Randomized Double-Blinded Prospective Trial of Fibrin Sealant Spray Versus Mechanical Stapling in Laparoscopic Total Extraperitoneal Hernioplasty

*Chan Shannon Melissa, MBChB, MRCSEd,**
*Teoh Anthony Yuen Bun, MBChB, FRCSEd (Gen), FHKAM (Surgery),**
Chan Kin Wing, MBBS, FRCS (Edin), FHKAM (Surgery),†
Tang Yiu Chung, MBChB, FRCS (Edin), FHKAM (Surgery),†
*Ng Enders Kwok Wai, MD, MBChB, FRCS (Edin), FHKAM (Surgery),**
and Leong Heng Tat, MBBS, FRCS (Edin), FHKAM (Surgery)†

Objective: The aim of the current study was to compare the clinical outcomes of mesh fixation with fibrin sealant (FS) spray or mechanical stapling (MS) in laparoscopic total extraperitoneal hernioplasty (TEP).

Background: The most appropriate method of mesh fixation is uncertain.

Methods: Between June 2007 and June 2011, consecutive patients with primary reducible unilateral inguinal hernia who underwent day-case laparoscopic TEP were recruited. Outcome parameters included the incidence of acute and chronic pain, recurrence rates, morbidity rates, analgesic requirements, quality-of-life (QOL) scores, and direct cost.

Results: During the study period, 130 patients were included in the study. Patients in the MS group had significantly worse pain scores on the day after operation ($P = 0.006$). Analgesic requirements were similar between the 2 groups ($P = 0.558$). At 6 months, no significant differences in the incidence of chronic pain were observed (at rest, after coughing or cycling). The incidence of seroma formation was similar between the 2 groups ($P = 0.64$), and no recurrences were observed at 1 year. No differences in the QOL scores were detected. The direct cost of the entire hospitalization in the FS group was less expensive ($P < 0.001$).

Conclusions: FS and MS are both effective methods of providing mesh fixation. FS was associated with reduced acute pain but not chronic pain. The rates of seroma formation were similar. However, the use of FS for mesh fixation was less.

Keywords: fibrin sealant spray, fibrin glue, fixation, inguinal hernia, laparoscopic total extraperitoneal hernioplasty, mechanical stapling, quality of life

(*Ann Surg* 2014;259:432–437)

Laparoscopic total extraperitoneal hernioplasty (TEP) is increasingly adopted as a surgical approach for patients suffering from primary unilateral inguinal hernia.[1] The procedure was shown to result in less postoperative pain and allows earlier return to normal activities.[2–4] However, chronic pain is still a major issue affecting the quality of life (QOL) of patients after TEP and the reported incidence was from 9.2% to 22.5%.[5–7] Mechanical stapling (MS) is frequently used for mesh fixation; however, it may result in nerve and tissue entrapment by staples and further contribute to chronic pain.[8] On the contrary, the use of fibrin sealant (FS) as an alternative for mesh fixation has also been described and it was shown to provide similar tensile strength as compared to MS in an animal model.[9] Several cohort studies and one randomized trial have suggested that mesh fixation with FS in TEP may reduce chronic pain[10] with increased incidence of seroma.[11-13] Despite the lack of supporting literature, FS was still recommended as the method of choice in mesh fixation during laparoscopic TEP.[14]

Recently, a spraying device for application of FS laparoscopically has become available. The device allows more efficient use and even distribution of FS at lower volumes. There was no previous randomized study on the use of this new device. Hence, the aim of the current study was to compare the clinical outcomes of TEP using FS versus MS for mesh fixation in patients suffering from primary unilateral inguinal hernia. We hypothesize that mesh fixation with FS can reduce the incidence of chronic pain after TEP hernioplasty when compared with MS.

PATIENTS AND METHODS

This was a prospective double-blinded randomized controlled trial performed at the Ambulatory Surgery Center of Alice Ho Miu Ling Nethersole Hospital in Hong Kong. Between June 2007 and June 2011, consecutive male patients aged from 18 to 70 years with reducible unilateral inguinal hernia undergoing day-case laparoscopic TEP under general anesthesia were considered eligible. Patients with bilateral hernia, recurrent hernia, partially reducible or strangulated hernia, large hernia (L3 or M3 Endohernia Society Groin Hernia Classification), body mass index more than or equal to 35 kg/m^2, previous abdominal incision (including previous contralateral hernia repair), peripheral neuropathy, coagulopathy or taking anticoagulation drugs, end-stage renal failure, cirrhosis, impaired cognitive function, and those who did not consent to study were excluded. This study was approved by the Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee. All patients provided written consent. The study was registered with Clinicaltrials.gov number NCT01727050.

Surgical Procedure

All operations were performed or supervised by 2 surgeons with experience of more than 50 laparoscopic TEP. Prophylactic antibiotics were given to all patients before the operation. The procedure was performed with a 3-port technique (one 10-mm and two 5-mm ports) that involved the development of the preperitoneal plane from the pubic bone to 2 to 3 cm superior to the anterior superior iliac spine.

From the *Department of Surgery, Prince of Wales Hospital, The Chinese University of Hong Kong; and †Ambulatory Surgery Unit, Alice Ho Miu Ling Nethersole Hospital, Tai Po, Hong Kong SAR, China.

Disclosure: This study was not supported by any research grant, and the authors do not have any disclosures (Clinicaltrials.gov identifier: NCT01727050).

Reprints: Teoh Anthony Yuen Bun, Department of Surgery, Prince of Wales Hospital, The Chinese University of Hong Kong. E-mail: anthonyteoh@surgery.cuhk.edu.hk.

ISSN: 0003-4932/13/25903-0432
DOI: 10.1097/SLA.0b013e3182a6c513

The direct or indirect sacs were identified and reduced or ligated. The vas deferens and spermatic cord were preserved. Patients were randomized after complete dissection of the posterior wall of the inguinal canal. They were randomly allocated to the FS spray (FS group) or MS (MS group) for mesh fixation. A 10×15 cm^2 lightweight Prolene mesh was then inserted and fashioned in the preperitoneal space to cover the hernia opening and fixed.

FS Spray

Patients randomized to the FS group would undergo mesh fixation with the use of FS spray (Tisseel; Baxter Healthcare, Deerfield, IL). It is a mixture of human fibrinogen and synthetic fibrinolysis inhibitor that forms a rubber-like mass and adheres to raw surfaces resulting in gluing of tissue. FS was applied using a laparoscopic applicator (Duplo-catheter; Baxter Healthcare, Deerfield, IL) connected to an insufflator machine, creating an aerosol form of the sealant and allowing even and precise application at desired areas. Two milliliters of FS were used in each patient, and it was applied along the inferior edge of the mesh. This area is traditionally avoided when MS is used for fixation due to presence of major vascular structures (Fig. 1).

Mechanical Stapling

Patients randomized to the MS group underwent mesh fixation with the use of a titanium mechanical stapler (Tacker TM; Covidien, Mansfield, MA). The principle of stapling was to use the minimal number of tacks and avoid bony prominences and vascular and neural structures (Fig. 1). Tacks were only applied superior to the iliopubic tract. In any patient, the maximum number of staples applied did not exceed 8 and the usual number of tacks that were required was between 4 and 6.

Postoperative Management

All patients were assessed postoperatively and discharged on the day of operation if they satisfied the criteria for same-day discharge. Combination tablets (acetaminophen 500 mg and phenyltoloxamine citrate 30 mg—Dologesics; Llorens Pharmaceuticals International Division, Miami, FL) were provided for 1 week and taken as required. Patients were then scheduled for follow-up at 2 weeks, 1 month, and 6 months after operation. All outcome assessments were performed by a designated nurse of the Ambulatory Surgery Center who was blinded to the type of mesh fixation.

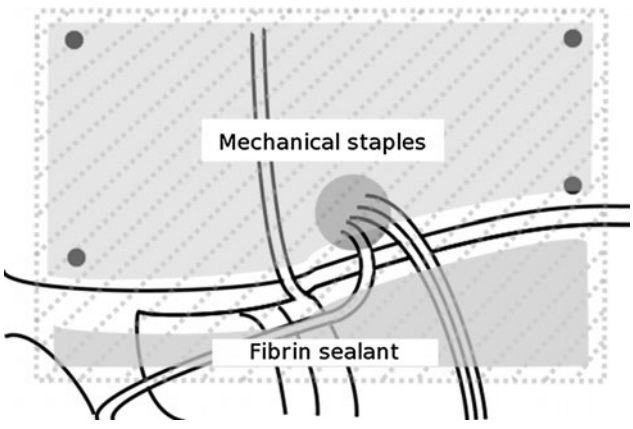

FIGURE 1. Figure demonstrating the locations where the mesh was fixed. MS was only applied superior to the iliopubic tract (in the superior shaded area) and the minimal number of tacks was used with avoidance bony prominences, vascular and neural structures. FS was applied to the inferior edge of the mesh in the area (in the inferior shaded area).

Outcome Parameters

The primary outcome was the incidence of chronic pain. Chronic pain was defined as the presence of any pain during any activity at 6-month follow-up. Secondary outcomes included analgesic requirements, morbidities, recurrence rates, QOL scores and direct cost. Baseline pain and QOL assessments were performed before the operation. Severity of pain was measured on a 4-point scale (*none*, *mild*, *moderate*, and severe) after various activities (at rest, coughing for 10 times and cycling for 5 minutes). In the first 7 days after operation, the patients were instructed to score the severity of pain at rest on a pain score assessment sheet at home. Thereafter, the patients were asked to score the severity of pain after various activities in person on follow-up at 4 weeks and 6 months after operation. QOL was evaluated by the validated Chinese (Hong Kong) version of SF-36 Health Survey questionnaire.[15] These parameters were assessed at 4 weeks and 6 months after operation.

Morbidites were defined by the following criteria. Wound infection was the presence of turbid discharge from the wounds with a positive culture. *Seroma* was defined as presence of a well-defined irreducible bulge at operative site with sonographic evidence of a fluid collection. *Recurrence* was the presence of a reducible lump at the groin area with radiological confirmation of a hernia. The hospital intranet was also searched for any unscheduled emergency department attendance or hospital admissions related to hernia operation within 30 days.

The direct cost of the groups included the total cost for the entire admission and was calculated by adding the costs of hospital stay, performed procedures, consumables, and management of major complications.

Sample Size Calculation and Statistical Analysis

The sample size was calculated by assuming a reduction in the incidence of chronic pain from 30% to 10% with FS spray, using 2-sided $P < 0.05$ as significant, achieving a power of 80%. The calculated sample size was 59 patients in each arm. Allowing maximum 10% loss to follow-up, 65 patients were needed in each arm. Randomization was done by opening sealed opaque envelopes containing computer-generated randomization codes in blocks of 10. Comparisons were made by χ^2 test or Fisher exact test where appropriate for categorical data and Student t test or Mann-Whitney U test for continuous data. The changes in QOL scores between groups were compared using Friedman test and Wilcoxon sign rank test with Bonferroni's correction. Analysis was based on intention-to-treat and a 2-sided $P < 0.05$ was considered significant. All statistical analyses were performed by statistical software SPSS version 20 (SPSS, Chicago, IL).

RESULTS

Between June 2007 and June 2011, a total of 130 patients were included into the study. One patient who defaulted follow-up was excluded from the analysis (Fig. 2). The baseline characteristics were similar between the 2 groups of patients (Table 1). No differences in the intraoperative details were observed, and this included the operation time, laterality of the hernia, size of the hernial defect, and the number of patients with perforation of the peritoneum. In 1 patient, the procedure was converted due to the presence of a sliding hernia with dense chronic adhesions to the spermatic cord.

In the early postoperative period, more patients in the MS group complained of moderate to severe pain on the day after operation ($P = 0.006$, Table 2). Thereafter, no differences in pain scales were detected between the groups from postoperative days 1

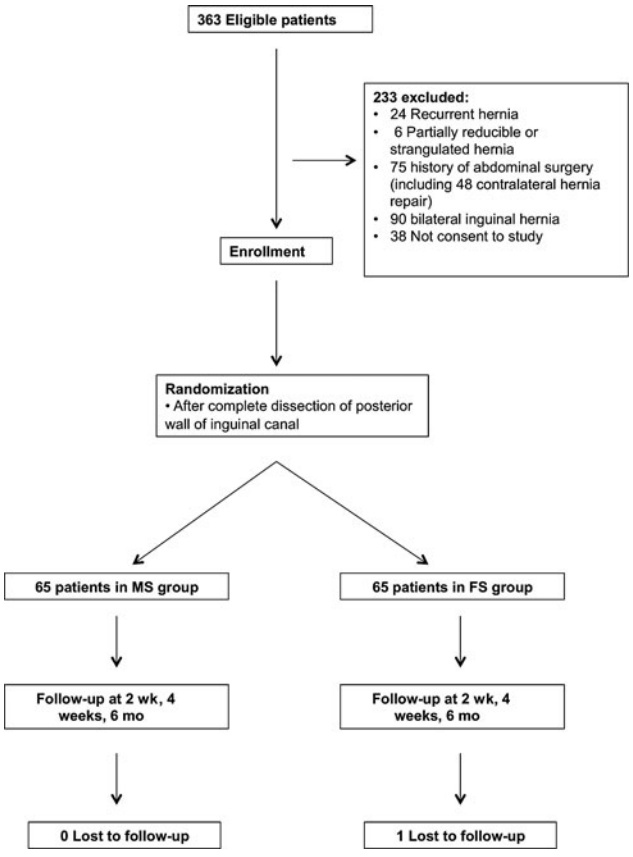

FIGURE 2. CONSORT flow diagram.

TABLE 1. Baseline Characteristics and Operative Details of the Study Population

	MS (N = 65)	FS (N = 64)	*P*
Age	53.31 (11.78)	52.77 (10.25)	0.781
American Society of Anesthesiology grading (I/II), %	54/11 (83.1/16.9)	45/19 (70.3/29.7)	0.099
Side (L/R), %	31/34 (47.7/52.3)	27/37 (43.8/56.2)	0.725
Type, %			0.791
Direct	24 (36.9)	20 (31.2)	
Indirect	38 (58.5)	41 (64.1)	
Both	3 (4.6)	3 (4.7)	
Operative time, min	73.09 (21.31)	75.84 (19.01)	0.441
Perforation of peritoneum, %	28 (43.1)	31 (48.4)	0.598
Size of hernia defect, cm	1.53 (0.63)	1.57 (0.64)	0.745
Conversion, %	1 (1.5)	0 (0)	1.000
Presence of pain assessed on a 4-point scale, %			
At rest			0.070
No pain	50	57	
Mild pain	15	6	
Moderate pain	0	1	
Coughing 10 times			0.077
No pain	42	48	
Mild pain	22	12	
Moderate pain	1	4	
Cycling 5 min			0.134
No pain	52	58	
Mild pain	13	6	

Values are expressed as mean (SD) unless otherwise specified.

TABLE 2. Comparison of Pain Among the 2 Groups

	MS (N = 65)	FS (N = 64)	*P*
Pain after operation (day 0)			**0.009**
None	8	7	
Mild	26	42	
Moderate	24	9	
Severe	5	3	
Missing	2	2	
Dologesic requirements (doses)	8.75 (8.54)	7.81 (9.17)	0.558
Pain at 4 weeks, %			
At rest			0.671
No pain	52	57	
Mild pain	9	6	
Moderate pain	1	1	
Missing	3	0	
Coughing 10 times			0.948
No pain	51	54	
Mild pain	10	9	
Moderate pain	1	1	
Missing	3	0	
Cycling 5 minutes			0.410
No pain	52	49	
Mild pain	9	13	
Missing	4	2	
Pain at 6 months, %			
At rest			0.364
No pain	56	58	
Mild pain	4	1	
Missing	5	5	
Coughing 10 times			0.364
No pain	59	56	
Mild pain	1	3	
Missing	5	5	
Cycling 5 minutes			1.000
No pain	56	56	
Mild pain	2	1	
Missing	7	7	

Values are expressed as mean (SD) unless otherwise specified. Boldface indicates significance.

to 7. Analgesic requirements were also similar among the 2 groups of patients ($P = 0.558$). Pain was then assessed at 4 weeks and 6 months after the operation under various conditions. At 4 weeks, there were no differences in the number of patients who experienced pain at rest ($P = 0.671$), after coughing for 10 times ($P = 0.948$, Fig. 3), or cycling for 5 minutes ($P = 0.410$, Fig. 4). Similarly at 6 months, no differences in the number of patients who experienced pain at rest were observed ($P = 0.364$). The incidences of pain after coughing for 10 times ($P = 0.364$, Fig. 5) and cycling for 5 minutes ($P = 1.000$, Fig. 6) were also similar between the 2 groups.

The overall morbidity rate was 7% and none of the patients had unscheduled admissions (Table 3). No patients suffered from recurrences. The rates of postoperative seromas were 0% for MS group and 3.4% for the FS group at 6 months ($P = 0.147$). The direct cost of the procedures was also compared (Table 4). Mesh fixation with MS (US \$3357.29 ± 49.8) was significantly more expensive than FS (US \$3182.00 ± 53.37) ($P < 0.001$, Table 4). QOL scores were similar between the 2 groups of patients when measured preoperatively and 4 weeks and 6 months after the operation (Fig. 7).

DISCUSSION

In the current study, FS spray was shown to have comparable efficacy to MS for mesh fixation in laparoscopic TEP for unilateral inguinal hernia. No patients in either group suffered from recurrences.

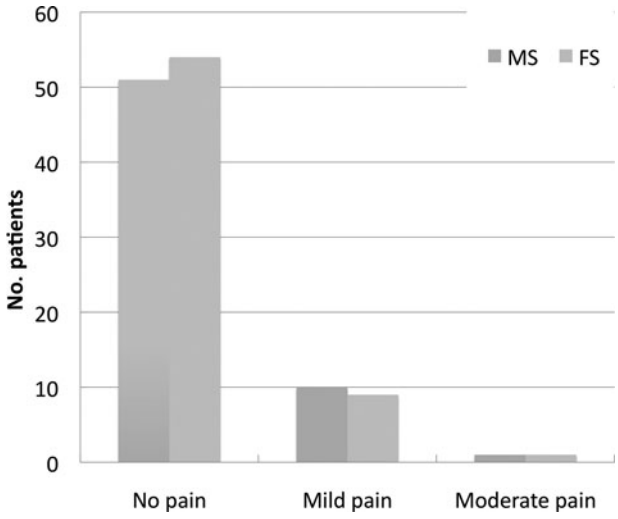

FIGURE 3. No difference in pain between the groups at 4 weeks after coughing for 10 times ($P = 0.948$).

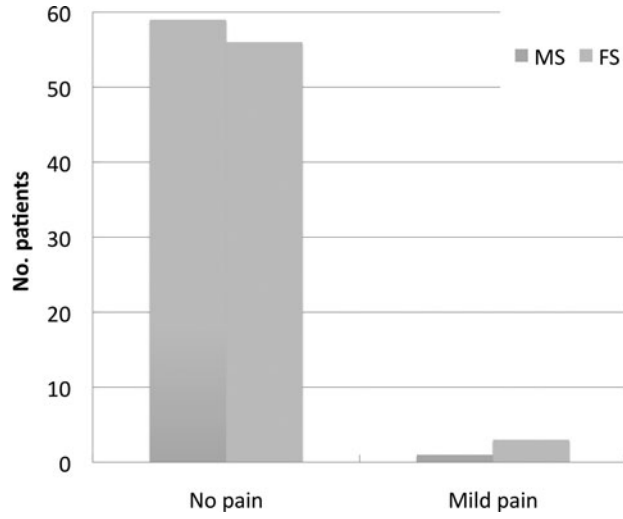

FIGURE 5. No difference in pain between the groups at 6 months after coughing for 10 times ($P = 0.364$).

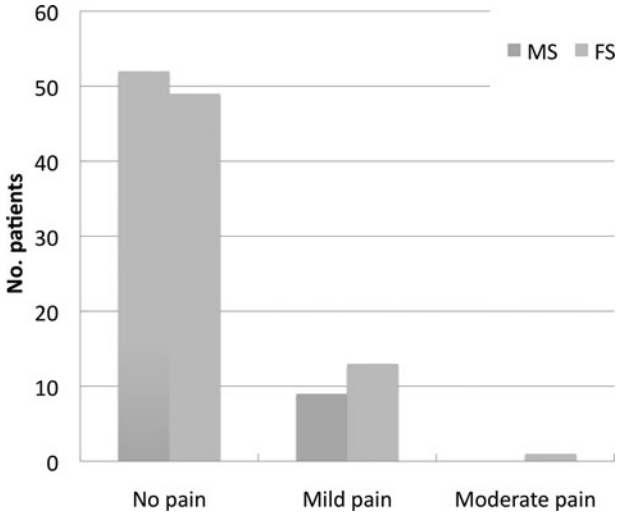

FIGURE 4. No difference in pain between the groups at 4 weeks after cycling for 5 minutes ($P = 0.410$).

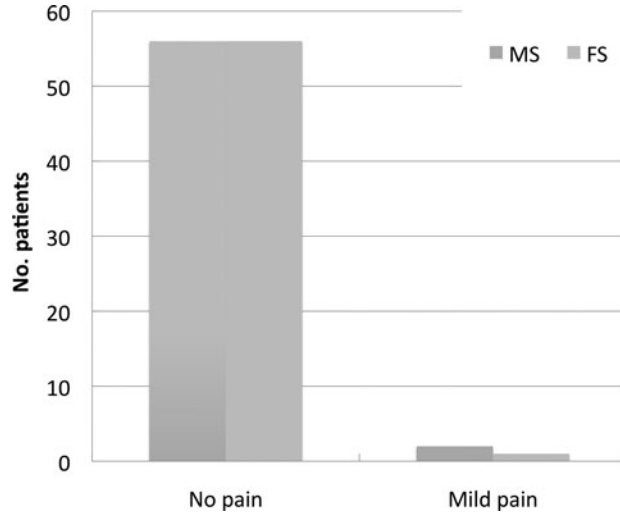

FIGURE 6. No difference in pain between the groups at 6 months after cycling for 5 minutes ($P = 1.000$).

Acute postoperative pain was significantly less for the FS group at the day after operation, whereas the incidence of chronic pain at 6 months was similar. Morbidities were also comparable, and the rates of seroma formation at 6 months were low in both groups. As a result, no differences in QOL scores were observed. However, the direct cost of the FS group was significantly less.

This study was unique in several aspects. First, there is a lack of randomized evidence in the literature and the current study is the second randomized study assessing the role of MS versus FS in laparoscopic TEP hernioplasty. Second, a strict inclusion criterion was adopted and this study only included patients with primary unilateral inguinal hernia without any history of prior abdominal or hernia surgery. This was to avoid the situation where prior surgery or the presence of a contralateral repair could introduce chronic pain resulting in bias. Furthermore, apart from a small difference in acute pain, there was no difference in incidence of chronic pain between the 2 groups. This is in contrast to results published in prior randomized studies where more chronic pain was present in the groups with mesh fixation by staples.[10–13] This may be partly explained by our technique of avoidance of bony prominences and usage of the minimal number of staples during MS. We also postulate that more staples may be required with the transabdominal preperitoneal (TAPP) approach to close the peritoneal opening resulting in more pain. Moreover, the number of patients who were lost to follow-up was very low and more than 99% of the patients completed follow-up. Finally, we demonstrated that the direct cost of the procedure was less in the FS group and this aspect was rarely addressed in previous studies.[14]

The literature is scarce on how different methods of mesh fixation compare to one another in laparoscopic hernioplasty. Despite this, FS was still recommended by the International Endohernia Society as the method of choice when fixation is required. In the only randomized study performed with the laparoscopic TEP approach, Lau[11] did not observe any difference in the incidence of acute and chronic pain during bilateral TEP. However, a significant reduction in

TABLE 3. Comparison of Postoperative Complications Among the 2 Groups

	MS (N = 65)	FS (N = 64)	*P*
Wound infection, %	2 (3.1)	5 (7.9)	0.273
Seroma formation, %			
4 wk	7 (11.3)	9 (14.1)	0.640
6 mo	0 (0)	2 (3.4)	0.147
Acute retention of urine, %	0 (0)	0 (0)	
Recurrence, %	0 (0)	0 (0)	
Unscheduled admissions	0 (0)	0 (0)	

TABLE 4. Breakdown and Comparison of Direct Cost Between the 2 Groups

	MS (N = 65)	FS (N = 64)	*P*
Total direct cost	3357.29 (49.80)	3182.00 (53.37)	**<0.001**
Hospital Stay	423.10 (0)	423.10 (0)	
Operation	2564.10 (0)	2564.10 (0)	
Consumables	347.05 (0)	166.67 (0)	
Management of complications	23.10 (49.74)	28.14 (53.37)	

Values are expressed as mean (SD) unless otherwise specified. All costs are shown in US dollar. Boldface indicates significance.

analgesic consumption and an increased incidence of postoperative seroma was observed in the FS group (17.4% vs 5.3%; $P = 0.009$). The increased incidence of seroma formation may be related to the enhanced inflammatory response caused by FS.[9] Yet, this increase in seroma rate was not observed in this study. The exact mechanism is uncertain but we believe that even application of the glue with the duplo-catheter may have a role in explaining this phenomenon. In our study, we used lightweight mesh instead of heavyweight because lightweight mesh conforms better to the myopectineal orifice. We postulate that this enabled us to fix the mesh with less glue and thus resulting in less seroma. Moreover, FS was applied to the inferior edge of the mesh to allow better fixation. This would not have been possible with MS because the region is a danger zone where staples could not be applied. Two other studies examined the role of FS for laparoscopic TAPP. Lovisetto et al[16] included 197 patients with inguinal or femoral hernia for laparoscopic TAPP. The patients in the FS group had significantly lower pain scores at 1, 3, and 6 months after operation. The time to return to normal activity was also significantly shorter, and improved QOL scores at 1 month were demonstrated. In another study, only 22 patients were included.[17] Lower pain scores were observed in the FS group, and seroma rates were similar among the 2 groups. However, this study may be underpowered to detect any true differences in the outcome parameters. In a recent meta-analysis assessing the role of FS for laparoscopic TEP, 3 retrospective studies and 1 prospective randomized study were included.[10] There was no difference in recurrence rates, but a higher incidence of chronic pain was observed with MS. There were also no significant differences in

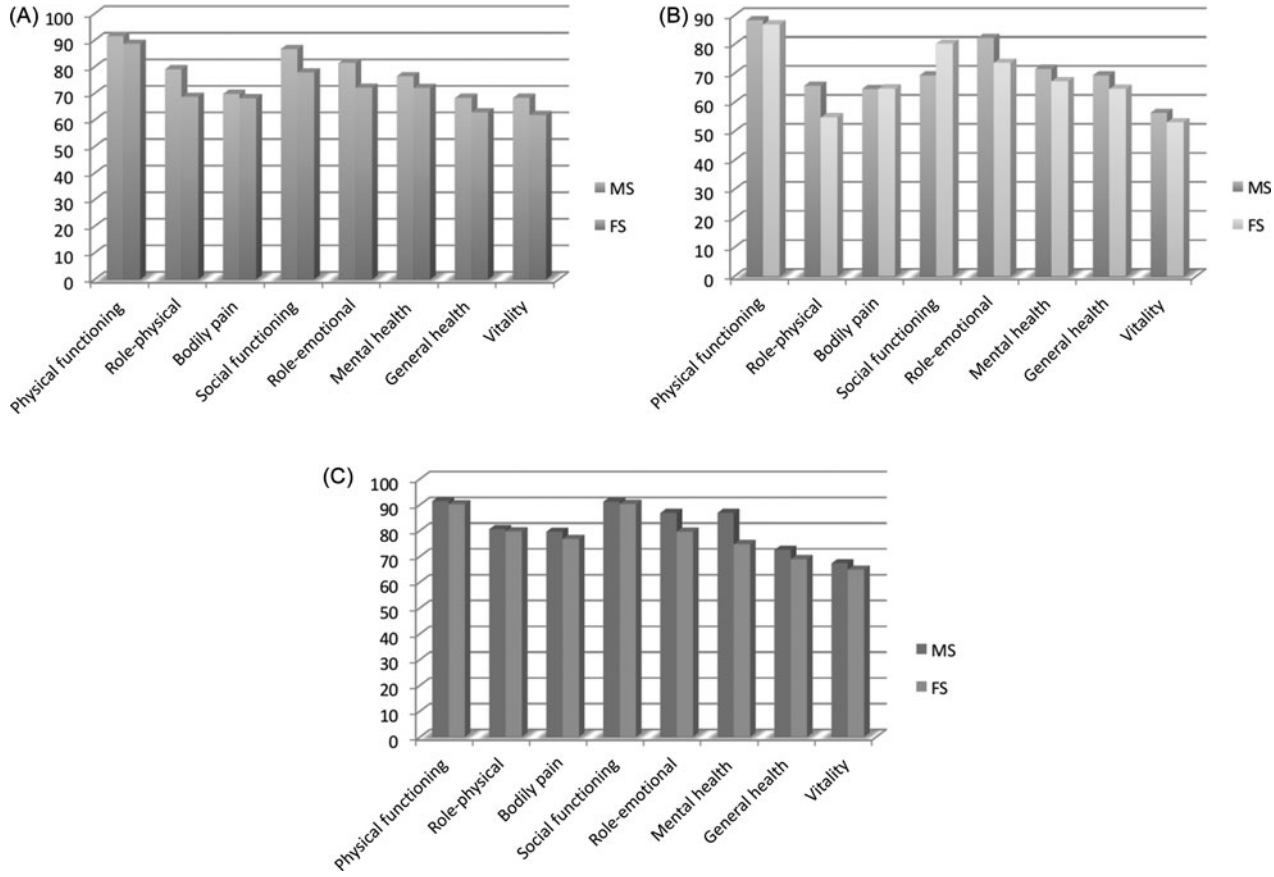

FIGURE 7. No difference in QOL scores preoperatively (A) and 4 weeks (B) and 6 months (C) postoperatively.

operative time, seroma formation, hospital stay, or time to return to normal activities. The current study adds further evidence to the body of literature supporting comparable rates of chronic pain with either method of mesh fixation.

There were a number of drawbacks to the current study. First, the incidence of chronic pain was less than 10% in both groups. This low rate of chronic pain may make the presence of any difference undetectable resulting in a type II error. Furthermore, the calculation of direct cost in this study may not be comparable with those of older studies as the cost of FS continues to diminish whereas that of MS remained similar throughout the last few years.

CONCLUSIONS

FS and MS are both effective methods of providing mesh fixation. FS was associated with reduced acute pain but not chronic pain. The rates of seroma formation were similar. However, the use of FS for mesh fixation was less expensive.

REFERENCES

1. National Institute for Clinical Excellence. *Laparoscopic Surgery for Inguinal Hernia Repair, Technology Appraisal 83*. London, UK: National Institute for Clinical Excellence; 2004.
2. Liem MS, van der Graaf Y, van Steensel CJ, et al. Comparison of conventional anterior surgery and laparoscopic surgery for inguinal hernia repair. *N Engl J Med*. 1997;336:1541–1547.
3. EU Hernia Trialists Collaboration. Laparoscopic versus open groin hernia repair: meta-analysis of randomized trials based on individual patient data. *Hernia*. 2002;6:2–10.
4. McCormack K, Scott NW, Go PM, et al. Laparoscopic techniques versus open techniques for inguinal hernia repair. *Cochrane Database Syst Rev*. 2003;1:CD001785.
5. Lau H, Patil NG, Yuen WK, et al. Prevalence and severity of chronic groin pain after endoscopic totally extraperitoneal inguinal hernioplasty. *Surg Endosc*. 2003;17:1620–1623.
6. 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.
7. Hindmarsh AC, Cheong E, Lewis MPN, et al. Attendance at a pain clinic with severe chronic pain after open and laparoscopic inguinal hernia repairs. *Br J Surg*. 2003;90:1152–1154.
8. Stark E, Oestreich K, Wendl K, et al. Nerve irritation after laparoscopic hernia repair. *Surg Endosc*. 1999;13:878–881.
9. Katkhouda N, Mavor E, Friedlander MH, et al. Use of fibrin sealant for prosthetic mesh fixation in laparoscopic extraperitoneal inguinal hernia repair. *Ann Surg*. 2001;233:18–25.
10. Kaul A, Hutfless S, Le H, et al. Staple versus fibrin glue fixation in laparoscopic total extraperitoneal repair of inguinal hernia: a systematic review and meta-analysis. *Surg Endosc*. 2012;26:1269–1278.
11. Lau H. Fibrin sealant versus mechanical stapling for mesh fixation during endoscopic extraperitoneal inguinal hernioplasty: a randomized prospective trial. *Ann Surg*. 2005;242:670–675.
12. Topart P, Vandenbroucke F, Lozac'h P. Tisseel vs tack staples as mesh fixation in totally extraperitoneal laparoscopic repair of groin hernias. *Surg Endosc*. 2005;19:724–727.
13. Schwab R, Willms A, Kroger A, et al. Less chronic pain following mesh fixation using a fibrin sealant in TEP inguinal hernia repair. *Hernia*. 2006;10:272–277.
14. Bittner R, Arregui ME, Bisgaard T, et al. Guidelines for laparoscopic (TAPP) and endoscopic (TEP) treatment of inguinal hernia [International Endohernia Society (IEHS)]. *Surg Endosc*. 2011;25:2773–2843.
15. Lam CL, Gandek B, Ren XS, et al. Tests of scaling assumptions and construct validity of the Chinese (HK) version of the SF-36 Health Survey. *J Clin Epidemiol*. 1998;51:1139–1147.
16. Lovisetto F, Zonta S, Rota E, et al. Use of human fibrin glue (Tissucol) versus staples for mesh fixation in laparoscopic transabdominal preperitoneal hernioplasty: a prospective, randomized study. *Ann Surg*. 2007;245:222–231.
17. Boldo E. Pain after laparoscopic bilateral hernioplasty: early results of a prospective randomized double-blinded study comparing fibrin versus staples. *Surg Endosc*. 2008;22:1206–1209.