Safety and effectiveness of a new-type domestic biologic mesh

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【**Abstract**】 **Objective** To evaluate the safety and effectiveness of a new biologic domestic mesh in inguinal hernia repairment. **Methods** A multicenter, randomized, parallel controlled clinical study was carried out, the patients with inguinal hernia were divided into control group using imported mesh and intervention group using domestic mesh, and they underwent Lichtenstein operation by the same group of surgeons during the same period to compare the clinical curative effect. **Results** A total of 194 patients from 3 clinical hernia centers were included in this study. There was no significant difference in terms of demographic characteristics, general situation and medical history. During a follow-up period of 6 months, no significant differences were noted between the two groups for foreign body reaction, homatoma, seroma, infection, groin pain, recurrence and etc. **Conclusions** This study suggests that the domestic biologic mesh is equivalent to imported mesh, regarding long-term outcomes as recurrence and complications. Domestic mesh has the advantages of low price and being easy to promote, which could be a better choice for inguinal hernia patients in China.

【**Key words**】 Hernia, inguinal; Herniorrhaphy; Comparative Study; Biologic Mesh

Inguinal hernia is a common and frequently-occurring disease in general surgery.

In adult patients with inguinal hernia, surgery is the only cure [1].

In 1984, the Lichtenstein Hernia Center in the United States invented tension-free hernia repair, opening a new chapter in hernia surgery. With the rapid development of materials science, various materials have been widely used in hernia repair, including polypropylene, polyester, polytetrafluoroethylene, polyvinylidene fluoride and other non-absorbable synthetic materials, polylactic acid, polyamide, etc. Esters and other absorbable synthetic materials, composite materials, animal-derived materials and allogeneic materials, etc. [2-4].

Biomaterials with collagen as the main body have the characteristics of rapid vascularization, light adhesion, resistance to infection, etc., can effectively solve the problem of poor histocompatibility of synthetic patches, and provide new options for the treatment of inguinal hernias [5]. There are about 2 million to 4 million cases of inguinal hernia in my country every year. However, most of the patches used in the clinic are imported products and the price is relatively high.

This study evaluated the safety and effectiveness of the domestic biological mesh by comparing the application and clinical efficacy of the domestic new biological mesh and the similar imported hernia patch in Lichtenstein surgery.

Data and Methods

1. General information

This study used a multi-center, randomized, open, parallel controlled clinical study to analyze the data of 194 inguinal hernia patients who met the inclusion criteria from November 2015 to May 2017. Beijing Chao-Yang Hospital, Capital Medical University (95 cases) , Tianjin People's Hospital (94 cases), and Tianjin Medical University General Hospital (5 cases). Patients with inguinal hernia were divided into 2 groups according to the ratio of 1:1, with 97 cases in each group. The test group used the hernia biologic mesh from Beijing Biosis Healing Biological Technology Co., Ltd, and the control group used the Biodesign Suigisi mesh from the American COOK company, which has been widely recognized and adopted at home and abroad, by the same group of physicians during the same period. Standard Lichtenstein procedure. The average age of the experimental group was 46 years old, with 83 males and 14 females; the average age of the control group was 49 years old, with 78 males and 19 females. The two groups were in terms of age, gender, race, height, weight, comorbidities, and history of surgery. In comparison, the difference was not statistically significant (Table 1). This study was approved and filed by the medical ethics committee of our hospital, and an informed consent form was signed with the patient or family member.

2. Method

1) Materials: The experimental group used SIS-HRP-8L series hernia biologic mesh produced by Beijing Biosis Healing Biological Technology Co., Ltd, with specifications of 6 cm×13 cm and 10 cm×15 cm. C-IHM series hernia biologic mesh (product name: Biodesign Surgisi) produced by COOK Company of the United States was used in the control group, with the same specifications of 6 cm×13 cm and 10 cm×15 cm.

2) Case selection: a) Inclusion criteria: 18 to 75 years old, no gender limit; clinically diagnosed as type II ～ V (Gilbert type [6]) patients with unilateral primary inguinal hernia; herniorrhaphy is required , no contraindications to surgery; patients voluntarily participate in clinical trials and sign informed consent, able to cooperate with clinical follow-up.

b) Exclusion criteria: Those who cannot accept porcine-derived devices due to religious or ethnic issues; those who have participated in clinical trials of other drugs or medical devices in the past 6 months; and those who have bilateral inguinal hernias, femoral hernias, incarcerated hernias, and recurrent hernias ; Patients with acute infection or poorly controlled lesions; patients with skin diseases around the surgical incision; with severe diseases that cause increased intra-abdominal pressure (such as severe prostatic hyperplasia,constipation or chronic cough; uncontrollable ascites caused by liver cirrhosis or tumor, etc.)

Severe heart, liver, and renal insufficiency (heart function: grade II and above; ALT or AST>2.5 times the upper limit of normal; serum creatinine> upper limit of normal); poorly controlled diabetic patients (2 consecutive monitoring Fasting blood glucose ≥8.8 mmol/L); those with severe heart, lung, and brain diseases, cancer, or AIDS; those with specific allergies; those with an expected lifespan of less than 6 months; those with mental abnormalities and no behavioral autonomy; pregnant or women who plan to become pregnant and breast-feeding women; other situations where the physician judges that they cannot participate in the trial.

2) Surgical method: use local anesthesia or epidural anesthesia. After the anesthesia is satisfied, routinely sterilize the drape, take the oblique incision between the inner and outer rings above the midpoint of the inguinal ligament, and cut it layer by layer until the spermatic cord is exposed. Cut the cremaster muscle longitudinally along the spermatic cord to look for the hernia sac. According to the defect area of the patient's posterior inguinal canal wall and the size of the hernia ring, a suitable hernia biologic mesh is selected, and the mesh is hydrated with sterile normal saline at room temperature for 5-10 minutes, use hernia biologic mesh to repair the posterior wall of the inguinal canal in accordance with the plain film tension-free herniorrhaphy;

(Lichtenstein procedure); absorb the suture to fix the patch during the operation. After the completion of the operation, complete hemostasis and suture the external oblique aponeurosis, deep fascia, and fascia. Superficial fascia, subcutaneous tissue and skin.

4) Observation and evaluation indicators: recurrence rate within 6 months after operation, patch infection, wound hematoma and seroma, postoperative chronic pain, allergic reaction, groin discomfort, orchitis/atrophy, scrotal hematoma, incision healing.

3. Statistical analysis

In this study, the quantitative indicators were described by the mean, standard deviation, median, minimum, and maximum value, and group t test or Wilcoxon rank sum test was used for comparison between groups,The classification index is expressed by the rate, and the $\chi 2$ test or the exact probability method is used for comparison, and the rank data uses the Wilcoxon rank sum test or the CMH test.

Table1 Comparison of the general conditions of patients in 2 groups

Programe	Index	Test group	Control group	Statistics	*P value*
Gende(%)	male	83(85.57)	78(80.41)	0.913	0.339
	female	14(14.43)	19(19.59)		
Race(%)	chinese	94(96.91)	94(96.91)	-	1.000
	other	3(3.09)	3(3.09)		
Age	Median(Min,Max)	47.74(18.67,72.80)	51.40(19.40,74.58)	1.078	0.281
Height(cm)	Median(Min,Max)	171.00(148.00,185.00)	170.00(155.00,186.00)	-0.678	0.498
Weight(kg)	Mean(Sd)	68.03(9.55)	68.20(11.06)	-0.115	0.909
Complications	no	62(63.92)	57(58.76)	0.543	0.461
(%)	yes	35(36.08)	40(41.24)		
History of surgery	no	55(67.90)	58(71.60)	0.263	0.608
(%)	yes	26(32.10)	23(28.40)		

Table 2 Comparison of intraoperative conditions of patients in 2 groups

Programe	Index	Test group	Control group	Statistics	*P value*
Hernia type (%)	Ⅱ	56(57.73)	54(55.67)	-	0.901
	Ⅲ	31(31.96)	30(30.93)		
	Ⅳ	4(4.12)	4(4.12)		
	Ⅴ	6(6.19)	9(9.28)		
Lesion side (%)	Left	35(36.08)	42(43.30)	1.055	0.304
	Right	62(63.92)	55(56.70)		
Intraoperative blood loss(ml)	Median(Min,Max)	5.00(0.00,10.00)	3.00(0.00,5.00)	-0.296	0.767
Time spent on surgery (min)	Median(Min,Max)	50.00(22.00,105.00)	45.00(30.00,90.00)	-0.322	0.748

Result

A total of 3 clinical research centers participated in this study, and a total of 202 patients were randomized. Among them, 194 patients successfully underwent standard Lichtenstein surgery using biological mesh and completed a 6-month postoperative visit.

1. Comparison of intraoperative conditions of patients in 2 groups

Both groups of patients successfully completed the operation. There was no statistically significant difference in hernia classification, intraoperative blood loss, and operation time between the two groups (P>0.05) (Table 2).

2. Conditions during hospitalization and postoperative complications

The average postoperative hospital stay of the experimental group was (1.94±0.90) days, and the average postoperative hospitalization time of the control group was (1.80±0.81) days, and the difference was not statistically significant (P=0.271); 13.04)h, the time for the control group to resume autonomous activities after surgery (50.27±13.38)h, the difference was not statistically significant (P=0.748); the number of days of antibiotics used in the experimental group was (0.11±0.59) d, and the control group used antibiotics after the operation the number of days was (0.08±0.37) d, and the difference was not statistically significant (P=0.995). Follow-up for 6 months after operation, 1 case in the test group recurred (1.03%), and no recurrence in the control group, the difference was not statistically significant (P=1); there were no cases of patch infection in the two groups; the groin between the two groups at each time point There was no statistically significant difference in discomfort, incision healing, hematoma/seroma, pain and other indicators （P＞0.05）（table 3）

3. Adverse events

In this clinical trial, a total of 67 cases of adverse events occurred after surgery, 83 times, with a total incidence of 34.55%. Among them, 13 cases developed postoperative fever, local seroma formation, wound swelling, etc., and improved after anti-inflammatory analgesia and other symptomatic support treatment; 10 of them developed postoperative immune detection C-reactive protein increase, which is considered to be related to personal physique. It was caused by the implantation of allogeneic biomaterials in the body. It was a normal clinical phenomenon. During the follow-up period, there was no discomfort or symptoms. One case had a postoperative inguinal hernia recurrence, which was confirmed to be a direct hernia recurrence after another operation. The inguinal hernia was performed again with a synthetic patch after the tension-free repair; 2 cases developed postoperative wound infection, and healed after 1 week of anti-infective treatment. there was no mesh infection. Among the adverse events, there were 37 cases (38.14%) in the control group and 30 cases (30.93%) in the test group, and the difference was statistically significant (P=0.365). There were 22 cases (22.68%) of the adverse events related to the mesh in the control group.

There were 14 cases (14.43%) in the experimental group, and the difference was statistically significant (P=0.196). The analysis results showed that there was no significant difference in the incidence of adverse events and the correlation with the study patch between the two groups.

During the trial, a total of 7 subjects had serious adverse events, of which 2 patients were judged to be possibly related to the research patch. They were subjects with selection numbers 0019 and 0058 from Tianjin People's Hospital, respectively. The patients had surrounding wounds after the operation. Redness, swelling and pain, diagnosed as "wound infection after operation", after the second-generation cephalosporin anti-infection, wound dressing change, negative pressure suction and other symptomatic treatment, the wound healed, consider the operation caused by the operation, it is judged that the serious adverse reaction may be related to the mesh. Serious adverse events occurred in 6 cases (6.19%) in the control group and 1 case (1.03%) in the control group, the difference was not statistically significant (P=0.118) (Table 4).

Discuss

Inguinal hernia is a common and frequently-occurring disease. Adult inguinal hernia cannot heal by themself. Surgery is the only reliable treatment. Tension-free inguinal hernia repair was invented in 1984 by Dr. Lichtenstein and his companions at the Lichtenstein Hernia Center in the United States. This method uses a mesh with good tissue compatibility to cover the inguinal hernia defect. It is widely used because of its relatively simple operation, fast postoperative recovery, and fewer complications [7-8].

With the rapid development of materials science, various hernia repair materials have been widely used in clinics. The materials include non-absorbable synthetic materials such as polypropylene/polyester/polytetrafluoroethylene/polyvinylidene fluoride, polylactic acid/polyethylene fluoride, etc. Lactone and other absorbable synthetic materials, composite materials, animal-derived biological materials, allogeneic biological materials, etc. The application of synthetic materials has made great progress in the therapeutic effect of hernia repair. Non-degradable materials can stimulate fibrous tissue proliferation through foreign bodies and chronic inflammation after implantation in the body to achieve the purpose of repairing defects. However, as the application time increases, the related complications caused by them become more and more prominent. Take the most widely used polypropylene material as an example. Due to the rough surface of the patch, direct contact between the patch and internal organs due to surgical operation or post-operative patch erosion will not only cause severe abdominal adhesion, but also Erosion of the intestinal wall, causing serious complications such as intestinal leakage [9].In addition, polypropylene material has the problem of patch shrinkage [10],

Table 3 Comparison of postoperative conditions in 2 groups (%)

Index	Group	Number of cases	During hospitaliza-tion	1 week after operation	1 month after operat-ion	3 month after operation	6 month after operation
Relapse	test group	97	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(1.03)
	Control group	97	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
	Statistics		-	-	-	-	(Fisher Exact probability method)
	P value		-	-	-	-	1.000
Patch infection	test group	97	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
	Control group	97	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
	Statistics		-	-	-	-	-
	P value		-	-	-	-	-
Discomfort in the groin area	test group	97	2(2.06)	4(4.12)	0(0.00)	0(0.00)	0(0.00)
	Control group	97	3(3.09)	9(9.28)	2(2.06)	0(0.00)	0(0.00)
	Statistics		0.204 CMH test	2.051 CMH test	2.010 CMH test	-	-
	P value		0.651	0.152	0.156	-	-
Redness and swelling of the incision	test group	97	0(0.00)	4(4.12)	2(2.06)	0(0.00)	0(0.00)
	Control group	97	0(0.00)	2(2.06)	1(1.03)	0(0.00)	0(0.00)
	Statistics		-	0.684 CMH test	0.337 CMH test	-	-
	P value		-	0.408	0.562	-	-
Hematoma/ seroma	test group	97	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(1.03)
	Control group	97	0(0.00)	3(3.09)	0(0.00)	0(0.00)	0(0.00)
	Statistics		-	3.031 CMH test	-	-	1.000 CMH test
	P value		-	0.082	-	-	0.317
Pain	test group	97	1(1.03)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
	Control group	97	2(2.06)	2(2.06)	0(0.00)	0(0.00)	0(0.00)
	Statistics		0.337 CMH test	1.807 CMH test	-	-	-
	P value		0.562	0.179	-	-	-
Allergy	test group	97	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
	Control group	97	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
	Statistics		-	-	-	-	-
	P value		-	-	-	-	-
	test group	97	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)

Orchitis/ Atrophy	Control group	97	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
	Statistics		–	–	–	–	–
	P value		–	–	–	–	–

Note: The pain score at each time point after the operation adopts the visual analog pain score method

Table 4 Comparison of the occurrence of adverse events in the 2 groups

Programe	Test group			Control group			P value
	Instance	Numbe	Percentage (%)	Instance	Numbe	Percentage (%)	
Adverse events	38	30	30.93	46	37	38.14	0.365
Adverse events related to the study patch	18	14	14.43	27	22	22.68	0.196
Serious adverse event	1	1	1.03	6	6	6.19	0.118
Serious adverse events related to the study patch	0	0	0.00	2	2	2.06	0.497

the results of the study show that the patch can shrink by 20% in length and 40% in area after being implanted in the body. Scarring and shrinkage formed in the later stage will cause the patch to be distorted, and its irregular and hard surface may irritate and damage the surrounding tissues, causing infection and skin sinus formation [11]. The pain, local foreign body sensation, and discomfort caused by scars and scar tissue sclerosis after synthetic patches are also difficult to overcome at present. In addition, once infection or recurrence occurs, a second operation is required to remove the mesh, which not only increases surgical damage and difficulty, but also increases the pain and economic burden of patients [12].

While the current hernia material scientists continue to explore and improve the development of composite materials, they have also conducted more in-depth research on biomaterials with collagen as the main body. The biomaterials that have been approved by the U.S. Food and Drug Administration(FDA) and have been tested for clinical use include: human dermis, pig intestinal submucosa, pig dermis, embryonic bovine dermis, etc.The hernia mesh used in this study is made of pig small intestine submucosa (SIS) as a raw material, by removing the serosal layer, muscle layer and mucosal layer of the pig small intestine, and undergoing a series of decellularization, deproteinization and disinfection, etc. Acellular tissue matrix (ACTM) prepared after processing [13]. Its principle of action is "endogenous induced regeneration", that is, the implant is dynamically degraded over time, accompanied by host cell

infiltration, proliferation, angiogenesis and collagen deposition, and finally achieves the process of tissue replacement and biological healing [14]. Therefore, compared with synthetic patches, biological patches have significant advantages such as good biocompatibility, no excessive scar tissue, no long-term chronic inflammation, and low degree of tissue adhesion.

At the same time, there are still some problems that need to be solved urgently in the application of biological patches. First, the clinical application found that the incidence of seromas around the patch after the implantation of the biological patch exceeds that of the synthetic patch [15]. In this study, 13 patients had postoperative pain, fever, and local wound swelling, and 4 of them were finally confirmed as seroma formation around the patch. Analyzing the reasons, relevant scholars believe that it may be related to the following factors: (a) The quality of the biological patch is larger than that of the synthetic patch; (b) After the implantation of the biological patch

The active surface area far exceeds that of synthetic patches. Therefore, how to obtain a more satisfactory biological patch by improving the preparation technology is the direction of further research by experts in hernia surgery and materials science. In addition, the recurrence of hernia after biological patch repair is still the focus of clinical attention. In this study, 1 patient had a recurrence of left-side direct inguinal hernia at 5 months after surgery, which is considered to be related to his previous history of benign prostatic hyperplasia and high long-term abdominal pressure. Compared with indirect hernias, direct weakness of the transverse abdominal fascia, the pressure in the abdominal cavity is more direct, and the recurrence rate is higher [16]. In clinical applications, it should be noted that for larger direct inguinal hernias, the posterior wall of the inguinal canal should be reinforced at the same time, and the defect area should be reduced as much as possible to increase the overlap between the biological patch and the surrounding vascularized tissue, especially the muscle tissue, to avoid degradation faster than regeneration. Local swelling and recurrence caused by unbalanced load-bearing tension. In summary, biological patch is safe and effective in tension-free inguinal hernia repair. The excellent rate of domestic patch is equivalent to that of imported similar products, and the price is low, easy to promote, and provides a better choice for inguinal hernia patients in my equivalent to that of imported similar products, and the price is low, easy to promote, and provides a better choice for inguinal hernia patients in my country.

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