Biologic Prosthesis Reduces Recurrence After Laparoscopic Paraesophageal Hernia Repair

A Multicenter, Prospective, Randomized Trial

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Objective: Laparoscopic paraesophageal hernia repair (LPEHR) is associated with a high recurrence rate. Repair with synthetic mesh lowers recurrence but can cause dysphagia and visceral erosions. This trial was designed to study the value of a biologic prosthesis, small intestinal submucosa (SIS), in LPEHR.

Methods: Patients undergoing LPEHR (n = 108) at 4 institutions were randomized to primary repair −1° (n = 57) or primary repair buttressed with SIS (n = 51) using a standardized technique. The primary outcome measure was evidence of recurrent hernia (≥2 cm) on UGI, read by a study radiologist blinded to the randomization status, 6 months after operation.

Results: At 6 months, 99 (93%) patients completed clinical symptomatic follow-up and 95 (90%) patients had an UGI. The groups had similar clinical presentations (symptom profile, quality of life, type and size of hernia, esophageal length, and BMI). Operative times (SIS 202 minutes vs. 1° 183 minutes, $P = 0.15$) and perioperative complications did not differ. There were no operations for recurrent hernia nor mesh-related complications. At 6 months, 4 patients (9%) developed a recurrent hernia >2 cm in the SIS group and 12 patients (24%) in the 1° group ($P = 0.04$). Both groups experienced a significant reduction in all measured symptoms (heartburn, regurgitation, dysphagia, chest pain, early satiety, and postprandial pain) and improved QOL (SF-36) after operation. There was no difference between groups in either pre or postoperative symptom severity. Patients with a recurrent hernia had more chest pain (2.7 vs. 1.0, $P = 0.03$) and early satiety (2.8 vs. 1.3, $P = 0.02$) and worse physical functioning (63 vs. 72, $P = 0.03$ per SF-36).

Conclusions: Adding a biologic prosthesis during LPEHR reduces the likelihood of recurrence at 6 months, without mesh-related complications or side effects.

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Traditionally, paraesophageal hernias were repaired by thoracotomy or laparotomy with morbidity around 20% and mortality of 2%.[1,2] The advent and later popularization of antireflux operations via the minimally invasive approach led to the development of a similar (laparoscopic) approach to the treatment of paraesophageal hernia (PEH). This approach called for the excision of the sac, a thorough esophageal mobilization, primary closure of the hiatus, and a Nissen fundoplication.[3,4] Laparoscopy appears to have some of the benefits of thoracotomy (the hiatus can be accessed easier, the esophagus can be dissected under direct vision and high mobilization of the esophagus is possible) and some of the advantages of the laparotomy (less morbidity, no need to collapse the lung, no need for postoperative chest tube). Indeed, most PEHs are currently repaired via a laparoscopic approach.

Hashemi et al in 2000 reported that patients who had had a repair of a PEH via the laparoscopic approach had a higher recurrence rate when compared with those operated on via thoracotomy and laparotomy.[5] The only other study comparing open and laparoscopic repair revealed a higher incidence of recurrence in the open repair group (8% vs. 0%),[6] but was also based solely on symptoms. Case series of laparoscopic paraesophageal hernia repair (LPEHR), which evaluate recurrent hiatal hernia by x-ray or endoscopy, have found the recurrence rate to be between 12% and 42%,[3,5,7] suggesting significant room for improvement.

It is not surprising that primary repair of the paraesophageal hiatal hernia by suturing the pillars of the diaphragm together under tension is at significant risk for disruption. With the development and wide application of mesh materials for tension-free repair of inguinal and ventral hernias, many surgeons have applied the technique of tension-free closure with a mesh to the hiatal hernia. Two randomized trials have demonstrated a significant reduction in recurrence rates by using synthetic mesh in large hiatal hernia repairs.[8,9] However, there are potential problems introduced by using synthetic mesh at the dynamic hiatus, such as mesh erosion, ulceration, stricture, and dysphagia.[9–11]

Recently, a number of biomaterials have been developed for hernia repair. The idea behind them is that a biologic scaffold, usually containing extracellular collagen, serves as a

temporary matrix, thus strengthening a natural hernia closure.[12,13] One such mesh is derived from porcine small intestinal submucosa (SIS) (Cook Surgical, Indianapolis, IN). A pilot study using SIS for PEH repair suggested that is was safe and possibly effective in reducing recurrence.[14]

In this study, we tested the hypothesis that the use of SIS to reinforce the closure of the hiatus in patients with PEHs would result in a lower recurrence rate and improved outcomes, without an increase in the complication rate.

MATERIALS AND METHODS

In 2002, 4 centers (University of Washington, Oregon Health Sciences University, Washington University St. Louis, and the Oregon Clinic) embarked on a prospective randomized trial in patients with symptomatic paraesophageal hernias. Eligibility for the trial is outlined in Table 1.

Surgical Technique

Five laparoscopic ports were used according to each center's routine. The short gastric and posterior gastric vessels to the base of the left crus were all divided. Circumferential dissection of the hernia sac from the hiatus and mediastinal structures was then performed. The sac was then first, everted over the gastroesophageal junction and then excised. Performance of a Collis gastroplasty for a foreshortened esophagus was left to the discretion of the operating surgeon. The hiatus was closed with interrupted suture (0 or 2-0 diameter). The closure was mostly posterior, but anterior sutures could be placed at the discretion of the surgeon.

For the SIS group, a piece of SIS (4-ply Surgisis, 7 × 10 cm, Cook Surgical) was prepared and cut in a U configuration. The SIS was placed with the U base overlying the posterior hiatal closure. It was then sutured to the diaphragm with interrupted, sutures to provide good contact between the SIS and diaphragm (Fig. 1). A Nissen fundoplication was then created between 2.5 and 3 cm in length over a 50–60 Fr Bougie.

TABLE 1. Patient Eligibility Criteria

Required characteristics
- A. Documented symptomatic paraesophageal hernia
  - 1. Greater than 5 cm hiatal hernia on UGI
  - 2. Evidence that the stomach or other viscera is present in the hernia and does not spontaneously reduce from the mediastinum
  - 3. Significant symptoms or signs of a paraesophageal hernia: heartburn, dysphagia, chest pain, shortness of breath, postprandial abdominal pain, early satiety, odynophagia, or chronic anemia
- B. Consenting adult ≥18 yr
- C. Must be able to participate in follow-up evaluation
- D. Has a telephone
- E. Free of cognitive or speech impairment

Exclusionary criteria
- A. Previous operation of the esophagus or stomach
- B. Associated gastrointestinal diseases that require extensive medical or surgical intervention that might interfere with quality of life assessment (eg, Crohn's disease)
- C. Emergent operation for acute volvulus

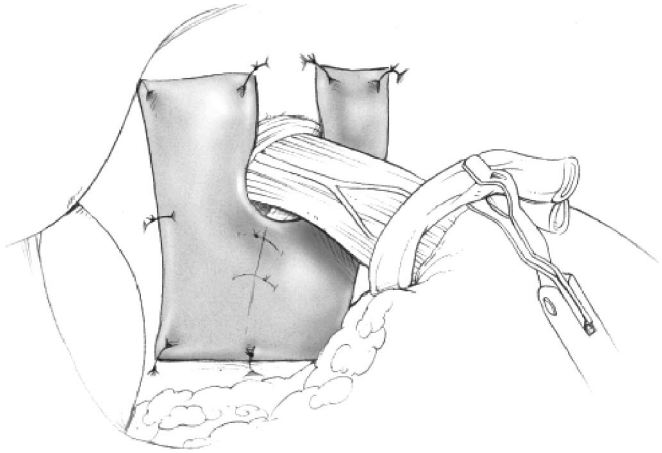

FIGURE 1. Schematic of SIS reinforced hiatal repair as performed in this trial.

Outcome Variables

Upper Gastrointestinal (UGI) Series (or Barium Swallow)

Preoperative and 6-month postprocedural UGI series were performed for each patient at their home institutions (University of Washington, Oregon Health Sciences University, Washington University St. Louis, and the Oregon Clinic). Based on the examination protocols at each institution, videofluoroscopy was used to assess the esophagus, stomach, and proximal small intestine with barium as the oral contrast material of choice. Preoperative exams were interpreted by the study clinicians at each institution and were used as the primary means of diagnosing PEH for inclusion within the study. Inclusion required fluoroscopic demonstration of a nonreducible hiatal hernia (type II or III), with stomach and/or other viscera (type IV hernia) contained in mediastinum.

A postprocedural UGI for each patient was performed at their respective medical centers 6 months after the surgery. To reduce reader variability, hard copies or digitized versions of these exams were reviewed at the coordinating center (University of Washington) by the same 2 radiologists (L.M. and J.N.) with over 36 combined years of experience in gastrointestinal imaging. The radiologists were both blinded to the treatment group and were asked to formulate a consensus interpretation based on the following 5-point scale (Fig. 2):

1. Intact fundoplication located below the diaphragm without any portions of stomach seen above the plication.
2. Intact fundoplication, but with indeterminate positioning. Plication seen within 2 cm of the level of the left hemidiaphragm.
3. Intact plication with probable small sliding hiatal hernia. Plication seen between 2 and 5 cm above the left hemidiaphragm.
4. Intact plication with a large sliding hiatal hernia (>5 cm above the left hemidiaphragm).
5. Slipped or disrupted fundoplication, portion of stomach present above the plication.

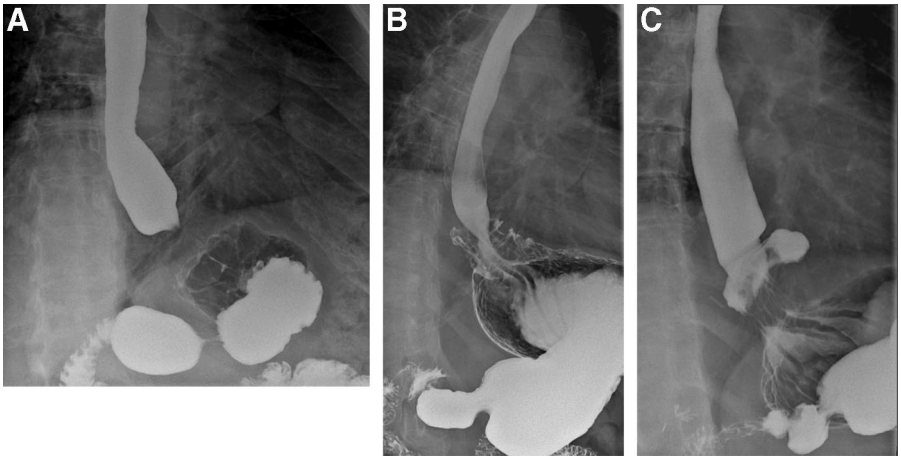

FIGURE 2. Upper gastrointestinal x-ray postoperative examples. A, Intact fundoplication located below the diaphragm. B, Intact fundoplication, but indeterminate positioning (fundoplication seen within 2 cm of the level of the left hemidiaphragm). C, Intact fundoplication with small sliding hiatal hernia (2–5 cm above the left hemidiaphragm).

When possible, distance measurements (in mm) were obtained using electronic calipers. All images for each examination were reviewed and the greatest linear distance from the level of the diaphragm adjacent to the fundoplication to the top of the wrap was recorded. For exams received as hard copy films, mechanical calibers were used in conjunction with recorded distance scales to obtain the measurements. In cases received where no calibration scales were found on the fluoroscopic spot images, the height of the nearest vertebral body was estimated from the overhead scout images and this height was then used on the fluoroscopic spot images to estimate the level of the plication.

Symptom Questionnaire

A standardized symptom questionnaire was administered upon enrollment, 2 to 4 weeks after operation, and 6 months after operation. Patients individually scored symptoms based on severity. The symptoms included were: heartburn, regurgitation, chest pain, dysphagia, abdominal pain, bloating, nausea, postprandial pain, and early satiety. The severity was scored using a visual analog score (VAS) in which the patient marked each symptoms from 0 to 10 (0 being no affect on life and 10 being extreme, incapacitating effect) from that symptom.

Quality of Life

The 36-item Health Survey (SF-36) was administered upon enrollment, 2–4 weeks after operation, and 6 months after operation. The SF-36 is a validated questionnaire measuring 8 health categories: physical functioning, role-physical, role-emotional, bodily pain, vitality, mental health, social functioning, and general health.[15] The SF-36 scores are standardized on a 100-point scale, with the worst score being 0 (poor quality of life) and the best being 100 (excellent quality of life). The results of the SF-36 were used to compare QOL before and after operation, as well as between groups. All data are presented as "norm-based" for consistency.

Intraoperative Data

For each patient, the following intraoperative data were collected:

Operative time in minutes measured from incision time to skin closure.

Operative time in minutes measured from incision time to skin closure.

Measurement of hiatal hernia defect in centimeters for 1) maximal distance between left and right crus and 2) anterior-posterior distance from apex of the hiatus to the posterior decussation of the left and right crus.

Length of intraabdominal esophagus after dissection completed at an insufflation pressure of 14 mm Hg.

All measurements were done with a flexible measuring tape and measured to the nearest 0.5 cm.

Additional Data

Upon enrollment, data were collected about medical comorbidities, body mass index (BMI), and other objective data performed during the patient workup, though not required for the study (pH monitoring, manometry, endoscopy).

Primary Outcome Measure

Recurrence rate (hiatal hernia >2 cm) was based on the results of an UGI done after 6 months. Need for reoperation secondary to wrap disruption, migration, or herniation at any time during the study period was assumed to constitute a recurrence.

Secondary Outcome Measures

Secondary outcome measures include symptom frequency and severity, QOL (SF-36), perioperative complications, and operative time.

Randomization

Randomization occurred via an automated phone system set up specifically for this study. Permuted block randomization with random block sizes for each institution was used to assign patients to primary hiatal closure (primary) or SIS reinforced hiatal closure (SIS).

Statistical Considerations

Data was collected and stored in a database developed at the institution of the principal investigator (University of

Washington). The data compilation, entry, and organization were performed electronically by the study coordinator.

Sample size was calculated before the trial as 71 patients per arm to have enough power to detect a 66% difference in recurrence rates (assuming a $\delta = 0.05$ and $E = 0.20$). Primary outcome measure (hernia recurrence) and complication rates were analyzed every 6 months, and a significant difference in either was used as criteria for stopping the trial early.

The value of the outcomes and their changes over time were compared between the primary and SIS groups. Groups were analyzed on an intent-to-treat basis. We tested for differences between pairs of groups as well as for differences over time within each of the groups. Two- and one-sample *t* tests were used for the quality of life scores and all quantitative operative outcomes to test for differences between groups and temporal changes within groups, respectively. Likewise, we used Mann-Whitney *U* and Wilcoxon's signed rank test to compare symptom frequency and severity scores and χ^2 and McNemar's test to compare presence of hernia and symptoms. Symptom severity and quality of life at 6 months were compared between those with and without hernia using linear regression of the outcomes with an adjustment for the baseline of the outcome. We built a multivariate logistic regression model to predict hernia recurrence using forward selection criterion. The factors considered in the model building included SIS/primary group, type of hernia, size of hernia (right to left, anterior-posterior, and the total area), esophageal length, BMI, and institution site. A *P* value of <0.05 was accepted to denote statistical significance.

The study was approved by the University of Washington Human Subjects Division, as well as by each of the participating institution's institutional review boards, and compliance of all standards were met. Patients who agreed to participate provided written informed consent. All data were protected according to HIPPA guidelines.

RESULTS

A total of 108 patients consented to the study and were enrolled and randomized according to established trial criteria. Fifty-one were randomized to the SIS arm and 57 to the primary arm. All patients were successfully contacted at 6 months for follow-up, although some patients had incomplete data: 7 had incomplete questionnaire data and 11 did not have an UGI.

Baseline Characteristics

Enrollment characteristics were similar between groups with regard to age, gender, BMI, and presenting symptoms (Table 2). There was a similar distribution of hernia types: type II (primary = 6, SIS = 8), type III (primary = 48, SIS = 40), type IV (primary = 4, SIS = 3).

Operative Data

There was no statistically significant difference between groups with regard to operative time, esophageal length, or the right to left hiatus dimensions (Table 3). There was a trend toward larger hiatal diameters (measured anterior to posterior) in the SIS group, but this was not statistically significant ($P = 0.07$). Collis gastroplasty was performed in 6 patients (4 primary and 2 SIS patients) for a foreshortened esophagus. Two patients were converted from laparoscopy to laparotomy, both in the primary group: one for a left gastric artery injury and the other for severe hepatomegaly.

TABLE 2. Baseline Characteristics of Treatment Groups at Randomization

	Primary (n = 57)	SIS (n = 51)	*P*
Age (yr)	64 ± 13	67 ± 11	NS
Female	43 (75%)	38 (75%)	NA
BMI (kg/m^2)	31.3 ± 4.9	30.2 ± 5.6	NS
Symptoms*			
Heartburn	5.3 ± 3.5	5.3 ± 3.1	NS
Regurgitation	5.4 ± 3.2	5.2 ± 3.1	NS
Chest pain	4.4 ± 3.7	3.7 ± 3.6	NS
Dysphagia	3.1 ± 2.9	3.1 ± 3.1	NS
Bloating	4.0 ± 3.3	4.1 ± 2.8	NS
Postprandial pain	4.1 ± 3.3	4.8 ± 3.4	NS
Early satiety	3.7 ± 3.4	4.4 ± 2.8	NS

Values are mean ± SD. NS, not significant; NA, not applicable.
*Symptom severity scored by visual analog scale (0–10).

TABLE 3. Operative Data

	Primary	SIS	*P*
Time (min)	185 ± 66	201 ± 69	0.22
Hiatus (R-L) (cm)	4.3 ± 2.4	4.2 ± 1.8	0.99
Hiatus (A-P) (cm)	5.8 ± 1.5	6.4 ± 2.0	0.07
Esophageal length (cm)	3.4 ± 0.9	3.2 ± 1.0	0.26
Collis gastroplasty	3 (5%)	2 (4%)	NA
Convert to open	2 (3.5%)	0	NA

Values are mean ± SD. NA, not applicable.

Complications

There were 10 (18%) complications in the primary group: pneumothorax (n = 6), 2 gastric and one small bowel perforations (n = 3), and splenic hematoma (n = 1). There were 12 (24%) complications in the SIS group: pneumothorax (n = 10) and bleeding (n = 1). One patient in the SIS group was reoperated on postoperative day (POD) 9 for a delayed gastric perforation that was unrelated to the SIS placement. Two patients died after discharge, at home; neither had an autopsy. Both of these patients were in the primary group. One death was thought to be secondary to a myocardial infarction (POD 14) and the other was thought to be caused by a massive pulmonary embolism (POD 7).

Symptom Results

There was a significant reduction in both the frequency and severity of presenting symptoms (heartburn, regurgitation, chest pain, dysphagia, abdominal pain, bloating, nausea, postprandial pain, and early satiety) 6 months after operation compared with the time of enrollment before LPEH repair (Table 4).

TABLE 4. Symptom Severity at 6 Months After LPEH Repair

	Primary	*P**	SIS	*P**
Heartburn	0.4 ± 0.8	<0.001	1.0 ± 2.3	<0.001
Regurgitation	0.6 ± 1.5	<0.001	1.1 ± 2.1	<0.001
Chest pain	1.1 ± 2.3	<0.001	1.5 ± 2.7	0.003
Dysphagia	0.8 ± 2.1	<0.001	1.4 ± 2.5	0.007
Bloating	1.9 ± 2.6	<0.001	2.6 ± 2.9	0.002
Postprandial pain	1.3 ± 2.4	<0.001	1.4 ± 2.4	<0.001
Early satiety	1.9 ± 2.1	0.003	1.5 ± 2.3	<0.001

Values are mean ± SD. Symptom severity scored by visual analog scale (0–10).
*Compared with preoperative scores.

Quality of Life Assessment

Quality of life, as assessed by the SF-36 questionnaire, was significantly improved with LPEH when measured 6 months after operation. Overall, all domains of the SF-36 improved (physical functioning, role limitations due to physical health, bodily pain, vitality, social functioning, role limitations due to emotional problems, and mental health) with the exception of general health perceptions (Fig. 3a). This improvement in quality of life appeared to be more pervasive among domains in the SIS group than it was in the primary group. While both primary and SIS groups had significant improvement in physical functioning, role limitations due to physical health, bodily pain, vitality, and social functioning, the SIS group also experienced improvements in role limitations due to emotional problems and mental health (Fig. 3b, c).

Hernia Recurrence

Ninety-five of 106 patients (90%) had a UGI performed and interpreted by the study radiologists. By our study defi-

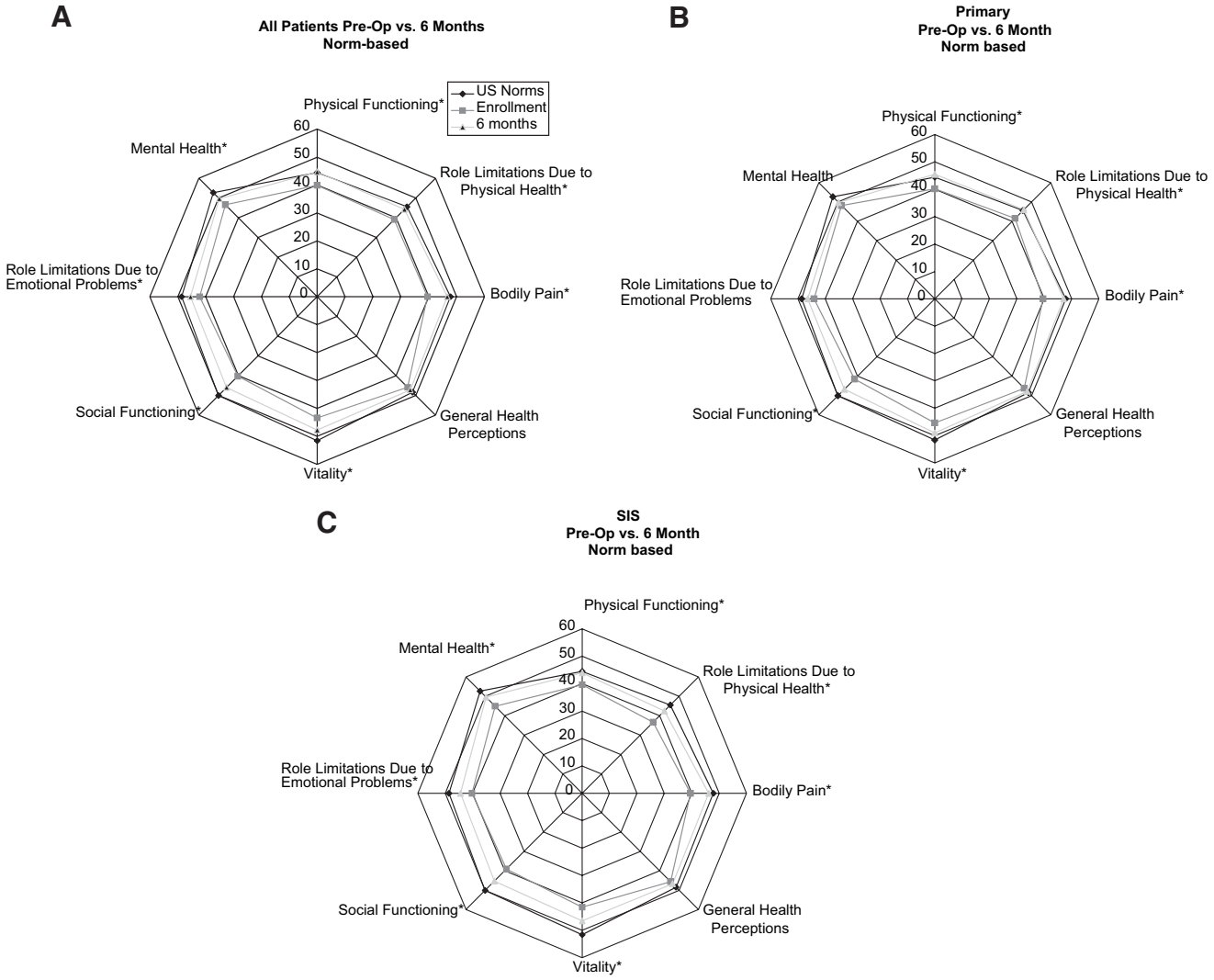

FIGURE 3. A, SF-36 results preoperative and 6 months after operation for all study patients. U.S. norms included for comparison. *Preoperative versus 6 months ($P \leq 0.01$). B, SF-36 results preoperative and 6 months after operation for primary group. U.S. norms included for comparison. *Preoperative versus 6 months ($P < 0.05$). C, SF-36 results preoperative and 6 months after operation for SIS group. U.S. norms included for comparison.*Preoperative versus 6 months ($P \leq 0.01$).

nition of recurrent hernia (>2 cm), there was a statistically significant reduction in hernia recurrence with SIS compared with primary repair: 12 patients (24%) in the primary versus 4 patients (9%) in SIS group ($P = 0.04$). Of the 16 patients with a recurrence, all were measured between 2 and 5 cm, except one patient (primary group) that had a hernia larger than 5 cm.

Multivariate Analysis

Based on a multivariate analysis (methods described earlier) of the following factors: SIS/primary group, type of hernia, size of hernia (right to left, anterior-posterior, and the total area), esophageal length, BMI, and institution site; the only factor that appeared to be related to hernia recurrence was placement of SIS mesh (odds ratio = 0.16, $P < 0.05$).

Effect of Recurrent Hernia

To determine the association of a recurrent hernia with outcomes, we compared the outcomes of patients with a recurrent hernia with those without a recurrence. After adjusting for baseline differences, both chest pain and early satiety were significantly more severe in those with recurrent hernias (Table 5). In addition, patients with recurrent hernias had lower scores on the physical functioning component of the SF-36.

DISCUSSION

Paraesophageal hernias have a relatively high recurrence (12%–42%) when treated via the laparoscopic approach and with primary repair.[3,5,7] Based on prior investigations, we hypothesized that a biomaterial, specifically SIS, might reduce the risk of recurrence without the potential risks associated with synthetic mesh.[14] The results of this trial suggest that LPEHR is effective at relieving symptoms associated with PEH and can be done with very little morbidity. Furthermore, this study confirms a substantial benefit of mesh reinforcement for LPEHR and is the first trial to demonstrate the efficacy of a biologic material for these hernia repairs. This finding is important, not only for LPEHR, but potentially for other hernia repairs and operations that would benefit from nonpermanent biologic support.

TABLE 5. Effect of Recurrent Hernia on Symptoms and Quality of Life (6 Months)

	No Hernia	Recurrent Hernia	$P^{\dagger}$
Symptoms*			
Heartburn	0.5 ± 1.3	1.1 ± 2.3	0.3
Regurgitation	0.8 ± 1.9	1.1 ± 2.0	0.9
Chest pain	1.0 ± 2.1	2.7 ± 3.4	0.03
Dysphagia	1.2 ± 2.4	0.6 ± 1.5	0.4
Bloating	2.3 ± 2.7	2.1 ± 3.0	0.6
Postprandial pain	1.1 ± 2.1	1.9 ± 2.5	0.3
Early satiety	1.3 ± 2.1	2.8 ± 2.1	0.02
SF-36			
Physical Functioning	72 ± 28	63 ± 38	0.03
Limitation–Physical Health	70 ± 29	61 ± 40	0.12
Bodily Pain	65 ± 26	58 ± 35	0.4
Health Perceptions	67 ± 21	60 ± 25	0.8

Values are mean ± SD.
*Symptom severity scored by visual analog scale (0–10).
†Linear regression adjusted for baseline.

Benefits of the Laparoscopic Approach in the Treatment of Paraesophageal Hernias

Since the first report LPEHR in 1991,[16] there has been debate about the best approach for repairing PEHs. It has been suggested that the laparoscopic approach, as with many operations, is associated with lower rates of morbidity, less pain, and faster recovery.[6] If true, this may be even more important in this patient population, since most patients with PEHs are older and likely to have associated medical comorbidities. Our study would support this assessment, as we had very few complications and most patients made a quick, unremarkable recovery. On the other hand, the mortality of nearly 2% observed in our study underlines the high risk that these patients have and the need for careful selection, especially since most patients with PEHs are in their seventh, eighth, and ninth decades of life. Other studies have clearly documented an increased morbidity and mortality with advanced age.[17] Still, despite a lack of good comparative data, we think that the laparoscopic approach is much safer in this high-risk group.

There are few studies that have collected prospective data on the clinical and quality of life outcomes from this operation. The best reports come from relatively large, single-institution case studies, which report that roughly 80% to 90% of patients experience substantial symptomatic improvement after LPEHR.[7,18–20] This trial, by collecting detailed, comprehensive information about each patient's state of health before and after operation, confirms that LPEHR confers a substantial benefit to patients with a PEH.

There remains a debate over access (laparoscopy vs. open) for PEH repairs, largely because recurrence rates after LPEHR, if critically investigated with imaging studies is quite high. Indeed, our study confirms this by demonstrating, with rigorous UGI follow-up, a recurrence rate of 24% for LPEH treated with primary closure of the hiatal defect.

Given that most recurrences are relatively small (<5 cm), are they clinically relevant? Previous investigations have suggested that most recurrences, especially when a fundoplication is part of the repair, are asymptomatic.[5,7] These observations, however, come from retrospective studies, which were based on subjective interpretation of medical records. By contrast, our trial was designed to measure the change in frequency and severity of symptoms in these patients. Our data showed significantly worse clinical outcomes in patients with recurrent hernias when compared with those without recurrence. Therefore, preventing a recurrent hernia is of critical importance in obtaining the best possible symptomatic outcome.

Use of Mesh

There are several reported ways to decrease recurrence. These include resection of the sac,[3] gastropexy,[21] addition of

a fundoplication with fixation of the top of the wrap to the undersurface of the diaphragm,[4] esophageal lengthening (Collis gastroplasty), and the use of thoracotomy to further mobilize the esophagus, resect the sac, and repair the hiatus.[5] Since most of these methods have not prevented hernia recurrence, many authors have advocated the use of prosthetic mesh materials.[8,22–24] This is logical since the use of mesh has become the standard of care for inguinal, ventral, and other types of hernias because it resulted in a drastic reduction in recurrence rates.

There are several reasons why primary suture approximation of the pillars of the crus is not enough in many cases. First, the hernia defect with an intrathoracic stomach is quite large, and closure is usually under tension. Second, the pillars are often quite thin and made of attenuated muscle, not fascia. Third, there are constant, frequently repeated episodes of stress on the diaphragm from breathing, cough, and Valsalva maneuvers. Indeed, there are 2 randomized trials that have shown a reduction in PEH recurrence rates with synthetic mesh compared with primary hiatal repair.[8,9]

However, the use of nonabsorbable mesh at the hiatus is not universally accepted because of its potential complications. The most devastating complication described is esophageal or gastric erosion, which is thought to result from the constant movement of mesh and diaphragm.[11] Since many such complications are not reported, it is likely that their prevalence exceeds those suggested in the literature.

The placement of synthetic mesh for hiatal repair is also associated with dysphagia. Most studies on the outcomes of hiatal mesh repair do not give detailed results of dysphagia, especially compared with no mesh.[8] So the magnitude of this problem is unclear, but there are reports of severe dysphagia after the use of mesh at the hiatus.[25] Synthetic material causes a significant inflammatory response and because it is rigid it is usually not amenable to endoscopic dilation.

Randomized Trials Using Mesh for Hiatal Hernia Repair

Two prospective, randomized clinical trials have shown that the use of mesh in laparoscopic hiatal hernia repairs prevents recurrences. However, unlike our trial, neither was done specifically for PEHs. The first published trial used polytetrafluoroethylene as an on lay circumferential ("key-hole") patch over a closed hiatus.[8] Seventy-two patients were enrolled and had different lengths of follow-up (median, 2.5 years), but there were no anatomic recurrences in the mesh group versus 22% in the group without mesh. The weakness of this study is the lack of objective clinical symptom follow-up. Therefore, it is not clear from this trial whether protection against recurrence results in better symptom control or if mesh is associated with negative side effects such as dysphagia.

The second trial used a 1 × 3 cm patch of polypropylene over the primary hiatal closure during laparoscopic Nissen fundoplication (not for PEHs).[9] A total of 100 patients were randomized, and by 1 year 8% of patients receiving mesh had a recurrence compared with 26% for those patients without mesh. Interestingly, there was no difference in the postoperative GERD symptoms (heartburn and regurgitation) between groups, but the mesh group did have a 3-fold higher rate of dysphagia in the first 3 months.

In both of these trials, mesh conferred a substantial reduction in the short-term recurrence rates, thus making a strong argument for routine mesh use. However, even these trials suggest this may come at a price. Indeed, neither of these trials documents better symptom and quality of life outcomes in patients receiving mesh, and the Granderath et al trial showed an increase in dysphagia with only a small piece of mesh placed over the posterior hiatal repair.[9]

Benefits of Biologic Mesh

In the last 5 years, there has been a lot of interest in the use of biomaterials in hernia repairs, as well as other applications. The theoretical benefits purported include: resistance to infection in contaminated surgical fields, avoidance of permanent foreign body, and a reconstruction that, in the end, is made of natural tissue. The premise is that these products, usually made of a matrix of acellular collagen, provide a scaffold for tissue remodeling that is stronger than native tissue.

SIS is an acellular xenograft consisting primarily of type I porcine collagen. Experimental evidence suggests that even though the scaffold provided by SIS rapidly degrades, the remodeled tissue is stronger than normal tissue healing.[12,13] Animal studies have shown that SIS is incorporated into the abdominal wall[26] and can even bridge defects in the diaphragm.[27] Furthermore, several human clinical studies have demonstrated safety and suggested good results in repairing abdominal wall hernias.[28–30]

Soon after the FDA approval of SIS as one of the first biologic materials for hernia repair, we hypothesized that it was promising for the vexing problem of PEH repair. Indeed, we thought that the use of SIS would minimize the risk of dysphagia observed by Granderath et al[9] and of mesh erosion because this biologic mesh material is flexible and is absorbed and incorporated by the body. Furthermore, we thought that the scaffold provided by SIS might lead to a stronger and long lasting repair. Because animal studies had shown that SIS led to substantial tissue contraction in the area of placement,[31] we decided not to place the mesh in a "key-hole" or circumferential manner to reduce the risk of stricture/dysphagia (Fig. 2).

We initially did a pilot study in 9 patients with especially difficult PEHs. There were no mesh-related complications and the short-term recurrence rate was low.[14] One of our coinvestigators also had experience with the use of this prosthesis. Desai et al created PEHs in dogs and repaired them with SIS.[31] None of the dogs developed a stricture, erosion, dysphagia, or recurrence at 1 year. Subsequently, other human cases series have reported using biomaterials for reinforced LPEHR confirming safety and good clinical results.[32,33]

While we have clearly shown that the use of SIS reduces the rate of short-term (within 6 months) recurrences, it is unclear whether this will confer long-term protection of recurrence. The fact that this prosthetic material is absorbed may, in theory at least, jeopardize the long-term success of the operation. However, other studies have shown that most recurrences after PEH repair occur early.[9,34] Moreover, since SIS is rapidly remodeled so that the strength of the native

mesh deteriorates within the first week, we expected to see the effects of this on recurrence rates within the first 6 months of repair.[12] Lastly, experimental evidence suggests that the tissue that replaces this biologic mesh is stronger than normal scar. Nevertheless, we plan to follow up this study with an investigation of these patients in the next few years to determine the validity of this assumption.

CONCLUSION

This study demonstrates that biologic prosthesis reinforced LPEHR results in a lower hiatal hernia recurrence rate than does primary LPEHR. The use of this mesh reduced the short-term hernia recurrence rate 2.5-fold. Preventing recurrent herniation at the hiatus is associated with superior clinical outcomes. Moreover, biologic, absorbable mesh is not associated with an increased rate of side affects or complications in the short term. Furthermore, because the foreign material is fully reabsorbed, it is not expected to lead to erosions, strictures, or ulcers, as has been seen with synthetic mesh. Biologic mesh reinforcement of the hiatal hernia repair should be strongly considered routinely during LEPHR.

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REFERENCES

1. Ellis FH, Crozier RE, Shea JA. Paraesophageal hiatus hernia. *Arch Surg*. 1986;121:416–420.
2. Pearson FG, Cooper JD, Ilves R, et al. Massive hiatal hernia with incarceration: a report of 53 cases. *Ann Thoracic Surg*. 1983;35:45–51.
3. Horgan S, Eubanks TR, Jacobsen G, et al. Repair of paraesophageal hernias. *Am J Surg*. 1999;177:354–358.
4. Oelschlager BK, Pellegrini CA. Paraesophageal hernias: open, laparoscopic, or thoracic repair? *Chest Surg Clin North Am*. 2001;11:589–603.
5. Hashemi M, Peters JH, DeMeester TR, et al. Laparoscopic repair of large type III hiatal hernia: objective follow-up reveals high recurrence rate. *J Am Coll Surg*. 2000;190:554–561.
6. Schauer PR, Ikramuddin S, McLaughlin MD, et al. Comparison of laparoscopic versus open repair of paraesophageal hernia. *Am J Surg*. 1998;176:659–665.
7. Mattar SG, Bowers SP, Galloway KD, et al. Long-term outcome of laparoscopic repair of paraesophageal hernia. *Surg Endosc*. 2002;16:745–749.
8. Frantzides CT, Madan AK, Carlson MA, et al. A prospective, randomized trial of laparoscopic polytetrafluoroethylene (PTFE) patch repair vs simple cruroplasty for large hiatal hernia. *Arch Surg*. 2002;137:649–652.
9. Granderath FA, Schweiger UM, Kamolz T, et al. Laparoscopic Nissen fundoplication with prosthetic hiatal closure reduces postoperative intrathoracic wrap herniation: preliminary results of a prospective randomized functional and clinical study. *Arch Surg*. 2005;140:40–48.
10. Paul MG, DeRosa RP, Petrucci PE, et al. Laparoscopic tension-free repair of large paraesophageal hernias. *Surg Endosc*. 1997;11:303–307.
11. Trus TL, Bax T, Richardson WS, et al. Complications of laparoscopic paraesophageal hernia repair. *J Gastrointest Surg*. 1997;1:221–228.
12. Badylak S, Kokini K, Tullius B, et al. Strength over time of a resorbable bioscaffold for body wall repair in a dog model. *J Surg Res*. 2001;99:282–287.
13. Gloecker DC, Sacks MS, Billiar KL, et al. Mechanical evaluation and design of a multilayered collagenous repair biomaterial. *J Biomed Mater Res*. 2000;52:365–373.
14. Oelschlager BK, Barreca M, Chang L, et al. The use of small intestine submucosa in the repair of paraesophageal hernias: initial observations of a new technique. *Am J Surg*. 2003;186:4–8.
15. Ware JE, Kosinski M, Dewey JE. *How to Score Version Two of the SF-36® Health Survey*. Lincoln, RI: QualityMetric, 2000.
16. Congreve DP. Laparoscopic paraesophageal hernia repair. *J Laparoendosc Surg*. 1992;2:45–48.
17. Flum DR, Koepsell T, Heagerty P, et al. The nationwide frequency of major adverse outcomes in antireflux surgery and the role of surgeon experience, 1992–1997. *J Am Coll Surg*. 2002;195:611–618.
18. Swanstrom LL, Jobe BA, Kinzie LR, et al. Esophageal motility and outcomes following laparoscopic paraesophageal hernia repair and fundoplication. *Am J Surg*. 1999;177:359–363.
19. Diaz S, Brunt LM, Klingensmith ME, et al. Laparoscopic paraesophageal hernia repair, a challenging operation: medium-term outcome of 116 patients. *J Gastrointest Surg*. 2003;7:59–66.
20. Edye MB, Canin-Endres J, Gattorno F, et al. Durability of laparoscopic repair of paraesophageal hernia. *Ann Surg*. 1998;228:528–535.
21. Kercher KW, Matthews BD, Ponsky JL, et al. Minimally invasive management of paraesophageal herniation in the high-risk surgical patient. *Am J Surg*. 2001;182:510–514.
22. Basso N, Rosato P, De Leo A, et al. 'Tension-free' hiatoplasty, gastrophrenic anchorage, and 360 fundoplication in the laparoscopic treatment of paraesophageal hernia. *Surg Laparosc Endosc*. 1999;9:257–262.
23. Muller-Stitch BP, Holzinger F, Kapp T, et al. Laparoscopic hiatal hernia repair: long-term outcome with the focus on the influence of mesh reinforcement. *Surg Endosc*. 2006;20:380–384.
24. Champion JK, Rock D. Laparoscopic mesh cruroplasty for large paraesophageal hernias. *Surg Endosc*. 2003;17:551–553.
25. Carlson MA, Condon RE, Ludwig KA, et al. Management of intrathoracic stomach with polypropylene mesh prosthesis reinforced transabdominal hiatus hernia repair. *J Am Coll Surg*. 1998;187:227–230.
26. Poulose BK, Scholz S, Moore DE, et al. Physiologic properties of small intestine submucosa. *J Surg Res*. 2005;123:262–267.
27. Sandoval JA, Lou D, Engum SA, et al. The whole truth: comparative analysis of diaphragmatic hernia repair using 4-ply vs 8-ply small intestinal submucosa in a growing animal model. *J Pediatr Surg*. 2006;41:518–523.
28. Eid GM, Mattar SG, Hamad G, et al. Repair of ventral hernias in morbidly obese patients undergoing laparoscopic gastric bypass should not be deferred. *Surg Endosc*. 2004;8:207–210.
29. Franklin ME, Gonzales JJ, Glass JL. Use of porcine small intestinal submucosa as a prosthetic device for laparoscopic repair of hernias in contaminated fields: 2-year follow-up. *Hernia*. 2004;8:186.
30. Helton WS, Fisichella PM, Berger R, et al. Short-term outcomes with small intestinal submucosa for ventral abdominal hernia. *Arch Surg.*2005;140:549–560.
31. Desai KM, Diaz S, Dorward IG, et al. Histologic results one year following bioprosthetic repair of paraesophageal hernia in a canine model. *Surg Endosc*. In press.
32. Strange PS. Small intestinal submucosa for laparoscopic repair of large paraesophageal hiatal hernias: a preliminary report. *Surg Technol Int*. 2003;11:141–143.
33. Johnson JM, Carbonell AM, Carmody BJ, et al. Laparoscopic mesh hiatoplasty for paraesophageal hernias and fundoplications: a critical analysis of the available literature. *Surg Endosc*. 2006;20:362–366.
34. Seelig MH, Hinder RA, Klinger PF, et al. Paraesophageal herniation as a complication following laparoscopic antireflux surgery. *J Gastrointest Surg*. 1999;3:95–99.

Discussions

DR. TOM R. DEMEESTER (LOS ANGELES, CALIFORNIA): This report on paraesophageal hernia emphasizes that this

disease is more diaphragmatic disease than a reflux disease, although commonly associated reflux disease, and there are 3 controversies that exist over this. One is the approach one makes–laparoscopic or open–the length of the esophagus, and the crural repair. Dr. Oelschlager's report focuses on the crural closure of the repair and the use of mesh. And he touches a little bit on the other 2 controversies.

Now, in regards to the use of mesh, I think that this report really emphasizes, as do others, that we need to add mesh to the support when we close the crura. It also introduces this new concept of a biological mesh to avoid the complications. So those are the positive things about the report.

Let me ask a few questions. What do we know about the durability of this new material? Do we have studies on it? You have a 9% hernia recurrence in the group that had the mesh at 6 months. Will that increase with time? What are your plans to follow along a little bit longer? And did you have to reoperate on any of those patients? If you did, what was the state of the mesh at the time you reoperated on them?

Now, your report also kind of touches a little bit on the length of the esophagus. In 6 patients you had to do a Collis gastroplasty to lengthen it. In 2 of those, you used mesh. Was there any effect of contamination and was there recurrence in patients who had the Collis gastroplasty and the mesh? Could you tell us about that?

And lastly, I know this is not a report on open versus laparoscopic approach to this problem, but I was struck by the very high complications–4 perforations, 1 left gastric artery injury, and 2 deaths. Granted, they were later, but these are older people, and the idea of the laparoscopic is to avoid those kinds of complications by having less invasive surgery. I was struck by that. And I wonder—in the face of this sort of evidence, and that seems to be the general level of complications in the literature with this laparoscopic approach to these giant hernias—what your comments are, whether or not we should persist with laparoscopic approach? Or should an open approach with an epidural on an elderly patient done faster give us a more permanent closure, even though we would use mesh in that situation as well?

Dr. Brant K. Oelschlager (Seattle, Washington): On your question of the durability of the material, obviously this is a relatively short-term outcome study on our initial results, so I obviously can't tell you the long-term durability of using this mesh in these repairs. I can tell you there is experimental evidence that the mesh is gone by the 6-month period, so we would assume that this mesh has been resorbed, completely remodeled, and we have native tissue at the hiatus at this time. We have not had the opportunity in this trial, fortunately, to reoperate on any of these patients. All the recurrences have been relatively small, and not required intervention. Our plan, amongst all the investigators, is to do longer follow-up and continue this trial to see if there is in fact durability of this repair. So I hope to be able to share that with you in the coming years.

As far as the question on the lengthening procedure, first of all, that was left to the discretion of the surgeon. In all patients at the time of operation, after of whatever was done to the esophagus to lengthen it, the esophagus was measured and in all cases had at least 2.5 centimeters intra-abdominal esophagus. There were no recurrences in patients who had a lengthening procedure and mesh placed, though this was a very small number of patients, so I am not sure we can draw any conclusions from that.

Then on your final question on the high complication rate, I would first say that surely this is a difficult operation. Whether you do it laparoscopically or open, I think it is a difficult operation. And usually we are operating, as you pointed out, in an elderly high-risk patient population. So complications, like myocardial infarction, are going to occur if you operate on these patients. I would disagree that the complication rate is very high. By far the most common listed complication was pneumothorax, though these were self-limited and there were no interventions for this. Likewise, only 1 of the perforations went unrecognized and required re-operation or adverse outcomes. In our experience we think the complication rate is lower than it would be with an open procedure. But, of course, this trial was not set up to compare laparoscopy to an open procedure for this particular operation.

Dr. Jeffrey L. Ponsky (Cleveland, Ohio): I want to congratulate Dr. Oelschlager and the other authors on a tremendous effort.

Your paper supposes that one of the major causes of recurrence is disruption of the hiatal repair. And you didn't mention it. You must have considered that total reduction of the sac and excision of the sac as well as the crural closure was important in the repair, and you didn't mention that.

Did the other authors in any of the other sites do any fixation of the wrap below the diaphragm such as a posterior gastropexy? Our group has had great success with an anterior as well as a posterior gastropexy in decreasing our recurrence rate just without using prosthesis.

Finally, I would like to know, in those patients—and I am sure there were a few—who you could not primarily close the crura below the esophagus, what did do you? Did you use the mesh as an interposition, or did you use some other prosthesis and then cover it with the bio mesh?

Dr. Brant K. Oelschlager (Seattle, Washington): On your question of techniques, the hernia sac was excised in all patients and the crura closed, all the things that we think should be important in paraesophageal hernia repairs.

On fixation of the wrap, this was the one hotly debated aspect when we sat down before the trial to try to standardize our technique. We came to the conclusion that since there

was no evidence that fixation of the fundoplication prevented recurrence and there was variability in our individual techniques, that we would get the best results to know what effect the mesh was having if each of the individual surgeons did the technique that they thought was best in their hands. So some investigators did fixate and some did not, otherwise our approach was the same.

On your final question of not being able to close the hiatus, we recognize this does occur. In this study we were able to close the crura in all these patients. If the crura could not be closed, a piece of permanent mesh was placed or whatever means the surgeon thought was best in that particular scenario, though this did not occur. We believe that SIS will work best as a buttress of a "closed" crura.

Dr. David W. Easter (San Diego, California): The line drawing in your presentation showed a posterior repair of the diaphragm with no need for anterior mesh coverage. We occasionally have had the need to place both anterior and posterior sutures in the diaphragm, selectively. Did you specify only posterior repairs? If you allowed anterior sutures in the diaphragm, did that contribute to your outcomes either way?

Dr. Brant K. Oelschlager (Seattle, Washington): We did specify where it would be placed before the trial for consistency. The reason we placed a U-shaped mesh instead of a keyhole circumferential is there are some animal studies showing that at the hiatus on reoperation of animals there is a fair amount of fibrosis and contraction of tissue in that area and we did not want to create dysphagia. And since we all agreed that we repair the hiatus mostly posteriorly (although we did allow some to be able to place anterior stitches at their discretion) and since we were going to buttress the repair, that we would use most of the mesh posteriorly to buttress the repair of the hiatus.

Dr. Jeffrey H. Peters (Rochester, New York): We shouldn't skip over the problem of dysphagia too quickly. If you look carefully, mesh-associated dysphagia appears in this and most other studies. Your dysphagia visual analog scores were twice as high in the mesh group although your numbers are relatively small. The study may be underpowered to conclude that there is no difference. Secondly, 25% recurrence at 6 months in the non-mesh group is appreciable! I echo what Dr. DeMeester said: Is it time that we stop doing lap repairs without mesh, and pursue either repair with mesh or perhaps even better an open repair?

Dr. Brant K. Oelschlager (Seattle, Washington): On the question of dysphasia, you are right, there is a numerical difference. If you look at the numbers on a 10-point analog scale, the average dysphagia rate was 0.8 for the non-mesh group and 1.4 for the mesh group (on a 10-point scale), with no statistical difference. There was really not anyone who had at least what we call moderate on our 10-point scale of dysphagia, 5 or greater. So you are right, if there is a difference, the study is probably underpowered to show that small difference. However, at such a mild severity I would question even if we did find a difference with more patients, whether it would be clinically significant.

On your other dicey question of should we should abandon laparoscopy, I don't think we should abandon laparoscopy. I think that there is a lot of benefit to be gained from the laparoscopic approach. Moreover, as you know, even in your study with open repair, there is a fairly high recurrence rate. Whether or not as high as with laparoscopy is debatable. But I would advocate, as I have advocated in the conclusions of this trial, that we probably should consider at least a piece of biologic mesh to cut the recurrence rates.

Dr. George W. Holcomb, III (Kansas City, Missouri): We have been using this technique in Kansas City at Children's Mercy Hospital over the last 5 years for acquired disease, that is transmigration of the fundoplication wrap, through the esophageal hiatus, and have not had a single recurrence following reinforcement of the hiatal closure with SIS. Have you transitioned to the 8-ply SIS?

Second, which suture material do you use when you secure the patch to the diaphragm? My personal feeling is that you need to use silk because that promotes an inflammatory response, which provides neovascularization and incorporation of the mesh into the native tissue. But I would be interested in your thoughts.

Dr. Brant K. Oelschlager (Seattle, Washington): Thank you for supporting the outcomes of our study with your personal experience. We used 4-ply mesh in this trial, which is less rigid and probably adequate. The sutures used were up to the individual surgeon. At the University of Washington, we tend to use silk, as you do, but I am not sure that it makes a difference.