Electrospun P(LLA-CL) Nanoscale Fibrinogen Patch vs Porcine Small Intestine Submucosa Graft Repair of Inguinal Hernia in Adults: A Randomized, Single-Blind, Controlled, Multicenter, Noninferiority Trial

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BACKGROUND: The aim of this study was to compare primary efficacy indicators of a low-cost, electrospun, nanoscale P(LLA-CL)/fibrinogen patch with a porcine small intestine submucosa patch for hernia repair.

STUDY DESIGN: A randomized, single-blind, controlled multicenter trial was performed in 3 hospitals in Shanghai. Eligible patients (20 to 75 years old) with primary unilateral, reducible groin hernias were randomly assigned (1:1) to electrospun nanoscale P(LLA-CL)/fibrinogen patch (experimental group) or porcine small intestine submucosa (control group) patch groups. Patients were treated with the Lichtenstein technique, and the primary endpoint was hernia recurrence at 33 months after surgery. The secondary endpoints were postoperative complications including groin pain and operative site infections.

RESULTS: Between July 2014 and February 2016, 172 patients were assigned to experimental (n = 86) and control (n = 86) groups. At 6-month follow-up, postoperative complications occurred in 5 patients (5 of 86, 5.81%) and 2 (2 of 86, 2.35%) patients in the control and experimental groups, respectively ($p < 0.05$). At 33-month follow-up, recurrence was observed in 2 patients (2 of 79, 2.53%) in the control group vs none in the experimental group (0 of 78) (the 95% CI difference between the experimental and control groups was -0.93% to 6.00% and within the preset noninferior margin of Δ10%). No significant differences were found in the degree of chronic pain and complications 33 months after surgery between the 2 groups.

CONCLUSIONS: Because the recurrence rates and postoperative complications after 33 months were not inferior in the experimental group, we believe that the P(LLA-CL)/fibrinogen patch, as a low cost alternative, has prospects for widespread clinical use. (J Am Coll Surg 2019;229:541−551.

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Abbreviations and Acronyms

ASA = American Society of Anesthesiologists
CFDA = China Food and Drug Administration
ECM = extracellular matrix
FAS = full analysis set
PPM = polypropylene mesh
PPS = per protocol set
SS = safety set
SIS = small intestinal submucosa
SVS = simple verbal scale
VAS = visual analog scale/score

More than 20 million patients undergo groin hernia repair every year worldwide, and synthetic permanent meshes have been used as a gold standard to prevent recurrence for decades.[1,2] With the increased success in terms of recurrence rates from 24% to 54% to 1% to 3%,[3,4] the focus has shifted toward other complications after surgery. Overall, the incidence of clinically significant chronic pain ranges from 10% to 12%.[4,5] Of the several underlying reasons, traumatic mesh fixation, inflammatory reactions, mesh shrinkage, and the resulting scar tissue formation may constitute important causes for iatrogenic neuropathic pain.[6] Additional surgery is often required to deal with these complications, which results in more pain and additional expense for patients.[7-9]

Biologic patches have been developed for hernia repair over the last 20 years. This technology involves the use of various decellularization techniques that are applied to dislodge cell components of animal tissues, such as the skin (Strattice, porcine dermal matrix; LifeCell)[10,11] or small intestinal submucosa (SIS) (Biodesign Surgisis; Cook Biotech[12,13] such that only the main components of the extracellular matrix (ECM) remain, including elastin and collagen. This type of acellular matrix can gradually degrade in vivo and induce regeneration of the local vasoganglion and tissue remodeling, thereby reducing the occurrence of complications.[14,15] A meta-analysis that compared synthetic permanent meshes with biologic patches following the Lichtenstein repair showed no difference in recurrence rates (median follow-up time, 18 months) and reported crude chronic pain rates of 2.1% for biologic patches and 7.6% for permanent meshes.[16]

Among the various biological surgery grafts, Biodesign Surgisis (Cook Biotech) is the most successful biologic graft developed to date.[12,13,17] It is an acellular matrix derived from porcine SIS without fixation of chemical cross-linking agents. This graft is mainly composed of type I or type III, and a small amount of type V or type VI, collagen fibers. However, the decellularization process of the SIS patch is complicated.[14] Moreover, if the heterogeneous antigenicity is not removed completely, it may critically affect safety and efficacy.[18] Therefore, the cost to manufacture it is much higher than that of the synthetic products, which is the main factor limiting its wide application.[19-21]

In our previous study, we blended polylactic acid-ε-caprolactone copolymer (P[LLA-CL]) with formulated porcine fibrinogen[22] to prepare nanoscale composite scaffold materials, which mimic the ECM using an electrospinning method. These materials promote chemotaxis adhesion of wound healing factors to the cells after implantation because of their large surface-to-volume ratio and super hydrophilicity. During self-degradation, regeneration of the local vasoganglion and tissue remodeling help repair the tissue defect and recovery of the normal structure and functions.[22] In our previously published papers, we stated that these materials are free from heterogeneous collagen, cell debris, and genetic material, eliminating the possibility of tissue calcification, as well as immunoreaction and endogenous retrovirus transmission from sources. Moreover, because they use electrospinning equipment in a clean environment for batch production, this process is simple and safety is controllable. The manufacturing costs are also comparable to costs of synthetic permanent meshes, which encourages their clinical use.[23] The materials were tested in a series of animal experiments by the State Food and Drug Administration Jinan Quality Supervision and Inspection Center for Medical Devices, PR China, and were approved by China's State Food and Drug Administration. The test results showed that the materials possess good biocompatibility and carry a low risk in biologic use.

Therefore, in this study, we compared the classic SIS patch with the P(LLA-CL/fibrinogen (P[LLA-CL]/Fg) patch, which was approved by the China Food and Drug Administration (CFDA) in August 2018, to analyze primary efficacy indicators. We investigated whether P(LLA-CL)/Fg patches are effectively degraded in clinical use to alleviate patient pain and reduce the surgical infection rate, as well as other complications.

METHODS

Study design and participants

In this randomized, single blind, controlled, multicenter, noninferiority clinical trial, we recruited 172 patients from 3 university hospitals in Shanghai, China, from July 3, 2014 to February 19, 2016. The relevant local clinical research ethics committees approved the study. The trial was registered retrospectively on October 13,

2017 (ChiCTR-INR-17010723). Full details of the trial protocol can be found at the registered trial data bank (www.chictr.org.cn).

Male subjects aged 20 to 75 years, who had a primary unilateral reducible hernia, with American Society of Anesthesiologists (ASA) physical stages I to III, were eligible for inclusion in the study. Classification of inguinal hernias has been done according to the groin hernia classification of the Committee of Hernia and Abdominal Wall Surgeons of the Chinese College of Surgeons.[24] Exclusion criteria were: recurrent hernia, incarcerated hernia, or bilateral hernia; any condition that might affect the correct evaluation of pain; patients who were noncompliant, blind, drug addicted, or had a mental illness including depression; patients who were allergic to the study materials or surgical contraindications including local infection or abnormalities detected during systemic examination; patients with a previous history of severe drug allergy or a history of asthma and diabetes; and evident abnormality in blood clotting or bleeding times, the heart, kidney, and liver, among other organs. A detailed description of the clinical trial was provided by physicians, and an informed consent form was provided by each enrolled patient or a surrogate decision maker.

Randomization and masking

A total of 172 patients with inguinal hernia from 3 university hospitals (Huadong Hospital, Fudan University, 10th People's Hospital, Tongji University, and Putuo Hospital, Shanghai University of Traditional Chinese Medicine) were selected and randomly assigned to the experimental (P[LLA-CL]/Fg) or control (porcine small intestine submucosa) patch group in a 1:1 ratio. The subjects who consented to take part in the study were assigned using sealed envelopes with computer-generated random allocation (PLAN program of SAS software) stratified by a trial statistician. The envelopes were provided at the trial sites and opened by independent assistants to enroll the patients.

Only surgeons giving the interventions were aware of the allocation. Patients, investigators, and data analysts were blind to the study-group allocation during the entire investigation. Patients were informed about their actual study group only after their last follow-up visit (27 to 40 months).

Procedures

All surgeons performing the intervention were invited to a specific training course organized in the training center located in the coordinating hospital (Huadong Hospital, Fudan University, Shanghai, China). The study protocol was provided during the training course to ensure that all participating surgeons used the same standard techniques in the study.

The surgical method for open tension-free inguinal hernia repair was a tension-free hernioplasty technique (Lichtenstein hernioplasty) performed on all patients using an in situ tailored patch (~6 × 14 cm). After a skin incision of approximately 5 to 6 cm, the inguinal canal was exposed by opening the aponeurosis of the external oblique muscle through the external ring. The genital branch of the genitofemoral nerve and the iliohypogastric nerve were identified and carefully preserved. A large space was then created beneath the external oblique aponeurosis by blunt dissection from the anterior superior iliac spine laterally to a point 2 cm medial to the pubic tubercle medially to eventually accommodate either patch. For patients with indirect hernia, the hernia sac was isolated and removed, and the remaining end of the hernia sac was then stitched to close the abdominal cavity. For patients with a hernia sac entering the scrotum, the near end of the hernia sac was isolated at the top and stitched, while the distal end stayed in place after hemostasis. The inner ring was then sutured to complete the repair. For patients with direct hernia, if the hernia sac was too large, an absorbable suture was used after hernia sac reduction. One end of the patch was trimmed into a circular shape that was consistent with the inner angle of the inguinal canal. Single-strand, nonabsorbable synthetic suture (Gauge No. 00) was used to fix the patch to the anterior rectus sheath of the pubic tubercle. The patch was slit (1 to 1.5 cm) from its lateral edge to accommodate the spermatic cord. The 2 slices were overlapped and sutured together to the inguinal ligament, restoring the inner ring. Closure of the aponeurosis of the external oblique abdominal muscle was performed using a continuous suture, leaving the spermatic cord in its natural subfascial position. Finally, the skin was sutured. Early mobilization as soon as possible after surgery was allowed, and drinking and eating were advised.

The trial process of patients with visit 1 to visit 6 (3 days, 1 week, 1, 3, 6, and 27 to 44 months postoperatively), including various medical disease symptoms, are summarized in eTable 2. The baseline characteristics of patients were recorded and collected during the screening period. Clinical symptoms, physical examination results, wound recovery data (recurrence, pain, infection, and other complications), adverse events, and medication use were recorded at 1 week and at 1, 3, 6, and 33 months after surgery. Additionally, laboratory tests including routine blood and urine analyses, liver and kidney function tests, immunologic examination at 3 months, and groin B-ultrasound at 3, 6, and 33 months

postoperatively were performed, and the results were carefully recorded.

Pain was evaluated using a simple verbal scale (SVS) and a visual analog scale (VAS) at different follow-up times. The SVS and VAS were used to measure each patient's degree of pain at rest and during coughing. In the 3 hospitals, a research nurse assessed patients 1 week after the operation for repair-related complications. Questionnaires were sent to all participants 6 months and 33 months after the operation. The questionnaire contained questions about return to usual activities, hernia-specific items, and some questions that were related to the use of various resources.

Outcomes

The primary endpoint was defined as the rate of hernia recurrences after 33 months. All patients were examined preoperatively and at 1 week and 1, 3, 6, and 33 months postoperatively; groin B ultrasound examinations were performed at 6 months and 33 months follow-ups. Secondary endpoints were perioperative SVS and VAS scores at predetermined visits, and postoperative complications such as wound infection, seroma, and hematoma. The outcomes of SVS and VAS were transformed into a number between 0 (which indicated the worst possible outcome) and 100 (which indicated the best possible outcome). Complications were assessed during all planned visits and in-between visits when patients came to the hospital. All data were collected by masked researchers.

Statistical analysis

Sample size was based on the primary endpoint (rate of hernia recurrences after 33 months) and determined based on the following formula: $n = [(Z_{1-\alpha}/2 + Z_{1-\beta})/(PT - PC-\delta)]\ 2 * [PT(1-PT) + PC(1-PC)]$, $\alpha = 0.025$, $\beta = 0.20$, noninferior dividing value $\delta = 10\%$. According to a published study, the recurrence rate of SIS patches (control group) was 4.9%;[17] therefore, we used 5% as the established recurrence rate. We assumed that the recurrence rate of the experimental group was comparable to that of the control group. The required number of cases in each group was calculated to be 75 for a total cohort of 150 cases. Assuming an exclusion rate of 10%, we required 150/0.9 = 168 cases in total, or 84 cases in each group.

Statistical analyses were performed using SAS version 9.3. The full analysis set population for recurrence rate determination was based on full analysis set (FAS) and the per protocol set (PPS). Safety analysis was based on a safety set (SS).

A chi-square test was used for comparisons between enumeration data sets. When the expected value was <5 in the 4-grid table, Fisher's exact test was used. An independent *t*-test was used for comparison between numerical data sets with a normal distribution. The Wilcoxon rank sum test was used for comparison between numerical data sets with a non-normal distribution.

For the recurrence rate 33 months after the operation, Fisher exact probability test was adopted to compare the difference between the 2 groups of patients. The difference in the postoperative recurrence free time was compared using survival analysis. The margin of noninferiority was -10% (with the permission of the ethics committee and Chinese authorities).

Secondary endpoints were postoperative pain and postoperative complications. Postoperative pain, which was assessed using SVS and VAS, was defined as pain still present more than 3 months after surgery. Postoperative complications were hematoma, seroma, postoperative infections, and other symptoms. Hematoma was defined as an accumulation of blood in the wound area, which needed surgical intervention. Seroma was defined as the accumulation of clear fluid in the surgical field, with clinical symptoms. Postoperative infections were defined as surgical site infections that occurred within 30 days of the operation. Other complications were scored within the categories scrotal effusion, bladder injury, spermatic cord and testicular ischemic orchitis, testicular atrophy, and others. Postoperative complication rates were compared using Fisher's exact test.

RESULTS

Between July 3, 2014 and February 19, 2016, we recruited 172 potentially eligible cases of hernia, with 86 subjects in the experimental group and 86 in the control group. No anesthetic complications or postoperative deaths occurred. At 6-month follow-up, 3 cases were incomplete; 2 of them (both in the control group) were lost to follow-up, and 1 patient (in the experimental group) developed an inflammation in the operative area (suspended). Therefore, the total number of patients was 172 in the FAS, 169 in the PPS, and 172 in the SS. At 33 months follow-up, 5 patients were lost in the control group and 7 in the experimental group; the total number of patients was 154 (Fig. 1).

All subjects were male and Han Chinese. The median age was 61 years in the control (interquartile range 53 to 66 years; range 20 to 75 years) and experimental groups (interquartile range 54 to 66 years; range 20 to 75 years). The baseline characteristics of the study population in both groups were similar ($p > 0.05$). Patients with ASA

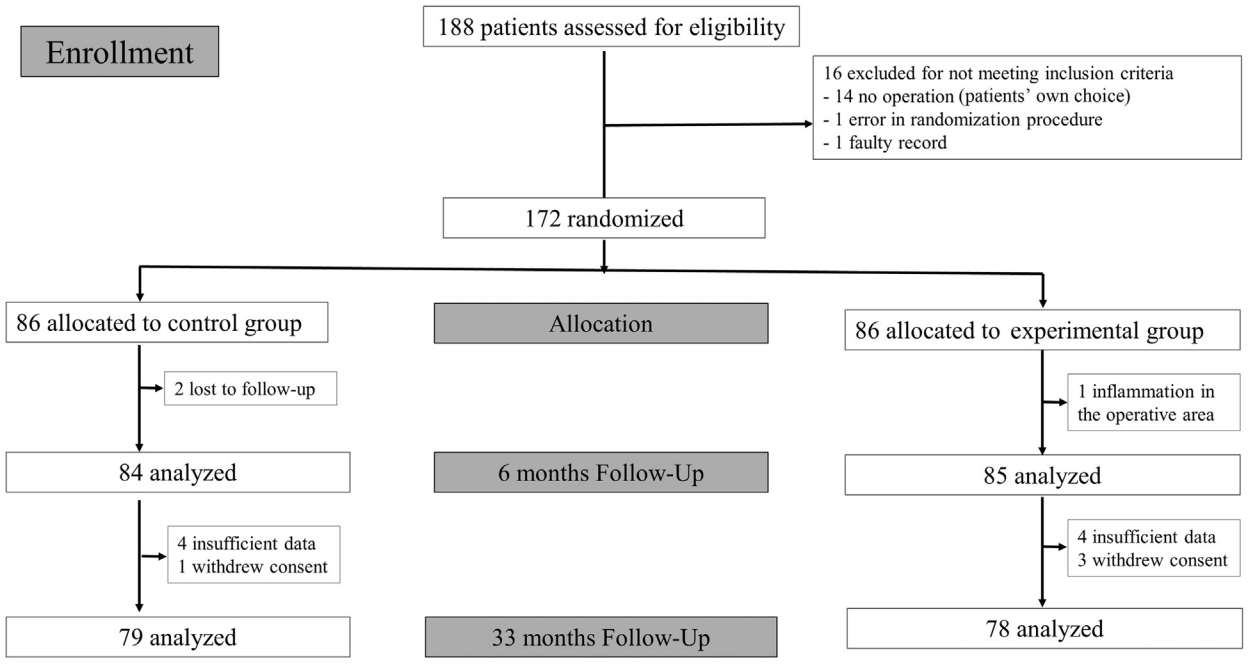

Figure 1. Flow diagram of study.

grades I and II accounted for 54.65% (n = 47) and 44.18% (n = 38) in the control group and 52.32% (n = 45) and 46.51% (n = 40) in the experimental group, respectively. Inguinal hernia type III accounted for 9.30% (n = 8) of patients in the experimental group and 8.23% (n = 7) in the control group. The majority of patients had type I or II hernia, and all were diagnosed with primary unilateral inguinal hernia. The shortest course of disease was 3 days; the longest was 50 years. No significant difference in baseline pain indicators or other vital signs (data not shown) were found between the 2 groups (Table 1).

At 33 months after surgery, the number (and rate) of cases without recurrence was 78 in the experimental group and 79 in the control group. Based on the Clopper-Pearson method, the 95% CI was 0.9538 to 1.000 in the experimental and 0.9115 to 0.9969 in the control group. The 95% CI difference between the experimental and control groups was -0.93% to 6.00% and within the preset noninferior margin of Δ10%. Therefore, the recurrence rate of the experimental group after 33 months was noninferior to that of the control group (Table 2).

No significant difference was found in SVS and VAS scores at rest between the 2 groups 1 week after surgery ($p > 0.05$). However, the difference in VAS scores during coughing in FAS patients was significantly different in the first week ($p = 0.045$). For 1, 3, and 6 months, as well as 33 months after surgery, no significant difference was found in the SVS or VAS scores at rest or during coughing between the 2 groups ($p > 0{\cdot}05$) (Table 3).

At 1 week after surgery, the number (and incidence) of other complications in the FAS population was 4 cases (4.65%) in the experimental group, including testis hydrocele (n = 1), early wound pain (n = 1), occasional tenderness in the right testis (n = 1), and hematoma at the surgical side (n = 1). Five cases (5.81%) in the control group included hematoma and seroma at the surgical site (n = 3), early wound pain (n = 1), and pain in the right testis (n = 1). No significant difference was found between the groups after 1 week ($p > 0.05$). However, the numbers (and incidences) of complications in FAS population at 1 month after surgery were 1 case of early wound pain (1.16%) in the experimental group and 7 cases (8.13%) in the control group, including 3 hematomas, 2 cases of early wound pain, and 2 others, which was significantly different ($p < 0.05$). At 3 months after surgery, the numbers (and incidences) of complications in the FAS population were 3 cases (3.48%) in the experimental group and 0 case (0.00%) in the control group, which was significantly different ($p < 0.05$). At 6 months after surgery, the numbers (and incidences) of complications in the FAS population were 2 (2.35%) in the experimental group and 5 (5.95%) in the control group ($p > 0.05$) comprising hematomas. At 33 months after surgery, no complications were recorded in either group (Table 4). All complications healed without further intervention.

Table 1. Baseline Characteristics of the Intention-to-Treat Population

Variable	Control group (n = 86)	Experimental group (n = 86)
Sex, male/female	86/0	86/0
Age, y		
Median (IQR)	61 (53–66)	61 (54–66)
Range	20–75	20–75
Height, cm		
Median (IQR)	170 (160–174)	170 (168–175)
Range	158–190	158–182
Weight, kg		
Median (IQR)	68 (62–74)	67 (62–74)
Range	49–100	49–100
BMI, kg/m^2		
Median (IQR)	23 (21–25)	23 (21–25)
Range	17–29	18–31
ASA preoperative evaluation, n (%)		
Grade I	47 (54.65)	45 (52.32)
Grade II	38 (44.18)	40 (46.51)
Grade III	1 (1.16)	1 (1.16)
Classification of inguinal hernia, n (%)		
Type I	27 (31.39)	22 (25.58)
Type II	52 (60.46)	56 (65.11)
Type III	7 (8.23)	8 (9.30)
Course of disease, mo		
Median (IQR)	6 (2–30)	6 (2–30)
Range	0.1–600	0.2–483
Resting state SVS, n (%)		
None	76 (88.37)	78 (90.69)
Slight	9 (10.46)	7 (8.13)
Moderate	1 (1.16)	1 (1.16)
Coughing state SVS, n (%)		
None	51 (59.30)	56 (65.11)
Slight	23 (26.74)	22 (25.58)
Moderate	9 (10.46)	8 (9.30)
Severe	2 (2.32)	0 (0.00)
Intolerable	1 (1.16)	0 (0.00)
Resting state VAS		
Median, n (IQR)	0 (0–0)	0 (0–0)
Range	0–55	0–55
Coughing VAS		
Median, n (IQR)	0 (0–15)	0 (0–11)
Range	0–92	0–84

Classification of inguinal hernia has been done according to the groin hernia classification of the Committee of Hernia and Abdominal Wall Surgeons of the Chinese College of Surgeons Chinese Medical Association.
ASA, American Society of Anesthesiologists; IQR, interquartile range; SVS, simple verbal scale; VAS, visual analog scale.

Two and 5 incidences of adverse events occurred in the experimental and control groups, respectively, which were possibly related to the intervention. Clinical manifestations were swelling of the surgical site accompanied by symptoms such as local pain or fever, but no significant difference was found between the 2 groups ($p > 0.05$). A total of 55 cases of adverse events in the experimental group and 18 cases in the control group occurred ($p < 0.05$) that were probably unrelated to the intervention. Among these adverse events, ultrasound examination only manifested as an echo abnormality in the surgical site, and body temperature and blood routine examinations were normal; inflammatory reactions or infections could be ruled out and the findings have been regarded as local regeneration reactions.

A total of 26 cases of adverse events that were definitely unrelated to the intervention were identified in the experimental group and 24 cases in the control group ($p > 0.05$). Among them, 11 cases of severe adverse events, which needed medical intervention, were reported (7 cases in the experimental group and 4 cases in the control group, $p > 0.05$). These adverse events included 2 cases of acute appendicitis, 5 wound healings, 1 case of acute pancreatitis, 1 postoperative fever, 1 myocarditis, and 1 pulmonary space-occupying lesion (Table 5).

DISCUSSION

The results of the clinical trial showed that electrospun nanoscale P(LLA-CL)/Fg patch repair for inguinal hernias was not inferior to the SIS patch; no differences in recurrence rates and postoperative complications were found between the patient groups.

Based on the materials used, repair grafts can be divided into synthetic and biologic grafts. Synthetic permanent meshes are still widely used in clinics due to their high mechanical strength, simple manufacturing process, and convenience of use. After implantation, the graft is enveloped in connective tissue because of foreign-body reactions. Formation of scar tissue enhances the mechanical strength of the repair, which also leads to the incidence of long-term complications (up to 17%).[25,26]

Biologic grafts are allogeneic or xenogeneic tissues with removed cellular components, leaving micro- and macroscale structural and functional ECM components. After implantation, grafts degrade over time and induce remodeling and regeneration of local tissue. Clinical studies have shown that the recurrence rate using porcine SIS is 4.9%,[12] The incidence and degree of chronic pain after surgery were significantly lower than in those patients using synthetic permanent meshes.[13,17] However, because the product is derived from porcine small intestine, it

Table 2. Primary Efficacy Index Analysis 33 Months after Operation

Variable	Control group	Experimental group	Effective difference (Miettinen Numinen) (experimental − control group)
33 mo postoperation, n	79	78	
Recurrence, n (%)	2 (2.53)	0	
Noninferiority analysis			
Clopper-Pearson 95% CI	91.15−99.69	95.38−100.00	−0.93−6.00

requires the artificial separation of the mucous layer, muscular layer, and outer membrane, as well as decellularization by adopted physical methods (such as multiple freeze-thaws or application of supercritical fluid) or chemical methods (such as SDS or Triton-X-100 detergent, alkaline and acidic solutions, or enzyme applications), which is time consuming (several days to weeks) and labor intensive.[14,20] In addition, some heterogeneous cell debris may be left behind, including DNA and α1,3-galactose antigen debris, which increase the risk of immunoreactions.[18-20] At the same time, because biologic meshes are created from SIS, the amount produced is limited and the cost is higher (3.3 to 15 US dollars/cm^2)[19-21,25] than that of synthetic permanent meshes (<1 US dollar/cm^2), making this technology difficult to be adopted widely in clinical practice due to cost considerations.

More recently, synthetic absorbable meshes consisting of a macroporous multifilament knitted construction of 2 different resorbable fibers have been developed. The first fiber of glycolide, lactide, and trimethylene carbonate is resorbed within the initial 4 months after implantation, and the second fiber (a copolymer of lactide and trimethylene carbonate) is completely resorbed after 3 years. Although the results for repairing sheep abdominal defects demonstrated that the deposition of collagen is more similar to native connective tissue,[27] the outcome of a 3-year clinical trial that included 35 cases of patients with inguinal hernia revealed that the recurrence rate was as high as 22.8%.[28]

We previously demonstrated that the scaffold prepared by electrospinning of P-(LLA-CL) blended with formulated porcine fibrinogen provides good support for cell growth and favorable cell-cell and cell-matrix interactions, since fibrinogen is a plasma protein that plays a pivotal role in wound healing and ECM remodeling.[22] In addition, the deposition of fibrinogen amino acid residues onto the scaffold surfaces improves its biocompatibility and hydrophilicity properties.[19] Furthermore, the host tissue response and biomechanical properties of the P(LLA-CL)/Fg patch were compared with those of the polypropylene mesh (PPM) in a canine abdominal defect model. Macroscopic, histologic, and biomechanical evaluation carried out over a 24-month period indicated that the P-(LLA-CL)/Fg patch could effectively induce and augment abdominal tissue regeneration. The degradation rate and the new tissue in-growth rate reached equilibrium within 2 weeks of implantation. Immunohistologic data demonstrated the presence of regenerated skeletal muscle tissue with P-(LLA-CL)/Fg patches, whereas the PPM exhibited dense fibrous encapsulation along the perimeter of the meshes.[23] Compared with the Biodesign Surgisis, the P(LLA-CL)/Fg patch possesses the following advantages. First, it can lower the risk of immunoreaction and tissue calcification. Second, it is easier to adjust the thickness, area, and shape of the product, making it easier to meet clinical demands. Third, the mechanical strength is moderate, and the speed of degradation matches the speed of regeneration. Finally, the use of electrospinning technology can essentially cut down production costs and enables its widespread use in primary hospitals.

In this study, a noninferior trial was used. The primary endpoint was determined considering that the recurrence rate was 5% according to previous reports and the number of patients needed to conduct the study was 150. According to the conventional assumption of a 10% exclusion rate, the total recruitment rate was calculated as follows: 150/0.9 = 168 cases. However, only 157 cases at 33 months were enrolled, with an exclusion rate of 14.7% and 4.7%, respectively, which met the needs of the trial.

The secondary endpoints were chronic pain and other complications such as wound infection, hematoma, and seroma. Postoperative chronic pain is a major complication after a synthetic permanent graft.[25] The incidence of chronic pain was reported to be more than 4.0% during a 2- and 3-year follow-up.[12] In this study, we report that the incidence rates of chronic pain in the control and experimental groups were 0.12% ± 0.64% vs 0.16% ± 0.60% and 0.26% ± 0.92% vs 0.28% ± 1.03% at 6 and 33 months, respectively. Except for significant differences in SVS and VAS scores in the coughing state of FAS patients 1 week after surgery ($p < 0.05$), no significant difference was found in the SVS or VAS scores at rest or during coughing between the 2 groups ($p > 0.05$).

Analysis of the relationship between adverse events and research devices is shown in Table 5. The higher incidence

Table 3. Simple Verbal Scale and Visual Analogue Scale Analysis at Different Time Points in the Control and Experimental Groups

	1 week postoperation		1 month postoperation		3 months postoperation		6 months postoperation		33 months postoperation	
Variable	**Control**	**Experiment**	**Control**	**Experiment**	**Control**	**Experiment**	**Control**	**Experiment**	**Control**	**Experiment**
Resting state SVS, n (%)										
None	24 (27.90)	30 (34.88)	64 (74.41)	68 (79.06)	81 (94.18)	81 (94.18)	83 (96.51)	83 (96.51)	72 (91.13)	70 (89.74)
Slight	50 (58.13)	39 (45.34)	21 (24.41)	17 (19.76)	5 (5.81)	5 (5.81)	3 (3.48)	3 (3.48)	7 (8.86)	6 (7.69)
Moderate	12 (13.95)	14 (16.27)	1 (1.16)	1 (1.16)	0	0	0	0	0 (0.00)	2 (2.56)
Severe	0 (0.00)	3 (3.48)	0	0	0	0	0	0	0	0
p Value	0.125		0.250		0.500		0.500		0.500	
Coughing state SVS, n (%)										
None	1 (1.16)	5 (5.81)	43 (50.00)	47 (54.65)	64 (74.41)	72 (83.72)	77 (89.53)	78 (90.69)	76 (96.20)	69 (89.61)
Slight	33 (38.37)	38 (44.18)	36 (41.86%)	33 (38.37)	22 (25.58)	14 (16.27)	8 (9.30)	7 (8.13)	2 (2.53)	5 (6.49)
Moderate	43 (50.00)	39 (45.34)	7 (8.13%)	6 (6.97)			1 (1.16)	1 (1.16)	1 (1.26)	3 (3.89)
Severe	9 (10.46)	4 (4.65)								
p Value	0.125		0.250		0.250		0.250		0.250	
Resting state VAS, mean ± SD	16.83 ± 16.68	18.24 ± 21.29	3.86 ± 8.36	3.73 ± 9.11	0.64 ± 3.14	0.83 ± 3.97	0.20 ± 1.55	0.57 ± 3.50	0.16 ± 0.60	0.26 ± 0.92
p Value	0.629		0.922		0.728		0.3713		0.421	
Coughing state VAS, mean ± SD	39.71 ± 21.44	33.18 ± 20.89	8.93 ± 13.40	8.16 ± 12.82	2.63 ± 5.93	1.89 ± 5.45	1.07 ± 6.04	1.78 ± 7.49	0.12 ± 0.64	0.28 ± 1.03
p Value	0.045*		0.701		0.395		0.495		0.244	

*Statistically significant.
SVS, simple verbal scale; VAS, visual analog scale.

Table 4. Complication Rates and Types at Different Follow-Up Time Points in the Control and Experimental Groups

Postoperative complication	1 week postoperation				1 month postoperation				3 months postoperation				6 months postoperation				33 months postoperation			
	Control (n = 86)		Experimental (n = 86)		Control (n = 86)		Experimental (n = 86)		Control (n = 86)		Experimental (n = 86)		Control (n = 84)		Experimental (n = 85)		Control (n = 79)		Experimental (n = 78)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Yes	5	5.81	4	4.65	7	8.13	1	1.16	0	0.00	3	3.48	5	5.95	2	2.35	0	0	0	0
Hematoma and serum swelling at surgical site	3	60.00	1	25.00	3	42.85	0	0.00	—	—	—	—	5	100.00	2	100.00	—	—	—	—
Early wound pain	1	20.00	1	25.00	2	28.57	1	100.00	—	—	—	—	—	—	—	—	—	—	—	—
Testis hydrocele	0	0.00	1	25.00	—	—	—	—	—	—	—	—	—	—	—	—	0	0.00	0	0.00
Other	1	20.00	1	25.00	2	28.57	0	0.00	0	0.00	3	100	—	—	—	—	—	—	—	—
n	5	81.00	4	82.00	7	79.00	1	85.00	0	86.00	3	83.00	5	79.00	2	83.00	0	79.00	0	78.00

Table 5. Analysis of the Relationship Between Adverse Events and Research Devices

Index	Experimental group		Control group		p Value
	n	%	n	%	
Possibly related cases*	2	2.32	5	5.81	0.443
Probably unrelated cases†	55	63.95	18	20.93	0.000
Definitely unrelated cases‡	26	30.23	24	27.90	0.867

*Swelling of the surgical site accompanied by symptoms.
†Ultrasound examination was only manifested as an echo abnormality in the surgical site. Patients without clinical symptoms, in whom body temperature and blood routine examination are normal, can rule out inflammatory reaction or infection.
‡Such as upper respiratory tract infection, acute gastroenteritis, etc.

of adverse events was the result of positive B-ultrasonography in the surgical site ($p < 0.05$). Because no clinical sign was found and routine blood examination was normal, inflammatory reactions or infection could be ruled out.

We came to the conclusion that the positive B-ultrasonography in the surgical site was related to the degradation of biologic materials after implantation in the human body and induced tissue regeneration, which was a normal response to the regeneration process. In the international guidelines for groin management,[4] the authors pointed out that if studies include seroma formation, only symptomatic seromas should be considered as a postoperative complication unlike tissue repair, which presents as a response to damage or loss of tissue, that leads to restoration of tissue continuity by scar tissue formation without the complete replacement of normal functional tissue. Complete tissue regeneration restores tissue structural and functional integrity through synthesis of new tissue that is specific and appropriate to that anatomic location, by mobilizing potential local regenerative ability.[14] The critical point is that the implanted scaffold material should release bioactive substances during the degradation process, therefore recruiting the cellular components and factors to gather locally and promote a more constructive remodeling with M_2 macrophage phenotypes rather than M_1 phenotypes, which trigger a series of regeneration programs afterwards and may be the reason for the low echo of ultrasound at the implant site. It could also explain the finding that cross-linked biomaterials and purely synthesized absorbable meshes, which do not release active substances effectively, have a low induction effect in vivo, and the recurrence rate and incidence of clinical complications are high.[26,28] However, the fibrinogen blended in the P(LLA-CL)/Fg patch is the starting protein of wound healing. Its degradation products, such as Arg-Gly-Asp sequence and fibrinogen

degradation product, may play a role through this pathway and are worthy of further study.

CONCLUSIONS

In conclusion, our results showed that the electrospun (LLA-CL)/Fg patch is noninferior to the SIS patch; both patches have identical safety profiles after 33 months. The P(LLA-CL)/Fg patch is a safe and effective treatment for open, tension-free inguinal hernia repair, and it combines the advantages of biologic biodegradable grafts with reduced production costs.

Author Contributions

Study conception and design: He, Tang

Acquisition of data: Li, Xiao, Yang, Hua, Qiu, Hu, Ping, Zheng

Analysis and interpretation of data: Li, Xiao, Hua, He, Tang

Drafting of manuscript: Li, Xiao, Hua

Critical revision: He, Tang

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eTable 1. International Committee of Medical Journal Editors (ICMJE) Data Sharing Statement

Question	Answer
Will individual deidentified participant data (including data dictionaries) be shared?	Yes
What data in particular will be shared?	Individual participant data that underlie the results reported in this article after deidentification
Will additional related documents be available (eg study protocol, statistical analysis plan)?	Study protocol, statistical analysis plan, clinical study report
When will the data become available and for how long?	9 to 36 months after article publication
Who will have access to the data?	Investigators whose proposed use of the data has been approved by an independent review committee
For what types of analyses will the data be available?	For individual participant data meta-analysis
By what mechanism will the data become available?	The data can be obtained by contacting the corresponding author directly up to 36 months after article publication.

eTable 2. Experimental Process

	Patient screening	Follow-up after operation				
	Visit 1	Visit 2*	Visit 3	Visit 4	Visit 5	Visit 6
Research phase	3 days before operation	Within 1 week	Month 1 ± 1 week	Month 3 ± 2 weeks	Month 6 ± 2 weeks	Average, 33 months
Sign informed consent	X					X
Inclusion/exclusion criteria	X					
History						
Demographic characteristic	X					
Complaint	X					
Clinical symptoms	X	X	X	X	X	X
Past medical history	X					
Physical examination						
Vital sign	X	X				
Physical sign	X	X	X	X	X	X
Classification	X					
Laboratory and assistant examination						
Blood and urine test†	X			X		
Hepatorenal function‡	X			X		
Immunology§	X			X		
ECG	X					
Groin B ultrasound	X			X	X	X
Evaluation		X	X	X	X	X
Recurrence	X	X	X	X	X	X
Pain	X	X	X	X	X	X
Infection	X	X	X	X	X	X
Other complication	X	X	X	X	X	X
Other						
Adverse event		X	X	X	X	X
Medication use	X	X	X	X	X	X

*Patients were normally discharged 3-4 days after surgery. The length of stay was extended if complications occurred.
†Blood tests included a red blood cell count, a white blood cell count and classification (ratio of neutrophils and lymphocytes), hemoglobin, and platelets. Urine tests included a white blood cell count, a red blood cell count, and urine protein content.
‡Hepatorenal function tests included glutamate transaminase, total bilirubin, albumin, globulin, urea nitrogen, and creatinine.
§Immunology tests included cellular immunity (CD3, CD4, CD8 cell percentage, CD4/CD8 cell ratio), humoral immunity (immune globulin, IgG, IgA, IgM, IgE, C-reactive protein, and complement C3, C4).