Randomized clinical trial

Randomized clinical trial of tissue glue *versus* absorbable sutures for mesh fixation in local anaesthetic Lichtenstein hernia repair

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Background: **Chronic pain may be a long-term problem related to mesh fixation and operative trauma after Lichtenstein hernioplasty. The aim of this study was to compare the feasibility and safety of tissue cyanoacrylate glue *versus* absorbable sutures for mesh fixation in Lichtenstein hernioplasty.**

Methods: **Lichtenstein hernioplasty was performed under local anaesthesia as a day-case operation in one of three hospitals. The patients were randomized to receive either absorbable polyglycolic acid 3/0 sutures (Dexon®; 151 hernias) or 1 ml butyl-2-cyanoacrylate tissue glue (Glubran®; 151 hernias) for fixation of lightweight mesh (Optilene®). Wound complications, pain, discomfort and recurrence were identified at 1 and 7 days, 1 month and 1 year after surgery.**

Results: **A total of 302 patients were included in the study. The mean(s.d.) duration of operation was 34(12) min in the glue group and 36(13) min in the suture group ($P = 0{\cdot}113$). The need for analgesics was similar during the first 24 h after surgery. Five wound infections (3·4 per cent) were detected in the glue group and two (1·4 per cent) in the suture group ($P = 0{\cdot}448$). The recurrence rate at 1 year was 1·4 per cent in each group ($P = 1{\cdot}000$). The rates of foreign body sensation, acute and chronic pain were similar in the two groups. Logistic regression analysis showed that the type of mesh fixation did not predict chronic pain 1 year after surgery.**

Conclusion: **Mesh fixation without sutures in Lichtenstein hernioplasty was feasible without compromising postoperative outcome. Registration number: NCT00659542 (http://www.clinicaltrials.gov).**

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Introduction

Lichtenstein hernioplasty is a tension-free open technique for inguinal hernia repair; a polypropylene mesh is used to support the inguinal muscular layer[1]. Chronic pain may occur after 10–30 per cent of procedures[2–5]. The pain may be caused by irritation or damage to the inguinal nerves by sutures or mesh[6], an inflammatory reaction against the mesh[7] or simply scar tissue[8,9]. Pain is often reported to be neuropathic in character, related to younger age, and exists during physical activity; it is more often associated with recurrent hernia surgery[2–5]. The routine use of mesh techniques reduces the risk of hernia recurrence compared with non-mesh methods[10].

Identification and preservation of inguinal nerves during surgery may also decrease the risk of chronic pain[11,12]. Pain is, however, related to both patient and surgical factors. Patients with a high preoperative physical activity score and high pain response to a standard heat stimulus may have a lower frequency of pain after hernia repair[13]. Furthermore, the use of a lightweight mesh may be associated with significantly less pain during exercise and reduced sensation of a foreign object compared with standard mesh[14–16].

The original technique for fixation of mesh in Lichtenstein hernioplasty used non-absorbable sutures placed medially near the pubic periostium and the upper corner of the mesh, and continuous sutures along the inguinal ligament[1,17]. Since that, others have described

using absorbable sutures[18], various tissue glues[19–21] or novel self-fixing mesh[22]. The aim of all these methods has been to try to reduce chronic neuropathic pain (and to speed up surgery).

The aim of the present study was to compare the early postoperative outcome (duration of operation, pain scores, wound complications) and 1-year results of Lichtenstein hernioplasty performed using cyanoacrylate glue or absorbable sutures for mesh fixation.

Methods

This was a randomized multicentre trial conducted in the ambulatory surgery unit of three hospitals in Finland. The study enrolment took place between June 2007 and May 2009. Four surgeons did all the surgery on study patients during their weekly operative schedule (average 3 patients per week per surgeon). They enrolled consecutive patients treated under their care. The study subjects were all over 18 years old with unilateral or bilateral inguinal hernia. Patients who fulfilled the criteria for day-case surgery received written and oral information about the aims and conduct of the study. Every included patient gave informed consent. The exclusion criteria were: known femoral hernia, large scrotal hernia, emergency operation for strangulated hernia, recurrent hernia, allergy to polypropylene and patient refusal. The ethics committees at the hospitals approved the study protocol.

Randomization

Randomization was done separately in each participating centre. Treatment allocation was by means of sealed, numbered envelopes opened in sequence. Each enrolled subject was assigned to suture or tissue glue fixation according to the allocation in the envelope.

Interventions

All surgeons were senior consultants with wide experience of open inguinal hernia surgery. Tension-free hernioplasty was done with a 9×13-cm trimmed lightweight polypropylene mesh (Optilene® 60 g/m^2; B. Braun, Melsungen, Germany). Indirect hernia sacs were either resected or inverted into the abdomen. Large direct hernias were also inverted into the abdomen with absorbable 3/0 Dexon® (United States Surgical, Norwalk, Connecticut, USA) sutures. A trimmed mesh was placed between the conjoint tendon, the inguinal ligament, the pubic bone and internal oblique aponeurosis, overlapping the inguinal ligament by about 0·5 cm[1,17]. In men, the spermatic cord was always passed through a slit in the mesh. Mesh fixation was either by absorbable polyglycolic acid 3/0 sutures (Dexon®) or 1 ml butyl-2-cyanoacrylate tissue glue (Glubran®; GEM, Viareggio, Italy). The exact technique of mesh fixation is shown in *Fig. 1*. The ilioinguinal, genitofemoral and iliohypogastric nerves were identified and preserved, if possible. Care was taken not to include the nerves within the sutures. In patients with bilateral hernia, each one was treated individually; the second operation began when the first had finished in order to time each operation precisely.

The procedures were carried out under local anaesthesia as an outpatient. Local anaesthesia was a 1 : 1 mixture of bupivacaine (Marcaine 5 mg/ml; AstraZeneca, London, UK) and Citanest®–adrenaline (10 mg/ml + 5 μg/ml; AstraZeneca) with a total volume ranging from 40 to 60 ml[23]. The operation time started when the surgeon performed infiltration anaesthesia and finished after skin closure.

After surgery the patient was observed for 60–120 min to check for wound haemorrhage, and then discharged from the ambulatory unit. No prophylactic antibiotics were used. A 0·5–1·0-mg bolus of intravenous alfentanil (Rapifen®; AstraZeneca) or 5–10 mg diazepam (Stesolid®; Actavis Nordic, Gentofte, Denmark) was administered if the patient felt pain during the operation. Ibuprofen or paracetamol was prescribed for postoperative pain.

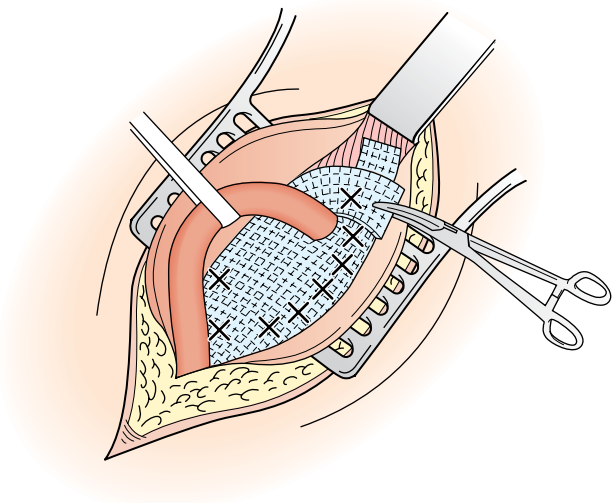

Fig. 1 Operative technique of mesh fixation. Either absorbable knots or 1–2 drops of tissue glue were positioned at the points marked X

Outcomes

The primary outcome of the study was the sensation of pain during the first year after operation. Secondary outcomes included duration of operation, wound complications, time to return to normal physical activities, recurrences, reoperations and sensation of a foreign object. Preoperative pain scores were acquired using a visual analogue scale (VAS; range 0–10) at rest. Operative details were recorded, including type and size of the hernia, duration of operation and bleeding. All postoperative complications were monitored carefully.

The patients were telephoned with a standard set of questions 1, 7 and 30 days after surgery; the questions were based on those from the Danish Hernia Database[3]. After 1 year, all patients were re-examined clinically, and when necessary by ultrasonography, to determine recurrence rates. Duration of sick leave, time to resumption of normal activities, chronic pain, recurrence, reoperations, need for analgesia, sensation of a foreign object and satisfaction were recorded at each time interval. Postoperative pain scores at rest were recorded at the same time intervals. Patients who reported wound haematoma, infection, recurrence or chronic pain were examined clinically by one of the operating surgeons. Wound infection was always confirmed using bacterial culture, and the frequency of infections was recorded 1 month after surgery.

For patients who did not work, the return to normal activity (walking, driving, sports) was evaluated. Chronic pain was defined as pain (VAS score at least 2) that persisted for more than 3 months after surgery. Hernia recurrence was diagnosed by clinical or ultrasound examination and confirmed at reoperation. The staff who conducted the postoperative assessment, and the patients themselves were blinded to the treatment allocation.

Statistical analysis

The power calculation was based on the presence of pain at 1 year after surgery, considering a 50 per cent difference between the groups as clinically significant (incidence of chronic pain at 12 months: suture fixation of mesh 30 per cent, glue fixation 15 per cent). Earlier studies have described chronic pain in 23–25 per cent of patients after Lichtenstein hernia repair with conventional fixation of mesh[3]. According to the power calculation, 120 subjects per treatment group were needed for the study to achieve a statistical power of 0·80 with an α of 0·05 (two-tailed). Allowing a dropout rate of 10–20 per cent during long-term follow-up, the study was set up to include randomization of 300 patients.

Pearson's χ^2 test or Fisher's exact test was used for analysis of categorical variables, and independent-samples t test or Mann–Whitney U test for numerical data. Risk factors for chronic postoperative pain were assessed by means of logistic regression analysis. In addition to the background variables, the criterion for variables entering the logistic regression analysis was two-tailed $P < 0{\cdot}250$ in univariable analysis. The final model was evaluated using a backward directed stepwise method (likelihood ratio), with exception of the fixation method (glue or suture), which was entered into all models. $P < 0{\cdot}050$ was considered statistically significant. Multiple dependent variables (VAS scores) measured at multiple time intervals (1 day, 7 days, 30 days and 1 year after operation) were modelled using the GLM repeated measures procedure. The effect of background variables (such as hospital, size of hernia and preoperative use of analgesia) was also examined. The possible co-variables of the models were age, duration of operation and preoperative pain. Owing to the complexity of the model the majority of the analysis was done separately. SPSS® version 17·0 for Windows® (SPSS, Chicago, Illinois, USA) was used for statistical analysis.

Results

During the study interval 1600 patients had an inguinal repair in the participating hospitals; 302 were included in the trial: 100 in hospital A, 80 in hospital B and 122 in hospital C. All patients who were randomized received the intended treatment, giving 151 patients in each group; 144 in the cyanoacrylate glue group and 142 in the suture group completed 1-year follow-up and were analysed (*Fig. 2*). Four patients had bilateral hernias.

There were no significant differences in patient characteristics between the two treatment groups, except that more right-sided inguinal hernias were included in the tissue glue group (*Table 1*). The operation was 2–4 min quicker in the glue group in the three hospitals, but the difference was not statistically significant ($P = 0{\cdot}113$) (*Table 2*). Eleven patients (3·6 per cent) remained in hospital overnight because of a postoperative haematoma (2) or for social reasons (9). Although over 95 per cent of patients were discharged between 1 and 4 h after surgery, more patients (for social reasons) stayed at the hospital overnight in the glue group ($P = 0{\cdot}032$). There were no other significant differences during the first 24 h or first week between the treatment groups. Although the local anaesthetic technique employed rendered the groin insensitive until late evening after surgery, over 90 per cent of patients in both groups needed analgesics

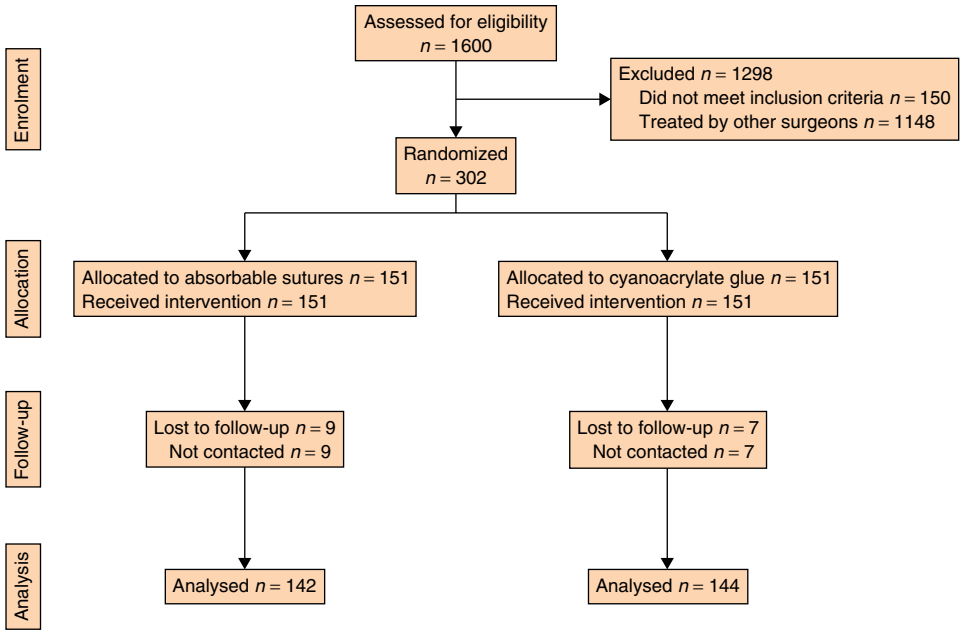

Fig. 2 CONSORT diagram of the trial

Table 1 Patient characteristics in suture and glue fixation groups

	Suture fixation ($n = 151$)	Glue fixation ($n = 151$)	P†
Age (years)*	53(15)	53(15)	0·679‡
Sex ratio (M : F)	135 : 16	131 : 20	0·477
Body mass index (kg/m^2)*	25(3)	25(3)	0·547‡
Side of hernia			0·017
Left	79 (52·3)	59 (39·1)	
Right	72 (47·7)	92 (60·9)	
Hernia type			0·217
Direct	55 (36·4)	41 (27·2)	
Indirect	90 (59·6)	104 (68·9)	
Combined	6 (4·0)	6 (4·0)	
Size of defect (cm)			0·503
< 1·5	50 (33·1)	55 (36·4)	
1·5–3·0	91 (60·3)	82 (54·3)	
> 3·0	10 (6·6)	14 (9·3)	
Preoperative use of analgesia	35 (23·2)	39 (25·8)	0·570
Preoperative pain score (VAS)*	4·0(2·5)	4·0(2·4)	0·118‡
Duration of symptoms (months)*	28(58)	18(28)	0·337‡

Values in parentheses are percentages, unless indicated otherwise; *values are mean(s.d.). VAS, visual analogue scale. †Fisher's exact test, except ‡Mann–Whitney *U* test.

Table 2 Operative and postoperative outcomes in the two groups

	Suture fixation	Glue fixation	P†
Duration of operation (min)*	36(13)	34(12)	0·113‡
Overnight admission	2 (1·3)	9 (6·0)	0·032
Outcome at 24 h	$n = 151$	$n = 151$	
Normal wound	137 (90·7)	140 (92·7)	0·770
Haematoma	14 (9·3)	11 (7·3)	
Need for analgesia	140 (92·7)	144 (95·4)	0·540
Pain score (VAS)*	5·0(2·3)	5·0(2·1)	0·242‡
Outcome at 7 days	$n = 147$	$n = 147$	
Normal wound	136 (92·5)	135 (91·8)	0·828
Haematoma	11 (7·5)	12 (8·2)	
Need for analgesia			0·962
Daily	50 (34·0)	49 (33·3)	
Sometimes	45 (30·6)	46 (31·3)	
None	52 (35·4)	52 (35·4)	
Pain-free walking	107 (72·8)	103 (70·1)	0·545
Normal car driving	113 (76·9)	115 (78·2)	0·692
Pain score (VAS)*	3·0(1·7)	3·0(1·8)	0·742‡

Values in parentheses are percentages, unless indicated otherwise; *values are mean(s.d.). VAS, visual analogue scale. †Fisher's exact test, except ‡Mann–Whitney *U* test.

in the first 24 h, but with no difference between groups ($P = 0·540$).

After 1 week, one-third of the patients needed analgesics every day, one-third sometimes and one-third not at all. The use of tissue glue for mesh fixation did not much affect the need for analgesia or result in less postoperative pain during the first month after surgery (*Table 3*). The postoperative pain response was similar in the two groups: mean VAS values peaked at up to 5 on the day after surgery and thereafter decreased to 1 during the following month.

There were five infectious wound complications in the glue fixation group compared with two in the suture

Table 3 Follow-up data after 1 month and 12 months

	Suture fixation	Glue fixation	*P*†
Outcome at 1 month	*n* = 147	*n* = 146	
Normal wound	143 (97·3)	138 (94·5)	0·234
Haematoma/swelling	4 (2·7)	8 (5·5)	
Infection	2 (1·4)	5 (3·4)	0·448
Need for analgesia			0·048
Daily	0 (0)	4 (2·7)	
Sometimes	18 (12·2)	11 (7·5)	
None	129 (87·8)	131 (89·7)	
Pain-free walking	144 (98·0)	143 (97·9)	1·000
Pain-free daily working	137 (93·2)	134 (91·8)	0·646
Pain score (VAS)*	1·0(1·3)	1·0(1·2)	0·204‡
Outcome at 12 months	*n* = 142	*n* = 144	
Recurrence	2 (1·4)	2 (1·4)	1·000
VAS score ≥ 2	22 (15·5)	29 (20·1)	0·318
Pain score (VAS)*	1·0(1·5)	1·0(1·8)	0·103‡
Scrotal or testicular pain	2 (1·4)	1 (0·7)	1·000
Sensation of foreign object	32 (22·5)	38 (26·4)	0·469
Not satisfied	7 (4·9)	9 (6·2)	0·627
Need for analgesia			1·000
Daily	1 (0·7)	1 (0·7)	
Sometimes	3 (2·1)	4 (2·8)	
None	138 (97·2)	139 (96·6)	
Pain-free walking	139 (97·9)	143 (99·3)	0·369

Values in parentheses are percentages, unless indicated otherwise; *values are mean(s.d.). VAS, visual analogue scale. †Fisher's exact test, except ‡Mann–Whitney *U* test.

group ($P = 0{\cdot}448$); overall 2·4 per cent (*Table 3*). One patient in each group needed reoperation and removal of part of the mesh because of persistent infection. Three other reoperations were required during follow-up, for haematoma evacuation (2) and recurrence (1).There were no other differences between the study groups in the first month (*Table 3*).

After 1 year there were four recurrent hernias (1·4 per cent), two in each group (*Table 3*). There were two lateral (one suture, one glue) and two medial (one suture, one glue) recurrences. Use of glue for mesh fixation did not decrease the rate of chronic pain (VAS score at least 2), which was reported in 51 (17·8 per cent) of 286 patients: 29 (20·1 per cent) in the glue group and 22 (15·5 per cent) in the suture group ($P = 0{\cdot}318$). Nine patients (3·2 per cent) still needed occasional or daily analgesics for the groin pain.

In univariable analysis of the whole study group, younger age ($P = 0{\cdot}005$), feeling of pain or need for analgesics before the surgery ($P = 0{\cdot}004$), and painful walking or car driving 1 week after surgery ($P = 0{\cdot}007$) predicted chronic pain. The method of mesh fixation had no influence on the sensation of chronic pain. In multivariable analysis, the odds ratio (OR) for chronic pain in the glue group compared with the suture group was 1·01 (95 per cent confidence interval 0·49 to 2·05; $P = 0{\cdot}988$) (*Table 4*). The sensation of foreign material was also similar between the study groups. In logistic regression analysis, preoperative VAS score remained an independent predictor (OR 1·33, 1·14 to 1·55; $P < 0{\cdot}001$) for chronic pain after Lichtenstein hernioplasty. In contrast, older age decreased the risk of chronic pain after hernia surgery (*Table 4*). The mean(s.d.) age of 51 patients who reported a VAS score of at least 2 was 49(15) years, compared with 55(15) years in 235 patients with a VAS score of 0–1 ($P = 0{\cdot}005$). The GLM repeated measures procedure showed a change in pain score over time; however, there was no significant difference between the groups. The duration of operation was the only other predictor of chronic pain.

Table 4 Results of logistic regression analysis to identify independent predictors of chronic pain 1 year after hernia repair

	Odds ratio	*P*
Preoperative VAS score	1·33 (1·14, 1·55)	< 0·001
Younger age	0·95 (0·92, 0·97)	< 0·001
Duration of operation	0·97 (0·94, 1·00)	0·048
Glue fixation	1·01 (0·49, 2·05)	0·988

Values in parentheses are 95 per cent confidence intervals. VAS, visual analogue scale.

Discussion

The present results indicated that the fixation of mesh during Lichtenstein hernia repair was feasible and safe with 1 ml of tissue glue, without compromising short-term or 1-year outcome. The mesh fixation method had no influence on the sensation of chronic pain after 1 year. The pain scores, immediate wound complications and 1-year recurrence rates in patients who had glue fixation were comparable to those in the suture fixation group. The duration of operation was slightly, but non-significantly, shorter in the glue group. Both fixation methods were modified from their original description[1,17], but it is likely that the use of non-absorbable sutures was not contributory. In the present study, absorbable sutures were used because the authors previously found them to be safe, with no increased risk of recurrence over use of non-absorbable sutures[18]. Recent register data from Sweden, however, suggested that absorbable sutures may double the risk of inguinal hernia recurrence in the short term[24].

Previous studies showed that laparoscopic hernioplasty using a lightweight mesh fixed by tissue glue was highly effective for preventing chronic pain compared with conventional staple fixation[25,26]. In laparoscopic

hernioplasty the fixation of mesh may not be necessary at all, although this needs confirmation[25,26]. In open hernioplasty, one small randomized trial compared sutures (59 patients), cyanoacrylate glue (56) and human fibrin glue (52) for mesh fixation[27]. Testini and co-workers[27] concluded that both tissue glues were better tolerated than sutures, because short-term morbidity was significantly higher in the suture group. Those authors used 3/0 polypropylene sutures to fix the mesh. They found no significant difference in morbidity between fibrin glue and cyanoacrylate[27], but some authors believe that cyanoacrylate glue is potentially cytotoxic *in vitro* when undiluted, and stiff to handle[28,29].

Cyanoacrylate has been used as a surgical tissue adhesive since the 1960s. Glubran-2® is a new cyanoacrylate surgical glue composed of *N*-butyl-2-cyanoacrylate and methacryloxysulpholane monomer[28]. It has been used for many surgical procedures including skin closure of abdominal wounds and suture reinforcement[27]. Many experimental studies in animals and preliminary non-randomized studies in humans have shown that both fibrin and cyanoacrylate glue fixation of mesh is feasible in inguinal hernia surgery[30–34]. Glue fixation may cause less damage to nerves, pubic periostium or vessels than conventional methods. Sutures, anchors, tacks and staples all have been linked to iatrogenic tissue trauma and neuropathic pain.

In the present study, glue fixation was found easier to perform than conventional sutures, particularly in obese patients. The surgery was carried out under local anaesthesia, which was rapid, less painful and effective for inguinal hernia repair[35]. Lightweight mesh was used. Recent biomechanical data indicated that tissue glue fixation (fibrin) was secure even for using lightweight large-pore monofilament polypropylene mesh[36].

It is well known that traditional inguinal hernioplasties (Bassini, Shouldice, McVay, etc.) may cause chronic pain owing to tension[2]. Yet chronic pain has also been reported in 10–30 per cent of patients after tension-free hernia repair[3,14–16]. In the present study, about 30 per cent of patients reported pain during walking after 1 week, and 15–20 per cent felt some pain at 1 year after surgery, comparable to findings of an earlier study[37]. Severe chronic pain was rare in the present study; only two patients reported daily use of analgesics after 1 year and no patient had reoperation for chronic pain. However, as the immediate pain response and the rate of long-term pain was not less in the glue group, the hypothesis of the study was not fulfilled.

The use of glue fixation had an economic impact. The additional cost of cyanoacrylate glue was about €100 per patient, but it slightly shortened the operating time. Although mesh fixation with cyanoacrylate glue was feasible, it had only a minor impact on the 1-year outcome in the present study.

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