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: guidelines for reporting parallel group randomized trials. (www.prisma-statement.org)

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ADDENDUM

Search strategy used for a systematic literature review on prevention of incisional hernias with mesh. A computerized search was performed within 12 databases (Embase, Medline, Web-of-Science, Scopus, Cochrane, Cinahl, Pubmed publisher, Lilacs, Scielo, ScienceDirect, ProQuest, Google scholar) on June 25th 2015.

Embase.com *839*

('surgical mesh'/exp OR (mesh* OR 4DDOME OR AIGISRx OR AlloDerm OR AlloMax OR 'Bard Composix EX' OR 'BIO-A Tissue Reinforcement prosthesis' OR CollaMend OR DermaMatrix OR DualMesh OR 'Evolution P3EM' OR FasLata OR FlexHD OR FortaGen OR 'IntePro Lite' OR InteXen OR NEOVEIL OR 'Parietex composite' OR Pelvicol OR Pelvisoft OR Pelvitex OR PerFix OR 'Peri-Strips Dry' OR PeriGuard OR Permacol OR Physiomesh OR SeamGuard OR Strattice OR Surgisis OR 'TiLoop Bra' OR Timesh OR Tutomesh OR Tutopatch OR Ultrapro OR Ventralex OR Veritas OR Vivosorb OR Vypro OR X-Repair OR XenMatrix):ab,ti) AND (prevention/exp OR prevention:lnk OR (prevent* OR protect* OR prophyla*):ab,ti) AND ('incisional hernia'/exp OR 'abdominal wall hernia'/de OR 'abdominal wall defect'/de OR 'abdominal surgery'/de OR 'abdominal wall closure'/de OR laparotomy/exp OR 'abdominal wall'/de OR (((incision* OR cicatri* OR scar* OR ventral*) NEAR/3 (herni*)) OR ((abdominal* OR transabdominal*) NEAR/3 (surger* OR clos* OR defect* OR wall*)) OR laparotom* OR (midline NEAR/3 incision*)):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline (ovid) *490*

("surgical mesh"/ OR (mesh* OR 4DDOME OR AIGISRx OR AlloDerm OR AlloMax OR "Bard Composix EX" OR "BIO-A Tissue Reinforcement prosthesis" OR CollaMend OR DermaMatrix OR DualMesh OR "Evolution P3EM" OR FasLata OR FlexHD OR FortaGen OR "IntePro Lite" OR InteXen OR NEOVEIL OR "Parietex composite" OR Pelvicol OR Pelvisoft OR Pelvitex OR PerFix OR "Peri-Strips Dry" OR PeriGuard OR Permacol OR Physiomesh OR SeamGuard OR Strattice OR Surgisis OR "TiLoop Bra" OR Timesh OR Tutomesh OR Tutopatch OR Ultrapro OR Ventralex OR Veritas OR Vivosorb OR Vypro OR X-Repair OR XenMatrix).ab,ti.) AND ("Primary Prevention"/ OR "prevention and control".xs. OR (prevent* OR protect* OR prophyla*).ab,ti.) AND ("Hernia, Ventral"/ OR "Hernia, Abdominal"/ OR abdomen/su OR laparotomy/ OR "abdominal wall"/ OR (((incision* OR cicatri* OR scar* OR ventral*) ADJ3 (herni*)) OR ((abdominal* OR transabdominal*) ADJ3 (surger* OR clos* OR defect* OR wall*)) OR laparotom* OR (midline ADJ3 incision*)).ab,ti.) NOT (exp animals/ NOT humans/)

Cochrane *30*

((mesh* OR 4DDOME OR AIGISRx OR AlloDerm OR AlloMax OR 'Bard Composix EX' OR 'BIO-A Tissue Reinforcement prosthesis' OR CollaMend OR DermaMatrix OR DualMesh OR 'Evolution P3EM' OR FasLata OR FlexHD OR FortaGen OR 'IntePro Lite' OR InteXen OR NEOVEIL OR 'Parietex composite' OR Pelvicol OR Pelvisoft OR Pelvitex OR PerFix OR 'Peri-Strips Dry' OR PeriGuard OR Permacol OR Physiomesh OR SeamGuard OR Strattice OR Surgisis OR 'TiLoop Bra' OR Timesh OR Tutomesh OR Tutopatch OR Ultrapro OR Ventralex OR Veritas OR Vivosorb OR Vypro OR X-Repair OR XenMatrix):ab,ti) AND ((prevent* OR protect* OR prophyla*):ab,ti) AND ((((incision* OR cicatri* OR scar* OR ventral*) NEAR/3 (herni*)) OR ((abdominal* OR transabdominal*) NEAR/3 (surger* OR clos* OR defect* OR wall*)) OR laparotom* OR (midline NEAR/3 incision*)):ab,ti)

Web-of-science *474*

TS=(((mesh* OR 4DDOME OR AIGISRx OR AlloDerm OR AlloMax OR "Bard Composix EX" OR "BIO-A Tissue Reinforcement prosthesis" OR CollaMend OR DermaMatrix OR DualMesh OR "Evolution P3EM" OR FasLata OR FlexHD OR FortaGen OR "IntePro Lite" OR InteXen OR NEOVEIL OR "Parietex composite" OR Pelvicol OR Pelvisoft OR Pelvitex OR PerFix OR "Peri-Strips Dry" OR PeriGuard OR Permacol OR Physiomesh OR SeamGuard OR Strattice OR Surgisis OR "TiLoop Bra" OR Timesh OR Tutomesh OR Tutopatch OR Ultrapro OR Ventralex OR Veritas OR Vivosorb OR Vypro OR X-Repair OR XenMatrix)) AND ((prevent* OR protect* OR prophyla*)) AND ((((incision* OR cicatri* OR scar* OR ventral*) NEAR/3 (herni*)) OR ((abdominal* OR transabdominal*) NEAR/3 (surger* OR clos* OR defect* OR wall*)) OR laparotom* OR (midline NEAR/3 incision*))) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR rabbit* OR rodent* OR pig OR sus OR swine* OR porcine OR monkey* OR dog OR sheep OR ovine) NOT (human* OR patient*)))

Scopus *697*

TITLE-ABS-KEY(((mesh* OR 4DDOME OR AIGISRx OR AlloDerm OR AlloMax OR "Bard Composix EX" OR "BIO-A Tissue Reinforcement prosthesis" OR CollaMend OR DermaMatrix OR DualMesh OR "Evolution P3EM" OR FasLata OR FlexHD OR FortaGen OR "IntePro Lite" OR InteXen OR NEOVEIL OR "Parietex composite" OR Pelvicol OR Pelvisoft OR Pelvitex OR PerFix OR "Peri-Strips Dry" OR PeriGuard OR Permacol OR Physiomesh OR SeamGuard OR Strattice OR Surgisis OR "TiLoop Bra" OR Timesh OR Tutomesh OR Tutopatch OR Ultrapro OR Ventralex OR Veritas OR Vivosorb OR Vypro OR X-Repair OR XenMatrix))

AND ((prevent* OR protect* OR prophyla*)) AND ((((incision* OR cicatri* OR scar* OR ventral*) W/3 (herni*)) OR ((abdominal* OR transabdominal*) W/3 (surger* OR clos* OR defect* OR wall*)) OR laparotom* OR (midline W/3 incision*))) AND NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR rabbit* OR rodent* OR pig OR sus OR swine* OR porcine OR monkey* OR dog OR sheep OR ovine) AND NOT (human* OR patient*)))

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(MH "surgical mesh+" OR (mesh* OR 4DDOME OR AIGISRx OR AlloDerm OR AlloMax OR "Bard Composix EX" OR "BIO-A Tissue Reinforcement prosthesis" OR CollaMend OR DermaMatrix OR DualMesh OR "Evolution P3EM" OR FasLata OR FlexHD OR FortaGen OR "IntePro Lite" OR InteXen OR NEOVEIL OR "Parietex composite" OR Pelvicol OR Pelvisoft OR Pelvitex OR PerFix OR "Peri-Strips Dry" OR PeriGuard OR Permacol OR Physiomesh OR SeamGuard OR Strattice OR Surgisis OR "TiLoop Bra" OR Timesh OR Tutomesh OR Tutopatch OR Ultrapro OR Ventralex OR Veritas OR Vivosorb OR Vypro OR X-Repair OR XenMatrix)) AND (MH "Preventive Health Care" OR MW prevention OR (prevent* OR protect* OR prophyla*)) AND (MH "Hernia, Abdominal" OR MH abdomen/su OR MH laparotomy OR (((incision* OR cicatri* OR scar* OR ventral*) N3 (herni*)) OR ((abdominal* OR transabdominal*) N3 (surger* OR clos* OR defect* OR wall*)) OR laparotom* OR (midline N3 incision*))) NOT (MH animals+ NOT humans+)

Pubmed publisher *14*

("surgical mesh"[mh] OR (mesh*[tiab] OR 4DDOME OR AIGISRx OR AlloDerm OR AlloMax OR "Bard Composix EX" OR "BIO-A Tissue Reinforcement prosthesis" OR CollaMend OR DermaMatrix OR DualMesh OR "Evolution P3EM" OR FasLata OR FlexHD OR FortaGen OR "IntePro Lite" OR InteXen OR NEOVEIL OR "Parietex composite" OR Pelvicol OR Pelvisoft OR Pelvitex OR PerFix OR "Peri-Strips Dry" OR PeriGuard OR Permacol OR Physiomesh OR SeamGuard OR Strattice OR Surgisis OR "TiLoop Bra" OR Timesh OR Tutomesh OR Tutopatch OR Ultrapro OR Ventralex OR Veritas OR Vivosorb OR Vypro OR X-Repair OR XenMatrix)) AND ("Primary Prevention"[mh] OR "prevention and control"[sh] OR (prevent*[tiab] OR protect*[tiab] OR prophyla*[tiab])) AND ("Hernia, Ventral"[mh] OR "Hernia, Abdominal"[mh] OR abdomen/su[mh] OR laparotomy[mh] OR "abdominal wall"[mh] OR (((incision*[tiab] OR cicatri*[tiab] OR scar*[tiab] OR ventral*[tiab]) AND (herni*[tiab])) OR ((abdominal*[tiab] OR transabdominal*[tiab]) AND (surger*[tiab] OR clos*[tiab] OR defect*[tiab] OR wall*[tiab])) OR laparotom*[tiab] OR (midline AND incision*[tiab]))) NOT (animals[mh] NOT humans[mh]) AND publisher[sb]

Google scholar

Mesh|meshes prevention|preventive|protective|protection|prophylactic|prophylaxis "incisional|cicatrical|scar|ventral hernia "|"abdominal|transabdominal surgery|closure|defect|wall"|laparotomy|"midline incision" -animal -animals -rats -mice

Lilacs *18*

Scielo *8*

(Mesh*) AND (prevent* OR protect* OR prophyla*) AND ("incisional hernia" OR "cicatrical hernia" OR "scar hernia" OR " ventral hernia" OR "abdominal hernia" OR "abdominal surgery" OR "abdominal closure" OR "abdominal defect" OR "abdominal wall" OR laparotom* OR "midline incision")

ScienceDirect *92*

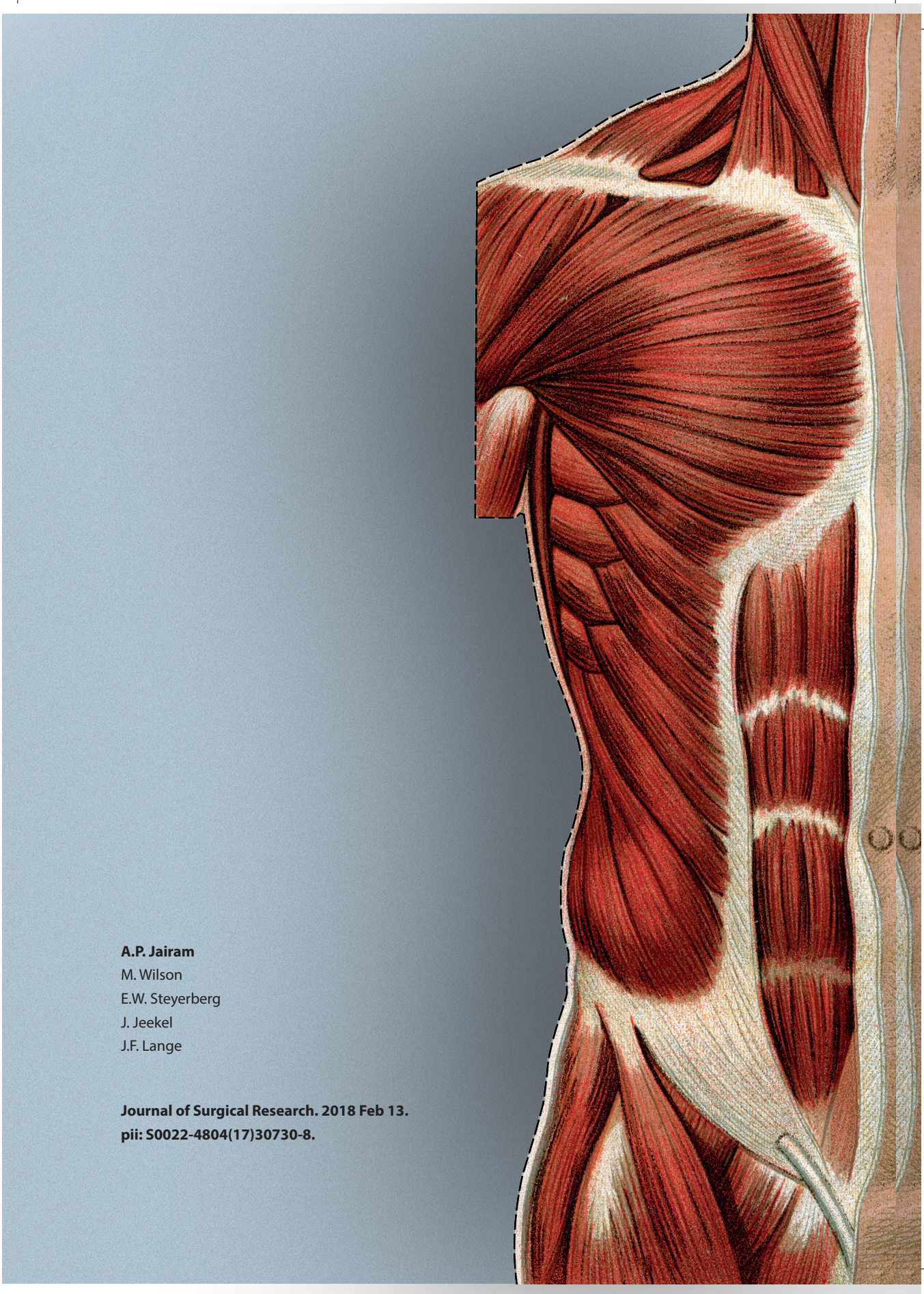
(Mesh*) AND (prevent* OR protect* OR prophyla*) AND ("incisional hernia" OR "cicatrical hernia" OR "scar hernia" OR " ventral hernia" OR "abdominal hernia" OR "abdominal surgery" OR "abdominal closure" OR "abdominal defect" OR "abdominal wall" OR laparotom* OR "midline incision") AND TOPIC (incisional hernia)

ProQuest *9*

(ti(Mesh*) OR ab(Mesh*)) AND (ti(prevent* OR protect* OR prophyla*) OR ab(prevent* OR protect* OR prophyla*)) AND (ti("incisional hernia" OR "cicatrical hernia" OR "scar hernia" OR " ventral hernia" OR "abdominal hernia" OR "abdominal surgery" OR "abdominal closure" OR "abdominal defect" OR "abdominal wall" OR laparotom* OR "midline incision") OR ab("incisional hernia" OR "cicatrical hernia" OR "scar hernia" OR " ventral hernia" OR "abdominal hernia" OR "abdominal surgery" OR "abdominal closure" OR "abdominal defect" OR "abdominal wall" OR laparotom* OR "midline incision"))

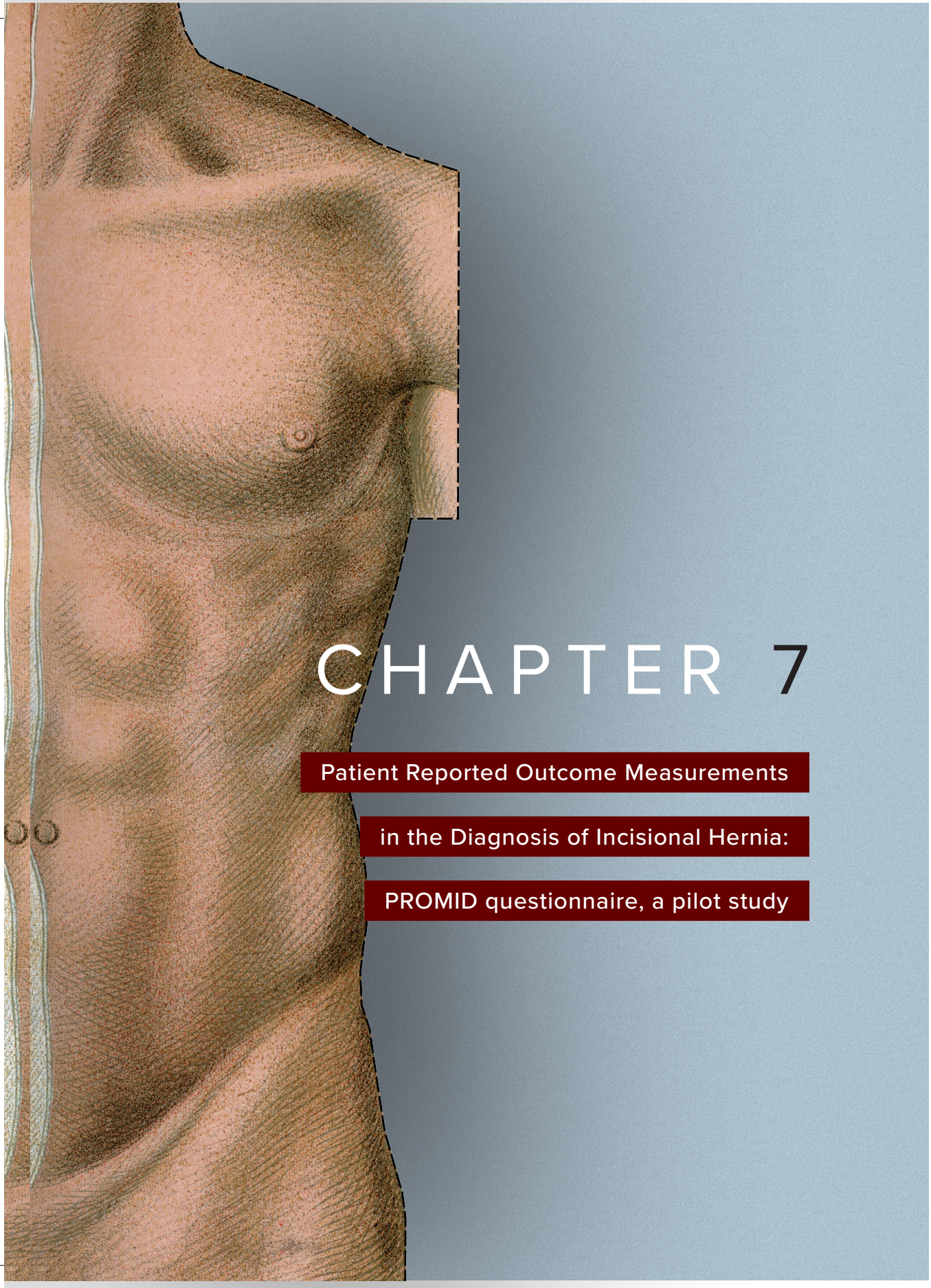
PART 2

New Tools, Techniques and Meshes in Ventral Hernia Surgery



A.P. Jairam
M. Wilson
E.W. Steyerberg
J. Jeekel
J.F. Lange

Journal of Surgical Research. 2018 Feb 13.
pii: S0022-4804(17)30730-8.



CHAPTER 7

Patient Reported Outcome Measurements in the Diagnosis of Incisional Hernia: PROMID questionnaire, a pilot study

ABSTRACT

Background: Incisional hernia (IH) is the most frequent complication after abdominal surgery. Long-term follow up is crucial. Patient reported outcome measurements (PROMS) are able to monitor patients' disease progression after treatment. Until now, there are no PROMS that assess patients after abdominal surgery or that detects patients with IH. We aimed to develop a reliable questionnaire to assist in diagnosing IH, called the 'PROMID questionnaire': Patient Reported Outcome Measurements in the Diagnosis of Incisional Hernias. In this pilot study, the reliability of this questionnaire is being determined.

Methods: Patients diagnosed with IH between 2013 and 2014 were included. A questionnaire with seven questions was developed. Patients were asked if they thought they had IH, if they felt any pain at the site of the scar and if they saw or felt a lump or a bulge. Furthermore, smoking history and patients' weight and height were taken into account. Patients were approached three times by telephone, with an interval of one week. Test-retest reliability, internal consistency and sensitivity were measured.

Results: 43 patients were included. Test-retest reliability was 1.0, and internal consistency was 0.56. The question regarding patients' pain was least consistent with other questions. The overall sensitivity of the questionnaire was 95%.

Conclusion: The PROMID questionnaire is a highly reliable questionnaire, but the internal consistency is modest. The clinical relevancy of pain in IH patients is essential. Therefore, this question will be kept in the current PROMID questionnaire. It needs further validation in a prospective cohort study, in order to use it as a diagnostic tool in the future to detect IH.

Keywords: incisional hernia, PROMs, quality of healthcare, questionnaire

INTRODUCTION

Incisional hernia (IH) is the most frequent complication after abdominal surgery. The incidence varies from 5% to 20% in the general population and rises up to 39% in high risk patients, such as AAA patients and patients with obesity [1, 2]. Yearly approximately 4000 IH operations are performed in the Netherlands [1]. IH can cause morbidity and mortality, due to obstruction or strangulation of the bowel, with a potential risk of perforation [3]. In addition it might induce back pain by truncal instability and psychological complaints by disturbed cosmesis. Thus, treatment of IH is an essential surgical challenge [4]. According to the literature, approximately 80 – 95% of all incisional hernias occur within three years after initial surgery [5]. Long-term follow up is therefore crucial in providing high quality care after abdominal surgery. However, the method of follow up remains a challenge. Long-term follow up with physical examination and imaging is time consuming and costly and demands devotion and dedication of patients and doctors [6]. Furthermore, not all patients will show up if they do not have any symptoms [6]. Other methods like postal questionnaires and telephone interviews, have been proposed as a method of follow up, but there is very little high-quality evidence on their reliability [6].

For several years now, a tool has developed to collect preoperative and postoperative data of patients' own assessment of their health-related quality of life regarding healthcare procedures. These so called 'Patient Reported Outcome Measurements (PROMs)' are currently being used in different countries, such as Sweden and the United Kingdom. The intention of PROMs is to screen patients and help in shared decision making. PROMs also intend to improve patient care and patient-doctor communication. Furthermore, PROMs can monitor disease progression, stimulate quality of health care and it can predict overall wellbeing [7-9]. PROMs can help to make subjective findings objective and measurable, like the impact of a treatment on quality of life [7-9]. In the United Kingdom, PROMs are developed for four surgical conditions; one of them is inguinal hernia. At this moment, there is no PROM questionnaire to monitor patients after abdominal surgery, even though IH is a frequently observed (long term) complication.

We aimed to develop a reliable questionnaire to assist in diagnosing IH in patients who have undergone abdominal surgery. This questionnaire could be used during follow up, since not all of these patients are monitored at the outpatient clinic by their doctor after many years. In this pilot study, the reliability of the PROMID questionnaire is being determined.

METHODS

The study was approved by the local ethics committee of the three hospitals that participated in this pilot study. Patients were selected from a database in the three different hospitals: Havenziekenhuis Rotterdam, IJsselland Ziekenhuis and Sint Franciscus Gasthuis. Patients were over 18 years and diagnosed with IH between 2013 and 2014. The diagnosis 'incisional hernia' was a clinical diagnosis, conducted by physical examination. Radiological examination was only performed in case there was any doubt regarding the diagnosis. All patients were either conservatively treated, or they were on the waiting list for surgery. Exclusion criteria were emergency surgery, or an insufficient understanding of the Dutch language.

A telephone questionnaire was developed consisting of seven questions (Table 1). Questions were developed in association with the department of Medical Psychology, who are well experienced in Quality of Life measurements, and formulating questions for these questionnaires. The questions were kept as simple as possible, and are thus applicable to the 'average' patient. The first four questions regarded symptoms that relate to the diagnose IH, and could only be answered with a 'yes' or a 'no'. The last three questions are known risk factors that contribute to the development of IH. Patients were called three times with an interval of one week between the phone calls, and the same questions were asked to measure the test-retest reliability. The questionnaire was taken by telephone by blinded researchers, who did not know what answers patients gave between the intervals. Most patients were aware of the diagnosis made by the surgeon, so they were not blinded. As stated earlier, only seven questions were asked to the patients. In this respect the call did not take much time and varied from 5 to 15 minutes.

Table 1. PROMID questionnaire

1.	Do you think you have an incisional hernia?
2.	Do you currently feel any pain at the site of the scar?
3.	Do you feel bulging or a lump at the site of the scar?
4.	Do you see bulging or a swelling at the site of the scar?
5.	What is your weight?
6.	What is your length?
7.	Do you currently smoke, or have you ever smoked before in your life on a daily base?

Statistical analysis

The aim of this pilot study was to determine the reliability of this questionnaire. This was done by measuring the test-retest reliability, the sensitivity, and the internal consistency. Data were analyzed using SPSS. Statistical analysis was done by using Spearman's rank correlation coefficient. Furthermore, sensitivity was calculated, and internal consistency was measured by Cronbach's alpha.

RESULTS

43 Patients with IH were randomly selected and were phoned between July 2014 and February 2015. The majority of patients was male (60%) and the mean age was 64 years old (SD: ± 14 years). All patients already visited the surgeon at the moment we called them, so they were aware of their diagnose 'incisional hernia'. 70% of patients diagnosed with IH was conservatively treated, and 30% were on the waiting list for an operation.

Patients were called three times with an interval of one week between phone calls. Since all included patients were diagnosed with IH, sensitivities could be calculated for each of the questions and a sum score of the questions. The first question was if patients thought they had IH. 39 Patients answered positively on this question positively, which gives a sensitivity of 91%. The second question regarded patients' pain at the site of the scar. Only 24 patients felt any pain at the site of the scar at the moment they were interviewed, the sensitivity of this question being 56%. The third question referred to whether patients felt a bulge or a lump at the site of the scar. 39 Patients did feel a lump or a bulge, which gives a sensitivity of 91%. The fourth question concerned if patients saw a lump or a bulge at the site of the scar. There were 38 patients who answered this question with a 'yes'. The sensitivity of this question being 88% (Table 2). The overall sensitivity of the questionnaire was 95%. The last three questions concerned risk factors for developing IH. The mean BMI was 29, and half of the patient group (47%) smoked or had ever smoked in the past.

The Pearson test-retest correlation coefficients were 1.0, which implied that patients repeatedly gave exactly the same answers on the questions on all measurement occasions. The internal consistency, measured by Cronbach's alpha, is 0.56. The question that was least consistent with the other questions was the second question; 'Do you currently feel any pain at the site of the scar?' If this question was deleted, Cronbach's alpha rose to 0.74.

The question if a patient feels a bulging or a lump at the site of the scar was most consistent with other questions. When leaving this question out of the questionnaire, the Cronbach's alpha dropped to 0.32.

Table 2. Sensitivity per question

Question		Sensitivity
1.	Do you think you have an incisional hernia?	91%
2.	Do you currently feel any pain at the site of the scar?	56%
3.	Do you feel bulging or a lump at the site of the scar?	91%
4.	Do you see bulging or a lump at the site of the scar?	88%

DISCUSSION

This pilot study reveals that the PROMID questionnaire is a highly reliable questionnaire. However, the internal consistency of the questions, measured by Cronbach's alpha, is only modest, with the question regarding patients' pain being least consistent.

IH is the most common complication after abdominal surgery [3]. Approximately 80% of IH develop in the first three years after abdominal surgery, but not all patients attend the outpatient clinic for that many years after their first operation [5]. However, long-term follow up is essential to monitor patients, in order to diagnose IH in time, and to prevent the morbidity and mortality rate [6]. In the current literature, long-term follow up by means of a questionnaire is not thoroughly investigated. Therefore, this pilot study is relevant. The main purpose of this study was to develop a highly reliable questionnaire. Three questions were based on complaints that patients with IH may experience: feeling pain at the site of the scar, and seeing or feeling a bulge or a lump. Furthermore, risk factors were taken into account, with smoking and obesity as commonly observed risk factors.

The questionnaire has a high test-retest reliability, with a correlation coefficient of 1.00. This is an excellent result implying that the answers to the questions are reliable. However, the internal consistency is only modest, with a Cronbach's alpha of 0.555. This means that this question does not fit the other questions, and it also implies that it does not measure the same topic as the other questions: the questions are not a closely related set of items. Statistical analysis showed that the low Cronbach's alpha was due to the question regarding patients' pain, which was least consistent and highly

heterogenic. When this question would be removed, the Cronbach's alpha would reach a higher number of 0.741, which is an acceptable scale. The reason for the low Cronbach's alpha rate might be the fact that pain is a general complaint, and is not very specific for patients with IH. Furthermore, not all patients with IH experience pain; literature shows that 60% of IH patients suffer from pain. Our results are comparable with the literature: 56% of patients answered positively to the question if they had pain at the site of their scar. Even though the pain question had a modest Cronbach's alpha, and was least consistent, the clinical relevancy of this question should be taken into account as well. Pain is an essential symptom of incisional hernia, and can indicate a symptomatic incisional hernia, which needs immediate care. Therefore, we decided to include this question in the questionnaire.

The most consistent question is if patients feel a lump. The sensitivity of this question was 91%. This implies that 91% of patients with IH felt a bulging or a lump at the site of the scar, and when this question would be left out, the Cronbach's alpha would drop to an insufficient number of 0.32. Several studies show that 67% of patients with IH might have symptoms of bulging. The discordance of these percentage rates might be due to the fact that the patients in this study already visited their surgeon and were aware of the diagnosis of IH and the complaints related to this.

In the past, several studies have been performed that validate questionnaires to detect recurrence in patients who have undergone groin hernia surgery [10, 11]. Haapaniemie et al. validated postal questionnaires as a method of follow up to diagnose patients with a recurrence after groin hernia repair. They showed a sensitivity and a specificity of their questionnaire of respectively 75% and 73% and still concluded that this is a solid basis for quality control. The included questions were if patients had any problems in the groin after wound healing, if the lump in the groin has recurred and if patients were satisfied with the results of operation [11]. Van den Heuvel et al. validated their PINQ-PHONE questionnaire, which is a validated method of follow-up after laparoscopic inguinal hernia repair. The sensitivity of the PINQ-PHONE has, in contrast to the questionnaire of Haapaniemie, an exceptional high number of 100%, which means that this questionnaire detected all groin hernia recurrences [10]. The PROMID study would be the first study validating a questionnaire to diagnose primary IH. Since IH is the most commonly seen complication after abdominal surgery, with a high morbidity as a result, it is of paramount importance to develop a validated questionnaire as a method of follow up to diagnose IH.

Essential to take into account is that both postal questionnaires and telephone interviews cannot replace physical examination, which is needed to diagnose a hernia [6]. Literature showed a high discordance between self-reported outcomes and medical chart abstraction to set the diagnosis of a hernia. This low level of agreement is based on the complexity of this diagnosis and shows that it cannot be made by patient reported outcome measurements alone [12].

The PROMID pilot study offers new future perspectives. The aim of this study was only to explore the reliability of the questionnaire, and it seems that it is a highly reliable questionnaire. The next step will be conducting a prospective cohort study, in order to validate the questionnaire. The questionnaire will be submit to patients, who have undergone a midline laparotomy in recent years. Furthermore, they will be invited to the outpatient clinic as well to perform physical examination. With these data, essential metrics such as sensitivity, specificity, positive predictive value and negative predictive value can be assessed.

Limitations

One of the main limitations of this study is non-response, which can introduce bias and is a major disadvantage of both postal questionnaires and telephone interviews [6, 13]. Telephone interviews are time consuming, in particular when patients have to be called repeatedly. This was applicable for this study as well. The advantage of our questionnaire is that it is a relatively short one. This might lead to more patients who are willing to cooperate and to response, which is also pointed out by Nakash et al.: implementing shorter questionnaires improve response rates [6, 14].

Another limitation which can possibly lead to bias, is the fact that 70% of interviewed patients were conservatively treated. The main reasons to operate IH are cosmetic reasons, (severe) pain or bulging complaints, and a (significant) risk of incarceration [4]. This conservatively treated patient group is more frequently asymptomatic, will therefore give answers of not having pain or bulging complaints. This can influence the sensitivity of the questions. However, only the pain question had a relatively low sensitivity, and the bulging questions had high sensitivities.

CONCLUSION

The PROMID questionnaire is a highly reliable questionnaire. The internal consistency on the other hand, is only modest. The question that is least consistent is the question regarding patients' pain. The clinical relevancy of pain in IH patients is essential,

and therefore this question will be kept in the current PROMID questionnaire. The questionnaire needs further validation in a prospective cohort study, with the aim to use it as a method of follow up to diagnose incisional hernia.

Compliance with ethical standards

The authors declare that they have no conflict of interest. Informed consent was obtained from all individual participants included in the study.

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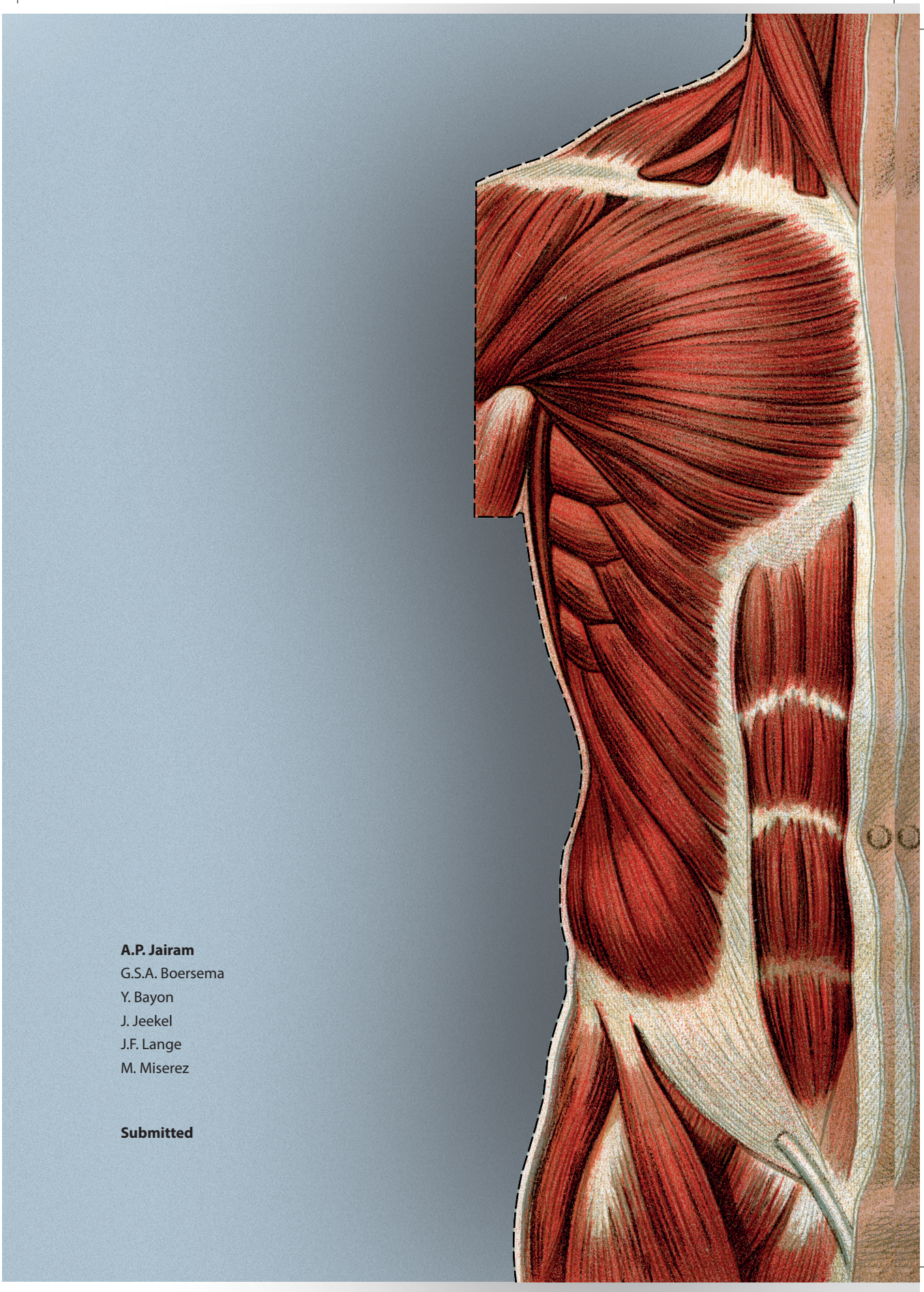

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Y. Bayon
J. Jeekel
J.F. Lange
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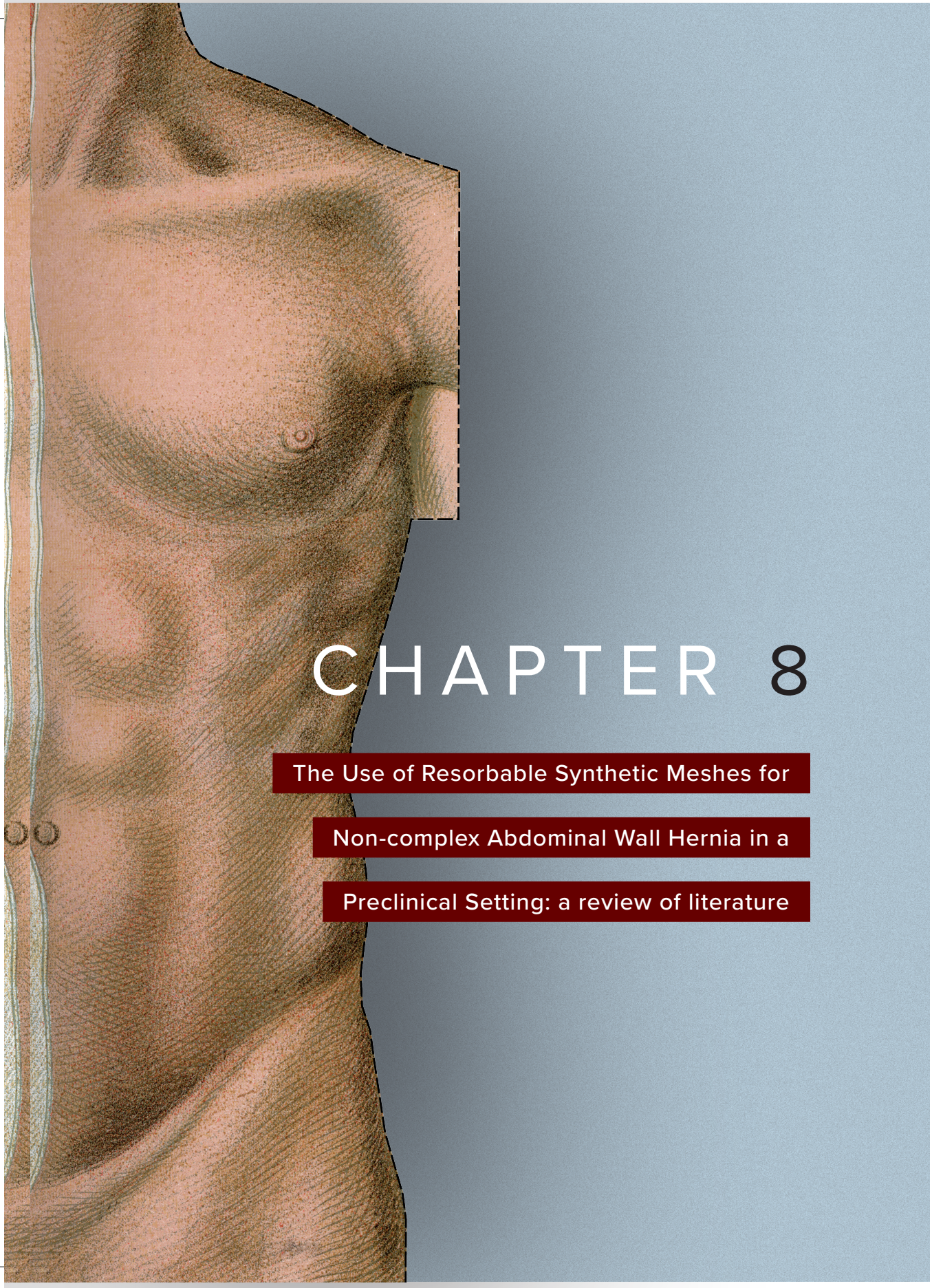

CHAPTER 8

The Use of Resorbable Synthetic Meshes for Non-complex Abdominal Wall Hernia in a Preclinical Setting: a review of literature

ABSTRACT

Background: Prosthetic materials for the repair of abdominal wall defects have been studied extensively to improve outcome. A new approach can be the use of a slowly resorbable synthetic mesh, which aims to combine advantages of both synthetic and biological meshes. The objective of this review is to give an overview of the physicochemical characteristics and biomechanical, histological, and macroscopic outcome (recurrence, adhesion formation) of the use of resorbable synthetic meshes, for treatment and prevention of abdominal wall hernias, based upon experimental studies.

Methods: A systematic review was conducted according to the PRISMA guidelines. Only experimental studies were included. Outcome parameters were resorption, degradation, organization of connective tissue, inflammatory response, tensile strength and amount of adhesion formation. Surgical characteristics were taken into account as well (type of defect, clean vs. contaminated model, position mesh, repair of the defect, recurrences).

Results: In total, eleven articles were included. Three absorbable synthetic meshes are currently available: GORE® BIO-A® mesh (Gore), TIGR® Matrix Surgical mesh (Novus Scientific) and Phasix™ mesh (Bard). Two studies concluded that, despite an early transient inflammatory reaction in the first months, remodelling was good in GORE® BIO-A®, 6-12 months after augmentation or suture line reinforcement with only minimal to moderate adhesions when used intraperitoneally. The TIGR® Matrix Surgical mesh shows only partial remodelling with a persistent foreign body reaction after one year. Phasix™ mesh seems to perform well in extraperitoneal implantation after one year in two studies, although the defect was also small. Only two studies directly compared two resorbable synthetic meshes under the same circumstances. The latter also included a number of animals where the meshes were used in a non-hernia model in contamination. No hernia recurrences or deaths of animals were described in all studies.

Conclusion: The use of resorbable synthetic meshes in the prevention or treatment of abdominal wall hernias seems safe according to the experimental studies that have been performed so far, since no serious complications have occurred. However, there is no evidence available that can support the advantages of resorbable synthetic meshes over the use of synthetic or biological meshes, mostly due to lack of good data. More experimental studies are needed, followed by randomized controlled trials and prospective registries in humans with a sufficiently long follow-up period, in order to reveal the potential advantages in clinical practice.

INTRODUCTION

Since a few decades, extensive research in the field of prosthetic materials for the repair of abdominal wall defects has been performed. All these materials aim to improve the result of simple tissue repair. The traditional synthetic polymeric materials are non-resorbable polyester (i.e. polyethylene terephthalate; PET), polypropylene, and polytetrafluoroethylene. These non-resorbable meshes were introduced in the late 1950s in the field of general surgery, urology, and gynaecology for various soft tissue reinforcement applications (1-5).

The use of non-resorbable synthetic biomaterials for the reinforcement of soft tissue weakness has led to a marked reduction of the hernia recurrence rate compared to primary suture (6). However, the use of a non-resorbable mesh is unfavourable in a contaminated field because of the risk of post-operative infection of the mesh. Also, a synthetic mesh represents permanent foreign body material, which may lead to (chronic) inflammation, excessive fibrosis, and complications of pain and even enterocutaneous fistula. Even though most of these meshes show sufficient strength, they can impair tissue regeneration (1).

In order to minimize the risk of complications, biological meshes have been introduced gradually (7). They consist of an extracellular matrix (ECM) that is derived from collagenous rich tissue, such as dermis, pericardium, or small intestinal submucosa from human or animal origin (8). The use of biological meshes may lead to a reduction of the foreign body and chronic inflammatory response (9). These implants are resorbable, easily colonized with host tissue and blood vessels, and are meant to induce site-specific remodelling by regenerating newly formed tissue (10). They are more infection resistant than synthetic materials. Biological meshes are favourable in case the surgical field is contaminated, but high-level evidence in long-term data of clinical outcome and complications is lacking. A disadvantage of biological meshes is the excessively high cost (8).

An alternative for abdominal wall repair and soft tissue reinforcement might be the use of a slowly resorbable synthetic mesh, which aims to combine advantages of both synthetic (no degradation shortly after implantation) and biological meshes (the "remodelling" aspects and better tolerance in case of contamination) and which is also less expensive than a biological mesh. Resorbable synthetic meshes maintain mechanical strength for a certain period. These meshes will gradually resorb, allowing rebuilding of connective tissue, although without clear remodelling properties (1, 7, 11, 12). In this way, this new generation of materials is different from the available quickly absorbing polyglactin

mesh (Vicryl® mesh; Johnson & Johnson). Experience with resorbable synthetic meshes is limited; several experimental studies and a few clinical studies have been performed so far. Some studies report "optimal tissue remodelling", however, the definition of this is often very unclear and certainly not standardised. There is not enough evidence yet that these meshes provide sufficient strength on the long-term after full resorption (11). Furthermore, it is not fully clear if these meshes can be safely used in patients at risk of infection. The objective of this review is to give an overview of the physicochemical characteristics and biomechanical, histological, and macroscopic outcome (recurrence, adhesion formation) of the use of resorbable synthetic meshes, for treatment and prevention of abdominal wall hernias, based upon experimental studies.

METHODS

We conducted a systematic review following the PRISMA guidelines. A systematic search was performed in MEDLINE, Embase, Web of Science, Scopus, PubMed Publisher, Google Scholar and the Cochrane Library, with a search period until September 2017.

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

Two reviewers (A.J. and G.B.) independently evaluated the identified records. All records were screened by title and abstract for eligibility and the full text of eligible records was assessed. Studies were included if they met the following inclusion criteria: experimental studies, investigating resorbable synthetic meshes, with or without comparison of synthetic and/or biological meshes for treatment and prevention of abdominal wall hernias. Articles had to be written in Dutch or English. Clinical studies and studies that investigated only biological or nonresorbable synthetic meshes were excluded.

The following outcome measurements were assessed: resorption (= disappearance of a substance from its initial place, due to physical or chemical phenomena), degradation (= loss of the performance or of the characteristics of substance or device, regardless of the mechanism), organization of connective tissue, inflammatory response, tensile strength and amount of adhesion formation. Surgical characteristics such as type of defect, clean or contaminated model, position of the mesh, repair of defect, and recurrences were taken into account. The following baseline study characteristics were extracted from all included studies: author, year of publication, animal species, number of included animals and follow-up period in months. Data were assembled 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 570 articles were identified after the removal of duplicates. After screening, 52 articles were considered relevant and the full text of these articles was evaluated. After assessment of the full text versions, 11 articles were suitable for inclusion in this (1, 7, 11-19). The reasons for exclusion can be found in the PRISMA flow diagram (Figure 1).

The included resorbable synthetic meshes are the GORE® BIO-A® mesh (Gore), TIGR® Surgical Matrix Mesh (Novus Scientific) and the Phasix™ mesh (Bard). Table 1 gives an overview of the baseline study characteristics of the included articles. Appendix 2 shows per mesh an overview of the type of defect and the surgical, histological, macroscopic and biomechanical characteristics. In the following sections the features of each mesh (as described by the company) and outcome parameters of the included studies are given.

GORE® BIO-A® mesh (Gore)

Features of the mesh

GORE® BIO-A® consists of one type of fiber; a synthetic bioabsorbable poly(glycolide:trimethylene carbonate) copolymer. According the Instructions for Use (IFU), GORE® BIO-A® is not designed to be a load-bearing prosthesis and is therefore not recommended for permanent bridging of fascial defects. Table 2.1 shows the features of the GORE® BIO-A® mesh as provided by the company. GORE® BIO-A® does not have data to provide on measurements as ball burst strength, strength retention in time and mechanical strength. According to the company, strength is not a required function in the performance of the product.

Outcome parameters

In total, eight studies investigated GORE® BIO-A® (7, 11-13, 16-19). The surgical, histological and biomechanical characteristics of the GORE® BIO-A® experiments are extensively described in Appendix 2.

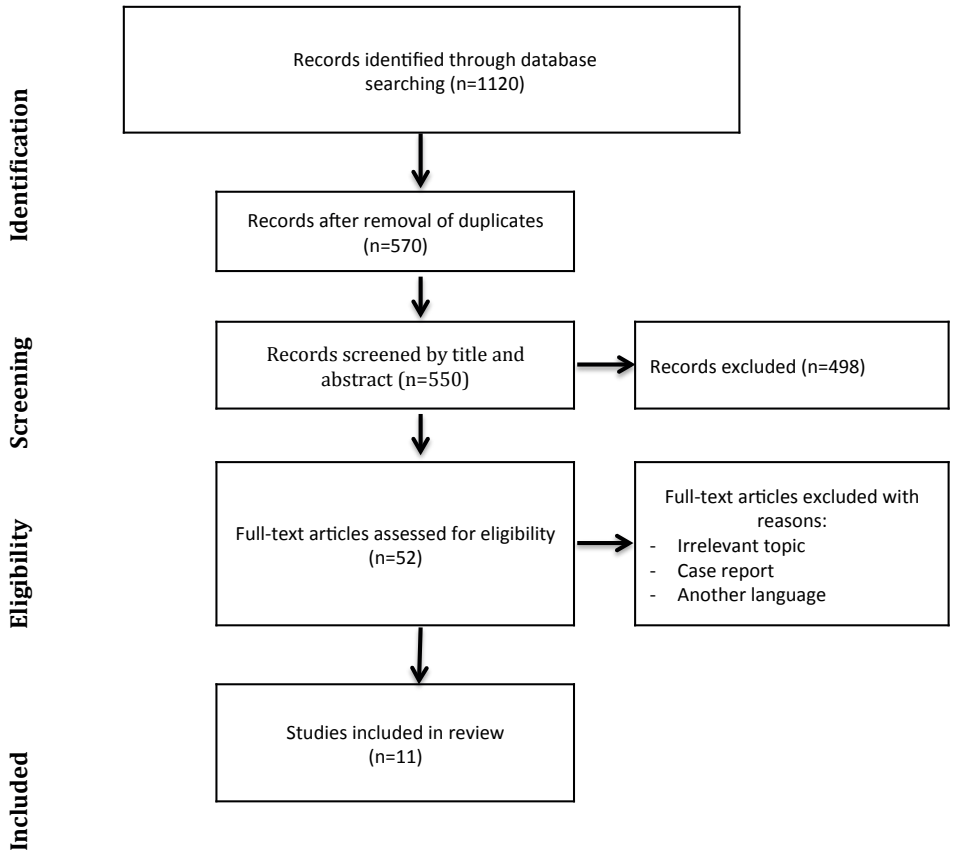

Figure 1. Prisma Flow Diagram

Peeters et al. performed a rabbit study. A full thickness midline abdominal wall defect (11x4cm) was created and meshes were placed intra-abdominally; afterwards the laparotomy was closed (mesh augmentation). At one-year follow-up, the meshes were completely degraded and a fibrous rim was present at the edges of the resorbed mesh. The connective tissue was dense and well organized and there was no undesirable inflammatory response. The tensile strength of the abdominal wall was comparable to native tissue. There were moderate intra-abdominal adhesions and no recurrences were observed (11). This was also applicable for the group who had undergone primary repair (control group).

Table 1. Study characteristics

Author	Year of publication	Total number of animals	Type of meshes investigated
Hjort et al.	2012	14 sheep	TIGR® Matrix Surgical Mesh, polypropylene
Lopez-Cano et al.	2012	65 rats	GORE® BIO-A®
Pascual et al.	2012	72 rabbits	GORE® BIO-A®, Strattice®,Tutomesh
Deeken et al.	2013	20 minipigs	Phasix™ mesh, P4HB plug
Martin et al.	2013	30 pigs	Native abdominal wall
Peeters et al.	2013	46 rabbits	GORE® BIO-A®, TIGR® Matrix Surgical Mesh, Permacol, Surgisis, polypropylene
Yeo et al.	2014	6 rabbits	GORE® BIO-A®
Pascual et al.	2014	9 rabbits	GORE® BIO-A®, Strattice®, Tutomesh
Sandor et al.	2014	21 vervets	GORE® BIO-A®, Physiomesh
Gruber-Blum et al.	2017	27 rats	GORE® BIO-A®, Strattice®, Veritas®
Stoikes et al.	2017	60 rats, 10 rabbits	GORE® BIO-A®, Phasix™ mesh

Lopez Cano et al. conducted a rat study: in 65 rats, a full thickness median incision along the linea alba was made (4cm length) in which a precut longitudinal GORE® BIO-A® prosthesis was inserted as a suture line reinforcement which was held in place with slowly resorbable sutures. After a 6 month follow-up the mesh was not fully resorbed. Degradation and dense, well-organized connective tissue was visible. A mild degree of inflammatory cells was seen at the site of remodelling. There was a significantly ($p<0.01$) increased tensile strength compared with the suture group (polydioxanone 2-0). More adhesions were present compared to the suture group, with a low Zülhke score of 1-2. It was concluded that GORE® BIO-A® for soft tissue suture line reinforcement GORE® BIO-A® is able to initiate constructive synthesis and remodelling of newly organized host tissue (13).

Pascual et al. conducted 2 studies: an in vivo study performed in 2012 (7) and a combined in vitro and in vivo study, conducted in 2014 (12). Here, we will focus only on the in vivo results. GORE® BIO-A® was compared with two different biological meshes: Strattice and Tutomesh. In the study from 2012, non-full layer defects of 3x3cm were created in the lateral wall of the abdomen of rabbits and were treated with an inlay mesh. After 180 days, a significant gain in biomechanical strength was seen. After 6 months of follow-up, degradation was almost complete and dense connective tissue was seen. The mesh was completely resorbed. Macrophage response remained high in GORE® BIO-A® until the 180th day. However, at six months follow up, inflammatory cells had disappeared (7). The study from 2014 showed that significantly more adhesions were seen in GORE®

BIO-A®, as well as the macrophage count (both 90 days after implantation). Thickness of neoperitoneum was 90 days after implantation greater for Strattice™ Tissue Mesh (Life Cell) and Tutomesh (Taureon) compared with GORE® BIO-A® (12).

Table 2.1. Features of GORE® BIO-A® (provided by the company)

Mesh type	**GORE® BIO-A® Tissue Reinforcement**
Material	Fiber of synthetic bioabsorbable poly(glycolide: trimethylene carbonate) copolymer
Structure	Non-woven, porous fibrous structure
Pore size	Pore size of between 20-120 micrometers
Ball burst strength	Gore does not have data to provide on this measurement.
Strength retention in time	Gore does not have data to provide on this measurement.
Mechanical strength (suture retention – parallel/ perpendicular)	Gore does not have data to provide on this measurement.
Total resorption time	6-7 months
Indications	Soft tissue reinforcement: - hernia repair as suture-line reinforcement - muscle flap reinforcement - general tissue reconstructions
Contraindications	Not for reconstruction of cardiovascular defects
Degradation	Combination of hydrolytic and enzymatic pathways
Reactions	Possible adverse reactions are those typically associated with any implantable prosthesis, and may include, but are not limited to, contamination, infection, inflammation, adhesion, fistula formation, seroma formation, hematoma, recurrence
Mesh available sizes	7x10cm, 8x8cm, 9x15cm, 10x30cm, 20x20cm, 20x30cm

Yeo et al. also investigated GORE® BIO-A® mesh in a clean rabbit model. Meshes were inserted in subcutaneous pockets without defect creation on the back of the animal (2x2cm fixated with slowly absorbable sutures). After 6 months, almost complete resorption/degradation took place. Soft tissue was newly formed with a few giant cells, which implies a moderate grade foreign body response (16).

Sandor et al. created a full thickness defect of 3x7 cm by removal of the fascia, rectus muscle, and peritoneum in 21 vervets. The mesh (4x8 cm) was placed intra-abdominally in an inlay position and was fixated with continuous 3/0 Prolene sutures. This study showed also full resorption and complete degradation of the mesh. After 6 months of

follow up, no inflammatory response was detectable and the tensile strength of the abdominal wall was lower (but not significantly) compared to the synthetic Physiomesh (17).

Gruber-Blum et al. recently published an experimental study. In this study two lateral full muscular defects (diameter 1 centimeter) were created in the abdominal wall of rats. The peritoneum was spared. Eleven days after primary surgery, rats were randomized to undergo onlay bridged placement of either GORE® BIO-A® mesh, Strattice® mesh or Veritas® mesh. Follow up took place after 30 and 60 days. GORE® BIO-A® mesh integrated well and was resorbed after 60 days follow up. Tissue integration was significantly higher in GORE® BIO-A® mesh compared to Strattice® mesh and Veritas®. After 60 days, a large amount of collagen was detected around the mesh fibers. Vascularisation of the mesh was superior compared to both Strattice® and Veritas® mesh. GORE® BIO-A® mesh led to a moderate foreign body reaction. A higher force of perforation was seen in GORE® BIO-A® mesh, when compared to native abdominal wall (18).

Stoikes et al. performed a rat study (non-contaminated), in which parameters such as resorption and inflammation were investigated, and a rabbit study (contaminated), in which inflammation and tensile strength were tested. In this experimental study, Phasix™ mesh and GORE® BIO-A® mesh were investigated and compared. In the rat study, 60 rats in total were included: in 30 rats Phasix™ mesh was implanted and in 30 rats GORE® BIO-A® mesh was implanted. A defect of 0.5 centimetres was created in the muscle layer. A mesh of 2 by 2 centimetres was placed into the subcutaneous plane and was fixated over the surgical defect. Follow up was until 24 weeks. It was concluded that Phasix™ mesh and GORE® BIO-A® mesh had a similar overall biocompatibility. A significantly higher host inflammatory response was seen in GORE® BIO-A® mesh in the first 4 weeks, compared to Phasix™ mesh ($p<0.01$). Furthermore, a greater macrophage infiltration was observed in GORE® BIO-A® mesh. Histological assessment showed also that GORE® BIO-A® mesh was initially thicker compared to Phasix™ mesh ($p<0.0001$). GORE® BIO-A® mesh has a more rapid resorption profile, compared to Phasix™ mesh. Resorption of GORE® BIO-A® mesh was complete after 24 weeks. At week 16, repair thickness transitioned into significantly thinner sites, in comparison with Phasix™ mesh. In the rabbit study, 20 New Zealand rabbits were included. In 10 rabbits, Phasix™ mesh was implanted, and in 10 rabbits, GORE® BIO-A® mesh was implanted. Follow up was until 7 days. In each animal, (bilateral) pockets were made subcutaneously along the back. Meshes were implanted into this pocket. Each mesh had a diameter of 3.8 centimetres and was inoculated with 10^8 CFU of MRSA (methicilline resistant Staphylococcus Aureus). Phasix™ mesh showed

significantly lower MRSA bacterial colonization, compared to GORE® BIO-A® mesh ($p<0.01$), 7 days after implantation. Furthermore, a greater ball burst strength was seen in Phasix™ mesh, in comparison with GORE® BIO-A® mesh ($p<0.001$) (19).

TIGR® Matrix Surgical Mesh (Novus Scientific)

Features of the mesh

TIGR® Matrix Surgical Mesh is a multifilament knitted mesh and consists of two types of fiber: a fast-resorbing fiber (40% of weight) and a slow resorbing fiber. According to the IFU, TIGR® mesh is marketed for reinforcement (i.e. no bridging) of soft tissue where weakness exists, but must always be separated from the abdominal cavity by peritoneum. The company explicitly excludes the repair of direct inguinal hernias. Table 2.2 shows the features of the TIGR® mesh as provided by the company.

Outcome parameters

In total, two studies were included which investigated the TIGR® mesh (1, 11). The surgical, histological and biomechanical characteristics of the TIGR® mesh are extensively described in Appendix 2.

Peeters et al. found in their rabbit study that after one year follow up, the mesh was only partially incorporated in the native abdominal wall. Filaments were surrounded with less organized collagen depositions. There was an intense foreign body reaction, with significantly more macrophages/foreign body giant cells than the GORE® BIO-A® mesh. Tensile strength was significantly higher compared with GORE® BIO-A®. There were significantly more adhesions than the GORE® BIO-A® group, but similar percentages of adhesions compared to the polypropylene mesh group. No recurrences of hernia were detected after one-year follow-up, as in the control group (11).

Hjort et al. performed a sheep study in which a full thickness abdominal wall defect (3x3cm) was created. Onlay TIGR® mesh was compared with an onlay polypropylene mesh (8x8cm, bridged). After a follow-up of three years, according to the authors, 'optimal tissue remodelling' was seen. The mesh was fully resorbed and degraded and replaced by newly formed collagen rich tissue, indicating that continuous tissue remodelling has taken place. The inflammatory response remained high in the first 24 months, which was mainly caused by recruitment of phagocytic cells around and between the filaments. Inflammation declined after 24 months and was absent at 36 months of follow-up. The tensile strength and adhesion percentages were not available in this study. No hernia recurrences were seen after 3 years (1).

Table 2.2. Features of TIGR® matrix (provided by the company)

Mesh type	TIGR®matrix
Material	Two types of fiber, consisting of: 1) fast-resorbing fiber (40 % of weight): copolymer of glycolide, lactide and trimethylene carbonate. 2) Slow-resorbing fiber (60 % of weight): copolymer of lactide and trimethylene carbonate
Structure	Multifilament knitted
Pore size	1 mm (at time of implantation) to 1x2 mm (at 4 months)
Ball burst strength	450 to 500 Newton, using ASTM D3787
Strength retention in time	Short term strength retention: 3 weeks (loss of 50% strength) Long term strength retention: up to 9 months
Mechanical strength (suture retention – parallel/ perpendicular)	40 Newton
Total resorption time	Fast-resorbing fiber 4 months, slow resorbing fiber 3 years
Indications	Soft tissue reinforcement where weakness exist: - hernia repair - abdominal wall defects - abdominal wall reinforcement - muscle flap reinforcement
Contra indications	- Reconstruction of cardiovascular defects - TIGR mesh must always be separated from the abdominal cavity by peritoneum - Not for use following planned intraoperative or accidental opening of the gastrointestinal tract - Repair of direct inguinal hernias
Degradation	Bulk hydrolysis
Reactions	Infection, inflammation, extrusion, erosion, adhesion, fistula formation, seroma formation, hematoma, and recurrence of the hernia or tissue defect
Mesh available sizes	10x15cm, 15x20cm, 20x30cm

Phasix™ mesh (Bard)

Features of the mesh

Phasix™ mesh is a monofilament knitted mesh and its fibers are composed of poly-4-hydroxybutyrate (P4HB). This is a natural polymer from the class of polyhydroxyalkanoates. Phasix™ mesh is indicated in patients where weakness exists, to reinforce soft tissue. Phasix™ biomaterials should not be used in repairs where permanent wound or organ support from the mesh is required. Table 2.3 shows the features of the mesh as provided by the company.

Table 2.3. Features of Phasix™ mesh (provided by the company)

Mesh type	**Phasix™Mesh**
Material	Fiber consisting of poly-4-hydroxybutyrate (P4HB)
Structure	Monofilament knitted
Pore size	Minor pore size: 362 microns, major pore size: 700 microns
Ball burst strength	149 Newton, using ASTM D3787
Strength retention in time	Loss of 50% strength after 8 weeks
Mechanical strength (suture retention – parallel/ perpendicular)	40 to 45 Newton
Total resorption time	12-18 months
Indications	Soft tissue reinforcement: - patients undergoing plastic and reconstructive surgery - soft tissue repair of ventral or inguinal hernias - other abdominal fascial defects that require the addition of a reinforcing or bridging material to obtain the desired surgical result
Contra indications	If permanent wound or organ support from the mesh is required
Degradation	Mostly hydrolysis and small amount of enzymatic degradation
Reactions	Infection, seroma, pain, mesh migration, wound dehiscence, adhesions, hemorrhage, hematoma, inflammation, extrusion and recurrence of the hernia or soft tissue defect
Mesh available sizes	10.2x15.2cm, 15.2x20.3cm, 20.3x25.4cm, 25.4x30.5cm

Outcome parameters

Three studies investigated the Phasix™ mesh (14, 15, 19). The surgical, histological and biomechanical characteristics of the Phasix™ mesh are extensively described in Appendix 2.

Deeken et al. conducted an experimental study with 20 minipigs. Bilateral abdominal wall defects of 3 cm were made in the anterior abdominal wall, using a preperitoneal bridging technique with a mesh of 10.2cm in diameter. The Phasix™ mesh significantly resorbed over time. This was measured by the molecular weight, which progressively decreased between measured time points. Collagen scores were consistent over time and showed a mixture of both mature and immature collagen, which was seen at all time points. There was a mild to moderate inflammatory response, which remained stable throughout the complete study. The burst strength of the abdominal wall remained also stable over time, but was significantly greater compared to the native abdominal wall. There were no recurrences after one year (14).

Martin et al. conducted an experimental study with 30 Yucatan pigs. A full fascial defect (diameter 2.5 centimetres) in the anterior abdominal wall was made. The mesh was placed in a preperitoneal position, and the abdominal wall defect was reinforced (augmentation) with a Phasix™ mesh. Evaluation of the functional performance was done at 72 weeks. In this study, Phasix™ mesh was investigated in an in vitro and in vivo model. In this paper, we focus on the in vivo results. A moderate chronic host inflammatory response was found around the mesh knots and monofilaments, and contained mainly macrophages, lymphocytes and giant cells. Phasix™ mesh has a higher strength in the first 16 weeks compared to the native abdominal wall. At the same time, relatively high stiffness occurs in the mesh scaffold, which indicates a natural fibrotic response during remodelling. After the 16th week, the ball burst strength decreases, as well as the relative stiffness, and the molecular weight decreases while the mesh degrades. There is no information regarding the recurrence rate (15).

Stoikes et al. performed a rat study (non-contaminated) and a rabbit study (contaminated), as described before. We refer to the Gore Bio-A section and to Appendix 2 for description of the results.

DISCUSSION

This review gives an overview of slowly resorbable synthetic meshes that are currently available on the market: GORE® BIO-A®, TIGR® Matrix Surgical mesh and Phasix™ mesh. Surgical, histological and biomechanical characteristics of these meshes for the treatment and prevention of abdominal wall hernias are highlighted. Only experimental studies were included. GORE® BIO-A® was more extensively described in literature than TIGR® Matrix Surgical mesh and Phasix™ mesh.

The occurrence of incisional hernia after a median laparotomy has an incidence that can increase up to 35%. Currently only non-resorbable synthetic meshes are used for hernia repair. However, permanent foreign body material can elicit a chronic inflammatory response. This response can cause symptoms like chronic postoperative pain, discomfort and mesh erosion. Furthermore synthetic meshes are contraindicated for hernia repair in a contaminated environment (1, 11, 20, 21). Under these circumstances biological meshes are possibly an alternative for the most complex cases, in patients at risk for complications of infection. Unfortunately these biological meshes seem to provide insufficient strength for adequate repair, especially in large abdominal defects with bridging of the defect, as reported by clinical studies (1, 11, 21, 22). In addition the costs of this variety of meshes are extremely high. Due to the disadvantages of both

synthetic and biological meshes, strategies focussed on the development of new type of meshes: slowly resorbable synthetic meshes were gradually introduced. This new generation of meshes aims to combine the advantages of both a synthetic mesh (no degradation shortly after implantation) and a biological mesh (the "remodelling" aspects and the better tolerance in case of contamination). Currently it is unclear in what way biological meshes really induce a site-specific remodelling of fascia- and muscle-like tissue or whether it is "just" a matured fibrotic scar that remains after full degradation, and whether the tensile strength of the new tissue in augmentation techniques has an equal strength as with the use of standard synthetic non-resorbable materials. The same question holds for the new generation of slowly absorbable synthetic materials discussed here in general, and in bridging vs. augmentation in particular (1, 11, 17). According to information from the manufacturers, the three commercially available materials have a wide range of pore size (0.02-2mm), strength retention (3 weeks – 9 months), and resorption time, they are resorbed (at least partially) between 4 months and 3 years. This is already a first problematic issue, since, apart from weight and pore size, there are no clear-cut criteria to describe in a standardised way the biomechanical properties of a mesh before implantation. Once this is established, a list of independent accredited laboratories with validated measurement tools needs to be installed. These materials degrade mainly by hydrolysis and do not seem to be intended to be used in case of bridging, although the exact indications and contra-indications based on the instructions for use from the manufacturers are ill defined. For TIGR Matrix, the contraindication for use in direct inguinal hernia repair is explicitely mentioned. However, most of the studies reported here with an acute defect used a bridging model (1, 7, 14, 17-19). The data presented in this review show the various aspects of resorbable synthetic meshes.

Essential parameters of resorbable synthetic meshes are remodelling, tensile strength, inflammation, adhesions and recurrence. No firm conclusion can be made based upon these experimental studies regarding remodelling. Different parameters influencing optimal remodelling of a resorbable synthetic mesh have to be taken into account: (1) the type and size of defect, (2) the level of contamination, (3) the surgical technique to repair the defect that has been applied (augmentation, bridging, inlay), (4) the specific characteristics of the mesh studied (resorption time and strength retention in time), and (5) the duration of follow up. Two studies concluded that, despite an early transient inflammatory reaction in the first months, remodelling was good in GORE® BIO-A® 6-12 months after augmentation or suture line reinforcement with only minimal to moderate adhesions when used intraperitoneally (11, 13). The latter study is the only one in this review reporting on hernia prevention. Interestingly it also seems to provide a sufficient support in an onlay bridging model up to 2 months (20), but this needs to be confirmed

with longer follow-up. The TIGR® Matrix Surgical mesh shows only partial remodelling with a persistent foreign body reaction after one year (1, 11). This finding might also be attributed to the fact that TIGR ® Matrix Surgical mesh consists of two distinct fibers. A strong repair with absent inflammatory response was seen in another onlay bridging model after 3 years, although the defect was small (3x3cm in sheep model) (1). This mesh cannot be used intraperitoneally because of the risk for adhesions, as stated in the IFU of the manufacturer. According to the manufacturer, also Phasix™ mesh cannot be used intraperitoneally, unless covered by an anti-adhesive barrier. Here again the mesh seems to perform well in extraperitoneal implantation after one year, although the defect was also small in both studies (3cm in minipig model (bridging) and 2.5 cm in Yucatan swine model (augmentation). These models may not reflect the performance of the mesh, in real clinical setting.

Only two studies directly compared two resorbable synthetic meshes under the same circumstances (11, 19). Only one of these included a macroscopic, histological and biomechanical analysis after one year (11). The other one is the only available study that included also a number of animals where the meshes were used in a contaminated setting, but only with an evaluation after 7 days, and in a non-hernia model (19). It is clear that these data need to be confirmed before sound conclusions can be drawn. Overall it can be stated that after implantation indeed at least some degree of remodelling occurs, but whether this can lead to strong fascial tissue of good quality in the long term remains completely unclear. This can only truly be assessed in bridging models. Also it is unclear what the clinical impact is of the degree of inflammation during or after remodelling, although in none of the studies it was seen that a (higher) inflammatory response led to short or long-term complications. In conclusion so far, the use of these materials seems safe, although it should be clear they have not been marketed to be used in contaminated settings, even though they are intended to be clinically used in these settings mainly.

This review paper has several limitations, inherent to the heterogeneity and quality of the selected publications. Apart from defect size and type, surgical techniques used were extremely variable. For instance, we know that inlay repair of incisional hernias with synthetic non-resorbable mesh in a clinical setting is prone to failure, yet this technique was used in two studies (7, 17). In addition, many different animal models were used and meshes were always placed in a clean environment, except in one study. Last but not least, outcome parameters were not standardised and only four studies had a follow-up of one year or longer (1, 8, 11, 15). This all makes it extremely difficult to extrapolate these results to humans. In order to overcome these limitations, a longer follow-up (at least longer than full resorption of the material) in a chronic standardized

validated large hernia model with an accepted surgical technique, adequate comparison groups and a fixed set of clearly defined and relevant outcome parameters is needed, before any statements can be made (23, 24).

Ideally, each experimental study has to stick to such a set of fixed independent and dependent parameters. In order to achieve this, we have set up a table with our own suggested parameters (Table 3). Research groups from different countries should work together in this, along with the industry. All these studies should be registered in order to avoid publication bias.

Table 3. Format fixed set of parameters

Surgical characteristics	**Physicochemical, Macroscopic, Histological, and Biomechanical outcome parameters**
Defect: acute / chronic	Resorption
Setting: clean / clean-contaminated/contaminated	Degradation
Position mesh: inlay / onlay / sublay / IPOM	Connective tissue
Repair of defect: augmentation / bridging	Inflammatory response
	Tensile strength
	Adhesion
	Recurrences

Experimental studies should be followed by clinical studies. At this moment several prospective clinical cohort studies regarding GORE® BIO-A® and TIGR® Matrix Surgical mesh have been published, with positive short-term results (25-27). No clinical study for the Phasix™ mesh has been published yet; several studies are currently being conducted and results will follow soon. Ideally, resorbable synthetic meshes should be compared with either synthetic meshes (in a clean setting) or biological meshes (in a contaminated setting). Unfortunately no randomized controlled trials have been conducted yet. Concurrently, we urge all surgeons to register their patient data in well-designed prospective registries, especially when new meshes are launched in order to detect as soon as possible (rare) potential adverse effects related to the safety of a specific material.

CONCLUSION

The use of resorbable synthetic meshes in the prevention or treatment of abdominal wall hernias seems safe according to the experimental studies that have been performed so far. Although a certain degree of remodelling occurs, it remains completely unclear

whether this can lead to strong fascial tissue of good quality in the long term. Currently, there is no clear experimental evidence available that can support the advantages of resorbable synthetic meshes over the use of synthetic or biological meshes in human settings, mostly due to lack of good data. More experimental studies are needed, using standardized models and parameters, followed by randomized controlled trials and prospective registries in humans with a sufficiently long follow-up period, in order to reveal the potential advantages in clinical practice.

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APPENDIX

Appendix 1: Syntax with search terms

Embase.com *284*

(hernioplasty/exp OR herniorrhaphy/exp OR hernia/de OR 'abdominal wall hernia'/exp OR 'abdominal wall defect'/de OR 'incisional hernia'/exp OR (hernia* OR hernio* OR ('abdominal wall' NEXT/1 defect*)):ab,ti) AND ('synthetic biology'/exp OR ((biomaterial/exp OR 'biodegradable implant'/exp) AND ('synthetic fiber'/exp OR polymer/de)) OR (((synth* OR polymer*) NEAR/3 (bio*)) OR biosynth* OR 'bio a' OR tigr OR tephaflex OR phasix OR (slow* NEAR/3 (resor* OR absor*))):ab,ti)

MEDLINE (OvidSP) *209*

(Herniorrhaphy/ OR hernia/ OR Hernia, Abdominal/ OR exp Hernia, Ventral/ OR (hernia* OR hernio* OR (abdominal wall ADJ defect*)).ab,ti.) AND (Synthetic Biology/ OR ((exp Biocompatible Materials/ OR Absorbable Implants/) AND (polymers/)) OR (((synth* OR polymer*) ADJ3 (bio*)) OR biosynth* OR bio a OR tigr OR tephaflex OR phasix OR (slow* ADJ3 (resor* OR absor*))). ab,ti.)

Cochrane Library *18*

((hernia* OR hernio* OR ('abdominal wall' NEXT/1 defect*)):ab,ti) AND ((((synth* OR polymer*) NEAR/3 (bio*)) OR biosynth* OR 'bio a' OR tigr OR tephaflex OR phasix OR (slow* NEAR/3 (resor* OR absor*))):ab,ti)

Web-of-science *209*

TS=(((hernia* OR hernio* OR ("abdominal wall" NEAR/1 defect*))) AND ((((synth* OR polymer*) NEAR/3 (bio*)) OR biosynth* OR "bio a" OR tigr OR tephaflex OR phasix OR (slow* NEAR/3 (resor* OR absor*)))))

Scopus *294*

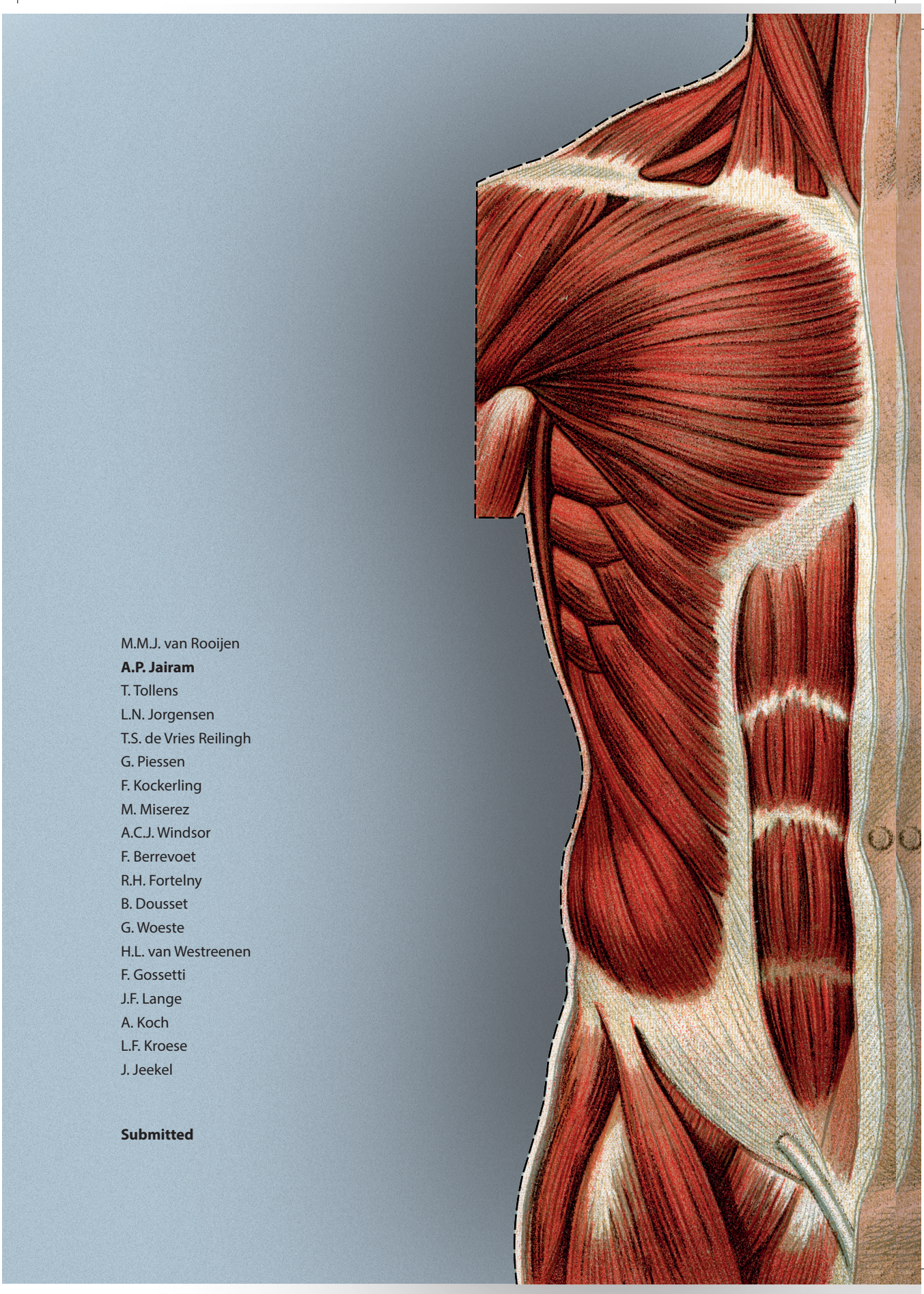
TITLE-ABS-KEY(((hernia* OR hernio* OR ("abdominal wall" W/1 defect*))) AND ((((synth* OR polymer*) W/3 (bio*)) OR biosynth* OR "bio a" OR tigr OR tephaflex OR phasix OR (slow* W/3 (resor* OR absor*))))) AND doctype(ar)

PubMed Publisher *5*

(Herniorrhaphy[mh] OR hernia[mh] OR Hernia, Abdominal[mh] OR Hernia, Ventral[mh] OR (hernia*[tiab] OR hernio*[tiab] OR abdominal wall defect*[tiab])) AND (Synthetic Biology[mh] OR ((Biocompatible Materials[mh] OR Absorbable Implants[mh]) AND (polymers[mh])) OR (((synth*[tiab] OR polymer*[tiab]) AND (bio*[tiab])) OR biosynth*[tiab] OR bio a OR tigr OR tephaflex OR phasix OR (slow*[tiab] AND (resor*[tiab] OR absor*[tiab])))) AND publisher[sb]

Google Scholar

hernia|hernioplasty|herniorrhaphy|"abdominal wall defect" biosynthetic|"bio synthetic"|"bio a"|tigr|tephaflex|phasix|"slowly resorbable|absorbable"



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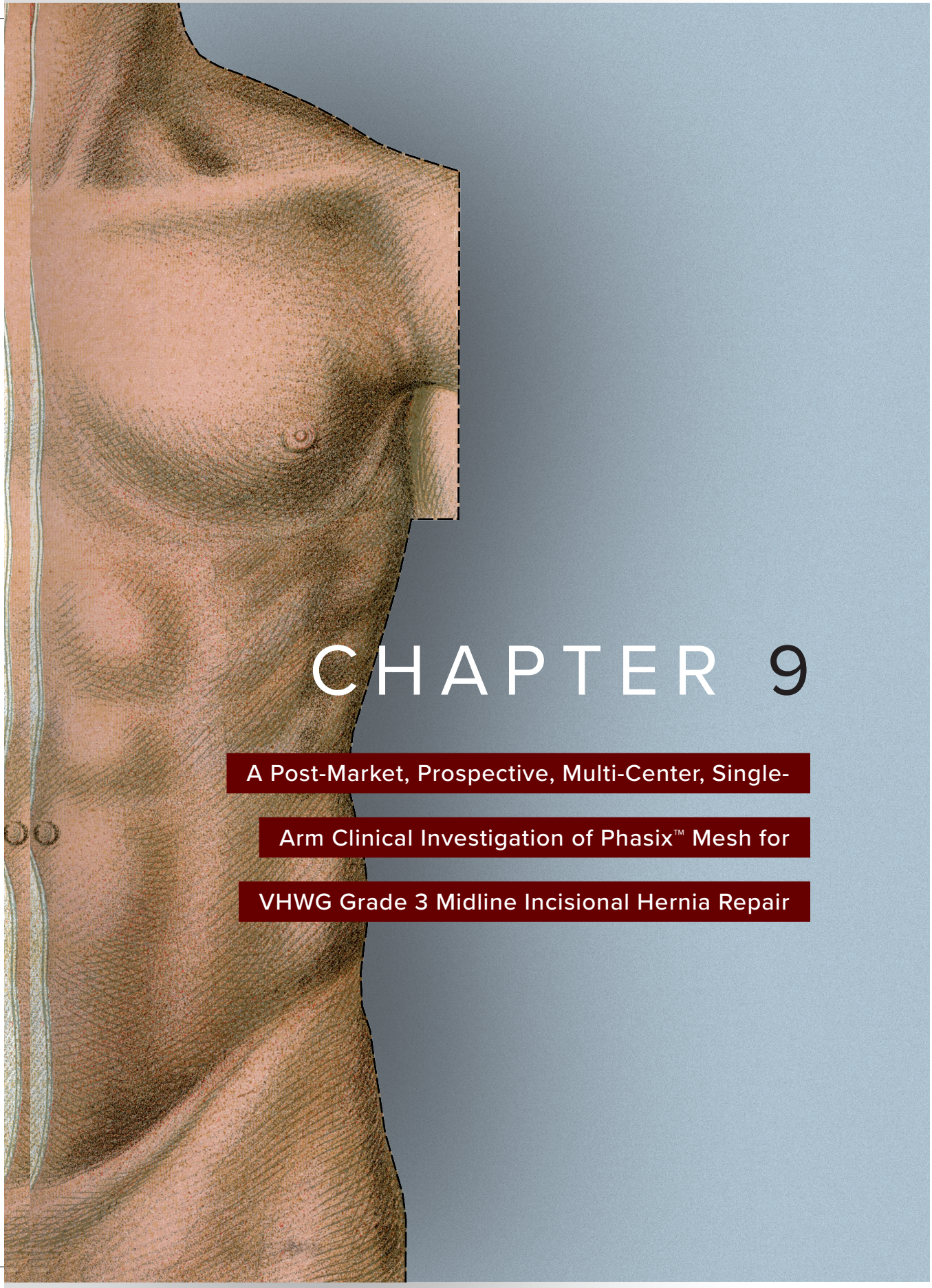
T. Tollens
L.N. Jorgensen
T.S. de Vries Reilingh
G. Piessen
F. Kockerling
M. Miserez
A.C.J. Windsor
F. Berrevoet
R.H. Fortelny
B. Dousset
G. Woeste
H.L. van Westreenen
F. Gossetti
J.F. Lange
A. Koch
L.F. Kroese
J. Jeekel

Submitted



CHAPTER 9

A Post-Market, Prospective, Multi-Center, Single-Arm Clinical Investigation of Phasix™ Mesh for VHWG Grade 3 Midline Incisional Hernia Repair

ABSTRACT

Background Incisional hernia is a frequent complication of midline laparotomy. The use of mesh in hernia repair has been reported to lead to fewer recurrences compared to primary repair. However, in Ventral Hernia Working Group (VHWG) Grade 3 hernia patients, whose hernia is potentially contaminated, synthetic mesh is prone to infection. There is a strong preference for resorbable biological mesh in contaminated fields, since it is more able to resist infection, and because it is fully resorbed, the chance of a foreign body reaction is reduced. However, when not crosslinked, biological resorbable mesh products tend to degrade too quickly to facilitate native cellular ingrowth. Phasix™ Mesh is a biosynthetic mesh with both the biocompatibility and resorbability of a biological mesh and the mechanical strength of a synthetic mesh. This multi-center single-arm study aims to collect data on safety and performance of Phasix™ Mesh in Grade 3 hernia patients.

Methods A total of 85 VHWG Grade 3 hernia patients will be treated with Phasix™ Mesh in 15 sites across Europe. The primary outcome is Surgical Site Occurrence (SSO) including hematoma, seroma, infection, dehiscence and fistula formation (requiring intervention) through 3 months. Secondary outcomes include recurrence, infection and quality of life related outcomes after 24 months. Follow-up visits will be at drain removal (if drains were not placed, then on discharge or staple removal instead) and in the 1st, 3rd, 6th, 12th, 18th and 24th month after surgery.

Conclusion Based on evidence from this clinical study, Phasix™ Mesh may become a preferred treatment option in VHWG Grade 3 patients.

BACKGROUND

Incisional hernia (IH) is one of the most frequent complications after midline laparotomy, with incidences varying from 10% to 20%, and even higher percentages occur in high-risk groups [1, 2]. IH can lead to a high morbidity and reduces quality of life [3, 4]. Due to the high IH incidence rates, hernia repair surgery is one of the most frequently performed surgical procedures [5]. The aim of hernia surgery is to relieve symptoms, to prevent complications or to resolve acute complications.

There are several options for hernia repair, including primary suture repair, synthetic or biologic material placement, repair with relaxing incisions, component separation and use of musculofascial flaps, utilizing both open and laparoscopic approaches [6-8]. Synthetic mesh repair procedures, either open or laparoscopic, lead to fewer recurrences compared to primary repair; recurrences after mesh are 7.7% compared to 23.8% after primary closure [1, 3, 9, 10]. Improved outcomes are believed to be related to reduced tension on the fascial edges and sutures when mesh is used in hernia repair procedures. Despite reducing hernia recurrence rates, the use of synthetic mesh has been associated with complications in approximately 17% of patients. These complications include infection, pain, adhesions, fistulae and foreign body reactions including increased inflammation and/or connective tissue deposition [3, 11]. Especially complex and large abdominal wall defects continue to pose a challenge to surgeons, which are associated with recurrence rates of up to nearly 40% [12].

It can be stated that synthetic mesh is more prone to infection than primary closure, and this poses a problem in potentially contaminated hernias like Ventral Hernia Working Group (VHWG) Grade 3 hernias [13] (Figure 1). The success of the mesh repair is jeopardized by potential contamination due to complicating factors like previous wound infection, the presence of a stoma or violation of the gastro-intestinal tract.

The use of a biological tissue matrix has been advocated in (potentially) contaminated hernias, because of their ability to resist infection, milder inflammatory response and more orderly collagen deposition than non-resorbable, synthetic meshes [14-16]. Most often, biological meshes are derived from human, porcine or bovine dermis, and these materials have been processed to acellular sheets of collagen and elastin. The development of resorbable mesh products has faced challenges related to the rate of absorption with complications arising when the mesh product is resorbed too quickly. Rapid resorption does not support sufficient healing if structural reinforcement is diminished during the tissue repair period.

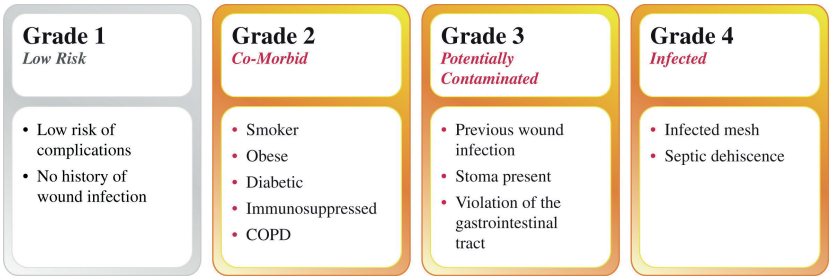


Figure 1. Ventral Hernia Working Group Grading System

Therefore, some meshes contain chemicals to induce additional crosslinking in the graft. This slows down the degradation process, causing the mesh to retain its strength for a longer period of time[17]. However, crosslinking in the mesh reduces its biocompatibility; causing delayed cellular infiltration and neovascularization [17-19]. Ideally, a resorbable mesh should have a high ability to resist infections and retain its functional strength for a sufficient period of time to allow native cellular ingrowth tissue remodeling, maturation of collagen and gradual shift of mechanical load.

Phasix™ Mesh is a commercially available biosynthetic mesh. It is a slowly resorbable mesh prepared from poly-4-hydroxybutrate which has been studied for use as a biomaterial for different medical applications due its strength and flexibility, biocompatibility and desirable degradation times [20-22]. Phasix™ Mesh is comparable in performance to traditional polypropylene mesh when using standard measures of mechanical strength (suture pullout, tear and ball burst strength) [23, 24]. Preclinical implantation studies indicate that Phasix™ Mesh retains approximately 70% of its original strength at 12 weeks [23]. Absorption of the mesh material will be essentially complete in 12-18 months [24]. Given the long-term strength retention observed in preclinical studies, it is anticipated that Phasix™ Mesh may result in low recurrence and complication rates with minimal pain and discomfort when used for hernia repair.

Rationale

From a general perspective, the current literature still is rather void of evidence-based guidelines regarding optimal choice of mesh. Simple, uncontaminated hernias are usually treated with synthetic mesh; biologic meshes are mostly used in potentially contaminated hernias, since post-operative mesh infection is anticipated.

Until now, the use of Phasix™ Mesh was studied primarily in patients up to VHWG Grade 2 [25]. Based on the data gained from this clinical study, additional evidence may be provided with a view to optimal selection of hernia repair material in a population of higher risk. Based on the combination of the features of the Phasix™ Mesh proven in previous clinical and non-clinical investigations, and based on evidence from the clinical study as described in this protocol, Phasix™ Mesh may become a preferred treatment option in VHWG Grade 3 patients.

METHODS

Objectives

The objective of this study is to collect additional data on safety and performance of Phasix™ Mesh in subjects requiring VHWG Grade 3 midline incisional hernia repair. Among others, Surgical Site Occurrence (SSO), hernia recurrence, pain, infection, reoperation and adverse events will be collected for subjects with a VHWG Grade 3 hernia meeting the study inclusion and exclusion criteria.

Design

The study has been designed as a post-market, prospective, single arm, multi-center, open-label study to collect data on performance and safety of Phasix™ Mesh in subjects with a VHWG Grade 3 midline hernia. This study will be conducted in 15 hospitals across Europe.

Participants

Subjects with a VHWG Grade 3 incisional hernia scheduled for hernia repair are eligible for this study and will be asked for informed consent at the outpatient clinic.

Inclusion criteria

All subjects who meet the following criteria listed below can be enrolled in the study:

- Age 18 years or older
- Diagnosis of an incisional midline hernia
- VHWG Grade 3 hernia
- Size of hernia >10 cm^2, measured intraoperatively
- Elective retro-rectus hernia repair
- Signed informed consent

Exclusion criteria

All subjects who meet the following criteria must be excluded from study enrolment:

Regarding the subject:

- Body Mass Index (BMI) > 35 kg/m^2
- Peritonitis
- Use or suspected future use of chemotherapeutic medication during any part of the study
- Known human immunodeficiency virus (HIV) infection
- Cirrhosis of the liver and/or ascites
- Pregnancy, plans to become pregnant during the study period or current breastfeeding
- Alcohol/substance abuse problem or a relapse within 12 months of the screening visit
- Involvement in another interventional clinical study in the last 30 days prior to informed consent signature
- Life expectancy of less than 2 years at the time of enrollment
- Known sensitivity to Phasix™ Mesh or component materials (subjects with known allergies to tetracycline hydrochloride or kanamycin sulfate)
- Any condition that, in the opinion of the investigator, would preclude the use of the study device or preclude the subject from completing the follow-up requirements

Regarding ventral hernia:

- More than 4 previous repairs of the hernia under observation
- The hernia repair requires more than a single piece of mesh
- Intact permanent mesh adjacent to the current hernia to be repaired

Regarding surgery:

- American Society of Anesthesiology class 4 or 5
- Surgical technique requires surgical bridge repair
- Complete removal of existing mesh from a prior hernia repair (in the same affected area) is not possible
- The hernia repair requires intraabdominal mesh placement

Study procedures

Screening

Subjects with a diagnosis of incisional midline hernia requiring surgical repair to close the defect who are presenting at the study site will be considered potential subjects for inclusion in this clinical study and should be pre-screened for study eligibility. If inclusion criteria are potentially met and no exclusion criteria are anticipated to be present at the time of pre-screening, the Investigator will invite the subject to participate in the study.

Informed Consent

Subjects will be asked to sign a written informed consent form. A copy of the informed consent will be provided to the subject.

Eligibility

Final eligibility will be determined intraoperatively. Subjects who fail to meet eligibility criteria should be considered screen failures and will be treated per hospital standard of care. Reason for screen failure will be documented.

Intervention

All subjects will undergo an open ventral repair of the hernia. All intraoperative inclusion and exclusion criteria will be verified.

Subjects will be administered perioperative antibiotics according to hospital protocol. Subjects will be prepared to undergo hernia repair with Phasix™ Mesh. The general instructions for the use of Phasix™ Mesh are supplied by the manufacturer.

Surgical technique

The surgical technique will require retro-rectus placement (onlay is allowed as an exception when retro-rectus placement cannot be achieved), using slowly resorbable sutures, with or without Component Separation Technique (CST). The peritoneum should remain posterior to the mesh upon completion of mesh placement. The mesh may be cut to shape or size desired for each specific application. The mesh is to be positioned so its edges extend beyond the margins of the defect by at least 5 cm. It is recommended that the mesh is fixated at approximately 5-6 cm intervals (6-12 absorbable sutures) around the periphery of the mesh. Defect closure must be confirmed. All skin incisions will be closed with staples/sutures and wounds will be dressed with sterile occlusive dressings.

Outcome parameters

Primary outcome

Primary outcome will be Surgical Site Occurrence (SSO) up to and including, the 3-month follow-up assessment. SSOs will be assessed by physical examination at each study visit through 3 months. SSO is defined as hematoma, seroma, surgical site infection, wound dehiscence, skin necrosis and fistula, all of which require intervention.

Secondary outcome

Secondary outcomes will be:

- Surgical Site Occurrence (SSO) after the 3-month follow-up assessment
- Surgical Site Infection (SSI)[26], is included in SSOs, but will also be analysed separately
- Hernia Recurrence rate (via physical exam, if uncertain via ultrasonography, CT or MRI)
- Pain at every follow-up point, measured with the Visual Analogue Scale (VAS)
- Device related adverse event incidence
- Rate of reoperation due to the index hernia repair
- Quality of Life assessments (Carolinas Comfort Scale™[27][a] and EuroQol-5D (EQ-5D) [28])
- Surgical procedure time as measured from incision to closure (skin to skin)
- Return to work
- Length of hospital stay (day of index surgery until day of discharge, LOS)

To measure these outcomes, the following data will be gathered at different points in time, and saved in an electronic case report form:

Pre-operative data

- Demographic data (age, sex, race, ethnicity) and medical history
- Information regarding the inclusion and exclusion criteria
- Height and weight (calculated to a BMI)
- Length and width of hernia
- Wound assessment
  - signs of infection
  - status and location of potential previous mesh
  - signs of necrosis
- Pain medication usage

- Pain (measured with VAS), discomfort (measured with Carolinas Comfort Scale™) and quality of life (measured with EQ-5D)

Peri-operative data

- Information regarding the inclusion and exclusion criteria
- Intra-operative evaluation of wound and abdomen
- Intra-operative assessment and description of hernia
- Intra-operative assessment of complications, e.g. enterotomy
- Surgical procedure
- Mesh details
- Fixation details
- Wound closure

Post-operative data

The following data will be collected at fixed follow-up visits, namely at drain removal (if applicable, otherwise at discharge or at staple removal), 1 month, 3 months, 6 months, 12 months, 18 months and 24 months (Table 1):

- Wound assessment
  - signs of infection
  - status and location of potential previous mesh
  - signs of necrosis
- Hernia recurrence (diagnosed with physical exam, if uncertain via ultrasonography, or via CT/MRI)
- Adverse events
- Device failure/malfunction/defects
- Pain (measured with VAS)
- Discomfort (measured with Carolinas Comfort Scale™)
- Quality of life (measured with EQ-5D)

In addition, pain medication usage will be collected at 12 and 24 months follow-up.

Withdrawal/Early Termination

A subject is considered an Early Termination if discontinuation occurs after study treatment and before 24 months follow-up. The site will attempt to bring the subject back to the hospital to complete all Early Termination visit study procedures: Physical examination, Pain measured with VAS, Carolinas Comfort Scale™, EQ-5D and collect adverse events. Reason for subject discontinuation will be documented when possible.

Sample size consideration

The expected rate of SSO at 3 months is 37% based on historical data (ranging from 21-53%)[29-32]. With 75 subjects, the accuracy of the estimated SSO will be ± 11% (i.e. half of the width of the 95% confidence interval of the estimated rate of SSO is 11%). The study plans to enroll 85 subjects for follow-up. Anticipating on an attrition rate of about 10%, 75 subjects will be evaluable to assess the primary endpoint of Surgical Site Occurrence (SSO) at 3 months.

Table 1. Summary of procedures performed per visit.

Study Procedure	Screening and Baseline	Index Surgery	Drain Removal/ Discharge	1, 3, 6 and 18 Month Visit	12 and 24 Month Visit	Early Term
Describe study to potential subject	**X**					
Obtain informed consent	**X**					
Collect demographics and medical history	**X**					
Verify eligibility criteria	**X**	**X**				
Physical examination	**X**		**X**	**X**	**X**	**X**
Placement of device		X				
Pain Scale (VAS)	**X**		**X**	**X**	**X**	**X**
Carolinas Comfort Scale™	**X**			**X**	**X**	**X**
EQ-5D	**X**			X	X	**X**
Collect Adverse Events		**X**	**X**	**X**	**X**	**X**
Collect pain medications	**X**				X	

Statistical analysis

There will be a modified intention-to-treat population (mITT), which consists of the subjects in whom Phasix™ Mesh has been implanted. The screen failures were not implanted, and therefore not used in the analysis. A per-protocol (PP) population may be created if there are subjects who have any major protocol deviations. However, all analyses will be primarily based on the mITT population.

Demographics and baseline characteristics will be summarized using the mITT population. Summary statistics for categorical variables will include frequency counts and percentages, and for continuous variables mean, standard deviation, minimum, median and maximum.

The primary endpoint is the SSO rate up to (including) 3 months (± 14 days) post device placement based on the mITT population. A 95% confidence interval will be reported for the SSO rate.

The SSO rate after 3 months, the hernia recurrence rates and surgical site infection rates until 1, 3, 6, 12, 18 and 24 months post device placement will be reported per visit along with their 95% confidence intervals based on the mITT population as secondary endpoints. Additionally, Kaplan-Meier analyses for the time from surgery to hernia recurrence and for the time from surgery to surgical site infection may be performed.

The secondary endpoints of VAS pain scale, Carolinas Comfort Scale™ and EQ-5D will be summarized based on the mITT population with mean, standard deviation, minimum, median and maximum presented by visit.

Device related adverse events will be tabulated by system organ class and preferred term. The number of subjects with a post procedure reoperation due to the index hernia repair will be presented by time intervals (until 1, 3, 6, 12, 18 and 24 months post device placement), surgical procedure duration of the index procedure (calculated as time of skin closure complete minus time of first incision) and length of hospital stay will be summarized descriptively. The time to return to work will be tabulated using summary statistics as well.

Safety parameters, such as adverse events, device deficiencies (mechanical failure, malfunction or defects), physical examination and pain medication, will be summarized using the mITT population.

Subgroup analyses will be performed by sex, sites (sites with few treated subjects can be combined) and other factors of interest.

No missing value imputation methods will be applied in any of the aforementioned analyses.

Safety

In this study, Adverse Events (AE) are defined as any undesirable clinical event occurring in the abdominal wall or the abdominal space, as well as any other undesirable clinical events judged to be related to the study device or surgical procedure regardless of anatomical region, from time of implantation to end of study participation. Abnormal laboratory results are also to be considered as AEs if the results are accompanied by clinical signs or symptoms. The investigator will assess the relationship of an AE to the study device or procedure and categorize them as 'definitely', 'possibly' or 'not related'.

An adverse device effect (ADE) is an AE related to the use of the mesh product implanted (e.g. insufficient or inadequate implantation, installation, operation or malfunction of the Phasix™ Mesh).

Serious adverse events (SAE) are the events that meet the definition of serious in the ISO 14155:2011.

All events will be followed to satisfactory resolution or stabilization.

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of AE, ADE or SAE. All SAEs and investigator-judged device related AEs that occur, must be reported to the sponsor within 24 hours of becoming aware of the event.

An independent safety monitoring committee will reassess safety of the study protocol and decide about potential adaptations if one of the following criteria are met:

- More than 4 device related SAEs within 3 months of Phasix™ Mesh implantation
- More than 1 device related recurrence within 3 months of Phasix™ Mesh implantation

The enrolment and treatment of new subjects are suspended until the impact of the study parameters (e.g. surgical technique, hernia size, mesh size, AE time-course) on the results is assessed. The follow-up for the subjects already treated continues.

Monitoring for accuracy and timely submission of data forms and compliance with the study protocol, meeting enrolment commitments and applicable regulations will take place by monitoring personnel.

Ethics

This study will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The Medical Ethical Committee of the Erasmus Medical Center and the Institutional Review Board of every participating hospital have approved the protocol. Written informed consent will be obtained from all subjects. All study data will be recorded in electronic Case Report Forms provided to the investigational site. Site and subject numbers will be used to track subject information throughout the study.

The sponsor of the study has taken out an insurance policy for all participants of the study, in the case of any negative consequences experienced due to the study or the medical device.

The results of the study will be published in a peer-reviewed journal and on clinicaltrials.gov, which is accessible for the public.

DISCUSSION

A major challenge in all hernia studies is the formulation of a clear definition on the severity or grade of the hernia. The difference between grade 3 and 4 hernias is not always clear, since the classification is more gradual than it seems. The definition for Grade 3 hernias used in this study is the same as the one of the Ventral Hernia Working Group in 2010, which excludes presence of infected mesh[13].

A discussion topic in this study is the absence of a control group. Because no standard treatment is recorded for VHWG Grade 3 hernias, comparing Phasix™ Mesh with synthetic mesh has been considered to be unethical, since the potential contamination of the hernia could cause complications when using a synthetic mesh . Comparing Phasix™ Mesh with just sutures (primary closure) would not be ethical either, due to the high recurrence rates associated with primary closure.

It was considered to compare Phasix™ Mesh with the treating surgeon's standard of care for VHWG Grade 3 hernias in each participating hospital. However, due to the lack of consensus on what standard of care for VHWG Grade 3 hernias is, this would lead to a very heterogenous control group. This justifies the single-arm design of the study.

CONCLUSION

This multicenter trial will collect additional data on safety and performance of Phasix™ Mesh in subjects with a VHWG Grade 3 midline hernia requiring surgical repair. Based on evidence from this clinical study, Phasix™ Mesh may become a preferred treatment option in VHWG Grade 3 patients.

List of abbreviations

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
BMI	Body Mass Index
CCS	Carolina Comfort Scale
CST	Component Separation Technique
CT	Computed Tomography Scan
EQ-5D	EuroQol-5D
HIV	Human Immunodeficiency Virus
IH	Incisional Hernia
LOS	Length of hospital Stay
mITT	Modified Intention-to-treat
MRI	Magnetic Resonance Imaging
PP	Per Protocol
SAE	Serious Adverse Event
SSI	Surgical Site Infection
SSO	Surgical Site Occurence
™	Trademark
VAS	Visual Analogue Scale
VHWG	Ventral Hernia Working Group

List of Declarations

Ethics Approval and consent to participate

This study will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The Medical Ethical Committee of the Erasmus Medical Center and the Institutional Review Board of every participating hospital have approved the protocol. Written informed consent will be obtained from all subjects. A model consent form will be available upon reasonable request. All study

data will be recorded in electronic Case Report Forms provided to the investigational site. Site and subject numbers will be used to track subject information throughout the study.

Consent for publication
Not applicable.

Availability of data and material
This is a protocol, therefore no collected patient data was used. Not applicable.

Competing interests
The study was funded and reviewed by C. R. Bard. (the sponsor).

Funding
C. R. Bard (the sponsor) has designed and financially supported this trial, and will as well conduct interim analyses on the collected data.

Author's contributions
MMJvR and APJ were major contributors in data acquisition and writing the manuscript. TT, LNJ, TSdVR, GP, FK, MM, ACJW, FB, RHF, BD, GW, HLvW, FG, AK, GWMT and JFL acquired data, revised and approved the protocol. LFK was a major contributor in data acquisition, reviewing and approving the manuscript. JJ was a major contributor in designing, reviewing and approving the manuscript.

Acknowledgements
Not Applicable.

Endnotes

[a] The CAROLINAS COMFORT SCALE™ questionnaire was created by and is licensed from the Division of Gastrointestinal and Minimally Invasive Surgery of Carolinas Medical Center, North Carolina

[b] Reprinted from Surgery, 148(3), The Ventral Hernia Working Group, Incisional ventral hernias: Review of the literature and recommendations regarding the grading and technique of repair, 544-558, Copyright (2010), with permission from Elsevier.

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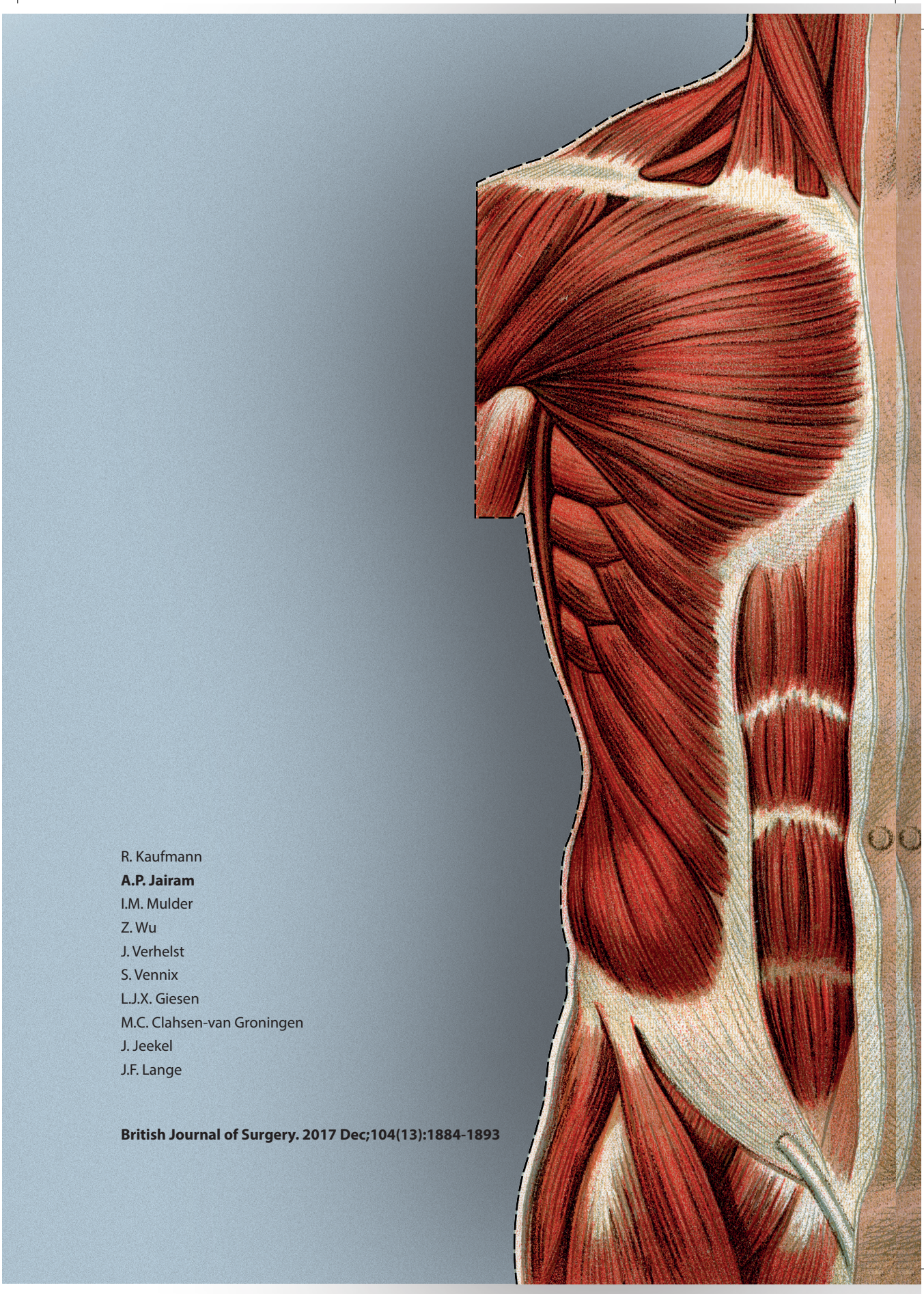
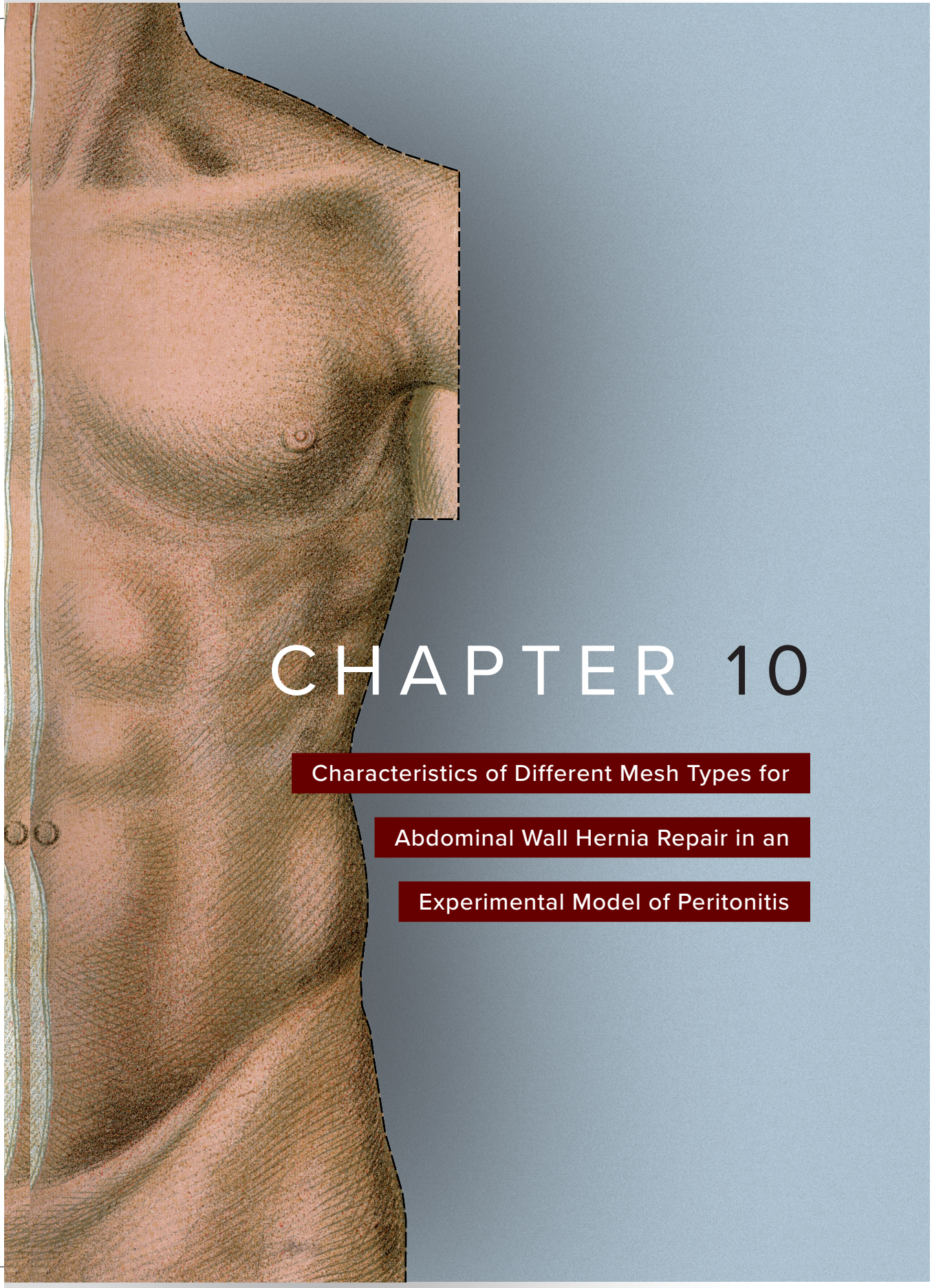


R. Kaufmann
A.P. Jairam
I.M. Mulder
Z. Wu
J. Verhelst
S. Vennix
L.J.X. Giesen
M.C. Clahsen-van Groningen
J. Jeekel
J.F. Lange

British Journal of Surgery. 2017 Dec;104(13):1884-1893



CHAPTER 10

Characteristics of Different Mesh Types for Abdominal Wall Hernia Repair in an Experimental Model of Peritonitis

ABSTRACT

Background: 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 h. 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 analysed.

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 per cent[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 places after implantation of the mesh. During this phase, there is incorporation of host fibroblasts and collagen replacement occurs. This so-called xenograft remodelling 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.

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 per cent, and 12-h 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 g 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 anaesthetized 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 per cent ethanol. The abdominal cavity was opened via a 3-cm midline incision. To induce peritonitis, the caecum ligation puncture model (CLP) was used[18]. The caecum was ligated just distal to the ileocaecal 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 per cent and were placed under a heating lamp to recover from anaesthesia.

After 24 h, all rats were again anaesthetized with a mixture of isoflurane and oxygen. They received a single dose of buprenorphine (0.05 mg/kg subcutaneously). The skin was desinfected with 70 per cent ethanol, the abdomen was reopened, and a bacterial culture swab taken to confirm faecal peritonitis. The necrotic or ischaemic part of the caecum 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 per cent and were placed under a heating lamp to recover from anaesthesia.

Mesh material

Five different meshes were analysed 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 behaviour were assessed using a 12-point wellness scoring system[19]. Animals were killed if they reached the humane endpoint (at least 20 per cent 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 days, 90 or 180 days after mesh placement. They were anaesthetized with a mixture of isoflurane and oxygen, the abdomen was shaved, and the skin desinfected with 70 per cent 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 (*Fig. 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.

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).

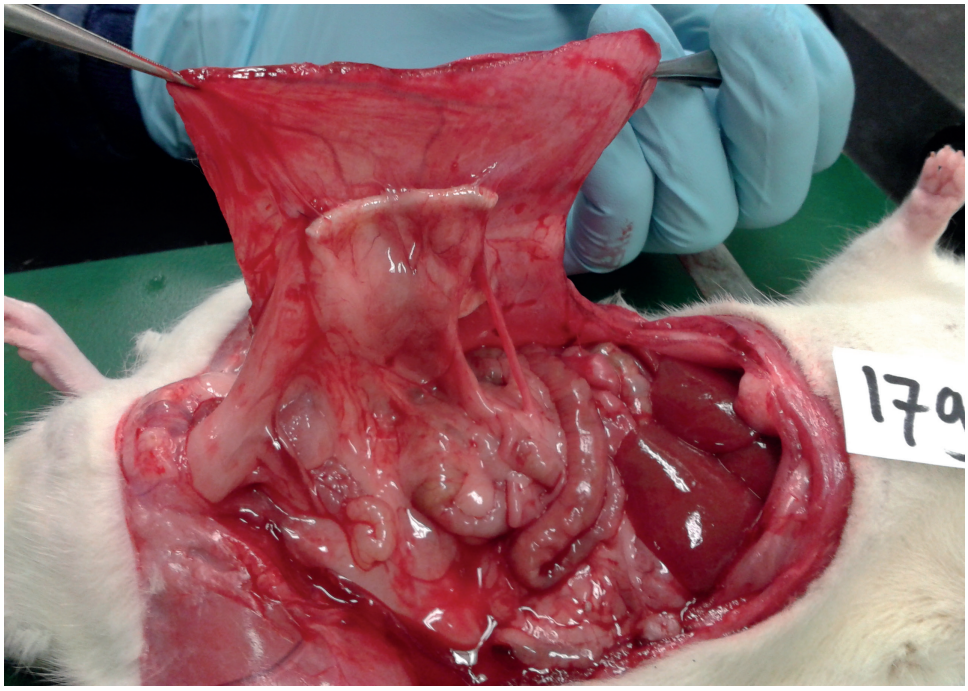


Figure 1. Photograph taken during sacrifice: Inner abdominal wall and the mesh site (cross-linked biological mesh)

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 (*Fig. S1*, supporting information). The

samples were fixed for 24 h in 4 per cent formalin and subsequently embedded in paraffin. Two 4-µm sections were cut and stained with either haematoxylin and eosin or sirius red, according to standard diagnostic procedure in the pathology department.

All slides were analysed blind by an experienced pathologist. Haematoxylin 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 per cent in amount of adhesions between the meshes. The expected mortality of the CLP model was 25 per cent. Aiming for a power of 80 per cent 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 (i.q.r.). 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 hour after induction of peritonitis and another 13 died in the next 24 hours after implantation of the mesh (overall mortality rate 13.3 per cent). 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 faecal 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 caecum and mesentery; no adhesions between bowel and mesh). The remaining 117 rats survived and could be analysed at the intended endpoint. The distribution of the surviving animals per study group is shown in *Table 1*.

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 behaviour, piloerection, ocular exudates, abnormal posture, shivering, diarrhoea and weight loss. Mean weight loss varied from 9.0 to 11.2 per cent, 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 caecum was macroscopically ischaemic in 89 per cent of the animals, necrotic in 4 per cent, and both ischaemic and necrotic in 7 per cent of the animals.

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/m²)	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. analysed					
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.

Incorporation of mesh

The percentage incorporation varied greatly between the mesh groups (*Table 2* and *Fig. 2*). At 180 days after implantation, it was highest for XCM™ Biologic (88(72-100) per cent), followed by Permacol™ (62(58-67) per cent), Parietene™ (57(32-87) per cent), Omyra® Mesh (54(40-66) per cent) and lowest for Strattice™ (21(10-30) per cent). Both XCM™ Biologic and Permacol™ showed significantly better incorporation than Strattice™ 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 12 to 51 per cent at different time points for different meshes (*Table 2* and *Fig. 3*). Shrinkage was most evident in XCM™ Biologic: 21(4-36) per cent at 30 days, 43(38-66) per cent at 90 days and 36(34-51) per cent at 180 days. Parietene™ showed the least shrinkage at 30 days after implantation (8(1-257) per cent). Strattice™ and Omyra® Mesh showed the least shrinkage 90 days after implantation (15 (13-20) per cent and 15 (9-20)per cent respectively). Strattice™ showed the least shrinkage 180 days after implantation (13(5-17) per cent). 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) per cent), followed by Permacol™ (7363-83) per cent), Parietene™ (70(60-80) per cent) and Omyra® Mesh (63(60-70) per cent), and lowest in Strattice™ (0(0-0) per cent). 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.

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 (i.q.r.). 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).

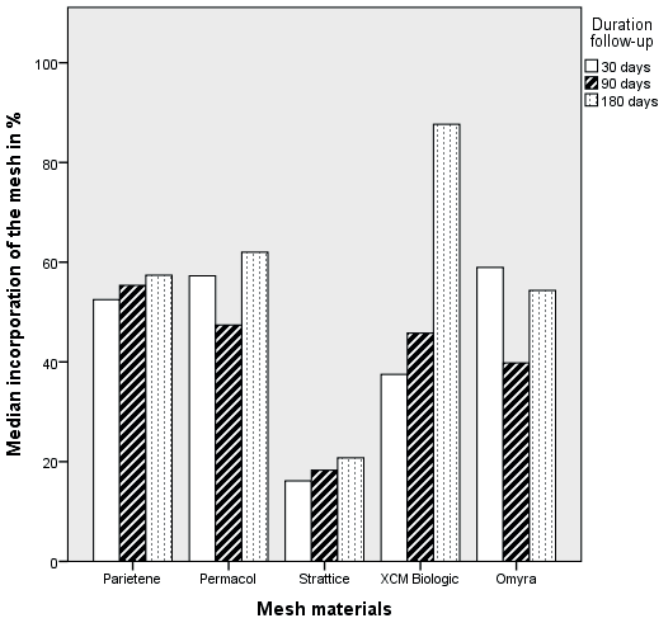


Figure 2. Median percentage incorporation of each mesh at 30, 90 and 180 days

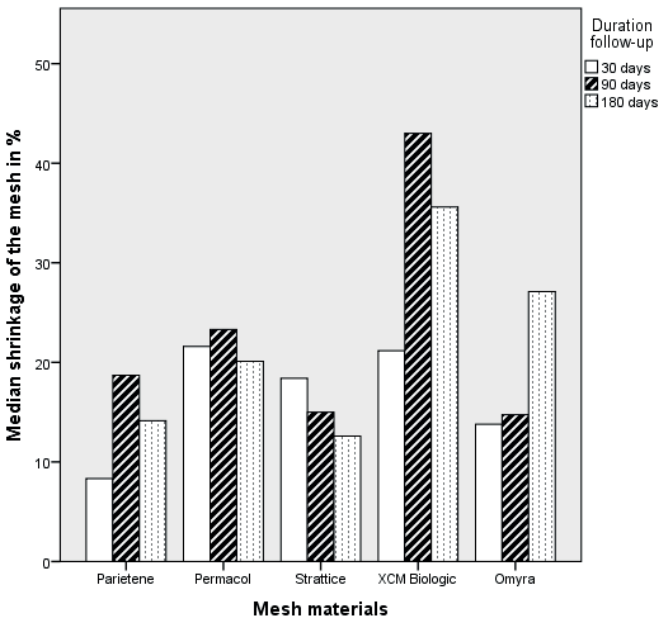


Figure 3. Median percentage shrinkage of each mesh at 30, 90 and 180 days

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 caecal 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 analysed. 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 haematoxylin 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*, *Figs S2–S5*, supporting information, online available). 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 per cent at various time points. XCM™ Biologic shrank excessively, by 21–43 per cent. 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 per cent 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 per cent of animals at the time of death. Both Deerenberg and colleagues[14] and the present study group studied Strattice™, Parietene™ and Omyra® Mesh. In the study of Deerenberg *et al.*[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 per cent 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 arepoly of different materials, their *in vivo* response was similar. Interestingly, Permacol™ is the only biological mesh in this study that mimicked the behaviour 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 behaviour 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. 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 behaviour 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.

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Disclosure: The authors declare no conflict of interest.

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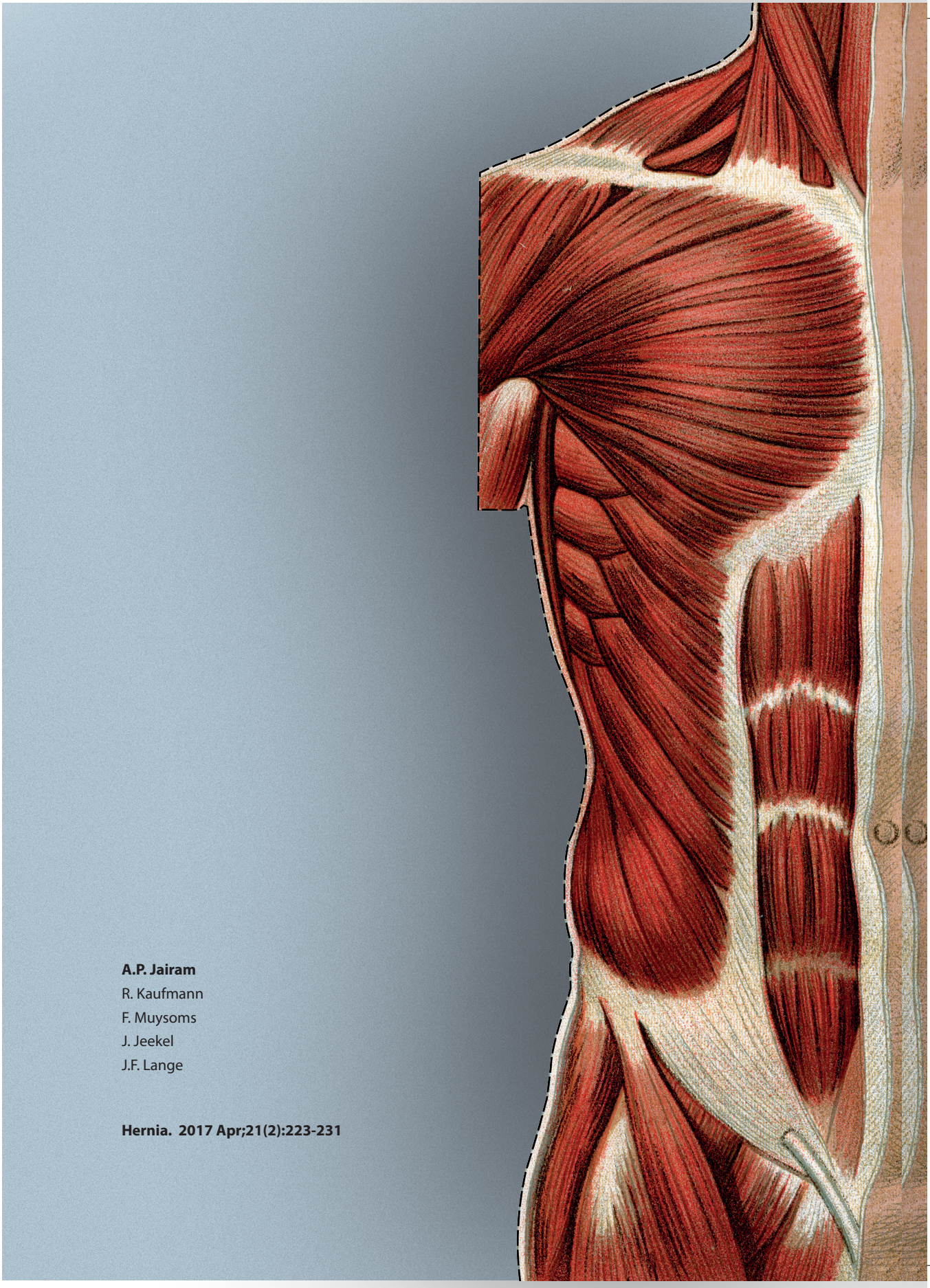
Supporting information

Additional supporting information may be found online in the supporting information tab for this article.

Table S1 Zühlke scoring system for adhesions (Word document)
Table S2 Abscess scoring system (Word document)
Table S3 Histological scoring system for inflammatory cell reaction (Word document)
Table S4 Histological scoring system for mesh-specific parameters (Word document)
Table S5 Collagen deposition (Word document)
Table S6 Results of histological evaluation (Word document)
Table S7 Results for mesh-specific parameters (Word document)
Figure S1 Schematic representation of tissue sampling for histopathology (Word document)
Figure S2 Haematoxylin and eosin staining of cross-linked biological mesh, without abscess (original magnification × 10) (Word document)
Figure S3 Haematoxylin and eosin staining of cross-linked biological mesh, without abscess (original magnification × 20) (Word document)
Figure S4 Sirius red staining of cross-linked biological mesh, without abscess (Word document)
Figure S5 Haematoxylin and eosin staining of cross-linked biological mesh, with abscess (original magnification × 2.5) (Word document)
Figure S6 Haematoxylin and eosin staining of cross-linked biological mesh, with abscess (original magnification × 10) (Word document)
Figure S7 Haematoxylin and eosin staining of cross-linked biological mesh, with abscess (original magnification × 20) (Word document)
Figure S8 Sirius red staining of cross-linked biological mesh, with abscess (Word document)
Figure S9 Haematoxylin and eosin staining of non-cross-linked biological mesh (XCM™ Biologic), without abscess (original magnification × 10) (Word document)
Figure S10 Haematoxylin and eosin staining of non-cross-linked biological mesh (XCM™ Biologic), without abscess (original magnification × 20) (Word document)
Figure S11 Sirius red staining of non-cross-linked biological mesh (XCM™ Biologic), without abscess (Word document)



A.P. Jairam
R. Kaufmann
F. Muysoms
J. Jeekel
J.F. Lange

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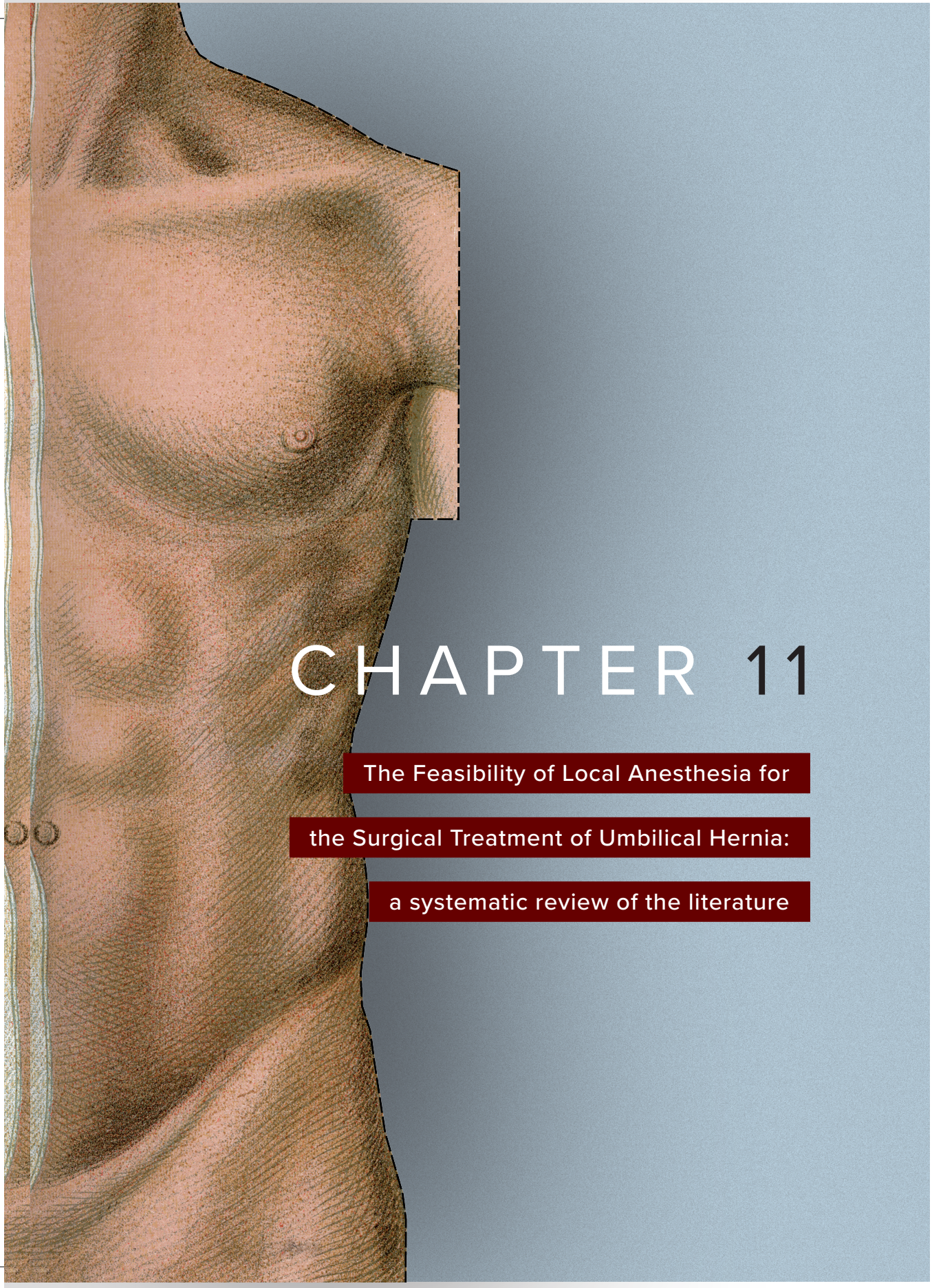

CHAPTER 11

The Feasibility of Local Anesthesia for the Surgical Treatment of Umbilical Hernia: a systematic review of the literature

ABSTRACT

Background: 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 9 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%. There were no postoperative deaths and no allergic reactions described for local anesthesia. The hernia recurrence rate varied from 2% to 7.4%. Almost 90% of umbilical hernia patients treated with local anesthesia were discharged within 24 hours, compared with 47% of patients treated with general anesthesia. The overall patient satisfaction rate varied from 89% to 97%.

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% of all abdominal wall hernias are defined as umbilical hernia [3], and the prevalence of umbilical hernia in the adult population is 2% [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 than general anesthesia or spinal anesthesia [7-13]. However, only 7% 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.

MATERIAL AND 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 MedicalVLibrary (Erasmus University Medical Center, Rotterdam, the Netherlands). A syntax with search terms was designed, which is available at Appendix 1.

Records identified 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 5 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, 9 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 9 included articles, 6 were prospective cohort studies, and 3 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 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.

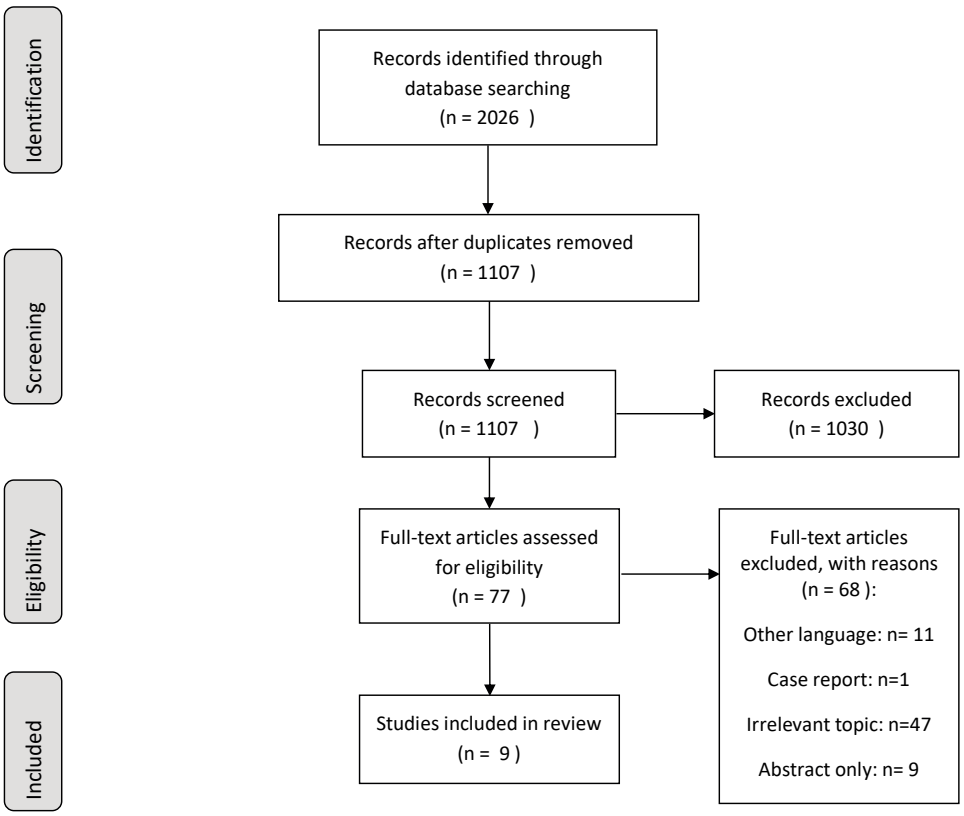

Figure 1. PRISMA flow diagram

Surgical technique

There were 2 studies in which a Mayo repair was performed, with the classical 'vest over pants' technique [19, 20]. Bennett et al. inserted a polypropylene soft mesh plug if the defect was < 2 cm. In case the defect was > 2 centimeter, a preperitoneal pocket was made and a polypropylene soft mesh was placed, with a 2 centimeter margin [14]. In the study of Kurzer et al. a cone polypropylene mesh was used for defects < 3 centimeter,

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

and a flat piece mesh for defects > 3 centimeter [2]. Garcia et al. used 1 centimeter 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 only one study umbilical hernia operations with meshes was performed [1, 3, 6, 19]. Dalenbäck et al. were the only authors who specified the type of surgical procedure for the type of anesthesia. A total of 162 patients underwent an umbilical hernia operation. Of the patients operated with a suture repair, 59% were operated under local anesthesia and 41% under general anesthesia. Of the patients receiving a mesh repair, 18% were operated under local anesthesia and 82% 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 4 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 our without sedatives) and the different types of anesthetic drugs that were used. The anesthetic drugs varied from the short acting lidocaine and xylocaine to the longer acting agent bupivacaine. Bennett et al. 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 et al. 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% of lean patients (BMI < 30) had a VAS of < 3, compared with 71.9% 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].

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	Lidocain 0.5%	Not applicable	
Bennett et al.	Not applicable	Not applicable	GA: not described LA: Xylocaine 2%, Bupivacain 0.5%
Dalenback et al.	Not applicable	Not applicable	GA: not described LA: not described
Garcia et al.	Not applicable	Lidocaine 1% + midazolam	Not applicable
Kulacoglu et al.	Not applicable	Lidocaine, bupivacaine 0.5% + midazolam and fentanyl	Not applicable
Kurzer et al.	Not applicable	Bupivacaine 0.25% + midazolam	Not applicable
Menon and Brown	Not applicable	Xylocaine 1% + Bupivacaine 0.5% + midazolam	Not applicable
Sinha and Keith	Not applicable	Not applicable	GA: not described LA: xylocaine 1%
Stabilini et al.			GA: not described LA: mepivacaine

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 et al. 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 et al. and Menon and Brown all included patients with umbilical hernia treated with local anesthesia alone. Kulacoglu et al. 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 (27045), *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)

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% (15/431), and ranged from 1% to 12.9% [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% and 0.7% ($p < 0.023$). 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%, and an overall percentage of 4.8%. All seromas either resolved spontaneously or were successfully treated with drainage [1, 3, 4, 21]. The second most frequent postoperative complication were hematomas (1%) [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 2 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, 3 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 3 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 4 articles measured a recurrence rate ranging from 2% to 7.4% [3, 4, 19, 21]. These 4 studies did not all mention which patients presented with a recurrence. Dalenbäck et al. 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 2 recurrences (out of 144 patients) in the general anesthesia group and 5 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 et al. showed that patients with umbilical hernia, operated under local anesthesia, stayed 122±58 min in hospital before discharge [1]. Sinha and Keith described that 89% of the patients in the local anesthesia group were discharged in less than 24 hours, compared with 47% of the patients in the general anesthesia group [21]. The other articles did not specify the duration of stay for the type of anesthesia or type of hernia. The longest mean duration of stay was 1.8 days (range: 3 hours – 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% till 97% 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% of their patient population was satisfied, according to the definition of Reitter. [21]. The remaining 3 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].

Table 4. Time to discharge

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

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]. These studies all 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 et al. showed that significantly more urinary retentions occurred in patients undergoing Lichtenstein hernia repair under spinal anesthesia [7]. Furthermore, the conversion rate to general anesthesia was lower for patients operated under local anesthesia (2%) than patients operated under spinal anesthesia (10%) [15]. Nordin et al. also showed that local anesthesia has significant cost advantages compared to spinal anesthesia and general anesthesia [12]. 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 all 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 et al. 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 et al. used a solution which consisted of 1% lidocaine, 1% 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%, 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% for mesh repair, rising up to 8% for suture repair [24, 25]. However, recently the cohort study of Christoffersen et al. showed that the total cumulated recurrence rate after primary repair was 10% for mesh repair and 21% for sutured repair after 55 months of follow up ($p = 0.001$) [26], which is a surprisingly high percentage. Dalenbäck et al. 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). 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 et al. 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. 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% 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% 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.

The present 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 aim 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 current available literature. Almost every outcome parameter is not specified for the patient group we aim 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.

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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

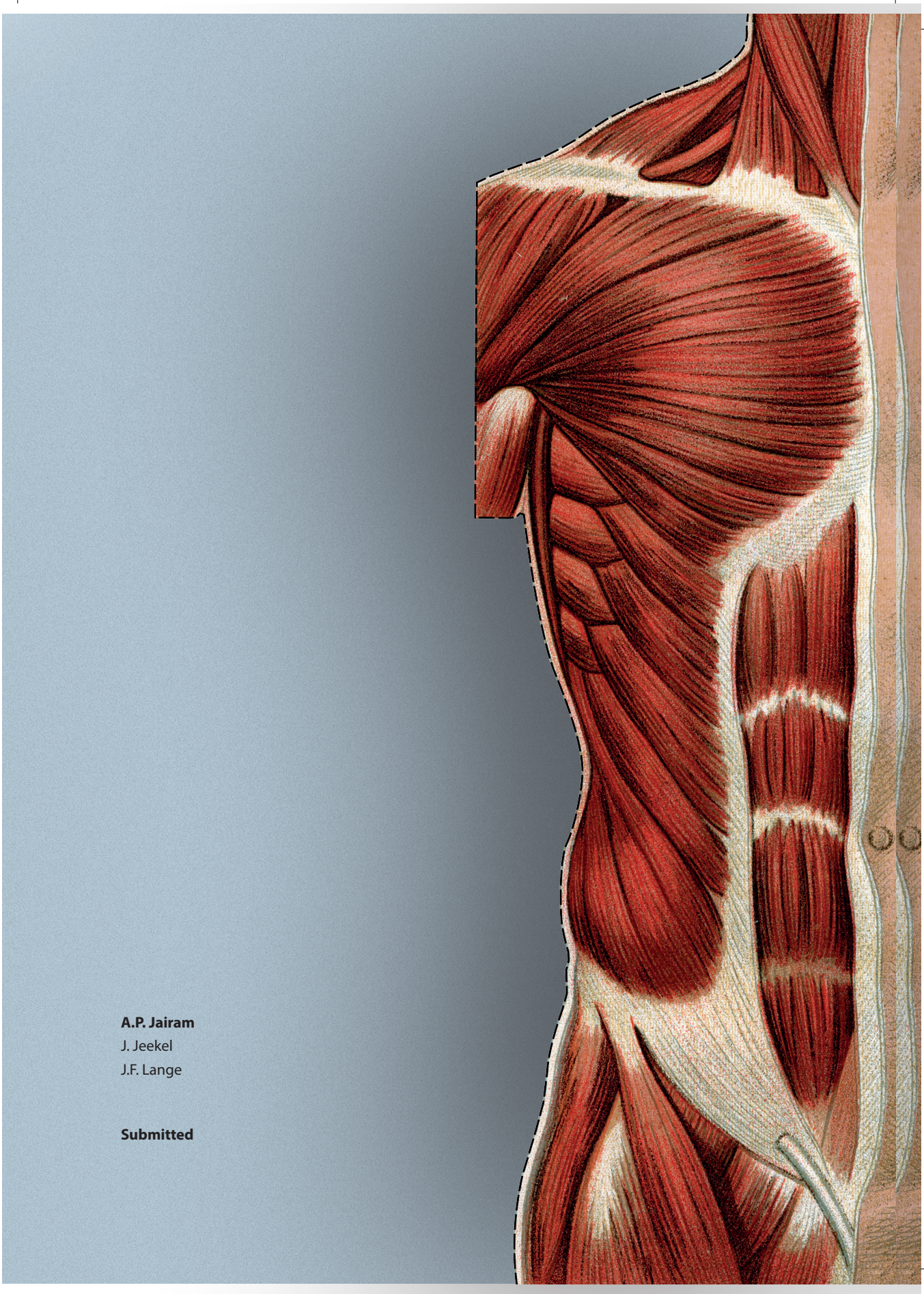
In Cochrane the following search strategy was performed: ((((umbilic* OR 'abdominal wall' OR ventral) NEAR/6 (herni* OR defect*)) OR exomphal*):ab,ti) AND ((((local OR topical OR region* OR infiltrat* OR conduct* OR block*) NEAR/3 (anesthe* OR anaesthe*)) OR ((ambula* OR day OR daycare OR outpatient*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



A.P. Jairam
J. Jeekel
J.F. Lange

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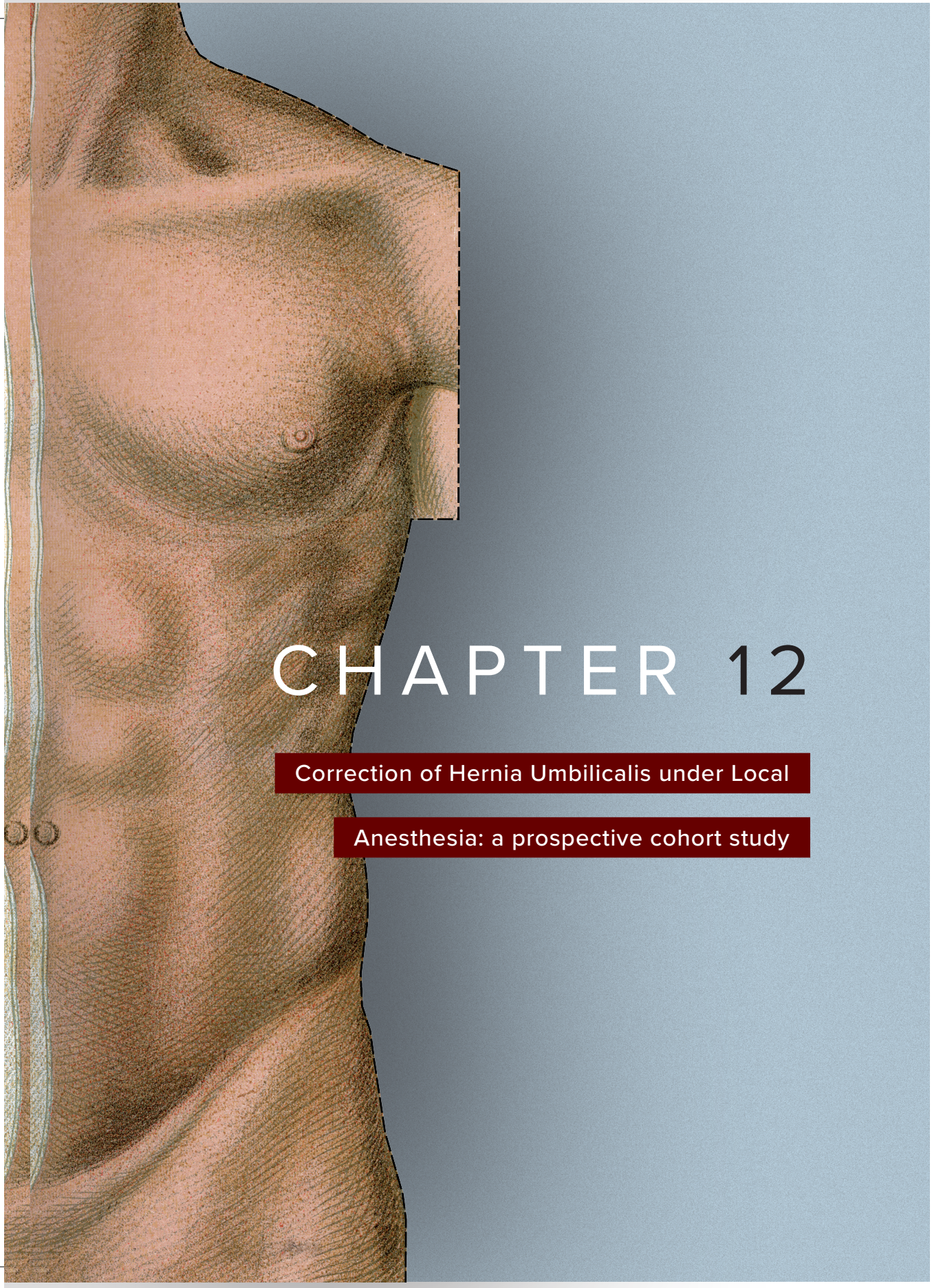

CHAPTER 12

Correction of Hernia Umbilicalis under Local Anesthesia: a prospective cohort study

ABSTRACT

Background: Most umbilical hernias are repaired under general anesthesia. Nowadays, it is becoming more common to undergo inguinal hernia surgery under local anesthesia. Local anesthesia has several advantages, such as less postoperative pain and early mobilisation of patients, which can lead to a shorter hospital stay. There is a lack of evidence regarding local anesthesia for umbilical hernia repair. In this prospective cohort study the feasibility and safety of local anesthesia in standardized circumstances will be investigated.

Methods: Patients from four different hospitals in the Netherlands were included. Patients could only be enrolled if they were aged ≥18 years and were diagnosed with an umbilical hernia. Patients were anesthetized with a local anaesthetic: Ropivacaine (0,75% 3 milligram per kilogram body weight), which was injected as a field block. Remifentanil (0,5 microgram/kg) was used as a sedative. The main endpoint of this pilot study is the feasibility and safety of local anesthesia in umbilical hernia repair.

Results: 30 patients were included. In 67% of patients, the defect was closed with primary sutures. None of the surgical procedures had to be ceased during surgery because of excessive pain. The use of local anesthesia did not lead to peri- or postoperative complications, allergic responses or postoperative deaths. All patients were discharged on the same day they were operated. A mean VAS of 1.8 was identified after surgery. No postoperative complications were identified after a follow up of two weeks.

Conclusion: Both patients and surgeons were positive about the surgical procedure with a local anaesthetic. It can be concluded that the use of local anaesthesia, using Ropivacaine as a local agent and Remifentanil as a sedative, is safe and feasible in umbilical hernia repair. The next step will be conducting a randomized controlled trial, in which local anesthesia will be compared with general anesthesia in umbilical hernia repair.

INTRODUCTION

Approximately 10% of all abdominal wall hernias are umbilical hernias (1). According to the European Hernia Society, an umbilical hernia (UH) is defined as a midline abdominal wall defect from three centimetres above up to three centimetres below the umbilicus (2). It can be present either at birth, or it can develop spontaneously throughout life, for example by increased intra-abdominal pressure, such as in COPD patients or patients with liver cirrhosis. The prevalence of UH in adult population is approximately 2% (3). Yearly, 4500 UHs are repaired in the Netherlands. Surgical repair can be performed by either suture repair or mesh repair. The recurrence rate of mesh repair is low, with a percentage of 1% (4).

Most of UHs are repaired under general anesthesia. Nowadays, it is becoming more common to undergo abdominal wall hernia surgery for small hernias under local anesthesia. Local anesthesia in the treatment of inguinal hernia has already been investigated thoroughly. Several studies have shown the advantages of the use of local anesthesia in groin hernia repair over the use of general or spinal anesthesia (5-11). However, unfortunately the use of local anesthesia is still not commonly applied in abdominal wall hernia repair among surgeons (11). Local anesthesia has several advantages, such as less postoperative pain, normal micturation and early mobilisation of patients, which can lead to a shorter duration of hospital stay. Until now, there is a lack of evidence regarding local anesthesia for UH repair. Jairam et al. performed a systematic review, in which nine (retrospective and prospective) cohort studies/case-studies were included (12). It was concluded that the advantages of local anesthesia could not be sufficiently demonstrated, due to the heterogeneity amongst included studies. In order to conduct an appropriate randomized controlled trial, in which local anesthesia will be compared with general anesthesia for UH repair, we aimed to start with a prospective cohort study at first. In this study the feasibility and safety of local anesthesia will be investigated.

METHODS

Between January 2015 and December 2017, patients were asked to participate. The local ethics committee of the Erasmus University Medical Center Rotterdam approved this study. Patients from three different hospitals were included: Havenziekenhuis Rotterdam, Maastricht Universitair Medisch Centrum and Spaarne Gasthuis Haarlem. Patients could only be enrolled if they were aged ≥18 years and were diagnosed with UH. Patients were excluded if they were pregnant, had UH> 3 centimetre in

diameter, a recurrence or if they had undergone previous abdominal surgery (either midline laparotomy or laparoscopic surgery). Other exclusion criteria were: emergency procedure, the presence of an incarcerated hernia, ascites or cirrhosis, an American Society of Anaesthesiologists (ASA) score IV and a BMI > 30. All patients gave written informed consent.

The main endpoint of this pilot study is the feasibility and safety of local anesthesia in UH repair. There were no secondary endpoints.

Patients were anesthetized with a local anesthetic: Ropivacaine (0,75% 3 milligram per kilogram body weight), which was injected as a field block. Patients also received preoperatively Remifentanil (0,5 microgram/kg), to reach a comfortable situation for the patient, without losing consciousness. The surgeon was instructed to reserve 5 milliliters of Ropivacaine, which could be administered if the patient still experienced severe pain (as escape medication).

Surgical repair was performed by para-umbilical incision, dissection of the hernia sac and restoration of the sac together with its contents into the abdominal cavity. The defect was primarily closed with absorbable monofilament interrupted sutures (PDS 2x0) in case the defect was <1 centimeter. In case the defect was ≥ 1 cm, a mesh was placed intraperitoneally or in the preperitoneal plane. The achieved overlap had to be at least 2 centimeters in each direction of the circular mesh. The mesh that was used in this pilot study was the Cabs'Air® mesh (Cousin, France). This mesh is a knitted monofilament polypropylene mesh with poly-L-lactic acid (PLLA), having an inflatable expansion balloon. For the intraperitoneal defect the Cabs Air Composite® mesh was used, which has a monofilament polypropylene side and an ePTFE side. In case the mesh had to be placed extraperitoneally, the Cabs Air Semi Resorbable (SR-6)® mesh was used. Closure of the subcutaneous tissue and skin was conducted by using a method chosen by the individual surgeon. Surgery took place at the operation room. A nurse anesthetist was present to monitor vital signs. During surgical repair of UH, the anesthesiologist was ready to intervene if necessary. The procedure was ceased if the local anesthetic did not adequately reduce the pain.

Visual Analogue Scale (VAS) evaluated postoperative pain. Patients were followed at the outpatient clinic after one week. After 2 weeks, they were asked to fill in the Short Form-36 questionnaire (SF-36), EuroQol-5D questionnaire (EQ-5D) and the VAS form again.

Statistical analysis of the VAS, SF-36 and the EQ-5D will be performed with the linear model. The measurements of VAS scores will be compared using the Mann-Whitney test.

RESULTS

In total, 30 patients were included. Table 1 shows the baseline and surgical characteristics. Almost 80% of patients were male, mean age being 57 years. In 67% of patients, the defect was closed with primary sutures. Patients did not experience excessive pain. Therefore, none of the procedures had to be ceased. During operation of all patients, vital signs remained stable. All patients were discharged on the same day they were operated. Postoperative pain was measured with the Visual Analogue Score (VAS). A mean VAS of 1.8 (SE 0.33) was identified.

Table 1. Baseline and surgical characteristics

Baseline characteristics	
Male gender, N (%)	24 (80%)
Age, mean (y)	57 y
Surgical characteristics	
Defect < 2 centimeters, N (%)	20 (67%)
Complications, N (%)	
- hematoma	0 (0%)
- seroma	1 (3.3%)
- surgical site infection	0 (0%)
Ceased surgical procedures, N (%)	0 (0%)
Overnight hospital admission, N (%)	0 (0%)

Two to four weeks after surgery, patients were seen at the outpatient clinic. None of the patients developed hematoma or a surgical site infection. One patient developed a seroma, which did not deed any surgical intervention. Mean VAS of 1 (SE 0.23) was identified during follow up. SF-36 and EQ-5D questionnaires were filled in by all patients. Table 2 shows the Quality-of-Life (QoL) scores.

Table 2. Quality-of-Life scores

	Mean (SE)
SF-36 domain	
Pain	79.03 (2.12)
Physical functioning	79.55 (2.25)
Physical health	72.42 (3.2)
Emotional problems	84.36 (3.84)
Energy or fatigue	72.30 (1.64)
Emotional wellbeing	74.90 (1.16)
Social functioning	83.00 (2.52)
General health	72.90 (2.40)
EQ-5D	0.82 (0.03)

DISCUSSION

This prospective cohort study reveals that the use of local anesthesia for the repair of UHs is safe and feasible. UH is a common surgical problem, with a number of 4500 repairs per year in the Netherlands alone. Currently, most UH repairs take place under general anesthesia. This is unfortunate, since local anesthesia might have several advantages, such as a shorter duration of hospital stay, cost-effectiveness, better immediate postoperative micturition, and less postoperative pain. Literature regarding local anesthesia in UH repair is scarce (1, 3, 12-19). This is in contrary to local anesthesia in groin hernia repair, which is investigated extensively. Van Veen et al. conducted a randomized controlled trial, in which local anesthesia was compared with spinal anesthesia in Lichtenstein hernia repair (11). It was found that patients who were operated under local anesthesia had significantly less pain after surgery. Duration of surgery was shorter in the local anesthesia group. Furthermore, significantly more urinary retention and more overnight admissions occurred after spinal anesthesia (11). Even though evidence shows that local anesthesia is superior compared to general or spinal anesthesia, patients are still more often operated with general or spinal anesthesia, for unknown reasons.

Due to the lack of convincing literature regarding UH and local anesthesia, a systematic review was performed by Jairam et al (12). This systematic review showed a high heterogeneity, with no consensus regarding injection technique, type of local anaesthetic, or conversions to general anesthesia. Only a few small prospective and

retrospective cohort studies have been performed until now (3, 13, 14, 16, 18). No randomized controlled trial has been conducted so far, providing level-1 evidence in showing the superiority of local anesthesia for the treatment of UH. This means that no firm conclusions can be made regarding postoperative complications, postoperative pain, or mortality. We therefore aimed to perform a well-conducted randomized controlled trial. The underlying prospective cohort study was initiated to evaluate the safety and feasibility of the performance of local anesthesia, since there was no consensus regarding type of anesthesia or the surgical technique. In addition, no information was available in literature regarding postoperative complications, postoperative pain, or mortality. Last but not least, it was noticed that most surgeons did not feel comfortable with local anesthesia for umbilical hernia repair. A learning curve in the following randomized controlled trial had to be avoided.

The inclusion of patients for this study, even in four hospitals of which three large teaching hospitals, proved to be difficult as, even after specific training in the local anaesthetic technique, surgeons and anaesthesiologists were still reluctant to include patients by habit. However, in this cohort the safety and feasibility of local anesthesia were demonstrated. None of the surgical procedures had to be ceased during surgery because of excessive pain. The use of local anesthesia did not lead to peri- or postoperative complications, allergic responses or postoperative deaths. Furthermore, a relatively low VAS score was measured directly after surgery, which is comparable with the VAS detected in the study of Van Veen et al (11). None of the patients needed overnight hospital admission. During visit at the outpatient clinic, no serious complications were observed: only one patient developed seroma without any consequence for the patient. VAS score was low during follow up (VAS 1, SE 0.23). Hopefully these results will convince surgeons of the need of a randomized controlled trial, in which the local anaesthetic of this pilot study will be compared with general anesthesia in patients undergoing UH repair.

CONCLUSION

This prospective cohort study is the first study in which the use of a local agent in UH surgery is prospectively investigated under standardized circumstances in a homogenous group of patients. Both patients and surgeons were positive about the surgical procedure with a local anaesthetic. It can be concluded that the use of local anaesthesia, using Ropivacaine as a local agent and Remifentanil as a sedative, is safe and feasible in UH repair.

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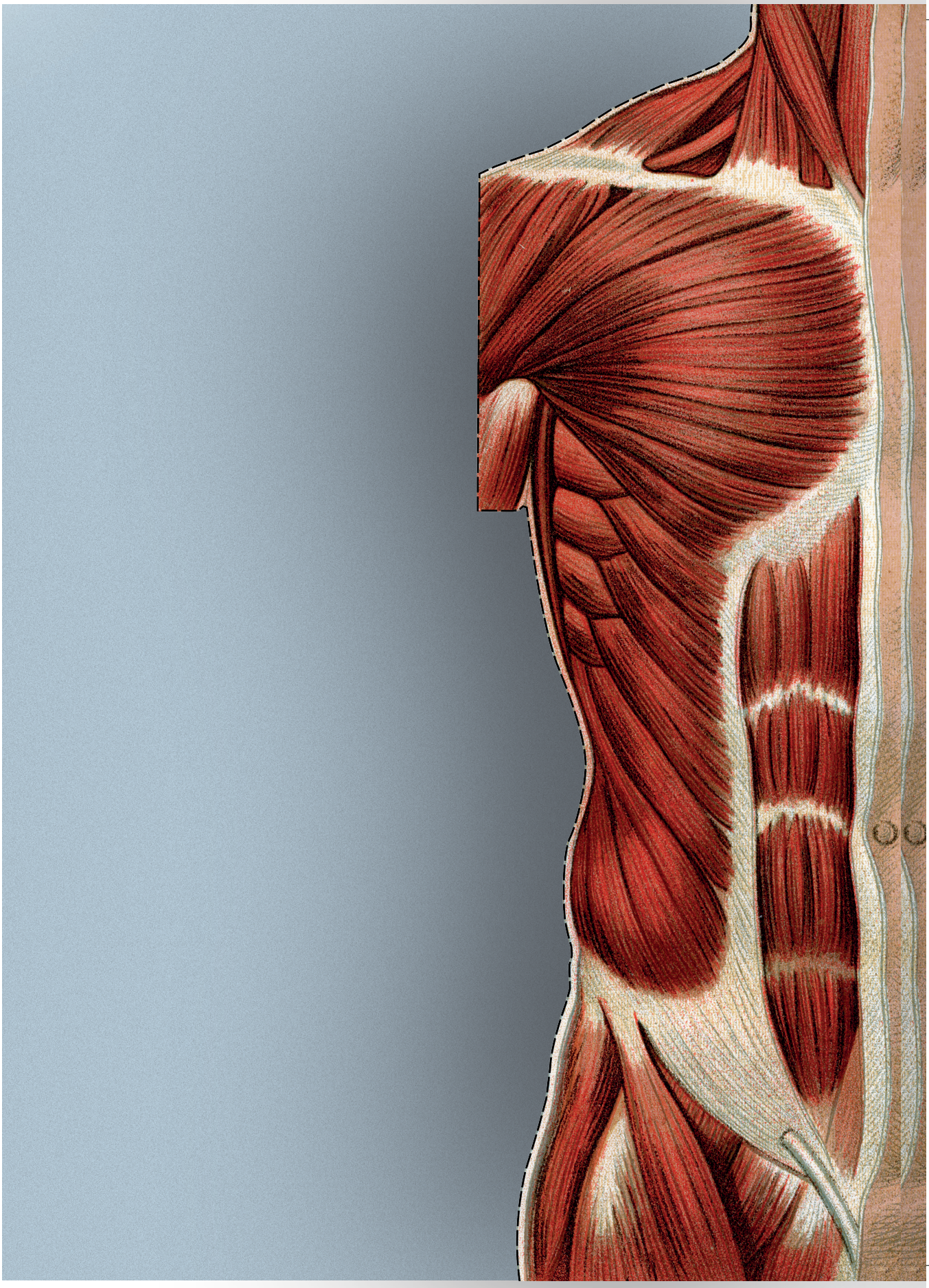
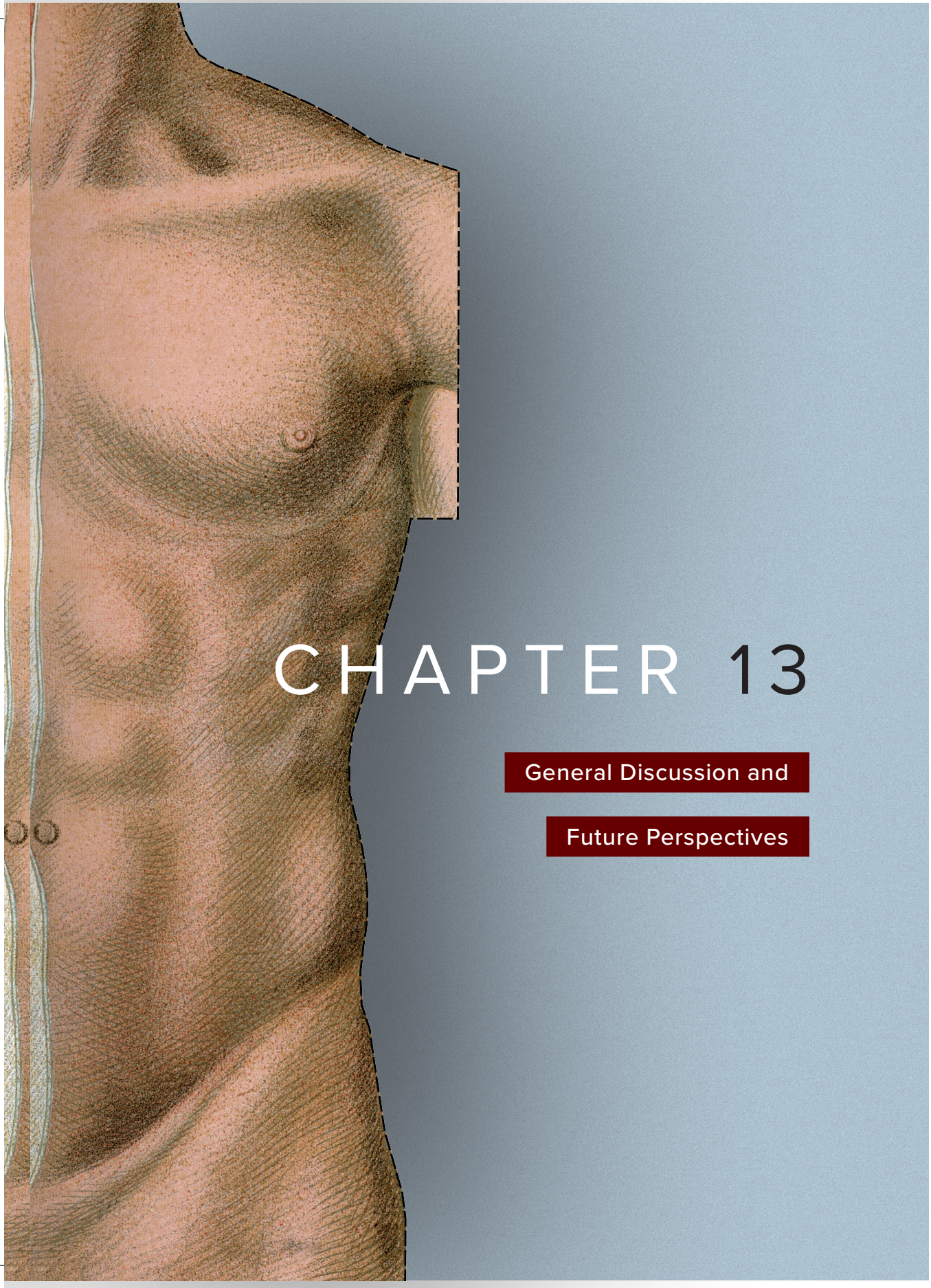
PART 3

Future Perspectives, Summary and Appendices





CHAPTER 13

General Discussion and Future Perspectives

DISCUSSION

Incisional hernia (IH) is the most frequent complication after abdominal surgery (8, 43). In the United States alone 200.000 IH repairs are performed each year, with a total cost of 3.2 billion dollars. It can be stated that IH has an unnecessary high (economic) burden on today's society (44-46). There are several factors that can contribute to a high IH incidence, such as patients' risk factors (obesity, aneurysm of the abdominal aorta, collagen diseases like Ehlers Danlos and Marfan), suture technique and type of incision (13-18). In the first part of this thesis it was investigated how incisional hernia could be prevented, what the complications are of mesh reinforcement and which costs it may bring on society.

Part I: Prevention of incisional hernia

Treatment of IH should be focussed on prevention of IH, taken into account high recurrence rates after mesh repair, mesh-related complications, high costs of IH and reduced quality of life. The first step towards prevention of IH is to answer the question what the most optimal technique is to close a laparotomy incision. Diener et al. and Van 't Riet et al. concluded that slowly resorbable continuous suturing of the abdominal wall leads to a significantly lower IH rate compared to interrupted suture (47, 48). It was also concluded that slowly resorbable sutures lead to less pain. Thus, slowly resorbable continuous sutures can achieve optimal fascial closure. Another factor that should be taken into account in order to prevent IH is the suture length to wound length ratio, first investigated by Jenkins, later by Israelsson et al. (49, 50) and by Deerenberg et al. in the STITCH trial. Their findings showed that a small bites suture technique (SL:WL ratio of 4:1) is more effective than the large bites technique for the prevention of incisional hernia in midline laparotomies (9).

The PRIMA trial focussed on prophylactic mesh reinforcement (43). The trial confirmed the positive results of earlier conducted studies, in which was shown that mesh reinforcement leads to a reduction of IH incidence (10, 28-30). In 2015, the European Hernia Society published guidelines on the closure of abdominal wall incisions. The Bonham Guidelines Group stated that 'prophylactic mesh augmentation in order to reduce the IH incidence after elective midline laparotomy in high-risk patients is suggested'. However, it was also stated that the evidence was weak and that larger trials were needed, in order to make a strong recommendation (2). These guidelines can be found in this thesis (Chapter 2). Recently, well-conducted large randomized controlled trials have been published and level-1 evidence has been provided (8, 43).

The PRIMA trial is the first large randomized controlled trial, with three randomisation arms, in which high-risk patients (AAA, BMI of >27), undergoing midline laparotomy, were included. These patients were randomized in either one of the three randomisation arms: (1) primary suture (PS), (2) onlay mesh reinforcement (OMR) or (3) sublay mesh reinforcement (SMR). The primary endpoint of this RCT was the IH incidence after follow-up of two years (43). The PRIMAAT trial, of Muysoms et al., included high-risk patients (AAA) as well. In this RCT patients were either randomized in a primary suture group or sublay mesh reinforcement group (8).

Both the PRIMA and PRIMAAT trial show results in favour of mesh reinforcement: the incidence of IH was significantly lower in the mesh reinforcement group, compared to the primary suture group. These findings confirm the outcome of most of the earlier conducted studies, both RCTs and prospective cohort studies. Until recently, it was unclear which surgical technique; either onlay or sublay mesh reinforcement was superior. In the PRIMA trial it was shown that onlay mesh reinforcement, compared with sublay mesh reinforcement and primary suture, leads to a statistically significant reduction of the IH incidence. Therefore, as this technique is much less challenging and time consuming compared to sublay, the onlay mesh reinforcement has the potential to become standard treatment in high-risk patients undergoing midline laparotomy. This finding is remarkable; since the assumption has always been that with regard to mesh infection that sublay mesh reinforcement is superior in comparison with onlay mesh reinforcement, even though there was no evidence for this finding. Chapter 4 presents the long-term results of the PRIMA trial.

In Chapter 3, the short-term results of the PRIMA trial are being discussed (51). Most of the earlier conducted RCTs focussed mainly on IH prevention and the short-term complications were often not described. This manuscript focussed on short-term results, i.e. the complications that occur in the first month after surgery. There were no differences between the three groups (primary suture (PS), onlay polypropylene mesh repair (MR), sublay polypropylene mesh repair (PMR)) regarding baseline characteristics or intraoperatieve characteristics. Furthermore, there were also no differences in intraoperative complications, such as bleeding, duration of surgery, or intestinal lesion. Patients receiving prophylactic mesh reinforcement did not attend the intensive care more often, nor did they receive more often blood transfusion or ventilation. There were no differences in admissions days between the three groups. Seromas occurred in 52% of patients. Significantly more seroma's were observed in the onlay prophylactic mesh reinforcement group (34%), compared with the primary suture group (5%) or with the sublay prophylactic mesh reinforcement group (13%). However, there were no differences between groups regarding surgical site infections (SSI), re-admissions

or re-interventions. Thus, the fact that there were more seromas in patients with onlay PMR, did not have any consequences for the patient. Other postoperative complications that were investigated were hematoma, fascial dehiscence, mesh infection and mesh removal, ileus and death. None of these postoperative complications occurred (significantly) more frequent in one of the treatment arms. After a follow-up of two years, no other complications were found. In total, 15% of the population died, with no significant differences in percentages between the three randomisation arms. It can be concluded that mesh reinforcement in high-risk patients undergoing midline laparotomy is a safe procedure (51).

A few meta-analyses regarding prevention of IH in patients undergoing PMR have been performed so far. After publication of the PRIMA trial, a new meta-analysis was conducted, in order to confirm the existing level-1 evidence. In this meta-analysis, 12 RCTs were included (8, 10, 28-30, 51-57). Studies were divided in high-risk of bias and low risk of bias. In general, IH occurred significantly less frequent in patients with PMR compared with PS patients. In the low risk of bias group, IH occurred significantly less in the PMR group compared with the PS group. No statistical differences were found for the high risk of bias group. Both onlay and retromuscular PMR lead to a significant reduction of the IH incidence compared with PS. Patients with an onlay PMR had a higher risk of developing seroma compared with patients who underwent PS. There was not a higher incidence of SSI in onlay PMR compared to PS. This meta-analysis showed that onlay prophylactic mesh reinforcement leads to a significantly lower incidence of IH with dimensions of the effect larger than with retromuscular mesh reinforcement. The findings of the MARIA meta-analysis can be found in Chapter 5.

It should be taken into account that the findings of the meta-analysis, prospective cohorts and RCTs are applicable on a certain patient group, who are operated under certain circumstances, using a specific surgical technique and a specific type of mesh. In most of the prevention studies, a synthetic non-resorbable mesh is being used, mostly polypropylene, in either onlay or sublay position. The mesh that was used in the PRIMA trial was a lightweight polypropylene mesh. In the PRIMAAT trial, a large pore, partially resorbable light-weight polypropylene mesh was used. The results are therefore only applicable for synthetic meshes. Even though it can be concluded that prophylactic mesh reinforcement can be safely performed in a clean setting, it is unclear how biological or biosynthetic meshes perform, especially on long-term. A systematic review of literature regarding prevention of incisional hernia with biological or biosynthetic meshes was conducted, in order to reveal the benefits of these meshes (58). Only four studies (two RCTs and two case-control) studies are available for the prevention of IH in midline laparotomies with biological or biosynthetic meshes (55, 57, 59, 60). After qualitative

assessment, it was concluded that the level of evidence on the efficacy and safety of biological meshes is very low (58). Furthermore, PMR can be considered safe in elective laparotomies. There is no evidence on how PMR behaves in emergency situations.

It can be concluded that level-1 evidence is provided for the prevention of IH with prophylactic mesh reinforcement in high-risk patients undergoing elective midline laparotomy. As a consequence, it should be considered to review and adapt the guidelines on the closure of the abdominal wall, based upon the most recently published trials.

Part II: New tools, techniques and meshes in ventral hernia surgery

Questionnaires: a new diagnostic tool?

Adequate, reliable long-term follow up is essential in providing high-quality care after midline laparotomies. It is known that 80-95% of all incisional hernias occur in the first three years after surgery (61). There are several methods of follow up, such as physical examination and radiological examination. Until now, physical examination at the outpatient clinic is the gold standard for follow up. However, routinely scheduled clinical visits are time consuming, costly and demand devotion of both patient and doctor (62). Furthermore, it is not always necessary to conduct a three year follow up after abdominal surgery and patients will not attend a physician if symptoms are absent. Another method of follow-up might be the use of questionnaires. However, there is little evidence on their reliability. Van den Heuvel et al. validated questionnaire in order to detect inguinal hernia recurrences (21). In this thesis, a questionnaire named PROMID (Patient Reported Outcome Measurement In Diagnosing IH), is developed in order to assist in diagnosing IH in patients who have undergone abdominal surgery. In a pilot study, the reliability, internal consistency and sensitivity of the PROMID questionnaire are being determined. The questionnaire regarded patients' symptoms. It was concluded that the PROMID questionnaire is a highly reliable questionnaire, with a test-retest reliability of 1.0. The internal consistency is modest. The overall sensitivity of the questionnaire was 95% (63). Currently, the PROMID questionnaire is being validated in a prospective cohort study, with the aim to use it as a diagnostic tool in order to diagnose IH.

Biological and biosynthetic meshes: the ideal mesh?

Until now the question, which mesh is the 'perfect' or 'ideal' mesh, remains unanswered**.** The difficulty of this question is related to the fact that it should be answered separately for each patient and is thus patient-specific. Currently, there are a wide variety of synthetic, biological and biosynthetic meshes available. We aimed to investigate both biological and synthetic meshes in a peritonitis rat model in order to assess in

vivo characteristics, such as shrinkage, incorporation of the mesh, adhesion formation, and abscess formation. The feasibility of using the biological mesh in a contaminated environment was evaluated. As such, there was also a search for the question: which mesh is the ideal mesh to use in this environment? Meshes that were investigated in the experimental study in this thesis were as follows: Permacol™ (cross-linked collagen), Strattice™ (non-cross-linked collagen), XCM™ Biologic (non-cross-linked collagen), Omyra® mesh (condensed polytetrafluoroethylene), and Parietene™ (polypropylene). Our experiment showed that XCM™ Biologic was superior when incorporation, macroscopic mesh infection and histological parameters like collagen deposition were taken into account. However, XCM™ Biologic did show a high percentage of shrinkage. There are no studies yet performed with XCM™ Biologic that assesses the shrinkage rates in a rat model. Interestingly, our experiment showed that there was little abscess formation for all meshes. This is in contrast with earlier conducted experimental studies (64). However, in these studies other meshes were investigated that showed high abscess rates, which could be attributed to the fact that the sub strain of Wistar rats was more infection resistant. Although biological meshes behave well in a contaminated field, the long-term data of outcome and complications are lacking. Furthermore, they are expensive. A new mesh that has been introduced on the market is the resorbable synthetic mesh. This mesh aims to combine advantages of both synthetic and biological meshes. Resorbable synthetic meshes maintain mechanical strength for a certain period, will gradually resorb and rebuild connective tissue. However, the actual remodelling properties are unclear. Many studies report that there is 'optimal tissue remodeling' (33, 40, 41, 65). However, the definition of this is unclear, not standardized, and furthermore, there is not enough evidence yet that these meshes provide sufficient strength on long-term (41). The synthetic resorbable meshes which are currently available on the market are GORE® BIO-A® mesh (Gore), TIGR® Surgical Matrix Mesh (Novus Scientific) and the Phasix™ mesh (Bard). Until now, a number of experimental studies with these meshes have been conducted (33, 40, 41, 66-69). A review in this thesis was conducted in order to give an overview of the characteristics and biomechanical, histological and clinical outcome of the use of resorbable synthetic meshes. This review was the first one that was published. There is currently no clear experimental evidence available that can support the advantages of resorbable synthetic meshes over the use of synthetic or biological meshes in human settings. Even though a certain degree of remodelling occurred, it remains unclear whether this can lead to strong fascial tissue of good quality on long term. This review showed a high heterogeneity: different animal models were used, and most of the meshes were placed in a clean environment. Used surgical techniques were extremely variable. Furthermore, outcome parameters were not standardized. This makes it all difficult to extrapolate to humans. At this moment, several prospective

clinical cohort studies for ventral hernia repair and inguinal hernia repair with GORE® BIO-A® and TIGR® Matrix Surgical mesh have been published, with good results (70-72). GORE® BIO-A® was used for single-staged contaminated ventral hernia repair (CDC class II and III) (73). The hernia recurrence rate after 24 months was 17%. TIGR® Matrix Surgical mesh was investigated in two clinical studies. One of these was a pilot study (71). Here, the mesh was used to prevent wound dehiscence and incisional hernia in 16 patients with three or more risk factors for the development of wound dehiscence or incisional hernia. After a follow-up of nine months, two complications were found (seroma and surgical site infection, both requiring treatment). No complications required re-operation, and no incisional hernia or wound dehiscence was seen. Another study performed with TIGR® Matrix Surgical mesh was done in patients with primary inguinal hernias, who were enrolled for Lichtenstein repair (72). No serious adverse events were reported after a follow-up of one year. After three-years of follow-up, high recurrence rates were seen in patients with medial (44%) and combined inguinal (33%) hernias. No recurrences were seen in patients with an isolated lateral inguinal hernia (LIH) (33). The first clinical results for the Phasix™ mesh will soon follow. This will be a prospective cohort study, in which 85 patients with a Ventral Hernia Working Group (VHWG) Grade 3 hernia will be treated with Phasix™ mesh. Primary outcome of the study is surgical site occurrence (SSO) in the first three months, including hematoma, seroma, infection, dehiscence and fistula formation (requiring intervention). Secondary outcomes include recurrence, infection and quality of life related outcomes after 24 months. The protocol of the Phasix™ mesh study can be found in Chapter 9.

Umbilical hernia and local anesthesia: a new feasible technique?

Little evidence is available regarding local anesthesia for the repair of umbilical hernias. Therefore, a review of literature was conducted. All included articles had a level of evidence of 2B, and there was no study conducted that investigated local anesthesia for umbilical hernias only. It was concluded that even though the use of local anesthesia seemed safe and feasible, the advantages were not sufficiently demonstrated. Therefore, a prospective cohort study was conducted. Here it was shown that the use of local anaesthesia, using Ropivacaine as a local agent and Remifentanil as a sedative, is safe and feasible in UH repair.

FUTURE PERSPECTIVES

Incisional hernia is still one of the most common complications after abdominal surgery, especially in high-risk patients. This thesis has focussed on prevention of incisional hernia by prophylactic mesh reinforcement. The key of preventing incisional hernia is

to avoid midline laparotomies. In an era in which laparoscopic surgery has taken its flight and has become standard daily practice, the expectation is that the incidence of incisional hernia will decline. However, it should be taken into account that laparoscopic surgery is not always possible, such as in specific emergency cases. Furthermore, laparoscopic surgery is not always standard daily practice in non-Western countries. Last but not least, laparoscopy can lead to trocar hernias. The use of mesh to prevent incisional hernia is thus indicated, even in countries in which a mesh is not affordable. In this respect the randomized controlled trial of Löfgren et al. showed that the use of a low-cost mesh (sterilized mosquito mesh) did not significantly differ in recurrence and postoperative complications, compared with a commercial mesh.

Incisional hernia is a frequent complication after abdominal (midline) surgery. Therefore, this topic needs far more attention in the surgical community than it currently gets. Education in how to close the abdomen should become structural part of the surgical training. Surgeons with a specific field of interest in hernia surgery should educate and train surgical residents. Anatomical skills and closing techniques of the abdominal wall should become a mandatory part of this training. In this way, the incidence of incisional hernia can be reduced.

With the level-1 evidence that is currently available regarding prophylactic mesh reinforcement, guidelines should be set up. This should be started in each individual country at their own surgical association or society. Furthermore, the European Hernia Society should adapt the guidelines on the closure of abdominal wall incisions. The Guidelines Group stated that more evidence was needed in order to make a strong recommendation regarding the use of prophylactic mesh augmentation in high-risk groups, which is currently the case.

The use of prophylactic mesh reinforcement is not the only option to prevent incisional hernias. The small bite suture technique, as investigated by Deerenberg et al., demonstrated that this technique is more effective compared with the large bites technique in the prevention of incisional hernia. Another prevention method that is currently still being investigated is the use of stem cell therapies or growth factors. The fundamental mechanism of the formation of incisional hernias is the failure of fascial wound healing. The use of stem cells or growth factors have been proposed as a new treatment and/or prevention option in abdominal wall repair. Both experimental and clinical research regarding this topic is ongoing and should be stimulated.

Individual patients' risk factors should be taken into account to select which patient will benefit most from prophylactic mesh reinforcement. Currently, most studies that have been performed regarded high-risk patients, such as patients with an aneurysm of the abdominal aorta or morbid obese patients. Further research is needed to identify other risk factors. Data from large prospective registries might be helpful to explore those risk factors. The Danish Ventral Hernia database is a very good example and other countries should follow this example. Collaboration between countries, developing one (worldwide) registry would be advantageous in order to analyse many research questions.

Which mesh is the 'ideal' mesh? The answer to this question is difficult to formulate, as the mesh choice is patient specific. Currently, there are over 200 different meshes available on the market, all with a specific indication. Many studies have been performed regarding synthetic meshes (prolene or polypropylene), but also on biologic meshes. Slowly resorbable synthetic meshes might be interesting, since it can combine 'best of both worlds'. Due to its slowly resorbable capacity, it can provide sufficient strength, which is needed to prevent the formation of incisional hernia. However, it might also lead to less chronic pain on long term or other mesh related complications. At this moment, clinical and experimental data are being published. The most important question is whether remodelling occurs and if this can lead to strong fascial tissue of good quality on long term. More experimental studies are needed, followed by randomized controlled trials and prospective registries.

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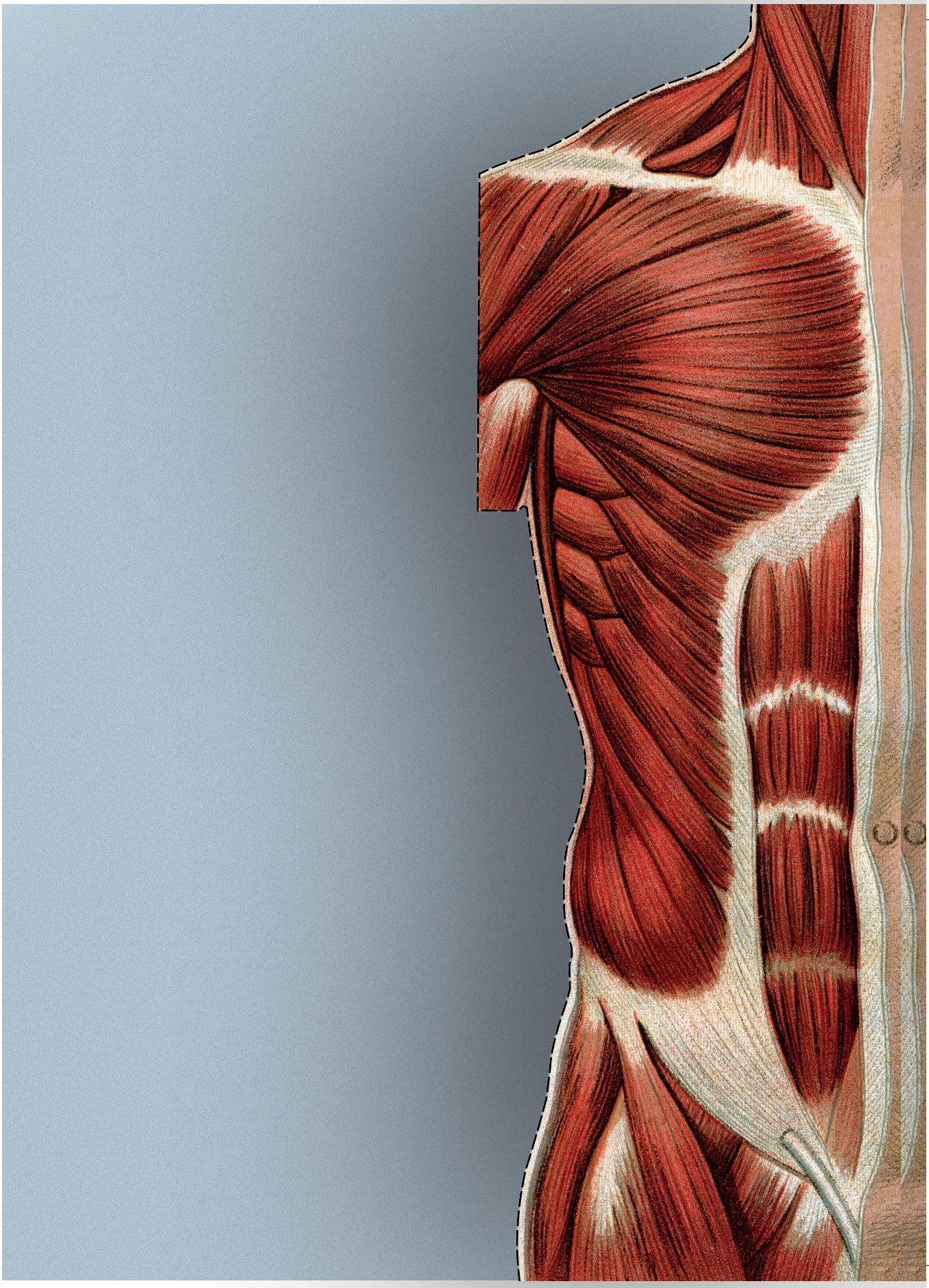
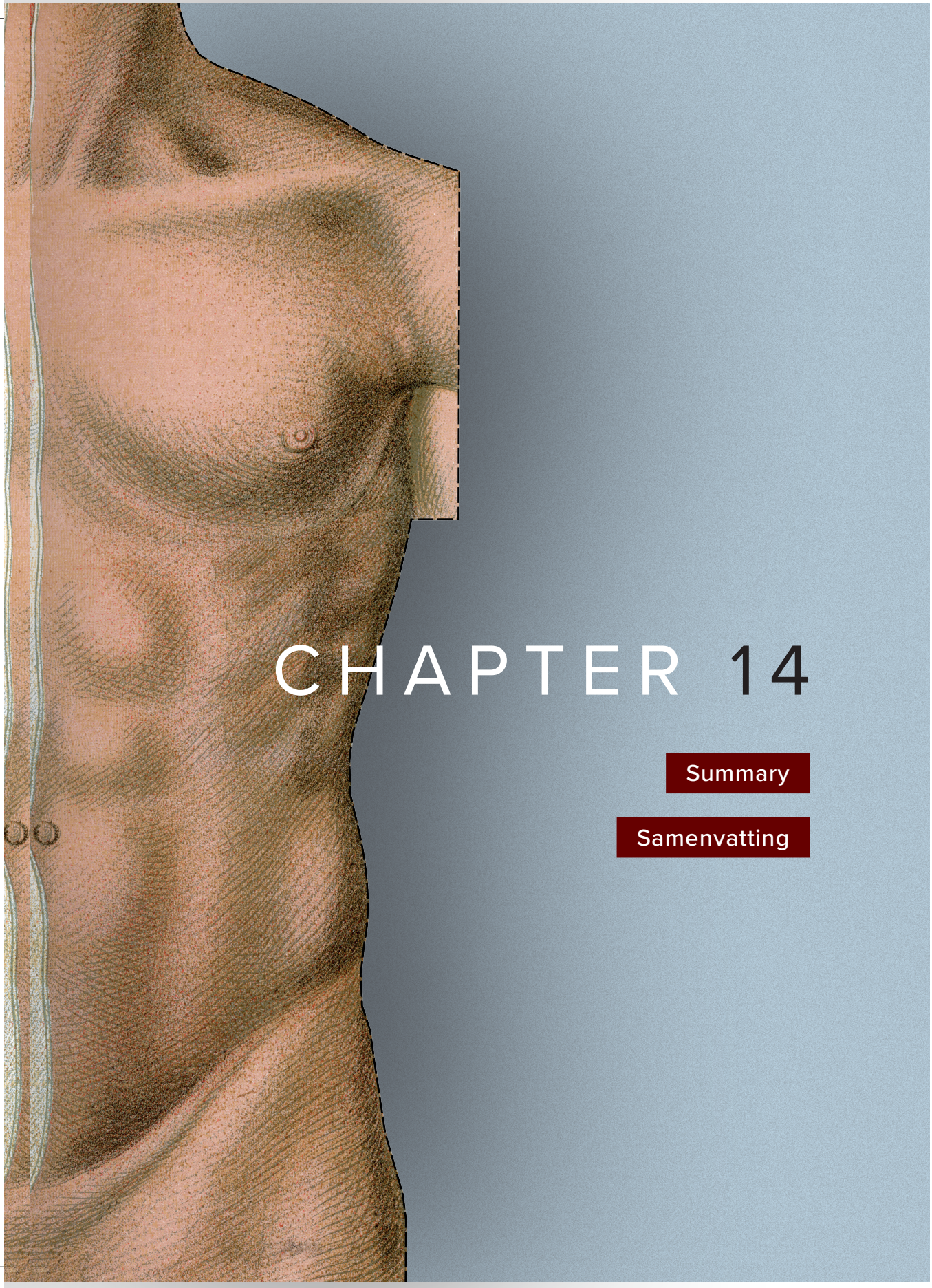




CHAPTER 14

Summary

Samenvatting

SUMMARY

In this thesis there are two parts. Part 1 focuses on the prevention of a major complication after abdominal wall surgery: incisional hernia. Part 2 focuses on the search for new tools, techniques and meshes in ventral hernia surgery.

Part I: Prevention of incisional hernia

Chapter 1 describes the subject of this thesis: the prevention of incisional hernia. Incisional hernia is one of the most frequently seen complications after abdominal surgery. Incidences vary from 10% to 20% in 'general population' and can increase up to more than 30% in high-risk groups. These incidences are unacceptable. The morbidity among patients with an incisional hernia is high. Furthermore, incisional hernia has a negative influence on patients' quality of life and body image. Thus, prevention of incisional hernia is of paramount importance. Incisional hernias can be prevented by prophylactic mesh reinforcement in patients undergoing midline laparotomy.

In **Chapter 2** the European Hernia Society Guidelines on the closure of abdominal wall incisions is presented. It was stated that the evidence regarding prophylactic mesh augmentation for an elective midline laparotomy in high-risk patients, in order to reduce incisional hernia, is weak. The Guidelines Development Group decided that larger trials are needed to make a strong recommendation.

In **Chapter 3** the short-term results of the PRIMA trial are described. High-risk patients, undergoing midline laparotomies were randomized in either primary suture of the abdomen, onlay mesh reinforcement or sublay mesh reinforcement. Postoperative complications after a follow-up of one month were investigated. Significantly more seromas were detected after OMR, compared with primary suture and compared with SMR. There were no statistically significant differences in other postoperative complications, such as surgical site infection (SSI), hematoma, reintervention or readmission.

In **Chapter 4** the long-term results of the PRIMA trial are presented. Patients in the onlay mesh reinforcement group developed significantly more frequent an incisional hernia, compared to patients who were allocated primary suture only (13% vs 30%, OR 0.37, 95%CI 0.20-0.69, p=0.0016). In the sublay mesh reinforcement group, more incisional hernias were identified compared to primary suture, however, this finding was not statistically significant (18% vs. 30%, OR 0.55, 0.30-1.00, p=0.05). Seromas were more frequent in patients with onlay mesh reinforcement (34/188) than in those assigned

primary suture (5/107, p=0.002) or sublay mesh reinforcement (13/185, p=0.002). The incidence of wound and surgical site infections, re-admission or re-interventions did not significantly differ between treatment groups.

In **Chapter 5** the results of a meta-analysis regarding the prevention of incisional hernias after midline laparotomies with prophylactic mesh reinforcement are presented: in total, twelve randomized controlled trials were included. The incisional hernia rate was significantly lower in patients with prophylactic mesh reinforcement compared with sutured closure (RR0.35, 95%CI 0.21-0.57, p<0.0001). Both onlay mesh reinforcement (RR 0.26, 95%CI 0.11-0.67, p= 0.005) as well as retromuscular mesh reinforcement (RR 0.28 95%CI 0.10-0.82, p= 0.02) led to a significant reduction of incisional hernias, compared with primary suture. In patients undergoing prophylactic mesh reinforcement, a higher occurrence of seromas was seen, however, there was no increase of surgical site infections.

In **Chapter 6** the results of a systematic review of literature are presented. This systematic review was performed to analyse the prevention of incisional hernias in midline laparotomies with a biological mesh. The level of evidence on the efficacy and safety of biological meshes for the prevention of incisional hernias was low. There were no studies comparing biological meshes with synthetic, non-absorbable meshes, for the prevention of incisional hernia. There was no evidence that a biological or biosynthetic mesh should be preferred to synthetic meshes, in order to prevent incisional hernia in patients undergoing midline laparotomy.

Part II: New tools, techniques and meshes in ventral hernia surgery

In **Chapter 7** the results of the PROMID pilot study are reported. In this pilot study, the reliability of a questionnaire was determined. The PROMID questionnaire is a questionnaire with seven questions (regarding syptoms of incisional hernia), and should assist in diagnosing incisional hernia, or it can be used in the future as a diagnostic tool to detect incisional hernia. It was found that the test-retest reliability was 1.0, and the internal consistency 0.56. The least consistent question was whether patients experience pain. For conclusion the PROMID questionnaire is highly reliable, but the internal consistency is only modest. The questionnaire will be validated in a prospective cohort study.

In **Chapter 8** a review of literature is given regarding the use of resorbable synthetic meshes for non-complex abdominal wall hernias in a preclinical setting. Currently, three resorbable synthetic meshes are available: GORE® BIO-A® mesh (Gore), TIGR® Matrix Surgical mesh and Phasix™ mesh (Bard). The use of resorbable synthetic meshes seems

safe. A certain degree of remodelling occurs, however, it is unclear whether this will lead to strong fascial tissue of good quality. At this moment, there is no evidence supporting the advantages of resorbable synthetic meshes over the use of synthetic or biological meshes. More experimental studies, using standardized parameters, are needed. Furthermore, randomized controlled trials and prospective registries with sufficient follow-up should be conducted in order to reveal the advantages in a clinical setting.

In **Chapter 9** the protocol of a prospective multicentre cohort study of Phasix™ mesh is presented. The aim of this clinical study is to include 85 patients with a VHWG grade 3 hernia, and to collect data on safety and performance of the Phasix™ mesh in this patient group. Primary outcome will be surgical site occurrence in the first three months after implantation. Secondary outcomes are recurrence, infection and quality of life. Follow-up will be up to 24 months.

In **Chapter 10** the characteristics of different mesh types for abdominal wall repair in an experimental rat model of peritonitis are reported. 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). 180 days after implantation, XCM Biologic® and Permacol™ had significantly better incorporation than Strattice™ ($p=0.003$ and $p=0.009$). Strattice™ had significantly fewer adhesions than XCM Biologic® and Permacol™. XCM Biologic® showed the most prominent shrinkage. This finding was not statistically significant. In this experimental study it was investigated whether there is an ideal mesh. XCM Biologic® is a new biological mesh and has shown good results in this study. The use of XCM Biologic® may be useful in patients with a contaminated incisional hernia.

In **Chapter 11** a systematic review is presented, in which the feasibility of the use of local anesthesia for the surgical treatment of umbilical hernia is described. Various anaesthetic agents were used and there was no consensus regarding the injection technique. The recurrence rate varied from 2% to 7.4%. Almost 90% of patients were discharged within 24 hours, compared with 47% of patients treated with general anesthesia. Local anesthesia for the treatment of umbilical hernia seems safe and feasible. However, there is a very high heterogeneity among studies, and the advantages are not sufficiently demonstrated, due to lack of data. A randomized controlled trial, comparing local versus general anesthesia for the treatment of umbilical hernia, should follow.

In **Chapter 12**, a prospective cohort study is presented, in which the safety and feasibility of local anesthesia are investigated. This is the first study in which the use of a local agent in UH surgery is prospectively investigated under standardized circumstances in

a homogenous group of patients. Both patients and surgeons were positive about the surgical procedure with a local anaesthetic. It can be concluded that the use of local anaesthesia, using Ropivacaine as a local agent and Remifentanil as a sedative, is safe and feasible in UH repair.

NEDERLANDSE SAMENVATTING

In **Hoofdstuk** 1 wordt het onderwerp van dit proefschrift: *'de preventie van littekenbreuken'* beschreven. Het optreden van een littekenbreuk is de meest frequente postoperatieve complicatie na abdominale chirurgie. Tegenwoordig is de incidentie nog steeds hoog, variërend van 10 tot 20% in de 'algemene populatie', oplopend tot meer dan 30% in hoog-risico groepen. Deze getallen zijn onacceptabel. Het hebben of krijgen van een littekenbreuk kent veel gevolgen: het kan leiden tot één of meerdere (her)operatie(s), tot complicaties en recidieven. Verder heeft het optreden van een littekenbreuk een negatieve invloed op de kwaliteit van leven van patiënten en brengt het hoge kosten met zich mee. De preventie van littekenbreuken is derhalve van essentieel belang, niet alleen voor de patiënt zelf, maar ook voor de samenleving als geheel. Littekenbreuken kunnen worden voorkomen door het plaatsen van een mesh (mat) tijdens het sluiten van de mediane laparotomie. Momenteel is het gebruik van een niet-oplosbare synthetische mesh als profylaxe de standaard.

Deel I: Preventie van littekenbreuken

Het eerste deel van dit proefschrift richt zich op de preventie van littekenbreuken.

In **Hoofdstuk 2** worden de resultaten van de European Hernia Society Guidelines weergegeven. Deze richtlijn beschrijft de beste methode om de buik te sluiten. Hier wordt vastgesteld dat het bewijs omtrent de profylactische mesh plaatsing in hoog risico-patiënten, die een mediane laparotomie hebben ondergaan, zwak is. Het besluit van de richtlijngroep is dan ook terecht dat er grotere gerandomiseerde trials nodig zijn om tot een sterke aanbeveling te komen.

In **Hoofdstuk 3** worden de korte-termijn resultaten van de PRIMA trial beschreven. In deze dubbelblinde gerandomiseerde trial werden hoog-risico patiënten, die een midline laparotomie ondergingen, gerandomiseerd in drie groepen: primair sluiten van de buik, onlay mesh ('onlay mesh reinforcement') of sublay mesh ('sublay mesh reinforcement'). Postoperatieve complicaties na follow-up van een maand werden onderzocht: er werden significant meer seromen gevonden in de groep, die onlay mesh reinforcement onderging, vergeleken met patiënten bij wie de buik primair werd gesloten en bij patiënten, die sublay mesh reinforcement ondergingen. Er waren geen statistisch significante verschillen in andere postoperatieve complicaties, zoals surgical site infections (SSI's), hematomen, re-interventies en heropnames.

In **Hoofdstuk 4** worden de lange-termijn resultaten van de PRIMA trial besproken. De incidentie littekenbreuken was significant hoger bij patiënten in de onlay mesh groep, vergeleken met patiënten bij wie de buik primair werd gesloten (13% vs 30%, OR 0.37, 95%CI 0.20-0.69, p=0.0016). In de sublay mesh groep was de incidentie littekenbreuken ook hoger, vergeleken met patiënten bij wie de buik primair werd gesloten. Deze bevinding was niet statistisch significant (18% vs. 30%, OR 0.55, 0.30-1.00, p=0.05).

In **Hoofdstuk 5** worden de resultaten van een meta-analyse gepresenteerd. In deze meta-analyse werd de preventie van littekenbreuken na mediane laparotomie door middel van een profylactische mesh onderzocht. In totaal werden 12 gerandomiseerde trials geïncludeerd. Het percentage littekenbreuken was significant lager in de patiëntengroep bij wie profylactisch een mesh werd geplaatst, vergeleken met patiënten bij wie de buik primair door middel van hechtingen werd gesloten (RR0.35, 95%CI 0.21-0.57, p<0.0001). Zowel in de onlay als in de sublay mesh groepen werd een significante reductie gezien van de littekenbreuk incidentie, vergeleken met de patiëntengroep bij wie de buik primair werd gesloten. In patiënten bij wie profylactisch een mesh werd geplaatst, werd wel een hogere incidentie van seromen, maar geen hogere incidentie van wondinfecties gezien.

In **Hoofdstuk 6** worden de bevindingen van een beschrijvende systematische review weergeven. Dit systematische review werd uitgevoerd om de rol van de biologische mat als profylaxe in de littekenbreukchirurgie vast te stellen. Geconcludeerd kan worden dat de mate van bewijs betreffende de effectiviteit en de veiligheid van biologische matten als profylaxe binnen littekenbreukchirurgie laag is. Tot op heden zijn er geen preventiestudies uitgevoerd waarin de biologische mat werd vergeleken met een synthetische, niet resorbeerbare mat. Er is geen bewijs dat een biologische mat de voorkeur heeft boven synthetische matten ter preventie van littekenbreuken bij patiënten, die een mediane laparotomie ondergaan.

Deel II: Nieuwe ontwikkelingen, technieken en meshes bij ventrale buikwandhernia's

Het tweede deel van dit proefschrift richt zich op nieuwe ontwikkelingen en technieken binnen het gebied van de chirurgie van ventrale buikwandhernia's. Tevens worden verschillende (nieuwe) meshes op de huidige markt besproken.

In **Hoofdstuk 7** worden de resultaten van de PROMID pilot studie vermeld. In deze pilot studie werd de betrouwbaarheid van een vragenlijst bepaald. De PROMID vragenlijst bestaat uit zeven vragen en hebben betrekking op symptomen, die kunnen optreden bij patiënten met een littekenbreuk. De PROMID vragenlijst zou kunnen helpen bij het

diagnosticeren van een littekenbreuk, of deze kan worden gebruikt in de toekomst als diagnosticum om een littekenbreuk te detecteren. De pilot studie toonde aan dat de vragenlijst een test-retest reliability van 1.0 heeft en dat de interne consistentie 0.56 is. De minst consistente vraag betrof de pijnbeleving met betrekking tot de symptomen van littekenbreuken. Er kan worden geconcludeerd dat de PROMID vragenlijst betrouwbaar is, maar dat de interne consistentie minimaal is. De vragenlijst zal in een prospectief cohort worden gevalideerd.

In **Hoofdstuk 8** wordt een review van de literatuur gepresenteerd betreffende het gebruik van resorbeerbare synthetische matten voor niet-complexe buikwandhernia's in een experimentele (preklinische) setting. Momenteel zijn er drie resorbeerbare synthetische matten verkrijgbaar op de markt: GORE® BIO-A® mesh (Gore), TIGR® Matrix Surgical mesh and Phasix™ mesh (Bard). Dit beschrijvende review laat zien dat het gebruik van langzaam resorbeerbare synthetische matten veilig lijkt. Er lijkt een zekere mate van remodelling op te treden, alhoewel het onduidelijk is of dit tot een sterke fascie van goede kwaliteit leidt. Momenteel is er niet genoeg bewijs beschikbaar waarbij wordt aangetoond dat het gebruik van resorbeerbare synthetische matten de voorkeur heeft boven synthetische of biologische matten. Het opzetten van meer experimentele studies (die gestandaardiseerde parameters gebruiken) en gerandomiseerde trials (met langdurige follow-up) zijn essentieel, om zo de voordelen van deze mat te onderzoeken.

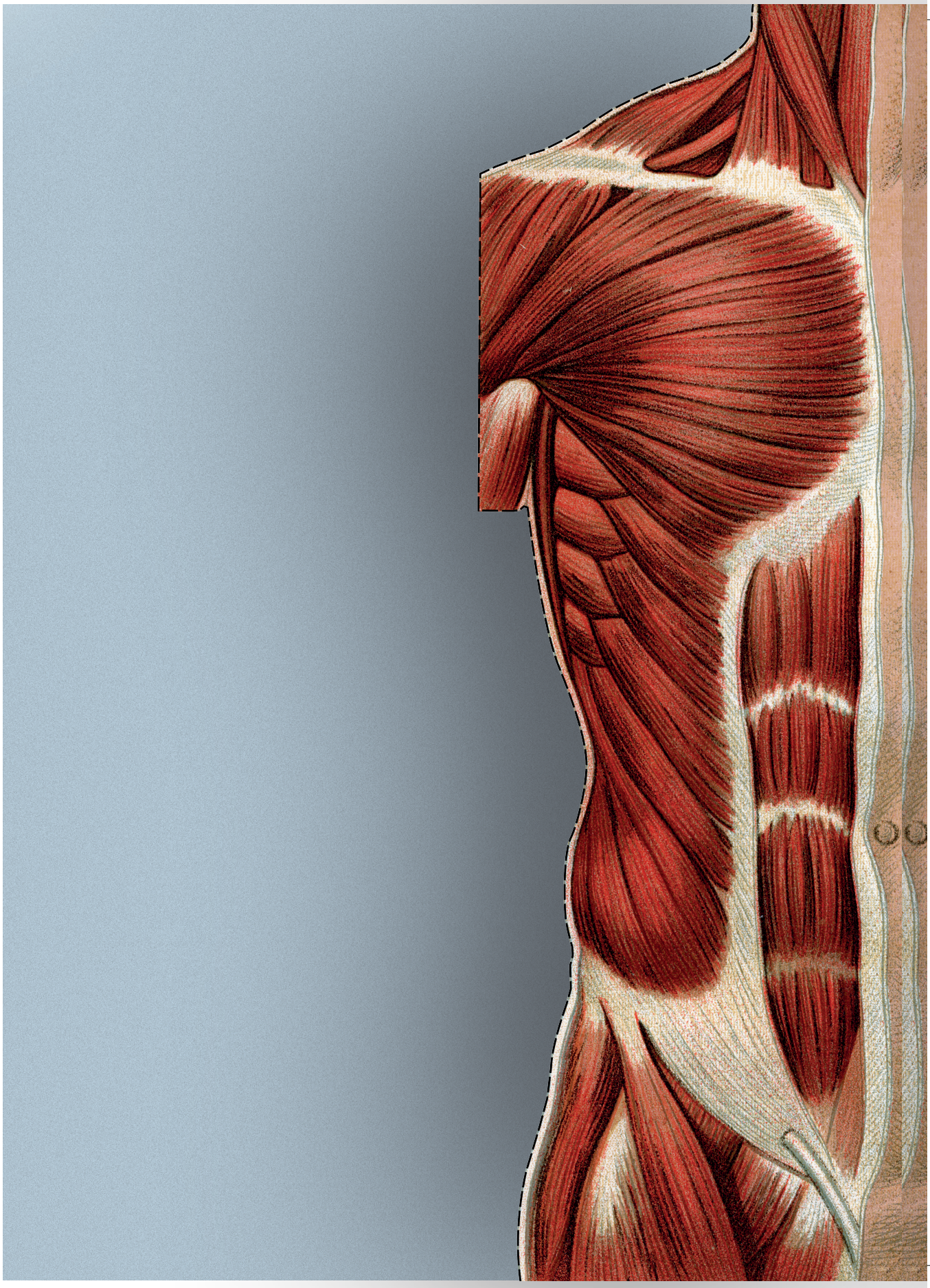
In **Hoofdstuk 9** wordt het protocol van een prospectieve multicentre cohort studie van de Phasix™ mesh (Bard) gepresenteerd. Het doel van deze klinische studie is om 85 patiënten met een VHWG graad 3 hernia te includeren en data betreffende de veiligheid en gebruik van de Phasix™ mesh in deze patiëntengroep te verzamelen. De primaire uitkomst is het optreden van surgical site occurences in de eerste drie maanden na implantatie. Secundaire uitkomstmaten zijn recidiefpercentage, infectie en kwaliteit van leven. De follow-up tijd zal 24 maanden beslaan.

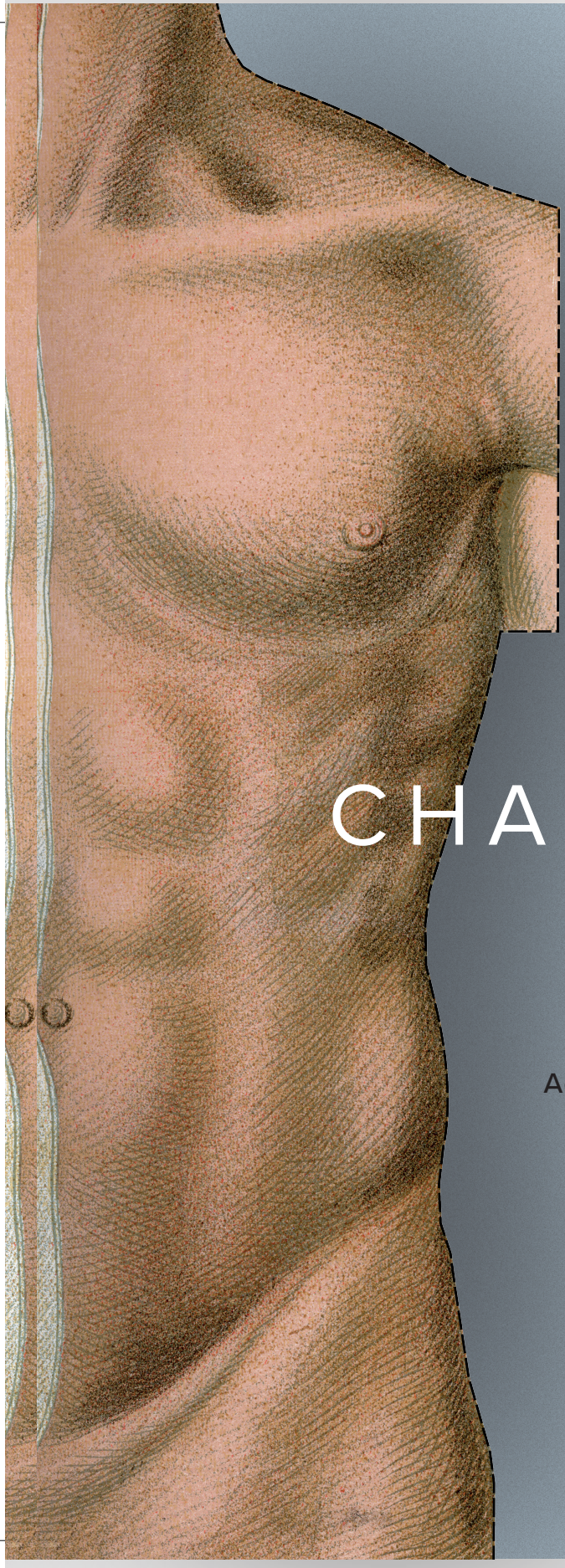
In **Hoofdstuk 10** worden de resultaten van een experimentele studie weergeven. In deze studie, uitgevoerd met ratten, worden de karakteristieken van verschillende typen mesh (voor de behandeling van buikwandhernia's) in een peritonitismodel beschreven. Er werden 5 meshes onderzocht: Permacol™ (cross-linked collagen), Strattice™ (non-cross-linked collagen), XCM Biologic® (non-cross-linked collagen), Omyra® Mesh (condensed polytetrafluoroethylene) en Parietene™ (polypropylene). 180 Dagen na implantatie bleek dat XCM Biologic® en Permacol™ een betere ingroei hadden dan Strattice™ ($p=0.003$ and $p=0.009$). Strattice™ had significant minder adhesies vergeleken met XCM Biologic® en Permacol™. XCM Biologic® toonde de meeste krimp. Deze bevinding was niet statistisch significant. In deze experimentele studie werd onderzocht of een

ideale mesh bestaat. Uit deze studie kwam naar voren dat XCM Biologic® een nieuwe biologische mat is, welke goede resultaten heeft laten zien in deze studie. Het gebruik van deze mesh kan nuttig zijn voor patiënten met een gecontamineerde littekenbreuk.

In **Hoofdstuk 11** wordt een systematische review gepresenteerd, waarin de haalbaarheid van het gebruik van lokale anesthesie voor de behandeling van navelbreuken wordt onderzocht. In de verschillende studies werden verschillende lokale anesthetica gebruikt en er was geen consensus betreft de injectietechniek. Het recidiefpercentage varieerde van 2% tot 7.4%. Lokale anesthesie voor de behandeling van navelbreuken lijkt veilig en haalbaar. Desondanks is er een grote heterogeniteit tussen de verschillende studies en zijn de voordelen van het gebruik van lokale anesthesie onder andere door het ontbreken van data niet duidelijk. Een gerandomiseerde trial, waarin lokale anesthesia met algemene anesthesia voor de behandeling van navelbreuken vergeleken wordt, zou de volgende stap moeten zijn.

In **Hoofdstuk 12** wordt een prospectief cohort gepresenteerd. In deze studie, waarin 30 patienten zijn geincludeerd, worden de veiligheid en haalbaarheid onderzocht van het gebruik van lokale anesthesie in patienten met een navelbreuk. Er werd geconcludeerd dat het gebruik van lokale anesthesie (Ropivacaine en Remifentanil), veilig en haalbaar is in het corrigeren van een navelbreuk.





CHAPTER 15

Appendices

Acknowledgements/ Dankwoord

List of Publications

PhD Portfolio

Curriculum Vitae

DANKWOORD

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LIST OF PUBLICATIONS

This thesis: accepted

Prevention of Incisional Hernias after Midline Laparotomy with Prophylactic Mesh Reinforcement: a meta-analysis and trial sequential analysis. **Jairam AP**, Lopez-Cano M, Garcia Alamino J, Antonio-Pereira J, Timmermans L, Jeekel J, Lange JF, Muysoms FE. British Journal of Surgery Open

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Other publications: accepted

Small bites versus large bites for closure of abdominal midline incisions (STITCH): a double-blind, multicentre, randomised controlled trial. Deerenberg EB, Harlaar JJ, Steyerberg EW, Lont HE, van Doorn HC, Heisterkamp J, Wijnhoven BP, Schouten WR, Cense HA, Stockmann HB, Berends FJ, Dijkhuizen FP, Dwarkasing RS, **Jairam AP**, van Ramshorst GH, Kleinrensink GJ, Jeekel J, Lange JF. Lancet. 2015 Sep 25;386(10000):1254-60.

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Clinical outcome and morphologic analysis after endovascular aneurysm repair using the Excluder endograft. Bastos Goncalves F, **Jairam A**, Voute MT, Moelker AD, Rouwet EV, Ten Raa S, Hendriks JM, Verhagen HJ. Journal of Vascular Surgery. 2012 Oct;56(4):920-8.

Other publications: submitted

Kaufman R, **Jairam AP**, Mulder IM, Wu Z, Verhelst J, Vennix S, Giesen LJX, Clahsen-van Groningen MC, Jeekel J, Lange JF. Non-cross-linked collagen mesh performs best in a non-contaminated rat model with intraperitoneal mesh placement. British Journal of Surgery

Book chapter

Jairam A, Van Ramshorst GH, Lange JF**.** Chapter: Wound Closure and Postoperative Hernia Prevention Strategies. Springer International Publishing Switzerland 2016. Y.W. Novitsky, Hernia Surgery.

PHD PORTFOLIO

Name PhD fellow: A.P. Jairam
Erasmus MC Department: Surgery

PhD period: June 2013 – Jan 2017
Promotor: prof. dr. J.F. Lange
Supervisoren: prof.dr. J. Jeekel, prof. dr. G.J. Kleinrensink

1. PhD training	Year	ECTS
General courses		
• Biomedical English Writing and Communication	2014	3.0
• Research Integrity	2014	0.3
• Laboratory animal science (Artikel 9)	2013	4.5
• BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2013	1.5
• Good Clinical Practice	2013	0.3
• Biostatical methods	2013	2.0
• Systematic Literature Retrieval Pubmed	2013	1.0
Presentations at inter(national) conferences		
• Club Hernie, Paris (oral)	2018	1.0
• ICENI, Londen (oral)	2018	1.0
• Hernientage, Koln (oral)	2018	1.0
• MAR Symposium, Barcelona (oral)	2017	1.0
• European Hernia Society, Vienna (oral)	2017	1.0
• European Hernia Society, Rotterdam (oral)	2016	1.0
• Chirurgendagen, Veldhoven (oral)	2016	1.0
• American Hernia Society, Washington DC (oral)	2016	1.0
• MAR Symposium, Barcelona (oral)	2015	1.0
• Club Hernie, Paris (oral)	2015	1.0
• World Hernia Congress Milan, Italy (oral)	2015	1.0
• RICH congress, Rotterdam (oral)	2014	1.0
• Chirurgendagen, Veldhoven	2013/2015	1.0
• Najaarsdag Heelkunde, Rotterdam	2014	1.0
Other		
• Journal club	2014-2017	2.0
• REPAIR	2013-2017	2.0

2. Teaching/ supervising	Year	ECTS
• Education medical students	2014-2017	2.0
• Examination of Basic Life Support medical students	2014-2017	1.0
• Master thesis	2016-2017	2.0

CURRICULUM VITAE

An Jairam werd geboren op 17 november 1986 in het toenmalige Eudokia ziekenhuis te Rotterdam. Haar basisschooltijd bracht ze door in Schiedam, en gedurende de middelbare school periode verhuisde het gezin naar Rotterdam. In 2005 behaalde ze haar middelbare school diploma op het Montfoort College in Rotterdam. In hetzelfde jaar werd ze ingeloot voor de studie Geneeskunde aan de Erasmus Universiteit Rotterdam. Haar oudste co-schap liep ze op de afdeling Chirurgie in het Reinier de Graaf Ziekenhuis te Delft (dr. M. Van der Elst). Voor haar keuze co-schap reisde ze af naar het St. Elisabeth Ziekenhuis Curaçao, waar ze op de Spoedeisende Hulp werkzaam was. In 2012 studeerde ze af en startte ze haar baan als ANIOS (arts-assistent niet in opleiding tot specialist) op de afdeling Chirurgie in het St. Franciscus Gasthuis (dr. G. Mannaerts). Vervolgens begon ze in 2013 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). Het promotie onderzoek heeft geleid tot dit proefschrift. In 2017 was ze werkzaam als ANIOS Chirurgie in het Maasstad Ziekenhuis, te Rotterdam (dr. R.A. Klaassen). Per 1 januari 2018 is ze begonnen als ANIOS Chirurgie in het Erasmus Medisch Centrum Rotterdam (dr. B.P.L. Wijnhoven).