Pain and convalescence following laparoscopic ventral hernia repair

Effect of different mesh fixation techniques

Jens Ravn Eriksen

This review has been accepted as a thesis together with three previously published papers by University of Copenhagen 1st of January 2011and defended on 6th of May 2011.

Tutor: Jacob Rosenberg.

Official opponents: Jørgen Berg Dahl, Agneta Montgomery & Michael Bau Mortensen.

Correspondence: Department, Department of Surgical Gastroenterology, Herlev Hospital, Herlev Ring vej 75, 2730 Herlev, Denmark.

E-mail: jravn@dadlnet.dk

Dan Med Bull 2011;58: (12) B4369

THE 3 ORIGINAL PAPERS ARE

I. Eriksen JR, Poornoroozy P, Jørgensen LN, Jacobsen B, Friis-Andersen HU, Rosenberg J. Pain, quality of life and recovery after laparoscopic ventral hernia repair. Hernia 2009; 13: 13–21.

II. Eriksen JR, Bech JI, Linnemann D, Rosenberg J. Laparoscopic intraperitoneal mesh fixation with fibrin sealant (Tisseel®) vs. titanium tacks: a randomised controlled experimental study in pigs. Hernia 2008; 12: 483–91

III. Eriksen JR, Bisgaard T, Assaadzadeh S, Jørgensen LN, Rosenberg J. Fibrin glue versus titanium tacks for mesh fixation in laparoscopic ventral hernia repair: a double-blinded randomised controlled trial. Br J Surg 2011; 98: 1537-45

DEFINITIONS

Short-Form 36 (SF-36)

The SF-36 questionnaire is a generic health-related quality of life questionnaire. It includes eight scale scores from which two summary measures can be calculated: the physical component score formed by 'physical functioning', 'role physical', 'bodily pain', and 'general health' perceptions, and the mental component score covered by the scores 'vitality', 'social functioning', 'role emotional' and 'mental health'. For all scales higher scores represent better functioning and outcome.

Fibrin sealant (FS)

FS is manufactured in Denmark under the commercial name Tisseel®. It is a two-component tissue glue composed of human derived fibrinogen and thrombin. When fused, the two components form an adhesive clot mimicking the last steps in the coagulation cascade. The product is degraded within two weeks after application.

Pain and its assessment

In 1986 the International Association for the Study of Pain defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [1]. When pain is measured in clinical settings it is important to acknowledge, that pain is complex and that pain scores reflect an individual's subjective sensation combined with emotional and cultural experience. Acute postoperative pain is caused by inflammation and tissue damage, also called nociceptive pain. A simple relation between the extent of tissue damage and the amount of pain reported by the patient is not apparent [2], and pain perception is influenced by many parameters including anesthesia method, postoperative analgesic regimens and surgical technique. Nociceptive pain is sensitive to opioid analgesics, local analgesics, paracetamol and non-steroidal anti-inflammatory drugs. Neuropathic pain is related to nerve damage and causes superficial paraesthesis. This pain type is only semi-sensitive to opioid. The term chronic pain is used when pain continues for more than three months postoperatively [3]. The theory behind chronic pain is the sequence of peripheral nerve injury, central sensitization, neural plasticity and dysfunctional adaptations of neurons in the pain-regulating system [4].

In Study I and Study III, pain was assessed quantitatively by patient-reported scores, measured on a visual analogue scale (VAS) and a verbal rating scale (VRS). A 0–100 mm VAS was used with 0 mm = no pain and 100 mm = worst possible pain. The VRS was constructed as '0' = no pain, '1' = light pain, '2' = moderate pain and '3' = severe pain. Both methods measure pain in a one-dimensional way. In practice, the visual analogue scales can be interpreted as a continuous interval scale. To asses the impact of pain on patients daily life, pain was measured both at rest and during activity.

Mesh

A mesh refers to a prosthetic net used for closure and reinforcement of hernia defects to obtain tension-free repairs. They consist of polypropylene, polyester or expanded polytetrafluoroethylene (ePTFE) and differ in pore size, barrier coating, prize and ease of handling.

All values and results referred in this PhD thesis are median (range) if not stated otherwise.

INTRODUCTION

A ventral hernia is defined as a fascial defect located to the abdominal wall (Figure 1). Primary ventral hernias are classified as umbilical, epigastric, Spighelian and lumbar hernias, and secondary ventral hernias are incisional hernias developed in former postoperative scars [5]. Ventral hernia repair is a common surgical procedure. In Denmark (5.5 million inhabitants) around 3500 ventral hernia repairs are done annually [6]. Most ventral hernias are small umbilical and epigastric hernias, but around 30 % of the procedures are incisional hernia repairs and half of these are performed laparoscopically [6].

The treatment of ventral hernia disease has evolved over decades. As open mesh repair was introduced instead of open suture repair, the overall recurrence rate significantly decreased from 63 % to 32 % [7]. Even for small hernia defects (<10 cm2) the recurrence rate dropped significantly from 67 % to 17 % when mesh was used [7]. For the first time it was documented that mesh repair reduced recurrence rate, and tension-free repair with mesh was accepted as the new gold standard.

At the same time laparoscopic ventral hernia repair (LVHR) was developed and introduced in 1993 [4]. A general optimism for minimal invasive surgery helped the technique to be quickly accepted and implemented, although no data had documented its superiority.

The first RCT comparing open and laparoscopic ventral hernia repair was published in 1999 [9]. Recently, a meta-analysis including 526 patients from eight randomized trials concluded, that laparoscopic repair resulted in less infectious complications and a tendency towards shorter hospital stay and fewer haemorrhagic complications, compared with open repair [10]. No difference in recurrence rate was found in the randomised trials, 3.4 % (lap) versus 3.6 % (open), and it equals the average recurrence rate of 4.5 % found in a pooled analysis of all published series with more than 50 LVHRs [11].

A low recurrence rate and acceptable complication rate after LVHR has turned the focus on pain. Laparoscopic surgery has often been considered as less painful than similar open surgery, but that is not the case in ventral hernia repair. Three RCTs comparing open vs. laparoscopic ventral hernia repair found no difference in acute or chronic pain between the two procedures [12–14]. It is a general clinical experience that patients suffer intense pain after LVHR and postoperative pain is one of the most challenging and remaining problems following LVHR. Unfortunately, no detailed data describing pain and convalescence after LVHR are available in the literature, and therefore, pain intensity and its impact on convalescence, quality of life and general well-being has remained unknown.

The use of titanium tacks for mesh fixation in LVHR is the most likely explanation of postoperative pain as this fixation technique can cause bleeding, haematoma, nerve injury and adhesions due to its invasive and permanent nature.

Based on this knowledge the overall objective of this PhD thesis was to modify existing operative techniques to reduce postoperative pain following LVHR.

The methodological strategy to achieve this goal was based on three steps:

1. Is there a problem and what is it? Examine the impact of postoperative pain after LVHR by a detailed quantification and description of pain and convalescence after LVHR (Study I).

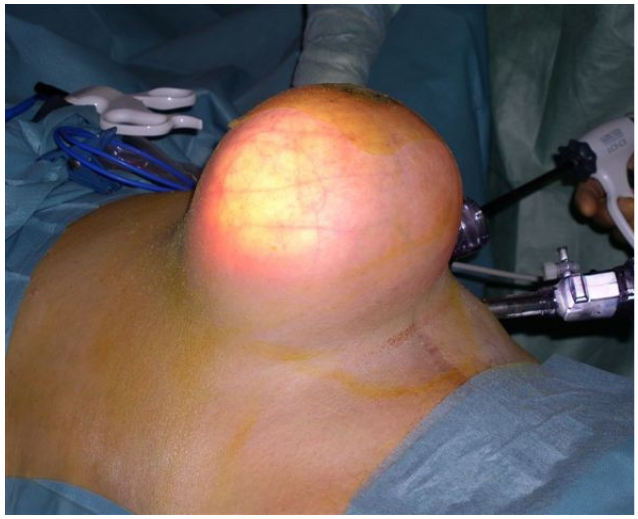

Figure 1
Laparoscopic repair of a large incisional hernia.

2. What can be done? Test the feasibility of intraperitoneal mesh fixation with fibrin sealant (instead of titanium tacks) using laparoscopic approach in a pig model (Study II).
3. Does it work? Performing a randomised, controlled, double-blinded, clinical trial, comparing fibrin sealant vs. titanium tacks for mesh fixation in LVHR (Study III).

PRESENTATION OF STUDY I, II AND III

Study I: Pain, quality of life and recovery after laparoscopic ventral hernia repair.

Aim - This prospective multicentre study was a descriptive study. The purpose was to characterize postoperative pain and convalescence after LVHR and identify areas for further research.

Methods - Between November, 2005, and May, 2006, 35 patients were prospectively included and operated in the four participating centres. Inclusion criteria was age between 18–80 years, ASA group I–III and a ventral hernia defect >3 cm at clinical examination. Standard laparoscopic technique under general anesthesia with double-crown tack fixation without sutures was used in all patients. The same mesh (Proceed® mesh) was used in all patients. The follow-up period was six months for all patients with clinical examination in the out-patient clinic one and six months postoperatively. Several preoperative, peroperative and postoperative assessments and registrations were obtained from each patient.

Preoperatively, at inclusion, sex, age, height, weight, employment status, physical demands at work, ASA group, former laparotomy and wound infection (y/n), smoking habits, and hernia location were registered.

Intraoperatively, duration of surgery, size of hernia defect and mesh, hernia sac content, number and size of trocars used, number of tacks used, estimated blood loss and other complications were registered.

Postoperatively, patients registered pain, general well-being, fatigue, bowel function and nausea daily from POD 0–7, at POD 14 and 30 and after six months. Furthermore, VRS pain scores related to three predefined locations (shoulder, incisional and intraabdominal) were measured by the patient. Quality of life was assessed by the SF–36 questionnaire, preoperatively and after

Table 1
Patient characteristics from Study I.

patient characteristics	N=32
Male	**19**
Age (years)	**57 (30-71)**
Body mass index (kg/m^2)	**29 (21-42)**
ASA class (I:II:III, no.)	**17:12:3**
Hernia localisation (%)	
a. umbilical	**16**
b. infraumbilical midline	**3**
c. supraumbilical midline	**53**
d. infraumbilical transverse	**16**
e. supraumbilical transverse	**12**
in-hospital data	
Hernia defect size (cm^2)	**41 (4-300)**
Mesh size (cm^2)	**319 (169-900)**
Operation time (min.)	**82 (28-202)**
Tacks used (no.)	**59 (23-90)**
Hospital stay (days)	**2 (0-5)**

one and six months. Patients overall satisfaction was reported using a VAS after one and six months. Predefined predictors of postoperative pain were number of tacks per patient, mesh size, BMI, age and hernia location.

Discharge was planned at POD 2 and patients were allowed to resume normal daily activities two days after the operation without any risk. All patients received oral acetaminophen (1g × 4 daily) and ibuprofene (600 mg × 3 daily) from POD 0–2. Analgesic use after POD 2 was registered by the patient.

All patients gave oral and written informed consent for participation in the study. The study was approved by The Danish Ethical Committee (KA05090m) and the Danish Data Protection Agency, and was performed in agreement with the Declaration of Helsinki.

Results - Three patients were excluded; one patient developed metastatic colonic cancer during follow-up and two patients had another mesh than described in the protocol. One patient was lost to follow-up on POD 3 and three patients were lost to six months follow-up. Patient characteristics and operative in-hospital data are presented in Table 1. At one month follow-up (n=31) and six month follow-up (n=28) no recurrences or severe complications were observed. 23% had clinical seromas after one month, but all had disappeared after six months.

Pain scores at rest and during activity are presented in Figure 2. Pain during activity reached preoperative values at POD 30 (p=0.148). The ratio of patients with pain score ≥ 50 at POD 2, POD 7 and after six months was 18/32 (56 %), 8/31 (26 %), and 2/28 (7 %), respectively. Average pain from POD 0–2 and POD 0–6 was 61 and 48, respectively. No significant correlation between pain and any of the predefined predictors of pain was found. VRS pain scores related to three predefined locations (shoulder, incisional and intraabdominal) showed significant difference in total VRS pain score over time, with intraabdominal pain being the most frequent complaint.

General well-being scores was back to baseline scores on POD 3 (p=0.06) and improved further until six months postoperatively, where patients reported significantly better general well-being scores compared with preoperative scores (median 99 vs. 69, p<0.001). A significant negative correlation between general well-being and pain at one month follow-up (rS= -0.64, p<0.001) and six months follow-up (rS= -0.8, p<0.001) was found.

The highest median fatigue score was 9 (range 1-10), measured on the day of surgery. It reached baseline scores on POD 30

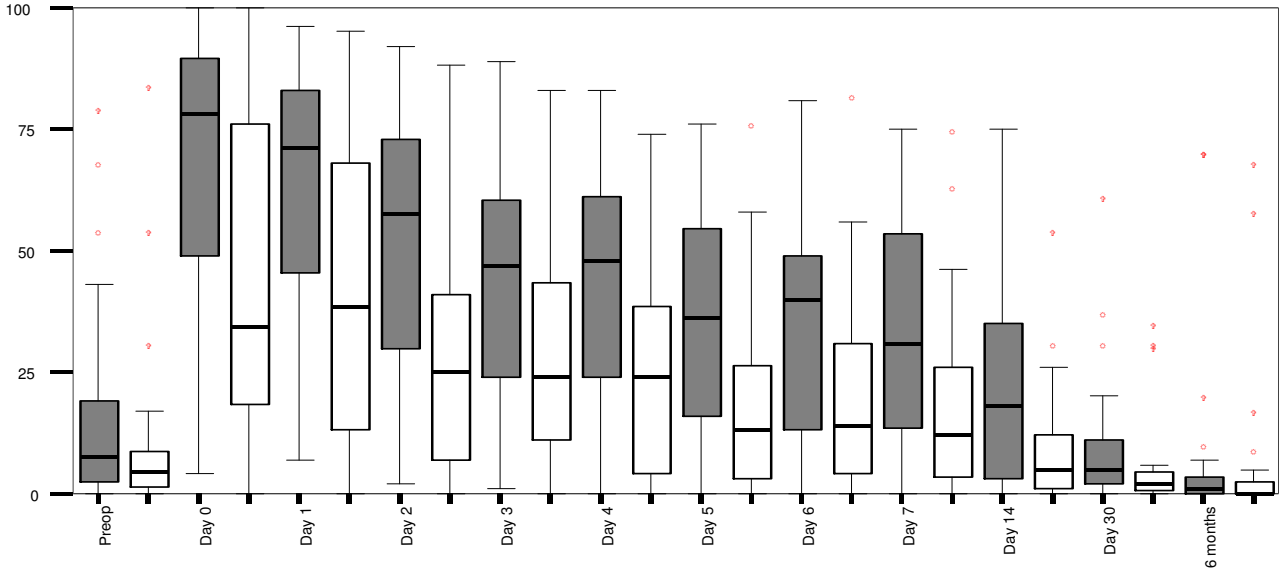

Figure 2
Daily postoperative median VAS pain scores after LVHR, Study I, during activity (grey boxes) and at rest (white boxes). Boxes represents 25-75th percentiles with median lines and range shown. Outliers and extremes are marked as red circles and crosses, respectively.

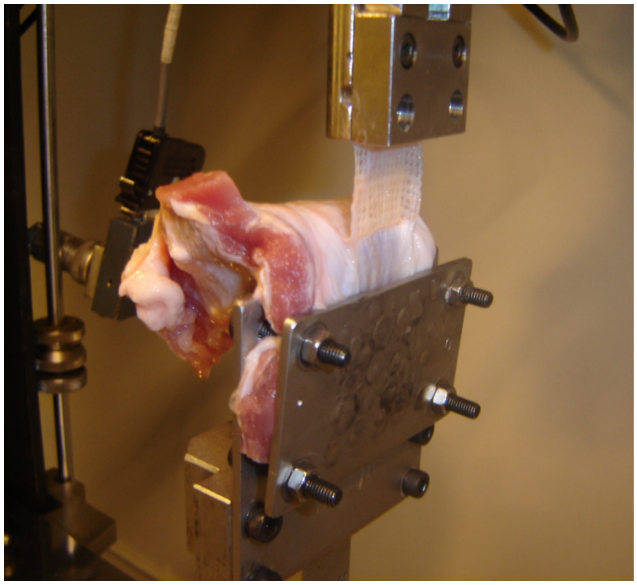

Figure 3
Mechanical peel test of prepared mesh-tissue sample placed in separate clamps in the Instron tensiometer. The mesh has been peeled off from the abdominal wall for a 1 cm distance in this situation.

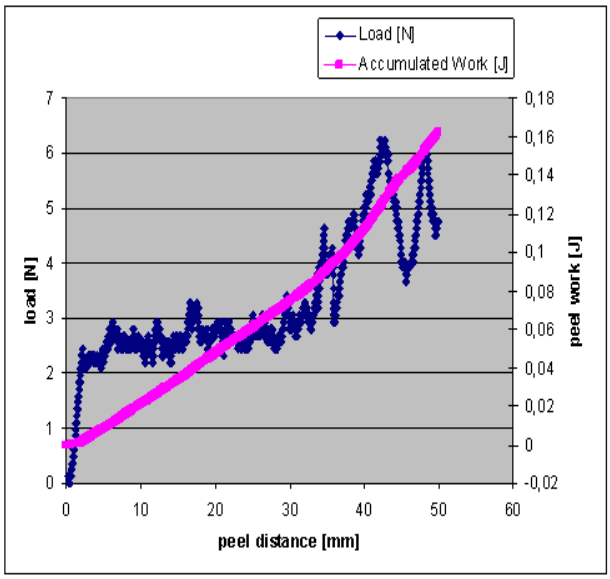

Figure 4
Example of load-peel length graph computed for all peel tests (n=36).

(p=0.46). At six months follow-up the fatigue score was significantly below baseline score (median 1 (range 1–7) vs. 3 (1–7), p=0.005). Complete general well-being and fatigue scores are illustrated in the original article (Fig. 4, Study I).

Bowel function was normalized in all patients on POD 4 and moderate to severe nausea (VRS score 2–3) was reported by 25 % of the patients at least at one time point during the first two postoperative weeks.

Patients resumed normal daily activity on POD 14 (1–38), independent of employment status (p=0.334).

Satisfaction score was 90 (3–100) on POD 30 and 98 (30–100) after six months (p=0.15). A significant negative correlation between satisfaction and pain during activity at one month follow-up (rS= -0.59, p<0.001) and six months follow-up (rS= -0.67, p<0.001) was found. Likewise, a significant positive correlation between satisfaction and general well-being at one month follow-up (rS=0.75, p<0.001) and six months follow-up (rS=0.76, p<0.001) was demonstrated.

Baseline quality of life scores for bodily pain and physical functioning were significantly below the Danish reference scores (p<0.005). On POD 30, three scores were significantly below baseline scores (role physical, bodily pain and physical component scale, p<0.005 for each). At six month follow-up, all eight scales were comparable to the scores of a Danish reference population and bodily pain score had increased significantly above baseline score (p<0.005). The physical and mental component scores were negatively correlated to pain at one month follow-up (rS= -0.46 and -0.47, p<0.02) and at six months follow-up (rS= -0.44, p<0.05 and rS= -0.63, p<0.001).

Conclusion - LVHR was associated with considerable postoperative pain and fatigue during the first postoperative month and it may have influenced patients´ time to resume normal daily activities. Pain was significantly correlated to patients' general well-being, satisfaction and quality of life after one and six months postoperatively. No single parameter could predict post operative pain, but postoperative pain was unacceptably high. The use of titanium tacks could be a likely cause. Alternative fixation methods are therefore necessary.

Limitations - This study had the limitations of a descriptive study. There may have been drawn conclusions about associations and correlations which were not causal. Many correlation tests were performed, as the study was explorative and hypothesis generating in its nature, but it also increased the risk of mass significance, though Bonferroni correction was made where appropriate. Selection bias and confounding may also be present, as no comparing group was present. Patients were included consecutively at all centres and the criteria's for participation nearly reflected normal day practice. Only patients with chronic pain or history of alcohol or drug abuse, patients receiving opioids or immunosuppressant drugs, patients with ASA score > III or acute operation or former LVHR, were excluded. Four centres participated in the study, which both strengthens and weakens the results at the same time, in terms of external and internal validity, respectively. To decrease the risk of reducing the internal validity, the surgical technique and postoperative care was standardized between centres.

The decision on when and how to assess outcomes in the postoperative period was a compromise to obtain the best possible patient compliance. As no measurements were made from POD 14 to POD 30, the exact time of return to baseline levels for several parameters may be uncertain.

Study II: Laparoscopic intraperitoneal mesh fixation with fibrin sealant (Tisseel®) vs. titanium tacks: a randomised controlled experimental study in pigs.

Aim - This randomised controlled experimental study was designed to investigate fibrin sealant (Tisseel®) vs. Titanium tacks for intraperitoneal mesh fixation. The aims of the study were 1) to test the technical applicability of laparoscopic mesh fixation using fibrin sealant in a pig model, 2) to evaluate strength of ingrowth,

adhesion formation and histological parameters, and 3) to compare two different meshes in this setting.

Methods - Nine 40–kg Danish Landrace female pigs were operated under aseptic and sterile conditions. Pneumoperitoneum was created through open access and three trocars were inserted in the left flank. Four 3×10 cm meshes (two Proceed® mesh and two MotifMESH®) were placed transversally over the midline from the xiphoid process towards the symfysis in each pig. Mesh fixation was performed using tacks (T) or fibrin glue (G), creating a total of four groups: Proceed®–tack (PT), Proceed®–glue (PG), MotifMESH®–tack (MT) and MotifMESH®–glue (MG). The intraperitoneal location and fixation method was randomly assigned for each mesh in each pig. All pigs were euthanized on POD 30 and the abdominal wall was removed for further examination.

The primary outcome of the study was strength of ingrowth between mesh and abdominal wall. Strength of ingrowth was measured by performing a mechanical peel test on all tissue samples using an electro-mechanic pc-linked Instron TT-CM tensile test machine (Fig. 3). The force required to peel the mesh from the tissue was measured continuously and load-peel length graphs were computed (Fig. 4). Strength of ingrowth was presented as peel work per area of mesh (J/m2) and peak force in Newtons per width of mesh in centimetres (Nmax/cm). All tacks were removed from the tissue samples before testing to obtain relevant and comparable test results. Complete tack removal was impossible in six samples. In these cases the load peaks produced by the tacks were subtracted afterwards.

Secondary outcome parameters of the study were grade and strength of adhesions to the mesh, shrinkage and displacement/folding of the mesh and histological parameters (fibrosis, inflammation and foreign body reaction). A detailed description of the evaluation of these parameters can be found in the original article (Paper II)

The study was conducted in accordance with the Danish law regarding use of laboratory animals and the study protocol was approved by the Danish Ministry of Justice, Animal Experiments Inspectorate (reg. no. 2006/561-1212).

Results - All nine pigs survived without complications until sacrifice. No significant difference in strength of ingrowth between fixation methods or mesh types was found. When the six samples that did not have all tacks removed before peel testing were removed from the statistical analyses, similar results were found.

No meshes were displaced from their initial position at autopsy but in two cases mesh folding was observed. The Proceed mesh shrank significantly more than MotifMESH (11 % vs. 4 %, p=0.002). There was no difference in grade of adhesions (%) between fixation methods (p=0.79) or mesh types (p=0.30). Similarly, no difference in strength of adhesions (grade 0–4) between fixation methods or mesh types was found (p>0.5). There was no significant difference in formation of fibrosis or inflammation between the different meshes or fixation methods. All samples showed foreign body reaction with giant cells.

Conclusion - Laparoscopic intraperitoneal mesh fixation with fibrin sealant was safe and technically feasible in a pig model. No significant differences between FS and titanium tacks were found in this study. Mesh folding and migration is an issue of concern, because it could result in recurrence in real patients.

Limitations – An experimental study cannot always answer clinical questions, but it can be used to test new ideas and techniques before using new techniques in humans. A potential weakness of this experimental study was that our model involved hernia-free pigs and smaller mesh sizes than used in humans. Because the main objective of this study was applicability of FS and strength of ingrowth, and not hernia repair, an ideal human-like model design was less important. Samples with irremovable tacks during peel test, was another potential weakness of this study. A correction was made by subtraction of the estimated ´tack work´ after the peel test was completed, but this correction technique may be unreliable and not reproducible. Therefore an additional statistical analysis without these specific samples was performed, and the results and conclusions were unchanged.

Financial reasons limited the study size to nine pigs, and because of the small sample size, a type 2 error may have been present. On the other hand, the randomised controlled design, with each pig being its own control, strengthened the results.

Study III: Fibrin sealant versus titanium tacks for mesh fixation in laparoscopic ventral hernia repair: a double-blinded randomised controlled trial.

Aim - This randomised, controlled, and double-blinded clinical trial was conducted to evaluate the effect of fibrin sealant for mesh fixation in LVHR.

Methods - Patients with umbilical hernia defects between 1.5 – 5 cm at clinical examination, age between 18–85 years and, ASA group I-III were eligible for inclusion in the study. Three hernia centres participated in the study and all surgeons were experienced laparoscopic hernia surgeons. None of the surgeons had experience with intraperitoneal FS application before study start. To standardize the operative procedure among centres, a one-day theoretical and technical training course on pigs was completed before study start. Consensus on the operative technique was obtained and demonstration videos were made for all participants.

The primary outcome was acute postoperative pain, defined as the average pain score from POD 0–2. POD 0 was the day of surgery. Secondary outcome parameters were fatigue, general well-being and time to resume normal daily activity. Questionnaires were completed by patients at inclusion, daily from POD 0 to POD10 and after one month. All patients were examined in the out-patient clinic on POD 10 and POD 30 and questionnaires were collected.

Sample size calculation was based on data from Study I. The average pain score from POD 0–2 was 59 (SD 22) and a type I error of 5 % and a type II error of 20 % was accepted. A minimal relevant difference in pain, measured on a 0–100 mm VAS, was set to 25 mm. Based on two-sided analysis, 13 patients were required in each group to evaluate the primary outcome parameter. It was decided to include a total of 40 patients (20 in each group) in the study. Statistical analyses were performed using non-parametric tests. The Mann-Whitney test was used for comparisons between independent groups. Paired intragroup comparisons were performed using Wilcoxon test. Chi-square test and Fisher´s exact tests were used to test for relationship between two categorical variables. Spearman's rank correlation test (rS) was used for correlation analysis.

Randomisation was performed as block randomisation and participants were randomly assigned to receive FS or titanium tacks for mesh fixation (ratio 1:1). Randomisation was carried out by the surgeon after the patient was anaesthetized. Patients, care givers and those assessing the outcomes were blinded to group assignment. Data was entered into a web-based registration

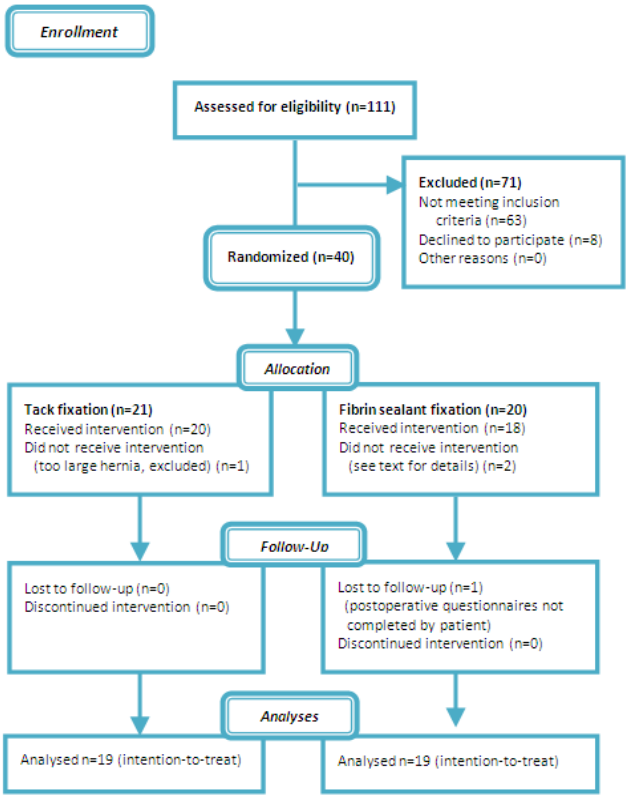

Figure 5

CONSORT diagram [84], showing the number and passage of patients for each intervention group through each stage of Study III.

Table 2

Consecutive list of all patients with an umbilical hernia referred to one of the three centers in the inclusion period that did not meet the inclusion/exclusion criteria (all listed).

	number of patients (n=63)
hernia defect < 1.5 cm at clinical examination	22
hernia defect > 5 cm at clinical examination	6
strangulated hernia (acute operation)	4
expected poor compliance (e.g. dementia, psychiatric disorders)	4
age < 18 years	3
known immune deficiency including current systemic steroid use	3
simultaneous operation for other hernia	3
not Danish speaking	2
current opioid medication	2
pregnancy	1
chronic liver disease (Child-Pugh B or C)	1
medical conditions contraindicating general anaesthesia: BMI 43	1
former laparoscopic umbilical herniotomy or open operation with mesh	0

system [15] by a project nurse. According to the protocol, excluded patients and drop-outs were only replaced if more than four patients were missing.

The study was approved by The Committees on Biomedical Research Ethics (H-B-2008-147) for the Capital Region of Denmark, the Danish Data Protection Agency and performed in agreement with the Helsinki II declaration and registered at clinicaltrials.gov before study start (ID number NCT00842842). Informed consent for participation was obtained from all included patients.

All patients were operated in a propofol-based general anesthesia without epidural blockade. Ketorolac (15–30 mg) was given intravenously if not contraindicated and ondansetron and dexamethasone was administerd in case of known postoperative nausea and vomiting. All patients received a single-dose of 1.5 g cefuroxime IV preoperatively. Same standard technique was used in all patients. The hernia sac was not resected and the hernia defect was not sutured. The hernia defect was measured, and if hernia diameter was above six centimetres the patient was excluded. In patients allocated to tack fixation, tacks were placed 1–2 cm apart in a double-crown fashion using the ProTack™ 5 mm fixation device. For FS fixation 4 ml Tisseel Duo Quick was used, giving a total amount of 8 ml fibrin glue. The 500 IU/ml thrombin unit was replaced with a 4 IU/ml thrombin formulation, to extend coagulation time [16]. The mesh was introduced through the 10 mm port and placed and orientated correctly on the intestines. A uniform layer of FS was applied using a manual application catheter and two graspers were used to place the mesh on the abdominal wall. The intraabdominal pressure was decreased to 6 mmHg for 5 to 10 minutes to observe continuous good and stable mesh position. If FS fixation was unsuccesful, fixation was converted to tacks. No transfascial fixation sutures or stay sutures were used. A 12 cm round Parietex Composite Mesh was used for all operations.

All patients discharged at the day of surgery if not pain, social conditions, or surgery late in the afternoon made overnight stay necessary. Patients were allowed to resume normal daily activities two days after the operation. All patients were given oral acetaminophen (1g × 4 daily) and a non-steroidal anti-inflammatory drug (ibuprofene 600 mg × 3 daily) during POD 0–2.

Results - 40 of 111 eligible patients were randomised and 19 patients in each group were available for analysis (intention to treat) after one month, Figure 5. A consecutive registration of patients not meeting inclusion criteria (n=63) are presented in Table 2. Two patients were excluded; one during surgery because of a too large defect (>7 cm) and one did not complete the questionnaires. These two patients remained in their allocation group for the intention-to-treat analysis.

Table 3 shows demographics and baseline characteristics of all evaluable patients in each group. Perioperative and postoperative summary results are presented in Table 4.

Pain scores reported in the two groups are illustrated in Figure 6a+b. No significant difference in preoperative pain scores was seen between groups. Patients in the FS group reported less pain at POD 0–2, both at rest (median 19 vs. 47, p=0·02) and during activity (38 vs. 60, p=0·01), see Table 4 and Figure 7a+b. Absolute difference between groups for the primary endpoint was 19 mm (95% CI 3–34 mm) at rest and 20 mm (95% CI 4–35 mm) at activity. Furthermore, patients in the FS group reported

Table 3

Baseline characteristics and demographics from Study III. Values are median (range) or number of patients. FS, fibrin sealant. [a] all acetaminophen.

	Tack group (n=19)	FS group (n=19)
age (years)	45 (31–67)	59 (34–69)
Men	13	14
body mass index (kg/m^2)	31.1 (24.8–38.8)	31.2 (19.0–38.3)
employment status (no/light work/hard work)	3/11/5	10/7/2
ASA class (I/II/III)	7/11/1	4/14/1
Smoker	4	6
daily preoperative analgesic use[a]	4	0
recurrent/primary hernia	5/14	2/17

Table 4

*Summary results for each group in Study III. All VAS scores from POD 0-2 or 0-10 are average scores for the given period. All values are medians (range). POD, postoperative day. FS, fibrin sealant. [a] oral morphine equivalent doses (mg). b one patient received a transverse abdominal plane block at postoperative day 1. *primary outcome **secondary outcome.*

	Tack group (n=19)	FS group (n=19)	p-value
Perioperative			
number of tacks per patient	27 (17–38)	-	
duration of surgery (min)	40 (23–130)	50 (30–90)	0.02
hospital stay (days)	0 (0–2)	0 (0–2)	0.22
peroperative hernia diameter (cm)	2.5 (1.5–4.0)	3.0 (2.0–6.0)	0.15
opioid use[a] at post anaesthesia care unit (mg)	30 (0–90)[b]	30 (0–120)	0.63
Postoperative			
normal daily activity (days)**	18 (1–95)	7 (1–66)	0.03
VAS pain POD 0–2, rest*	47 (6–91)	19 (3–74)	0.02
VAS pain POD 0–2, activity*	60(18–96)	38 (6–98)	0.01
VAS pain POD 0–10, rest	32 (2–73)	10 (2–59)	0.03
VAS pain POD 0–10, activity	40 (6–74)	21 (2–67)	0.03
VAS discomfort POD 0–2**	55 (14–94)	41 (6–87)	0.01
VAS discomfort POD 0–10**	38 (8–63)	22 (5–55)	0.02
fatigue POD 0–2**	8 (3–10)	7 (2–10)	0.07
fatigue POD 0–10**	5 (2–8)	4 (1–7)	0.23
VAS satisfaction POD 30	99 (26–100)	99 (51–100)	0.89

Table 5

Frequencies of patients reporting moderate to severe pain defined as VRS ≥ 2 or VAS ≥ 50 in relation to postoperative day (POD). VRS verbal rating scale 0–3, VAS visual analogue scale 0–100. FS, fibrin sealant. § p= 0.02 (Chi-square test).

	Tack group (n=19)		FS group (n=19)	
	VRS ≥ 2	VAS ≥ 50	VRS ≥ 2	VAS ≥ 50
POD 0	12 (63)	14 (74)	11 (58)	10 (53)
POD 2	12 (63)	12 (63)	7 (37)	5 (26)§
POD 7	6 (32)	4 (21)	3 (16)	2 (11)
POD 10	4 (21)	3 (16)	1 (5)	0
POD 30	1 (5)	1 (5)	0 (0)	0

significantly lower pain scores during POD 0–10 compared with the tack group (Table 4 and Figure 7a+b). At POD 30, pain was significantly below preoperative values in the FS group (median 0 (range 0–3) vs. 1 (0–47) at rest, p=0.02, and 0 (0–33) vs. 3 (0–53) at activity, p=0.03), but not in the tack group (0 (0–82) vs. 5 (0–38) at rest, p=0.14, and 1 (0–82) vs. 16 (0–71) at activity, p=0.054). The proportion of patients with moderate to severe pain, defined as VRS score ≥2 or VAS score ≥50, at different time points are listed in Table 5.

Patients' self-reported discomfort scores are illustrated in Figure 6c. The average discomfort score from POD 0–2 and POD 0–10 was significantly less in the FS group compared with the tack group (Table 4 and Figure 7c). Fatigue scores are illustrated in Figure 6d and no significant difference was found between groups (Table 4 and Figure 7d).

The FS fixation procedure was significantly more time consuming than the tack procedure (median 50 minutes vs. 40 minutes, p=0.02) (Table 4). No significant difference in hospital stay, hernia diameter, or morphine consumption in the post anesthesia care unit was found between groups (Table 4). Correlation analysis between number of tacks used per patient and pain from POD 0–2, showed no significant relation (rS=0.10, p=0.67).

Patients in the FS group resumed normal daily activity faster than patients in the tack group, POD 7 (1–66) versus POD 18 (1–95), respectively (p=0.03). Patients that resumed normal daily activity quickly also reported lower pain scores at POD 0-2, both at rest (rS=0.35, p=0.03) and during activity (rS=0.43, p=0.008).

Patient satisfaction was high in both groups at one-month follow-up, with no significant difference between groups (Table 4).

There was no difference in 30–day morbidity between groups. Seromas were found in 34 % of the patients (seven in the tack group and six in the FS group), haematomas at trocar sites in 18 % (three and four patients in tack and FS group, respectively), superficial skin infections in 8 % of the cases (one in the tack group and two in the FS group), and one patient in the FS group developed an asymptomatic skin erythema. All haematomas, infections, and the erythema had disappeared at POD 30 follow-up, but eight patients still had clinical seromas (three in the FS group and five in the tack group). In two cases, recurrence was ruled out by ultrasound examination showing a seroma in one patient and a haematoma in another. There was no difference between the tack vs. FS group in the number of patients using non-steroidal anti-inflammatory drugs (9 vs. 5, p=0.18), paracetamol (3 vs. 3) or morphine (3 vs. 2) from POD 2 to POD 30. Three patients were readmitted to hospital after discharge during follow-up. Two

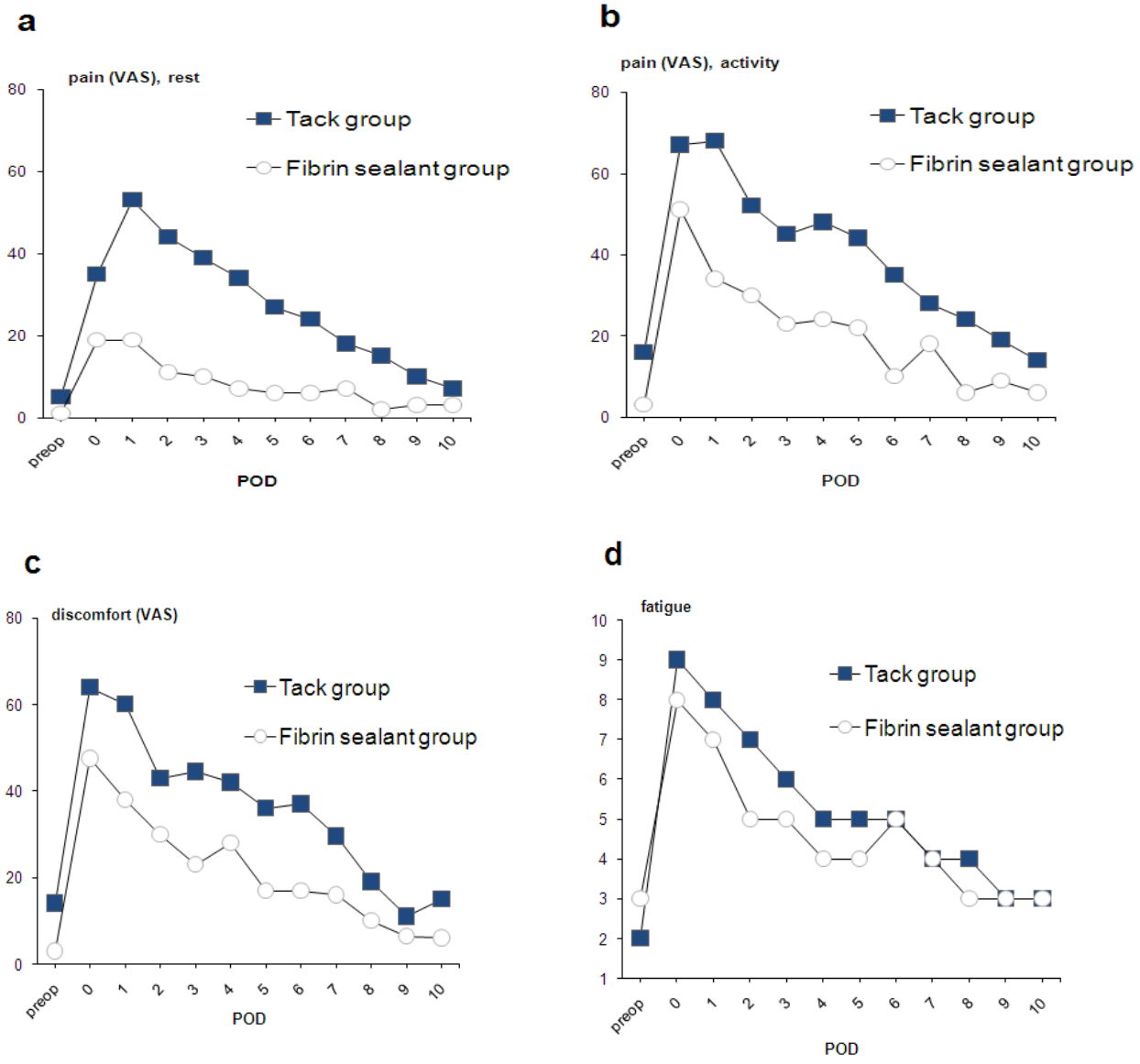

Figure 6

Patient-reported outcome measures in both groups until postoperative day 10. VAS pain scores at rest (a) and during activity (b), VAS discomfort scores (c), and fatigue scores (d) are illustrated. Values are medians. POD 0, postoperative day 0 (day of surgery).

readmissions, although without overnight stay, was due to pain (one in tack and one in FS group) and in one case the patient was observed two days in hospital due to subileus (tack group), but recovered uneventfully. No adverse events or side effects were observed.

Conclusion - Mesh fixation with FS instead of titanium tacks in LVHR of defects ≤ 5 cm significantly improved outcome in terms of less acute pain and discomfort and a shorter convalescence period. The results are very encouraging as postoperative pain has remained an unsolved clinical problem following LVHR. Long-term follow-up must show the value of FS fixation in terms of chronic pain and recurrence.

Limitations – Although the trial was conducted in perfect agreement with the protocol, it had potential weaknesses. Firstly, recurrence is an important outcome parameter in hernia surgery; especially when new techniques are tested. In this study recurrence was evaluated clinically at follow-up. Sometimes, distinction between a seroma and a recurrence can be difficult, as show in two patients in the present study. Therefore, an ultrasound examination or CT scan was performed if there was any doubt, as in everyday clinical practice. Secondly, follow-up time was short and recurrences are known to present years after the operation. Recurrence was not an outcome parameter but was considered a safety parameter, and therefore long-term follow-up is important. Another potential weakness was the multicentre design with three locations. Efforts as consensus meetings, training course on pigs, preparation of demonstration videos and instruction manuals and one coordinating centre with a full-time project nurse was done to minimize the risk of violating the internal validity of the study. Sample size calculation was based on the results from Study I, which also included larger hernia defect, than in the present study.

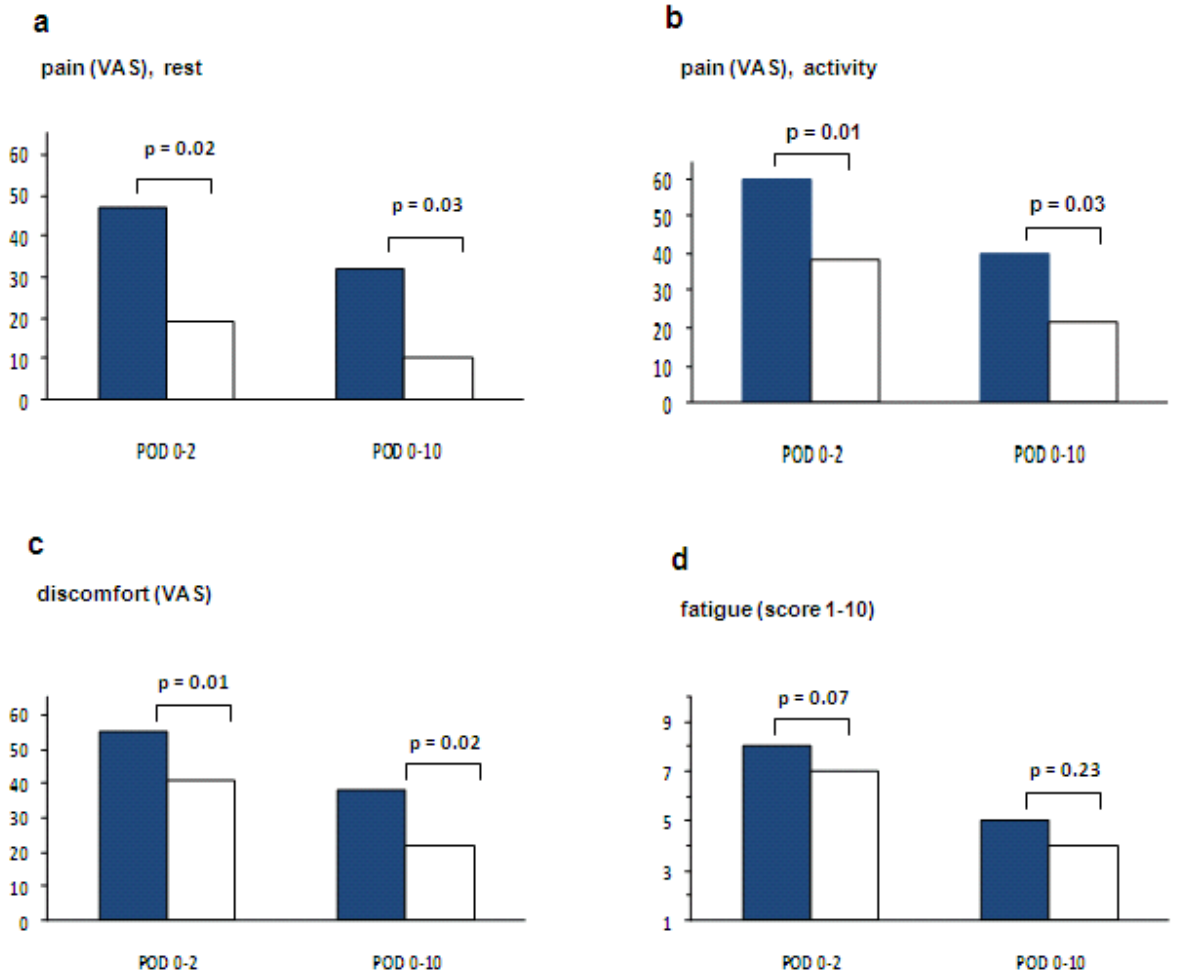

Figure 7

Patient-reported scores from day 0-2 and 0-10 for both groups. VAS pain score at rest (a), VAS pain score during activity (b), VAS discomfort scores (c) and fatigue scores (d). Values are medians. POD, postoperative day. track group, Fibrin sealant group.

A potential bias in our study was the baseline imbalance in age. Patients in the tack group were younger than patients in the glue group (median 45 vs. 59 years, p=0.01). Young patients are known to report higher pain scores than older patients [17] and therefore age difference between groups has potential clinical importance. If randomization was performed correctly, as was the case in the present study, chance could be the only explanation for differences between randomization groups at study start. A correlation test (Spearman) between pain and age concluded, that around 14 % of the observed difference in pain between groups could be attributed to the difference in age (rS = -0.38, p=0.02).

DISCUSSION

As illustrated in Figure 8, LVHR with tacks is a very painful procedure compared with other laparoscopic standard procedures and at least as painful as open ventral hernia repair. When fibrin sealant is used instead of tacks, the pain burden after LVHR is comparable to that reported after laparoscopic cholecystectomy (Figure 8).

The absolute difference in VAS pain score between the two groups in Study III was 20 mm. Determination of the minimal clinically significant difference (MCSD) in pain experience, measured on a VAS, is important, as clinical significant difference not necessarily equals a statistical significant difference. The discriminative skill of a VAS has been evaluated in several studies and the MCSD to be registered on a 0–100 mm VAS has been found to be between 9-13 mm [18–20]. This seems to be true in all parts of the VAS scale as MCSD was not affected by the severity of pain [18].

Reduction of acute pain tends to decrease the period of convalescence, morbidity and incidence of chronic pain [21]. In Study III it was documented, that reduction of acute postoperative pain after LVHR consequently reduced the time of convalescence significantly. No difference in morbidity or complication rate was seen, but the study was not designed to answer such questions.

Whether acute pain can result in chronic pain is uncertain. Severe acute postoperative pain has been correlated to chronic pain [22] but it is still debated whether peri-operative pain treatment can reduce the incidence and severity of chronic pain.

Chronic pain has been reported in 22 % of patients three months after LVHR [14] and in up to 7 % of patients six months postoperatively [Study I]. Chronic pain significantly affects patient

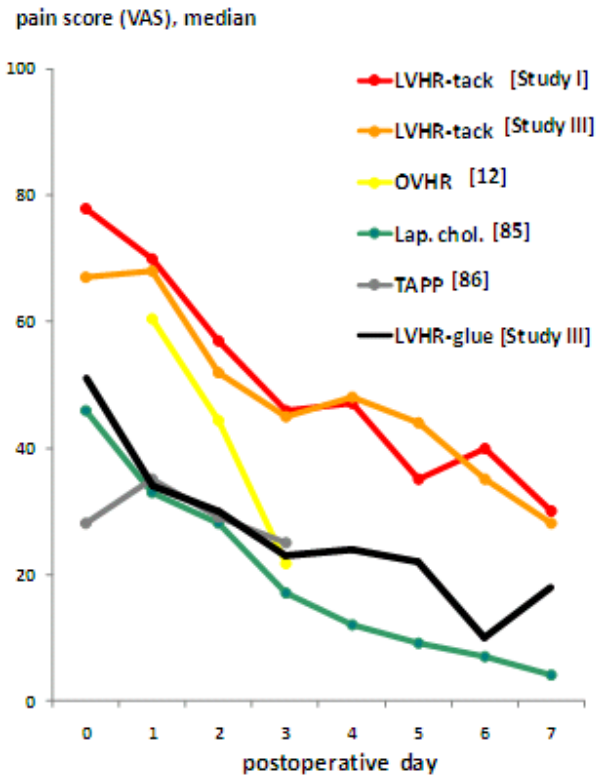

Figure 8

Pain scores on 0–100 mm visual analogue scale (VAS) after different laparoscopic procedures. LVHR, laparoscopic ventral hernia repair. OVHR, open ventral hernia repair. FS, fibrin sealant. Lap. chol, laparoscopic cholecystectomy. TAPP, transabdominal preperitoneal inguinal hernia repair.

satisfaction, general well-being and quality of life in a negative direction, up to six months postoperatively [Study I].

Time of convalescence depends on actual recommendations given about physical restrictions and information about postoperative pain [23]. When patients were specifically instructed to resume normal daily activity after LVHR at POD 2 without any risk, they actually resumed normal daily activity after 7 days when FS was used and 18 days if titanium tacks were used for mesh fixation (Study III). Furthermore, it is now evident that severe acute pain correlates with prolonged time of convalescence (Study III).

Significant postoperative fatigue is a well-known phenomenon after abdominal surgery and gynaecologic operations, but orthopaedic patients do not suffer postoperative fatigue at all [24]. Postoperative fatigue has been defined as "and indefinable weakness throughout the body after doing only minor tasks" [25]. The aetiological background of fatigue is poorly understood, but can in part be explained by circulating cytokines (IL-6) released due to the acute inflammatory response in tissue trauma (surgery) and as a consequence of postoperative catabolism and muscle loss due to impaired mobility and nutrition, postoperatively.

Patients reported high fatigue scores after LVHR, but fatigue was unaffected by fixation method and pain score (Study III). It has been claimed that the sensation of fatigue during the first two postoperative days can be in part mediated by pain [26]. This could explain the very high fatigue scores in the immediate postoperative period in Study I and Study III.

Mesh fixation technique

Invasive non-degradable fixation

Titanium tacks with or without transfascial sutures have traditionally been used to ensure safe initial mesh fixation. Some advocate for the use of sutures because of higher tensile strength compared with tacks [27] but others found sutures to increase adhesion formation [28].

In three clinical studies, one non-randomised [29] and two randomised non-blinded trials [30, 31], tacks was compared with sutures for mesh fixation in LVHR.

In the non-randomized study, 50 patients underwent LVHR. No difference in acute or chronic pain, narcotic use or other relevant parameters was found [29]. Comparable results were published recently from a randomized trial including 199 patients in three treatment arms: double crown fixation with tacks, tacks and non-absorbable sutures or tacks and absorbable sutures [30]. No significant difference in postoperative pain up to three months postoperatively was found between the groups. In the study by Beldi et al. patients in the suture group reported significantly more pain than patients in the tack group after six weeks, but no difference was found after six months [31].

Furthermore, no difference in recurrence rate has been found between tack and suture fixation.

Invasive degradable mesh fixation

Degradable mesh fixation products such as AbsorbaTack™ and I-Clip™ have been introduced on the market, claiming to reduce postoperative pain and intraabdominal adhesions. No comparative studies have been published, but an inhomogeneous feasibility study using I-Clip™ for mesh fixation in different laparoscopic hernia procedures showed no recurrences [32], but pain scores or sick leave was not registered.

The AbsorbaTack™ is made of an absorbable synthetic polyester copolymer derived from lactic and glycolic acid and degrades within one year postoperatively. The suggested positive effect on postoperative pain has not been documented yet, but hopefully an ongoing randomized trial comparing AbsorbaTack™ and ProTack™ will provide some answers [33]. Laparoscopic intracorporeal suturing of the mesh was performed in another interesting study using the DaVinci robot system. The patients (n=11) reported a low median VAS pain score of 3 on POD 1, maybe due to the avoidance of tacks and transfascial sutures [34]. The DaVinci system facilitates intracorporeal suturing combining intuitive hand movements with the laparoscopic approach, but the setup is expensive and time-consuming. Nevertheless, the positive results from the pilot study encouraged the group to proceed with a randomised trial (ongoing) comparing conventional LVHR and robot-assisted LVHR with pain as the primary outcome parameter [35].

Non-invasive degradable mesh fixation

Non-invasive degradable products such as fibrin sealant and cyanoacrylate glues have been used for mesh fixation in hernia repairs. Generally, they are not registered for that purpose, but Tisseel® has recently been registered in the United Kingdom. The first publication describing the experience with FS in LVHR was a case series published in 2007 [36]. Hernia defects were < 7 cm in diameter and VAS pain scores were obtained from 30 of 40 included patients. The highest mean 0–10 VAS pain score reported was 2 at POD 1–3. No pain was observed from POD 7. The mean follow-up period was 16 months and no recurrences or severe

complications were reported. Today it seems evident that FS is superior to tacks for mesh fixation in terms of acute pain reduction after LVHR (Study III). Only two further studies of the clinical use of FS for intraperitoneal mesh fixation have been published, that is a case report of paraesophageal hernia repair [37] and a series of intraperitoneal on-lay mesh (IPOM) repairs of inguinal hernias [38].

Cyanoacrylate glue is a synthetic tissue adhesive and has been evaluated to some extend for mesh fixation. Two small randomized studies compared cyanoacrylate glue with sutures in Lichtenstein repairs and both found less early pain in the glue groups [39, 40]. It has been investigated for laparoscopic mesh fixation in experimental studies as well [41], but only one (retrospective) clinical study has been published [42]. TAPP inguinal hernia repair in 76 patients using either fibrin glue or cyanoacrylate glue for mesh fixation were evaluated. After three months 10 % of the patients reported mild pain [42]. Unfortunately, the authors did not comment on technical differences of application in the two techniques. Probably many surgeons find cyanoacrylate glue imperfect for mesh fixation purposes due to reports on impaired mesh integration [43], heat-induced inflammation and necrosis of nerves and blood vessels [44] and the fact, that cyanoacrylate glue may obliterate the laparoscopic instruments.

A recent meta-analysis of FS for mesh fixation in laparoscopic inguinal hernia repair concluded, that the technique was safe and feasible and reduced pain [45] in transabdominal preperitoneal (TAPP) repair [46, 47] and analgesic consumption in total extraperitoneal (TEP) repair [48], compared with tacks.

No mesh fixation

A simple way to prevent pain caused by fixation materials would be to use no fixation at all. A self-adhering mesh for this purpose has been evaluated both experimentally [49] and clinically [50] in the extraperitoneal position. Only two studies have compared tacks versus no fixation, both in TEP repairs. There was a tendency towards less pain in the no fixation group [51, 52]. The special self-gripping mesh, however, can not in its present form be used for LVHR because the grips do not adhere to the peritoneal surface.

Analgesic interventions

Local anaesthetics

Great efforts have been put into research of pain control through local anaesthetics. The theory behind is basically prevention of afferent nociceptive nerve transmission from the surgical site to the spinal cord, thus reducing local inflammatory response and pain perception. It is well-documented that local anaesthetics at incisional sites reduce pain after laparoscopic surgery and LVHR specifically [53, 54]. Catheter-based continuous local anaesthetic infusion reduces the use of opioids and recovery after colonic resections [55]. Rosen et al. conducted a randomized trial (n=73) in LVHR, comparing continuous 0.5 % bupivacaine or saline infiltration (infusion rate 2 ml/h) via a catheter placed transcutaneously into the hernia sac just above the mesh [56]. No difference in pain, narcotic use, time to restore bowel function or length of hospital stay was found between the groups. Correct and accurate positioning of the catheter may influence the analgesic effect observed using this method and limits its reproducibility. Intraperitoneal installation of local anaesthetics has positive effect on postoperative pain after laparoscopic fundoplication [57] and cholecystectomy [58], but the technique has not been investigated in LVHR.

In a recent systematic review concerning the use of perioperative intravenous lidocaine infusion for improving postoperative analgesia it was concluded, that the treatment was safe and resulted in significant reductions in postoperative pain and opioid consumption [59]. No studies specifically addressed the effect of lidocaine infusion in LVHR. Another study tested the analgesic effect of a lidocaine patch, Lipoderm®, placed on the exterior abdominal wall after LVHR [60]. Originally, the Lipoderm® patch was constructed for treatment of postherpetic neuralgia. Thirty patients were randomised for patch 12 hours per day for three days or nothing (no placebo group). The authors found less pain in the patch group at discharge but no difference in postoperative analgesic requirements.

Compartment blocks

Local anaesthetics can also be administered as ´compartment block´ techniques, e.g. the rectus sheath block and the transversus abdominis plane block (TAP block). The rectus sheath block is administered using ultrasound guidance [61] and can reduce acute pain [62], also compared with intraperitoneal and intraincisional application [63], but is probably not better than local infiltration to reduce pain after umbilical hernia repair [64]. The TAP block is an analgesia technique used for pain control after operations involving the anterior abdominal wall [65]. The procedure is relatively easy and can be applied bed-side [66]. A local anaesthetic is distributed ultrasound-guided into the neuro-fascial plane between the internal oblique and the transversus abdominis muscles. If correctly administered it will affect nerves T7-L1 [67] making it relevant for both upper and lower abdominal surgery. It can be administered as a bolus and has a known opioid-sparing effect as part of multimodal analgesic regimens in many procedures such as caesarean delivery [68], appendectomy [69], cholecystectomy [70], open hysterectomy [71] and open colonic resection [72]. By placing a catheter for infusion it could be an interesting alternative to epidural analgesia [73]. Epidural analgesia is an invasive procedure and keeps the patient in hospital during treatment. In some patients it is required for postoperative pain control [Study I] but no studies have compared epidural analgesia with other analgesic regimens after LVHR. At present epidural analgesia should be restricted to patients with severe acute pain to reduce opioid use.

A long-lasting local anaesthetic as bupivacaine normally has an analgesic effect for 6-8 hours when used as infiltration. In compartment blocks the absorption is reduced, prolonging the analgesic effect. Long-lasting local anaesthetics are not yet available but could probably eliminate the use of infusion catheters. Unfortunately, no studies have evaluated the effect of bilateral TAP block in LVHR, although it would be highly relevant.

Type of anaesthesia

Propofol-based general anesthesia reduces postoperative nausea and vomiting compared with gas anesthesia [74] and is generally used in combination with short acting opioids in LVHR.

LVHR under spinal anaesthesia may be feasible [75] but not equal to or better than general anesthesia. Until further randomized studies have proven better, this procedure should be restricted to selected patient categories, where general anesthesia is troublesome, as urinary retention, hypotension, bradycardia and even cardiac arrest are known complications [76].

Other pain-modulating interventions
Glucocorticoids administered systemically has proven anti-inflammatory and antihyperalgesic effects. A preoperative single dose of dexamethasone can reduce postoperative pain, nausea and fatigue and improve general-well being and convalescence after many surgical procedures [77], but the optimal dose is still debated. No studies concerning the effect of glucocorticoids in LVHR are available.
The positive effect of the anti-convulsant gabapentine on postoperative pain, analgesic requirements and nausea has been proven after laparoscopy [78] and abdominal hysterectomy and spinal surgery [79], but no studies in LVHR have been published. The mechanism of action is central and its proven effect on neuropathic pain [80] and possible role as a protective pain-modulating premedication [81] in combination with standard analgesic regimens should be further evaluated in LVHR. The effect of pregabalin, a derivate of gabapentine, on acute pain has been studied in several studies and a recent review concluded that the effect of pregabalin on acute postoperative pain remains uncertain [82].

CONCLUSION
The studies making the basis of the present PhD thesis has added new and important knowledge to laparoscopic treatment of ventral hernias. First of all, a detailed quantification and analysis of pain and recovery have shown that LVHR is associated with extensive acute postoperative pain which negatively affects patients' quality of life, general well-being and satisfaction. Secondly, experimental intraperitoneal mesh fixation without titanium tacks is technically feasible using fibrin sealant as sole fixative, with no difference between the two procedures in strength of fixation. Lastly, fibrin sealant significantly reduces acute pain, discomfort and convalescence compared with titanium tacks in a clinical setting.

Laparoscopy has solved many problems, but new problems have evolved. Pain is a significant clinical problem after LVHR with a high impact on patients' general well-being, quality of life and patient satisfaction.

Some analgesic interventions have well-documented pain-reducing effects in LVHR and others have proven to reduce pain in other abdominal procedures, but not in LVHR specifically. In LVHR, high-quality studies are lacking to make evidence-based guidelines, but in conclusion, some summary statements on prevention and reduction of pain after LVHR can be given based on the results of the present PhD thesis and review of the current literature:

- FS significantly reduced acute pain, discomfort and convalescence compared with titanium tacks.
- Tacks and sutures are equal mesh fixation methods with respect to postoperative pain and recurrence.
- Local anaesthetics at incisional sites may reduce postoperative pain.
- Catheter-based continuous local anaesthetic infusion above the mesh had no effect on pain.
- The pain modulating effect of glucocorticoids, gabapentine or pregabalin in LVHR have not been investigated.
- The pain limiting effect of perioperative intravenous lidocaine infusion has not been investigated.
- The pain limiting effect of TAP block has not been investigated.
- The potential pain limiting effect of degradable stapling devices has not been investigated.
- Use of a self-gripping mesh to reduce pain cannot be recommended at present as no studies are available.

LVHR is often recommended in case of disabling or socially invalidating symptoms or for cosmetic reasons, but watchful waiting can be a safe alternative to surgery, preventing potential severe complications overriding the initial complaint. The results of an ongoing study of watchful waiting in patients with ventral hernias can hopefully add important knowledge to this field [83].

RESEARCH IMPLICATIONS
The pain issue must have first priority in future research in LVHR and initial steps have been taken to improve outcome. First of all, long-term follow-up must show the value of FS fixation in terms of chronic pain and recurrence. Future studies using fibrin sealant should include larger hernia defects and incisional hernias, as the operative technique may be different. Also, ongoing research will hopefully answer the questions about pain reduction using degradable stapling devices instead of titanium tacks and robot-assisted LVHR instead of conventional LVHR. Moreover, research on the applicability of self-adhering meshes to avoid fixation would be interesting as would studies of new meshes with incorporated growth-factors to fasten and strengthen ingrowth. The TAP block is a very interesting and simple technique that has proved its effect in many other abdominal procedures and a randomized trial in LVHR should be conducted. Furthermore, the use of glucocorticoids, gabapentine, or lidocaine infusion in relation to LVHR are other interesting areas that should be investigated further.

SUMMARY
Severe pain is usual after laparoscopic ventral hernia repair (LVHR). Mesh fixation with titanium tacks may play a key role in the development of acute and chronic pain and alternative fixation methods should therefore be investigated.
This PhD thesis was based on three studies and aimed to

1. assess the intensity and impact of postoperative pain by detailed patient-reported description of pain and convalescence after LVHR (Study I),
2. evaluate the feasibility of fibrin sealant (FS) for mesh fixation in an experimental pig model (Study II), and
3. investigate FS vs. tacks for mesh fixation in LVHR in a randomised, double-blinded, clinical controlled study with acute postoperative pain as the primary outcome (Study III).

In Study I – a prospective descriptive study - 35 patients were prospectively included and underwent LVHR. Scores of pain, quality of life, convalescence, fatigue, and general well-being were obtained from each patient. Follow-up was six months. Average pain from postoperative day (POD) 0–2 and POD 0–6 measured on a 0–100 mm visual analogue scale (VAS) was 61 and 48, respectively. Pain scores reached preoperative values at POD 30. The incidence of severe chronic pain was 7%. No parameter predicted postoperative pain significantly. Significant correlations were found between pain, and general well-being (r_S= -0·8, $p<0·001$), satisfaction (r_S= -0.67, $p<0.001$), and quality of life score (r_S= -0.63, $p<0.001$) six months postoperatively. Patients resumed normal daily activity at POD 14.

In Study II – a randomised experimental study in pigs – nine pigs were operated laparoscopically with insertion of two different meshes fixed with either FS or tacks. All pigs were euthanized on POD 30. The primary outcome parameter was strength of ingrowth between the mesh and the anterior abdominal wall. A mechanical peel test was performed for each tissue sample. The secondary outcome parameters were grade and strength of adhesions to the mesh, shrinkage and displacement/folding of the mesh and histological parameters. All nine pigs survived without complications until sacrifice. No meshes were displaced from their initial position at autopsy, but in two cases mesh folding was observed. No significant difference in strength of ingrowth was found between different fixation methods or mesh types. Furthermore, no significant difference was found in grade or strength of adhesions or any histological parameters.

In Study III – a randomised, controlled, double-blinded, multicenter trial - 40 patients with umbilical hernia defects between 1.5 – 5 cm, were randomly assigned to receive FS or titanium tacks for mesh fixation in LVHR. Patients, care givers and those assessing the outcomes were blinded to group assignment. The primary outcome was average pain from POD 0-2 (VAS score). Secondary outcome parameters were fatigue, general well-being and time to resume normal daily activity. Follow-up was one month for all. Patients in the FS group reported significantly less pain at POD 0–2 (median VAS 38 (range 6–98) vs. 60 (18–96), p=0.01). Absolute VAS score difference between groups was 20 mm (95% CI 4–35 mm) at activity, and 19 mm (95% CI 3–34 mm) at rest. Patients in the FS group reported significantly less discomfort from POD 0–2 and POD 0–10, compared with the tack group. No significant difference was found in fatigue score between groups. No significant difference in hospital stay, hernia diameter, or morphine consumption in the post anesthesia care unit was found between groups. Patients in the FS group resumed normal daily activity at POD 7 (1–66) versus POD 18 (1–95) in the tack group (p=0.03). No recurrences were observed. No adverse events or side effects were observed. No significant differences in predefined complications were found between groups.

In conclusion, pain is a significant clinical problem after LVHR with impact on general well-being, quality of life and patient satisfaction. This issue must have first priority in future ventral hernia repair research. It is now documented, that the simple application of fibrin glue instead of titanium tacks for mesh fixation in LVHR of defects < 5 cm significantly reduced acute pain, discomfort and the period of convalescence. Long-term follow-up will show the value of FS fixation in terms of chronic pain and recurrence. As FS potentially may solve many of the outcome problems associated with LVHR, future studies should include larger hernia defects including large incisional hernias, as the operative technique may be different.

ABBREVIATIONS

ASA	American Society of Anesthesiologists
LVHR	Laparoscopic ventral hernia repair
POD	Postoperative day
POD	0 day of surgery
BMI	Body mass index = weight (kg)/height2 (cm)
RCT	Randomised clinical trial
VAS	Visual analogue scale
VRS	Verbal rating scale
FS	Fibrin sealant
CI	Confidence interval

REFERENCES

1. Merskey H (Eds.) and International Association for the Study of Pain Subcommittee on Taxonomy. Classification of chronic pain syndromes and definitions of pain terms. Pain Suppl 1986; 3: S1–226.
2. Turk D, Melzack R. Handbook of Pain Assessment. 2nd ed. New York: Guilford Press; 2001.
3. Loeser JD, Butler SH, Chapman CR et al. Bonica's management of pain. 3rd ed. Lippincott Williams & Wilkins; 2001.
4. Romundstad L, Stubhaug A. Glucocorticoids for acute and persistent postoperative neuropathic pain. What is the evidence? Anesthesiology 2007; 107: 371–3.
5. Muysoms FE, Miserez M, Berrevoet F et al. Classification of primary and incisional abdominal wall hernias. Hernia 2009; 13: 407–14.
6. Homepage of the Danish Ventral Hernia Database, www.herniedatabasen.dk (assessed September 15, 2010).
7. Burger JW, Luijendijk RW, Hop WC et al. Long-term follow-up of a randomized controlled trial of suture versus mesh repair of incisional hernia. Ann Surg 2004; 240: 578–83.
8. LeBlanc KA, Booth WV. Laparoscopic repair of incisional abdominal hernias using expanded polytetrafluoroethylene: preliminary findings. Surg Laparosc Endosc 1993; 3: 39–41.
9. Carbajo MA, Martín del Olmo JC, Blanco JI et al. Laparoscopic treatment vs. open surgery in the solution of major incisional and abdominal wall hernias with mesh. Surg Endosc 1999; 13: 250–2.
10. Forbes SS, Eskicioglu C, McLeod RS et al. Meta-analysis of randomized controlled trials comparing open and laparoscopic ventral and incisional hernia repair with mesh. Br J Surg 2009; 96: 851–8.
11. Eriksen JR, Gögenur I, Rosenberg J. Choice of mesh for laparoscopic ventral hernia repair. Hernia 2007; 11: 481–92.
12. Misra MC, Bansal VK, Kulkarni MP et al. Comparison of laparoscopic and open repair of incisional and primary ventral hernia: results of a prospective randomized study. Surg Endosc 2006; 20: 1839–45.
13. Barbaros U, Asoglu O, Seven R et al. The comparison of laparoscopic and open ventral hernia repairs: a prospective randomized study. Hernia 2007; 11: 51–6.
14. Asencio F, Aguiló J, Peiró S et al. Open randomized clinical trial of laparoscopic versus open incisional hernia repair. Surg Endosc 2009; 23: 1441–8.
15. Rosenberg J, Henriksen N, Jørgensen LN. Multicenter data acquisition made easy. Trials 2010; 11: 49.
16. Fortelny RH, Petter-Puchner AH, Ferguson J et al. A Comparative Biomechanical Evaluation of Hernia Mesh Fixation by Fibrin Sealant. J Surg Res 2010 [Epub ahead of print] doi:10.1016/j.jss.2010.06.001
17. Ip HY, Abrishami A, Peng PW et al. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. Anesthesiology 2009; 111: 657–77.
18. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain Emerg Med J 2001; 18: 205–7.
19. Todd KH. Clinical versus statistical significance in the assessment of pain relief. Ann Emerg Med 1996; 27: 439–41.
20. Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? Acad Emerg Med 1998; 5: 1086–90.
21. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery - a review of predictive factors. Anesthesiology 2000: 93: 1123–33.

22. Bisgaard T, Rosenberg J, Kehlet H. From acute to chronic pain after laparoscopic cholecystectomy: A prospective follow-up analysis. Scand J Gastroenterol 2005; 40: 1358–64.
23. Bisgaard T, Klarskov B, Rosenberg J et al. Factors determining convalescence after uncomplicated laparoscopic cholecystectomy. Arch Surg 2001; 136: 917–21.
24. Rubin GJ, Hardy R, Hotopf M. A systematic review and meta-analysis of the incidence and severity of postoperative fatigue. J Psychosom Res 2004; 57: 317–26.
25. Christensen T, Bendix T, Kehlet H. Fatigue and cardiorespiratory function following abdominal surgery. Br J Surg 1982; 69: 417–9.
26. Bautmans I, Njemini R, De Backer J et al. Surgery-induced inflammation in relation to age, muscle endurance, and self-perceived fatigue. J Gerontol A Biol Sci Med Sci 2010; 65A: 266–73.
27. Van´ Riet M, de Vos van Steenwijk PJ, Kleinrensink GJ et al. Tensile strength of mesh fixation methods in laparoscopic incisional hernia repair. Surg Endosc 2002; 16: 1713–6.
28. Winslow ER, Diaz S, Desai K et al. Laparoscopic incisional hernia repair in a porcine model. What do transfixion sutures add? Surg Endosc 2004; 18: 529–35.
29. Nguyen SQ, Divino CM, Buch KE et al. Postoperative pain after laparoscopic ventral hernia repair: a prospective comparison of sutures versus tacks. JSLS 2008; 12: 113–6.
30. Wassenaar E, Schoenmaeckers E, Raymakers J et al. Mesh-fixation method and pain and quality of life after laparoscopic ventral or incisional hernia repair: a randomized trial of three fixation techniques. Surg Endosc 2010; 24: 1296–302.
31. Beldi G, Wagner M, Bruegger LE et al. Mesh shrinkage and pain in laparoscopic ventral hernia repair: a randomized clinical trial comparing suture versus tack mesh fixation. Surg Endosc 2010 [Epub ahead of print] DOI 10.1007/s00464-010-1246-0
32. Lepere M, Benchetrit S, Bertrand JC et al. Laparoscopic resorbable mesh fixation. Assessment of an innovative disposable instrument delivering resorbable fixation devices: I-Clip™. Final results of a prospective multicentre clinical trial. Hernia 2008; 12: 177-83.
33. http://clinicaltrials.gov/NCT00749268 (assesed September 14, 2010)
34. Tayar C, Karoui M, Cherqui D et al. Robot-assisted laparoscopic mesh repair of incisional hernias with exclusive intracorporeal suturing: a pilot study. Surg Endosc 2007; 21: 1786–9.
35. http://clinicaltrials.gov/NCT00908193 (assesed September 14, 2010)
36. Olmi S, Scaini A, Erba L et al. Use of fibrin glue (Tissucol) in laparoscopic repair of abdominal wall defects: preliminary experience. Surg Endosc 2007; 21: 409–13.
37. Fortelny RH, Petter-Puchner AH, Glaser KS. Fibrin sealant (Tissucol) for the fixation of hiatal mesh in the repair of giant paraesophageal hernia. A case report. Surg Laparosc Endosc Percutan Tech 2009; 19: e91–4.
38. Olmi S, Scaini A, Erba L et al. Laparoscopic repair of inguinal hernias using an intraperitoneal onlay mesh technique and a Parietex composite mesh fixed with fibrin glue (Tissucol). Personal technique and preliminary results. Surg Endsoc 2007; 21: 1961-4.
39. Nowobilski W, Dobosz M, Wojciechowicz T et al. Lichtenstein inguinal hernioplasty using butyl-2-cyanoacrylate versus sutures. Preliminary experience of a prospective randomized trial. Eur Surg Res 2004; 36: 367–70.
40. Helbling C, Schlumpf R. Sutureless Lichtenstein: first results of a prospective randomised clinical trial. Hernia 2003; 7: 80–4.
41. Ladurner R, Drosse I, Seitz S et al. Tissue attachment strength and adhesion formation of intraabdominal fixed meshes with cyanoacrylat glues. Eur J Med Res 2008; 13: 185–91.
42. Agresta F, Baldazzi GA, Ciardo LF et al. Lightweight partially absorbable monofilament mesh (polypropylene/poliglecaprone 25) for TAPP inguinal hernia repair: initial experience. Surg Laparosc Endosc Percutan Tech 2007; 17: 91–4.
43. Fortelny RH, Petter-Puchner AH, Walder N et al. Cyanoacrylate tissue sealant impairs tissue integration of macroporous mesh in experimental hernia repair. Surg Endosc 2007; 21: 1781–5.
44. Toriumi DM, O'Grady K. Surgical tissue adhesives in otolaryngology-head and neck surgery. Otolaryngol Clin N Am 1994; 27: 203–9.
45. Schäfer M, Vuilleumier H, Mare LD et al. Fibrin sealant for mesh fixation in endoscopic inguinal hernia repair: is there enough evidence for its routine use? Surg Laparosc Endosc Percutan Tech 2010; 20: 205-12.
46. Olmi S, Scaini A, Erba L et al. Quantification of pain in laparoscopic transabdominal preperitoneal (TAPP) inguinall hernioplasy indentifies marked differences between prosthesis fixation systems. Surgery 2007; 142: 40–6.
47. Lovisetti F, Zonta S, Rota E et al. Use of human fibrin glue (Tissucol) versus staples for mesh fixation in laparoscopic transabdominal preperitoneal hernioplasty. A prospective, randomized study. Ann Surg 2007; 245: 222–31.
48. Lau H. Fibrin sealant versus mechanical stapling for mesh fixation during endoscopic extraperitoneal inguinal hernioplasty: a randomized prospective trial. Ann Surg 2005; 242: 670–5.
49. Hollinsky C, Kolbe T, Walter I et al. Comparison of a new self-gripping mesh with other fixation methods for laparoscopic hernia repair in a rat model. J Am Coll Surg 2009; 208: 1107–14.
50. Chastan P. Tension-free open hernia repair using an innovative self-gripping semi-resorbable mesh. Hernia 2009; 13: 137–42.
51. Koch CA, Greenlee SM, Larson DR et al. Randomized prospective study of totally extraperitoneal inguinal hernia repair: fixation versus no fixation of mesh. JSLS 2006; 10: 457–60.
52. Taylor C, Layani L, Liew V et al. Laparoscopic inguinal hernia repair without mesh fixation, early results of a large randomised clinical trial. Surg Endosc 2008; 22: 757–62.
53. Coughlin SM, Karanicolas PJ, Emmerton-Coughlin HM et al. Better late than never? Impact of local analgesia timing on postoperative pain in laparoscopic surgery: a systematic review and metaanalysis. Surg Endosc 2010. [Epub ahead of print] DOI 10.1007/s00464-010-1111-1.
54. Bellows CF, Berger DH. Infiltration of suture sites with local anesthesia for management of pain following laparoscopic ventral hernia repairs: a prospective randomized trial. JSLS 2006; 10: 345–50.
55. Beaussier M, El'Ayoubi H, Schiffer E et al. Continuous preperitoneal infusion of ropivacaine provides effective analgesia and accelerates recovery after colorectal surgery: A

randomized, double-blind, placebo-controlled study. Anesthesiology 2007; 107: 461–8.
56. Rosen MJ, Duperier T, Marks J et al. Prospective randomized double-blind placebo-controlled trial of postoperative elastomeric pain pump devices used after laparoscopic ventral hernia repair. Surg Endosc 2009; 23: 2637–43.
57. Palmes D, Röttgermann S, Classen C et al. Randomized clinical trial of the influence of intraperitoneal local anaesthesia on pain after laparoscopic surgery. Br J Surg 2007; 94: 824–32.
58. Kehlet H, Gray AW, Bonnet F et al. A procedure-specific systematic review and consensus recommendations for postoperative analgesia following laparoscopic cholecystectomy. Surg Endosc 2005; 19: 1396–415.
59. McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. Drugs 2010; 70: 1149–63.
60. Saber AA, Elgamal MH, Rao AJ et al. Early experience with lidocaine patch for postoperative pain control after laparoscopic ventral hernia repair. Int J Surg 2009; 7: 36–8.
61. Dolan J, Lucie P, Geary T et al. The rectus sheath block: accuracy of local anesthetic placement by trainee anesthesiologists using loss of resistance or ultrasound guidance. Reg Anesth Pain Med 2009; 34: 247–50.
62. Smith BE, Suchak M, Siggins D et al. Rectus sheath block for diagnostic laparoscopy. Anaesthesia 1988; 43: 947–8.
63. Azemati S, Khosravi MB. An assessment of the value of rectus sheath block for postlaparoscopic pain in gynecologic surgery. J Minim Invasive Gynecol 2005; 12: 12–5.
64. Isaac LA, McEwen J, Hayes JA et al. A pilot study of the rectus sheath block for pain control after umbilical hernia repair. Paediatr Anaesth 2006; 16: 406–9.
65. Petersen PL, Mathiesen O, Torup H et al. The transversus abdominis plane block: a valuable option for postoperative analgesia? A topical review. Acta Anaesthesiol Scand 2010; 54: 529–35.
66. Niraj G, Kelkar A, Fox AJ. Application of the transversus abdominis plane block in the intensive care unit. Anaesth Intensive Care 2009; 37: 650–2.
67. Bonnet F, Berger J, Aveline C. Transversus abdominis plane block: what is its role in postoperative analgesia? Br J Anaesth 2009; 103: 468–70.
68. Belavy D, Cowlishaw PJ, Howes M et al. Ultrasound-guided transversus abdominis plane block for analgesia after Caesarean delivery. Br J Anaesth 2009; 103: 726–30.
69. Niraj G, Searle A, Mathews M et al. Analgesic efficacy of ultrasound-guided transversus abdominis plane block in patients undergoing open appendicectomy. Br J Anaesth 2009; 103: 601–5.
70. El-Dawlatly AA, Turkistani A, Kettner SC et al. Ultrasound-guided transversus abdominis plane block: description of a new technique and comparison with conventional systemic analgesia during laparoscopic cholecystectomy. Br J Anaesth 2009; 102: 763–7.
71. Carney J, McDonnell JG, Ochana A et al. The transversus abdominis plane block provides effective postoperative analgesia in patients undergoing total abdominal hysterectomy. Anesth Analg 2008; 107: 2056–60.
72. McDonnell JG, O'Donnell B, Curley G et al. The analgesic efficacy of transversus abdominis plane block after abdominal surgery: a prospective randomized controlled trial. Anesth Analg 2007; 104: 193–7.
73. Niraj G, Kelkar A, Fox AJ. Oblique sub-costal transversus abdominis plane (TAP) catheters: an alternative to epidural analgesia after upper abdominal surgery. Anaesthesia 2009; 64: 1137–40.
74. Gupta A, Stierer T, Zuckerman R et al. Comparison of recovery profile after ambulatory anesthesia with propofol, isoflurane, sevoflurane and desflurane: a systematic review. Anesth Analg 2004; 98: 632–41.
75. Tzovaras G, Zacharoulis D, Georgopoulou S et al. Laparoscopic ventral hernia repair under spinal anesthesia: a feasibility study. Am J Surg 2008; 196: 191–4.
76. Senthil Kumar M, Dehran M. Laparoscopic hernia repair with the patient under combined spinal epidural anesthesia: cardiac arrest. Surg Endosc 2009; 23: 922–3.
77. Jakobsen J. Preoperative single-dose intravenous dexamethasone during ambulatory surgery: update around the benefit versus risk. Curr Opin Anaesthesiol 2010. [Epub ahead of print] DOI:10.1097/ACO.0b013e32833ff302.
78. Mohammadi SS, Seyedi M. Effects of gabapentin on early postoperative pain, nausea and vomiting in laparoscopic surgery for assisted reproductive technologies. Pak J Biol Sci 2008; 11: 1878–80.
79. Mathiesen O, Møiniche S, Dahl JB. Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure. BMC Anesthesiol 2007; 7: 6.
80. Power I. Recent advances in postoperative pain therapy. Br J Anaesth 2005; 95: 43–51.
81. Dahl JB, Mathiesen O, Møiniche S. Protective premedication: An option with gabapentin and related drugs? A review of gabapentin and pregabalin in the treatment of postoperative pain. Acta Anaesthesiol Scand 2004; 48: 1130–6.
82. Dahl JB, Mathiesen O, Kehlet H. An expert opinion on postoperative pain management, with special reference to new developments. Expert Opin Pharmacother 2010; 11: 2459–70.
83. http://clinicaltrials.gov/ NCT00351455 (assesed September 14, 2010).
84. Schulz KF, Altman DG, Moher D, CONSORT group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. PLoS Med 2010; 7: e1000251. doi:10.1371/journal.pmed.1000251
85. Bisgaard T, Klarskov B, Rosenberg J et al. Characteristics and prediction of early pain after laparoscopic cholecystectomy. Pain 2001; 90: 261–9.
86. Pokorny H, Klingler A, Scheyer M et al. Postoperative pain and quality of life after laparoscopic and open inguinal hernia repair: results of a prospective randomized trial. Hernia 2006; 10: 331–7.