NEW INSIGHTS IN CHRONIC PAIN AFTER COMMON OPERATIONS

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NEW INSIGHTS IN CHRONIC PAIN AFTER COMMON OPERATIONS

NIEUWE INZICHTEN IN CHRONISCHE PIJN NA GANGBARE OPERATIES

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Voor mijn lieve vader

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CHAPTER 1 Introduction

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INTRODUCTION

Chronic postoperative pain

The first publication that identified surgery as major risk factor for chronic pain appeared in 1998 gaining increasing interest since. [1] Chronic postoperative pain (CPP) is experienced by 5 to 50% of patients after various common operations of which 5% experience CPP of severe intensity. This is a significant number when the huge number of operations conducted is considered. [2,3] CPP leads to disability, repeated clinical encounters, consultations with anesthesiologists and other specialists, additional imaging studies, and extra costs in various ways. Hence the consequences of CPP are significant, not only in terms of a reduced quality of life for the individual patient but also with regard to the burden to health care and social and economic support systems. [4]

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[5] CPP is normally considered to be pain that persists or keeps coming back for more than three months postoperatively or exceeding the expected healing time. Other causes for CPP such as infection or cancer have to be ruled out and CPP is not pain continuing from the original condition. [5]

The pathophysiological concept of CPP remains difficult to determine. It was initially thought to be primarily neuropathic, but ongoing nociception might also play a role according to neurophysiological assessments. [6] There is often no precise demarcation between nociceptive and neuropathic pain and diagnosis is complicated by the influence of social, genetic and psychological factors.[7] According to the Committee of the International Association for the Study of Pain (IASP) neuropathic pain arises after injury to nerves or sensory transmitting systems in the spinal cord and brain. A key feature of this type of pain is the combination of sensory loss (negative phenomena) and spontaneous paradoxical hypersensitivity (positive phenomena) located within and beyond the damaged nerve innervation territory. The hypersensitivity can mask the sensory loss and is often burning, sharp or stabbing in character. Neuropathic CPP may arise direct postoperatively and then persist in the absence of any peripheral noxious stimulus or ongoing peripheral inflammation. Infrequently neuropathic CPP arises months to years after the operation. Nociceptive CPP results from activation of nociceptors of peripheral sensory neurons by inflammatory mediators. For example, this might be due to a continuous inflammatory reaction around foreign material like the mesh used to repair inguinal hernia. This may also lead to subsequent inflammatory nerve damage inflicting neuropathic CPP. [8,9] Nociceptive pain is often more difficult to describe. It is mostly characterized as aching, gnawing or pulling without abnormal cutaneous sensations.

Given that only subsets of surgical patients develop CPP, there may be factors that predispose an individual to develop CPP. These predictive factors are usually divided in patient-specific and surgery-specific factors and subdivided into preoperative, intra-operative, and

postoperative factors. [3,10] Important patient related factors are moderate to severe preoperative pain lasting more than one month, psychological vulnerability, female gender, younger age and genetic predisposition. Thereafter the overall severity (not maximum severity) of pain over the first seven days after surgery plays a role. However, particularly with regard to this risk factor, it is very difficult to differentiate between causality and association.[3,11] Of the surgery specific factors, the surgical approach, the surgical technique and the duration of the operation seem to be important: operations that reduce nerve injury, like minimal invasive procedures, seem to be superior. [3,10]

The problem of CPP is not limited to major surgery as it is even the most common and serious long-term complication after inguinal hernia repair, a relatively minor operation, together with laparotomy representing the commonest operations performed worldwide. [12]

Chronic pain after laparotomy

The burden of adhesions

Adhesions result from fibrin exudates that follow any kind of trauma to the parietal peritoneum caused by inflammation or surgery. These fibrin exudates form temporary adhesions until the fibrinolytic system absorbs the fibrin. Absorption is delayed in the presence of ischemia, inflammation or foreign bodies like meshes which are probably the most common biomaterials implanted in surgical medicine. In these conditions adhesions can mature and remain. Postoperative adhesion formation is the most common complication of abdominal and pelvic surgery and comprise a lifelong risk for various clinical entities like small bowel obstruction, infertility and complications during subsequent surgery.[13] Whether adhesions can also be held responsible for CPP remains a subject of debate although nerve fibers are found frequently (78%–100%) in intra-abdominal adhesions. Thereafter adhesions are thought to cause pain indirectly by restricting organ motion. However most patients with postoperative intra-abdominal adhesions are asymptomatic. This was illustrated by the findings of *Ditzes et al* who found no more CPP in patient operated because of complicated appendicitis compared to uncomplicated appendicitis which elicits less adhesions formation. [14]

In literature the exact prevalence of CPP after laparotomy varies. One study reported a prevalence of 18% in patients four years after laparotomy for gastrointestinal malignant or non-malignant conditions. Another study reported an incidence of 40% in patients after laparotomy for small bowel obstruction.[15] These patients experience a significant reduced QOL which is independent of cancer status.[2] In 35-50% of patients with CPP, in which diagnostic tools have been exhausted, the only pathological findings are adhesions found at laparoscopy. Whether these patients will benefit from laparoscopic adhesiolysis is still subject of discussion and the procedure has its own significant morbidity because of iatrogenic enterotomy. Thereafter CPP frequently recurs which can be explained by reformation of adhesions, increased severity of adhesions and the novo adhesion formation. Thereafter it should be realized that unexplained CPP can be part of centrally mediated disorders of

gastrointestinal pain, formerly known as functional abdominal pain syndrome. This reflects a range of gastrointestinal symptoms believed to have a central origin, where central dysregulation of pain is the major contributor. Among this is the centrally mediated abdominal pain syndrome (CAPS) resulting from central sensitization with disinhibition of pain signals rather than increased peripheral afferent excitability. Characteristics are the expression pain of varying intensity, urgent reporting of intense symptoms, minimizing a potential role for psychosocial contributors, frequently seeking for health care, request for narcotic analgesics, focusing attention on complete symptom relief, taking limited personal responsibility for self-management, and requesting diagnostic studies. These are characteristics comparable with the patient population presenting with CPP. CAPS / CPP management relies on a strong patient-physician relationship, early incorporation of non-pharmacological therapies, and referral for behavioral health therapies when needed.[16]

Chronic pain after inguinal hernia surgery

The inguinal hernia

The word 'hernia' is derived from the Greek word kele/hernios which means bud or offshoot. A hernia is a protrusion of parietal peritoneum, the 'peritoneal sac', through a preformed or secondarily established defect in the abdominal wall. Inguinal (groin) hernia is a common condition with an incidence of 6 to 12 per cent in adult males and increasing with age reaching 22.8% in persons aged 60-74 year. [17] It affects men more often than women. The natural course of inguinal hernias is usually slow, but they can reach impressive sizes (Figure 1). Important intrinsic risk factors for the development of primary inguinal hernia include: in-

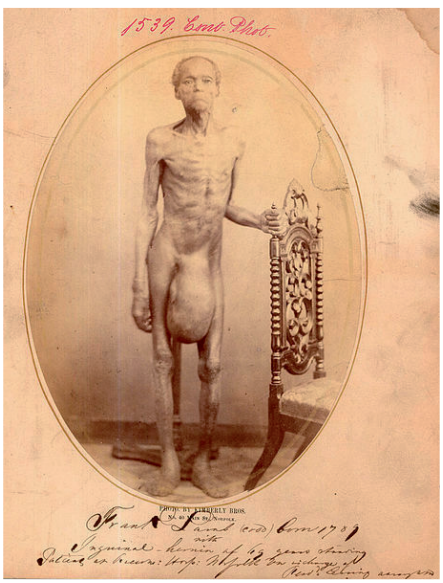

Figure 1. A man with a 69 years history of inguinal hernia. The patient, Frank Lamb, was a slave in North Carolina and since he was 9 years old suffered from left inguinal hernia. Nevertheless he was forced to hard, daily labor. As a result an important scrotal hernia developed. From: Otis Historical Archives of "National Museum of Health and Medicine".

heritance, a previous contralateral hernia, gender, age and abnormal collagen metabolism. Important acquired risk factors are prostatectomy and obesity. Since there is a low complication risk (incarceration or strangulation) in asymptomatic or minimally symptomatic men watchful waiting for minimal or asymptomatic inguinal hernias is safe. However the crossover rate to surgery is high due to the development of complaints or pain.

The history of hernia surgery

Hernias and their treatment were already described by the The Egyptians (1500 BC), Phoenicians (900 BC) and Ancient Greeks (400 BC). [18] Various non-surgical treatments were described including bloodletting, tobacco enemas, herbal dressings, special diets and compression devices or inguinal belts that were supposed to maintain the hernia sac inside the body cavity as they are still used today. [19] Surgical techniques were restricted to inguinal hernias complicated by incarceration or strangulation. They consisted of cauterization causing a stricturing scar like a permanent groin belt (Figure 2) or wide excision of the sac with surrounding skin and all its contents including hemicastration because of the spermatic duct running close to or stucked to the hernia sac. During the operation incarcerated patients were positioned upside down to facilitate reduction of the hernia (Figure 3). These surgical techniques carried a high risk of permanent stoma or death from bleeding, peritonitis and infection. [20,21] Operations were only done to save lives and not to reduce groin discomfort. Hence recurrence rates were not given a second thought, as immediate survival was the surgeons' major preoccupation. [22]

Figure 2. Cautorisation of inguinal hernia by the Arabics in the 12th century

It was not until the mid-1700s, the so called Age of Dissection, when there became an understanding of the inguinal anatomy and the nature of hernia development leading to the first major steps in finding a solution to the problem. [18] Important anatomical structures were identified and named after the anatomists or surgeons: Gimbernat's ligament (1793), the transverse fascia and Cooper's ligament (1804), Poupart's Ligament, Hasselbach's triangle, and the iliopubic tract (1814). [20,22]

Figure 3. Resection of an inguinal hernia in

Edoardo Bassini (1844-1924) was an Italian surgeon who was the first to realize that the problem was more within the diseased anatomy and physiology of the inguinal canal than in the surgical technique itself: „In order to achieve a radical cure of hernia it is absolutely essential to restore those conditions in the area of the hernial orifice, which exist under normal conditions". [27,28]

This understanding together with the recent anatomical knowledge led to the introduction in 1884 of the first durable inguinal hernia repair technique in which the inguinal floor was completely reconstructed. After complete incision of the fascia transversals, a triple layer consigned of fascia transversalis, aponeurosis of the musculus transversus abdominis and musculus obliquus internus (conjoint tendon), was sutured to the inguinal ligament (Poupart). This technique was long time the golden standard for inguinal hernia surgery in Europe. Other suture techniques were designed by the Canadian surgeon Shouldice (1890-1965) and the American surgeon McVay of which the latter popularized his concept of inguinal hernia repair using Cooper's ligament instead of the inguinal ligament.[29]

In the nineteen century various techniques using woven soft metal grafts as a reinforcement material (mesh) were used and found to be unsatisfactory. In1935 Wallace Carothers, a chemist at Dupont, discovered a method to create synthetic polymers and he is credited with the creation of nylon. The "era of plastics" was ushered leading to the introduction of polyester and polypropylene meshes. Initially the mesh was used to reinforce the posterior wall of the inguinal canal after performing a standard repair as in „tense" repairs hereby reducing recurrence rates. Until 1984 when Irvin Lichtenstein announced: „There is evidence

that to incise a strong posterior layer and, then, to reconstruct it as in the Bassini, Shouldice or McVay repair is inappropriate, disruptive and even meddlesome. The application of a wide sheet of harmless prosthetic mesh, one which serves only to strengthen such a floor, is harmless and should reduce the incidence of recurrences".[30] He, or more precisely his colleague Alex Shulman, introduced a "tension free" mesh repair. This technique has become the gold standard in open tension free hernioplasties due to its effectiveness, easiness to perform, safety and low rate of complications and recurrences. Furthermore it can be performed under local anesthesia in a day care setting.

The first laparoscopic inguinal hernia repair was described in 1979 and in1989 a prosthetic mesh was introduced during laparoscopic hernia repair. Various laparoscopic techniques were developed of which the TAPP (transabdominal pre-peritoneal) and TEP (totally extraperitoneal) have become the most common techniques used today.

Prosthetic meshes have revolutionized hernia surgery because rates of recurrence and chronic postoperative inguinal pain (CPIP) are significantly lower than in autologous repair. This is thought to be related to the ability to use a tension free technique rather than the mesh itself. However the downside of CPIP remains. The reported frequency of CPIP after Lichtenstein repair varies widely because of different definitions used. In 2000, Poobalan et al reviewed the literature of CPIP and found incidences ranging from 0% to 63%. [23] A similar range was reported by Aasvang and Kehlet in an update. [8] The overall incidence of moderate to severe CPIP that interferes with daily living is estimated to be around 10–12%. [24] Debilitating CPIP affecting normal daily activities or work ranges from 0.5 to 6%. [9] This is largely exceeding the incidence of recurrence making CPIP the most important complication of inguinal hernia repair today. Regarding the high number of repairs, the incidence of 11% and the fact that CPIP is especially effecting young otherwise healthy males, CPIP must be considered a major health problem with significant socio-economic impact. [25,26] Improvements in clinical outcome therefore have great medical and economic impact.

Patients with CPIP commonly experience both nociceptive and neuropathic pain. For neuropathic pain to occur one of the four nerves that cover the sensory innervation of the inguinal region and lower abdomen have to be damaged during hernia repair. When the inguinal region is approached anteriorly three nerves are at risk: the iliohypogastric nerve which supplies the region cranially to the pubic tubercle and more laterally to the hip region, the ilioinguinal nerve covering sensation to the base of the pubic area and inner thigh, the genital branch of the genitofemoral nerve innervating the scrotum or labia majora. The lateral femoral cutaneous nerve is rarely affected during Lichtenstein repair because of its lateral position, but can be damaged when tackers are used to fixate the mesh during TEP repair. The pain can often be intensified by stretching of the hip joint, coughing, sneezing, sexual intercourse and tension of the abdominal muscles causing nerve traction or compression.[9,27] Nerves can be damaged due to dissection during operation, entrapment by the mesh and sutures to secure the mesh and postoperative complications like inflam-

mation (periostitis, foreign body reaction to mesh or sutures). Neuropathic pain can be felt in or around the inguinal scar and radiating into the skin area innervated by the damaged nerve. Nociceptive pain can often be aggregated by applying pressure to the mesh and can develop after some months because of mechanical pressure by mesh displacement or contraction.

Recently new mesh products have been developed which offer the potential to decrease CPIP. In this research a semi-resorbable self-fixing mesh is investigated. It is presumed that the self-fixing properties minimize entrapment neuropathy by omitting sutures or tackers. In addition the light weight construction of the mesh is known to reduce the amount of foreign body reaction thereby minimizing inflammatory damage to the surrounding tissue and nerves.

AIM OF THE THESIS

The first part of the thesis addresses CPP after laparotomy judged to be caused by adhesions. It aims to assess long term results of laparoscopic adhesiolysis as a treatment for CPP. The second part of the thesis addresses CPP after inguinal hernia repair (CPIP). It aims to determine whether a self-gripping mesh for open inguinal hernia repair according to Lichtenstein influences the incidence of CPIP. The third part focuses on the methodological quality and comparability of studies addressing CPIP after Lichtenstein hernioplasty. It aims to assess whether study outcomes are valid and can be compared to each other to make firm conclusions about the best treatment or prevention method for CPIP.

OUTLINE OF THE THESIS

In the **first part** of the thesis CPP judged to be caused by adhesions will be addressed

In **Chapter 2** the long term follow up of a randomized controlled trial comparing laparoscopic adhesiolysis and laparoscopy alone in patients with CPP after abdominal surgery will be evaluated.

In the **second part** studies are presented to evaluate a self-gripping mesh for Lichtenstein repair of primary inguinal hernias in adult patients.

In Chapter 3 and 4 the results of a long term follow-up retrospective study (**Chapter 3**) and a multi-center randomized controlled double blinded trial (**Chapter 4**) comparing a self-gripping mesh and a sutured mesh for Lichtenstein hernioplasty will be presented. It is hypothesized that a self-gripping mesh not needing traumatic fixating devices will reduce the incidence of CPIP, because there is less risk of nerve entrapment (neuropathic pain) or muscle and periosteal damage (nociceptive pain) by the sutures. This effect is supposed to

be enhanced by the macroporous lightweight structure of the mesh thereby reducing the foreign body reaction which may cause inflammatory damage to surrounding nerve and muscle fibers causing nociceptive and neuropathic pain.

In **Chapter 5** the effect of a self-gripping mesh is further investigated in a meta-analysis of published randomized controlled trials comparing the self-gripping mesh with a sutured mesh for the Lichtenstein hernioplasty. While a number of meta-analysis on this subject have already been published this meta-analysis is thought to be of value because at this time new studies with larger populations and longer follow-up periods can be included which is essential for judging effects on CPIP.

The self-gripping mesh has micro hooks made of polylactic acid (PLA) on its lower surface which ensure tissue gripping of the mesh. **Chapter 6** will report the influence of these PLA micro hooks on the biocompatibility of the mesh by using a proved in vitro model of human derived macrophages.

In the **third part** the quality and comparability of the literature on CPIP is reported

In **Chapter 7** the uniformity and quality of studies addressing CPIP after Lichtenstein hernioplasty will be reviewed. It will be questioned whether there is uniformity in collecting data, definition of the outcome parameter CPIP and method of presenting outcomes.

Chapter 8 and 9 will summarize and discuss the conclusions of this thesis and **Chapter 10** will provide future perspectives.

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PART 1

CHRONIC PAIN AFTER ABDOMINAL SURGERY: ADHESIOLYSIS

CHAPTER 2

12 Year Outcomes of Laparoscopic Adhesiolysis in Patients with Chronic Abdominal Pain: A Randomized Clinical Trial

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Surgery 2017

ABSTRACT

Objective

To evaluate long term effects of laparoscopic adhesiolysis for treating chronic abdominal pain.

Background

Laparoscopic adhesiolysis as a therapy for chronic pain is still controversial and long term effects are not known.

Methods

One hundred patients with abdominal pain attributed to adhesions were randomized to laparoscopic adhesiolysis or a placebo group with laparoscopy alone. Pain relief was assessed after 12-year follow-up.

Results

Seventy-three percent fulfilled the long term follow up. Compared to the placebo group (n=31), patients in the adhesiolysis group (n=42) were significantly less often pain free (8 versus 13, P=0.033, RR=1.3). This caused the adhesiolysis group to have a higher intake of analgesics (26 versus 16, P=0.379, RR 1.2, 95% CI 0.8-1.8), seek of medical consultants (14 versus 6, P=0.186, RR1.33, 95% CI 0.9-1.9) and rate of additional surgery (8 against 1, P=0.042, RR=1.67, 95% CI 1.208-2.318). Both groups continued to have improved pain and quality of life scores.

Conclusion

This is the first long term placebo controlled trial regarding the use of laparoscopic adhesiolysis for treating chronic abdominal pain. Laparoscopic adhesiolysis was less beneficial than laparoscopy alone in the long term. Secondly, there was a powerful and long lasting placebo effect of laparoscopy. Since adhesiolysis is associated with an increased risk at surgical complications, avoiding this treatment will result in less morbidity and health care costs.

INTRODUCTION

Attempts to determine the cause of chronic abdominal pain are often challenging. Intra-abdominal adhesions seems to be the cause in 35% to 50% of patients.[1] Whether these patients would benefit from laparoscopic adhesiolysis is a topic of discussion since success rates in literature range between 38% - 87%. [2] This was reason to perform a randomized double-blind placebo controlled trial regarding the use of laparoscopic adhesiolysis for treating patients with chronic abdominal pain attributed to adhesions. Patients were randomized to either laparoscopic adhesiolysis (n=52) or laparoscopy alone (placebo group, n=48). The treatment arms were revealed to them at one year. At that time patients in the placebo group could request to have laparoscopic adhesiolysis. The 1-year results were published in The Lancet in 2003 and showed no benefit for the adhesiolysis group over the placebo (laparoscopy alone) group. [3] The outcomes after 12 years of follow-up are reported here.

METHODS

Study design

This multi-center randomized controlled trial, included patients with chronic abdominal pain likely to be caused by adhesions from previous abdominal surgery. Chronic abdominal pain was defined as continues or intermittent abdominal pain of at least six months' duration. After excluding other pathology (see exclusion criteria) included patients underwent a diagnostic laparoscopy to confirm the adhesions and to exclude serious morbidity not visible with other diagnostics. If during laparoscopy adhesions were the only pathology present, patients were randomly assigned either to laparoscopic adhesiolysis or no treatment. For the randomization and surgical procedures we refer to the original article.[3] Patients were unaware of their treatment assignment and the outcome assessment was blinded. Abdominal pain and quality of life (QOL) were assessed pre-operatively and at 3, 6 and 12 months of follow-using a visual analog scale (VAS), verbal rating pain change score (VRCS) and the short form 36 (SF-36). After 12 months randomization was disclosed and placebo group patients with persisting abdominal pain could request laparoscopic adhesiolysis. After 12 year follow-up pain, QOL, medical history and analgesic intake were analyzed to assess the long term effects of laparoscopic adhesiolysis.

The study was approved by the ethics committee of each participating hospital. The study is registered with clinicaltrials.gov; the NCT ID is NCT02839564 .

Outcome measures

Primary outcome: long term pain relief.

Secondary outcomes: QOL, long-term complications, analgesic intake, rate of consulting medical doctors and additional surgery because of persisting abdominal pain.

Patients

Inclusion criteria:

Patients aged 18 years and above with chronic abdominal pain that was likely to be caused by adhesions due to previous abdominal surgery were recruited. Before attributing abdominal pain to the existence of adhesions all patients had an extensional diagnostic work-up to exclude other pathology.

Exclusion criteria:

1. Current treatment by psychologist or psychiatrist
2. Use of laxatives, sedatives, morphine, antipsychotics, antidepressants, or drugs that stimulate the central nervous system
3. Abnormal outcome of standardized non-invasive diagnostics:
    - Biochemical investigation
    - Lactose tolerance tests or H2 respiration test
    - Feces analysis of worms and worm eggs
    - Ultrasound or CT scan of the abdomen
    - Radiographic studies of small and large bowel (or colonoscopy)

Statistics

Analysis was by intention-to-treat (ITT) according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. [4] Preceding observations and a least squares regression were used in case of missing data. Proportions were compared with the Chi-square test and Fisher's exact test. The Mann-Whitney U-test was used to analyze outcomes of the VRCS, VAS and SF36 . Changes compared to baseline were analyzed with the Student's t-test and Wilcoxon's signed rank test. The applied significance level was 5%. Statistical Analysis was performed using SPSS Statistical software (version 22.0, SPSS inc., Chicago, USA)

RESULTS

A total of 80 patients (80%) were traced back for the 12-year follow-up (Figure 1). Five of them had died due to causes unrelated to abdominal pathology and 2 patients were demential and therefore excluded. Of the remaining 73 patients, 42 were allocated to laparoscopic adhesiolysis and 31 to placebo (laparoscopy alone). Of the 31 patients in the placebo group, 12 underwent subsequent laparoscopic adhesiolysis after patients had their treatment arms revealed to them at one year. Baseline characteristics are shown in Table 1. By chance,

patients randomized to adhesiolysis had longer pre-study duration of pain than did patients randomized to the placebo group (30 vs 18 months).

Regarding the primary outcome 8 (19%) patients in the adhesiolysis group reported complete relief of abdominal pain against 13 (42%) patients in the placebo group (P=0.033, RR=1.3) (Figure 2). In both groups VAS scores improved significantly (P>0.05, Table 2) during the first 6 months of follow up and this was maintained throughout the remaining follow-up.

In accordance with the improved VAS scores both groups continued to register improved QOL scores especially for the items physical functioning, daily activities, social functioning, pain and vitality. Thereafter there was a significantly further improvement compared to twelve months of follow-up for daily activities and physical functioning in the adhesiolysis group and pain and vitality in the placebo group.

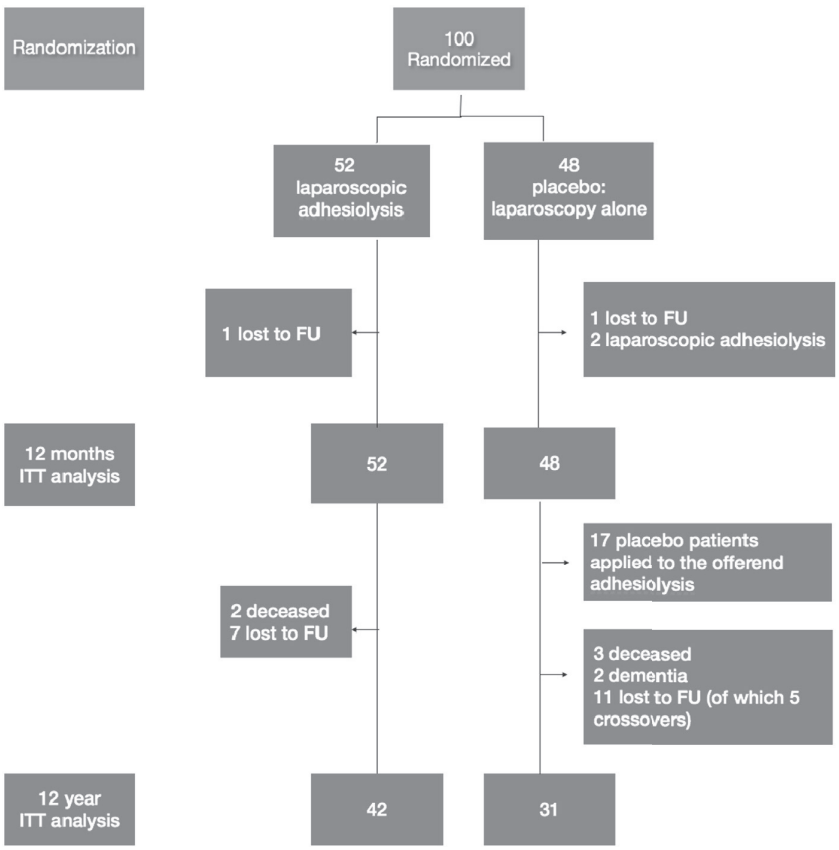

Figure 1. Trial Profile

Flow diagram according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines; ITT = intention to treat; FU = follow up

Table 1. Patients and baseline characteristics

Characteristics	Adhesiolysis group n = 42	Placebo group n=31
General features:		
Age in years	45.1 (13.5)	48.8 (12.1)
Female/male	38/4	28/3
Body mass index	24.2 (18-37)	24.2 (19-30)
Pain factors:		
VAS score	57.4 (18.2)	55.8 (17.3)
MOS SF-36 score	35.3 (16.2)	33.5 (15.2)
Duration of abdominal pain in months	30 (7-235)	19 (6-179)
Adhesion assessment:		
Adhesions between organs:		
Incidence	2 (0-7)	2 (0-6)
Severity	2 (0-24)	3 (0-24)
Adhesions between organs and the abdominal wall:		
Incidence	1 (0-4)	1 (0-5)
Severity	3 (0-16)	4 (0-16)
Number of previous abdominal operations:	2.8 (1.5)	2.7 (1.5)
Type of previous operation: (no. of patients):		
Open appendectomy	24	20
Gynecological procedures	38	36
Open bowel resections	6	14

Data are given as mean (standard deviation) or median (range)

Table 2. Results of VAS and MOS SF-36 scores for the adhesiolysis and control group after 3, 6, 12 months and 12 years.

	Adhesiolysis group		Placebo group		P-value
	No. of patients	Score (mean SEM)	No. of patients	Score (mean SEM)	
VAS					
0 months	52	57.2	48	56.0	
6 months	52	38.6 ± 3.5	48	40.2 ± 4.2	0.77
12 months	52	38.9 ± 3.4	48	40.5 ± 3.7	0.63
12 year	42	34.1 ± 4.2	31	28.6 ± 5.1	0.29
MOS SF-36 score (pain part)					
0 months	52	35.1	48	33.8	
6 months	51	51.2 ± 3.0	47	50.1 ± 3.5	0.73
12 months	51	51.0 ± 3.3	47	49.7 ± 3.2	0.84
12 year	42	60.7 ± 29.1	31	62.3 ± 29.2	0.81

Data are given as mean ± standard error of mean (sem); VAS = visual analogue scale; MOS SF-36 = medical outcomes study with 36 item short-form health survey

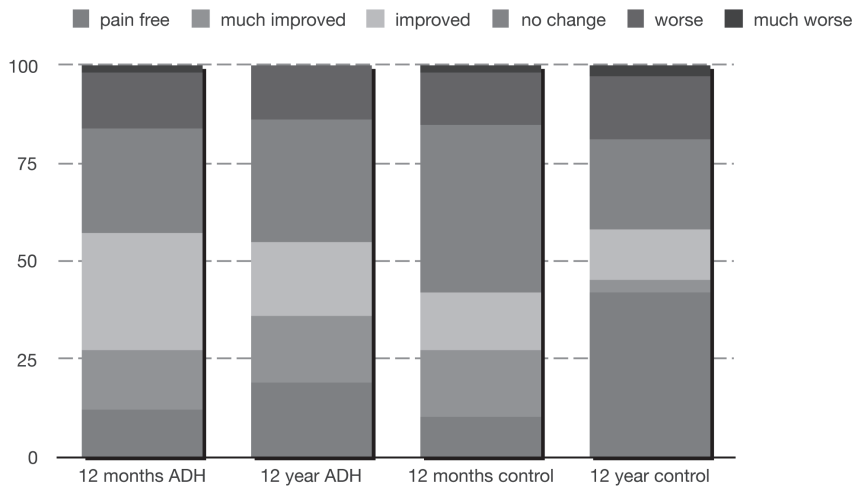

Figure 2. Verbal rating pain change scores after twelve months and twelve year
Change of pain (VRCS score) for patients in the adhesiolysis and control group at 12 months and 12 year of follow up compared with baseline (percentage of patients).
Significantly fewer patients in the adhesiolysis group reported being pain free compared to the non-adhesiolysis group (P=0.033, RR=1.3, Chi-square test).
ADH = adhesiolysis

Pain killers to relief abdominal pain were taken by 26 (62%) patients in the adhesiolysis group versus 16 (52%) patients in the placebo group (P=0.379, RR 1.72, 95% CI 0.8-1.8) (Table 4). Persisting abdominal pain was reason to seek other consultants for 14 (33%) adhesiolysis patients and six (19%) placebo patients of which five had crossed over to adhesiolysis (P=0.186, RR1.33). Consulted were general surgeons, internists, gynecologists and neurologists (P=0.186, RR1.33). Patients were diagnosed with Irritable Bowel Syndrome, gastritis, abdominal cutaneous nerve entrapment syndrome (ACNES), cholecystolithiasis, small bowel obstruction, ovarian cystic disease and mild diverticulitis. Another two were diagnosed with pancreatitis, which was regarded as a new disease because of normal serum amylases at preoperative work-up before trial participation).

Eight (19%) patients in the adhesiolysis group compared to one patient in the placebo group underwent additional surgery because of persisting abdominal pain (P=0.042, RR=1.67, 95% CI 1,208-2,318). The patient in the placebo group was actually a crossover patient and had a second adhesiolysis performed during long term follow-up. Of the patients in the adhesiolysis group three underwent a second adhesiolysis, two were operated because of ACNES, two because of ovarial cysts and one underwent an uterus extirpation.

Three long term complications were reported all appearing in the adhesiolysis group. There was one non strangulated cicatricial hernia and two admissions because of a small bowel obstruction. One was treated conservatively and one needed adhesiolysis.

Table 3. Medical history of patients in the adhesiolysis and placebo group regarding chronic abdominal pain for the period between the short term analysis at 12 months and long term follow-up after 12 year.

	Adhesiolysis group No. (%)	**Placebo group No. (%)**	**P-value RR CI 95%**
Use of painkillers			
Yes	26 (62)	16 (52)	P = 0,379
No	16 (38)	15 (48)	RR 1,72
			CI95% 0,79-1,812
Medical analysis			
Yes	14 (33)	6 (19)	P=0.186
		among which are 5	RR 1,33
		crossover patients	CI95% 0,903-1,944
No	28 (67)	25 (81)	
Re-operations			
Yes	8 (19)	1 (3)	P=0,042
		= crossover patient	RR: 1.67
No	34 (81)	30 (97)	CI95% 1,208-2,318
Type of re-operation:			
Adhesiolysis	3	1	
Uterus extirpation	1	-	
Ovarian cystectomy	2	-	
Neurectomy	2	-	
Incisional hernia	1	-	
Euthanasia because of pain	1	-	

Analysis were with Fisher's exact test

DISCUSSION

A randomized double blind placebo controlled trial was performed regarding the use of laparoscopic adhesiolysis for treating chronic abdominal pain. Compared were laparoscopic adhesiolysis to laparoscopy alone (placebo group). The one year results showed no benefit for the adhesiolysis group over the placebo (laparoscopy alone) group. After the 12 year the same findings were evident and even slightly worse for the adhesiolysis group.

Comparing our results to literature is challenging because of heterogeneity in study methods and consequently the reported outcomes with success rates laparoscopic adhesiolysis ranging between

16.7-97%. Since the surgical techniques differ only slightly between the studies, the discrepancy in success rates seems mostly due to methodological inconsistencies like the use of non-validated pain measurement tools, lack of a baseline measurement, low numbers of follow-up and inclusion of patients who had complaints not attributable to

adhesions. [5-18]. One other randomized controlled trial addressing this subject was found. This well performed short term study by Peters et al reported no benefit of laparoscopic adhesiolysis over adhesiolysis alone which is line with our short and long term results. [3,5] The long term results are probably even underestimated, since the placebo patients that did not crossover to adhesiolysis did much better overall. Because of the intention to treat analysis these crossover patients are kept in the placebo group thereby underestimating the value of just the diagnostic laparoscopy.

In addition to the conclusion that laparoscopic adhesiolysis is inferior to just diagnostic laparoscopy / placebo, not overlooking the additional drawback of a higher peroperative morbidity (3% vs 0.1%), a second conclusion emerged from the study. [3] The laparoscopy alone showed to have a persisting and enlarging placebo effect during long term follow up, which as far as we know has not been previously reported. Clinical trials of surgical therapies are known for their placebo effects, but long term results are lacking.[19] This may be due to the fact that surgical trials incorporating a placebo arm are rare and of short duration, because of debates on the ethics and feasibility of placebo in surgery. [20]

The question arises how the longevity of the placebo effect can be explained. A placebo response is a psychobiological phenomenon in which expectations of benefit have an important role.[21] if the perceived pain reduction with placebo matches the expectations of the patient it induces a sense of assurance.[22] This causes a positive feedback loop maintaining pain reduction in placebo arms over long periods.[23] The mechanisms responsible for the initial pain reduction in the both arms of this study might be the assurance that no serious pathology was found during the laparoscopy. The subsequent positive feedback loop turned out to be weaker in the adhesiolysis group which may be explained by the fact that laparoscopic adhesiolysis still inflicts new trauma to the sensitive peritoneum. This trauma results in neo-formation and reestablishment of adhesions with as long-term result, recurrent abdominal pain[24]. This decreasing success rate of adhesiolysis over time was described by Vrijland as well. [2]

The conclusion that there is no advantage of adhesiolysis above placebo is weakened by the fact that by chance, patients randomized to adhesiolysis had longer pre-study duration of pain compared to the patients randomized to the placebo group (30 vs 18 months). In the first analysis no evidence was found that this is a factor that modifies treatment effect.[3] However it can be of influence on the long term results since preoperative pain is a risk factor for persistent post-surgical pain. For example because it may have caused persisting neurophysiologic changes and pain-related pathology like psychological vulnerability or stress. These factors are likely to be present in this patient population although patients under treatment of a psychologist or psychiatrist were not eligible for trial participation. [25] This is however no assurance that psychological instability is not present illustrated by the fact that one crossover patient decided to have euthanasia because he was being sick of living with chronic abdominal pain.

It is not clear why a considerable part of the placebo group applied to have adhesiolysis as yet, especially because of the same short term results compared to placebo. Probably the assurance after diagnostic laparoscopy that no serious morbidity was found did not provide enough relief to match the expectations of the patients needed for attenuating a positive feedback loop. Persisting pain may have caused them to hope that doing something is still better than to do nothing. Thereafter disease profit of ongoing medical attention may have been a driving factor.

A strong feature of this long term follow up study is the high number of patients after a long period of time (73% after twelve year) and few missing data. The reason patient participation at twelve year was more complete for the adhesiolysis group is not clear, but since the response rate is high for both groups, response bias is less likely.

CONCLUSION

Laparoscopic adhesiolysis is not a beneficial treatment for patients with chronic abdominal pain attributed to adhesions and even results in worse outcome. Besides the risk of inadvertent enterotomy patients undergoing laparoscopic adhesiolysis have a smaller chance of becoming pain free, take more pain killers, have a higher consultation of medical doctors and are re-operated more often for persisting pain. Avoiding this treatment modality will result in less morbidity and health care costs. This study shows the powerful way in which placebo controlled trials can show non-efficacy of surgical therapies and the placebo effect to be powerful and long lasting. Without well-designed placebo controlled trials of surgery, ineffective surgical treatment may continue unchallenged.

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PART 2

CHRONIC PAIN AFTER INGUINAL HERNIA REPAIR:

A SELF-GRIPPING MESH

CHAPTER 3

A more than 5 year experience with a self-gripping mesh for the Lichtenstein hernioplasty.

Marijke Molegraaf
Dingeman Swank
Johan Lange

ABSTRACT

Purpose

Aim was to evaluate the long term effects of a self-adhering mesh not needing traumatic fixation devices on the incidence of chronic postoperative inguinal pain (CPIP) and recurrence rate after inguinal hernioplasty according to Lichtenstein.

Methods

Two groups of fifty consecutive patients, operated in 2008 with the self-gripping mesh (Progrip mesh, Covidien / Medtronic) or with a suture fixating polypropylene mesh, were selected from a population of adult males with primary unilateral inguinal hernia. All patients were sent a SF-36 questionnaire and VAS score in December 2010. Three years later they were interviewed about recurrence and CPIP.

Results

41 study patients and 42 control patients were available for both points of follow-up. After a median follow up 30 months incidence of CPIP was 14.6% in the self-gripping mesh group and 23.8% in the suturing mesh group. After a median follow-up of 67 months this was reduced to 4.8% respectively 9.8% (NS). At 30 months CPIP affected daily life in 1 patient in the self-gripping group (2.4%) and 3 patients in the suturing group (7.1%) (NS). After 67 months this was reduced to 0% respectively 2.4% (NS). Severe pain (VAS>70) was only seen in the suturing mesh group. Two recurrences were detected in the self-gripping mesh group and one in the sutured mesh group (NS). Operating time was significant shorter for the self-gripping mesh (p=0.000).

Conclusion

The findings presented here reflect the longest experience to date with the self-gripping mesh for inguinal hernioplasty. Although the self-gripping mesh appears not to reduce CPIP, it is efficient with no more recurrences and significantly reduced operating time.

INTRODUCTION

The open Lichtenstein and endoscopic inguinal hernia techniques are still recommended as the best evidence-based options for the repair of a symptomatic primary unilateral inguinal hernia, providing the surgeon is sufficiently experienced in the specific procedure [1]. In recent years chronic postoperative inguinal pain after hernioplasty (CPIP) gained much attention. CPIP has been defined as pain lasting more than three months after surgery [2]. The reported frequency of CPIP varies widely because of different definitions used. In 2000, Poobalan et al reviewed the literature of CPIP and found incidences ranging from 0% to 63% [3]. A similar range was reported by Aasvang and Kehlet in an update [4]. The overall incidence of moderate to severe CPIP is estimated to be around 10–12% [1]. Since surgical repair of groin hernias is one of the most commonly performed operations in the Western world and CPIP is especially effecting young otherwise healthy males, CPIP must be considered a major health problem [5]. The etiology of CPIP is multifactorial among which is the surgical repair technique [1]. This includes aspects like type of mesh used, its structure and interaction with tissue, method of fixation of the prosthetic material and handling of the cutaneous nerves [6]. The use of non-absorbable sutures for mesh fixation has been cited as an important etiologic factor because of tension at anchor sites, additional foreign body reaction and entrapment of muscle and nerve fibers [7]. A solution for this problem might be a self-gripping mesh (Parietene ProGrip®; Covidien): a polypropylene mesh with a one-sided coating of polylactic acid fiber hooks anchoring the mesh on to the tissue rendering additional fixating devices unnecessary. A number of clinical studies including clinical trials have been published to date comparing this particular mesh to the classic PPL mesh [8]. Preliminary results have shown shorter operative times and lower incidences of CPIP. However, there is a lack of data about recurrence and chronic pain results in extended follow-up. The present study aims to report the long term differences in prevalence of CPIP and recurrence between a sutured mesh and a self-gripping mesh. It is presumed that a self-gripping mesh induces less CPIP and sensory loss without enhancing recurrence rate.

METHODS

In the department of general surgery of the Groene Hart Hospital, Gouda, The Netherlands, two groups of fifty patients, operated in 2008 with the self-gripping mesh (R/Progrip, Covidien USA) or with a suture fixating polypropylene mesh (Prolene, Ethicon, USA), were consecutively selected from a population of adult male patients with primary unilateral inguinal hernia, operated by two surgeons, performing the self-gripping mesh-technique and by six other surgeons, performing the suture fixating mesh technique. Exclusion criteria

for both groups were incarcerated inguinal hernia, ASA>3, coexisting chronic groin pain and being incapacitate. The self-adhesive mesh was introduced in the department in 2007.

All operations were performed by a surgeon or by a trainee under supervision. Operations were performed under spinal or general anesthesia in day care setting. Tension-free hernioplasty was performed with a 6×11 cm Prolene mesh or 12x8 cm Parietene ProGrip Mesh. The hernioplasty was accomplished according to the open tension-free repair of Lichtenstein. The incision, dissection of the sac in relation to the type of hernia, dissection of the anterior inguinal floor and closure of the wound with absorbable sutures were similar in all patients. The ilioinguinal, genitofemoral (genital branch) and iliohypogastric nerves were identified and preserved if possible in each case. In case of damage to the nerve or interfering with mesh or sutures the nerve was excised. Indirect hernia sacs were inverted or in case of a large sac transfixed at the base and excised. Direct sacs were inverted with absorbable sutures. Finally a local anesthetic (50mg chirocaine soluted in 10ml NaCl) was administered into the wound in both groups of patients. Operating time was scored starting from skin incision to completion of skin closure.

After informed consent patients from both groups were sent a SF-36 questionnaire and VAS score in december 2010 to assess the degree of CPIP and interference with activities of daily living. Three years later, January 2014, a telephone call was made and patients were asked about recurrence of the hernia and the existence of CPIP or sensory loss in the operated groin area and whether the pain interfered with social activities and work. In the case of CPIP they were asked to grade their present groin pain on a visual analogue scale. Data about medical history, per- and postoperative complications and operation details were collected from the clinical database.

Progrip mesh

The Parietene Progrip Mesh [manufactured by Medtronic (Group Covidien)] is a monofilament mesh composed of polypropylene and resorbable polylactid acid (PLA) micro hooks for tissue gripping. Mesh fixation by the micro hooks to the underlying groin tissue is achieved instantly after exerting light pressure on the mesh. After the company the PLA micro hooks will be completely resorbed after 15 months and only the low-weight (40 g/m2) monofilament polypropylene (PP) will be left in situ. The mesh has an oval shape with a self-gripping flap to be placed around the spermatic cord at the internal ring. The flap can be opened and reclosed facilitating corrections during mesh placement. There is a right and left sided version for optimal fitting of the mesh to the anatomical area.

Technic of mesh placement

In the suturing group the mesh was positioned against the posterior wall of the inguinal canal and sutured to the aponeurotic tissue over the pubic bone with a non-absorbable monofilament suture overlapping the pubic bone by 1.0 to 1.5cm (avoiding the pubic

periosteum). With a running PDS 2.0 suture the lower edge of the mesh was fixed to the inguinal ligament. Then the mesh was incised to create two tails which were placed around the spermatic cord in order to create a prosthetic internal ring. Both tails were overlapping each other with a single non-absorbable monofilament suture. Interrupted sutures were used to fixate the upper edge of the mesh to the conjoint tendon.

The Progrip mesh was placed tension free over the posterior wall of the inguinal canal overlapping the pubic bone and inguinal ligament by 1cm. The self-gripping flap was closed loosely around the spermatic cord as described by Chastan [25]. Fixation was achieved by applying light pressure on the mesh. No fixating suture(s) were applied.

Outcomes

The primary outcome of the study was the prevalence of CPIP with pain defined as a VAS score >10 [14]. Chronic pain was regarded as mild (VAS 10–30), moderate (VAS 31–60) or severe (VAS 70–100) [14]. Secondary outcomes included wound complications, operating time and recurrence rate.

Statistics

The statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) for Windows, version 9´01 (SPSS, Chicago, Illinois, USA). All tests were two sided and $P < 0.05$ was considered significant. Dichotomous categorical data were compared using Pearson's Chi-squared test or Fisher's exact test for smaller groups. Continuous data were expressed as median (range) and compared with the Mann-Whitney U test.

RESULTS

Within the group of 100 patients 83 patients (n=41 self-gripping mesh; n=42 suturing mesh) were available for long term follow-up (mean 67 months). Demographic details of patients and hernia types are shown in Table 1. There was no significant difference in response rate and characteristics between the two groups.

The median duration of operation was 37 min for the self-gripping and 47 min for the sutured mesh ($p<0.001$, Mann-Whitney U test, Table II). No perioperative complications were observed. Three post-operative complications occurred, all in the suturing mesh group (not significant, NS)): one postoperative hematoma, one seroma and one infection (epididymitis). At the end of the study (median FU 67 months) two recurrences were detected in the self-gripping group and one in the suturing group (NS).

At the first cross sectional analysis in December 2010 (median follow up 30 months, range 26-35, Table III) CPIP defined as VAS>10 mm was reported by 14.6% patients in the self-gripping mesh group and by 23.8% patients in the suturing mesh group (OR 0.55, CI

0.179-1.681). CPIP affected daily life in 2.4% of the self-gripping group and 7.1% of the suturing group (NS).

At the second cross-sectional analysis in January 2014 (median follow up 67 months, range 63-72, Table IV) CPIP was reported by 4.8% respectively 9.8% (OR 0.59, CI 0.145-2.008) and affecting daily life in 0% respectively 2.4% (NS).

In those patients who reported CPIP, pain intensity was mostly classified as mild pain (VAS 10-30, Table III and IV). Severe pain (VAS>70) was only seen in the sutured mesh group. Two patients in this group were referred to a pain team. Sensory loss was reported by 15 (36.6%) patients in de self-gripping group and 25 (61%) patients in the suturing mesh group (P0.0367).

Table 1. Patient and hernia characteristics

	Suturing Mesh N=41	**Self-gripping Mesh N=42**
Age**	66 (24-89)	68 (21-89)
Sex ratio (F:M)	0:41	0:42
Body mass index (kg/m2) **	24.8 (18.2–31.0)	25·0 (20.2-30.4)
Type of work*		
Sedentary	13 (31.7)	11 (26.2)
Physical	11 (26.8)	12 (28.6)
Unemployed/retired	17 (41.4)	19 (45.2)
Side of hernia*		
Left	24 (58.5)	23 (54.8)
Right	17 (41.5)	19 (45.2)
Type of hernia*:		
Direct	12 (29.3)	10 (23.8)
Indirect	26 (63.4)	28 (66.7)
Combined	3 (7.3)	4 (9.5)
Operator*:		
Resident	35 (85.4)	38 (90.5)
Surgeon	6 (14.6)	4 (9.5)
Anesthesia*:		
General	13 (28.6)	12 (31.7)
Spinal	28 (71.4)	30 (68.3)
Follow up ** (months)	67 (63-72)	67 (64-72)

*values in parentheses are percentages; **Values are median (range)

Table 2. Results

	Suturing Mesh N=41	Self-gripping Mesh N=42	P
Operating time**	47 (34-87)	37 (17-97)	0.000 ¥
Neurectomy *	3 (7.3)	6 (14.3)	0.483$
Complications*:			
Recurrence	1 (2.4)	2 (4.2)	0,616 $
Hematoma	1 (2.4)	0	0.517 $
Seroma	1 (2.4)	0	0.517 $
Wound infection	1 (2.4)	0	0.517 $
Testicular atrophy	0	0	
Prevalence of CPIP (%)			
median FU 30 months*	10 (23.8)	6 (14.6)	0.312§
median FU 67 months*	4 (9.8)	2 (4.8)	0.353§
Interference with daily activities (%)			
median FU 30 months*	3 (7.1)	1 (2.4)	0.317§
median FU 67 months*	1 (2.4)	0	0.517 $
Sensory loss	25 (61)	15 (36.6)	0.037§

*values in parentheses are percentages; **Values are median (range); ¥ Mann–Whitney *U* test; $ Fisher's Exact Test; § Pearson χ^2 test.

Table 3. VAS scores of the first cross-sectional analysis, median follow-up 30 months, OR for CPIP 0.55 (CI 0.179-1.681)

	Chronic pain					
	<10	10-30	31-70	>70	median VAS	range
Self-gripping mesh	35	5	1	0	0	0-40
Suturing mesh	31	7	2	1	5	0-80

Table 4. VAS scores of the second cross-sectional analysis, median follow-up 67 months, OR for CPIP 0,54 (CI 0.145-2.008)

	Chronic pain					
	<10	10-30	31-70	>70	median VAS	range
Self-gripping mesh	40	2	0	0	0	0-20
Suturing mesh	38	2	1	0	15	0-40

DISCUSSION

Our data indicate that a self-gripping Progrip mesh not needing additional suturing is safe and effective also after long term follow-up of 67 months. Compared to a sutured mesh there were no significant differences in incidence of CPIP (2% resp. 4%) and recurrences (4.2% resp. 2.4%). Furthermore the self-gripping mesh is easy to perform reflected in significant reduced operating times. It was expected that this self-gripping mesh bypassing traumatic fixation devices would lead to a reduction in CPIP compared to meshes traumatically fixated with sutures or staples. This hypothesis was based on the assumption that atraumatic fixation of a mesh would reduce the risk of compression and entrapment of muscle and nerve fibers leading to less muscle ischemia and neuroma formation [9]. Indeed removal of sutures can be an effective treatment in patients with pain [10]. Further on despite Lichtenstein being a tension-free method, fixation devices will still cause tension at anchor sites [7]. Finally no fixation devices mean less foreign material and possibly a reduction of the foreign body reaction. This foreign body reaction is known to cause inflammatory damage to surrounding tissues and nerves and may induce a surplus of scar tissue leading to stiffness of the abdominal wall and a foreign body sensation [11]. When using the Parietene Progrip mesh the need for traumatic fixating devices is bypassed by small absorbable micro hooks on the surface of the mesh. Chastan was the first to report the initial promising clinical experience with this self-gripping mesh [12]. Since his publication a number of prospective studies and randomized controlled trials have compared the self-gripping mesh with a sutured mesh in Lichtenstein hernioplasty. Somme studies suggested that the incidence of CPIP was significantly reduced by using this mesh [13] while other studies did not confirm that [14]. The absence of a significant reduction of CPIP when using a self-gripping mesh may have several explanations. First the onset of CPIP is multi-factorial and not only caused by surgical related factors, but is also influenced by patient related factors. Patient risk factors for the onset of CPIP include young age, obesity, preoperative pain and pre-existing pain syndrome [6]. Surgical risk factors do not only include type of mesh fixation, but also the repair technique itself, inadvertent nerve injury, postoperative infection, hernia recurrence and type of prosthetic material [15]. It was argued that the reduction in foreign material by the absence of fixation devices would reduce the sometimes harmful effects of the foreign body reaction. However there is still the mesh causing this immune response. Thereafter it may have been too simplistic to suppose that the main difference between the meshes was the absence or presence of permanent sutures. The composition of the self-gripping mesh is different in that it has polylactic acid micro hooks on its surface. The inflammatory response to these micro hooks may differ from the response to polypropylene and sutures, affecting the extent of scar tissue formation and the probability of chronic nerve irritation. Further on establishing the anterior space as well as addressing the hernia sac should cause the same measure of trauma to the tissue irrespective of mesh attachment strategy. The results of the

Progrip mesh are in line with studies comparing another way of atraumatic fixation with fibrin sealant and glue fixation. A recent meta-analysis showed that there was no significant reduction in CPIP using glue or fibrin sealant compared to sutures or staples [16]. Apparently the surgical trauma to the groin itself plays a crucial role in the development of CPIP. When performing a pre-peritoneal inguinal hernioplasty there remains the risk of injuring the inguinal nerves by other ways than fixation devices, e.g. by transection (neurectomy), by blunt or sharp dissection, diathermic heat or entrapment of the inguinal nerves by the mesh itself.

Recurrence rate was the same for both groups after a long term of 67 months suggesting the micro hooks provide satisfactory mesh fixation or at least equivalent to sutures. This is in accordance with median-term follow-up studies [14]. Some even report no recurrent cases after 24 months with the use of the Progrip mesh [12]. The difference may be due to our extended follow-up of 67 months or due to the fact that most patients were operated by supervised residents instead of surgeons.

Duration of surgery with the self-gripping mesh was significantly shorter. This must be due to the lack of requirement for sutures to secure the Progrip mesh and is consisting with other studies. [17]. This is an important benefit of the Progrip mesh. Currently, the self-gripping mesh costs 2.5 times more than the comparable mesh of only polypropylene, but these increased costs are compensated by the reduced utilization of the operating room.

There are important limitations to the underlying study. Causes of CPIP are multifactorial. The number of patients included in this study is insufficient to show all important differences. Other drawbacks of the current study is that it was cross-sectional, not randomized and the analysis of the questionnaire was not blinded.

In conclusion, the findings presented here reflect the longest experience to date with the self-gripping Progrip mesh for inguinal hernioplasty. The self-gripping mesh appears safe and efficient with no more recurrences and significantly reduced operating time.

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HIPPO
TRIAL

CHAPTER 4

The HIPPO trial

A randomized double-blind trial comparing self-gripping Parietex Progrip mesh and sutured Parietex mesh in Lichtenstein hernioplasty
A Long-term Follow-up Study

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ABSTRACT

Objective

To evaluate the effect of a self-gripping mesh (Progrip) on the incidence of chronic postoperative inguinal pain (CPIP) and recurrence rate after Lichtenstein hernioplasty.

Background

Chronic pain is the most common complication of inguinal hernioplasty. One of the causes may be the use of sutures to secure the mesh.

Methods

Adult male patients undergoing Lichtenstein hernioplasty for a primary unilateral inguinal hernia were randomized to a self-gripping polyester mesh or a sutured polyester mesh. Follow-up took place after 2 weeks, 3, 12, and 24 months. Pain and quality of life were assessed using the Verbal Rating Scale, Visual Analog Scale, and Short Form 36. CPIP was defined as moderate pain lasting at least 3 months postoperatively.

Results

There were 165 patients in the Progrip mesh group and 166 patients in the sutured mesh group. The incidence of CPIP was 7.3% at 3 months declining to 4.6% at 24 months and did not differ between both groups. Pain and quality of life scores were significantly improved after 2 years. Hernia recurrence rate after 24 months was 2.4% for the Progrip mesh and 1.8% for the sutured mesh (P 0.213). The mean duration of surgery was significant shorter with the Progrip mesh (44 vs 53 minutes, $P < 0.001$).

Conclusion

The self-gripping Progrip mesh does not reduce CPIP rates. Outcomes of the Progrip mesh are comparable to the Lichtenstein technique with the additional advantage of a reduced operation time. NCT01830452.

INTRODUCTION

Surgical repair of groin hernias is one of the most commonly performed operations in the Western world. [1] Use of a prosthetic mesh became popular since recurrence and chronic postoperative inguinal pain (CPIP) rates are significantly lower than in autologous repair. [1,2] In 1984 Lichtenstein popularized routine use of a heavy weight polypropylene mesh fixed with non-absorbable sutures to create a tension-free hernioplasty, thereby further minimizing postoperative discomfort. [1-4] However the occurrence of CPIP remains and is challenging modern inguinal hernia surgery. [5]

The onset of CPIP is multifactorial with patient related factors and technical factors[6-8] Among the technical factors are the repair technique, nerve handling, postoperative complications and type of prosthetic material and its fixation. [5,9-12] Several meta-analysis have shown that lightweight macroporous meshes are associated with a reduced foreign body reaction (FBR) reducing CPIP and foreign body feeling, although the incidence of severe CPIP is not decreased. [12-14] Since the use of penetrating mesh fixation can cause entrapment of muscle and nerve fibers focus of interest has switched to atraumatic fixation. [15,16] Fibrin sealant and n-butyl-2 cyanoacrylate (NB2C) glues have been reported to yield beneficial results. [17-21] The same was true for the use of absorbable sutures. [22] Another atraumatic way of mesh fixation may be found in the self-adhering Parietex Progrip mesh [manufactured by Medtronic (Group Covidien)]. This mesh incorporates a one side coating of resorbable polylactic acid micro hooks providing atraumatic anchorage of the mesh in the underlying tissue bed. This self-gripping mesh is supposed to reduce CPIP in bypassing traumatic fixating devices and using low-weight / large pore monofilament polyester hereby reducing the FBR. A number of clinical trials have been published to date comparing this specific mesh to a sutured mesh during Lichtenstein repair. However, there is little data on recurrence and CPIP in extended follow-up. The present study aims to report the clinical outcomes of a randomized controlled double blinded trial with a follow-up of two years.

METHODS

The HIPPO trial was a two center double blind randomized controlled trial conducted at two teaching hospitals, the Groene Hart Hospital and St Franciscus Hospital, The Netherlands. The aim was to compare two types of fixation for the same type of mesh in ventral inguinal hernia repair according to Lichtenstein as described by Amid[4]; a lightweight (46 g/m^2) polyester mesh sutured with 3-0 polypropylene was compared to a lightweight (38 g/m^2 after polylactic acid resorption) polyester mesh with self-gripping micro hooks (Parietex Progrip mesh, Medtronic (Covidien)). Before the start of the trial, experience with the Progrip mesh was gained by performing more than 50 procedures per center with this self-gripping

mesh. In addition Dr Chastan, the inventor of the Progrip mesh, was invited to the clinic to teach the correct technique of mesh placement. [23]

Outcomes

Pain was assessed using a 6-point verbal rating scale (VRS) for day average pain and a visual analogue scale (VAS) for pain during daily activities and in rest. The primary outcome was the between group difference in the incidence of CPIP which was defined as moderate or more severe pain (VRS 3-6) lasting at least three months post-operatively. Secondary outcomes were the quality of life (QOL) which was assessed with the MOS SF-36 (medical outcomes study with 36 item short-form health survey), recurrence rate, perioperative and postoperative complications (e.g. wound infection, -hematoma or -seroma needing intervention such as antibiotic treatment or drainage, urinary retention after spinal anesthesia defined as bladder volume of >500cc needing catheterization), operating time, length of hospital stay, mesh sensation and time until retaining daily activities.

Inclusion and exclusion criteria

All male patients aged ≥ 18 years with an uncomplicated primary unilateral inguinal hernia were eligible. Exclusion criteria were American Society of Anesthesiologists (ASA) ≥ 4 or impairment to adequate follow up (e.g. mental retardation, foreign language speaker, psychiatric disorder). Eligible patients received oral and written information about the trial and had to sign inform consent before participation. Preoperative baseline measures were obtained by filling in the VRS, VAS, SF36 and Dutch Inguinal Hernia questionnaire (to be validated). Pre-operative patient characteristics recorded were age, body mass index, medical history and employment status (Table 1).

Blinding and randomization

Randomization was performed by the operating theatre nurse using an official online randomization program. The outcome of randomization was known by the surgeon not earlier than time of mesh placement. The investigator assessing the patient on the outpatient department and the patients themselves were not informed about the type of mesh that was placed and operation reports were coded.

Follow-up

Follow-up was at 2 weeks, 3, 12 and 24 months post-operatively to review pain, QOL and complications. At each moment of follow-up patients had to fill out the same questionnaires as before the operation.

Table 1. Baseline demographic data

	Sutured mesh	Progrip mesh
No. of patients	170	169
Age, yr *	61.4 ± 16.2	63.1 ± 14.6
BMI (kg/m^2)*	24.98 ± 3.72	24.90 ± 3.45
Symptomatic hernia	50 (29.4)	48 (28.4)
Pre-operative VAS at rest *	68 ± 12	56 ± 17
Comorbidity		
Smoking	50 (28.3)	61 (35.2)
Use of anticoagulants	21 (12.0)	25 (14.7)
Diabetes Mellitus	8 (4.8)	9 (5.5)
COPD	6 (3.6)	5 (3.0)
ASA fitness grade		
1	98 (59.0)	96 (58.5)
2	63 (38.0)	63 (38.4)
3	5 (3.0)	5 (3.4)
Work situation		
Full time, salaried	68 (41.0)	50 (30.5)
Full time, entrepreneur	16 (16.9)	19 (11.6)
Unemployed	82 (49.6)	95 (57.9)
Daily lifting		
0-5 kg	15 (9.0)	25 (15.2)
5-10 kg	84 (50.6)	79 (48.2)
10-15 kg	26 (15.7)	22 (13.8)
>15 kg	41 (24.7)	38 (23.2)

Values in parenthesis are percentages unless indicated otherwise;
* Values are mean ±SD; ASA American Society of Anesthesiologists; COPD Chronic Obstructive Pulmonary Disease

Surgical procedure

Patients were operated under protocoled general or spinal anesthesia by surgeons and supervised residents. Antibiotic prophylaxis was given according to the recommendations of the EHS. The inguinal hernia were corrected according to Lichtenstein, as described by Amid et al. [3,4] In the sutured mesh group a lightweight polyester mesh (Parietex Mesh, Medtronic (Covidien)) was fixed with non-absorbable 3-0 polypropylene (Ethicon, Johnson & Johnson, USA). In the Progrip mesh group a Parietex Progrip mesh was placed according to the description provided by Chastan. [23] In general, no fixating suture(s) were necessary, though in line with Chastan's recommendations it was allowed by study protocol to place one absorbable stitch at the pubic tubercle if concern existed for adequate overlap inferomedially. This extra stitch was recorded in the operation report.

The inguinal nerves were handled conform the recommendations of the EHS and Wijsmuller et al; as a rule the nerves were preserved, but in case of damage or interference with the mesh they were cut and nerve endings were buried. [10,24] It was recommended that, in the case of a large hernia sac, transection of the hernia sac was performed and the distal hernia sac was left undisturbed, in order to prevent ischemic orchitis. If necessary, a large direct hernia was sutured tension-free with continuous soluble sutures until a flat posterior wall was created with a normal internal ring.

Operation characteristics recorded were nerve identification and handling, the type of the hernia and the size of the hernia defect, extra stitches and the duration of the operation in minutes.

Post-operative pain control and recovery

After hernia repair the wound was locally infiltrated with analgesics. Post-operative analgesics included paracetamol 1 gram 4 times daily, diclofenac 50 gram 3 times daily and opioids when indicated. According to the EHS no limitations were placed on patients following inguinal hernia operation.

Sample size calculation

The primary endpoint was the incidence of CPIP. A difference of 10 in post-operative VAS score between the intervention and control group was considered to be the minimum relevant clinical difference. According to the power analysis, 169 patients per treatment group were needed to achieve this with a power of 80% with an alpha of 5%. The calculation was made with a two-sided test for the VAS pain score at 3 months. Based on a pilot study the standard deviation was set at 20.

Statistics

Analysis was by intention-to-treat however patients that were lost to follow-up within 3 months were excluded, because no primary endpoint data were available. The CONSORT 2010 Statement guidelines were followed for reporting this clinical trial. [25] Missing data were imputed on the basis of available preceding observations and by use of least squares regression. Statistical comparisons were made using the Wilcoxon test for continuous data and the Pearson chi squared test for ordinal data. The Wilcoxon test was used to analyze the SF36 scores and nominal operative parameters. $P<0.05$ was considered statistically significant.

Ethical approval

The study was approved by the Regional Ethics Review Boards and conducted in accord with the ethical standards of the Helsinki Declaration of 1975. The trial protocol has been posted in the http://www.clinicaltrials.gov protocol registration system (identifier NCT01830452). There are no sources of funding.

RESULTS

During study enrollment from 2011 to 2013 395 patients with a primary unilateral inguinal hernia were assessed for eligibility of which 339 patients were finally included. Patients were randomized to the Parietex Progrip Mesh (n=169) or traditional Lichtenstein hernia repair with a sutured mesh (n=170) (Fig. 1). Demographic characteristics were comparable

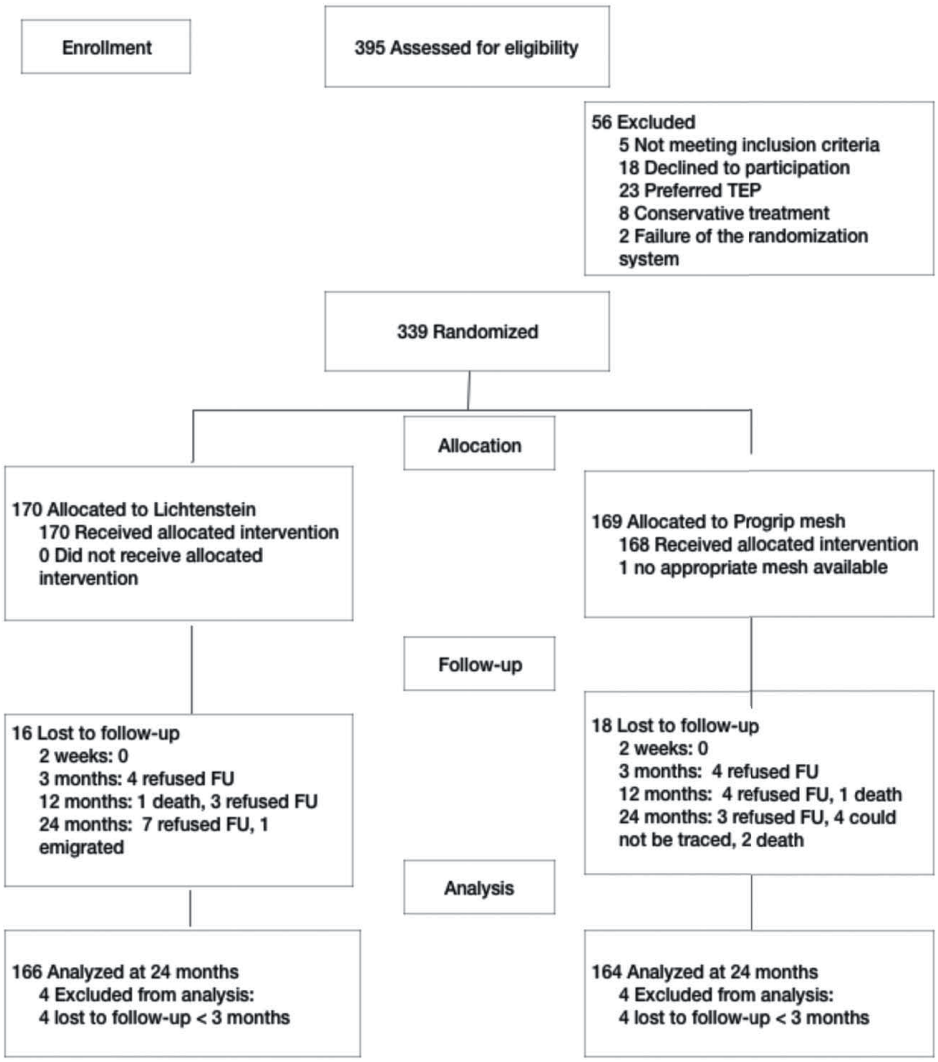

Figure 1. CONSORT flowchart depicting number of patients during the stages of the study and the reasons for loss to follow-up

between both groups (Table 1). One patient randomized to the Progrip mesh did not receive the allocated mesh, because no appropriate Progrip mesh was available. The rate of follow-up was 97.6% after three months declining to 90% after 24 months. Among the patients lost to follow-up were four patients (1%) who died from causes unrelated to the inguinal hernia repair and more than 12 months after surgery. Another four patients in each group were lost to follow up before the primary outcome could be measured at 3 months post-operatively and they were therefore excluded from the analysis. At 24 months 166 patients were analyzed in the sutured mesh group and 165 patients in the Progrip mesh group.

Baseline pain scores

Pre-operative pain scores were comparable between the groups (P>0.05). In the Progrip mesh group 48 (28.4 %) patients had preoperative inguinal pain defined as VRS3-6. In the sutured mesh group this number was 50 (29.4 %). The mean VAS for preoperative pain at rest was 56 ± 17 and 68 ± 12 in the Progrip resp. sutured mesh group.

Operative data

There were no significant differences in the operation and hernia characteristics between both groups, especially not for the nerve identification and nerve resection rate. Most patients were operated by residents under supervision of a surgeon and under spinal anesthesia (Table 2). Twenty-eight repairs with the Progrip group were done with an extra single stitch near the pubic bone.

Primary outcome

There were no significant differences between the self-gripping and sutured mesh group with regard to the primary outcome (Figure 2). The incidence of CPIP at 3 months was 7.3% (n=12) patients in the Progrip mesh group and 6.6% (n=11) patients in the sutured mesh group (P = 0.57). The incidence of CPIP declined during follow-up. After 12 months the incidence was 5.2% respectively 4.7% for the Progrip mesh and sutured mesh (p = 0.65) declining to 4.6 % respectively 5% after 24 months (p = 0.78).

Secondary outcomes

The number of patients with inguinal pain after 24 months was significantly declined compared to baseline (P>0.001). The mean VAS scores in rest and during daily activities showed the same decline from 3 months and on worth and were not statistically different between both groups at neither point of follow-up (Figure 3).

Along with the decline in prevalence of CPIP and mean VAS scores during follow-up there was a decline in number of patients reporting to have numbness or foreign body feeling in the groin region or limitations during work or daily activities because of CPIP (Table 3).

Table 2.

	Sutured mesh n=166		Progrip mesh n=1645		*P*
Operation performed by					
Surgeon	36 (21.8)		29 (17.7)		0.663
Resident	27 (16.4)		32 (19.5)		
Junior resident + Surgeon	98 (59.4)		97 (59.1)		
Junior resident + Senior resident	5 (2.4)		6 (3.7)		
Hernia characteristics					
Indirect	96 (57.8)		108 (65.9)		0.561
Direct	39 (23.5)		32 (19.5)		
Combined	31 (18.7)		23 (14.0		
Type of anesthesia					
Spinal	119 (71.7)		123 (75)		0.947
General	47 (28.9)		41 (25)		
Inguinal nerves:					
Number Identified or resected	Identified	Resected	Identified	Resected	I: 0.494
Ilioinguinal nerve	84 (68.3)	28 (20.0)	86 (67.7)	35 (24.6)	R: 0.445
Iliohypogastric nerve	44 (26.5)	10 (7.1)	38 (23.2)	6 (4.2)	
Genital branch of genitofemoral nerve	13 (7.8)	1 (0.7)	19 (11.6)	3 (2.1)	
Posterior reinforcement	23 (14)		20 (12.3)		0.964
Narrowing of the internal orifice	23 (14)		23 (14.2)		
Extra suture medial / near pubic bone	-		28 (17.3)		

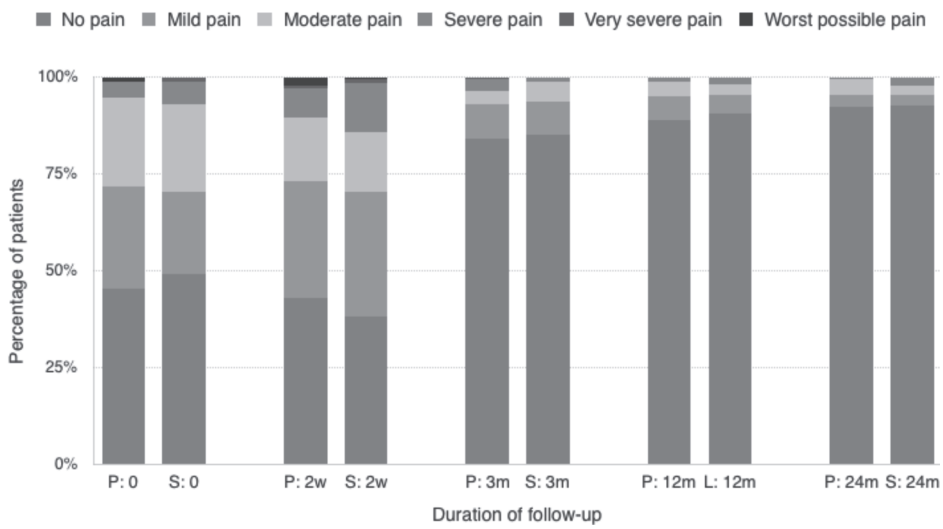

Figure 2. Verbal Rating Scale score for day average pain at different stages of follow-up for the self -gripping mesh and sutured mesh
m = months; P = Progrip mesh group; S = sutured mesh group; w = weeks.

Table 3. Secondary outcomes

	Sutured mesh	Progrip mesh	P
Operation time (min.)*	44.4 ± 7.2	53.4 ± 12.5	<0.001
Length of hospital stay (days)*	1.3 (0.61)	1.2 (0.72)	0.999
Time until retaining work activities (days) **	21.1 (2-32)	22.7 (2-36)	0.947
Post-operative complications:			
Seroma	8 (4.8)	6 (3.7)	0.147
Hematoma needing surgical nettoyage	1 (0.6)	1 (0.6)	
Wound infection treated with antibiotic	4 (2.4)	2 (1.2)	
Recurrence rate at 24 months	3 (1.8)	4 (2.5)	0.285
Mesh sensation			
2 weeks	101 (61.6)	101 (61.6)	0.901
3 months	94 (57.3)	94 (57.3)	0.434
12 months	67 (40.9)	67 (40.9)	0.698
24 months	37 (22.6) †	37 (22.6) †	0.411
Numbness			
2 weeks	91 (54.8)	85 (51.8)	0.961
3 months	78 (47.0)	71 (43.3)	0.589
12 months	59 (35.5)	44 (26.8)	0.086
24 months	28 (16.7) †	24 (14.6) †	0.479

Values in parenthesis are percentages unless indicated otherwise; * Values are mean ± SD
** Values are median (range) † The number is significantly declined (P=0.000) compared with 2 weeks post-operatively

After 24 months this decline was significant (P=0.000) compared to two weeks post-operatively. There was no significant difference between the groups.

QOL The overall QOL scores (SF36) and the pain part of the SF36 were significantly improved (P=0.000) at 1 and 2-year of follow-up compared to the pre-operative phase (Figure 4). There was no significant difference between the two groups.

Operating time The mean duration of surgery was significant longer for the sutured mesh (53.4 ± 12.5 min) compared to the Progrip mesh (44.4 ± 7.2 min) (p=0.001) (Table 3). Use of the Progrip mesh reduced the mean operating time with 17%.

Hospital stay No difference was observed in the length of hospital stay between the groups. Almost 90% of patients were discharged from the hospital at the day of surgery. The other 10% (mean age >70) had one overnight stay mainly because of social reasons.

Complications Wound complications occurred in nine patients that received the Progrip mesh and 13 patients with a sutured mesh: six respectively eight patients had seroma

formation, one patient in both groups had an hematoma needing drainage in the operating room and two respectively four wound infections needed treatment with antibiotics (Table 3). Urinary retention after spinal anesthesia was detected in 3 of 199 (2.5%) patients in the Progrip mesh group and 4 of 123 (3.3%) patients in the sutured mesh group.

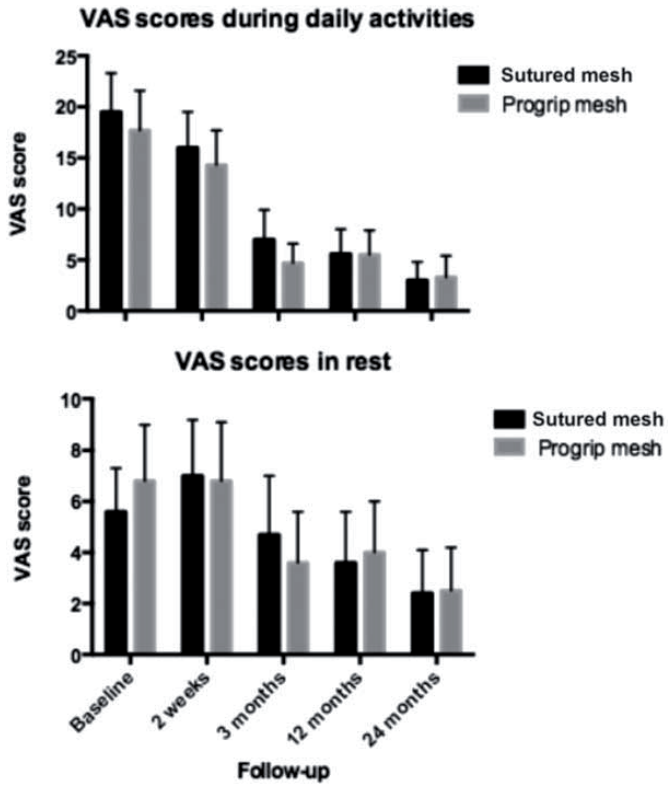

Figure 3. Visual Analog Scale (VAS) scores during daily activities and in rest for the Progrip mesh and sutured mesh. VAS scores were measured on a 1 to 100 mm scale and measured before operation (baseline measure) and postoperatively after 2 weeks, 3, 12, and 24 months. Values are mean (95% confidence interval).

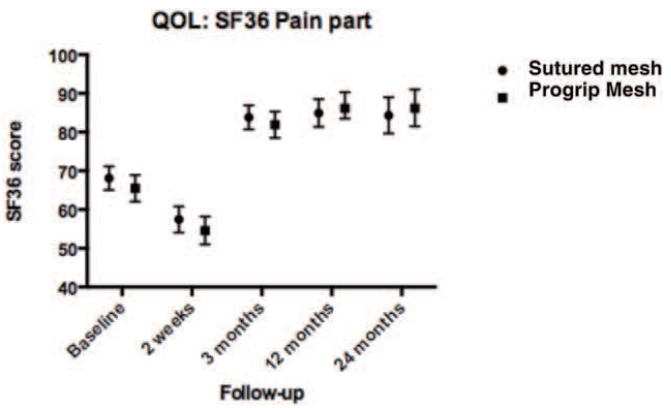

Figure 4. Pain part of the SF-36 quality of life score
SF- 36 = short form 36; differences with baseline are all significant except for 2 weeks of follow-up ($P < 0.001$).

Recurrence The rate of hernia recurrence after 24 months was 2.4% in the Progrip mesh group and 1.2% in the sutured mesh group (P=0.213). Two recurrences in the Progrip group occurred in the first three months of follow-up. Both patients were operated by the same surgeon. The presence of a medial stitch did not influence recurrence rates.

DISCUSSION

Chronic pain is the main challenge of modern inguinal hernia surgery. In this double blind randomized controlled trial it was hypothesized that a self-adhering (Progrip) polyester mesh not needing traumatic fixation devices will cause less CPIP compared to a sutured polyester mesh. This hypothesis was not confirmed. The incidence of CPIP and the distribution of pain severity and QOL scores were almost the same for both type of fixating techniques. However the Progrip mesh showed to have a similar outcome profile compared to the Lichtenstein technique, especially the same rate of recurrence after a follow-up of two years. The main advantage of the Progrip mesh seems to lie in its efficiency since operation times were significantly reduced.

The results presented here are in line with the results of previous randomized controlled trials. Except for the results presented by Kapischke et al trials comparing a sutured with a self-adhering mesh did not find reduced pain scores in favor of the self-adhering mesh. [26,27-33] Apart from this, the reported incidence rates of CPIP vary widely among the trials. This can be caused by the heterogeneity in outcome parameters with different definitions of CPIP, timing and duration of follow-up and way of presenting outcomes. In the HIPPO trial the overall incidence of CPIP was 7.3% at 3 months declining to 4.6% at 24 months. This decrease of CPIP over time is in accordance with the findings of Eker et al (LEVEL-trial) and others concluding that spontaneous resolution of CPIP is the natural course.[34-36] However the incidence of CPIP was still high after 24 months. This may be caused by the definition of CPIP which included all patients with moderate or more severe pain regardless whether it was influencing daily activities. Also, most patients were operated by trainee surgeons. The suggestion of Kingsnorth that a greater CPIP reduction with self-adhering devices may become apparent with less experienced surgeons, was not confirmed here. [26]

The self-adhering mesh did not result in lower pain rates which may be due to the multifactorial onset of CPIP. Besides patient related factors there are multiple surgery related factors. [37,38] Of all these factors only the type of fixation was changed, but factors like handling of the inguinal nerves, the surgical approach and experience of the surgeons were unchanged. Thereafter the introduction of mesh and fixation devices will elicit a foreign body reaction (FBR) which is material dependent. In the HIPPO trial it was thought to use the same type of mesh in both groups, with the only difference the absence or presence of permanent sutures. However this is only true after the absorption of the polylactic acid

micro-hooks. Until that time the inflammatory response to polylactic acid micro hooks may differ and being more harmful compared to the response to polyester alone. This FBR is under current investigation of our research group. A third reason for the absence of reduced pain rates with the Progrip mesh may be the extra absorbable suture nearby the pubic tubercular placed in 17.3% of patients in the Progrip mesh group. Whether efforts should be made to avoid this suture to minimize the risk for postoperative neuralgia was investigated by Kingsnorth et al and Kohler at al. [27,39] They found that, among self-gripping mesh patients, those with medial fixation had significantly higher pain scores direct post-operatively and at 1- and 3-month follow-up. [27,39] Though at 1 year post-operatively no differences could be observed in terms of CPIP. In addition the medial stitch did not seem to influence the recurrence rate which is in line with the results of this trial.

In the HIPPO trial there were seven recurrences in the overall series, four of which were in the Progrip mesh group which was not significant different from the sutured mesh group. This is in line with other long term follow-up studies.[30,40].

The duration of operation was the only outcome parameter to be significantly different in favor of the Progrip mesh. The lack of requirement for sutures to secure the Progrip mesh reduced the operative time significantly with 17%. This result is consistent with most other studies. [26-30,41,42]. To date no cost effectiveness study has been performed comparing the two mesh repair techniques. Currently, the self-gripping mesh is three times more expensive than the non-self-adhering polyester mesh. The similar short- and long-term results of the 2 groups enable surgeons to evaluate if raising the number of hernia repairs performed on a specific operating list would compensate for the higher price of the Progrip mesh.

To our knowledge, the HIPPO trial is the first RCT investigating the Progrip mesh combining a large number of patients (n=330) with a long term follow-up of 24 months. Another strong feature of this trial compared to others is the use of the same type of mesh in both groups except for the additional micro hooks on the Progrip mesh. A potential limitation is that patients were operated by different surgeons and surgeons in training and that nerves were not routinely searched for although this reflects the common situation in teaching hospitals. The results found could certainly have been strengthened by clinical examination at 24 months and quantitative sensory testing.

CONCLUSION

This large scale double blind randomized controlled trial with a follow up of 24 months shows that Lichtenstein repair with a self-gripping Progrip mesh does not reduce the incidence of CPIP , but has comparable hernia recurrence rates and is significantly faster to perform.

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CHAPTER 5

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

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Surgery 2017

ABSTRACT

Background

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

Methods

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

Results

In the present meta-analysis the outcomes of 10 RCTs enrolling 2541 patients were pooled. The mean follow-up was 24 months (range 6 to 72 months). There was no significant difference in the incidence of chronic pain [odds ratio = 0.93, 95% confidence interval (CI) (0.74-1.18)], recurrence [odds ratio = 1.34, 95% CI (0.82-2.19)], or foreign body sensation [odds ratio = 0.82, 95% CI (0.65-1.03)], between the self-gripping mesh and sutured mesh group for all moments of follow-up. The mean operating time was significantly shorter [odds ratio = -7.58, 95% CI (-9.58- -5.58)] in the self-gripping mesh group.

Conclusion

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

INTRODUCTION

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

METHODS

The systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[25] All trials published

up to January 2017 comparing a self-gripping mesh and a conventional sutured mesh for the Lichtenstein procedure were identified. The literature search was performed in the following databases: Embase, Medline Ovid, CINAHL EBSCOhost, Cochrane, Web of science, Scopus, and Google scholar. The search strategy was designed by a Biomedical Information Specialist of the Medical Library (Erasmus University Medical Center, Rotterdam, the Netherlands). A syntax with search terms was prepared and both the syntax and the search strategy are available in Appendix 1.

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

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

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

Data Analysis

A random effects model was used to calculate a pooled mean of the data, taking into account both the variance between studies and study populations and the variance within a study.[29] For continuous data the mean difference with a 95% confidence interval (CI) was calculated, for dichotomous data the effect measures odds ratio (OR) and risk ratio (RR) with 95% CI were calculated to evaluate the statistical difference between outcomes. Since RevMan 5.3 excludes trials with zero events when calculating an OR or RR, also a risk difference (RD)

was calculated in which zero event trials were included. Outcomes were displayed in forest plots. Statistical heterogeneity was assessed by calculating the test statistic Cochran's Q. The consistency of study effects was tested using I^2 statistic.[30] I^2 values of 0-25% was assigned as low, 25-50% moderate and 75-100% as high. In addition, the overall effect was provided for each total or subtotal. Two-sided $p \leq 0.05$ was considered statistically significant. Analysis were performed using RevMan 5.3.

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

RESULTS

In total, 464 articles were identified after the removal of duplicates. After screening of these records 42 articles were found eligible for full-text assessment. After assessment of the full text versions, nine articles were suitable for inclusion in this meta-analysis. Another article was identified though a monthly mail summarizing recently published articles.[31] During the writing of the meta0analysis the long term results of two already included studies were published and included in the meta-analysis.[32,33] A PRISMA flowchart of the literature search is shown in Figure 1.

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

Methodologic quality of included studies

The quality assessment of the study methods according to the Cochrane guidelines is given in Table 2 including a Jadad Score. Three of the ten included studies scored less than 4 points. The quality of two trials was poor (2 points) due the absence of an adequate randomization technique or no information about it, absence of blinding, no power calculations, and no baseline score.[34,35] The quality of one trial was moderate (3 points) due to the absence of blinding and baseline scoring.[36] The study reported by Fan et al. scored 5 points although it was not powered for the outcome CPIP and did not provide a definition nor an assessment method of CPIP.[31]

Four studies did not perform a baseline pain score while pre-operative pain is a well-known risk factor for CPIP.[31,36-38] Four studies only performed a quantitative assessment of CPIP and no qualitative assessment with some kind of QOL score.[34-36,39]

Some trials compared different types of meshes in the two study groups instead of only changing the way of mesh fixation (polypropylene and polyester, and heavy and low weight).[31,33,35,40]

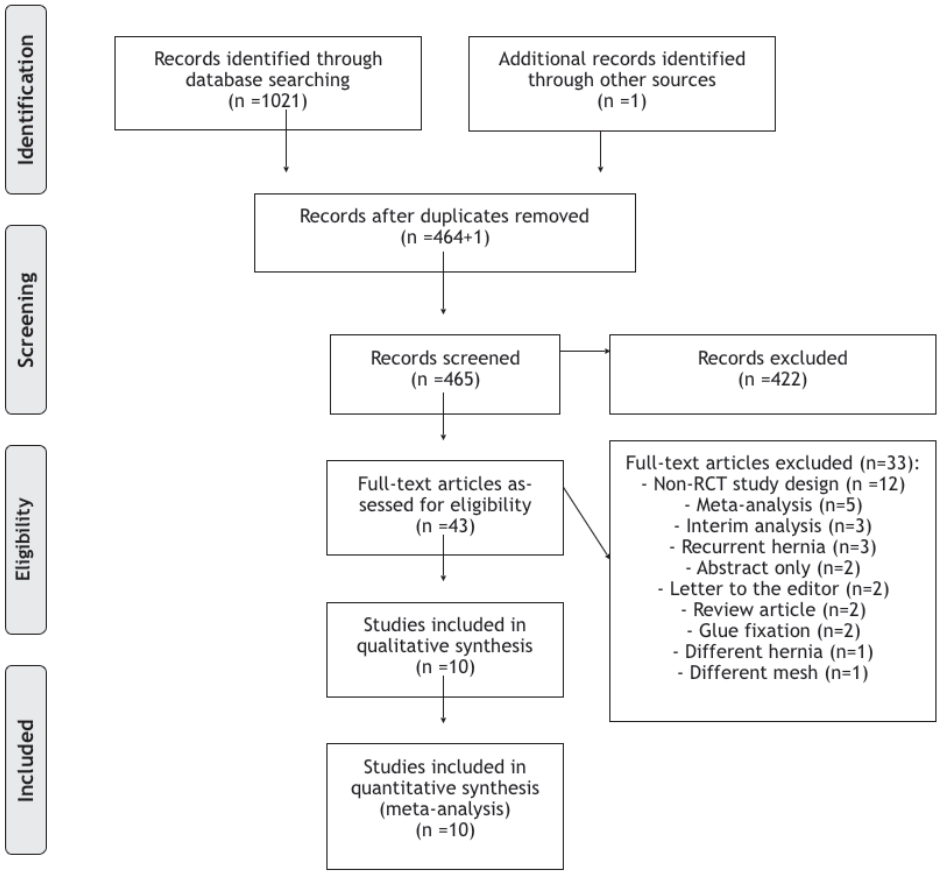

Figure 1. PRISMA Flow Diagram

CPIP definition

Besides Esteban et al. and Fan et al., all authors provided a definition of the primary or secondary outcome parameter CPIP.[31,38] Three studies referred to the definition provided by the International Association for the Study of Pain (IASP) which states that 'chronic pain is any pain that persists beyond the normal tissue healing time usually taken to be 3 months.[35,39,41,42] Three other studies used a threshold of a minimal VAS score of ≥ 30/100[43], 40/100[36], or 45/150[44] after which discomfort was regarded to be pain. Three authors used a time frame of 6[32] or 12[33,43] months.

Meshes

In the study group, patients were treated with either a polypropylene self-gripping mesh (Parietene Progrip mesh, 64%) or a polyester self-gripping mesh (Parietex Progrip mesh, 36%). In the control group different meshes were used (i.e. heavy weight polypropyl-

ene[31,33,35,40], low weight polypropylene[38], Parietene Light[39,43,44], Parietex Light[42] or Optilene LP[32]. Five studies assessed meshes of the same material, construction, and weight in both the study group and the control group except for the additional polylactic acid micro hooks on the study group mesh.[38,39,42,43]

Chronic pain

CPIP was assessed in all trials and nine of them reported the incidence of chronic pain according to the definition used in their study protocol.[31-33,35,36,38,39,42,43] Incidence rates were analyzed separately for the different moments of follow-up (3, 6-12, 24, 36, 72 months). Heterogeneity between the trials was very unlikely (P=0.87, Q/df< 1, I^2 0%). For all moments of follow-up, there was no significant difference in the incidence of CPIP between the self-gripping mesh and sutured mesh group [3 months OR = 0.89, 95% confidence interval (CI) (0.48–1.64), 6-12 months OR = 1.00, 95% CI (0.75–1.34), 24 months OR = 1.00, 95% CI (0.39-2.61)], 36-72 months OR = 0.77, 95% CI (0.38-1.58)]. The forest plot is shown in Figure 2A. A subgroup analysis (Figure 2B) accounting for mesh weight and including only studies that used a light weighted mesh in both the study and control group also showed no difference in CPIP rates between the self-gripping mesh and sutured mesh OR = 0.89 95% CI (0.68-1.16)].[32,34,42,45,46]

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

A combined analysis of the quantitative assessment of CPIP – reflecting the influence of CPIP on daily life – was not possible, since the four studies that used this kind of measure (SF12, SF36, AAS) did not provide full outcomes.[42-44,47] The separate studies did not find significant differences in the QOL scores between the two meshes, except for Pierides et al. who found significantly improved social functioning in favor of the self-gripping mesh.[45]

Foreign body sensation

Five studies reported the rate of FBS. There was no heterogeneity amongst the trials (P=0.86, Q/df< 1 and I^2 0%). No one reported a significant in between group difference for the rate of FBS although the combined analysis showed a trend towards less FBS in the self-gripping mesh group. (Figure 3) A subgroup analysis (not shown) corrected for mesh weight also did not reach significance. Incidences were declining during follow up except for the study population of Zwaans et al who reported an higher incidence after three years compared to one year postoperatively.[33]

Table 1A+B. Characteristics of included studies

First Author Year of publication	Study Design	Sample Size	Type of meshes	FU (months)	Validated Assessment Tool(s)	CPIP definition	Outcomes	Baseline score	Power analysis
Chatzimavroudis 2014	RCT	25 25	Parietene Progrip. HW Polypropylene	3,12,2**4**	VAS	IASP	1, 3, 4, 5, 6	no	no
Esteban 2014	RCT	45 45	Parietene Progrip LW polypropylene (Microval1)	12	VAS	NG	1, 3, 6	no	no
Fan 2017	RCT	22 23	Parietex Progrip. Polypropylene	1/4, 1,3,12,24,72	NG	NG	1,2,3,4,5, 6	no	yes, but powered for operation time
Jorgensen 2012	RCT	163 171	Parietene Progrip. Parietene light	1,12	VAS, SF12	VAS>30 at 12 months	1,3,4,6	yes	yes
Molegraaf	RCT	166 164	Parietex Progrip. Parietex light	1/2,3,12,24	VAS, SF36, VRS	IASP	1,2,3,4,6	yes	yes
Nikkolo 2015	RCT	70 75	Parietex Progrip Optilene LP	1/2,1,6, 36	SF36. VAS	pain during different activities more than 6 months	1,2,4,5	yes	yes
Pierides 2012	RCT	198 196	Parietene Progrip. Parietene light	1/2,12	first two weeks VAS	IASP	1,2,3,5,6	yes	yes
Porrero* 2014	RCT	89 89	Parietene progrip. HW Polypropylene	1/4,12	VAS	VAS ≥4 >3 months	1,3,4,5, 6	no	yes
Sanders 2014	RCT	270 287	Parietex progrip. Parietene light	1/4, 1,3,12	VAS 150, SPS, AAS	VAS 45/150 persisting at least 3 months	1,3,4,5,6	yes	yes
Zwaans 2017	RCT	168 170	Parietene Progrip. HW Polypropylene	12, 36	VRS, VAS 150	pain on VRS after 1 year	1,2,3,4,6	yes	yes

*Bilateral hernia; FU = Follow up; CPIP = chronic post-operative inguinal pain; RCT = Randomized Controlled Trial; HW = heavy weight; LW = light weight; NG=not given; IASP = International Association for the Study of Pain; VAS = Visual Analog Scale; SPS = Surgical Pain Scale; SF12 = Short Form 12; SF36 = Short Form 36; VRS = Verbal Rating Scale
Outcome parameters: 1: CPIP; 2: Foreign body sensation 3: recurrence; 4: operation time; 5: acute pain; 6: wound complications (seroma, hematoma, infection)

Table 1A+B. Characteristics of included studies

First Author Year of publication	Type of anesthesia Progrip/Sutured mesh	Operation team	Extra stitch	Nerve handling
Chatzimavroudis 2014	General anesthesia	Experienced surgeons	Chastan**	Nerves were identified and preserved.
Esteban 2014	Spinal anesthesia	Experienced surgeons	No	Nerves were preserved but not systematically search for
Fan 2017	17/19 spinal anaesthesia 5/4 general anesthesia	Experienced surgeons or supervised advanced surgical trainees P>0.05*	No	Nerves were protected
Jorgensen 2012	22/16 local anesthesia 2/4 spinal anesthesia 77/81 general anesthesia	Experienced surgeons	No	Attention was paid to identification and preservation of nerves. Any nerve division was recorded
Molegraaf 2017	123/119 spinal anaesthesia 41/47 general anesthesia	Experienced surgeons or supervised surgical trainees. P>0.05*	Chastan**	according to Wijsmuller et all***; nerve divisions were recorded
Nikkolo 2015	1/0 local anesthesia 7/11 spinal anesthesia 93/89 general anesthesia	Experienced surgeons or supervised surgical trainees. P>0.05*	No	All nerves in the inguinal canal were identified and preserved when possible
Pierides 2012	63/61 local anesthesia with iv sedation 34/34 spinal anesthesia 3/5 general anesthesia	Experienced surgeons		All nerves in the inguinal canal were identified and preserved when possible
Porrero 2014	Regional anesthesia	Experienced surgeons	No	All nerves in the inguinal canal were identified and preserved when possible
Sanders 2014	17/20 local anesthesia with iv sedation 17/16 spinal anesthesia 66/65 general anaesthesia	Experienced surgeons	Chastan**	according to Wijsmuller et all***; nerve divisions were recorded
Zwaans 2017	133/139 spinal anesthesia 49/42 general anesthesia	Experienced surgeons or supervised surgical trainees. P>0.05*	No	All nerves in the inguinal canal were identified and preserved when possible. nerve divisions were recorded

iv = intra venous; * no significant difference in experience level per study group; **Chastan: one suture (2-0 polypropylene suture, Prolene, Ethicon, Johnson & Johnson, USA) is allowed to be placed superficially to the pubic tubercle to prevent mesh dislocation.[49]

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

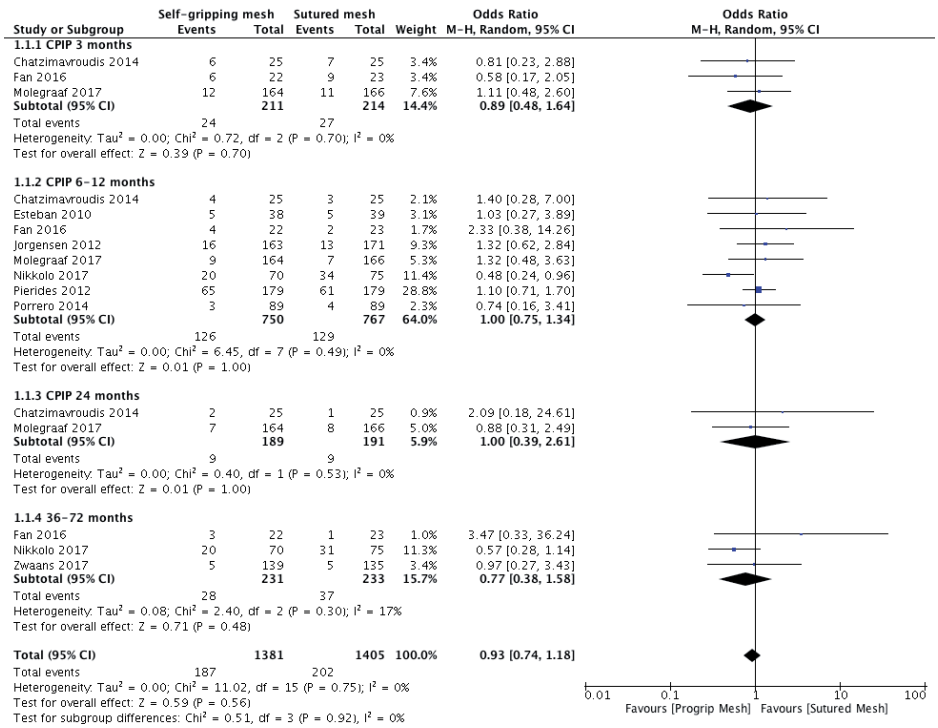

Figure 2A. Incidence of CPIP

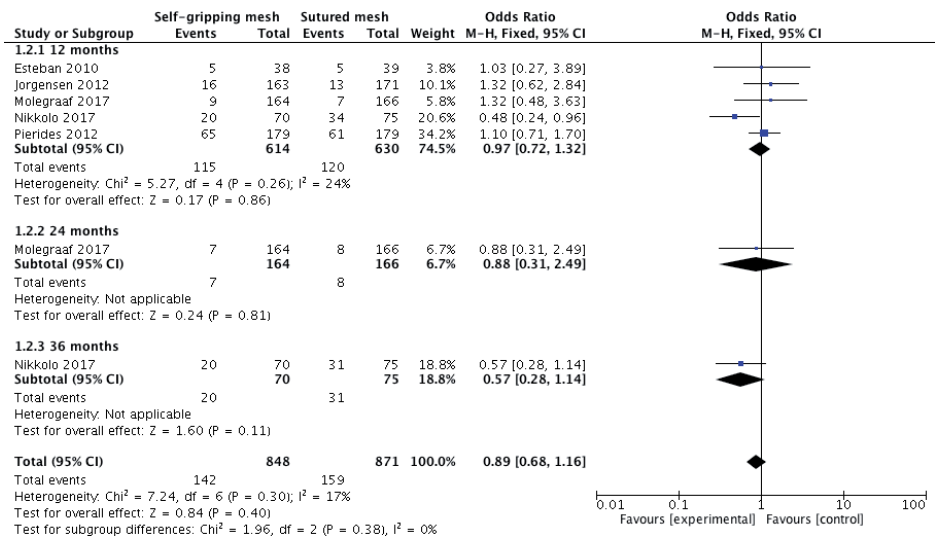

Figure 2B. Incidence of CPIP including only light weighted meshes

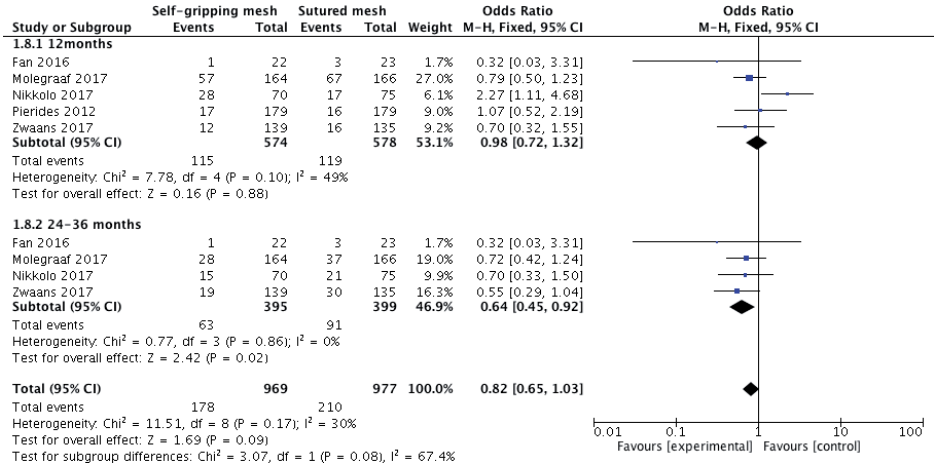

Figure 3. Foreign body sensation

Recurrences

All trials reported recurrence rates after 12 months of follow-up, 2 studies also provided recurrence rates after 24 months[35,42], 2 after 36 months [32,33] and 1 after 72 months[31]. There was no heterogeneity amongst the trials (P=0.41, Q/df< 1 and I^2 4%). The difference in recurrence rate between the self-gripping mesh group and the sutured mesh group was not significant neither at 12 months [OR = 1.19, 95% CI (0.61 to 2.31), nor at 24 months [OR = 1.06, 95% CI (0.27 to 4.17)] nor at 36 months [OR = 0.95, 95% CI (0.18 to 5.14)]. A RD analysis showed the same results [12 months RD = 0.00, 95% CI (-0.01 to 0.01), 24 months RD = 0.00, 95% CI (-0.03 to 0.03)] (Figure 4).

Extra stitch in the self-gripping mesh group

In seven of the ten studies in this meta-analysis no extra sutures were placed in the self-gripping mesh group.[31-33,38-40,43] The three studies that allowed an extra stitch according to the instructions of Chastan did not perform a subgroup analysis.[35,42,48 49]

Nerve handling and paresthesia

Except for Esteban et al. all trials tried to identify and preserve the inguinal nerves and four reported the actual rates of nerve identification and resection. [33,42,44,46] The techniques of nerve division of a suspected injured nerve were not clear from the study methods and numbers were not always recorded (Table 1B). Five studies investigated post-operative numbness in the groin region.[32,33,39,42,43] They found no significant difference in numbness between the two mesh fixation methods and also reported comparable rates of nerve resection for the two study groups. Sanders et al. performed a subgroup analysis on the impact of nerve resection and mesh fixation method on CPIP and found that when the

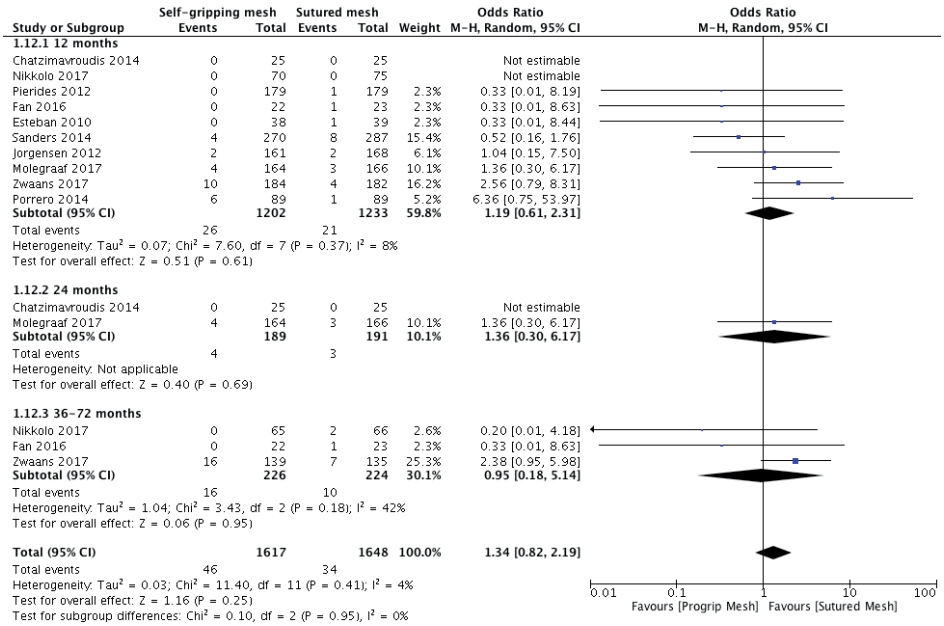

Figure 4. Recurrence rate

iliohypogastric nerve was preserved, postoperative pain was significantly lower in the self-gripping mesh group than the sutured mesh group at all follow-up points from discharge to 1 year postoperatively. There was no significant difference between the groups when the iliohypogastric nerve was resected.[48] Zwaans et al reported no relation between hypoesthesia or hyperesthesia and previous neurectomy.[33]

Operation duration

Five studies reported mean operating time with SD and could contribute to the combined analysis (Figure 5). The mean operating time was significantly shorter in the self-gripping mesh group than in the sutured mesh group [mean difference was -7.58, 95% CI (-9.58 - -5.58)]. There was a high heterogeneity direction of effect and the effect size was high and

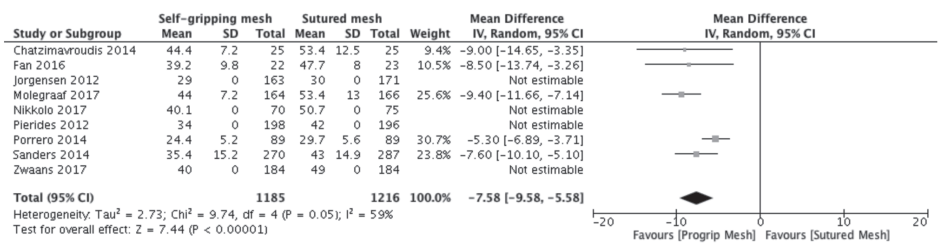

Figure 5. Operation Duration

significant, Z = 7.44 (P < 0.00001). The trials which could not contribute to the combined calculation confirmed this significant reduction in operating time for the self-gripping mesh. The mean reduction in operation time ranged from 1.[43] to 10 minutes (=17%).[42]

DISCUSSION

Chronic pain and recurrence are the main complications of inguinal hernia surgery and needs to be studied during long-term follow-up. Recently four large trials published their long-term results comparing the self-gripping mesh with a sutured mesh for open inguinal hernia repair and therefore a new meta-analysis was performed, focusing on these long-term results.[31,33,42,48] In line with the individual studies the meta-analysis showed no significant benefits regarding the incidence of CPIP, FBS and recurrence rate. The main advantage of the self-gripping mesh thus lies in its efficiency thereby significantly reducing operative times. Previous meta-analysis reported similar outcomes but the inclusion of studies with short term follow-up, low inclusion rates or no randomization limits their conclusions .[21-23,50] The negative results should be interpreted through surgical- and patient- related factors as well as methodological factors.

Before looking at the pathophysiological factors of CPIP there are methodological issues to address when a study fails to reach its primary outcome.[51] First, is there an indication of benefit using a self-gripping mesh? It was hypothesized that a self-gripping lightweight mesh would lower the incidence of CPIP, because of avoiding traumatic suture fixation, and reducing the amount of foreign body reaction because of its material reduced structure. Although this hypothesis is reasonable because of expected reduction of neuropathic and nociceptive pain stimuli, it is however too simplistic. Only the fixation method and material weight of the mesh are changed, but not for example the surgical approach, which still needs dissection in a neuralgic plane. Therefore some will wonder why to perform an open anterior approach at all, since laparoscopic techniques have shown faster recovery times and lower chronic pain risk.[52,53] This disregards the obligation that surgeons have to tailor treatments based on expertise, local/national resources, and patient related, and hernia related factors. For high-risk inguinal hernia patients with extensive co-morbidities or patients with pelvic scarring, an open mesh repair (under local anesthesia) is still the preferred technique as is the case for recurrent inguinal hernia after laparoscopic repair according to the world guidelines for groin hernia management 2016.

A second contributor in failing of the primary outcome may be studies to be underpowered since half of the studies enrolled less than one hundred patients. This meta-analysis should address the limitations of study size of individual RCTs, however not all RCTs could contribute to the combined analysis, because of differences in outcome measures. The combined analysis for the between group difference in incidence of CPIP after 6-12 months

was based on the response of 750 patients in de self-gripping mesh group and 767 patients in the sutured mesh group. After 36 months, these numbers were 231 respectively 233 per group for the incidence of CPIP and recurrence rate. Hence the long-term conclusions about CPIP and recurrence rate are still based on relatively low patient numbers which lowers the strengths of the results.

Other questions to be asked are whether the trials had deficiencies in their treatment regimen, the population studied, and the trial conduct. The latter is a focus of concern for two studies since they had an inadequate randomization technique, no blinding, no power calculations, and no baseline score.[34,35] In addition two other studies did not perform a baseline pain score while pre-operative pain is a well-known risk factor for CPIP.[31,36] Thereafter four studies lacked to perform a qualitative assessment of CPIP to evaluate the influence of CPIP on daily life and well-being.

Meta-analysis should be conducted when a group of studies is sufficiently homogeneous in terms of subjects involved, interventions, and outcomes to minimize performance and measuring bias so to provide a meaningful summary. This was reason to include only RCTs that compared the two meshes for a Lichtenstein hernia repair in adult patients with a primary hernia. Recurrent hernias were excluded because this is a risk factor for the development of CPIP. Although the strict inclusion criteria there was still heterogeneity amongst the trials in this meta-analysis, caused by clinical and methodological variation. Firstly, the hernia repairs were performed by different surgeons and with different levels of experience (trainees, general surgeons, hernia specialists). It is known that there is a substantial disparity between the state-of-the-art Lichtenstein repair and its application in general practice, especially with respect to steps that are suggested to play a role in the origin of chronic groin pain.[54] Other clinical variations that could modify the intervention effect were different types of anesthesia (spinal, general, regional), use of different meshes in the conventional Lichtenstein group (both heavy weight and light weight), differences in the way of nerve handling, timing of follow-up and whether an extra stitch was allowed for the self-gripping mesh. However, this clinical heterogeneity reflects daily practice and will therefore be of less influence on the generalizability of the results. Methodological variation was caused by the variable definitions and assessment methods for CPIP and the unstandardized way of presenting outcomes. This caused that only comparisons could be made for between group differences in CPIP rates, but not for incidence rates of CPIP overall or special subgroups. This methodological heterogeneity is a common problem in hernia research and is hindering comparison of outcomes to draw firm conclusion.[55-57]

Regarding surgical factors there are several discussions specific for the self-gripping mesh. First there is discussion on the influence of the extra stitch in the self-gripping mesh group; this stitch is placed near the neuralgic pubic tubercle to prevent a medial recurrence. The RCTs in this meta-analysis did not perform subgroup analysis whether the stitch induced more CPIP in patients. However a recent evaluation of the Herniamed register did not find

a correlation. The same applies to recurrence rates.[58] From this it may be concluded, that although seemingly of no influence on CPIP rates, it could be recommended to avoid the single stitch in this neuralgic place especially in the case of small or medium size hernias. A second consideration is the influence of the additional polylactic acid micro hooks. It is possible that the presence of micro-hooks and their disintegration exaggerates the foreign body reaction leading to inflammatory damage to surrounding nerves. This was not seen in experimental models and human studies are not available.[59] However since CPIP and FBS rates are not increased for the micro hook added meshes the inflammatory reaction to these micro hooks seems be of less influence. But since the foreign body reaction decreased over time there may be a relation with the resorption of the micro hooks which are completely resorted at 12 months postoperatively. Zwaans and colleagues were the only one to report increased FBS during follow-up especially for their heavy weight sutured mesh group. Thereafter a possible augmented inflammatory reaction may be counterbalanced by the light weight nature of the self-gripping mesh, since light weight meshes are known to induce less fibrosis and hence less FBS. This brings us to the third factor of discussion, the influence of the light weight microporous structure of the Progrip mesh. This was supposed to augment the pain reducing effect of the atraumatic fixation, but they together failed to do so.

Nerve injury, during dissection or mesh placement and fixation (or afterwards by the inflammatory reaction), is regarded to be one a the most important causative factors for CPIP and therefore nerve handling is important to report.[60] Almost all studies reported trying to identify and protect the nerves and to resect nerves that were accidentally damage or in the way of mesh placement, but only four studies reported identification and resection rates.[33,42,44,46] These were comparable for the self-gripping and sutured mesh groups hence do not seem to influence the between group results. Sanders et al and Zwaans et al performed sub analysis after the effect of neurectomy and found no significant influence of neurectomy on the rates of CPIP or an altered sensation in the groin.[33,44]

Finally, patient-related risk factors need to be addressed. Known risk factors for the development of CPIP are moderate to severe preoperative pain >1 month, psychological vulnerability, female gender, younger age and genetic predisposition. They are often underestimated compared to surgical factors, but there is increasing awareness of the individual variance in foreign body reaction and sensory disturbances that may or may not lead to CPIP. Hence these patient related risk factors need to be considered in the indication for surgery, which in the futures can be facilitated with tests like genotyping and quantitative sensory testing.[9,60-62]

In this meta-analysis we did not address acute post-operative pain, because we wanted to report the long term results of self-gripping mesh. However acute post-operative pain is one of the strongest and most consistent risk factors for CPP urging an approach of so-called "preventive or preemptive analgesia" by the use of pre-operative local anesthesia.[63-65].

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

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CHAPTER 6

Influence of polylactic acid supplementation on the biocompatibility of a polyester mesh for hernia repair using an in proved in vitro model

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Nienke Grotenhuis
Johan Lange

ABSTRACT

Background

Chronic pain is the main complication in inguinal hernia surgery. Among the etiologic factors are mesh fixation and biocompatibility. To bypass mesh fixation, supplementary polylactic acid micro-hooks were added to a lightweight monofilament polyester mesh to provide for self-gripping properties in inguinal hernia repair. This study was designed to evaluate the influence of this additional polylactic acid on the biocompatibility of polyester mesh by determining the direction of the foreign body response (FBR). The direction of FBR is mainly determined by macrophages.

Methods

The self-gripping polyester mesh (Parietex Progrip) was compared to a pure polyester mesh (Parietex). To investigate the reaction of macrophages to these meshes, macrophages were cultured in our human macrophage in vitro model and pro- and anti-inflammatory cytokines were measured in the culture medium.

Results

There was no significant difference between the two meshes in the production of pro inflammatory cytokines by M1 macrophages and anti-inflammatory cytokines by M2 macrophages. The two meshes had almost the same M1/M2 index.

Conclusion

It was concluded that polylactic acid micro-hooks does not seem to have a significant influence on the FBR of macrophages. Biocompatibility of a composited polyester polylactic acid self-gripping mesh seems to be comparable to a standard polyester mesh.

INTRODUCTION

Meshes for abdominal wall hernia repair are probably the most common used biomaterials implanted in surgery. The use of a prosthetic mesh is the gold standard in hernia repair, since recurrence rates are significantly lower compared to autologous repair [1]. The downside of mesh implantation includes mainly chronic pain, foreign body feeling, and infection. Chronic postoperative inguinal pain (CPIP) is a prominent issue in inguinal hernia repair research as its persisting appearance is a severe complication, occurring in 11% of patients [2].

The onset of CPIP is multifactorial with patient and surgery related factors.[3,4] Of the surgical factors nerve damage plays a pivotal pathophysiological role and may be caused by transection (neurectomy), blunt or sharp dissection, diathermic heat or entrapment of the inguinal nerves by the mesh or sutures [2]. Furthermore the implanted prosthetic material (mesh and sutures) in the inguinal canal elicits an inflammatory and fibrotic response that imparts strength to the hernia repair, but on the other side causes neuropathological effects in adjacent nerves by thickening of collagen layers around axons and generalized axonal degradation and loss [5,6]. This inflammation or foreign body reaction (FBR) is highly material dependent. Weight reduced large pore size meshes seem to result in a diminished FBR and consequently less chronic pain and foreign body sensation during the first post-operative year [7]. Regarding fixation, meta-analysis on the use of atraumatic fixation of the mesh with glue are inconclusive. One reports no benefit on the use of glue [8] in contrast to others we report a reduction of CPIP [9,10] whereas De Goede et all only found glue to reduce acute pain but not CPIP.[11] Subsequent meta-analysis The same is seen for the use of atraumatic devices or materials like glue to secure the mesh to the anterior wall [11-13].

A combination of atraumatic fixation and light weight material is found in the self-gripping Parietex Progrip mesh. This bi-component knit of polyester (PET) incorporates resorbable polylactic acid (PLA) micro hooks on one side of the mesh, which provides atraumatic anchorage of the mesh in the underlying tissue instantly after application. Tissue-gripping is achieved during the following twelve months and does not require additional fixation. After resorption of the PLA-part of the mesh, only the low-weight PET fabric (40 g/m^2) remains in the groin area, providing the long-term wall reinforcement. Besides to ease initial surgical handling, this self-gripping mesh is supposed to reduce CPIP in bypassing traumatic fixating devices and eliciting a reduced inflammation and FBR, because of the low-weight large pore size monofilament knit. However, a number of randomized controlled trials and meta-analysis did no report reduced CPIP rates [14-20]. An explanation may be found in the PLA micro-hooks to elicit a different, more harming inflammatory reaction thereby reducing the mesh biocompatibility.

Biocompatibility of a mesh can be expressed as the ability of the device to perform its intended function, with the desired degree of incorporation in the host, without excessive fibrosis and inflammatory damage to nerves and tissue [21]. Macrophages have an important

role in directing the intensity and balance of the host immune response. Macrophages can have different phenotypes, with pro-inflammatory (M1) and anti-inflammatory/wound healing (M2) on both ends of the spectrum. These two types are influenced by different factors and produce different cytokines (Table 1). From the release of cytokines by macrophages, an artificial M1/M2 index can be calculated indicative for a more pro- or anti-inflammatory reaction of macrophages to meshes. This is greatly influenced by the biophysical nature of the material with which the macrophages interact [22,23].

This study was designed to evaluate the influence of additional PLA on the mesh and how it influences the acute response of macrophages by assessing the cytokine profile of macrophages seeded on the mesh by the use of our earlier published in vitro model of human primary macrophages [24]. We determined the production of pro- and anti-inflammatory cytokines to investigate the reaction of macrophages to the PLA addition to a polyester (Parietex) mesh.

Table 1. Main characteristics of M1 and M2 macrophages

	M1	**M2**
Function	pro-inflammatory anti-fibrogenic tissue destructive	anti-inflammatory pro-fibrogenic promote FBGC formation
Genes	*TNFα* *IL* 6	*CD* 206 *CCL* 18
Stimulators *used in the study protocol*	LPS IFN-γ	IL-4
Cytokines (proteins) *most discriminative ones*	MIP-1α or CCL3 TNFα MCP-3 IL-1β IL-6	CCL5 CCL18 IL-1RA MDC

FBGC=Foreign Body Giant Cell, IL=interleukin, MIP=macrophage inflammatory protein, TNF=tumor necrosis factor, LPS=lipopolysaccharide, IFN=interferon, MCP=monocyte chemotactic protein, RA=receptor antagonist, RANTES=regulated upon activation normal T-cell expressed and secreted, MDC=macrophage derived chemokine, CCL=chemokine ligand

METHODS

A full description of monocyte isolation, validation of read out parameters and macrophage culturing has been published previously by our team [24]. A summarize will be given for proper understanding of the results presented.

Monocyte isolation

Ficoll density gradient (Ficoll-Paque™ PLUS, GE Healthcare) was used to isolate monocytes from 3 buffy coats of healthy donors, obtained from the blood bank (SanquinBloodbank, Rotterdam, the Netherlands). [24]

Meshes

Macrophage reaction was tested for a bicomponent semi-resorbable knit of non-absorbable monofilament polyester and resorbable monofilament polylactic acid (PLA). The results were compared to a low weight polyester mesh (Parietex. Both meshes were from Sofradim Production, A Medtronic Company, Trevoux, France (Table 2).

Table 2. Mesh materials used

Trade name	Chemical component	Type	Filament / constitution	Pore size (mm)	Mass (g/m^2)
Parietex LW	PET	Non-absorbable	Monofilament	1.5x1.5	46
Parietex Progrip	PET + PLA	Non-absorbable PET and absorbable PLA	Bicomponent, both monofilaments	Macro: 1.8 x 1.8	82 after adsorption of PLA: 49

LW = low weight; PLA = polylactic acid; PET = polyester
All were from Sofradim Production, A Medtronic Company, France

Culturing macrophages on biomaterials

The meshes were cut into pieces of 1.5 by 1.5 cm. After seeding samples were placed in a 24-well non-adherent plate (NUNC, non-treated multiplate, Rochester, NY, USA) and cultured for a total of 3 days in serum free X-vivo 15 medium. The samples were harvested after 3 days for protein production and DNA analysis.

Cytokine analysis

We previously determined a panel of proteins and genes to define several distinguishing markers for pro- and anti-inflammatory macrophages using lipopolysaccharide (LPS) + interferon (IFN)-γ and interleukin (IL)-4 stimulated macrophages. Protein production was measured for nine proteins; macrophage inflammatory protein (MIP)-1α (or chemokine ligand (CCL) 3), tumor necrosis factor (TNF)α, interleukin (IL)-1β and interleukin (IL)-6 as pro-inflammatory M1 markers, macrophage derived chemokine (MDC or CCL22), monocyte chemotactic protein (MCP)-3, regulated upon activation normal T-cell expressed and secreted (RANTES or CCL5), interleukin (IL)-1RA and chemokine ligand (CCL) 18 as anti-inflammatory M2 markers. Although IL-6 and RANTES are known to be able to act either pro-inflammatory or anti-inflammatory, depending on the environment [24], in our monolayer experiments with stimulated macrophagesIL-6 gene expression was higher in LPS+IFNc stimulated macrophages than in IL-4 stimulated macrophages. Therefore IL-6 was

selected as pro-inflammatory marker. RANTES protein levels on the other hand were higher in IL-4 stimulated cells than in LPS+IFNc stimulated cells and therefore selected in our model as an anti-inflammatory marker. [24] Cytokine measurement was done using an eight-plex Milliplex (Millipore) and a CCL18 DuoSet ELISA (R&D, Minneapolis, MN, USA).

DNA measuring

The amount of protein was corrected for the number of cells by measuring DNA. The seeded meshes after 3 days of culture were harvested in 0.1%Triton/PBS (Sigma–Aldrich) and stored at -20°C. Later the samples were analyzed with CyQUANT© cell proliferation assay kit (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's recommendation.

Statistics

The biomaterial experiments were performed with three different donors, each donor in triplicate. All data are presented as scatter dot plots with each dot representing one single measurement with the mean of the different donors. To compare the effect of the four materials on macrophage subtype, a relative M1/M2 index was calculated. The percentage of the mean production per cytokine was calculated, followed by dividing the mean percentage of M1 cytokines (MIP-1a, TNFa, MCP-3, IL-1b, IL-6) by the mean percentage of M2 cytokines (MDC, RANTES, IL-1RA and CCL18) per sample. Groups were compared in SPSS (20.0, IBM Corporation, Armonk, New York, USA) using a Kruskal–Wallis test (independent samples median test) and a Mann–Whitney test because the data were not normally distributed. Differences were considered statistically significant when $p < 0.05$. [13]

RESULTS

No significant difference in the amount of DNA per sample was found between the two meshes (Figure 1). No significant difference was found between the production of pro-

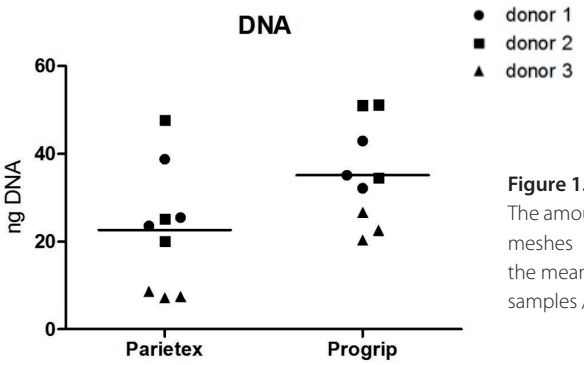

Figure 1. Amount of DNA per sample
The amount of DNA per sample for each of the two meshes is shown. The horizontal bar represents the mean amount of DNA. n = 3 donors with three samples / donor.

inflammatory cytokines by macrophages on Parietex or Parietex Progrip. The pure polyester (Parietex) mesh induced a higher amount of all pro-inflammatory cytokines compared to the Progrip mesh, albeit not significant (Figure 2).

For the anti-inflammatory cytokines the same trend was seen (Figure 3). The pure polyester mesh had a higher mean production of anti-inflammatory cytokines compared to the self-gripping polyester mesh, but this difference was not significant. The calculated M1/M2 index was almost the same for both meshes (Figure 4).

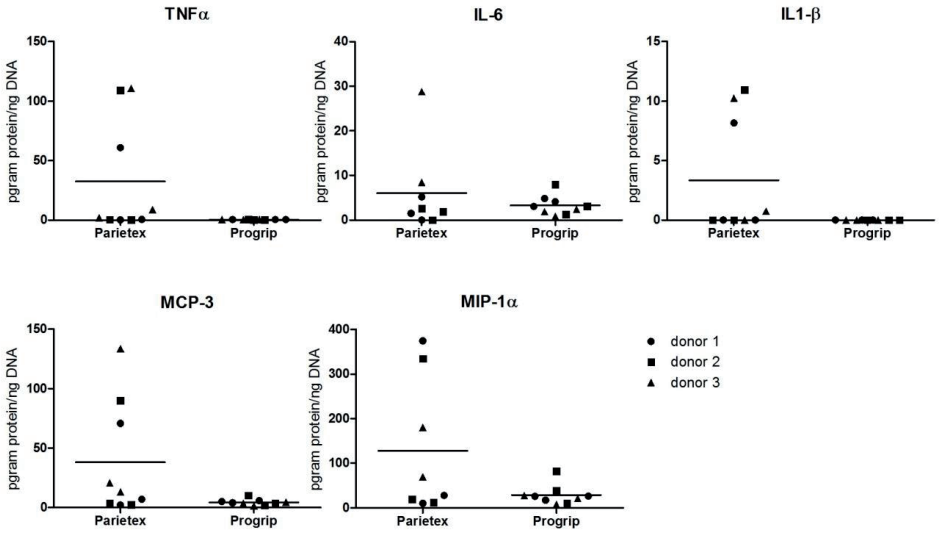

Figure 2. Pro-inflammatory cytokine production
Shown is the macrophages' protein production in picogram (pg) for the Parietex and Parietex Progrip mesh. Measurement took place 3 days after seeding and culturing the macrophages on the meshes The amount of pg protein is corrected for nanogram (ng) DNA per sample. There were 3 samples per donor and 3 different donors. The horizontal bar represents the mean production of pg protein per ng DNA.

DISCUSSION

To reduce the burden of chronic post-operative inguinal pain (CPIP) and enhance surgical handling of meshes manufacturers continue to develop new meshes with different materials, construction and properties. The purpose of this study was to evaluate the biocompatibility of a self-gripping polyester mesh supplemented with self-adhering polylactic acid micro hooks to provide an atraumatic tissue adherence of the mesh. Biocompatibility was determined by analyzing the production of pro- and inflammatory cytokines in an already proven in vitro model of healthy human primary macrophages [24]. To facilitate comparison of the Parietex Progrip mesh with a Parietex mesh a relative M1/M2 index was calculated for each biomaterial.

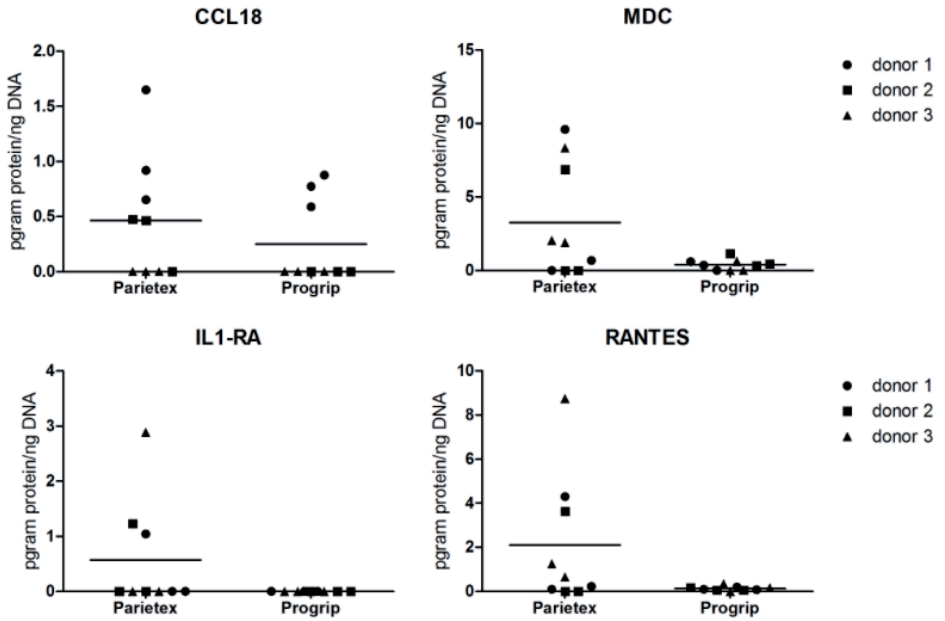

Figure 3. Anti-inflammatory cytokine production
Picogram protein corrected for nanogram DNA per sample, 3 samples per donor, 3 different donors

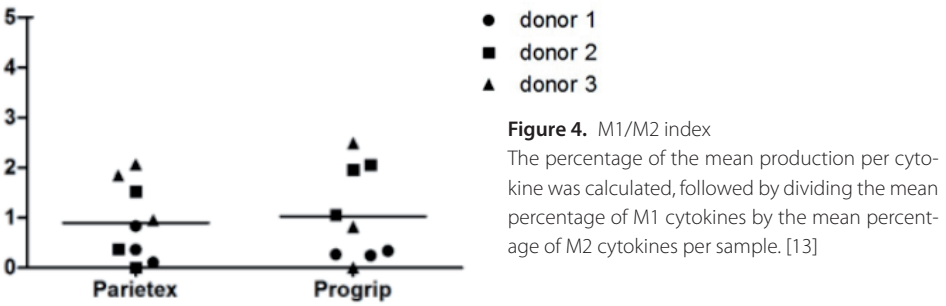

Figure 4. M1/M2 index
The percentage of the mean production per cytokine was calculated, followed by dividing the mean percentage of M1 cytokines by the mean percentage of M2 cytokines per sample. [13]

The balance between M1 and M2 macrophage reaction plays a critical role in the healing and remodeling of injured tissues and acceptance and ingrowth of meshes [25]. Mesh propensity to influence the M1 and M2 macrophage response reaction on a constructive way depends on the biomaterial composition, e.g. the type of polymer, the material weight and dimension, the filament structure and pore size. [6,21,26-29] Surgical meshes are mainly made of non-absorbable polymers like polypropylene (PP) or polyester (PET). To enhance mesh properties PLA was added to a polyester mesh. This synthetic biodegradable polymer was first used as biodegradable suture in the 1960s with the purpose to avoid a chronic foreign

body reaction. [30] Although it has been used in surgery for many years now, it has never been used before for the construction of surgical meshes.

Meshes combining absorbable and non-absorbable materials mostly elicit a typical host response; there is an increased inflammatory reaction with greater macrophage and lymphocyte infiltration accompanied by a greatly reduced FBR with limited fibrosis, because the absorption of the absorbable fibers reduces the amount of foreign material persisting in the host [6]. The enhanced infiltration of macrophages and lymphocytes is needed to degrade and phagocyte the absorbable material [22]. Phagocytosis of implanted biodegradable materials is enhanced by MMPs that can degrade the implanted material [23] Expression of MMPs is promoted by the pro-inflammatory cytokines IL-1β and TNFα suggesting M1 macrophage dominance[22]. Interestingly, no increased pro-inflammatory reaction was seen for the polyester-polylactic-acid composite self-gripping mesh. Macrophages seeded on the composited Parietex Progrip mesh produced a commensurate amount of both pro-inflammatory and anti-inflammatory/repair proteins. The FBR was comparable to the reaction elicited by the pure polyester mesh reflected in the same M1/M2 index. Junge et all experienced the same when investigating the influence of poliglecaprone 25 (Monocryl) supplementation on the biocompatibility of a polypropylene mesh. [31]

It turned out that the polylactic micro-hooks did not alter the acute response of the macrophages, inducing no extra inflammatory response. Polylactic-acid degrades much slower than for instance the polyglycolic -acid and the collagen film of the Parietex Composite™ mesh, for which we found in previous research indeed an increased pro-inflammatory response [24]. Whether this attenuated response also leads to less inflammatory damage to tissue and nerves is not clear. At least no reduced levels of CPIP are found for the Parietex Progrip mesh [19,20,32]. Probably other surgical factors like the dissection, nerve trauma and the presence of mesh in the inguinal canal and contacting the nerves play a more important role in the development of CPIP. The limited fibrotic reaction that was found for the self-gripping mesh may help in mesh integration and a reduced foreign body feeling [33]. At least recurrence rates are reported to be comparable to a sutured mesh.[16,34]

It is difficult to simulate the complex host response elicited by biomaterials in an in vitro model and to translate the results to the in vivo situation. Limitations are the artificial circumstances eliminating surgical factors, the monocellular evaluation without other immune cells involved in the FBR like mast cells and fibroblasts. Moreover, we used different blood samples which reacted differently to the biomaterials. However this is the same in real life and can be used to make sub analysis for specific patient populations like obese or diabetics. Although these limitations, an in vitro model gives an indication of the initial FBR and allows the comparison of this response between biomaterials. It will help to investigate whether some unwanted side effects as chronic postoperative inguinal pain are due to the type of mesh implanted or are dependent on other factors like the repair technique.

To conclude, polylactic-acid micro hooks supplemented to a polyester self-gripping mesh does not seem to influence the acute response of macrophages in an experimental model using human derived macrophages; the inflammatory cytokine profile is comparable with a mere polyester mesh.[24]

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PART 3

CHRONIC PAIN: ASSESSMENT IN LITERATURE

CHAPTER 7

Uniformity of chronic pain assessment after inguinal hernia repair, a critical review of literature

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European Surgical Research 2017

ABSTRACT

Background

Chronic postoperative inguinal pain (CPIP) is the most common long-term complication of inguinal hernia repair. As such procedures are routinely performed, CPIP can be considered a significant burden for global health care. Therefore, adequate preventative measures relevant to surgical practice are investigated. However, as no golden standard research approach is currently available, study methods and outcome measures differ between studies. The current review aims to provide a qualitative analysis of the literature to point out if outcomes of CPIP are valid and comparable facilitating recommendations on the best approach to prevent CPIP.

Methods

A systematic review of recent studies investigating CPIP was performed, comprising studies published in 2007-2015. Study designs were analyzed regarding the applied CPIP definitions, the use of validated instruments, the availability of a baseline score and a minimal follow-up of twelve months.

Results

Eighty eligible studies were included. In 48 studies, 22 different definitions of CPIP were identified of which the definition provided by the International Association for the Study of Pain was most often applied. Of the included studies, 53 (66%) studies used 33 different validated instruments to quantify CPIP. There were 32 (40%) studies that assessed both pain intensity (PI) and Quality of Life (QOL) with validated tools, 41% and 4% had a validated assessment of only PI respectively QOL and 15% lacked a validated assessment. The visual analogue scale and Short Form 36 were most commonly used for measuring PI (73%) and QOL (19%). Assessment of CPIP was unclear in 15% of the included studies. A baseline score was performed by 45% of the studies and 75% had a follow-up of at least 12 months.

Conclusion

The current literature addressing CPIP after inguinal hernia repair has a variable degree of quality and lacks uniformity in outcome measures. Proper comparison of study results to provide conclusive recommendations for prevention methods for CPIP therefore remains difficult. These findings reaffirm the need for a uniform and validated assessment with uniform reporting of outcomes to improve the burden that CPIP poses for a significant surgical patient population.

INTRODUCTION

Chronic postoperative inguinal pain (CPIP) is the most common complication following inguinal hernia repair, occurring in roughly 20% of patients. [1,2] As inguinal hernia repair is a routinely performed surgical procedure, the frequent occurrence of CPIP constitutes a significant burden on surgical care. [3] As a result, CPIP has provided a strong incentive to optimize preventive and therapeutic strategies, yielding a large amount of investigative studies over the recent decades. However Subsequent reviews have been faced with significant heterogeneity in study methods and outcomes. The heterogeneity of available studies is largely attributable to the varying application of CPIP definitions, different timing of post-operative assessment utilizing different measurements and the lack of standardized reporting of outcome results. Such heterogeneous data may be considered insufficient as a basis for consensus which needs uniform and validated study designs to ensure adequate scientific evidence for clinical decision-making. [4]. As a solution, the working group The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [5] and the International Association for the Study of Pain (IASP) [6] recommended core outcome domains to be considered in the development of studies investigating CPIP. These core domains are comprised of pain intensity (PI), consequences of chronic pain on physical and emotional functioning and the participants' rating of overall improvement. In addition, these core outcomes should be measured prospectively with a minimal follow-up of 1 year using two or more standardized assessment tools.

Furthermore, the National Institute for Health and Clinical Excellence (NICE) has emphasized the importance of utilizing prospective study designs to address these core outcome domains, in order to standardize definitions and assessment methods of pain. [7] The aim of the current review is to investigate whether the recommendations made in 2005 by the IMMPACT, IASP and NICE have led to improved uniformity and quality in the design of studies focusing on CPIP to a degree that allows the formation of conclusive recommendations to reduce the onset of CPIP.

METHODS

Search strategy

The literature search was performed using several databases, which were Medline in PubMed, Embase and the Cochrane Library. The following mesh terms were combined: 'hernia, inguinal', 'chronic pain', 'herniorraphy', 'Lichtenstein'. To ensure that the search would yield a complete overview of current literature, the MeSH terms were used in conjunction with free text word combinations as this search strategy would also cover papers without appropriate MeSH terms and papers not yet fitted with MeSH terms. The search was re-

stricted to articles published in the English language from 2007 to 2015 to obtain the most recent studies that were relevant to the aim of this review.

Inclusion criteria

Studies

Prospective studies and study protocols with the Lichtenstein method as the referring technique were included, irrespective of the application or method of randomization. Also, to suit the purpose of this review, studies were included regardless of sample size, publication status and whether it concerned single or multi centered studies.

Patients

As this study focuses on the adult patient population, all patients aged 18 years and above were included. All types of hernia (primary or recurrent, uni- or bilateral) that were investigated were included for both adult male and female populations to ensure broad applicability of our results in a large and diverse patient population in clinical practice.

Interventions

Correction of an inguinal hernia irrespective of the surgical technique

Outcomes

CPIP is among the primary or secondary outcomes

The review process was performed in two steps. First, all abstracts were subjected to the eligibility criteria, consulting the full-text papers in case of doubt about whether the study met these criteria. Next, all full-text papers of the selected abstracts were read and analyzed in full to make a final decision about inclusion.

Outcomes of interest

According to the recommendations of the IMMPACT, IASP and NICE all included_studies were scored for the presence of:

(1) formal definition of CPIP
(2) validated measurement of both PI and the effects of CPIP on daily functioning or QOL
(3) duration of follow up of at least 12 months
(4) baseline score: preoperative measurement of PI and QOL

One point was assigned to a study for the availability of each of the above mentioned aspects, after which each study was assigned an overall methodological quality score ranging from 0 to 4.

RESULTS

Using the strategy described above, the search yielded 234 hits (see PRISMA flowchart in Figure 1). After applying the search limitations, 109 articles remained eligible for inclusion. Following critical review of these full-text articles, 29 articles were excluded for not meeting the inclusion criteria. The reasons for exclusion at this stage were retrospective study design, the article being a review or comment, a lack of CPIP among the primary or secondary outcomes. Also, studies reporting the long term follow-up of another included study were considered redundant and were therefore excluded.

Following critical review, eighty studies fitted the eligibility criteria. Among these studies, 52 articles described RCT's and 38 studies had a comparative study design (Table 1). Most studies investigated the Lichtenstein technique using different meshes (n=10), fixation methods (Progrip mesh n=13, glue n=10), analgesia (n=3) and method of nerve handling (n=5). Other studies compared the Lichtenstein technique to pre- or retroperitoneal mesh placement: totally extra peritoneal (TEP) repair (n=12), Prolene Hernia System (PHS) repair (n=4), plug and patch (n=4), Kugel (n=2), trans inguinal preperitoneal (TIPP) repair (n=1), transabdominal preperitoneal (TAPP) repair (n=5) . Seven studies compared Lichtenstein hernioplasty with non-mesh techniques: Maloney Darn repair, (MDR, n=2), Shouldice (n=1), Desarda (n=1), suture repair (n=2). In 55 studies, CPIP was the primary outcome measure, in the other studies CPIP was among the secondary outcomes.

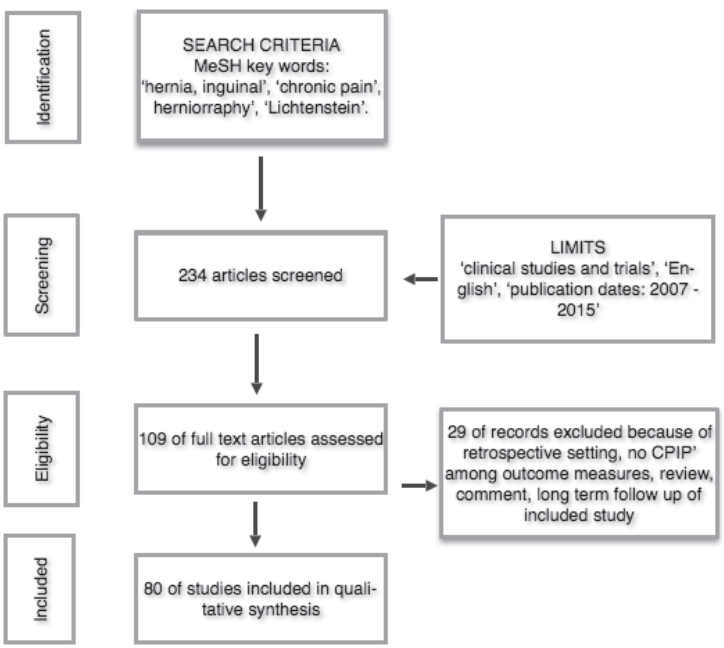

Figure 1. PRISMA flow chart

Table 1. Characteristics of the included studies and the score system

First author	Year	Study Design	Research question	N (total)	Measurement tool(s)	PI + QOL assessed with validated tool	Mean length of FU (months)	FU ≥ 12 months	CPIP defined	Basement score	SCORE
Abd El Maksoud (36)	2014	RCT	L / MDR	227	VAS		12	x			1
Anadol (52)	2011	P	L / Progrip mesh	51	VAS, ' questionnaire '		24	x	x		2
Andresen (74)	2013	RCT	L / Onstep approach	282	VAS, AAS, CCS	x	12	x	x		3
Beldi (43)	2008	P	L / suture repair / TEP	96	VAS, SF36, von Frey filaments	x	3		x		2
Bellows (53)	2011	RCT	L: synthetic / biological mesh	172	AAS, BPI , WBF, PAS	x	24	x	x		3
Belyansky (76)	2011	P	L / TEP / TAPP	2499	CCS	x	12	x	x		3
Bignell (29)	2014	RCT	L / TAPP	120	SF-12v2, PIQ-6	x	12	x		x	3
Bochicchio (84)	2014	RCT	L: synthetic / biological mesh	95	SF-36v2, VAS	x	12	x	x	x	4
Bracale (37)	2014	RCT	L: sutures / glue	102	-		15	x			1
Bury (30)	2012	RCT	L with 3 types of mesh	396	VAS, ' questionnaire '		62	x			1
Caliskan (64)	2010	P	nerve management	54	VRS, VAS		6		x		1
Campanelli (25)	2012	RCT	L: sutures / glue	319	SF-36v2, VAS	x	12	x	x	x	4
Champault (8)	2007	P	L / TEP / polypropyleen mesh / Glucamesh	349	VAS, 'a validated questionnaire'	x	24	x			1
Champault (22)	2011	P	Progrip mesh	186	VAS, SF12	x	3			x	2
Chastan (13)	2009	P	Progrip mesh	52	VAS		12	x		x	2
Chatzimavroudis (59)	2014	RCT	L / Progrip mesh	50	VAS		12	x	x		2
Dalenback (14)	2009	RCT	L / PHS / plug and patch	472	VAS, 'a standardised scored FAT 2 protocol'	x	36	x		x	3
Demetrashvili (23)	2011	RCT	L / TAPP	52	VAS		36	x			1

Table 1. Characteristics of the included studies and the score system (continued)

First author	Year	Study Design	Research question	N (total)	Measurement tool(s)	PI + QOL assessed with validated tool	Mean length of FU (months)	FU ≥ 12 months	CPIP defined	Basement score	SCORE
Dhankbar (60)	2014	RCT	L / TEP	72	VAS, SF36v2	x	3		x	x	3
Dhumale (18)	2010	P	L	1164	' questionnaire '		2		x		1
Eker (32)	2012	RCT	L / TEP	660	VAS		60	x		x	2
Eklund (48)	2010	RCT	L / TEP	1370	IPQ, VAS, FIS	x	60	x	x	x	4
Eklund (40)	2007	RCT	L / TAPP	1512	VAS, ' a validated questionnaire ', FIS	x	60	x	x	x	4
El-Awady (46)	2009	P	L	40	SF36		9		x	x	2
Ferranti (15)	2009	P	Self regulating prothesis	214	-		24	x			1
Fortelny (38)	2014	RCT	L: sutures / glue	38	VAS, SF36	x	12	x		x	3
Fricano (49)	2010	P	Modificated L	406	PIC, VRM, ' questionnaire '		6		x		1
Frisen (24)	2011	P	L: resident / surgeon	200	SS, IPQ	x	3			x	2
Garcia Urena (77)	2011	P	Progrip mesh	256	VAS, ' questionnaire '		6		x		1
Holzheimer (9)	2007	P	L	300			12	x			1
Honigmann (41)	2007	RCT	L: Local anaesthesia	264	VAS, PMD, SF36.	x	12	x	x	x	4
Jain (69)	2009	P	L: sutures/glue	80	- (VAS was used for acute pain)		12	x	x		2
Jeroukhimov (61)	2014	RCT	L: non-absorbable / absorbable sutures	200	VRS		12	x	x		2
Jorgensen (81)	2012	RCT	L / Progrip mesh	334	VAS		12	x	x	x	3
Kapischke (50)	2010	RCT	L / Progrip mesh	50	VAS, ' telephone interview'		6		x		1
Karakayali (19)	2010	RCT	nerve management	240	VAS, SF6, MPQ	x	12	x			2
Karakayali (10)	2007	P	L / Shouldice	100	VAS, EMG, ' questions about daily complaints '		12	x			1

Table 1. Characteristics of the included studies and the score system (continued)

First author	Year	Study Design	Research question	N (total)	Measurement tool(s)	PI + QOL assessed with validated tool	Mean length of FU (months)	FU ≥ 12 months	CPIP defined	Basement score	SCORE
Kim-Fuchs (55)	2012	RCT	L: sutures / glue	264	' a questionnaire '		60	x	x		2
Kingsnorth (79)	2012	RCT	L / Progrip mesh	302	VAS 0-150mm, SPS		12	x		x	2
Koch (11)	2008	RCT	L: HW mesh / LW mesh	317	VAS, SHS	x	2			x	2
Koning (56)	2012	RCT	L / TIPP	302	VAS, SF36, PPT	x	12	x	x		3
Kouhia (16)	2009	RCT	L / TEP	99	-		24	x		x	2
Kucuk (70)	2010	RCT	L / MDR	306	-		6		x		1
Kurmann (85)	2014	RCT	L: Local anaesthesia	357	VAS		12	x	x	x	3
Langeveld (20)	2010	RCT	L / TEP	660	0-6 weeks: VAS, SF36, after six weeks: interview	x	60	x			2
Lauscher (12)	2008	P	L / TEP	491	NAS, ' a validated questionnaire '	x	58.6	x			2
Lionetti (33)	2012	RCT	L: sutures / glue	148	VAS, ' a questionnaire '		12	x			1
Magnusson (34)	2012	RCT	L / PHS / UHS	309	VAS, SF36, ' a questionnaire '	x	12	x		x	3
Malekpour (44)	2008	RCT	L: nerve management	121	VAS, ' a questionnaire '		12	x	x		2
Myers (51)	2010	P	L / TEP	314	SF36		60	x	x		2
Negro (25)	2011	P	L: sutures / glue	520	VAS		12	x		x	2
Nienhuijs (42)	2007	RCT	L / Kugel	172	VAS, ' a pain questionnaire '		3		x	x	2
Nienhuijs (62)	2014	RCT	L / PHS / MPR	270	VDS, VAS	x	86	x	x		3
Nikkolo (88)	2010	RCT	L: HW mesh / LW mesh	35	VAS, SF36	x	12	x	x	x	4
Nikkolo (89)	2014	RCT	L : different pore size meshes	134	VAS, SF36	x	6		x		2
Paajanen (78)	2011	RCT	L: absorbable sutures / glue	59	VAS		12	x	x	x	3
Paajanen (82)	2013	RCT	L: 3 types of mesh	228	VAS, interview based on the DHD		56	x	x	x	3

Table 1. Characteristics of the included studies and the score system (continued)

First author	Year	Study Design	Research question	N (total)	Measurement tool(s)	PI + QOL assessed with validated tool	Mean length of FU (months)	FU ≥ 12 months	CPIP defined	Basement score	SCORE
Pedano (72)	2012	P	Progrip mesh	181	-		17	x	x		2
Pielacinski (26)	2011	RCT	L / absorbable mesh	358	VAS, VRS		6				0
Pierides (35)	2012	RCT	L / Progrip mesh	358	VAS, ' a questionnaire '		12	x		x	2
Pierides (27)	2011	RCT	L / PHS	232	' a questionnaire '		60	x			1
Quyn (57)	2012	P	L / Progrip mesh	132	SF36		12	x	x		2
Reinpold (71)	2011	P	nerve management	781	VAS, interview, 'a standardised questionnaire'		60	x	x	x	3
Ripetti (75)	2014	RCT	L / Trabucco / Valenti	162	-		96	x	x		2
Ruiz-Jasbon (67)	2014	P	L	40	VAS, IPQ	x	36	x	x	x	4
Sadowski (54)	2011	RCT	L: polypropylene / polyester	78	VAS, IPQ, 'a questionnaire '	x	3		x	x	3
Sanders (47)	2009	RCT	L / Perfix Plug / ProLoop plug	295	VAS		12	x	x		2
Sanders (86)	2014	RCT	L / Progrip mesh	557	VAS, SPS	x	12	x		x	3
Shen (80)	2012	RCT	L: sutures / glue	110	VAS		12	x	x	x	3
Singh (58)	2011	RCT	L / TAPP / TEP	117	SF36, SPS	x	12	x	x	x	4
Smeds (21)	2010	P	nerve management	525	VAS		3			x	1
Smietanski (63)	2009	P	L with monofilament mesh	212	VAS		36	x	x		2
Smietanski (90)	2008	RCT	L: HW mesh / LW mesh	392	SF36, VAS	x	12	x	x	x	4
Smietanski (65)	2011	RCT	L: HW mesh / LW mesh	202	SF36, VAS	x	60	x	x		3
Staal (45)	2008	P	L / Kugel	172	VAS, PDI	x	3		x	x	3
Szopinski (73)	2012	RCT	L / Desarda	216	VAS, ShS	x	36	x	x		3
Veen (68)	2007	RCT	L / suture repair	153	' a questionnaire '		129	x	x		2
Wong (28)	2011	RCT	L: glue / sutures	56	VAS		6				0

Table 1. Characteristics of the included studies and the score system (continued)

First author	Year	Study Design	Research question	N (total)	Measurement tool(s)	PI + QOL assessed with validated tool	Mean length of FU (months)	FU ≥ 12 months	CPIP defined	Basement score	SCORE
Yalcin (17)	2009	P	L: local anesthesia	115	VAS		12	x			1
Yilmaz (83)	2013	P	L / Progrip mesh	60	VAS		4		x	x	2
Column total						33		60	49	36	

FU = Follow-up; RCT = Randomized Controlled Trial; P = Prospective; / = versus; L = Lichtenstein; MDR = Modified Darn Repair; TEP = Total Extra Peritoneal Repair; TAPP = Trans Abdominal Pre Peritoneal Repair; PHS = Prolene Hernia System; UHS = UltraPro Hernia System; MPR = Mesh plug Repair; HW = Heavy weight; LW = Light weight; TIPP = Trans Inguinal Pre Peritoneal repair; VAS = Visual Analog Scale; AAS = Activities Assessment Scale; CCS = Carolinas Comfort Scale; SF36 = Short Form Health Survey 36; BPI = Brief Pain Inventory; WBF = Wong Baker Faces rating scale; PAS = Pain Assessment Survey; SF-12v2 = Short Form Health Survey 12 version 2; PIQ = Pain Impact Questionnaire (QualityMetric, USA); VRS = Verbal Rating Scale; IPQ = Inguinal Pain Questionnaire; PIC = Pain Intensity Scale; VRM = Verbal rating Model; SS = Sergel Score; PMD = Pain Matcher device (Cefar Medical AB, Lund, Sweden); MPQ = Mc Gill Pain Questionnaire; EMG = Electromyelogram; SPS = Surgical Pain Scale; SHS = Short Health Scale; NAS = Numeric Analog Scale; VDS = Verbal Descriptor Scale; PDI = Pain Disability Index; ShS = Sheffield Scale

1 CPIP Definition

A definition of CPIP was lacking in 31 (39%) studies (Tabel 1). [8-38] In the other 49 (61%) studies, a total of 22 different definitions of CPIP were identified (Table 2). Almost half (n=23) of these studies applied the definition provided by the IASP, which is "chronic pain is pain

Table 2. Overview of the different definitions of Chronic Post-operative Inguinal Pain (CPIP) used in the included studies

First author	Definition of CPIP
n=49 (61%)	
Anadol ((52), Beldi (43), Bellows (53), Chatzimavroudis (59), Dhankhar (60), Eklund (32, 48), El-Awady (46), Fricano (49), Honingman (41), Jeroukhimov (61) , Kapischke (50), Kim Fuchs (55), Koning (56), Malekpour (44), Myers (51), Nienhuijs (42, 62), Quijn (57), Sanders (47), Sadowski (54), Singh (58), Staal (45) (n=23)	IASP: any VAS lasting >3 months
Andresen (74)	Pain-related impairment of function at 6 months defined as AAS > 8.3 Pain that impairs daily function at the 12-month
Jain (69), Ripetti (75)	Proportion of patients with pain that impairs daily function at 12 months
Smietanski (63, 65, 90)	Pain lasting >12 months (Kehlet)
Caliskan (64)	Pain lasting >1 months
Ruiz-Jasbon (67)	Pain at 36 months
Pedano (72)	Invalidate pain > 3 months
Yilmaz (83)	VAS >0 at 4 months
Campanelli (25), Jorgensen (81)	VAS >30 at 12 months
Kurmann (85)	VAS as ≥30 in any quality (at rest, lying, walking, climbing stairs, and bending over) at 3 months
Garcia Urena (77)	VAS >3 at 3 and 6 months
Bochicchio (84)	Any VAS at 3 and 12 months
Kingsnorth (79)	VAS 45/150 lasting >3 months
Shen (80)	moderate or greater pain (VAS > 4) in the inguinal area at 3 months
Belyansky (76)	CCS >1 lasting >3 months
Kucuk (70)	Pain lasting >2 months and requiring painkillers
Nikkolo (88, 89)	Pain at rest at 6 months
Paajanen (78)	VAS >2 lasting >3 months
Paajanen (82)	VAS > 3 at 12 months
Reinpold (71)	Pain once a fortnight lasting >6 months
Szopinski (73)	Moderate or strong pain lasting >6 months
Veen (68)	Pain interfering with daily activities

IASP = International Association for the Study of Pain; VAS = Visual Analogue Scale; AAS = Activities Assessment Scale; CCS = Carolina Comfort Scale; > = more than

that persists beyond three months post-operatively". [39-62] The remaining half (n=26) used multiple definitions of CPIP, which can be categorized and summarized as follows. First, there was heterogeneity in the post-operative time period after which pain was classified as chronic. This "chronic" timeframe ranged between 1 and 36 months. [63-67] Second, some studies included the quantitative factor pain intensity in their definition of CPIP, which was either expressed using descriptive terms [68-75], a visual analogue scale (VAS) score or a QOL score [31,76-85].

In addition to incorporating a definition of CPIP, 31 (39%) studies provided a categorization of pain severity (Table 3). In half of the studies, the categorization consisted of reporting the effect of CPIP on daily life using nine different validated or non-validated criteria (Table III). [33,40,48,52,58,61,62,68,73,79,86] The remaining studies used a categorization of pain severity based on visual or numerical analog scale measurements (VAS or NAS). [8,10,19,22,23,50,56,71,73,81,87-89] The subsequent categorization of pain intensity was highly heterogenic (Figure 2). Some studies incorporated a minimal pain intensity score to distinguish between clinically relevant or minor CPIP. [14,31,71,74,76]

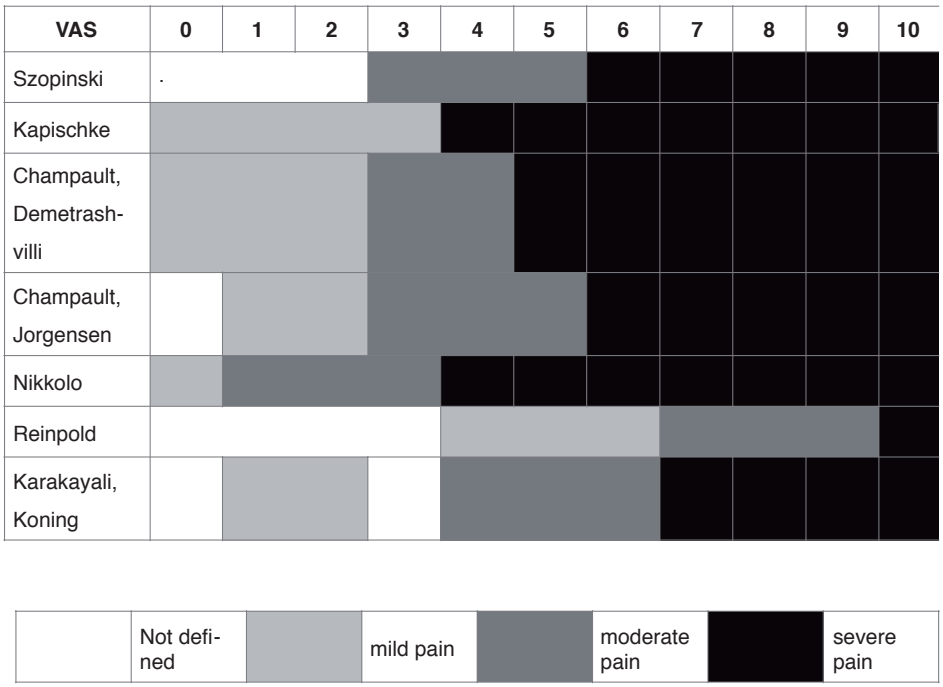

Figure 2. Categories of CPIP based on VAS score

Table 3. Overview of the different definitions and categories of pain severity

First author	Categories of CPIP
Anadol (52)	"intolerable pain" = "intractable" or "hard to live with" and those pain which requires pain medication and/or medical consultation
Szopinski (73)	**Sheffield scale:** 0 = no pain 1 = no pain at rest but it appears during movement 2 = temporary pain at rest and moderate during movement 3 = constant pain at rest and severe during movements
Eklund (40, 48), Smietanski (90)	mild = occasional discomfort or pain not interfering with daily activities moderate = discomfort or pain occasionally interfering with daily activities severe = discomfort or pain interfering with daily activities
Veen (68)	pain and discomfort whether or not interfering with daily activity
Lionetti (33)	**Cunningham's criteria:** Mild = occasional pain or discomfort that did not limit activity, with a return to pre-hernia lifestyle Moderate = pain preventing return to normal preoperative activities (inability to continue any sports or to lift objects without pain) Severe = pain constantly or intermittently present but so severe as to impair normal activities, such as walking.
Jeroukhimov (61)	Mild = occasional pain or discomfort that did not limit daily activity and did not require pain medicine. Moderate = pain that interfered with a return to normal everyday activity with rare analgesic requirement. Severe = pain that incapacitated the patient, occurred at frequent intervals, or interfered with everyday activities with a frequent need for painkillers.
Nienhuijs (62)	Pain was graded into non/mild/moderate and severe using a Verbal Discriptor Scale (VDS) for different aspects of life
Kingsnorth (79), Sanders (47), Singh (58)	**Surgical Pain Scale**: measures pain while at rest, during normal activities, during work or exercise, and pain unpleasantness.
Belyansky (76)	relevant pain = CCS>1
Ruiz-Jasbon (67), Sadowski (54)	pain yes or no in different situations according to **Inguinal Pain Index**: if yes a score on a VAS was asked
Andresen (74)	moderate to severe pain = VAS 4-10
Campanelli (25)	relevant pain = VAS>30
Dalenbäck (14)	severe = VAS >70
Champault (8), Demetrashvili (23)	mild = VAS <30, moderate = VAS <50, severe or debilitating = VAS >50
Champault (22) , Jorgensen (81)	mild = VAS 1–30, moderate = VAS 31–60, severe = VAS>60
Nikkolo (88, 89)	mild = VAS 1-10, moderate = VAS 11-50, severe = VAS >50
Reinpold (71)	not relevant CP: mild CP = VAS 1-3, relevant CP: moderate CP= VAS 4–6, strong CP= VAS 7–9, very strong CP =VAS 10
Karakayali (10, 19), Koning (56)	mild = VAS 1-30, moderate = VAS 40-70, severe = VAS>70
Szopinski (73)	moderate = VAS 30-54, strong = VAS>54
Kapischke (50)	low to medium = VAS 0-40; medium to strong = VAS >40
Lauscher (12)	weak = NAS 1-3, moderate/severe = NAS>3

VAS - Visual Analog Scale, in the studies ranging from 0=10 or 0=100; NAS = Numeric Analog Scale; CCS = Carolinas Comfort Scale; CP= chronic pain

Table 4. The number of studies that uses validated or non-validated assessment tools to measure CPIP

Type of assessment tool used	Number of studies (%)
No information given	8 (10%)
Non validated questionnaire: separated questions, written or by interview	19 (24%)
As a single measurement tool	4
In combination with a validated pain intensity score	12
In combination with a validated pain intensity and QOL score	3
Only validated questionnaire(s) or pain intensity scale (number of different tools n = 30)	53 (66%)

QOL = quality of life;

Table 5. Tools used to measure CPIP

Shortening	Full name	Number of studies it is used in
AAS	Activities Assessment Scale	3
BPI	Brief Pain Inventory	1
CCS	Carolinas Comfort Score	2
DHD	Danish Hernia Database questionnaire	1
FAT	Functional Ability test	1
FIS	Functional Index Score	2
IPQ	Inguinal Pain Questionnaire	4
MPQ	Mc Gill Pain Questionnaire	1
NAS	Numeric Analog Scale	1
PAS	Pain Assessment Survey	1
PDI	Pain Disability Index	1
PIQ-6	Pain Impact Questionnaire	
PIC	Pain Intensity Scale	1
PPT	Pin Prick Test	1
PMD	Pain Matcher Device	2
SF12 / SF12v2	Short Form 12 / Short Form 12 version 2	2
SF36 / SF36v2	Short Form 36 / Short Form 36 version 2	16
SF-6D	Short Form – 6 Dimensions	1
SHS	Short Health Scale	2
SPS	Surgical Pain Scales	3
ShS	Sheffield Scale	1
SS	Sergel Score	1
VAS-100mm	Visual Analog Scale 0-100mm	57
VAS-150mm	Visual Analog Score 0-150mm	1
VDS	Verbal Discriptor Scale	1
VRM	Verbal Rating Model	1
VRS	Verbal Rating Scale (0-100)	3
VRS-4	Verbal Rating Scale (0-4)	1
WBF	Wong-Baker Faces Rating Scale	1
FF	von Frey Filaments	1
	a validated questionnaire '	3

Table 6. Tools used to assess QOL and or pain intensity

Quality of Life (QOL) or Functional assessment	Pain Intensity (PI)	QOL + PI
Activities Assessment Scale	Numeric Analog Scale	Carolinas Comfort Score
Activity Restriction Questionnaire	Pain Intensity Scale	Brief Pain Inventory
Danish Hernia Database questionnaire	Pain Matcher Device	Mc Gill Pain Questionnaire
Functional Ability Test	Pin Prick Test	Short Health Scale
Functional Index Score	Surgical Pain Scale	Inguinal Pain Questionnaire
Pain Disability Index	Sheffield Scale	
Short Form 12 / 12-2v	Sergel Score	
Short Form 36	Visual Analog Scale 0-100mm	
Short Form – 6 Dimensions	Visual Analog Score 0-150mm	
Pain Impact Questionnaire	Verbal Rating Model	
	Verbal Rating Scale	
	Verbal Discriptor Scale	
	Wong-Baker Faces Rating Scale	

2.1 CPIP Assessment Tool(s)

Fifty-three (66%) studies used only validated instruments for the assessment of CPIP. However, among these studies, 33 different validated instruments were identified (Table 4, 5, 6). [11,13,14,17,19,21,26,28,29,32,36,38,41,43,45,47,48,51,53,56-65,79,90]

In 19 (24%) studies, non-validated instruments were used. [10,18,20,27,30,33-35,40,42,44,49,50,52,54,65,68,71,77,82] The majority of these studies described these instrument using non-specific phrases such as 'a questionnaire was used' or 'patients were interviewed'. Of these studies, fifteen utilized a non-validated instrument in conjunction with a VAS [10,30,33-35,40,42,44,50,52,71,77,82], VRS [49], Inguinal Pain Questionnaire (IPQ) [54], or Functional Index Score (FIS) [40].

In 8 (10%) studies there was no information provided about how data was collected [9,15,16,37,70,72,75].

Thirty-one (39%) studies provided definitions of the severity of CPIP (Table 3). Fifteen studies defined pain severity in terms of pain intensity according to the score on a Visual analog scale (VAS) or numerical analog scale (NAS). The categories of pain intensity based on VAS scores were heterogenic and thus not comparable.

2.2 Validated assessment of both pain intensity and QOL

Thirty-two (40%) studies had a validated assessment of both PI and QOL, [11,14,19,20,22,24,29,31,34,38,40,41,43,45,48,53,54,56,58,60,62,65,67,73,74,76,84,86-90], 33 (41%) respectively 3 (4%) studies there was only a validated assessment of PI [8,10,13,17,21,23,25,26,28,30,33,35,36,42,44,47,49,50,52,59,61,63,69,71,77,78,80-83,85] or QOL [46,51,57].

Table 7. Methodological Quality Score

	overall		2007 - 2010		2011 - 2015		
	N	%	N	%	N	%	
	80		**33**		**47**		
4 points	9	11%	5	15%	4	9%	
		100%		56%		44%	
3 points	21	26%	2	6%	19	40%	
		100%		10%		90%	
2 points	30	38%	15	45%	15	32%	
		100%		50%		50%	
1 point	18	23%	11	34%	7	15%	
		100%		61%		39%	
0 points	2	2%	0	0%	2	4%	
		100%		0%		100%	
							P=0.005

The methodological quality and comparability of the literature on CPIP was analyzed by scoring the included studies for:
(1) CPIP is defined thereby making use of standard internationally practiced criteria
(2) both PI and effects of CPIP on QOL are measured thereby making use of validated assessment tools
(3) sufficient follow up of at least 6 months
(4) availability of a baseline score e.g. preoperative measurement of PI and QOL
One point each was assigned for the availability of one the above mentioned aspects and each study was assigned an overall methodological quality score ranging from 0 to 4.
* Chi squared test

In 12 (15%) studies there was neither a validated assessment of PI nor QOL. [9,15,16,18,27,37,55,68,70,72,75]

The majority of studies investigating PI used VAS measurements, while QOL was most often examined using the SF36 questionnaire. (Table I and VI). Of the instruments that incorporate the assessment of both PI and QOL, the Inguinal Pain Questionnaire (IPQ) was used most.

3 Duration of follow-up of at least 12 months

The duration of follow-up ranged from 6 weeks to 96 months. Sixty (75%) studies had a follow-up of 12 months or longer with a median of 12 months (Table I).

4 Availability of a baseline score

A baseline score was performed by 45% (36/80) of the included studies (Table I).

Methodological quality score

The full amount of 4 points was scored by 11% of the studies, 26% scored 3 points, 38% scored 2 points, 23% scored 1 point and 2% scored 0 points (Table 7). When comparing the periods 2007-2010 and 2011 until to date there is a significant improvement of the Methodological quality score (P=0.005). The highest score was for the criterion to have a minimum of 12 months of follow up, second highest was the availability of a CPIP definition, on the third place was the performance of a baseline measurement and the worst was scored on the availability of a validated assessment of both PI and QOL.

DISCUSSION

The results from this review demonstrate that the current scientific literature investigating the management of CPIP after inguinal hernia repair is flawed due to lack of adherence to, and existence of commonly accepted definitions of the primary outcome, standards in study methodology and instrument tools. We found that, although the majority of studies provided similar definitions of CPIP, the variable interpretation of such definitions does not enable adequate comparisons, opposes uniformity and therefore obstruct evidence-based clinical decision making. Similarly, despite the fact that the majority of included studies did use a validated assessment tool to quantify CPIP, we found that a total of 33 different tools were used among these studies. The measurements of PI and QOL, which are both included in the recommendations of the IMMPACT and IASP, were performed using non-validated tools in a majority of studies. Furthermore, the majority of these studies provided no pre-operative baseline measurements of CPIP which clouds the interpretation of outcome findings.

Despite the efforts put forth by the scientific community, it appears that the current scientific literature about CPIP is heterogeneous to a degree that limits meta-analysis. Interestingly, the clinical relevance of this conclusion is not limited to the current state of scientific literature. Similar conclusions were drawn by Kehlet et al, who stated that no proper recommendations to prevent or treat CPIP could be made based on the sparse scientific evidence available over a decade ago. [4]. Based on their findings, they issued a call for uniformity and provided recommendations for an optimal study design as a solution for the heterogeneity. A more recent study published in 2007 by Hanswijck de Jonge et al. concluded that the measurements of pain and discomfort scores remained highly heterogeneous as studies evaluated CPIP by different types of instruments of varying quality and accuracy. [91]

Most of the included studies reported CPIP as the primary outcome. At a fundamental scientific level, the primary outcome of a study is the outcome parameter to be measured and compared, either to the control group in a comparative study or to results from the literature in non-comparative studies. Such a comparison to literature requires the unam-

biguous definition of the primary endpoint to provide conclusions of scientific and clinical value. To further enhance the comparability of scientific literature, it is of great importance to comply with standardized international definitions and to adhere to accepted categorizations of outcome measures. In the case of current CPIP literature, we found that 39% of studies lacked a definition of the primary outcome. When a definition was provided, it was often a non-standardized as we were able to identity 22 different CPIP definitions across the remaining 49 studies (Table II). The IASP definition of chronic pain was most frequently used, which states that 'chronic pain is any pain that persists beyond the normal tissue healing time usually taken to be 3 months' [39]. The other, non-standardized definitions diverged with respect to duration, intensity and severity. It appears that expert opinions disagree regarding the cut-off points between acute pain and chronic pain. This could be expected, considering that the IASP also uses different definitions for chronic pain and persistent postsurgical pain (PPSP), which is defined as 'pain that develops after a surgical intervention and lasts at least two months excluding other causes for the pain' [6]. Aasvang and Kehlet argued that given the possibility of an ongoing inflammatory reaction to a prosthetic mesh, CPIP should be measured at least six months postoperatively. [92] Others used a minimum duration of twelve months based on an earlier article of Kehlet et al [4].

The definition of CPIP provided by the IASP is based solely on a time factor as it regards discomfort to be pain scoring any VAS above zero. Alternative definitions incorporated a pain intensity factor in their CPIP definition. For example, such definitions state that a patient needs to express at least a VAS score of 2 or 3 on a scale of 10 to be considered as painful. Others added descriptive term of pain severity in their CPIP definition (Table II) such as discomfort or pain happening once a fortnight, requiring painkillers or interfering with daily activities. These different and seemingly arbitrary thresholds of pain severity and duration in the various definitions of chronic pain influence the incidence and prevalence rates of chronic pain and hinders comparisons between studies. In a recently published international expert consensus article, CPIP is defined as 'chronic inguinal post-operative pain that still exists and affects daily life six months post-operatively'.[93] However the Herniasurg Group, working on the World Guidelines for Groin Hernia Management, is now proposing to modify the IASP definition to include only chronic pain that is present from 3 months after surgery and which lasts beyond 6 months after surgery.

To generate high-quality evidence for the best preventive and treatment strategies for CPIP, it is imperative to use validated scales. To further enhance the comparability of scientific studies, these scales are ideally standardized and clearly described in the manuscript. [94] Since 33 different instruments could be identified among the included studies, it seems that consensus about the optimal instrument for the assessment of CPIP is still lacking.

Several pain assessment tools have been developed to measure different aspects of pain. Pain intensity is mostly measured using verbal rating scales (VRS), numerical rating scales (NRS) and visual analog scales (VAS). [95] In this review, we found that the VAS was

predominantly used (73% of studies). However, these PI scales only provide a global estimation of a patient's experience of pain, without considering all relevant aspects and consequences of chronic pain. To elaborate, chronic pain has a major impact on physical, emotional, and cognitive function. Furthermore, chronic pain can negatively affect patients' social life and their ability to work and secure an income which also has economic implications that extend beyond health care. [96] The importance of identifying the repercussions of chronic pain as perceived by the patient was demonstrated by Fredheim et al. [97] They found that patients with non-cancer related chronic pain reported a QOL that was lower when compared to the QOL of terminal cancer patients. IMMPACT and Kehlet et al therefore emphasized that, in order to perform a meaningful assessment of chronic pain, it is required to utilize quantitative measurement tools in conjunction with multidimensional qualitative tools like health-related QOL instruments to adequately assess the impact of chronic pain. [4,5] The Medical Outcome Survey Short-Form-36 (MOS SF-36 or SF36) is generally considered to be the gold standard in QOL measurement. The advantage of the generic SF36 is its broad implementation as it is well known by regulatory bodies and physicians. In addition, the SF36 is suitable for comparing changes in QOL between different diseases and treatments. However, some authors including Heniford et all argue that a disease-specific QOL measure is preferable to assess the impact of CPIP on QOL and patient satisfaction. [98] In this review, four hernia-specific QOL measures were identified among eight studies: the Carolina Comfort Scale (CCS) [76], the Inguinal Pain Questionnaire (IPQ [48], Activities Assessment Scale (AAS) [53] and a questionnaire based on the Danish Hernia Database (DHD). [99] Some studies used rating scales like the VAS to measure QOL. [62] There are also questionnaires available that incorporate assessment of PI (sensory dimension) and the degree of interference of chronic pain with aspects of daily life (reactive dimension). Examples of such questionnaires are the general McGill Pain Questionnaire, Short-Health Scale, Brief Pain Inventory (BPI) [100] and the hernia specific CCS and IPQ. Besides questionnaires, objective methods like pain evoked responses and quantitative sensory testing are gaining popularity but are not yet utilized on a regular basis. Deciding upon the appropriate questionnaire to use will likely remain challenging as long as consensus is lacking.

The majority of reviewed studies lacked a baseline measurement of PI and QOL. This is unfortunate, as baseline measurements are necessary for meaningful interpretation of postoperative results. Furthermore, preoperative pain is a known risk factor for developing CPIP and therefore holds clinical relevance that might be undermined when it is not incorporated into studies investigating CPIP. [101]

To reiterate, the literature concerning treatment and prevention of CPIP is highly heterogenic and inconsistent. Since a consensus measure is the only way to bring about more standardized and comparable results, CPIP literature will benefit from a common standard. This common standard should include one clear definition for the outcome measure CPIP, incorporating pain duration, pain intensity and the effects of chronic pain on daily activities.

Also, a common study methodology is needed that uses well-defined standard outcome parameters which are evaluated with validated instruments and a sufficient period of follow-up. Whether certain types of measurement tools should be recommended to further improve the uniformity among studies is open for discussion, for example by the Hernia-Surge Group that is currently designing a global guideline for the management of groin hernia. We recommend an easy to use, hernia-specific score incorporating assessment of both PI and QOL. Finally baseline measuring should become common practice and follow-up be done on standardized time points.

However, without an ambitious implementation plan designed to reach targeted groups, the impact of a common standard could be disappointing. Global recognition and awareness is essential and may be performed through the world wide hernia societies.

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PART 4

SUMMARY

DISCUSSION

FUTURE PERSPECTIVES

CHAPTER 8 Summary

In **Chapter 1** the subject of the thesis, chronic pain after common operations, is introduced. Common operation such as laparotomy, laparoscopy and inguinal hernia surgery can cause high rates of post-operative chronic pain leading to functional impairment, reduced quality of life and social- and economic consequences. These consequences together with high incidence rates makes that chronic post-operative pain must be considered as a major health problem. The exact cause of the pain is not always clear and both patient- and surgical related factors are of influence.

PART 1 CHRONIC PAIN AFTER ABDOMINAL SURGERY: ADHESIOLYSISYES

In the **first part** of the thesis chronic pain after abdominal surgery judged to be caused by adhesions is addressed

Chapter 2 reports the long term results of a randomized placebo controlled trial assessing the benefit of laparoscopic adhesiolysis in 100 patients with chronic abdominal pain attributed to adhesions. After 12-year follow-up patients in the adhesiolysis group were significantly less often free of pain (RR=1.30), had a higher intake of analgesics (RR=1.20), consulted medical specialists more often (RR=1.33) and had a higher rate of additional surgery (RR=1.67) because of persisting pain. Thus it was concluded that laparoscopic adhesiolysis was less beneficial than laparoscopy alone in the long term and that there is a powerful and long lasting placebo effect of laparoscopy. Since adhesiolysis is associated with an increased risk at surgical complications, avoiding this treatment will result in less morbidity and health care costs.

PART 2 CHRONIC PAIN AFTER INGUINAL HERNIA REPAIR: A SELF-GRIPPING MESH

In the **second part** studies are presented on the results of a self-gripping mesh for Lichtenstein repair of primary inguinal hernias in adult patients.

Chapter 3 describes the 5 year results of the patient cohort of 83 patients that was used as a pilot study for the HIPPO trial which compared a self-gripping mesh with a sutured mesh for the Lichtenstein hernioplasty (Chapter 4). CPIP was defined as any VAS score above zero lasting more than three months post-operatively. After a median follow up of 30 months 14.6% of patients in the self-gripping mesh group (n=41) reported CPIP compared to 23.8% in the suturing mesh group (n=42). After a median follow-up of 67 months this was reduced to 4.8% respectively 9.8%. It was also asked whether CPIP affected daily life. After 30 months this was true for 1 patient in the self-gripping mesh group (2.4%) and 3 patients in the sutured mesh group (7.1%). After 67 months this was reduced to 0% respectively 2.4%.

Severe pain (VAS>70) was only seen in the suturing mesh group. Two patients in the self-gripping mesh group and one in the sutured mesh group experienced a recurrent hernia. The operating time was shorter for the self-gripping mesh, because no time was needed to suture the mesh. This was the only outcome that different significantly between both groups.

Chapter 4 presents the results of the HIPPO trial. This randomized double blinded multi-center trial compared a self-gripping mesh with a sutured mesh for the Lichtenstein hernio-plasty. Results are based on 331 patients that were followed for 2 years. It turned out that the self-gripping mesh had comparable rate of CPIP, recurrence and other post-operative complications compared to the sutured mesh. The overall incidence of CPIP after 24 months was 4.6% and for recurrence rate this was 2.4% for the Progrip mesh and 1.8% for the sutured mesh. Patients reported significantly better pain and quality of life scores throughout the follow up period. The only significant difference that was found was the mean duration of surgery was 17% reduced for the self-gripping mesh.

In **Chapter 5** the long term results of the self-gripping mesh were further explored with a systematic review and meta-analysis of 10 RCTs enrolling 2541. Mean follow-up was 24 months (range 6-72 months). It had to be concluded that the self-gripping mesh is no solution to lower the incidence of CPIP; it has comparable results to a sutured mesh regarding the incidence of CPIP, recurrence and other late morbidity. However conclusions on long-term results are still based on relatively small patient numbers due to heterogeneity in CPIP definition, assessment, and presentation of outcome. The main advantage of the self-gripping mesh is its efficiency with consist significantly reduced operation times.

Chapter 6 presents the results of an in vivo study examining the reaction of macrophages to the self-gripping mesh which contains additional polylactic acid micro hooks on its lower surface. It turned out that the macrophages produced comparable amounts of pro- and anti-inflammatory cytokines to the self-gripping mesh and a standard mesh without the polylactic acid. Therefor it was concluded that polylactic acid does not have negative effects on mesh biocompatibility.

PART 3 CHRONIC PAIN: ASSESSMENT IN LITERATURE

In the **third part** the quality and comparability of the literature on chronic pain after inguinal hernia surgery is reported

Chapter 7 reports a_systematic review addressing the quality and uniformity of recent studies investigating CPIP. Eighty eligible studies were included. Only half of the studies provided a definition of their primary outcome CPIP and 22 different definitions of CPIP were identified. The chronic pain definition of the International Association for the Study of Pain was most often applied. Only 66% of the studies used a validated tool to evaluate CPIP

and 33 different tools were identified. The visual analogue scale and Short Form 36 were most commonly used for measuring PI (73%) and QOL (19%). When investigating chronic pain it is important not only to quantify CPIP but also to explore the repercussions for the quality of life. This was done by only 40% of the studies. A baseline score was performed by 45% of the studies and 75% had a follow-up of at least 12 months. It was concluded that the current literature addressing CPIP after inguinal hernia repair has a variable degree of quality and lacks uniformity in outcome measures. Proper comparison of study results to provide recommendations for prevention methods for CPIP therefore remains difficult.

CHAPTER 9 Discussion

Acute postoperative pain is followed by CPP in 10–50% of individuals after common operations and can be severe in 2-10% of these patients.[1] CPP must be regarded a major health problem because of its negative effect on QOL, social relationships and employment and because of its micro- and macro-economic drawbacks.

Whether CPP after abdominal surgery may be caused by adhesions is questionable. More certain is the inefficiency of laparoscopic adhesiolysis as a treatment method. It may reduce pain in the initial phase after treatment but there is no evidence for long-term efficacy of adhesiolysis for CPP (**Chapter 2)**.[2,3] Other drawbacks of laparoscopic adhesiolysis are the high rate of incompleteness of adhesiolysis especially in the case of so called 'cocoon' adhesions and the risk of bowel injury. Furthermore, it is important to realize that the development of CPP is multifactorial, influenced not only by surgical factors but also by physical, psychological, genetic and social factors. Examples of patient related risk factors are young age, female gender, expectations, lower preoperative optimism, anxiety for the operation and ineffective coping mechanisms.[4-6] In addition people who already experience chronic pain preoperatively are at greater risk to develop CPP after surgery. This may be due not only to genetic susceptibility or psychosocial characteristics, but also to changes in the nervous system.[1,7] It is hypothesized that persistent nociceptive input from injured peripheral nerves causes long lasting neuroplastic changes to the central nervous system with reduction in thresholds, amplification of responses and nervous hyperexcitability. This central sensitization increases the risk of CPP.[1] All these factors may explain why some patients develop CPP and others do not. A good illustration is given by Aasvang et al. He showed by quantitative sensory testing (QST) that sensory dysfunction as a result of nerve damage is apparent in many patients after groin hernia repair, both patients with and without CPP. [7,8]

The second part of this thesis focusses on chronic postoperative inguinal pain (CPIP) after inguinal hernia repair. Tension-free mesh techniques have revolutionized the procedure, but CPIP is still a challenging complication. Nerve injury is often cited as the most prominent causative factor. One way by which nerves can be damage is mechanical entrapment by devices used to fixate the mesh. [5] Every surgeon is aware of the risk of nerve entrapment in fixation sutures which causes the patient to have immediate severe postoperative pain. Rapid reoperation to release the entrapped nerve gives instant pain relief and when performed under local anesthesia the patient can sometimes exactly tell the surgeon which stitch has to be removed. In addition these penetrating sutures, staples and tacks may cause tension at anchor sites, additional foreign body reaction and periostitis when placed through the periosteal layer of the pubic bone.[9,10] Despite all this the atraumatic self-gripping mesh did not turn out to reduce the incidence of CPIP; the distribution of pain severity and QOL scores are comparable with a standard sutured mesh (**Chapters 2-4**). This should be interpreted through surgical- and patient- related factors as well as methodological factors.

Starting with the surgical factors it can be argued that the micro hooks are also inflicting trauma to the underlying tissues and nerves. This may be true, only that the ilioinguinal and

iliohypogastric nerve are protected by an investing fascia of the internal oblique muscle and a layer of areolar connective tissue. The genital branch of the genitofemoral nerve is covered by the deep cremasteric fascia. The micro hooks penetrate the tissue for 0.5mm which is not enough to penetrate the protecting perineural tissue, which of course should be left intact during dissection. A second point of discussion is that not all surgeons implementing the self-gripping mesh perform a truly sutureless procedure, because of concerns about recurrence. These concerns may be induced by the experience that the micro hooks are less sticking to the connective tissue (overlying the pubic bone: the area of a medial recurrence) compared to the muscle tissue. Thereafter extra suture fixation is in line with the recommendations made by Philipe Chastan. This French surgeon was involved in the development of the Progrip mesh and the first to publish his experiments with the Progrip mesh. He recommended surgeons to place one absorbable stitch at the pubic tubercle if concern exists for adequate overlap inferomedially to prevent recurrent hernia. Others have taken over this recommendation and because the surgeons participating in the HIPPO trial were trained by Chastan during a masterclass, this extra stitch was allowed to be placed in the trial protocol. However there are concerns about the effect of the extra stitch in this neuralgic position. Regarding our own RCT (**Chapter 4**) it was known that two participating surgeons as a rule placed this extra stitch in all patients regardless of the size or location of the hernia. We did not found increased pain levels or CPIP rates for the patients operated by these two surgeons. Of the RCTs included in the meta-analysis (**Chapter 5**) some surgeons consistently did not place the extra suture whilst others recommended case by case use of additional suture fixation in the self-gripping mesh group. None of the studies performed subgroup analysis whether the stitch induced more CPIP in patients. A retrospective analysis by Kohler et al of the Herniamed register did not show a correlation between the extra medial stitch and CPIP rates in more than 800 cases. The same applied to recurrence rates.[11] From this it may be concluded, that although seemingly of no influence on CPIP rates, it could be recommended to avoid the single stitch in this neuralgic place.

The Adhesix mesh (Bard, USA) is another concept of self-gripping meshes. In contrast to the Progrip mesh it is not based on mechanical fixation, but it has a synthetic adhesive coating made of polyethylene glycol (PEG) / polyvinylpyrolidone (PVP) and activated by moist tissue. Only one clinical trial on Adhesix™ mesh has been published and reported promising results without recurrences after Lichtenstein repair, but follow up was only three months. [12] A retrospective study with a follow up of three year reported 7% of patients with CPIP. [13] There are no RCTs comparing the Progrip and Adhesix mesh. Gruber-Blum et al compared both self-gripping meshes in an animal experimental model and showed a significantly higher dislocation tendency for the Adhesix mesh compared to the Progrip mesh. The reason for this was not clear and requires further investigation. [14]

How about other non-traumatic fixating devices like fibrin sealant, n-butyl-2 cyanoacrylate (NB2C) glues or the self-adhesive mesh? The present literature on the effect of glue

versus sutures on the rate of CPIP is not very conclusive. There are five meta-analysis, one concluded that glue did not provide any significant advantage [15], one concluded that there is insufficient evidence to promote fibrin sealant [16], two showed a reduction of CPIP [17,18], but one of these underlined the poor quality of the trials [19], and another study concluded that glue contributed to reduce postoperative pain and early chronic pain (3-6 months) but not late chronic pain [20].

To conclude, there is insufficient evidence to promote glue or self-gripping meshes rather than suture fixation during Lichtenstein hernioplasty. In addition, meta-analysis exploring other open mesh techniques using the Prolene Hernia system (PHS) or other mesh plugs have shown no difference in the rate of CPIP for the open mesh techniques.[21,22]

The trials investigating the Progrip mesh assumed that CPIP is mainly caused by neuropathic pain caused by mechanical entrapment of nerve fibers by devices used to secure the mesh, however entrapment can also be caused by the mesh itself and neuropathy is not only mechanically induced. Nerves can also be damaged during the dissection and diathermic heat. In addition there is a role for the immune system. The implanted mesh (and sutures) elicits an inflammatory and fibrotic response that imparts strength to the hernia repair, but on the other side may cause neuropathological effects in adjacent nerves. This immune response, also called the foreign body reaction (FBR), is highly dependent on mesh biocompatibility which is mainly determined by its material and structure. The Progrip mesh is a composited macroporous mesh made of standard monofilament polyester or polypropylene supplemented with resorbable polylactic acid (PLA) micro hooks**.** Since the Progrip mesh did not reduce CPIP rates an important question is whether the material characteristics or disintegration of the PLA micro hooks trigger possible inflammatory reactions which negatively affect the occurrence of CPIP. In an experimental rat model by Kolbe et al, no increased tissue reaction could be determined in comparison with conventional polypropylene. [23] Studies in humans are not available. Since macrophages play an important role in directing the intensity and balance of the host immune response we analyzed the macrophages reaction to the Progrip mesh in an in vitro model of human primary macrophages and determined the production of pro- and anti-inflammatory cytokines. (**Chapter 6**). Macrophages seeded on the Progrip mesh produced a commensurate amount of both pro-inflammatory and anti-inflammatory/repair proteins compared to a pure polyester mesh reflected in the same M1/M2 index. It was concluded that the polylactic micro-hooks did not alter the acute response of the macrophages. Whether this also means comparable inflammatory damage to tissues and nerves is not clear, because of the limitations in translating the results of the in vitro model to the in vivo situation. First it is a mono cellular evaluation not enchanting for all the other cells involved in the FBR. Thereafter the artificial circumstances eliminate surgical factors. Nevertheless the in vitro model will help to investigate whether some unwanted side effects as CPIP are likely to be due to the type of mesh implanted or that other factors might be more important.

Of the surgical factors only the type of mesh fixation was changed in the HIPPO trial. The anterior approach to the inguinal hernia / orifice still encompassed dissection during which tissues and nerves can be damaged. The inguinal nerves run in the plane anteriorly to the transversalis fascia. Therefore some might wonder why to perform an open anterior approach at all. The laparoscopic posterior techniques have shown faster recovery times and lower CPIP risk.[24,25] However this disregards the surgeons' obligation to tailor treatment based on expertise, local/national resources, and patient and hernia related factors. For high-risk patients with extensive comorbidities or patients with pelvic scarring an open mesh repair (under local anesthesia) is still the preferred technique as is the case for recurrent inguinal hernia after laparoscopic repair according to the world guidelines for groin hernia management 2016.

Other surgical factors that may be of influence on CPIP are handling of the inguinal nerves and hernia sac, type of anesthesia, experience of the surgeon and postoperative complications. [4,26] Due to randomization these factors were evenly distributed among the two groups in de HIPPO trial (**Chapter 4**). Regarding the experience of the surgeon, it was suggested by Kingsnorth that the Progrip mesh would show its benefit especially in the hands of inexperienced surgeons less able to identify nerves and keeping them away from the mesh or accidentally suturing the periostal layer of the pubic bone.[27] Although not proving, this suggestion was not confirmed by the results of the HIPPO trial in which most patients were operated by residents.

Besides surgical factors methodological factors have to be addressed when interpreting the literature on CPP. The burden of CPP for a significant surgical patient population and global health care has driven many investigators to find adequate preventative measures relevant to surgical practice. One drawback of published CPIP literature is the lack of consensus regarding the definition of CPP and a golden standard research approach. Study methods and outcome measures differ highly between studies making it difficult to compare study results and to conduct meta-analysis and systematic reviews. Thereafter validity is sometimes questionable with studies lacking baseline measures, power calculations, lack of control groups to adjust for confounders, unblinded pain assessment by the study investigator itself, assessment of pain by telephone interviews or using unvalidated questionnaires, no definition of the primary outcome parameter, insufficient follow-up etc. However it is always easy to point out the mistakes of others. Sometimes a retrospective cohort study is just used to have a quick indication of a research question after which a formal RCT can be deployed. We did it the same way with the HIPPO trial. Furthermore the trials in this thesis also have their imperfections; we did not see all patients on the outpatient clinic for follow-up, we did not perform quantitative sensory testing to analyze sensory dysfunction, we could have performed a more exhaustive evaluation of patient related risk factors for CPIP, there was no uniformity in the type of anesthesia and operating surgeons, we did allow the extra stitch in the HIPPO trial, we did not perform subgroup analysis…..

So clinical trials in their essence are hardly ever perfect and researchers learn by the way. However it would be helpful and beneficial for the quality and comparability of research to have a broad accepted and well defined disease specific uniform research strategy with pre-defined outcome measures, follow-up times and validated assessment tools.

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CHAPTER 10 Future perspectives

It is clear that CPP is common and may develop more or less after the whole spectrum of surgical treatments. Therefore it is important to accept that CPP can arise after surgery and to raise awareness amongst healthcare professionals and patients alike.[1] Information on CPP has to be a component of informed consent for surgery. Some patients, if given accurate data about the risk of CPP, might decide against having operations that are not entirely necessary. Thereafter, CPP needs to be considered in the indications for surgery, especially in the case of inguinal hernia surgery and chronic abdominal pain since not cure but quality of life is the main outcome of it. The evaluation and advice of a dedicated anesthesiologist part of the hospitals pain team may add in this. Last, the awareness of CPP has to lead to more attention to intra- and post-operative pain management since the intensity of pain in the days and weeks after an operation is one of the strongest and most consistent risk factors for CPP. The approach of so-called "preventive or preemptive analgesia" by the use of pre-operative local anesthesia has to become common practice.[2-4].

As CPP is notoriously difficult to treat it is desirable to prevent its development. Besides focusing on surgery related factors, patient related factors deserve the same attention or even more. It is known that some patients are more at risk to develop CPP than others. Hence it would be advantageous to have a pre-operative patient specific risk model for the occurrence of CPP. This risk model may contain

1) General patient related risk factors
2) Results of Quantitative Sensory Testing (QST); a systematic review of predictive experimental pain studies of QST has already shown that the preoperative pain response to a nociceptive stimulus correlates with the intensity of early postoperative pain. This is not very accurate yet so further fine tuning is required.
3) Genotyping; there seems to be a genetic susceptibility for CPP. Identification of certain 'pain genes and enzymes' like the COMT genes, GTP hydroxylase and DQB1*03:02 HLA haplotype are already promising. [5].

Preoperative psychometric evaluations of vulnerability, anxiety, depression and pain catastrophizing have shown to be less predictive.[6]

In patients that turned out to be at very high risk for CPP the medical indication for surgery has to be called into question.

Regarding surgical factors during hernia surgery, it would be helpful to get more insight in the clinical and personal surgical performance. A national or (preferably) international registry of inguinal hernia patients can add in this. Good examples are the EuraHS and the Danish Hernia Registry or a national registry within the Dutch Institute for Clinical Auditing. These registries can also be used to answer various research questions that require large patient cohorts. It is of utmost important that everyone is willing to participate in the registry, that data are inputted correctly and completely. Registration will also facilitate more uniform operative notes that record all steps that may be involved in the occurrence

of postoperative pain. This will also help surgeons and residents to pay attention to these important steps in inguinal hernia surgery.

Another problem is that many modifications of the Lichtenstein technique are practiced and compliance among surgeons and residents with Amid's guidelines is variable. [7] [8] This may be a lack of unawareness, skepticism or inadequate anatomical knowledge. Since residents learn the technique from their supervising senior residents and surgeons there is a risk of inconsistencies to sustain. Regarding the complexity of inguinal hernia surgery, especially with regard to a three nerve-sparing approach, outcomes may be improved when inguinal hernia surgery is only performed and taught by certified abdominal wall hernia surgeons as is the case for all other surgical treatments. They should be familiar with the repair techniques, anatomy, especially the most common inguinal nerve distribution patterns and variants, mesh related issues, risk factors for CPIP and local anesthesia techniques. Only in that case surgical patient specific "fine tuning" would be possible.

Thereafter a revision of residents training should be considered. A survey among Dutch residents (presented at the World Congress on Hernia Surgery 2016) revealed that most residents start with inguinal hernia surgery before a full understanding of the anatomy and with limited laparoscopic skills. This is not an efficient way of learning.[9] Since case numbers can no longer be guaranteed in the operation room and society no longer accepts morbidity that is associated with trainee errors, residents better prepare themselves outside the OR [10]. This will also enable them to focus on more complex issues inside the operating room and take the maximal teaching experience out of the exposure in the OR. Outside training programs are already part of the training of surgical trainees, but inguinal hernia surgery is under represented and / or scheduled too late in the curriculum. Thereafter most still focus on the open procedures and hands on inguinal hernia courses are not a regular part of the program. Resources such as the Surgical Council on Resident Education (SCORE) may help to enhance common knowledge. In addition simulation enables residents to practice manual dexterity and their knowledge of the anatomy and different steps of repair techniques and would be a perfect preparation or warming up for OR experience especially when used in a distributed manner.[11]

CPIP and CPP literature will benefit from a common standard formulated by an international collaboration of dedicated abdominal wall hernia surgeons like the Hernia Surge Group. This common standard should contain a clear definition of CPIP. Considering the effect of CPIP on daily life this definition has to include not only a measure of time and pain intensity but also a description of pain-related impairment. Other elements which may be part of this common standard are a description of the ideal study methodology. This may enhance the comparability and quality of studies. Items to be included are at least 1) baseline scoring of pre-operative pain, QOL and risk factors for CPIP, 2) well-defined standard outcome parameters, 3) detailed assessment of the location, characteristics, and evolution of painful symptoms and associated changes in neurologic function, 4) follow-up

by independent assessors on standardized time points during at least 2 year, 5) standard validated measurement tools, 6) uniform nerve management. Regarding point 5 an easy to use, hernia-specific tool incorporating assessment of both PI and QOL is strongly recommended. Good examples are the Inguinal Pain Questionnaire and the Caroline Comfort Scale. However, without an ambitious implementation plan designed to reach targeted groups, the impact of a common standard could be disappointing. Global recognition and awareness is essential and may be accomplished through the world wide hernia societies.

Finally, CPP is expressed against a complex physiological, genetic, and psychosocial background, which contributes not only to the conversion of somatosensory activity into a pain experience, but also to the amplitude of a reaction to the pain sensation and to related changes to mood and behavior. The complex way in which these factors interplay with each other needs a multidisciplinary pre- and post-operative approach directed by the (hernia) surgeon in narrow collaboration with an anesthesiologists dedicated to CPP and able to address the psychosocial factors involved in CPP.

To conclude, due the multifactorial etiology of CPP it is virtually impossible to isolate a single causative factor responsible in the development of CPP. Only a multipronged approach can provide a strong tool to reduce the impact of CPP. Prevention still remains the panacea to CPP.

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APPENDICES

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INTRODUCTIE

Chronische postoperatieve pijn (CPP) is een veelvoorkomende complicatie na openbuik operaties of liesbreukoperaties. Dit leidt bij patiënten tot een verminderde kwaliteit van leven en mede door de prevalente aard van deze ingrepen ook tot economische gevolgen doordat mensen meer gezondheidszorg consumeren en soms niet in staat zijn om te werken. Tot wel 50% van de patiënten ervaart chronische pijn na operaties waarvan 5% ernstige pijn heeft. In de introductie van dit proefschrift (hoofdstuk 1) wordt een overzicht gegeven van de definitie, pathofysiologie en behandeling van CPP. De precieze oorzaak van CPP is niet geheel duidelijk, maar bekend is dat zowel patiënt gebonden als operatie gerelateerde factoren een rol spelen Risicofactoren zijn onder andere het hebben van ernstige pijn gedurende meer dan een maand voor de operatie, psychologische kwetsbaarheid, het vrouwelijke geslacht, jonge leeftijd, maar ook genetische factoren. Op het chirurgische vlak zijn de chirurgische techniek, benadering en duur van de operatie als risicofactor geïdentificeerd. Pijn kan worden onder verdeeld in weefselpijn (nociceptieve pijn) en zenuwpijn (neuropatische pijn). Nociceptieve pijn ontstaat ten gevolge van weefselbeschadiging (zoals bij een operatie) of ontsteking. Neuropatische pijn ontstaat door de beschading van een zenuw welke vervolgens pijnsignalen blijft afgeven naar de hersenen. Bij neuropatische pijn is men nooit zonder pijn, omdat de zenuwbeschadiging niet weg gaat. Zenuwpijn is vaak scherp van aard alsof er met naalden geprikt wordt of kan lijken op een elektriciteit schok.

DEEL 1 CHRONISCHE PIJN NA BUIK OPERATIES: HET NUT VAN ADHESIOLYSE

In het **eerste deel** van dit proefschrift wordt ingegaan op chronische pijn ten gevolge van littekenweefsel, adhesies, ontstaan na een open buik operatie.

In **hoofdstuk 2** worden de lange termijn resultaten beschreven van een placebo gecontroleerd onderzoek naar het nut van laparoscopische adhesiolyse (het doornemen van adhesies tijdens een kijkoperatie) bij patiënten met buikpijn toegeschreven aan postoperatieve adhesies. Na 12 jaar bleken de patiënten die behandeld waren met laparoscopische adhesiolyse significant vaker nog pijn te hebben (RR=1.30), meer pijnstillers te gebruiken (RR=1.20), vaker een medisch specialist te consulteren (RR=1.33) en vaker opnieuw te zijn geopereerd (RR=1.20) vanwege persisterende buikpijn in vergelijking met patiënten die alleen een kijkoperatie hadden ondergaan zonder aanvullende adhesiolyse. Er wordt dan ook geconcludeerd dat laparoscopische adhesiolyse niet zinvol is in de behandeling van chronische buikpijn op basis van adhesies maar ook dat een kijkoperatie een langdurig placebo effect kan hebben. Aangezien adhesiolyse gepaard kan gaan met chirurgische complicaties wordt geadviseerd deze behandeling te mijden.

DEEL 2 CHRONISCHE PIJN NA LIESBREUK HERSTEL: EEN ZELF KLEVENDE MAT

In het **tweede deel** van dit proefschrift worden de effecten op chronische post operatieve pijn van een zelf klevende mat voor het herstel van een liesbreuk bij volwassen patiënten beschreven. Het herstel van de liesbreuk gaat volgens de Lichtenstein plastiek, een van de meest gebruikte technieken om een liesbreuk te herstellen. Bij de Lichtenstein plastiek wordt de breukpoort in de lies afgedicht door aan de voorzijde van de buikwand een mat te plaatsen over deze breukpoort heen. Hierna wordt de mat gefixeerd met niet oplosbare hechtingen.

Hoofdstuk 3 beschrijft de vijf jaar resultaten van een cohort van 83 patiënten die als pilotstudie gebruikt zijn voor de HIPPO trial (Hoofdstuk 4). De hypothese was dat het gebruik van een zelf klevende mat voor het herstel van een liesbreuk volgens de Lichtenstein plastiek minder post operatieve pijn geeft in vergelijking met een mat die wordt gefixeerd met hechtingen. Chronische post-operatieve inguinale pijn (CPIP) was gedefinieerd als elke VAS (pijn) score groter dan 0, die drie maanden na de operatie nog aanwezig was. Na een follow-up van 30 maanden meldde 14.6% van de patiënten in de groep met de zelfklevende mat (n=41) CPIP ten opzichte van 23.8% van de patiënten in de standaard Lichtenstein plastiek groep (n=42). Na een follow-up van 67 maanden was de incidentie van CPIP gedaald naar 4.8% respectievelijk 9.8%. CPIP was van invloed op de dagelijkse kwaliteit van leven in 2.4% respectievelijk 7.1% van de patiënten na 30 maanden en 0% respectievelijk 2.4% na 67 maan-den. Ernstige pijn (VAS>70) werd alleen gezien in de standaard Lichtenstein groep. Het recidief percentage was 4.8% voor de zelf klevende mat en 2.4% voor de standaard mat. De operatietijd was significant korter voor de zelfklevende mat. Deze resultaten waren de basis voor het starten van de de HIPPO trial, die beschreven is in **Hoofdstuk 4**. Dit dubbel blinde gerandomiseerde onderzoek vergelijkt een zelf klevende mat met een mat gefixeerd met niet oplosbare hechtingen voor het herstel van een liesbreuk volgens de Lichtenstein plastiek. De resultaten zijn gebaseerd op een groep van 331 patiënten die 2 jaar lang gevolgd zijn. De zelf klevende mat had een vergelijkbare incidentie van CPIP, recidief hernia en andere post-operatieve complicaties als de gehechte mat. De incidentie van CPIP na 24 maanden was 4,6% voor de gehele groep. Het recidief percentage was 2.4% voor de zelfklevende mat en 1.8% voor de gehechte mat. De operatietijd was significant (17%) korter voor de groep waarbij de zelfkle-vende mat gebruikt werd.

In **hoofdstuk 5** zijn de lange termijn resultaten van de zelf klevende mat verder onderzocht middels een systematische review van de literatuur waarna een meta-analyse van 10 gerandomiseerde onderzoeken met in totaal 2541 patiënten is verricht. De gemiddelde follow up was 24 maanden (varierend tussen 6-72 maanden). Uit de analyse kon worden geconcludeerd dat de zelf klevende mat geen oplossing biedt voor het ontstaan van CPIP. De incidentie van CPIP, recidief hernia en andere lange termijn morbiditeit was vergelijkbaar voor beide matten. Echter hierbij moet wel worden opgemerkt dat conclusies nog altijd

gebaseerd zijn op relatief korte follow-up en kleine aantallen patiënten ten gevolge van heterogeniteit in de definitie en meting van CPIP en de wijze waarop uitkomsten worden weergegeven. Het belangrijkste voordeel van de zelf klevende mat is zijn efficiëntie hetgeen leidt tot een significante verkorting van de operatietijd.

Hoofdstuk 6 presenteert de resultaten van een in vivo studie naar de reactie van macrofagen op de polymelkzuur haakjes aan de onderzijde van de zelfklevende mat. De reactie van macrofagen en de productie van pro- en anti-inflammatoire cytokinen was vergelijkbaar voor de zelf klevende mat en een standaard polypropyleen mat zonder de polymelkzuur haakjes. De polymelkzuur haakjes lijken dus geen negatieve invloed te hebben op de biocompatibiliteit van de mat.

DEEL 3 CHRONISCHE PIJN: DE BEOORDELING

In **deel drie** wordt in gegaan op de kwaliteit en uniformiteit van de literatuur betreffende chronische pijn na liesbreuk operaties.

Hoofdstuk 7 vermeldt de resultaten van een systematisch literatuur onderzoek naar de kwaliteit en uniformiteit van onderzoeken naar CPIP. In het systematische onderzoek werden 80 studies geïncludeerd. Slechts de helft hiervan vermeldde een definitie van de primaire uitkomstmaat CPIP. In totaal werden 22 verschillende definities geïdentificeerd waarvan de definitie van de Internationale organisatie voor de studie naar pijn (IASP) de meest gebruikte definitie was. In 66% van de studies werd gebruik gemaakt van een gevalideerde vragenlijst om de aanwezigheid van CPIP te evalueren en er werden 33 verschillende vragenlijsten geïdentificeerd. De visual analogue scale (VAS) en de Short Form 36 (SF36) waren de meest gebruikte gevalideerde vragenlijsten voor het meten van pijn intensiteit en de kwaliteit van leven. Bij het onderzoeken van chronische pijn is het belangrijk om niet alleen de kwantiteit van de pijn te meten maar om ook de effecten ervan op het dagelijks leven te meten. Dit werd gedaan door slechts 40% van de studies. Een 0 meting werd verricht in 45% van de studies en 75% vervolgde de patiënten tenminste 12 maanden.

Er werd geconcludeerd dat de huidige literatuur naar CPIP na herstel van een liesbreuk zeer varieert in kwaliteit en er een gebrek is aan uniformiteit. Dit bemoeilijkt een goede vergelijking tussen de uitkomsten van de studies en daarmee het maken van breed gefundeerde aanbevelingen voor de preventie van CPIP.

CURRICULUM VITAE

Marijke Molegraaf werd geboren op 20 augustus 1984 in Rotterdam samen met haar broer en zus. Haar jeugd bracht ze door in Barendrecht. Nadat ze in 2002 cum laude haar Gymnasium diploma behaalde aan de CSG Johannes Calvijn te Rotterdam, is zij geneeskunde gaan studeren aan de Universiteit Leiden. Tijdens de opleiding kreeg ze de mogelijkheid haar passie voor reizen te combineren met onderzoek en coschappen in onder andere Indonesië, Nepal en Suriname. In 2008 studeerde zij af en begon haar chirurgische carrière in het Groene Hart Ziekenhuis in Gouda. Hier werd zij door Dr. D. Swank en Dr. C. Baeten geïnspireerd tot het opzetten van haar eigen trial naar de invloed van een zelf klevende mat op chronische pijn na liesbreuk operaties. Dit leidde al snel tot een opleidingsplek voor de Heelkunde. Haar opleiding tot chirurg volgde ze in het Groene Hart Ziekenhuis in Gouda (Dr. R. Ottow, Dr. R. Schmitz), Leids Universitair Medisch Centrum in Leiden (Prof. dr. J. Hamming) en het Jeroen Bosch Ziekenhuis in Den Bosch (Dr. K. Bosscha, Dr. O. Koning) met als aandachtsgebied vaatchirurgie. Tijdens haar periode in het LUMC reisde zij via de Morogoro support foundation (Dr. M. Visser, Prof. D. F. Breedveld) opnieuw naar het buitenland om te opereren in het St. Kizito Hospital, Mikumi, Tanzania. Ondertussen bemachtigde ze een promotieplek bij de REPAIR groep in het Erasmus MC onder leiding van Prof.dr. J. Lange. Inmiddels is zij Europees gecertificeerd vaatchirurg en als fellow vaatchirurgie werkzaam in het Amphia Ziekenhuis te Breda.

LIST OF PUBLICATIONS

Molegraaf MJ, Baeten C, Swank J, Less chronic pain after Lichtenstein hernioplasty using the self-gripping Parietene Progrip Mesh, a 5 year follow-up retrospective study.

Molegraaf MJ, Torensma B, Grotenhuis B, de Ridder V, Lange J, Swank J, The HIPPO trial, a randomized double-blind trial comparing self-gripping parietex progrip mesh and sutured parietex mesh in Lichtenstein hernioplasty, a long-term follow-up study, Annals of Surgery 2017

Molegraaf MJ, Kaufmann R, Lange JF, Comparison of a self-gripping mesh and a sutured mesh in Lichtenstein Hernioplasty; a Meta-analysis, Surgery 2017

Molegraaf MJ, Grotenhuis N, Lange JF, Influence of polylactic acid supplementation on the biocompatibility of a polyester mesh for hernia repair using a in proved in vitro model Submitted

Molegraaf MJ, Torensma B, Grotenhuis B, de Ridder V, Lange J, Swank J, 12 Year outcomes of laparoscopic adhesiolysis in patients with chronic abdominal pain: a randomized clinical trial, Surgery 2017

Molegraaf MJ, Lange J, Wijsmuller AH, Uniformity of chronic pain assessment after inguinal hernia repair, a critical review of literature, European Surgical Research. 2017

LIST OF PRESENTATIONS

Less chronic pain after Lichtenstein hernioplasty using the self-gripping Parietene Progrip Mesh, a Pilot study
SEOHS 2009

The Need to learn (hernia surgery)
1st World Conference on Abdominal Wall Hernia Surgery, Milaan, 2015
invited speaker

The HIPPO trial, a randomized double blind trial comparing self-gripping Parietex Progrip Mesh and sutured Parietex Mesh in Lichtenstein hernioplasty; a long term follow-up study
European Hernia Society Conference, Rotterdam, 2016

Influence of polylactic acid supplementation on the biocompatibility of a polyester mesh for hernia repair using an in proved in vitro model
European Hernia Society Conference, Wenen, 2017

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Lieve Wouter, je bent het mooiste wat mij overkomen is. Je werd een fijne afleidende factor hetgeen mijn promotie goed heeft weten te vertragen, maar zonder jouw onvoorwaardelijke steun, vertrouwen, adviezen, humor en liefde was het überhaupt niet gelukt. Nu jij nog. En daarna nog meer tijd om samen te genieten van de toekomst! Ik hou van je!

PHD PORTFOLIO

Name PhD student:	Marijke Molegraaf
Erasmus MC Department:	Surgery
Research School:	REPAIR
PhD period:	July 2012 - Okt-2017
Promotor(s):	Prof. Dr. Johan F. Lange
Supervisors:	Prof. Dr. Johannes Jeekel
	Prof. Dr. Gert-Jan Klein Rensink

	Year	ECTS
Courses		
- Precourse RICH congress	2010	1.0
- Basic introduction course on SPSS	2012	1.0
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek)	2012	1.5
- Hernia course, Covidien, Hamburg	2013	1.0
- Laparoscopic component separation technique by Prof. Dr. Lars N. Jorgensen, Kopenhagen	2016	1.0
- Precourse European Hernia Congres, Wenen	2017	1.5
Presentations		
- Regionale Wetenschapsdag Regio Leiden - ' De HIPPO trial: Hernia Inguinalis Parietex versus Parietex Progrip Onderzoek'	2010	1.0
- Assistentencarrousel Groene Hart Ziekenhuis- ' The femoral hernia'	2010	1.0
- Regionale Wetenschapsbespreking, LUMC - 'The HIPPO trial, a randomized double blind trial comparing self-gripping Parietex Progrip Mesh and sutured Parietex Mesh in Lichtenstein hernioplasty; a long term follow-up study'	2012	1.0
- SEOHS, Amsterdam - 'Less chronic pain after Lichtenstein hernioplasty using the self-gripping Parietene Progrip Mesh, a Pilotstudy'	2012	1.0
- World Congress on Hernia Surgery, Milaan - 'The Need to learn (hernia surgery)'	2015	1.0
- European Hernia Congres, Rotterdam - 'The HIPPO trial, a randomized double blind trial comparing self-gripping Parietex Progrip Mesh and sutured Parietex Mesh in Lichtenstein hernioplasty; a long term follow-up study'	2016	1.0
- Wetenschapsdag Jeroen Bosch Ziekenhuis - ' The HIPPO trial'	2016	1.0
- European Hernia Congres, Wenen - ' Influence of polylacid acid supplementation on the biocompatibility of a polyester mesh for hernia repair using a in proved in vitro model'	2017	1.0
Conferences and seminars		
- Regionale Wetenschapsbespreking, LUMC	2010	1.0
- RICH: 6th Rotterdam Interactive Congress on Hernia	2010	1.0
- SEOHS, Amsterdam	2012	1.0
- 5th International Hernia Congress, New York	2012	1.0
- World Congress on Hernia Surgery, Milaan	2015	1.0
- European Hernia Congres, Rotterdam	2016	1.0
- Wetenschapsdag Jeroen Bosch Ziekenhuis	2016	1.0
- European Hernia Congres, Wenen	2017	1.0

-	Chirurgendagen	2016-2017	6.0
Teaching			
-	Klinisch les hernia's, Groene Hart Ziekenhuis	2010	1.0
-	Practicum introductie cursus eerste jaars assistenten Heelkunde, Orthopedie, Plastische chirurgie	2014-2016	4.0
Totaal			34