Randomized, Controlled, Blinded Trial of Tisseel/Tissucol for Mesh Fixation in Patients Undergoing Lichtenstein Technique for Primary Inguinal Hernia Repair

Results of the TIMELI Trial

Giampiero Campanelli, MD, Manuel Hidalgo Pascual, MD,† Andreas Hoeferlin, MD,‡ Jacob Rosenberg, MD,§ Gérard Champault, MD,|| Andrew Kingsnorth, MD,¶ and Marc Miserez, MD#*

Objective: Test the hypothesis that fibrin sealant mesh fixation can reduce the incidence of postoperative pain/numbness/groin discomfort by up to 50% compared with sutures for repair of inguinal hernias using the Lichtenstein technique.

Background: Inguinal hernia repair is the most common procedure in general surgery, thus improvements in surgical techniques, which reduce the burden of undesirable postoperative outcomes, are of clinical importance.

Methods: A randomized, controlled, patient- and evaluator-blinded study (Tissucol/Tisseel for MEsh fixation in LIchtenstein hernia repair [TIMELI]; trial NCT00306839) was conducted among patients eligible for Lichtenstein repair of uncomplicated unilateral primary inguinal small–medium sized hernia. Patients were subject to mesh fixation with either fibrin sealant or sutures. Main outcome measures were visual analogue scale (VAS) assessments for "pain," "numbness," and "groin discomfort" on a scale of 0 = best and 100 = worst outcome. The primary endpoint was a composite that evaluated the prevalence of chronic disabling complications (VAS score >30 for pain/numbness/groin discomfort) at 12 months after surgery.

Results: In total, 319 patients were randomized between January 2006 and April 2007 (159 fibrin sealant, 160 sutures). At 12 months, the prevalence of 1 or more disabling complication was significantly lower in the fibrin sealant group than in the sutures group (8.1% vs 14.8%; $P = 0.0344$). Less pain was reported in the fibrin sealant group than in the sutures group at 1 and 6 months ($P = 0.0132$; $P = 0.0052$), as reflected by a lower proportion of patients using analgesics in the fibrin group over the study duration (65.2% vs 79.7%; $P = 0.0009$). Only 3 of 316 patients (0.9%) experienced recurrence. The incidences of wound-healing complications and other adverse events were comparable between groups.

Conclusions: Fibrin sealant for mesh fixation in Lichtenstein repair of small–medium sized inguinal hernias is well tolerated and reduces the rate of pain/numbness/groin discomfort by 45% relative to sutures without increasing hernia recurrence (NCT00306839).

(*Ann Surg* 2012;255:650–657)

Inguinal hernia repair is the most common procedure in general surgery,[1] with an estimated 2800 procedures per million population performed each year in Europe and the United States.[2] In view of the frequency with which this operation is performed, even small improvements in surgical technique carry major implications for reducing the burden of undesirable postoperative outcomes. Until relatively recently, the clinical outcome of main focus was the rate of recurrence, leading to reoperation. Over the last decade, advances in hernia surgery techniques have reduced the rate of recurrence such that prevention of chronic pain has evolved to become the key target for improving clinical outcomes after inguinal hernia surgery.[3]

Chronic pain has been defined in various ways. The International Association for the Study of Pain defines chronic pain as pain lasting more than 3 months.[4] In terms of assessing chronic pain after inguinal hernia surgery, Aasvang and Kehlet[3] argue that given the possibility of an inflammatory reaction to prosthetic mesh, chronic pain should be measured at 6 months or more after herniorrhaphy. Using this criterion, they estimate that the prevalence of chronic postherniorrhaphy pain is around 12%, based on a review of available studies, although this estimate rises to 27% when pain is the primary outcome measure.[3] Similarly, in their meta-analysis of laparoscopic versus open inguinal hernia repair outcomes, McCormack et al define "persisting pain" as pain as close to 12 months after operation as possible, and put the prevalence of persisting pain at 16.6%, with less persisting pain in the laparoscopic groups.[5] More recent analyses of persisting pain 1 year after inguinal hernia repair are consistent with this in terms of prevalence.[6]

The impact of chronic pain on quality of life is complex to measure, but appears to pivot on restriction of activities of daily living. A large Danish study found that at 1 year after repair of inguinal hernias, 17% of 1166 patients reported restrictions during work, sport, or leisure as a result of chronic groin pain.[2] Other complications also impact significantly on well-being, such as numbness or groin discomfort (eg, due to a foreign body sensation), which is sometimes used as a measure of less severe pain, not requiring analgesia. In most studies, the rate of discomfort is at least comparable with that of chronic pain, ranging from 11% to 27% of patients.[7,8] Numbness is more commonly evaluated than discomfort, and the meta-analysis of McCormack et al[5] reported a prevalence of 13.4% after open hernia repair. This form of sensory dysfunction has been shown to be significantly correlated with chronic pain.[9]

The incidence of chronic pain differs between surgical techniques used, with most debate focusing on the merits of open versus laparoscopic hernia repair. Indeed, current European Hernia Society

From the *Department of Surgical Sciences, University of Insubria-Varese, Multimedica Santa Maria Hospital, Castellanza, Varese, Italy; †Hospital Universitario 12 de Octubre, Madrid, Spain; ‡Hernienpraxis-Mainz, Mainz, Germany; §Department of Surgery, Herlev Hospital, University of Copenhagen, Herlev, Denmark; ||CH Jean Verdier, Bondy, France; ¶Peninsula Medical School, Derriford Hospital, Plymouth, UK; and #Department of Abdominal Surgery, Gasthuisberg University Hospital, Leuven, Belgium.

Disclosures: This investigator-driven study was proposed and coordinated by Professor Giampiero Campanelli with funding and support from Baxter Healthcare. Assistance with data management, data analysis and development of the clinical study report was provided by MAPI Clinical Research Organization and was funded by Baxter Healthcare. Editorial assistance with the production of this manuscript was provided by Alpha-Plus Medical Communications Ltd (UK) and was funded by Baxter Healthcare.

Reprints: Giampiero Campanelli, MD, University of Insubria-Varese, Department of Surgical Sciences, Multimedica Santa Maria Hospital, Viale Piemonte 70, 21053 Castellanza, Varese, Italy. E-mail: Giampiero.Campanelli@multimedica.it.

ISSN: 0003-4932/12/25504-0650
DOI: 10.1097/SLA.0b013e31824b32bf

(EHS) guidelines recommend mesh repair (Lichtenstein or endoscopic) for uncomplicated primary unilateral or bilateral hernias.[10] The Lichtenstein technique for inguinal hernia repair is the standard open tension-free mesh-onlay method that is widely popular and produces low rates of complications and recurrence.[11] Sutures are generally used to secure the prosthetic mesh but may contribute to chronic pain or other problems such as numbness or groin discomfort, presumably through tension or nerve compression.[12] This triggered a search for less traumatic means of mesh fixation and led to trials with human fibrin sealant (Tissucol/Tisseel, Baxter Healthcare, Deerfield, IL). Promising initial findings with fibrin sealant in this setting[13–16] justified further evaluation in a randomized, controlled, double-blind clinical trial and prompted the design and implementation of the TIMELI (TIssucol/Tisseel for MEsh fixation in LIchtenstein hernia repair) study.

The primary objective of the TIMELI study was to evaluate the chronic complications of pain, numbness, or groin discomfort after repair of small–medium sized inguinal hernias using the Lichtenstein technique, comparing mesh fixation with fibrin sealant or sutures. The rationale and design of this study have been reported in detail by Campanelli et al.[17] The trial has been conducted under the auspices of the EHS.

METHODS

Study Design

This randomized, controlled, patient- and evaluator-blinded study enrolled patients from 7 centers in 7 European countries. Our hypothesis was that the prevalence of chronic, moderate to severe pain/numbness/groin discomfort after repair of inguinal hernias using the Lichtenstein technique would be reduced in patients receiving fibrin sealant, specifically Tissucol/Tisseel, compared with the established practice of using sutures to secure the prosthesis.

This study was performed in compliance with the ethical principles of the World Medical Association Declaration of Helsinki (2004 version) and Good Clinical Practice, local laws, and the bioethics policy of Baxter Healthcare as funder of the study. Independent ethics committees and health authorities in each country approved the study protocol. All patients provided written informed consent. This study is registered with the US National Institutes of Health clinical trials database (www.clinicaltrials.gov), number NCT00306839.

Patients

Patients were eligible if they met the following criteria: men aged between 18 and 80 years who were active (normal daily activities); diagnosed with an uncomplicated unilateral primary inguinal hernia or an uncomplicated bilateral hernia (L1–L2 or M1–M2 according to the EHS Groin Hernia Classification),[18] provided that only one hernia was operated upon during the 12 months of study follow-up; eligible for elective inguinal hernia repair using the Lichtenstein technique.

Exclusion criteria included the following: recurrent, scrotal, incarcerated, or femoral hernia; large hernia (L3 or M3 EHS Groin Hernia Classification); body mass index (BMI) $\geq 35\,kg/m^2$; concomitant abdominal surgery; ongoing long-term analgesic or steroid treatment; previous treatment or hypersensitivity to bovine aprotinin; patients receiving clopidogrel or warfarin therapy (unless therapy is interrupted and changed to low-molecular-weight heparin); known abuse of alcohol or drugs; Child-Pugh class C hepatic cirrhosis; known immunodeficiency; severely compromised health which, in the opinion of the investigator, was likely to affect patient compliance; and having received another investigational drug or device within the previous 30 days.

Procedures

Most patients were scheduled for day surgery and randomization took place in the 24 hours before surgery. Patients were randomly allocated to mesh fixation with Tissucol/Tisseel or mesh fixation with sutures (control group) by means of computerized randomization, in block sizes of 2, 4, or 6. The randomization procedure was stratified on the basis of the study site to ensure balance between study groups at each site. Patients and evaluators were blinded to the method of surgical fixation. Surgical staff members were not permitted to divulge this information to patients or other staff.

Each patient underwent inguinal hernia repair by the Lichtenstein technique,[19] performed by a surgeon experienced in this technique. Details of the surgical procedures are fully reported by Campanelli et al.[17] Briefly, patients received local, regional, or general anesthesia depending on the study center. Hernia size, as determined preoperatively, was reassessed and confirmed intraoperatively. Nerves were preserved if possible. However, where nerve resection did occur, this was recorded[20] and the nerve was cut, ligated, and implanted into the muscles according to Lichtenstein.[19,21] Each patient received an 8 cm × 15 cm macroporous, heavyweight polypropylene flat mesh, tailored before implantation. Absorbable suture was permitted to narrow the internal ring (one stitch) or to repair the posterior wall with a direct hernia (one or two stitches). A single nonresorbable polypropylene 2/0 stitch fixed mesh-mesh ends of the internal ring around the spermatic cord laterally. In the control group, the mesh was fixed with sutures as described for the classical Lichtenstein technique, that is, with running suture fixation to the inguinal ligament with polypropylene 2/0 and resorbable interrupted sutures on internal oblique muscle aponeurosis.[19] For patients in the fibrin sealant group, 2 mL of Tissucol/Tisseel was prepared according to the manufacturer's instructions (Baxter Healthcare, Deerfield, IL, United States; 1 mL of fibrinogen and 1 mL of thrombin solution). Before the mesh was positioned, 0.5 mL of fibrin sealant was applied dropwise using the Duploject device provided by the manufacturer (no spraying) on the pubic tubercle and the mesh pressed on it for 2 minutes. The remainder (1.5 mL) was sprayed over the entire surface of the mesh in a thin layer. A video detailing the fibrin sealant application technique was provided to all participating surgeons.

Closure of the external fascia and skin was performed according to a standardized procedure,[17] using running subcuticular suture (Vicryl 2/0) for the superficial layers. Local infiltration of the abdominal wall was allowed at the end. Skin sutures (Monocryl 3/0) and Steristrips were used for the skin. Drains were not used routinely.

Nonsteroidal anti-inflammatory drugs were given for 3 days, up to 3 times per day as needed for postoperative pain relief. Patients were instructed not to lift anything during the first 2 weeks after surgery.

Patient Assessment and Follow-Up

Assessments included a preoperative visit within 14 days of the planned date of hernioplasty (visit 1). In hospital, patients were assessed intraoperatively and until hospital discharge (visit 2), followed by outpatient visits 1 week, 1 month, and 6 months (visits 3, 4, and 5, respectively), with a final evaluation taking place at 12 months after surgery (visit 6). Each patient was asked to complete an SF-12v2 quality-of-life questionnaire[22] at visits 1, 4, 5, and 6.

Pain was evaluated by patient self-assessment preoperatively (visit 1) and at visits 3 to 6, using a 100 mm visual analogue scale (VAS), where 0 mm = no pain and 100 mm = worst conceivable pain. All VAS scores were ascertained by a blinded evaluator, who explained the scale to patients verbally. Patients were asked to recall the worst pain experienced during the period since the last evaluation.

VAS scores were also obtained for numbness (defined as paraesthesia in the groin) and for groin discomfort, at visits 1 and 3 to 6.

Study Endpoints

The primary endpoint was a combined measure that evaluated the prevalence of moderate to severe chronic pain and/or numbness and/or groin discomfort—at 12 months after surgery (visit 6), or where visit 6 data were missing, visit 5 data were based on the last observation carried forward (LOCF). This combined endpoint was chosen to allow a robust overall quantitative assessment of three overlapping, moderate–severe complications that occur at relatively low frequency. Patients' VAS scores for pain, numbness, and discomfort were classified as "none" (0 mm), "mild" (1–30 mm), "moderate" (31–60 mm), or "severe" (61–100 mm). Patients with all three VAS scores 30 mm or less were not included in the primary endpoint analysis.

Secondary outcome measures included (1) early postoperative pain—defined as pain within 30 days and scoring more than 30 mm on the VAS pain score 1 week or 1 month after the operation (at visits 3 and 4); (2) mid-term postoperative pain—defined as VAS pain score more than 30 mm at visit 5; (3) proportion of patients without early or chronic pain (ie, VAS pain score 30 mm or less at months 1, 6, and 12 [visits 4, 5, and 6]); (4) analgesic use for management of groin pain; (5) hernia recurrence, confirmed by a blinded examiner; (6) overall wound-healing complication rate, including hematoma/seroma 10 mL or more, wound infection including initiation of antibiotics for suspected wound infection, and bruising/ecchymosis; (7) safety based on adverse events (intraoperative and during physical examinations at each visit); (8) duration of surgery; (9) length of hospital stay (assessed at week 1 [visit 3]); (10) time to return to normal daily activities, assessed at months 1, 6, or 12 (visits 4, 5, or 6); (11) quality of life—assessed by SF-12v2 questionnaire[22] completed preoperation at months 1, 6, and 12 (visits 1, 4, 5, 6); and (12) patient satisfaction—assessed by asking patient "would you like to have the same operation again?" at month 12 (visit 6).

The investigators entered study data into an electronic clinical report form via a secured web site. SF-12v2 questionnaires were completed on paper and sent directly to the clinical research organization for analysis. Throughout the study, monitors from an independent data monitoring committee visited the investigators regularly to conduct quality control checks to ensure the validity and accuracy of recording and overall adherence to study protocol. Collected data were entered by double entry and computerized checks were performed to ensure consistency of the data.

Statistical Analysis

The sample size estimation was based on the projected prevalence of at least one of the complications of chronic pain, numbness, or groin discomfort (rating moderate to severe in intensity) at 12 months after hernia repair. This was estimated to be 25% in the control group, based on data from recent literature,[5,7,23,24] and a predicted prevalence of 12.5% in the fibrin sealant group, giving a total sample size of 328 patients, based on a dropout rate of 10%, a power of 80% and two-sided tests at the 5% significance level.

The primary efficacy analysis was performed on two data sets—the intention-to-treat (ITT) population, comprising all randomized subjects who underwent the surgical procedure and who had at least one late follow-up evaluation (at 6 or 12 months), and the per protocol population, that is, all ITT patients without a major protocol violation. For the primary endpoint, the two groups were compared using a mixed logistic regression analysis with surgical center as a random variable. Categorical variables were compared using the χ^2 or Fisher exact test. Quantitative variables were compared using a *t* test or, in cases of nonnormal distribution, by Mann-Whitney-Wilcoxon test. Safety variables (adverse events) were compared for all patients in the ITT population who underwent surgery. Results were considered statistically significant if $P \leq 0.05$.

RESULTS

Patient enrollment started in January 2006 and ended in April 2007, with last study visit on May 25, 2008. A total of 325 patients were assessed for eligibility and 319 of these randomized to fibrin sealant (n = 159) or sutures (n = 160). Of the randomized patients, 1 in the fibrin sealant group and 2 in the sutures group failed to undergo surgery as scheduled and were not included in the ITT efficacy population (n = 316). The per protocol population comprises all ITT patients minus seven patients in the fibrin sealant group and one in the sutures group who were excluded due to major protocol violations (Fig. 1).

Preoperative Assessment

The baseline characteristics of the study population are given in Table 1. Overall, 53% had a right-sided hernia, and 98% and 97% of patients had normal scrotal examination by location and volume, respectively. The most common comorbidity was hypertension, affecting 49 of 110 study patients with at least one other pathology (45%). The fibrin sealant group had slightly more smokers than the sutures group (27.8% vs 18.4%, $P = 0.045$ [χ^2 test]).

Mean preoperative VAS scores in the overall study population are summarized in Table 1; only 15.2% of all patients were completely free of pain/numbness/groin discomfort.

Preoperatively, 80.1% of the quality of life SF-12v2 questionnaires were considered exploitable for assessment. At baseline (visit 1), the mean (±SD) physical component summary score was 47.9 ± 8.5, whereas the mean (±SD) mental component summary score was 51.7 ± 9.4, with higher scores indicating better quality of life (maximum score of 100).

Intraoperative Assessment

No statistically significant differences between the two study arms (fibrin sealant vs sutures) were observed on any of the parameters assessed intraoperatively: (a) the majority of the study population were receiving prophylactic antibiotics related to the surgery (75.6% overall); (b) in terms of the relative proportions of main hernia type

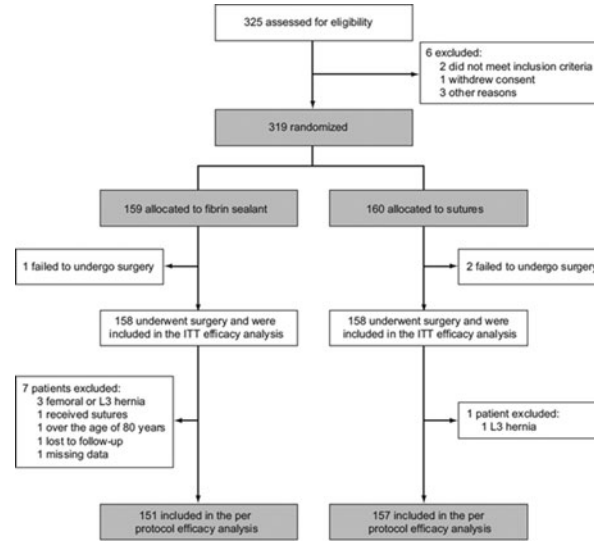


FIGURE 1. Trial profile.

TABLE 1. Baseline Characteristics of the ITT Population at Preoperative Visit*

	Fibrin Sealant (n = 158)	Sutures (n = 158)	Total (n = 316)
Median age, yrs (Q1;Q3)	58.0 (46;65)	59.0 (48;66)	59.0 (47;65)
BMI, Mean (SD), kg/m^2	25.5 (2.9)	25.5 (2.6)	25.5 (2.7)
General health*			
ASA I/II	148 (94.2%)	153 (96.9%)	301 (95.6%)
ASA III	9 (5.7%)	5 (3.2%)	14 (4.4%)
Level of activity			
Sportive—professional or leisure	77 (48.7%)	83 (52.5%)	160 (50.6%)
Nonsportive	81 (51.3%)	75 (47.5%)	156 (49.4%)
Employment status			
Employed (full/part time)	100 (64.1%)	98 (62.8%)	198 (63.5%)
Retired	51 (32.7%)	55 (35.3%)	106 (34.0%)
Most frequently reported comorbidities and concomitant diseases (%)			
Smoker†	27.8%	18.4%	23.1%
Hypertension‡	43.9%	45.3%	44.5%
Hypercholesterolemia‡	3.5%	15.1%	9.1%
Pain as assessed by VAS*			
No pain (0 mm)	56 (35.4%)	59 (37.3%)	115 (36.4%)
Any pain (1–100 mm)	102 (64.6%)	99 (62.7%)	201 (63.6%)
Mean pain score (mean [SD]) (mm)	21.4 (23.3)	21.3 (22.9)	21.3 (23.0)
Median pain score (mm)	20	20	20
Numbness as assessed by VAS*			
No numbness (0 mm)	113 (71.5%)	110 (69.6%)	223 (70.6%)
Any numbness (1–100 mm)	45 (28.5%)	48 (30.4%)	93 (29.4%)
Mean numbness score (mean [SD]) (mm)	7.8 (17.5)	8.5 (18.0)	8.1 (17.7)
Median numbness score (mm)	0	0	0
Groin discomfort as assessed by VAS*			
No groin discomfort (0 mm)	51 (32.3%)	47 (29.7%)	98 (31.0%)
Any groin discomfort (1–100 mm)	107 (67.7%)	111 (70.3%)	218 (69.0%)
Mean groin discomfort score (mean [SD]) mm	22.7 (23.7)	23.4 (23.0)	23.0 (23.3)
Median groin discomfort score (mm)	15	20	20
Complete absence of pain/numbness/groin discomfort (VAS = 0 mm)*	27 (17.1%)	21 (13.3%)	48 (15.2%)

*χ^2 testing (or Exact Fisher testing, in cases of a theoretic value < 5) indicated no significant differences between qualitative categorical groups.

†Student *t* testing (or Mann-Whitney-Wilcoxon testing, in cases of nonnormality of distribution) indicated no significant differences between groups, except for smoking ($P = 0.045$).

‡Note that there were 110/316 patients with at least one comorbidity (57 in the fibrin sealant and 53 in sutures group, respectively).

VAS = visual analogue scale, ranging from 0 mm (no pain/numbness/discomfort) to 100 mm (worst conceivable pain/numbness/discomfort).

based on the EHS classifications, 23% were L1, 13% M1, 33% L2, and 30% M2; (c) handling of ilioinguinal, iliohypogastric, and genitofemoral nerves was also comparable: recognition (98.1 vs 97.5%) and preservation (80.3 vs 76.6%), in the fibrin sealant and suture group, respectively (Table 2); and (d) the mean incision size was 62.5 mm [SD 16.5; range 40–120]. The relationship between nerve type, handling of nerves, and pain was not predefined as an endpoint of this study.

Efficacy Analysis

Primary Study Endpoint

The incidence of at least one moderate–severe complication (pain and/or numbness and/or groin discomfort [VAS scores > 30 mm]) at 12 months LOCF was 8.1% (95% CI [confidence interval] 4.2–13.6) in the fibrin sealant group and 14.8% (95% CI 9.6–21.4) in the sutures group, representing a significant reduction in favor of fibrin sealant ($P = 0.0344$, mixed logistic regression analysis) (Fig. 2).

The incidence of at least one moderate–severe complication 1 year after surgery in an active subpopulation was 5.9% (95% CI 2.2–12.5) with fibrin sealant and 13.1% (95% CI 7.2–21.4]) with sutures ($P = 0.0329$, mixed logistic regression analysis). The same comparison in retired patients was statistically nonsignificant (12.8% [95% CI 4.8–25.7] and 18.5% [95% CI 9.3–31.4] with fibrin sealant and sutures, respectively).

Secondary Study Endpoints

Early and mid-term postoperative pain. Figure 3 summarizes the assessment of pain, numbness, and groin discomfort at time points throughout the study. In terms of the proportion of patients experiencing early and mid-operative moderate–severe pain (VAS > 30 mm), no significant differences were observed between the fibrin sealant and sutures groups (50/152 [32.9%] vs 61/157 [38.9%] at 1 week; 14/152 [9.2%] and 18/157 [11.5%] at 1 month; and 9/147 [6.1%] vs 18/154 [11.7%] at 6 months, respectively).

Patients with no or mild pain (VAS ≤ 30 mm) and use of analgesic drugs. There was no significant difference in the proportion of patients reporting no or mild pain (VAS ≤ 30 mm) at 1, 6, and 12 months in the fibrin sealant and sutures groups (127/150 [84.7%] and 125/156 [80.1%], respectively). However, there was an overall reduced use of analgesia throughout the study period in the fibrin sealant group versus the sutures group (65.2% vs 79.7%, respectively; $P = 0.0009$).

Recurrences. The hernia recurrence rate was very low, with only three patients experiencing recurrence, 1 in the fibrin sealant group and two in the sutures group (0.94% overall). None of the recurrences occurred within the first 3 months of follow-up.

Wound-healing complications. At least one wound-healing complication occurred in 25.2% of patients, most commonly fluid collection for which there were no reoperations (puncture excluded) or bruising/ecchymoses. Wound, abscess, or mesh infections

TABLE 2. Nerves Seen and Nerves Preserved During the Surgery (ITT Population)

	Fibrin Sealant (n = 158)	Sutures (n = 158)	Total (n = 316)
Nerves seen*	154/157 (98.1%)	154/158 (97.5%)	308/315 (97.8%)
Ilioinguinal nerve	145/154 (94.2%)	140/154 (90.9%)	285/308 (92.5%)
Iliohypogastric nerve	133/154 (86.4%)	135/154 (87.7%)	268/308 (87.0%)
Genitofemoral nerve	111/154 (72.1%)	116/154 (75.3%)	227/308 (73.7%)
Nerves preserved	126/157 (80.3%)	121/158 (76.6%)	247/315 (78.4%)
Nerves cut†	31/157 (19.7%)	37/158 (23.4%)	68/315 (21.6%)
Ilioinguinal nerve	20/31 (64.5%)	18/37 (48.6%)	38/68 (55.9%)
Iliohypogastric nerve	18/31 (58.1%)	24/37 (64.9%)	42/68 (61.8%)
Genitofemoral nerve	9/31 (29.0%)	9/37 (24.3%)	18/68 (26.5%)

n = number of patients. Value are in n (%).
*One or more nerves identified during surgery; † one or more nerves cut during surgery.

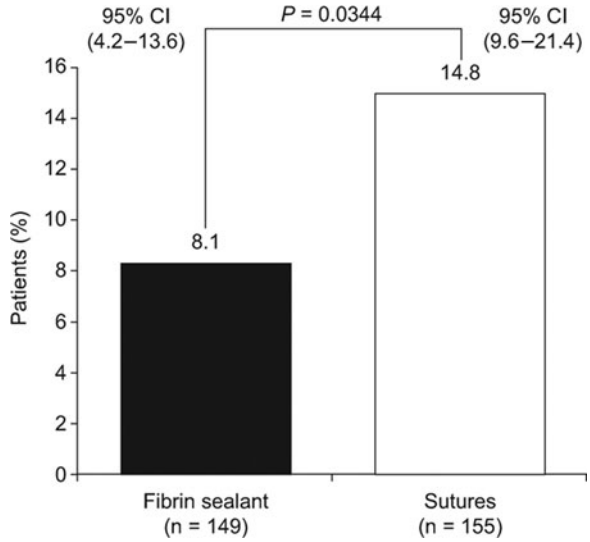


FIGURE 2. Proportion of patients with one or more complications (moderate–severe pain/numbness/groin discomfort) at study endpoint (12 months or 6 months [LOCF]; ITT population). A moderate–severe complication is pain/numbness/groin discomfort with a VAS score of > 30 mm. *P* value derived from mixed logistic regression analysis.

were rare (1.3%). No significant differences were noted between groups.

Intraoperative complications. Intraoperative complications, mostly light bleeding, were reported in 17/158 (10.8%) patients in the fibrin sealant group and 13/158 (8.2%) in the sutures group.

Postoperative complications other than wound-healing complications. One week after surgery, postoperative urological complications based on testicular examinations were reported in 11 patients (3.5%), urinary retention in four patients (1.3%) and other postoperative complications (mainly excessive scarring) reported in 13 patients (4.2%). However, by 1 month, the total number of patients with postoperative urological complications had fallen to 3 (1.0%). No significant differences were noted between groups.

Mean duration of surgery. The mean duration of surgery (skin to skin) was 40.7 minutes (SD 12.0; range 20–115), with no significant difference between the two groups: 39.8 ± 12.1 minutes (fibrin sealant) versus 41.5 ± 11.9 minutes (sutures).

Hospital stay and time to return to normal activities. Mean length of hospital stay was 17 hours (SD 16 hours; range 3–72), with only 20% of patients needing to stay in hospital for more than 1 day. No significant differences between groups were noted.

Likewise, there were no significant differences between the two study groups on time to return to normal daily activities: median time was 14 days for the fibrin sealant group (95% CI 13–17) and 15 days for the sutures group (95% CI 14–16) (Kaplan-Meier analysis).

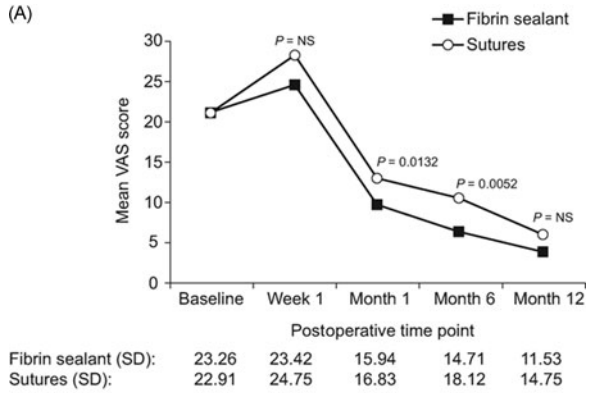
Quality of life evaluations (SF-12v2 questionnaire) and patient satisfaction. Numerical improvements from baseline seen in the fibrin sealant group relative to sutures in terms of general health at 1, 6, and 12 months were not significant (Fig. 4). Physical and mental component summary scores were similar between groups at each time point (Fig. 4), as were scores on individual SF-12v2 domains (data not shown). Regarding patient satisfaction with the overall procedure, more patients in the fibrin sealant group than in the sutures group answered positively when asked if they would have the same procedure again (98.7% vs 92.2%; $P = 0.0035$).

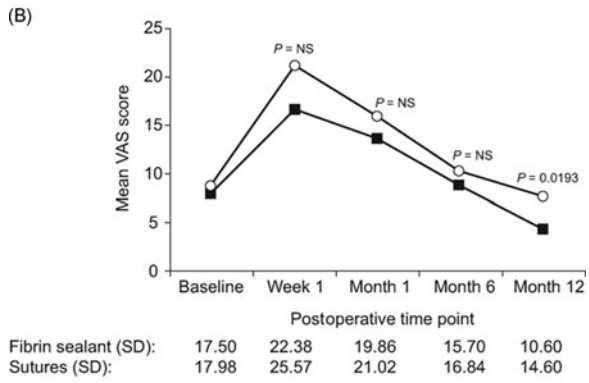
Safety Evaluation

During the study, 15 patients (9.5%) in the fibrin sealant group and eight patients (5.1%) in the sutures group reported at least one adverse event ($P = 0.0926$). Adverse events were attributed to study product in three patients in the fibrin sealant group (1.9%: one excessive pain; one scar pain; one testicular pain hydrocele) and in two patients in the sutures group (1.3%: one hematoma, one delayed wound closure). Most adverse events were mild or moderate and resolved without sequelae, but at least one serious adverse event was reported by seven patients in the fibrin sealant group (coronary artery occlusion, gastric ulcer hemorrhage, cholelithiasis, pulmonary embolism, pulmonary infarction, hip arthroplasty, cerebrovascular accident resulting in death) and three patients in the sutures group (heart valve replacement, road traffic accident, cerebrovascular accident) during the 12-month follow-up period. None of these adverse events was classed as related to the study products. Only one death was reported during the study (0.63% mortality; fibrin sealant group). This was a cerebrovascular accident, which occurred in an 84-year-old patient 187 days after the operation and was not considered related to the study product.

DISCUSSION

Tissucol/Tisseel, the fibrin sealant used in this study, is a biodegradable and biocompatible combination of human-derived fibrinogen and thrombin activated by calcium chloride, which leads to the formation of a matrix of polymerized fibrin fibers. There have been numerous reports of initial positive findings using fibrin sealant in the setting of hernioplasty, which highlight its adhesive and hemostatic properties and potential to promote wound healing and fibroblast





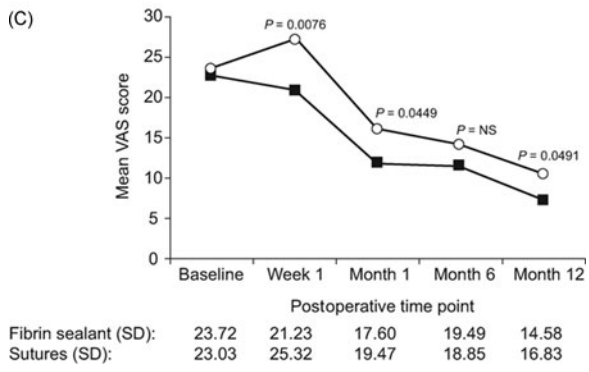
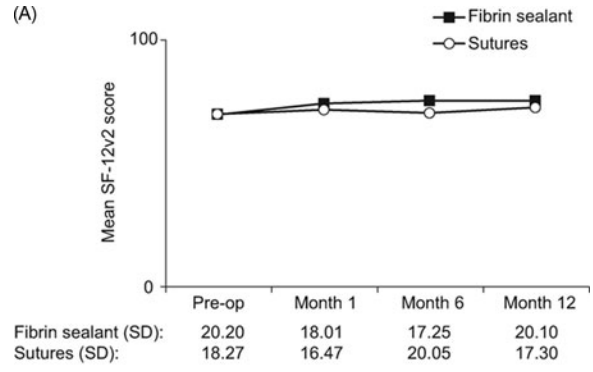
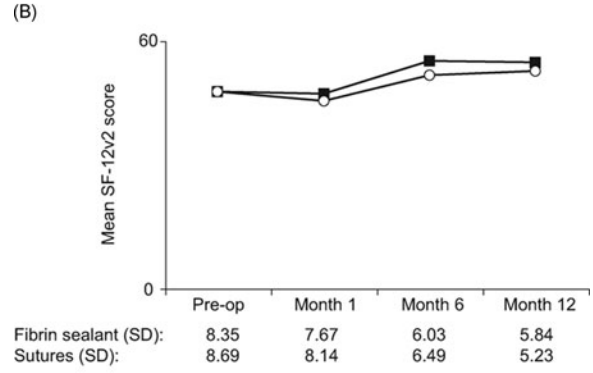


FIGURE 3. VAS scores (mm) for pain (A), numbness (B), and groin discomfort (C) before and after hernia repair with either fibrin sealant or sutures (ITT population). *P* values derived from nonparametric mixed covariance analysis. VAS = visual analogue scale, ranging from 0 mm (no pain/numbness/discomfort) to 100 mm (worst conceivable pain/numbness/discomfort).





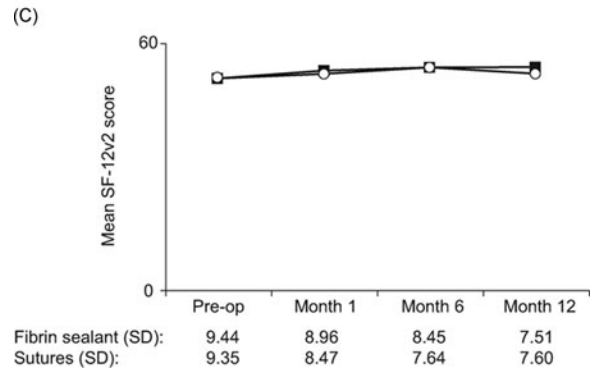


FIGURE 4. Change in SF-12v2 on general health (A), physical component (B), and mental component (C) summary scores at 1, 6, and 12 months after hernia repair with either fibrin sealant or sutures (ITT population). Larger positive change indicates greater improvements in quality of life.

proliferation.[13–16] In addition, compression of nerves by suture material, staples, and tacks can cause persistent neuropathic pain, which may be reduced through use of fibrin sealant.[25]

Our findings support the results of smaller, published trials and observational studies of fibrin sealant as a means of mesh fixation for various forms of hernia repair. In a randomized trial of fibrin sealant versus sutures or staples for the fixation of the polypropylene mesh during incisional hernia repair and associated dermolipectomy in overweight patients, Fernández-Lobato et al[13] demonstrated that patients receiving Tissucol/Tisseel had significantly fewer postoperative complications, shorter hospital stay and required less wound care. In an uncontrolled study, Canonico et al[14] followed 80 patients who had undergone sutureless Lichtenstein repair of primary unilateral hernia, with Tissucol/Tisseel as a means of mesh fixation. Two patients reported pubic pain at 6 months but were free of pain by 12 months; no other early or late complications were observed. Hidalgo et al[15] conducted a controlled study to compare the complication rate associated with Lichtenstein hernioplasty in 55 patients with bilateral inguinal hernias, in whom mesh fixation was undertaken with sutures on the right hernia, and with sealant on the left hernia. There were no recurrences or reports of chronic pain at 1 year after surgery.

The possibility that fibrin sealant might offer additional benefits over standard sutures for mesh fixation during hernia repair

provided the rationale for this randomized, double-blind, controlled multicenter trial. The new findings presented clearly demonstrate that the use of fibrin sealant as a means of mesh fixation in Lichtenstein repair for small–medium sized hernias significantly reduces the prevalence of moderate–severe complications compared with sutures at 12 months. The prevalence of moderate–severe chronic pain and/or numbness and/or groin discomfort was reduced by 45%. Notably, fibrin sealant appeared to be most effective in active patients. These primary findings were paralleled by a concomitant reduction in the number of patients requiring analgesia throughout the whole study period, and improved patient satisfaction with the overall procedure, with significantly more patients in the fibrin sealant group expressing satisfaction than in the sutures group.

Comparing the primary endpoint in the active versus retired population, two interesting remarks can be made. First of all, active patients reported less pain than retired patients. This is in contradiction with the current literature. The EHS guidelines on the treatment of inguinal hernia in adult patients describe level 2A evidence that the risk of chronic pain decreases with age.[10] Second, fibrin sealant appeared to be significantly effective only in active patients (55% reduction in the incidence of the primary endpoint vs a 30% reduction in retired patients). The reasons for both findings remain unclear. It may be that the lower number of patients in the retired subgroup (approximately 30% of the study population) had some effect on the results. In addition, age, employment status, and the level of activity are only three different parameters having a possible influence on the development of chronic pain. Therefore, a more thorough post hoc analysis is planned to include the above-mentioned parameters and also the role of the individual nerve recognition and nerve handling on moderate or severe chronic pain, discomfort, and/or numbness in each patient.

No significant differences between study groups were seen on any other secondary outcome measures. The rate of recurrence was very low. Both intervention groups had low rates of postoperative complications and adverse events, with the fibrin sealant group experiencing slightly more adverse events and serious adverse events ($P =$ nonsignificant). None of the serious adverse events were considered to be related to the study product.

The predicted rate of moderate–severe complications used for the sample size calculation was 25% for the sutures group and 12.5% for the fibrin sealant group, respectively. The actual rates obtained were much lower than these values (14.8% and 8.1%, respectively), yet a statistically significant difference was still achieved on the primary endpoint, providing additional support for our hypothesis that fibrin sealant reduces the rate of chronic, moderate–severe complications after hernia repair. The lower rates overall may be a reflection of the level of expertise of the participating study centers or cultural differences in the perception and reporting of pain.

In our study, the improvement in the primary outcome measure of chronic, moderate–severe pain and/or numbness and/or groin discomfort noted in the fibrin sealant group relative to the sutures group was not reflected by a concomitant improvement in quality of life (as assessed by the SF-12v2 questionnaire). The reasons for this inconsistency are unknown but may relate to the fact that the trial was not powered for this endpoint. Clearly, further study is required to explore the effect of hernia surgery outcomes on quality of life and everyday activities.

In terms of study weaknesses, our choice of a novel primary study endpoint—a composite of chronic pain/numbness/groin discomfort at 12 months after herniorrhaphy—may conceivably receive some scrutiny. Although it does allow capture of overlapping complications (moderate to severe, VAS > 30 mm) occurring in both study populations, it does not provide any direct information on the impact of the mesh fixation methods on quality of life. Thus, although the complications included in the primary composite were described as "disabling" in the published description of the TIMELI study methodology,[17] one might question whether moderate complaints such as pain/numbness/groin discomfort are really disturbing in all patients; this will depend on different factors such as patient activity status. This composite endpoint was devised to capture information on the three principal moderate–severe complications that may occur after this procedure, with the goal of providing a robust overall quantitative assessment of three overlapping parameters that occur at relatively low rates, thereby providing a powerful measure to assess the impact of procedural changes in the clinical trial setting. Combining the endpoints increases the event rate, thereby increasing the statistical power and efficiency of the trial. This approach is often utilized in randomized clinical trials with low frequency outcomes, such as cardiovascular or perioperative anesthesia trials.[26] In addition, the results of this study were limited to small- and medium-sized hernias, as large (scrotal) L3 or M3 EHS classified hernias were excluded from the study, so further investigation would be warranted to see whether the benefits of fibrin sealant might also extend to this patient population. Another point to note is that quality of life evaluations were assessed using a generally applicable questionnaire (SF-12v2). A specifically developed hernia questionnaire could potentially provide more relevant insight on the impact of fibrin sealant on postoperative patient outcomes and the effect on everyday activities[27–29]; however, at the time of protocol development these assessment instruments were not available. As with any clinical trial, it remains to be seen whether the reported findings translate to the real world. However, given that centers from seven European countries were involved in this study, and the primary efficacy results were comparable between them, we believe that our methods and findings are highly generalizable and encourage other investigators to consider using this outcome measure in designing future trials of hernia surgery techniques. Although fibrin sealant was associated with a significant reduction in the rate of moderate–severe complications at 1 year after surgery versus sutures, no significant improvements were observed in terms of duration of surgery or hospital stay or time to return to normal daily activities. However, the criteria for a return to normal daily activities in the study protocol were brief and nonstandardized, meaning that the sensitivity to detect a difference in recovery time between treatment groups may have been reduced. Nonetheless, many will agree that the possibility to minimize the incidence of moderate–severe complications after such a routinely performed surgical procedure is a cost-benefit rationale for choosing fibrin sealant over sutures for mesh fixation.

The cost-benefit of any intervention is always an important consideration. In Europe, Tissucol/Tisseel typically costs approximately 100 Euros per milliliter. Therefore, the cost associated with the use of this fibrin sealant for mesh fixation in Lichtenstein hernia repair is predictably greater than sutures alone. Although no significant improvements were observed in this study on surgical time, duration of hospital stay, or time to return to normal daily activities, it is ultimately up to society to decide how much they are willing to pay to reduce the incidence of chronic moderate–severe complications for improved patient outcomes.

In conclusion, our study shows that fibrin sealant is a well-tolerated and effective means of mesh fixation for the repair of small- and medium-sized inguinal hernias using the Lichtenstein technique. The reduction of long-term moderate–severe complications after hernia repair is the most significant challenge that hernia surgeons are currently facing, and the use of fibrin sealant will help reduce the considerable burden of morbidity that characterizes this frequently performed surgery.

ACKNOWLEDGMENTS

The authors thank Maurice Bagot d'Arc, MD, from Baxter Healthcare for funding and support and Florence Poulenard, Claire

Josso, Anne-Lise Bertrand, Stéphanie Chrétin, and Séverine Oudin of MAPI Clinical Research Organization, Lyon, France, for data management, analysis, and development of the clinical study report. The role of Alpha-Plus Medical Communications Limited (UK) in assisting with developing the first draft of the manuscript and editing subsequent drafts is acknowledged.

Following is the list of TIMELI Investigators and coinvestigators—Investigators: G. Campanelli (principal and coordinating investigator), Milan, Italy; G. Champault, Bondy, France; M. Hidalgo, Madrid, Spain; A. Hoeferlin, Mainz, Germany; A. Kingsnorth, Plymouth, UK; M. Miserez, Leuven, Belgium; J. Rosenberg, Herlev, Denmark. Coinvestigators: C. Barrat, Bondy, France; M. J. Castillo, Madrid, Spain; J. L. Eymar, Madrid, Spain; A. Marcos, Madrid, Spain; M. Cavalli, Milan, Italy; C. Polliand, Bondy, France.

REFERENCES

1. Rutkow IM, Robbins AW. Demographic, classificatory, and socioeconomic aspects of hernia repair in the United States. *Surg Clin North Am*. 1993;73(3):413–426.
2. Bay-Nielsen M, Perkins FM, Kehlet H. Pain and functional impairment 1 year after inguinal herniorrhaphy: a nationwide questionnaire study. *Ann Surg*. 2001;233:1–7.
3. Aasvang E, Kehlet H. Chronic postoperative pain: the case of inguinal herniorrhaphy. *Br J Anaesth*. 2005;95:69–76.
4. Pain IAftSo. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. *Pain Suppl*. 1986:S1–S226.
5. McCormack K, Scott NW, Go PM, et al. Laparoscopic techniques versus open techniques for inguinal hernia repair. *Cochrane Database Syst Rev*. 2003;(1):CD001785.
6. McCormack K, Wake B, Perez J, et al. Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation. *Health Technol Assess*. 2005;9:1–203, iii–iv.
7. Kumar S, Wilson RG, Nixon SJ, et al. Chronic pain after laparoscopic and open mesh repair of groin hernia. *Br J Surg*. 2002;89:1476–1479.
8. Verstraete L, Swannet H. Long-term follow-up after Lichtenstein hernioplasty in a general surgical unit. *Hernia*. 2003;7:185–190.
9. Cunningham J, Temple WJ, Mitchell P, et al. Cooperative hernia study. Pain in the postrepair patient. *Ann Surg*. 1996;224:598–602.
10. Simons MP, Aufenacker T, Bay-Nielsen M, et al. European Hernia Society guidelines on the treatment of inguinal hernia in adult patients. *Hernia*. 2009;13:343–403.
11. Amid PK, Lichtenstein IL. Long-term results and current status of the Lichtenstein open tension-free hernioplasty. *Hernia*. 1998;2:89–94.
12. Helbling C, Schlumpf R. Sutureless Lichtenstein: first results of a prospective randomised clinical trial. *Hernia*. 2003;7:80–84.
13. Fernandez Lobato R, Garcia Septiem J, Ortega Deballon P, et al. Tissucol application in dermolipectomy and incisional hernia repair. *Int Surg*. 2001;86:240–245.
14. Canonico S, Santoriello A, Campitiello F, et al. Mesh fixation with human fibrin glue (Tissucol) in open tension-free inguinal hernia repair: a preliminary report. *Hernia*. 2005;9:330–333.
15. Hidalgo M, Castillo MJ, Eymar JL, et al. Lichtenstein inguinal hernioplasty: sutures versus glue. *Hernia*. 2005;9:242–244.
16. Benizri EI, Rahili A, Avallone S, et al. Open inguinal hernia repair by plug and patch: the value of fibrin sealant fixation. *Hernia*. 2006;10:389–394.
17. Campanelli G, Champault G, Hidalgo Pascual M, et al. Randomized, controlled, blinded trial of Tissucol/Tisseel for mesh fixation in patients undergoing Lichtenstein technique for primary inguinal hernia repair: rationale and study design of the TIMELI trial. *Hernia*. 2008;12:159–165.
18. Miserez M, Alexandre JH, Campanelli G, et al. The European hernia society groin hernia classification: simple and easy to remember. *Hernia*. 2007;11:113–1116.
19. Amid PK. Lichtenstein tension-free hernioplasty: its inception, evolution, and principles. *Hernia*. 2004;8:1–7.
20. Alfieri S, Rotondi F, Di Giorgio A, et al. Influence of preservation versus division of ilioinguinal, iliohypogastric, and genital nerves during open mesh herniorrhaphy: prospective multicentric study of chronic pain. *Ann Surg*. 2006;243:553–558.
21. Amid PK. Causes, prevention, and surgical treatment of postherniorrhaphy neuropathic inguinodynia: triple neurectomy with proximal end implantation. *Hernia*. 2004;8:343–349.
22. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey. Construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34:220–233.
23. Franneby U, Sandblom G, Nordin P, et al. Risk factors for long-term pain after hernia surgery. *Ann Surg*. 2006;244:212–219.
24. Neumayer L, Giobbie-Hurder A, Jonasson O, et al. Open mesh versus laparoscopic mesh repair of inguinal hernia. *N Engl J Med*. 2004;350:1819–1827.
25. Callesen T, Bech K, Nielsen R, et al. Pain after groin hernia repair. *Br J Surg*. 1998;85:1412–1414.
26. Myles PS, Devereaux PJ. Pros and cons of composite endpoints in anesthesia trials. *Anesthesiology*. 2010;113:776–778.
27. Franneby U, Gunnarsson U, Andersson M, et al. Validation of an Inguinal Pain Questionnaire for assessment of chronic pain after groin hernia repair. *Br J Surg*. 2008;95:488–493.
28. McCarthy M, Jr, Jonasson O, Chang CH, et al. Assessment of patient functional status after surgery. *J Am Coll Surg*. 2005;201:171–178.
29. Heniford BT, Walters AL, Lincourt AE, et al. Comparison of generic versus specific quality-of-life scales for mesh hernia repairs. *J Am Coll Surg*. 2008;206:638–644.

