Randomized clinical trial

Randomized clinical trial of fibrin sealant *versus* titanium tacks for mesh fixation in laparoscopic umbilical hernia repair

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Background: The use of tacks for mesh fixation may induce pain after surgery for ventral hernia. The aim of this study was to compare postoperative pain after laparoscopic ventral hernia repair (LVHR) with conventional mesh fixation using titanium tacks *versus* fibrin sealant (FS).

Methods: This randomized clinical trial included patients with an umbilical hernia defect ranging from 1·5 to 5 cm at three Danish hernia centres. Participants were assigned randomly to FS or titanium tack fixation. The primary outcome was acute pain, defined as the mean pain score on days 0–2 after surgery, measured on a 0–100-mm visual analogue scale (VAS).

Results: Forty patients were included, of whom 38 were available for intention-to-treat analysis after 1 month. Patients in the FS group reported less pain than those in the tack group on days 0–2, both at rest (median 19 *versus* 47 mm; $P = 0{\cdot}025$) and during activity (38 *versus* 60 mm; $P = 0{\cdot}014$). The absolute difference in pain score between groups was 19 (95 per cent confidence interval 3 to 34) and 20 (4 to 35) mm at rest and during activity respectively. Patients in the FS group resumed normal daily activity earlier (after median 7 *versus* 18 days; $P = 0{\cdot}027$) and reported significantly less discomfort. No recurrences were observed.

Conclusion: Mesh fixation with FS in LVHR was associated with less acute postoperative pain, discomfort and a shorter convalescence than tack fixation. Long-term follow-up is needed to show whether the effect of FS fixation persists in terms of chronic pain and recurrence. Registration number: NCT00842842 (http://www.clinicaltrials.gov).

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Introduction

Information about pain after laparoscopic ventral hernia repair (LVHR) is limited, but a few studies have reported that pain is an important limiting factor for convalescence[1–3]. Although the laparoscopic technique is minimally invasive, many patients report severe and long-lasting pain after operation affecting general well-being and quality of life[1]. Mesh fixation with titanium tacks with or without sutures may play a key role in the development of postoperative pain, as shown for inguinal hernias[4–7].

Fibrin sealant (FS) has been used successfully for extraperitoneal mesh fixation in open ventral hernia repair[8] and laparoscopic inguinal hernia repair[4–7]. It is unknown whether mesh fixation with FS reduces pain after LVHR, as no clinical studies have been published. Experimental studies have shown FS to be as effective as titanium tacks for mesh fixation in LVHR in terms of strength of ingrowth and adhesion formation[9,10], but mesh dislocation has also been reported[11]. This randomized double-blind trial was conducted to evaluate the effect of FS for mesh fixation in LVHR for umbilical hernia.

Methods

All patients referred with a symptomatic umbilical hernia were registered consecutively and evaluated according to the study protocol for participation in the trial. Between August 2009 and March 2010 all eligible patients at three

participating centres were assessed and included in the study. Between September 2009 and May 2010, they were assigned randomly to either tack fixation or FS and underwent hernia repair. The study was approved by the Committees on Biomedical Research Ethics for the Capital Region of Denmark and the Danish Data Protection Agency, and performed in agreement with the Helsinki II declaration. All eligible patients received verbal and written information. Informed consent for participation was obtained from all included patients.

Inclusion criteria were: symptomatic umbilical hernia with a diameter of 1·5–5 cm at preoperative clinical examination, age 18–85 years, Danish speaking and American Society of Anesthesiologists (ASA) grade I–III. Exclusion criteria were: previous laparoscopic umbilical herniotomy or open operation with mesh, strangulated hernia (acute operation), previous or current use of opioid medication, expected poor compliance (for example owing to dementia, psychiatric disorders), chronic liver disease (Child–Pugh grade B or C), known immune deficiency including current systemic steroid use or other immunosuppressive treatment, pregnancy, medical conditions contraindicating general anaesthesia, simultaneous operation for another hernia, or hernia defect larger than 6 cm measured during the operation.

Surgical procedure

Three hernia centres participated in the trial and all surgeons were experienced in laparoscopic hernia repair. None had experience with intraperitoneal FS application before the start of this study. To standardize the operative procedure among centres, a 1-day theoretical and technical training course on pigs was completed before the study. Consensus on the operative technique was obtained and demonstration videos were made for all participants.

All patients had surgery under propofol-based general anaesthesia. Epidural blockade was not used. Ketorolac (15–30 mg) was given intravenously if not contraindicated. Ondansetron and dexamethasone were given only to patients with a history of postoperative nausea and vomiting. All patients received a single intravenous dose of 1·5 g cefuroxime before surgery. Pneumoperitoneum was established in the left side of the abdomen using a Veress needle or by open access, according to the surgeon's preference. Maximal intra-abdominal pressure was set to 12 mmHg. Trocar sites were infiltrated with a total of 20 ml 0·5 per cent bupivacaine without adrenaline (epinephrine). A 30° optic inserted through a 10-mm trocar, a 5-mm and a 10-mm working trocar were all placed in the left side of the abdomen. Adhesions to the hernia sac, including preperitoneal fat and the falciform ligament in the area of the mesh, were taken down using electrocautery scissors (*Video S1*, supporting information). The hernia sac was not resected and the defect was not sutured. The hernia defect was measured, and the patient excluded if the diameter exceeded 6 cm.

A 12-cm round Parietex™ Composite mesh (Sofradim, Trevoux, France; part of Covidien, North Haven, Connecticut, USA) was used for all operations. For FS fixation two packs of 2 ml Tisseel® Duo Quick (Baxter Healthcare, Vienna, Austria) were used, giving a total of 8 ml sealant. The 500-unit/ml thrombin unit was replaced with a 4-unit/ml thrombin formulation, to extend the coagulation time[12]. For tack fixation the ProTack™ 5-mm fixation device (Covidien) was used with tacks placed 1–2 cm apart in a double-crown fashion. In patients allocated to FS, the mesh was introduced through the 10-mm port, and placed and orientated correctly on the intestine. A uniform layer of FS was applied to the mesh using a manual application catheter (30-cm DuploSpray® MIS Applicator without spray function; Baxter Healthcare). Two graspers were used to place and temporarily fix the mesh on the abdominal wall. The intra-abdominal pressure was then decreased to 6 mmHg for 5–10 min until the mesh position was stable. The graspers were used to ensure good contact between the mesh and the abdominal wall, especially along the edge of the mesh. Trocars were removed and the abdominal cavity was exsufflated passively. If fixation was unsatisfactory with FS, the mesh was fixed with tacks, as defined in the protocol. No transfascial fixation sutures or stay sutures were used.

All patients were scheduled for discharge on the day of surgery, unless social conditions or surgery late in the afternoon made an overnight stay necessary. They were allowed to resume normal daily activities 2 days after operation. All patients were given oral paracetamol (1 g four times daily) and a non-steroidal anti-inflammatory drug (600 mg ibuprofen three times daily) on the day of surgery and for 2 days thereafter.

Randomization and masking

Block randomization was performed. The randomization sequence was generated by a computer, and sealed envelopes with code and allocation group were prepared in blocks of four. Randomization was performed by the surgeon after the patient had been anaesthetized to ensure enough time to prepare the frozen FS (30–45 min). Later randomization would have prolonged the operating time unacceptably. All patients, caregivers and those assessing the outcome parameters were blinded to the

group assignment. Data from case report forms and questionnaires were entered into a web-based registration system[13] by a project nurse. Anonymized data were extracted from the database and the randomization code was broken only after final analysis. According to the protocol, excluded patients and dropouts were not replaced. Only if more than four patients dropped out was a new block included.

Study endpoints

The primary outcome was acute postoperative pain, defined as the mean pain score on days 0 to 2 after surgery, measured on a 0–100-mm visual analogue scale (VAS). Day 0 was the day of surgery. Secondary outcome measures were fatigue, discomfort (general well-being) and time to resumption of normal daily activities.

Assessment of outcome parameters

Questionnaires were completed by the patient before operation at the time of inclusion, daily on days 0–10 following hernia repair and after 1 month, always at 20.00 hours.

Pain was measured on a VAS ranging from 0 mm (no pain) to 100 mm (worst pain imaginable), both at rest and during activity, and also by means of a verbal rating scale (VRS) (0, no pain; 1, slight pain; 2, moderate pain; 3, severe pain). Fatigue was measured using a ten-point ordinal fatigue scale (1, fit; 10, fatigued)[14] and discomfort on a 1–100-mm VAS (0 mm, extremely comfortable; 100 mm, extremely uncomfortable). Patient satisfaction was measured on a 0–100-mm VAS (0, most unsatisfactory) on day 30 after surgery. Analgesic use in addition to that prescribed by the hospital was registered by the patient at home until day 30.

All patients were examined in the outpatient clinic on days 10 and 30 after hernia repair by the specialist project nurse and questionnaires were collected. The presence of predefined medical and surgical complications was registered at each follow-up visit. Recurrence was considered a safety parameter; it was evaluated clinically at all visits and by ultrasonography in case of doubt.

Statistical analysis

The sample size calculation was based on data from a prospective study of LVHR[1]. The mean(s.d.) pain score on days 0–2 after surgery was 59(22) mm, and a type I error of 5 per cent and a type II error of 20 per cent was accepted. A minimum relevant difference in VAS pain score 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 trial.

Data were presented as median (range) unless indicated otherwise. Non-parametric methods were used in all statistical analyses. The Mann–Whitney *U* test was used for comparisons between independent groups. Paired intragroup comparisons were performed using the Wilcoxon test. Categorical variables were compared by means of Fisher's exact test. Spearman's rank correlation test (r_s) was used for correlation analysis. One-way repeated-measures ANOVA was used to test whether the mean of the dependent variable (pain) differed with respect to the categorical variable (time). A multiple regression analysis with backward elimination was carried out to identify significant predictors of postoperative pain. All data were based on intention-to-treat analysis. $P < 0{\cdot}050$ was considered statistically significant. Statistical analyses were performed using SAS® 9.1 for Windows® (SAS Institute, Cary, North Carolina, USA).

Results

During the study interval, 40 of 111 eligible patients were included in the study at the three centres (*Fig. 1*). Reasons for exclusion of 63 patients according to predefined criteria are shown in *Table S1* (supporting information). One patient allocated to the tack group was excluded during the operation because the hernia diameter was 7 cm. Two patients allocated to the FS group required tack fixation during surgery (at two different centres) owing to technical failure of the sealant. Both patients remained in the FS group for the intention-to-treat analysis. One patient allocated to the FS group did not complete the postoperative questionnaires and was therefore lost to follow-up.

Patient demographics and baseline characteristics are summarized in *Table 1*. There was no significant difference in baseline (preoperative) pain scores, but *post hoc* analysis showed a significant baseline imbalance in age between the tack and FS groups (median 45 *versus* 59 years respectively; $P = 0{\cdot}014$). There was no difference in age ($P = 0{\cdot}762$), pain at rest (0·787), pain during activity ($P = 0{\cdot}951$) or other parameters between the three centres.

Duration of surgery was significantly longer in the FS group (median 50 *versus* 40 min; $P = 0{\cdot}016$) (*Table 2*). There was no significant difference in hospital stay, hernia diameter, or opioid consumption in the recovery room between groups (*Table 2*). No significant correlation was

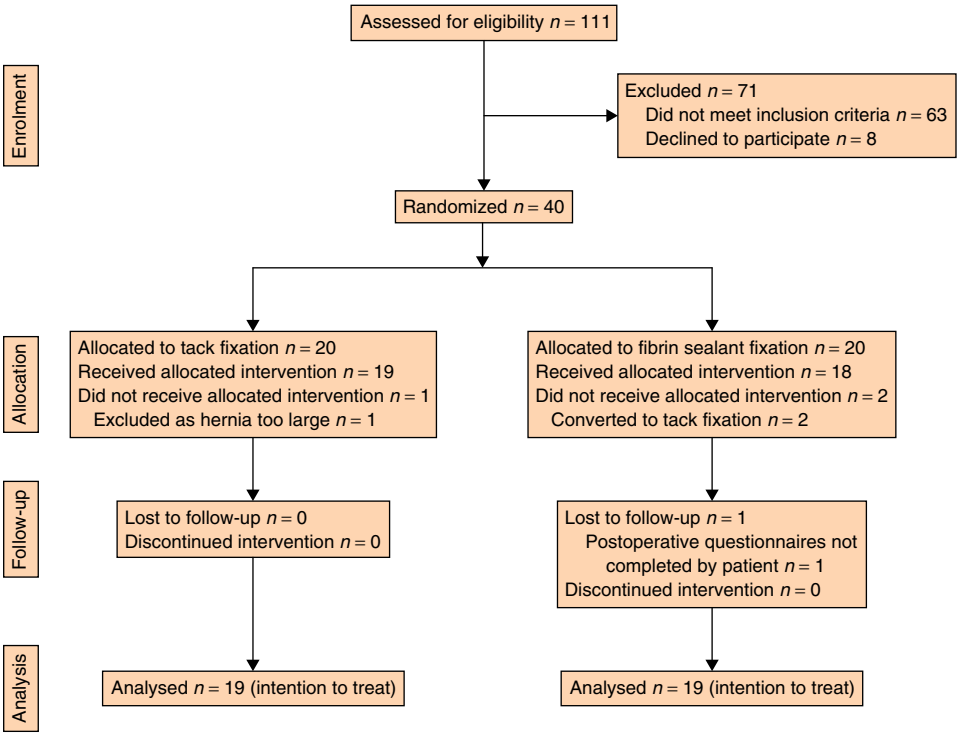

Fig. 1 CONSORT diagram[15] for the trial

Table 1 Patient demographics and baseline characteristics

	Tack fixation ($n = 19$)	Fibrin sealant ($n = 19$)	P‡
Age (years)*	45 (31–67)	59 (34–69)	0·014§
Sex ratio (M : F)	13 : 6	14 : 5	1·000
Body mass index (kg/m^2)*	31·1 (24·8–38·8)	31·2 (19·0–38·3)	0·238§
Employment status			0·058
Not working	3	10	
Light work	11	7	
Heavy work	5	2	
ASA grade			0·728
I	7	4	
II	11	14	
III	1	1	
Smoker	4	6	0·543
Daily preoperative analgesic use†	4	0	0·105
Hernia type			
Primary	14	17	
Recurrent	5	2	0·405
Preoperative pain score (0–100 VAS)*			
At rest	5 (0–38)	1 (0–47)	0·265§
During activity	16 (0–71)	3 (0–53)	0·299§

*Values are median (range). ASA, American Society of Anesthesiologists; VAS, visual analogue scale. †All paracetamol. ‡Fisher's exact test, except §Mann–Whitney U test.

found between number of tacks used per patient and pain on days 0–2 ($r_s = 0·10$, $P = 0·663$).

Evaluation of pain

Pain scores from 0–2 days after surgery were significantly lower in the FS group than in the tack group, both at rest and during activity (*Table 2*, *Fig. 2a,b*, *Fig. 3*). Patients in the FS group had significantly lower pain scores over the first 10 days after hernia repair. On day 30, pain scores in the FS group were significantly below preoperative values, both at rest (median (range) 0 (0–3) *versus* 1 (0–47) mm respectively; $P = 0·025$) and during activity (0 (0–33) *versus* 3 (0–53) mm; $P = 0·027$). No difference was found between pain scores at 30 days and preoperative scores in the tack group: 0 (0–82) *versus* 5 (0–38) mm at rest ($P = 0·138$) and 1 (0–82) *versus* 16 (0–71) mm during activity ($P = 0·054$).

The proportion of patients suffering moderate to severe pain, defined as a VRS score of at least 2 or a VAS score of at least 50, was significantly higher on day 2 in the tack group compared with the FS group (12 of 19 *versus* 5 of 19 respectively; $P = 0·049$). There were no differences between the two groups in moderate to severe pain on days 0, 7, 10 and 30. After Bonferroni

Table 2 Perioperative details and outcome data

	Tack fixation ($n = 19$)	Fibrin sealant ($n = 19$)	Mean difference*	P‡
Perioperative data				
No. of tacks per patient	27 (17–38)	–		
Duration of surgery (min)	40 (23–130)	50 (30–90)		0·016
Hospital stay (days)	0 (0–2)	0 (0–2)		0·221
Perioperative hernia diameter (cm)	2·5 (1·5–4·0)	3·0 (2·0–6·0)		0·151
Opioid use in recovery room (mg)†	30 (0–90)	30 (0–120)		0·645
Postoperative scores				
Pain (0–100 VAS)				
Days 0–2, at rest	47 (6–91)	19 (3–74)	19 (3, 34)	0·025
Days 0–2, during activity	60 (18–96)	38 (6–98)	20 (4, 35)	0·014
Days 0–10, at rest	32 (2–73)	10 (2–59)	15 (2, 27)	0·028
Days 0–10, during activity	40 (6–74)	21 (2–67)	14 (2, 27)	0·031
Discomfort (0–100 VAS)				
Days 0–2	55 (14–94)	41 (6–87)	16 (2, 30)	0·010
Days 0–10	38 (8–63)	22 (5–55)	13 (2, 24)	0·025
Fatigue (score 0–10)				
Days 0–2	8 (3–10)	7 (2–10)	1·1 (−0·3, 2·4)	0·074
Days 0–10	5 (2–8)	4 (1–7)	0·8 (−0·4, 2·0)	0·230
Time to resumption of normal daily activities (days)	18 (1–95)	7 (1–66)	11 (−2, 24)	0·027
Satisfaction (0–100 VAS), day 30	99 (26–100)	99 (51–100)	−5 (−18, 7)	0·891

Values are median (range), except *mean difference (95 per cent confidence interval). All visual analogue scale (VAS) scores are mean scores for the interval shown. †Oral morphine equivalent doses. One patient in the tack group received a transverse abdominal plane block on the day after surgery. ‡Mann–Whitney U test.

correction for multiple comparisons, the difference on day 2 was not significant ($P = 0·49$, Bonferroni correction for 10 comparisons). The hypothesis of no time effect on postoperative pain was rejected in a one-way repeated measure ANOVA ($P < 0·001$).

Baseline variables that correlated significantly with increased postoperative pain (pain measured on VAS during activity on days 0–2) by univariable analysis (r_s), included: randomization to the tack group ($P = 0·011$), increasing age in years ($P = 0·019$) and daily preoperative analgesic use before surgery ($P = 0·018$). A multiple regression analysis with backward elimination using all significant parameters from the univariable analysis showed that tack fixation group was the only significant predictor of postoperative pain.

Evaluation of secondary endpoints

Patients in the FS group reported significantly less discomfort than those in the tack group, measured as mean discomfort score on days 0–2 and days 0–10 (*Table 2*, *Fig. 2c*). There was no difference in fatigue scores between groups (*Table 2*, *Fig. 2d*).

Patients in the FS group resumed normal daily activities significantly earlier than those in the tack group (after 7 (1–66) *versus* 18 (1–95) days respectively; $P = 0·027$) (*Table 2*). When the outliers in both groups (66 days and 95 days) were excluded from the analysis, the difference was still significant (7 (1–45) *versus* 16 (1–45) days; $P = 0·023$).

A significant positive correlation between time to resumption of normal daily activities and pain scores on days 0–2, both at rest and during activity, was found (at rest: $r_s = 0·35$, $P = 0·032$; during activity: $r_s = 0·43$, $P = 0·008$). There was no significant difference in employment status between groups (*Table 1*), and no significant correlation between time to resumption of normal daily activities and employment status ($r_s = -0·025$, $P = 0·882$). Patient satisfaction on day 30 after surgery was excellent, with no difference between groups (*Table 2*).

Postoperative complications

Nine patients in the tack group and five in the FS group registered use of non-steroidal anti-inflammatory drugs after day 2 ($P = 0·179$). Paracetamol was used by three patients in each group, and morphine by three patients in the tack group and two in the FS group, during follow-up.

No significant differences in morbidity between groups were found after 30 days (*Table 3*). Eight patients (3 in the

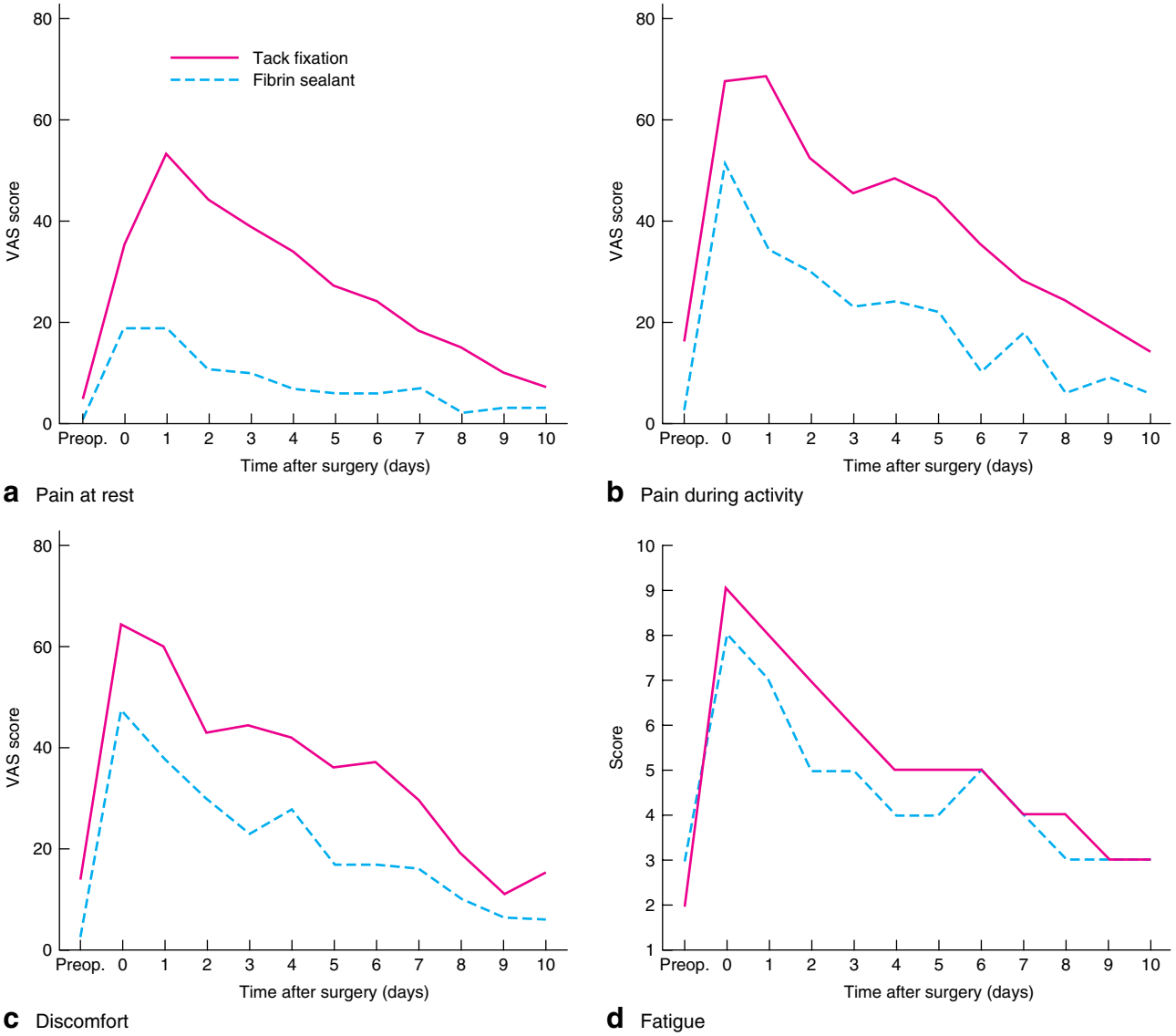

Fig. 2 Changes in patient-reported outcome measures during the first 10 days after hernia repair: **a** pain scores on visual analogue scale (VAS) at rest, **b** VAS pain scores during activity, **c** VAS discomfort scores and **d** fatigue scores. Values are medians. Day 0 is the day of surgery

Table 3 Postoperative complications within 30 days of surgery

	Tack fixation ($n = 19$)	Fibrin sealant ($n = 19$)
Seroma	7	6
Haematoma	3	4
Superficial infection	1	2
Skin erythema	0	1
Readmission	2	1
Recurrence	0	0

FS group and 5 in the tack group) still had a clinical seroma on day 30. Two patients with a suspected recurrence had an ultrasound examination, but neither had a recurrent hernia; a seroma was found in one and a haematoma in the other. The readmission rate was low in both groups (*Table 3*). Readmissions were for pain (1 in each group) without the need for an overnight stay, and suspected subileus (1 in tack group) treated conservatively with an uneventful recovery. No adverse events or side-effects were observed.

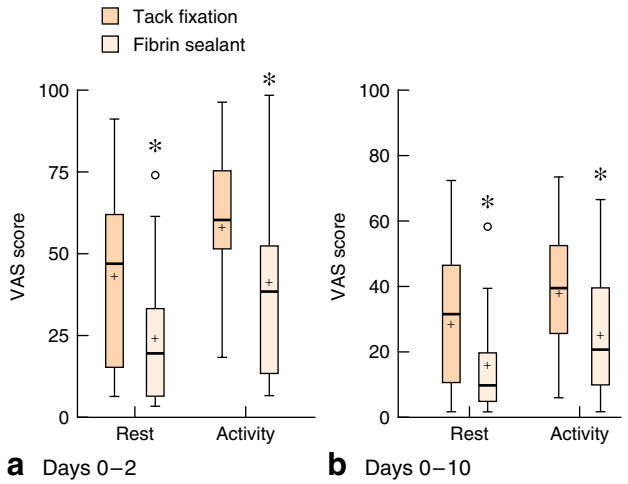

Fig. 3 Patient-reported pain scores at rest and during activity from **a** days 0–2 and **b** days 0–10 after hernia repair. Mean (plus sign), median (horizontal line within box), interquartile range (box), and range (error bars) excluding outliers (circles) are shown. $*P < 0{\cdot}050$ *versus* tack group (Mann–Whitney U test)

Discussion

Mesh fixation in patients with a small umbilical hernia was associated with significantly reduced acute postoperative pain when FS was used rather than tack fixation. Analysis of secondary outcome parameters showed that FS significantly improved general well-being and decreased time to resumption of normal daily activities. No recurrences were detected in the month after surgery, substantiating the immediate technical feasibility of the procedure. The results are promising as postoperative pain has remained an unsolved clinical problem following LVHR.

Some limitations of the study deserve mentioning. There was a significant imbalance in age between the groups. Age is a well known predictor of postoperative pain[16], but a multiple regression analysis found that age did not significantly influence or predict postoperative pain in the present study. The difference in operating time of 10 min in favour of tack fixation was small and had no major clinical relevance. This trial was not scheduled to address any cost issues and no data on cost differences were presented.

The judgement of whether a certain significant difference is clinically relevant is subjective. In the sample size calculation a difference of 25 mm on a 0–100-mm VAS was deemed clinically relevant. The discriminative ability of a VAS has been evaluated in several studies, which found the minimum clinically significant difference on a 0–100-mm scale to be between 9 and 13 mm[17–19]. In the present study, the absolute difference in VAS score during activity on days 0–2 between groups was 20 mm, so the specified minimum relevant difference of 25 mm was not achieved. This may be a limitation of the study, but the authors still believe that the results are clinically important and relevant. Pain was measured both at rest and during activity, and there may have been a type I error as the two parameters are closely related, but the risk was minimal.

Some would argue that only small umbilical hernias were investigated, that laparoscopic surgery is 'too complicated' for such a minor procedure, and that the results are not applicable to the 'general' patient with ventral hernia. The considerable effect reported for small hernia defects calls for further studies in larger hernias. A median hernia diameter of 3·0 cm and body mass index of 31·2 kg/m^2 for patients in the FS group, and the fact that recurrent hernias were also included, justify the laparoscopic approach. The decision to include only umbilical hernias was made to ensure a uniform study population and standard operative technique. By limiting the maximum diameter of included hernias to 5 cm, a minimum of 3 cm overlap and use of the same mesh size was possible in all patients. Furthermore, three centres participated in the trial, which strengthened the external validity of the results. Use of 4 units/ml thrombin solution instead of the manufactured 500 units/ml thrombin unit might have altered the strength of fixation. However, a recent study by Jenkins and colleagues[20] found equivalent acute fixation strength to the peritoneum for FS containing 4 units/ml compared with 500 units/ml thrombin.

To date, only one non-randomized study has reported use of FS for intraperitoneal mesh fixation in LVHR[21]. All hernia defects were smaller than 7 cm in diameter and four temporary holding sutures were used to place the mesh. VAS pain scores were obtained from 30 of the 40 included patients and the highest mean score reported during the first 3 days after surgery was 20 mm; no pain was observed from day 7[21]. The mean follow-up was 16 months and no recurrences or severe complications were reported. The pain scores in the first 3 days after surgery were consistent with the pain scores measured at rest in the FS group in the present study. Three clinical studies, one non-randomized[22] and two randomized non-blinded[2,23] trials, compared tacks with sutures for mesh fixation in LVHR. Two studies reported no difference in acute or chronic postoperative pain between groups[2,22]. In the study by Beldi and colleagues[23], patients in the suture group reported significantly more pain after 6 weeks but not after 6 months, compared with patients in the tack group. Long-term follow-up is needed to show the value of FS fixation in terms of chronic pain and recurrence. Future studies may include larger hernia defects and large incisional hernias.

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Patient exclusions according to predefined criteria (Word document)

Video S1 Intraperitoneal onlay mesh repair with fibrin glue (wmv file)

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Commentary

Randomized clinical trial of fibrin sealant *versus* titanium tacks for mesh fixation in laparoscopic umbilical hernia repair (*Br J Surg* 2011; 98: 1537–1545)

This article describes a well performed randomized trial investigating whether gluing the mesh reduces postoperative pain compared with use of tacks in laparoscopic umbilical hernia repair. As one of many unanswered questions in hernia repair regarding reduction of pain, this is a welcome addition to sparse evidence. However, the study does not indicate unequivocally that gluing mesh is superior to tacking. The study was performed in patients with a small hernia and the short follow-up does not allow conclusions to be drawn concerning long-term recurrence risk. The difference in postoperative pain is small, and a significant difference in age, preoperative pain and employment rate could all explain the difference found in favour of gluing. Sensitivity analysis was performed, but the small numbers showed very wide confidence intervals which makes the clinical relevance questionable. The results are not generalizable. The most important reason for not implementing gluing could be associated costs, but costs are not reported. In my hospital the cost difference for glue and extra operating time compared with use of tacks would exceed €500 per operation.

However, the results do suggest that the use of fibrin glue for small hernias achieves a slightly, although clinically questionable, lower risk of postoperative pain in the short term. Personally I would not yet advocate its use. Whether glue is safe for larger hernias and does not present a risk factor for recurrence remains uncertain and needs to be addressed. Animal studies indicate that certain mesh types should not be glued to the peritoneum[1]. Loosening, shrinkage and migration of mesh, and how to prohibit dislocation, are important aspects that need further clinical research. The type of material, how much overlap, what defect can be safely bridged, and the role of transfascial sutures, resorbable *versus* non-resorbable tacks and fibrin glue, are all still under investigation. Whether fibrin glue will cause fewer adhesions and reduce pain without a higher recurrence rate remains to be confirmed, but the strategy appears promising.

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