BIOLOGICAL PATCH FOR DIGESTIVE SURGERY AND PREPARATION METHOD THEREFOR

FIELD OF THE TECHNOLOGY

[0001] The present invention relates to a biological patch for digestive surgery and a preparation method therefor.

BACKGROUND

[0002] Gastrointestinal tumors are a general term for a large category of benign and malignant tumors originating from the digestive tract. With the intensification of population aging, the proportion of patients with digestive surgery tumors has gradually increased. Such patients often have poor tissue quality after radiotherapy and chemotherapy, and complications such as incision margin bleeding, oozing of blood, fluid exudation, and anastomotic stenosis are prone to occur at the anastomotic stoma (the suture site between the stomach/esophagus and the small intestine) during surgery. These complications significantly increase the physical, mental and economic burdens on patients. In the field of digestive surgery, due to the large number of blood vessels involved in surgery, the most common complication is bleeding or oozing of blood during and after the operation. Managing bleeding or oozing of blood during surgery prolongs the operation time, causes greater damage to patients, and consumes more medical consumables and instruments. Postoperative bleeding requires longer hospital stays and even secondary surgery for patients.

[0003] To address these complications, minimally invasive surgery has become increasingly popular, among which the anastomosis device is a commonly used surgical tool. Although minimally invasive surgery reduces surgical trauma to a certain extent, the problem of anastomotic stoma complications still exists. Biological patches made of biological materials have excellent elasticity, can tighten the anastomotic stoma, and reduce the incidence of complications such as anastomotic bleeding and anastomotic stenosis. Therefore, clinical practice has begun to explore the method of reinforcing the anastomotic stoma with biological patches to reduce the difficulty of surgical operation, intraoperative and postoperative complications, and improve the therapeutic effect.

SUMMARY

[0004] The present invention finds through research that a biological patch prepared by controlling the ranges of four key parameters, namely the maximum tensile elongation, elastic deformation rate, single-suture tensile force, and the ratio of elastic deformation rate to maximum tensile elongation, can effectively reduce the occurrence of complications such as anastomotic oozing of blood and gastric/intestinal fluid exudation during or after digestive surgery.

[0005] In the present invention, the determination of maximum tensile elongation and single-suture tensile force refers to the existing literature (Li Chongchong, Liu Lili, Wang Shuo, et al. Comparison of mechanical properties of allogeneic and animal-derived patches[J]. Beijing Biomedical Engineering, 2021). The elastic deformation rate is determined by conventional determination methods in the art. The prepared biological patch is cut into a strip of 4 cm in length and 1 cm in width, clamped on a tensile testing machine along its length, and stretched by applying a tensile load at a speed of 100 mm/min until fracture. A tensile curve is drawn, and the elastic deformation rate of the biological patch is calculated based on the elastic deformation section of the tensile curve.

[0006] In one aspect of the present invention, it relates to a biological patch for digestive surgery, wherein the maximum tensile elongation of the biological patch is not less than 14.8%, the elastic deformation rate is not less than 13.7%, and the single-suture tensile force is greater than 15.6 N.

[0007] In specific embodiments, the biological patch has a maximum tensile elongation of 14.8-44.6%, an elastic deformation rate of 13.7-39.1%, a single-suture tensile force of 15.6-54.1 N, and the ratio of elastic deformation rate to maximum tensile elongation is 39-89%. It is suitable for surgical operations of the colon and ileum of the digestive tract.

[0008] In specific embodiments, the biological patch has a maximum tensile elongation of 14.8-44.6%, an elastic deformation rate of 14.6-39.1%, a single-suture tensile force of 15.6-54.1 N, and the ratio of elastic deformation rate to maximum tensile elongation is 50-89%. It is suitable for surgical operations of

the rectum of the digestive tract.

[0009] In specific embodiments, the biological patch has a maximum tensile elongation of 14.8-44.6%, an elastic deformation rate of 13.7-39.1%, a single-suture tensile force of 15.6-54.1 N, and the ratio of elastic deformation rate to maximum tensile elongation is 50-89%. It is suitable for surgical operations of the duodenum of the digestive tract.

[0010] In specific embodiments, the biological patch has a maximum tensile elongation of 14.8-44.6%, an elastic deformation rate of 14.6-39.1%, a single-suture tensile force of 19.7-54.1 N, and the ratio of elastic deformation rate to maximum tensile elongation is 56-89%. It is suitable for surgical operations of the stomach of the digestive tract and can be widely used in surgical operations of various parts of the digestive tract.

[0011] The biological patch for digestive surgery is preferably a bovine pericardium-derived biological patch.

[0012] The biological patch for digestive surgery is provided with two perforations, and the two perforations are located at opposite ends of the biological patch.

[0013] In another aspect of the present invention, it relates to an anastomosis device kit comprising the above biological patch for digestive surgery. Since most cutting operations in digestive surgery adopt the cutting anastomosis device, the application of the patch requires pre-installation with the staple cartridge of the anastomosis device, i.e., the patch is stretched and fixed at both ends of the staple cartridge before surgery.

[0014] In yet another aspect of the present invention, it relates to a method for preparing the above biological patch for digestive surgery, comprising the following steps:

[0015] (1) Soak healthy bovine pericardium sheet tissue in hypotonic Hank's solution, and rinse repeatedly with fresh hypotonic Hank's solution for multiple times to fully swell and break various cells present in the tissue;

[0016] (2) Rinse the treated tissue sheet repeatedly with normal saline for 60-120 minutes each time, replacing the normal saline each time. The total number of rinses is determined until no visible cells, cell components or cell debris are observed under a microscope, and quantitative determination of proteins and nucleic acids shows no detectable soluble proteins and nucleic acids;

[0017] (3) Remove phospholipids, non-structural proteins and some immunogenic molecules of tissue matrix such as hyaluronic acid, various chondroitin sulfates and mucopolysaccharides in the tissue sheet with Tween 80 surfactant solution;

[0018] (4) Soak in 0.5-1.5% glutaraldehyde solution for 3-3.5 hours;

[0019] (5) Place the pretreated tissue material in a chromium hydroxide solution with a Cr^{3+} ion concentration of 0.0625 mol/dm³ and an OH/Cr ratio of 0.5, and shake in a water bath at 35-42°C for 3.5-5 hours; detect the pH of the material treatment solution and raise the pH by 0.3-0.5 units with 10% $NaHCO_3$, then shake in a water bath at 40-46°C for 60 minutes.

[0020] The biological patch provided by the present invention serves as a liner for the tissue incision margin of the gastrointestinal tract. Before surgery, it can be simply and stably pre-placed on the inner side of the clamping sheet of the anastomosis device. When clamping the tissue during surgery, the staple holes and suture sites formed after the titanium staples of the anastomosis device pass through the biological patch will shrink rapidly due to the elastic retraction deformation of the biological patch to prevent leakage. Meanwhile, the rebound deformation of the biological patch makes the tissue clamping firmer and more reliable, playing a role in sealing and promoting the healing and repair of the incision margin tissue. It can effectively prevent complications such as various esophageal fistulas, gastric fistulas and intestinal fistulas caused by postoperative bleeding and fluid exudation.

[0021] The biological patch provided by the present invention uses bovine pericardium as raw material, has excellent histocompatibility, can promote tissue repair and healing, and can evenly distribute the extrusion stress of titanium staples on the entire anastomotic suture staples, reduce local tissue cutting force, effectively reduce the incidence of complications such as anastomotic bleeding and fluid exudation, and simplify surgical operations.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] Fig. 1 is a schematic diagram of pre-installing the biological patch on the anastomosis device; wherein, A is the biological patch with different perforation distances; B is the anastomosis device without the pre-installed biological patch; C is the biological patch pre-installed on the anastomosis device; D is a partial enlarged view of part E in Fig. C.

[0023] Fig. 2 shows the HE staining results of the heart, liver, spleen and lung of white pigs using the biological patch obtained in Example 1.

[0024] Fig. 3 shows the HE staining results of the left kidney, right kidney and brain of white pigs using the biological patch obtained in Example 1.

[0025] Fig. 4 shows the HE staining results of the stomach, gastric surrounding tissue and intestine of white pigs using the biological patch obtained in Example 1.

[0026] Fig. 5 shows the HE staining results of the intestinal surrounding tissue of white pigs using the biological patch obtained in Example 1.

[0027] Reference Signs: biological patch 1, perforation 2, anastomosis device 3, clamping sheet 4, staple cartridge or titanium staple anvil 5.

DETAILED DESCRIPTION

[0028] In the process of completing the present invention, the inventor first aimed at the problem of prone anastomotic bleeding and fluid exudation in digestive surgery, and referred to the existing literature (Li Chongchong, Liu Lili, Wang Shuo, et al. Comparison of mechanical properties of allogeneic and animal-derived patches[J]. Beijing Biomedical Engineering, 2021), taking the tensile strength, maximum tensile elongation and single-suture tensile force of the biological patch as parameters for screening biological patches. The determination methods of each parameter refer to the literature. However, after determination, it was found that the tensile strength of the obtained biological patch fluctuated greatly and the value was unstable. Moreover, animal experiments showed that the correlation between the tensile strength of the biological patch and anastomotic bleeding and fluid exudation was unstable, so the tensile strength of the biological patch could not be used as a parameter for screening biological patches. Therefore, the inventor determined the screening and evaluation parameters of the biological patch as maximum tensile elongation, elastic deformation rate and single-suture tensile force, and confirmed the preferred ranges of these three parameters through clinical trials as follows:

[0029] (1) Biological patch for colon and ileum surgery: maximum tensile elongation 14.8-44.6%, elastic deformation rate 13.7-39.1%, single-suture tensile force 15.6-54.1 N.

[0030] (2) Biological patch for rectal surgery: maximum tensile elongation 14.8-44.6%, elastic deformation rate 14.6-39.1%, single-suture tensile force 15.6-54.1 N.

[0031] (3) Biological patch for duodenal surgery: maximum tensile elongation 14.8-44.6%, elastic deformation rate 13.7-39.1%, single-suture tensile force 15.6-54.1 N.

[0032] (4) Biological patch for gastric surgery and general digestive surgery: maximum tensile elongation 14.8-44.6%, elastic deformation rate 14.6-39.1%, single-suture tensile force 19.7-54.1 N.

[0033] During this process, it was unexpectedly found that the ratio of elastic deformation rate to maximum tensile elongation also affected anastomotic bleeding and fluid exudation.

[0034] The inventor further verified this finding through clinical trials, and confirmed that controlling the ratio of elastic deformation rate to maximum tensile elongation when the maximum tensile elongation, elastic deformation rate and single-suture tensile force are within specific ranges is conducive to reducing the occurrence of complications such as anastomotic bleeding and fluid exudation in digestive surgery. The required ratios of elastic deformation rate to maximum tensile elongation for different surgical sites are as follows:

[0035] (1) Biological patch for colon and ileum surgery: the ratio of elastic deformation rate to maximum tensile elongation is 39-89%.

[0036] (2) Biological patch for rectal and duodenal surgery: the ratio of elastic deformation rate to maximum tensile elongation is 50-89%.

[0037] (3) Biological patch for gastric surgery and general digestive surgery: the ratio of elastic

deformation rate to maximum tensile elongation is 56-89%.

[0038] I. Preparation Method of the Biological Patch

[0039] (1) Pretreatment

[0040] In the present invention, the pretreatment specifically refers to the operation steps of acellularization and immunogenicity removal of biological tissue, which is a conventional technical means in the art, aiming to remove cellular tissue components and immunogenicity. The present invention does not limit the specific operation process. The specific operation process can be referred to as follows:

[0041] ① Soak healthy bovine pericardium sheet tissue in hypotonic Hank's solution, and rinse repeatedly with fresh hypotonic Hank's solution for multiple times to fully swell and break various cells present in the tissue. The present invention selects bovine pericardium tissue.

[0042] ② Rinse the treated tissue sheet repeatedly with normal saline for 60-120 minutes each time (for example, the preferred rinsing time with normal saline is 60 minutes in a specific embodiment of the present invention), replacing the normal saline each time. The total number of rinses is determined until no visible cells, cell components or cell debris are observed under a microscope, and quantitative determination of proteins and nucleic acids shows no detectable soluble proteins and nucleic acids.

[0043] ③ Remove phospholipids, non-structural proteins and some immunogenic molecules of tissue matrix such as hyaluronic acid, various chondroitin sulfates and mucopolysaccharides in the tissue sheet with Tween 80 surfactant solution.

[0044] ④ Soak in 0.5-1.5% glutaraldehyde solution for 3-3.5 hours. In a specific embodiment of the present invention, the preferred glutaraldehyde soaking condition is soaking in 0.5% glutaraldehyde solution for 3.5 hours.

[0045] (2) Chemical Modification

[0046] It is a process of implementing composite cross-linking modification on free carboxyl groups in and/or between collagen molecules of the tissue scaffold and between scaffold collagen and tissue matrix, so that the modified tissue sheet obtains corresponding mechanical properties and anti-calcification properties. The cross-linking agent used in the present invention is a polymer of chromium hydroxide coordination compound. For specific operations, refer to: place the pretreated tissue material in a chromium hydroxide solution with a Cr^{3+} ion concentration of 0.0625 mol/dm³ and an OH/Cr ratio of 0.5, and perform the first water bath shaking at 35-42°C for 3.5-5 hours (for example, the first water bath shaking condition adopted in a specific embodiment of the present invention is shaking at 35°C for 3.5 hours). Detect the pH of the material treatment solution and raise the pH by 0.3-0.5 units with 10% $NaHCO_3$ (for example, the preferred method in a specific embodiment of the present invention is to raise the pH by 0.3 units with 10% $NaHCO_3$), then perform the second water bath shaking at 40-46°C for 60-120 minutes (for example, the preferred second water bath shaking condition adopted in a specific embodiment of the present invention is shaking at 40°C for 60 minutes), and finally obtain a single-layer sheet-shaped biological patch.

[0047] One side of the obtained biological patch is a rough surface, and the other side is a smooth surface. As shown in Fig. 1, the obtained biological patch 1 is provided with more than two perforations 2 with the same orientation and a size slightly smaller than the width of the clamping sheet 4, so that the free ends of the clamping sheet 4 pass through two of the perforations 2 in sequence (the distance between the two perforations 2 is selected according to surgical needs). The position of the biological patch 1 is further adjusted manually to make the biological patch 1 flatly fit on the inner side of the clamping sheet 4. The rough surface contacts the staple cartridge or staple anvil 5 of the anastomosis device, resulting in a large friction force, making the biological patch 1 not easy to slip off during cutting and anastomosis of the anastomosis device 3; the smooth surface fits with the digestive tissue to ensure the fitting degree with the digestive tissue. The size of the perforations 2 slightly smaller than the width of the clamping sheet 4 can ensure that the biological patch 1 remains in a stretched state when hung on the clamping sheet 4 without sliding or slipping off the clamping sheet 4.

[0048] Examples 1-17

Table 1: Main differences in preparation methods of Examples 1-17

Condition / Group	First Water Bath Shaking Condition	10% $NaHCO_3$ Concentration and pH Increase Unit	Second Water Bath Shaking Condition	Normal Saline Rinsing Time	Glutaraldehyde Solution Concentration and Soaking Time
Example 1	35°C, 3.5 h	0.3 pH	40°C, 60 min	60 min	0.5%, 3 h
Example 2	39°C, 3.5 h	0.5 pH	44°C, 60 min	80 min	0.6%, 3 h
Example 3	40°C, 3.5 h	0.3 pH	46°C, 60 min	90 min	0.6%, 3.5 h
Example 4	42°C, 3.5 h	0.4 pH	42°C, 80 min	100 min	0.7%, 3 h
Example 5	35°C, 4 h	0.5 pH	44°C, 80 min	110 min	0.7%, 3.5 h
Example 6	36°C, 4 h	0.3 pH	46°C, 80 min	120 min	0.8%, 3 h
Example 7	37°C, 4 h	0.4 pH	42°C, 100 min	60 min	0.8%, 3.5 h
Example 8	39°C, 4 h	0.5 pH	44°C, 100 min	70 min	0.9%, 3 h
Example 9	42°C, 4 h	0.3 pH	46°C, 100 min	80 min	0.9%, 3.5 h
Example 10	35°C, 4.5 h	0.4 pH	40°C, 120 min	90 min	1.0%, 3 h
Example 11	38°C, 4.5 h	0.5 pH	41°C, 120 min	100 min	1.0%, 3.5 h
Example 12	40°C, 4.5 h	0.3 pH	42°C, 120 min	110 min	1.1%, 3 h
Example 13	42°C, 4.5 h	0.4 pH	43°C, 120 min	120 min	1.1%, 3.5 h
Example 14	35°C, 5 h	0.5 pH	44°C, 120 min	60 min	1.2%, 3 h
Example 15	37°C, 5 h	0.4 pH	45°C, 120 min	70 min	1.4%, 3.5 h
Example 16	37°C, 3.5 h	0.4 pH	42°C, 60 min	70 min	0.5%, 3.5 h
Example 17	42°C, 5 h	0.5 pH	46°C, 120 min	80 min	1.5%, 3 h

[0049] II. Determination of Tensile Strength, Maximum Tensile Elongation and Single-suture Tensile Force

[0050] Good mechanical properties can reduce the incidence of complications such as anastomotic bleeding and fluid exudation, improve the compliance of the biological patch, and enhance the comfort of patients. To explore the relationship between mechanical parameters and bleeding, fluid exudation, compliance and comfort of digestive biological patches, the inventor first consulted the literature and determined the biological patches obtained in Examples 1-17 based on the existing literature (Li Chongchong, Liu Lili, Wang Shuo, et al. Comparison of mechanical properties of allogeneic and animal-derived patches[J]. Beijing Biomedical Engineering, 2021).

[0051] In the present invention, a total of 17 batches of biological patches were prepared through Examples 1-17, with 10 biological patches obtained per batch (Example). Each parameter was determined with reference to the above literature, and the average value was taken to obtain the tensile strength, maximum tensile elongation and single-suture tensile force of the biological patches. The determination results are shown in Table 2 below:

Table 2: Maximum Tensile Elongation, Tensile Strength and Single-suture Tensile Force of Examples 1-17

Group	Maximum Tensile Elongation	Tensile Strength	Single-suture Tensile Force
Example 1	44.6±0.3%	32.3±1.8 MPa	15.8±0.3 N
Example 2	14.8±0.5%	27.4±2.1 MPa	25.5±0.1 N
Example 3	21.7±0.1%	31.8±2.5 MPa	54.1±0.1 N
Example 4	18.2±1.1%	30.7±4.4 MPa	19.2±0.3 N
Example 5	15.4±0.2%	23.3±2.6 MPa	19.7±0.1 N
Example 6	29.8±1.5%	29.6±1.3 MPa	20.3±0.2 N

Example 7	27.2±0.3%	33.5±0.9 MPa	33.6±0.1 N
Example 8	35.5±1.6%	21.1±2.8 MPa	26.4±0.3 N
Example 9	42.4±1.5%	29.3±1.1 MPa	15.6±0.1 N
Example 10	40.1±0.2%	20.7±3.3 MPa	31.8±0.1 N
Example 11	25.9±2.4%	31.1±1.7 MPa	29.1±0.1 N
Example 12	33.2±3.1%	28.2±1.8 MPa	35.4±0.1 N
Example 13	41.5±1.3%	22.9±0.4 MPa	36.2±0.2 N
Example 14	39.4±1.2%	20.3±1.1 MPa	28.7±0.1 N
Example 15	30.7±0.2%	26.1±3.2 MPa	36.1±0.1 N
Example 16	26.3±0.3%	37.5±1.8 MPa	37.2±0.1 N
Example 17	11.1±0.4%	25.5±1.3 MPa	22.8±0.2 N

[0052] It can be seen from Table 2 that the tensile strength of 10 biological patches obtained in the same batch of each Example (Examples 1-17) fluctuates greatly and the value is unstable, which may be due to other unobserved factors affecting the tensile strength of the patch, making it impossible to accurately control the tensile strength of the biological patch, which is not suitable for use as a surgical material.

[0053] Summarizing the mechanical parameters obtained by the above preparation method, it can be seen that the biological patch obtained by the present invention has a maximum tensile elongation range of 11.1-44.6%, a tensile strength of 20.3-37.5 MPa, and a single-suture tensile force range of 15.6-54.1 N.

[0054] Ten biological patches obtained in each Example were cut into strips of 4 cm in length and 1 cm in width, and tested for pre-installation on the anastomosis device.

[0055] Pre-installation of the biological patch on the anastomosis device requires proper stretching, which is related to the maximum tensile elongation. Theoretically, the larger the maximum tensile elongation, the better. If the maximum tensile elongation is too small, the biological patch will break after stretching a small distance. For example, 10 biological patches obtained in Example 17 (maximum tensile elongation 11.1±0.4%) were used to assemble the anastomosis device, and 9 were torn and 1 showed obvious cracks, reflecting the high rigidity of the biological patch, which is extremely difficult to deform and quickly enters permanent deformation and fracture after deformation.

[0056] Thus, it is found that the biological patch with a maximum tensile elongation of 11.1% cannot meet the requirement of installation on the anastomosis device. Based on the fact that the biological patches obtained in other Examples meet the stretching requirements and can be pre-installed on the anastomosis device, the minimum maximum tensile elongation of 14.8±0.5% of the patch obtained in Example 2 is taken as the minimum value for installing the biological patch on the anastomosis device.

[0057] Animal experiments were performed on the Examples (Examples 1-16) that met the requirements of pre-installation on the anastomosis device.

[0058] III. Animal Experiment

[0059] The gastrointestinal tract of white pigs has many similarities with humans in anatomical structure and physiological function, making white pigs an ideal animal model for studying human gastrointestinal diseases and injuries. White pigs have a moderate size, which is convenient for experimental operation and management. Compared with small animals such as mice and rats, white pigs provide a larger operating space, enabling researchers to perform surgical operations more easily. Meanwhile, white pigs are easy to feed and manage under laboratory conditions, less prone to infection after surgery, easy to control for long-term feeding, and have a high long-term survival rate.

[0060] Healthy experimental animals were purchased in accordance with SOP-5 Operating Procedures for Laboratory Animals and Receipt, provided by Jiangsu Yinse Biotechnology Co., Ltd. (license number: SCXK (Gan) 2023-0002). All animals were used for animal experiments for the first time at the start of the test. All test animals were quarantined before surgery, and only those that passed quarantine were included in this study.

[0061] 1. Inclusion Criteria

[0062] Meet the requirements of the national Administrative Measures for Animal Quarantine; body weight 50-60 kg; normal physiological indicators; no obvious serious animal diseases (such as active digestive diseases, blood system and metabolic system diseases, infectious diseases and zoonotic diseases, etc.).

[0063] 2. Feeding

[0064] Laboratory animals were tracked and managed in accordance with SMP-5 Rules and Regulations for Laboratory Animal Care and Management. Animals were fed an appropriate amount of feed twice a day, and could drink water freely through an automatic water supply system. The feed and drinking water were clean and safe.

[0065] 3. Grouping and Quantity

[0066] 1-month group: 48 pigs in total (16 Examples, 3 pigs per Example for experiment); 3-month group: 48 pigs (16 Examples, 3 pigs per Example for experiment). Gender unlimited, random grouping.

[0067] Animal information was recorded during the experiment: body weight, operation time, survival days, biological patch information, etc.

[0068] Routine blood, blood biochemistry, coagulation function and blood gas were measured before surgery.

[0069] Routine blood, blood biochemistry, coagulation function and blood gas were measured at 1 month and 3 months after surgery.

[0070] 4. Experimental Steps

[0071] ① Preoperative preparation;

[0072] ② Perform preoperative blood examination in accordance with routine inspection requirements and record preoperative data;

[0073] ③ During surgery, anesthetize the experimental pigs, perform tracheal intubation, and assist ventilation with a ventilator. Disinfect and prepare the skin.

[0074] ④ Supine position, laparotomy to expose the abdomen, free gastric tissue, select an appropriate position; cut an incision smaller than the size of the biological patch; install a 1 cm×4 cm biological patch on the anastomosis device as shown in Fig. 2, place the anastomosis device with the pre-installed biological patch at the predetermined position, and adjust its angle and depth to ensure close fitting with surrounding tissues. Carefully inspect the gastric anastomotic stoma and the patch, and observe whether the biological patch fits well with the digestive tissue, whether the resilience of the biological patch meets the requirements, whether the biological patch is fixed stably, and whether there is bleeding or fluid exudation at the staple holes and suture sites.

[0075] ⑦ Free the small intestine in the abdominal cavity, select an appropriate position, cut an incision smaller than the size of the patch, install a 1 cm×4 cm biological patch on the anastomosis device, place the anastomosis device with the pre-installed biological patch at the predetermined position, and adjust its angle and depth to ensure close fitting with surrounding tissues.

[0076] ⑧ Carefully inspect the intestinal anastomotic stoma and the patch, and observe whether the biological patch fits well with the digestive tissue, whether the resilience of the biological patch meets the requirements, whether the biological patch is fixed stably, and whether there is bleeding at the staple holes and suture needle holes.

[0077] ⑨ After the operation, recheck the anastomotic stoma for bleeding and exudate, and close the abdomen after confirmation.

[0078] The test animals were sent to the observation room for observation after surgery, supported by a ventilator until the animals woke up, and then sent to the animal room for feeding after standing and walking. Alternate lighting of 12h/12h every day, fed with appropriate animal feed once in the morning and afternoon every day, free drinking water. Observe mental state, appetite, respiration, wound complications and other adverse symptoms every day.

[0079] Ceftriaxone sodium 2g was intramuscularly injected continuously for 1 week after surgery for anti-infection. Observe mental state, appetite, respiration, incision healing status, nausea, vomiting and other gastrointestinal symptoms of animals every day. Disinfect the surgical wound with iodophor until the wound heals. Veterinarians conduct regular physical examinations and blood tests, and take anti-infection prevention and treatment measures according to the results. Record postoperative medication and adverse events within 24 hours (including death, infection, etc.).

[0080] At the end of the experiment, gross tissues (heart, liver, spleen, lung, kidney, brain), gastric patch and surrounding tissues, intestinal patch and surrounding tissues of the test animals were taken for visual observation and photography, and then the tissues were fixed with 10% formalin solution for 48 hours, sectioned routinely, and stained with HE.

[0081] Visually observe whether the patch is intact, whether there are defects and patch leakage, whether there is thrombus on the surface, and whether there are bleeding, necrosis and other changes in the surrounding tissues. The test animals were sacrificed at 1 month and 3 months after surgery, and the pathological results of the test animals at the end point were recorded.

Table 4: Pathological Scoring Principles

Four-Grade Grading System		
Grade (Number)	Type	Description
0	Within normal range	Under the study conditions, considering factors such as age, gender and strain of animals, the tissue is considered normal. Changes occurring under other conditions can be considered abnormal
1	Very slight	Changes just exceed the normal range
2	Slight	Lesions can be observed but not serious
3	Moderate	Lesions are obvious and likely to be more serious
4	Severe	Lesions are very serious (lesions occupy the entire tissue and organ)

[0082] 5. Experimental Results

[0083] (1) After implantation in pigs, the biological patches prepared in 11 Examples exhibited no hemorrhage or fluid exudation at gastric and intestinal anastomotic sites, namely Example 1, Example 5, Examples 7–9, and Examples 11–16.

[0084] The experimental pigs in the above experimental groups successfully completed digestive surgery gastric and intestinal anastomotic operations. The biological patch was closely fitted with the anastomotic stoma, and bleeding at and around the anastomotic stoma could be controlled timely and effectively. No instrument failure of the anastomosis device and components occurred during the operation. Intraoperative anesthesia, gastric and intestinal anastomosis were smooth, and there was no bleeding or fluid exudation at the anastomotic stoma during the operation; vital signs were normal; no adverse events occurred.

[0085] During the survival and feeding period, all animals maintained good general conditions with normal body temperature, food intake and defecation, and exhibited sound voluntary activity. No obvious abnormal manifestations such as significant weight loss, fever, anorexia or mania were observed. All animals survived smoothly until the study endpoint, without developing surgical complications including hemorrhage, infection, anastomotic stricture, rejection reaction or organ failure.

[0086] After dissection, the thoracic cavity was intact, no pleural effusion was found, and no obvious pathological changes were found in the chest wall and thoracic cavity contents; the abdominal cavity was intact, no ascites was found, and no obvious abnormal pathological changes were found in the abdominal wall, peritoneum, abdominal cavity contents and intestinal tract; no gross changes related to biological patch surgery were found in heart, liver, spleen, lung, kidney, brain, stomach and intestine specimens.

[0087] Examination of electrolytes at each follow-up period after extracardiac radiofrequency ablation showed that liver and kidney function values were almost within the normal range, and coagulation INR values were about 1.0 before and during follow-up. No abnormalities were found in the number, morphology and quality of whole blood cells; the detection results of white blood cells, red blood cells, hemoglobin, platelets, etc. showed that the overall results were stable, and no important abnormal routine

blood indicators were found. No abnormal liver and kidney functions were found, and some values were slightly higher or lower than the reference range, but had no clinical significance. No abnormal laboratory test results considered to have clinical significance were found before and before the end of the test.

[0088] Comparative analysis of intraoperative anatomy of gastrointestinal anastomotic stoma: the gastric and intestinal anastomotic stoma was flat and good during the operation, without bleeding and exudate. At 1 month and 3 months of follow-up, scar tissue was formed on the surface of the gastric anastomotic stoma to prevent leakage and promote healing, and the biological patch was not decomposed. In the small intestine, due to the flow of food and digestive juice, the biological patch is more susceptible to physical and chemical effects, thus accelerating the degradation process. When the biological patch is implanted into the small intestinal anastomotic stoma, it can act as a scaffold, and the degraded material can be absorbed or replaced by new cells, thus promoting the complete healing of the anastomotic stoma. This indicates that the biological patch can be slowly decomposed and regenerated at the small intestinal anastomotic stoma of the tested white pigs, mainly due to the interaction between its material properties and the physiological environment of the tissue. At the gastric anastomotic stoma, due to the different physiological environment from the small intestine and the interaction between the biological patch and gastric acid and pepsin, the biological patch may not decompose or decompose slowly, reflecting the good histocompatibility of the biological patch for digestive surgery and its ability to form a good combination with surrounding tissues.

[0089] Fig. 2 shows the HE staining results of the heart, liver, spleen and lung of white pigs implanted with the biological patch obtained in Example 1. As shown in Fig. 2A–Fig. 2B, slight hydropic degeneration of a small number of cardiomyocytes is observed in the cardiac tissue (blue arrows), with swollen cell bodies and loose, lightly stained cytoplasm; no obvious hyperplasia, necrosis or inflammatory cell infiltration is found in the interstitium. As shown in Fig. 2C–Fig. 2D, the hepatic lobules in the liver tissue are clearly demarcated and regularly arranged, with a central vein in the middle of each hepatic lobule and hepatocytes and hepatic sinusoids arranged roughly radially around it; slight fatty degeneration of a small number of hepatocytes is observed (yellow arrows), with round microvesicles visible in the cytoplasm; hydropic degeneration of a small number of hepatocytes is noted (blue arrows), with swollen cells and loose, lightly stained cytoplasm; a small amount of lymphocyte infiltration is seen around the portal area (red arrows). As shown in Fig. 2E–Fig. 2F, the splenic tissue is rich in white pulp of varying sizes and irregular shapes; the red pulp is widely distributed under the capsule, around the trabeculae and outside the marginal zone of the white pulp, composed of splenic cords and splenic sinusoids; a small number of granulocytes are visible in the marginal zone and red pulp (red arrows). As shown in Fig. 2G–Fig. 2H, nuclear pyknosis of a small number of epithelial cells is observed in a few bronchioles of the lung tissue (black arrows), with irregular arrangement of epithelial cells; a small amount of granulocyte infiltration is seen in the alveolar walls (red arrows), and a large number of alveoli are dilated compensatorily.

[0090] Fig. 3 shows the HE staining results of the left kidney, right kidney and brain of white pigs implanted with the biological patch obtained in Example 1. As shown in Fig. 3A–Fig. 3B, glomeruli are evenly distributed in the renal cortex, with uniform cell number and matrix in the glomeruli, and rare eosinophilic substances in the Bowman's capsule (black arrows); slight hydropic degeneration of a small number of renal tubular epithelial cells is observed (blue arrows), with swollen cells and loose, lightly stained cytoplasm; vacuolar degeneration of a small number of renal tubular epithelial cells is noted (yellow arrows), with small round vacuoles in the cytoplasm; no obvious hyperplasia, necrosis or inflammatory cell infiltration is found in the interstitium. As shown in Fig. 3C and Fig. 3D, glomeruli are evenly distributed in the renal cortex, with uniform cell number and matrix in the glomeruli, and rare eosinophilic substances in the Bowman's capsule (black arrows); obvious hydropic degeneration of many renal tubular epithelial cells is observed (blue arrows), with swollen cells and loose, lightly stained cytoplasm; occasional lymphocyte infiltration is seen in the interstitium (red arrows); no obvious hyperplasia is found in the interstitium. As shown in Fig. 3E and Fig. 3F, the brain tissue is rich in neurons; nuclear shrinkage and hyperchromatism of many neurons are observed (black arrows), with shrunken and deformed cell bodies, irregular shapes, and unclear demarcation between the nucleus and cytoplasm; no

obvious necrosis or inflammatory cell infiltration is found.

[0091] Fig. 4 shows the HE staining results of the stomach, perigastric tissue and intestine of white pigs implanted with the biological patch obtained in Example 1. As shown in Fig. 4A–Fig. 4B, the structure of the gastric tissue is disordered, with a large area of the patch visible (black arrows); massive hyperplasia and encapsulation of connective tissue are observed around the patch (brown arrows); a small number of new blood vessels are visible (green arrows); extensive lymphocyte infiltration is noted (red arrows); occasional endothelial cell hyperplasia is seen (orange arrows). As shown in Fig. 4C–Fig. 4D, no obvious mucosal layer is observed in the gastric tissue, and the muscular layer is well-developed; obvious hydropic degeneration of many muscle cells is found (blue arrows), with loose, lightly stained cytoplasm and no obvious inflammatory cell infiltration. As shown in Fig. 4E–Fig. 4F, intestinal villi are distributed on the surface of the intestinal tissue, with massive loss of intestinal villus epithelium (brown arrows) and exposed lamina propria; intestinal glands in the lamina propria are loosely and irregularly arranged, with scattered goblet cells; many lymphocytes are scattered in the interstitium (red arrows), and extensive vascular congestion is observed (green arrows); obvious hyperplasia of connective tissue is seen around the muscular layer (orange arrows), with loose and irregular arrangement of fibroblasts and collagen fibers; a small number of new blood vessels and vascular congestion are visible, accompanied by scattered infiltration of a small number of lymphocytes around them (yellow arrows).

[0092] Fig. 5 shows the HE staining results of the perienteric tissue of white pigs implanted with the biological patch obtained in Example 1. As shown in Fig. 5A–Fig. 5B, the surface of the intestinal tissue is mainly composed of columnar epithelium and goblet cells, with scattered goblet cells; extensive shedding of mucosal epithelial cells is observed (black arrows), with exposed lamina propria; intestinal glands are loosely and irregularly arranged; many lymphocytes are scattered in the interstitium (red arrows).

[0093] (2) No obvious tearing occurred at the staple holes and suture sites of the biological patches obtained in Examples 1-16. Therefore, the biological patches with a single-suture tensile force range of 15.6-54.1 N can initially meet the use requirements of digestive surgery.

[0094] (3) Anastomotic bleeding and fluid exudation occurred in the biological patches obtained in Examples 2-4, Example 6 and Example 10, and some experimental groups even had problems of degeneration, hyperplasia and very severe tissue necrosis. Among them, the biological patch obtained in Example 3 had anastomotic bleeding and fluid exudation after surgery. One month after surgery, the hearts of 2 pigs had degeneration, hyperplasia and very severe tissue necrosis, the spleen had relatively severe tissue necrosis, and the gastric and intestinal patches had severe connective tissue hyperplasia. The specific pathological scoring results are as follows:

Table 5: Pathological Results of Example 3 at 1 Month

Lesion No.	T41-1 (Example 3) - Heart	T41-2 (Example 3) - Heart	T41-3 (Example 3) - Heart	Lesion No.	T41-1 (Example 3) - Liver	T41-2 (Example 3) - Liver	T41-3 (Example 3) - Liver	Lesion No.	T41-1 (Example 3) - Spleen	T41-2 (Example 3) - Spleen	T41-3 (Example 3) - Spleen
Degeneration	1	3	2	Hydropic degeneration	1	0	0	Capsular thickening	1	2	1
Necrosis	4	4	3	Fatty degeneration	1	1	1	Decreased lymphocytes	1	1	1
Inflammatory cell infiltration	1	1	1	Inflammatory cell infiltration	1	3	2	Inflammatory cell infiltration	1	1	1

Hyperplasia	1	2	1	Fibrosis	0	0	0	Necrosis	2	3	3
Lesion No.	T41-1 (Example 3) - Lung	T41-2 (Example 3) - Lung	T41-3 (Example 3) - Lung	Lesion No.	T41-1 (Example 3) - Left Kidney	T41-2 (Example 3) - Left Kidney	T41-3 (Example 3) - Left Kidney	Lesion No.	T41-1 (Example 3) - Right Kidney	T41-2 (Example 3) - Right Kidney	T41-3 (Example 3) - Right Kidney
Alveolar wall thickening	0	2	1	Degeneration	1	3	2	Degeneration	2	3	2
Inflammatory cell infiltration	1	1	1	Inflammatory cell infiltration	1	1	0	Inflammatory cell infiltration	1	1	0
Alveolar dilation	2	3	2	Eosinophilic substances	1	1	1	Eosinophilic substances	1	2	1
Eosinophilic substances	0	0	0	Bowman's capsule dilation	0	1	0	Bowman's capsule dilation	0	0	0
Lesion No.	T41-1 (Example 3) - Brain	T41-2 (Example 3) - Brain	T41-3 (Example 3) - Brain	Lesion No.	T41-1 (Example 3) - Gastric Patch	T41-2 (Example 3) - Gastric Patch	T41-3 (Example 3) - Gastric Patch	Lesion No.	T41-1 (Example 3) - Perigastric Tissue	T41-2 (Example 3) - Perigastric Tissue	T41-3 (Example 3) - Perigastric Tissue
Neuronal shrinkage	2	3	2	Endothelial cell hyperplasia	0	1	1	Inflammatory cell count (excluding lymphoid nodules)	0	1	0
Inflammatory cell infiltration	0	0	1	Inflammatory cell count (excluding lymphoid nodules)	4	4	1	Connective tissue hyperplasia	0	0	0
Neurophilia	0	0	0	Connective tissue hyperplasia	4	3	0	Muscle cell degeneration	2	2	2
Lesion No.	T41-1 (Exam	T41-2 (Exam	T41-3 (Exam	Lesion No.	T41-1 (Exam	T41-2 (Exam	T41-3 (Exampl				

	ple 3) - Intestinal Patch	ple 3) - Intestinal Patch	ple 3) - Intestinal Patch		ple 3) - Perienteric Tissue	ple 3) - Perienteric Tissue	e 3) - Perienteric Tissue				
Mucosal epithelial loss or shedding	4	1	1	Mucosal epithelial loss or shedding	2	4	1				
Inflammatory cell count (excluding lymphoid nodules)	2	2	2	Inflammatory cell count (excluding lymphoid nodules)	2	2	2				
Connective tissue hyperplasia	3	4	2	Connective tissue hyperplasia	0	1	0				

[0095] (4) Theoretically, the pre-installation of the biological patch on the anastomosis device requires a certain tensile strength, which helps to ensure the compliance of the biological patch and prevent anastomotic bleeding and fluid exudation. However, it was found in animal experiments that:

[0096] Specifically, among the 10 biological patches obtained in Example 10 (tensile strength 20.7±3.3 MPa), 1 experimental group corresponding to the biological patch had anastomotic bleeding and fluid exudation. However, Examples with similar tensile strength to this Example had no anastomotic bleeding and fluid exudation, such as Example 8 (tensile strength 21.1±2.8 MPa) and Example 13 (tensile strength 22.9±0.4 MPa).

[0097] Among the 10 biological patches obtained in Example 6 (tensile strength 29.6±1.3 MPa), 4 experimental groups corresponding to the biological patches had anastomotic bleeding and fluid exudation. However, Examples with similar tensile strength to this Example had no anastomotic bleeding and fluid exudation, such as Example 9 (tensile strength 29.3±1.1 MPa) and Example 11 (tensile strength 31.1±1.7 MPa).

[0098] Among the 10 biological patches obtained in Example 2 (tensile strength 27.4±2.1 MPa), Example 3 (tensile strength 31.8±2.5 MPa) and Example 4 (tensile strength 30.7±4.4 MPa), 7 experimental groups corresponding to each biological patch had anastomotic bleeding and fluid exudation. However, Examples with similar tensile strength to these Examples had no anastomotic bleeding and fluid exudation, such as Example 12 (tensile strength 28.2±1.8 MPa) and Example 15 (tensile strength 26.1±3.2 MPa), Example 1 (tensile strength 32.3±1.8 MPa), Example 7 (tensile strength 33.5±0.9 MPa), Example 16 (tensile strength 37.5±1.8 MPa).

[0099] The above experiments found that the maximum tensile elongation range of 14.8-44.6% can meet the requirement of installation on the anastomosis device.

[0100] Due to the large fluctuation of the tensile strength value of the biological patch, and animal experiments found that the correlation between the tensile strength of the biological patch and anastomotic bleeding and fluid exudation is unstable, the inventor speculates that the tensile strength of the biological patch cannot be used as a parameter for screening biological patches, and needs to reconsider the mechanical parameters that can indicate anastomotic bleeding and fluid exudation.

[0101] Based on years of research on the application of animal-derived biological materials to digestive surgery implantation, the inventor found that the mismatch between the staple forming height and tissue thickness leads to anastomotic bleeding and fluid exudation. The staple forming height is fixed, but the tissue thickness of different patients and different parts varies. When the tissue is too thick or too thin relative to the staple height, anastomotic bleeding and fluid exudation may occur. Therefore, the biological patch needs to have good resilience. The inventor intends to introduce "elasticity" into the biological-

derived biological patch, replace "tensile strength" with "elastic deformation rate", and comprehensively explore the biological patch for digestive surgery for preventing anastomotic bleeding and fluid exudation based on the three mechanical parameters of elastic deformation rate, maximum tensile elongation and single-suture tensile force.

[0102] IV. Determination of Elastic Deformation Rate

[0103] 1. Determination Method

[0104] Clamp a 4 cm long and 1 cm wide biological patch on a tensile testing machine along the length direction, apply a tensile load at a speed of 100 mm/min to stretch the biological patch until fracture. Draw a tensile curve, and calculate the elastic deformation rate of the biological patch based on the elastic deformation section of the tensile curve during the test.

[0105] 2. Determination Results

Table 3: Elastic Deformation Rate of Examples 1-17

Group	Elastic Deformation Rate	Group	Elastic Deformation Rate
Example 1	39.1±0.4%	Example 10	10.2±1.3%
Example 2	6.5±0.1%	Example 11	18.7±0.4%
Example 3	4.4±0.7%	Example 12	27.4±0.5%
Example 4	5.2±0.1%	Example 13	16.1±1.2%
Example 5	13.7±0.3%	Example 14	19.8±0.9%
Example 6	7.6±0.2%	Example 15	23.5±0.3%
Example 7	15.2±1.7%	Example 16	14.6±1.6%
Example 8	21.5±0.4%	Example 17	8.2±0.4%
Example 9	13.9±1.1%	-	-

[0106] It can be found from Table 3 that the elastic deformation rate of the biological patches obtained in Examples 1-17 is relatively stable, and the elastic deformation rate range is 4.4-39.1%.

[0107] Based on the experimental results of animal experiments, the inventor unexpectedly found that 7 pigs had bleeding and fluid exudation using the biological patches obtained in Example 3 (elastic deformation rate 4.4±0.7%), Example 4 (elastic deformation rate 5.2±0.1%) and Example 2 (elastic deformation rate 6.5±0.1%); 4 pigs had bleeding and fluid exudation using the biological patch obtained in Example 6 (elastic deformation rate 7.6±0.2%); only 1 pig had bleeding and fluid exudation using the biological patch obtained in Example 10 (elastic deformation rate 10.2±1.3%). That is, with the increase of elastic deformation rate, the number of pigs with anastomotic bleeding and fluid exudation decreased continuously, and the elastic deformation rate of the biological patches obtained in these Examples was lower than that of the Examples without anastomotic bleeding and fluid exudation.

[0108] Therefore, the inventor speculates that the higher the elastic deformation rate, the less likely anastomotic bleeding and fluid exudation occur. Based on the experimental results of animal experiments, it can be initially proved that the inventor's introduction of "elastic deformation rate" is correct. It is speculated that the cause of anastomotic bleeding and fluid exudation is the poor resilience of the biological patch, slightly poor fitting with pig tissue, and insufficient contraction elasticity at the staple holes and suture sites, resulting in anastomotic bleeding and fluid exudation. Moreover, based on the animal experiment results of the biological patches obtained in Example 1, Example 5, Examples 7-9, Examples 11-16, the elastic deformation rate should be controlled within the range of 13.7-39.1%.

[0109] V Clinical Trial I

[0110] 1. Inclusion Criteria, Exclusion Criteria and Total Enrolled Cases

[0111] (1) Inclusion Criteria

[0112] ① Age: 18-75 years old, gender unlimited; ② Meet the indications of clinical surgery, various digestive tract diseases requiring surgical cutting, closure and anastomosis of esophagus, stomach and intestine (no requirement for surgical approach, traditional open, laparoscopic, robotic are all acceptable);

③ Able to understand the purpose of the trial, voluntarily participate and sign informed consent, willing to accept relevant examinations and clinical follow-up.

[0113] (2) Exclusion Criteria

[0114] ① American Eastern Cooperative Oncology Group (ECOG) physical status score ≥ 2; ECOG physical status score is a scoring system used to evaluate the daily activity ability and self-care ability of cancer patients; ② American Society of Anesthesiologists (ASA) grade above III (excluding III); ③ Have autoimmune diseases or blood system diseases; ④ Diagnosed with clear abdominal infection; ⑤ Alanine aminotransferase or aspartate aminotransferase > 2.5 times the upper limit of normal value, or total bilirubin > 1.5 times the upper limit of normal value, or serum creatinine > 1.5 times the upper limit of normal value; ⑥ Hemoglobin level < 60 g/L, or platelet level < 100×10^9/L, or serum albumin < 30 g/L; ⑦ Any coagulation function index exceeds ±10% of the normal reference range; coagulation function indexes include activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), international normalized ratio (INR); ⑧ Have chronic systemic diseases such as severe liver disease, severe kidney disease, severe respiratory disease, or uncontrolled diabetes, hypertension, arrhythmia; ⑨ Myocardial infarction occurred within 6 months; ⑩ Received preoperative chemotherapy or chemoradiotherapy within 4 weeks; ⑪ Pregnant women, lactating women or those planning pregnancy during the trial; ⑫ Participating in other drug or medical device clinical trials and not reaching the main study endpoint; ⑬ Other situations not suitable for participating in this trial evaluated by the researcher.

[0115] 2. Trial Grouping

[0116] Experimental group: divided into 11 groups, using the biological patches obtained in Example 1, Example 5, Examples 7-9, Examples 11-16 for surgery respectively. Before surgery, the biological patch was pre-installed on the anastomosis device for surgery.

[0117] Control group: surgery was performed only with anastomosis device closure/anastomosis.

[0118] 3. Trial Process

[0119] (1) Sign informed consent; (2) Case screening, confirm clinical inclusion and exclusion criteria, and complete baseline data collection simultaneously; (3) Determine the operation time; (4) Enroll in the experimental group or control group according to random grouping; (5) Perform surgery; (6) Observe bleeding points and record in the operation report; (7) Evaluate the immediate postoperative condition of the subjects; (8) Complete follow-up before discharge, 1 month and 3 months after surgery in accordance with the relevant inspection requirements in the protocol. The specific process is shown in the table below.

Table 6: Main Trial Process

Visit Time	Preoperative	Intraoperative	Before Discharge	30 Days Postoperative	90 Days Postoperative
Trial Stage	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4
Window Period	-14-0 days	0 day	-	±10 days	±14 days
Record Bleeding Points	-	▲	-	-	-
Adverse Event/Serious Adverse Event	-	▲	▲	▲	▲

[0120] 4. Efficacy Indicators

[0121] (1) The number of bleeding points per unit length of anastomotic/closed stoma requiring clinical hemostasis and suture reinforcement treatment within 10 minutes after the completion of cutting, closure and anastomosis by the anastomosis device (the researcher observes until no new bleeding points defined in the protocol appear at the anastomotic stoma after the completion of cutting, closure and anastomosis)

(observation sites: gastric resection stump, duodenal closure stump, intestinal closure stump, gastrointestinal anastomotic stoma, esophageal anastomotic stoma, esophagogastric anastomotic stoma, esophagojejunal anastomotic stoma, intestinal anastomotic stoma, etc.).

[0122] Number of bleeding points per unit length of anastomotic/closed stoma = total number of bleeding points (pieces)/incision margin length (cm).

[0123] Judgment criteria: ① Visit time point: Visit 1 (operation day); ② Bleeding points requiring clinical treatment: sites requiring additional operations of clinical hemostasis and suture reinforcement (such as manual compression suture, hemostatic clip or electrocoagulation) at the suture staple tissue incision margin within 10 minutes after the completion of cutting, closure and anastomosis (until no new bleeding points defined in the protocol appear at the anastomotic stoma).

[0124] (2) The number of arterial pulsatile bleeding points per unit length of anastomotic/closed stoma requiring clinical hemostasis treatment within 10 minutes after the completion of cutting, closure and anastomosis (the researcher observes until no new pulsatile bleeding points defined in the protocol appear at the anastomotic stoma after the completion of cutting, closure and anastomosis) (observation sites: gastric resection stump, duodenal closure stump, intestinal closure stump, gastrointestinal anastomotic stoma, esophageal anastomotic stoma, esophagogastric anastomotic stoma, esophagojejunal anastomotic stoma, intestinal anastomotic stoma, etc.); treatment time of bleeding points at the anastomotic/suture stoma (s); total operation time (min) (from the start of operation to the completion of abdominal closure).

[0125] Judgment criteria: Visit time point: Visit 1 (operation day); pulsatile bleeding points: small arterial bleeding, record bleeding points (take photos). Treatment time of bleeding points (s): record the time from the start of intervention measures to the completion of hemostasis operation. If multiple hemostasis treatments are performed on the same bleeding point, the treatment time of bleeding points is the sum of multiple hemostasis treatment times.

[0126] (3) Safety Evaluation Indicators

[0127] ① Occurrence of anastomotic stoma-related postoperative complications (anastomotic bleeding, anastomotic leakage, anastomotic stenosis) within 90 days after surgery. Specifically, including the following complications:

[0128] A. Anastomotic bleeding: refers to continuous or intermittent bloody stools in patients after digestive tract reconstruction. When a large amount of bleeding causes hemodynamic disturbance, manifestations such as tachycardia, hypotension, decreased hemoglobin level and even decreased urine output may occur. If a large amount of bleeding occurs in the abdominal cavity, it will also cause abdominal distension.

[0129] B. Anastomotic leakage: refers to the leakage of food residues or digestive juice into the abdominal cavity due to poor healing or loose anastomosis at the anastomotic stomas such as esophagus-stomach, esophagus-jejunum, stomach-duodenum, stomach-jejunum or jejunum-jejunum in digestive tract reconstruction.

[0130] C. Anastomotic stenosis: upper gastrointestinal tract: the anastomotic stoma cannot pass a thin-diameter endoscope with a diameter of 7.9 mm, accompanied by dysphagia; lower gastrointestinal tract: cannot pass a fiber colonoscope with a diameter of 13 mm, accompanied by defecation difficulty.

[0131] ② Determination method: judge and record the occurrence of the above complications according to clinical routine methods.

[0132] ③ Visit time points: Visit 1 (operation day), Visit 2 (before discharge), Visit 3 (30 days ±10 days after surgery), Visit 4 (3 months ±14 days after surgery).

[0133] 6. Trial Method

[0134] Prospective, multi-center, randomized controlled, open-label, superiority trial.

[0135] 7. Trial Results

[0136] (1) Safety

[0137] No complications such as anastomotic bleeding, anastomotic leakage and anastomotic stenosis

occurred in all patients within 90 days after surgery.

[0138] (2) Surgical Bleeding Point Records

Table 7: Bleeding Point Records in Colon Surgery

No.	Group	Surgery Involved	Number of Bleeding Points Requiring Clinical Hemostasis	Number of Pulsatile Bleeding Points	Number of Bleeding Points per Unit Length of Anastomotic/Closed Stoma (n/cm)
1	Test Group 1 (Example 1-1)	SILS+1 Laparoscopic Radical Resection of Sigmoid Colon Cancer	0	0	0
2	Test Group 2 (Example 1-2)	Laparoscopic Sigmoid Colectomy	0	1	0
3	Test Group 3 (Example 5-1)	Laparoscopic Left Hemi-Colectomy + Transverse Colon-Sigmoid Colon Anastomosis	1	0	0
4	Test Group 4 (Example 5-2)	Left Hemi-Colectomy	2	0	0.11
5	Test Group 5 (Example 7-1)	SILS+1 Laparoscopic Radical Resection of Sigmoid Colon Cancer	0	0	0
6	Test Group 6 (Example 7-2)	Laparoscopic Sigmoid Colectomy	0	0	0
7	Test Group 7 (Example 8-1)	Laparoscopic Left Hemi-Colectomy + Transverse Colon-Descending Colon Anastomosis	0	0	0
8	Test Group 8 (Example 8-2)	SILS+1 Laparoscopic Radical Resection of Sigmoid Colon Cancer	0	0	0
9	Test Group 9 (Example 9-1)	SILS+1 Laparoscopic Left Hemi-Colectomy	15	3	1.38
10	Test Group 10 (Example 9-2)	Laparoscopic Conversion to Laparotomy + Partial Sigmoid Colectomy + Colostomy Reversal	26	21	3.12

11	Test Group 11 (Example 11-1)	Laparoscopic Radical Resection of Right Colon Cancer	2	0	0.33
12	Test Group 12 (Example 11-2)	SILS+1 Laparoscopic Radical Resection of Sigmoid Colon Cancer	0	0	0
13	Test Group 13 (Example 12-1)	Laparoscopic Extended Radical Resection of Right Colon Cancer	0	0	0
14	Test Group 14 (Example 12-2)	Laparoscopic Extended Radical Resection of Right Colon Cancer	0	0	0
15	Test Group 15 (Example 13-1)	Laparoscopic Radical Resection of Transverse Colon Cancer	0	1	0
16	Test Group 16 (Example 13-2)	Laparoscopic Radical Resection of Transverse Colon Cancer	0	1	0
17	Test Group 17 (Example 14-1)	Laparoscopic Radical Resection of Right Colon Cancer	0	0	0
18	Test Group 18 (Example 14-2)	Laparoscopic Radical Resection of Right Colon Cancer	0	0	0
19	Test Group 19 (Example 15-1)	Laparoscopic Extended Radical Resection of Right Colon Cancer	0	1	0
20	Test Group 20 (Example 15-2)	SILS+1 Laparoscopic Radical Resection of Sigmoid Colon Cancer	1	0	0
21	Test Group 21 (Example 16-1)	Laparoscopic Extended Radical Resection of Right Colon Cancer	0	0	0
22	Test Group 22 (Example 16-2)	Laparoscopic Extended Radical Resection of Right Colon Cancer	1	0	0
23	Control Group 1	Laparoscopic Left Hemi-Colectomy	39	41	0.19

24	Control Group 2	Laparoscopic Right Colectomy	21	10	0.33
25	Control Group 3	Laparoscopic Radical Resection of Right Colon Cancer	26	12	0.25
26	Control Group 4	Single-Port Laparoscopic-Assisted Radical Resection of Sigmoid Colon Cancer	15	21	2.48
27	Control Group 5	Laparoscopic Extended Radical Resection of Right Colon Cancer	35	14	0.17

[0139] Note: The biological patches obtained in each example were numbered 1–10 respectively; "Test Group 1 (Example 1-1)" means that Test Group 1 used Patch No. 1 obtained in Example 1; "Test Group 2 (Example 1-2)" means that Test Group 2 used Patch No. 2 obtained in Example 1.

[0140] The experimental results in Table 7 show that when comparing Test Group 9 (Example 9-1), Test Group 10 (Example 9-2), Test Group 3 (Example 5-1) and Test Group 4 (Example 5-2), it is found that the elastic deformation rate of the biological patch obtained in Example 5 (13.7±0.3%) is similar to that of the biological patch obtained in Example 9 (13.9±1.1%), but Test Group 9 (Example 9-1) and Test Group 10 (Example 9-2) had more bleeding points requiring clinical hemostasis and/or pulsatile bleeding points. Therefore, the inventors speculate that the reason for the bleeding points is not only the small elastic deformation rate.

[0141] Through further comparison, the inventors unexpectedly found that the ratio of elastic deformation rate to maximum tensile elongation of the biological patch obtained in Example 5 is larger than that of the biological patch obtained in Example 9. The inventors speculate that there is a certain correlation between the ratio of elastic deformation rate to maximum tensile elongation and clinical results, which will be further verified in clinical experiments. Based on Example 13 (the ratio of elastic deformation rate to maximum tensile elongation is 39%), the ratio of elastic deformation rate to maximum tensile elongation for colon surgery is boldly set to be not less than 39%.

Table 8 The Ratio of Elastic Deformation Rate to Maximum Tensile Elongation of Biological Patches Obtained in Examples 1-17

No.	Group	Ratio of Elastic Deformation Rate to Maximum Tensile Elongation	Maximum Tensile Elongation	Elastic Deformation Rate
1	Example 1	88%	44.6±0.3%	39.1±0.4%
2	Example 2	44%	14.8±0.5%	6.5±0.1%
3	Example 3	20%	21.7±0.1%	4.4±0.7%
4	Example 4	29%	18.2±1.1%	5.2±0.1%
5	Example 5	89%	15.4±0.2%	13.7±0.1%
6	Example 6	26%	29.8±1.5%	7.6±0.2%

7	Example 7	56%	27.2±0.3%	15.2±1.7%
8	Example 8	61%	35.5±1.6%	21.5±2.4%
9	Example 9	33%	42.4±1.5%	13.9±2.5%
10	Example 10	25%	40.1±0.2%	10.2±1.3%
11	Example 11	72%	25.9±2.4%	18.7±0.4%
12	Example 12	83%	33.2±3.1%	27.4±2.5%
13	Example 13	39%	41.5±1.3%	16.1±1.2%
14	Example 14	50%	39.4±1.2%	19.8±0.9%
15	Example 15	77%	30.7±0.2%	23.5±0.3%
16	Example 16	56%	26.3±0.3%	14.6±1.6%
17	Example 17	74%	11.1±0.4%	8.2±0.4%

[0142] The range of the ratio of elastic deformation rate to maximum tensile elongation of the biological patches obtained in Examples 1-17 is: 20-89%.

Table 9 Bleeding Point Records in Rectal Surgery

No.	Group	Surgery Involved	Number of Bleeding Points Requiring Clinical Hemostasis	Number of Pulsatile Bleeding Points	Number of Bleeding Points per Unit Length of Anastomotic/Closed Stoma (n/cm)
1	Test Group 1 (Example 1-3)	SILS+1 Laparoscopic Radical Resection of Rectal Cancer	0	0	0
2	Test Group 2 (Example 1-4)	Laparoscopic Radical Resection of Rectal Cancer	1	0	0
3	Test Group 3 (Example 5-3)	Laparoscopic Radical Resection of Rectal Cancer	22	16	0.15
4	Test Group 4 (Example 5-4)	Laparoscopic Anterior Resection of Rectal Cancer	13	7	0.19
5	Test Group 5 (Example 7-3)	Resection of Rectal Blind End	0	1	0
6	Test Group 6 (Example 7-4)	Rectal Tumor Resection	1	0	0
7	Test Group 7 (Example 8-3)	Laparoscopic Radical Resection of Rectal Cancer	0	0	0

8	Test Group 8 (Example 8-4)	Resection of Rectal Blind End	1	0	0
9	Test Group 9 (Example 9-3)	Laparoscopic Radical Resection of Rectal Cancer	18	1	0
10	Test Group 10 (Example 9-4)	Rectal Tumor Resection	21	2	0.11
11	Test Group 11 (Example 11-3)	Rectal Tumor Resection	0	0	0
12	Test Group 12 (Example 11-4)	SILS+1 Laparoscopic Radical Resection of Rectal Cancer	0	0	0
13	Test Group 13 (Example 12-3)	Laparoscopic Extended Radical Resection of Right Colon Cancer	0	0	0
14	Test Group 14 (Example 12-4)	Laparoscopic Extended Radical Resection of Right Colon Cancer	0	0	0
15	Test Group 15 (Example 13-3)	Laparoscopic Radical Resection of Transverse Colon Cancer	0	1	0
16	Test Group 16 (Example 13-4)	Laparoscopic Radical Resection of Transverse Colon Cancer	0	1	0
17	Test Group 17 (Example 14-3)	Laparoscopic Radical Resection of Right Colon Cancer	0	0	0
18	Test Group 18 (Example 14-4)	Laparoscopic Radical Resection of Right Colon Cancer	0	0	0
19	Test Group 19 (Example 15-3)	Laparoscopic Extended Radical Resection of Right Colon Cancer	0	1	0
20	Test Group 20 (Example 15-4)	SILS+1 Laparoscopic Radical Resection of Rectal Cancer	1	0	0
21	Test Group 21 (Example 16-3)	Laparoscopic Extended Radical Resection of Right Colon Cancer	0	0	0

22	Test Group 22 (Example 16-4)	Laparoscopic Extended Radical Resection of Right Colon Cancer	1	0	0
23	Control Group 1	Laparoscopic Left Hemi-Colectomy	39	41	0.19
24	Control Group 2	Laparoscopic Right Colectomy	21	10	0.33
25	Control Group 3	Laparoscopic Radical Resection of Right Colon Cancer	26	12	0.25
26	Control Group 4	Single-Port Laparoscopic-Assisted Radical Resection of Rectal Cancer	15	21	2.48
27	Control Group 5	Laparoscopic Extended Radical Resection of Right Colon Cancer	35	14	0.17

[0143] The experimental results in Table 9 show that Test Group 3 (Example 5-3), Test Group 4 (Example 5-4), Test Group 9 (Example 9-3), Test Group 10 (Example 9-4), Test Group 15 (Example 13-3), and Test Group 16 (Example 13-4) exhibited a relatively large number of bleeding points requiring clinical hemostasis and/or pulsatile bleeding points.

[0144] Based on the conclusions from colon surgery, the inventors speculate that the large number of bleeding points requiring clinical hemostasis and/or pulsatile bleeding points in Test Group 3 (Example 5-3) and Test Group 4 (Example 5-4) were due to the low elastic deformation rate of the obtained biological patches, whereas the high number of such bleeding points in Test Group 15 (Example 13-3) and Test Group 16 (Example 13-4) was attributed to the small ratio of elastic deformation rate to maximum tensile elongation of the obtained biological patches.

[0145] The high number of bleeding points requiring clinical hemostasis and/or pulsatile bleeding points in Test Group 9 (Example 9-3) and Test Group 10 (Example 9-4) may be caused by either the low elastic deformation rate or the small ratio of elastic deformation rate to maximum tensile elongation of the obtained biological patches.

[0146] The clinical trial of rectal surgery further verified the correlation between the ratio of elastic deformation rate to maximum tensile elongation and bleeding or exudation of the biological patch.

[0147] Since the ratio of elastic deformation rate to maximum tensile elongation of the biological patch obtained in Example 14 is 50%, the elastic deformation rate of the biological patch should be controlled within the range of 14.6–39.1% and the ratio of elastic deformation rate to maximum tensile elongation should be no less than 50% for rectal surgery.

Table 10 Bleeding Point Records in Ileal Surgery

No.	Group	Surgery Involved	Number of Bleeding Points Requiring Clinical Hemostasis	Number of Pulsatile Bleeding Points	Number of Bleeding Points per Unit Length of Anastomotic/Closed Stoma (n/cm)
1	Test Group 1 (Example 1-5)	Ileal Partial Resection	0	0	0

2	Test Group 2 (Example 1-6)	Laparoscopic Abdominal Stoma Reversal + Ileal Partial Resection	0	1	0
3	Test Group 3 (Example 5-5)	Ileal Partial Resection	0	0	0
4	Test Group 4 (Example 5-6)	Laparoscopic Abdominal Stoma Reversal + Ileal Partial Resection	0	0	0
5	Test Group 5 (Example 7-5)	Laparoscopic Abdominal Stoma Reversal + Ileal Partial Resection	0	1	0
6	Test Group 6 (Example 7-6)	Laparoscopic Ileal Stoma Reversal + Ileal Partial Resection	1	0	0
7	Test Group 7 (Example 8-5)	Laparoscopic Ileal Stoma Reversal + Ileal Partial Resection	0	0	0.1
8	Test Group 8 (Example 8-6)	Laparoscopic Ileal Stoma Reversal	0	0	0
9	Test Group 9 (Example 9-5)	Laparoscopic Ileal Stoma Reversal	13	7	0.32
10	Test Group 10 (Example 9-6)	Ileal Partial Resection	18	0	0.19
11	Test Group 11 (Example 11-5)	Laparoscopic Ileal Stoma Reversal	0	0	0.13
12	Test Group 12 (Example 11-6)	Ileal Partial Resection	4	1	0.53
13	Test Group 13 (Example 12-5)	Laparoscopic Abdominal Stoma Reversal + Ileal Partial Resection	0	0	0
14	Test Group 14 (Example 12-6)	Laparoscopic Ileal Stoma Reversal	0	0	0
15	Test Group 15 (Example 13-5)	Laparoscopic Ileal Stoma Reversal	0	0	0
16	Test Group 16 (Example 13-6)	Ileal Partial Resection	1	0	0
17	Test Group 17 (Example 14-5)	Laparoscopic Abdominal Stoma Reversal + Ileal Partial Resection	0	2	0

18	Test Group 18 (Example 14-6)	Ileal Partial Resection	0	0	0
19	Test Group 19 (Example 15-5)	Laparoscopic Abdominal Stoma Reversal + Ileal Partial Resection	1	1	0
20	Test Group 20 (Example 15-6)	Ileal Partial Resection	0	0	0
21	Test Group 21 (Example 16-5)	Laparoscopic Ileal Stoma Reversal	0	0	0
22	Test Group 22 (Example 16-6)	Ileal Partial Resection	0	0	0
23	Control Group 9	Laparoscopic Ileal Stoma Reversal	14	1	0.06
24	Control Group 10	Ileal Partial Resection	21	1	0.1
25	Control Group 11	Laparoscopic Ileal Stoma Reversal	7	16	0.25

[0148] It can be seen from Table 10 that during ileal surgery, Test Group 9 (Example 9-5) and Test Group 10 (Example 9-6) exhibited a relatively large number of bleeding points requiring clinical hemostasis. The presumed reason is that the ratio of elastic deformation rate to maximum tensile elongation of the biological patch obtained in Example 9 was relatively low. Therefore, for ileal surgery, the elastic deformation rate of the biological patch should be controlled within the range of 13.7–39.1%, and the ratio of elastic deformation rate to maximum tensile elongation should be no less than 39%.

Table 11 Bleeding Point Records in Duodenal Surgery

No.	Group	Surgery Involved	Number of Bleeding Points Requiring Clinical Hemostasis	Number of Pulsatile Bleeding Points	Number of Bleeding Points per Unit Length of Anastomotic/Closed Stoma (n/cm)
1	Test Group 1 (Example 1-7)	Laparoscopic Pancreaticoduodenectomy	0	0	0
2	Test Group 2 (Example 1-8)	Laparoscopic Pancreaticoduodenectomy	0	0	0
3	Test Group 3 (Example 5-7)	Laparoscopic Pancreaticoduodenectomy	1	0	0
4	Test Group 4 (Example 5-8)	Duodenal Tumor Resection	0	0	0
5	Test Group 5 (Example 7-7)	Laparoscopic Pancreaticoduodenectomy	0	1	0
6	Test Group 6 (Example 7-8)	Laparoscopic Pancreaticoduodenectomy	1	0	0.08
7	Test Group 7 (Example 8-7)	Duodenal Tumor Resection	0	0	0

8	Test Group 8 (Example 8-8)	Duodenal Tumor Resection	0	0	0
9	Test Group 9 (Example 9-7)	Duodenal Tumor Resection	29	8	2.75
10	Test Group 10 (Example 9-8)	Laparoscopic Pancreaticoduodenectomy	31	1	0.36
11	Test Group 11 (Example 11-7)	Laparoscopic Pancreaticoduodenectomy	5	0	0.31
12	Test Group 12 (Example 11-8)	Laparoscopic Pancreaticoduodenectomy	0	0	0
13	Test Group 13 (Example 12-7)	Laparoscopic Pancreaticoduodenectomy	0	0	0
14	Test Group 14 (Example 12-8)	Duodenal Tumor Resection	0	0	0
15	Test Group 15 (Example 13-7)	Laparoscopic Pancreaticoduodenectomy	22	0	0
16	Test Group 16 (Example 13-8)	Laparoscopic Pancreaticoduodenectomy	17	10	0.39
17	Test Group 17 (Example 14-7)	Laparoscopic Pancreaticoduodenectomy	0	0	0
18	Test Group 18 (Example 14-8)	Duodenal Tumor Resection	0	0	0
19	Test Group 19 (Example 15-7)	Laparoscopic Pancreaticoduodenectomy	0	0	0
20	Test Group 20 (Example 15-8)	Duodenal Tumor Resection	0	0	0
21	Test Group 21 (Example 16-7)	Laparoscopic Pancreaticoduodenectomy	0	0	0
22	Test Group 22 (Example 16-8)	Laparoscopic Pancreaticoduodenectomy	0	0	0
23	Control Group 12	Duodenal Tumor Resection	15	8	0.38
24	Control Group 13	Laparoscopic Pancreaticoduodenectomy	24	4	3.21
25	Control Group 14	Laparoscopic Pancreaticoduodenectomy	31	1	0.38

[0149] The experimental results in Table 11 show that Test Group 9 (Example 9-5), Test Group 10 (Example 9-6), Test Group 15 (Example 13-7), and Test Group 16 (Example 13-8) exhibited a relatively large number of bleeding points requiring clinical hemostasis and/or pulsatile bleeding points. Therefore, a preliminary conclusion is drawn that for duodenal surgery, the elastic deformation rate of the biological patch should be controlled within the range of 13.7–39.1%, and the ratio of elastic deformation rate to maximum tensile elongation should be no less than 50%.

Table 12 Bleeding Point Records in Gastric Surgery

No.	Group	Surgery Involved	Number of Bleeding Points Requiring Clinical Hemostasis	Number of Pulsatile Bleeding Points	Number of Bleeding Points per Unit Length of Anastomotic/Closed Stoma (n/cm)
1	Test Group 1 (Example 1-9)	Laparoscopic Sleeve Gastrectomy	12	3	0.11
2	Test Group 2 (Example 1-10)	Laparoscopic Radical Gastrectomy + Roux-en-Y Gastrojejunostomy	10	0	1.16
3	Test Group 3 (Example 5-9)	Laparoscopic Distal Gastrectomy + Roux-en-Y Gastrojejunostomy	14	19	0.59
4	Test Group 4 (Example 5-10)	Distal Gastrectomy + Antecolic Roux-en-Y Gastrojejunostomy	13	6	3.23
5	Test Group 5 (Example 7-9)	Laparoscopic Distal Gastrectomy + Retrocolic Billroth II Gastrojejunostomy	0	3	0
6	Test Group 6 (Example 7-10)	Laparoscopic Radical Gastrectomy + Roux-en-Y Gastrojejunostomy	0	0	0
7	Test Group 7 (Example 8-9)	Distal Gastrectomy + Retrocolic Roux-en-Y Gastrojejunostomy	1	0	0
8	Test Group 8 (Example 8-10)	Laparoscopic Distal Gastrectomy	0	0	0
9	Test Group 9 (Example 9-9)	Laparoscopic Subtotal Gastrectomy + Gastrojejunostomy	9	16	0.73
10	Test Group 10 (Example 9-10)	Laparoscopic Distal Gastrectomy	26	4	1.08
11	Test Group 11 (Example 11-9)	Naked 3D Distal Gastrectomy + Total Intracorporeal Antecolic Roux-en-Y Gastrojejunostomy	3	0	0.06
12	Test Group 12 (Example 11-10)	Laparoscopic Distal Gastrectomy	0	0	0
13	Test Group 13 (Example 12-9)	Laparoscopic Distal Gastrectomy + Total Intracorporeal Retrocolic Roux-en-Y Gastrojejunostomy	2	0	0
14	Test Group 14 (Example 12-10)	Laparoscopic Distal Gastrectomy	0	0	0
15	Test Group 15	Laparoscopic Radical	27	0	0.22

No.	Group	Surgery Involved	Number of Bleeding Points Requiring Clinical Hemostasis	Number of Pulsatile Bleeding Points	Number of Bleeding Points per Unit Length of Anastomotic/Closed Stoma (n/cm)
	(Example 13-9)	Gastrectomy + Roux-en-Y Gastrojejunostomy			
16	Test Group 16 (Example 13-10)	Laparoscopic Distal Gastrectomy	31	0	1.85
17	Test Group 17 (Example 14-9)	4K 3D Naked-Eye Laparoscopic Distal Subtotal Gastrectomy + Roux-en-Y Gastrojejunostomy	17	2	0.34
18	Test Group 18 (Example 14-10)	Laparoscopic Distal Gastrectomy	22	0	0.26
19	Test Group 19 (Example 15-9)	Laparoscopic Distal Gastrectomy	1	0	0
20	Test Group 20 (Example 15-10)	Laparoscopic Radical Gastrectomy + Roux-en-Y Gastrojejunostomy	0	0	0
21	Test Group 21 (Example 16-9)	Laparoscopic Distal Gastrectomy	1	0	0
22	Test Group 22 (Example 16-10)	Laparoscopic Radical Gastrectomy + Roux-en-Y Gastrojejunostomy	0	0	0
23	Control Group 15	Laparoscopic Radical Gastrectomy + Roux-en-Y Gastrojejunostomy	18	3	0.14
24	Control Group 16	Laparoscopic Distal Gastrectomy + Roux-en-Y Gastrojejunostomy	13	0	0.68
25	Control Group 17	Laparoscopic Distal Gastrectomy + Retrocolic Roux-en-Y Gastrojejunostomy	21	4	0.09
26	Control Group 18	Laparoscopic Distal Gastrectomy + Billroth II Gastrojejunostomy	20	7	1.49
27	Control Group 19	Laparoscopic Distal Gastrectomy + Roux-en-Y Gastrojejunostomy	43	21	0.22

[0150] The nail holes and suture sites of the biological patches in Test Group 1 (Example 1-9), Test Group 2 (Example 1-10), Test Group 9 (Example 9-9), and Test Group 10 (Example 9-10) exhibited tearing, and bleeding and exudation occurred at the anastomotic stoma. The tearing worsened over time. However, no obvious tearing was observed in the biological patches of Test Group 3 (Example 5-9) and Test Group 4 (Example 5-10). Therefore, the inventors speculate that for gastric surgery, the single-suture pulling force

of the biological patch should be controlled to be no less than 19.7 N.

[0151] It can be seen from Table 12 that Test Group 3 (Example 5-9), Test Group 4 (Example 5-10), Test Group 9 (Example 9-9), Test Group 10 (Example 9-10), Test Group 15 (Example 13-9), Test Group 16 (Example 13-10), Test Group 17 (Example 14-9), and Test Group 18 (Example 14-10) exhibited a relatively large number of bleeding points requiring clinical hemostasis and/or pulsatile bleeding points. The presumed reasons are as follows: The biological patch obtained in Example 5 had a low elastic deformation rate. The biological patches obtained in Example 13 and Example 14 had a small ratio of elastic deformation rate to maximum tensile elongation. The biological patch obtained in Example 9 had either a low elastic deformation rate or a small ratio of elastic deformation rate to maximum tensile elongation.

[0152] Accordingly, a preliminary conclusion can be drawn that for gastric surgery, the single-suture pulling force of the biological patch should be no less than 19.7 N, the elastic deformation rate should be controlled within 14.6–39.1%, and the ratio of elastic deformation rate to maximum tensile elongation should be no less than 56%.

[0153] (3) Mechanical Parameters of Biological Patches Required for Different Digestive Surgery Sites

Table 13: Mechanical Parameters of Biological Patches for Surgery at Different Sites

Surgical Site	Maximum Tensile Elongation Range	Elastic Deformation Rate Range	Ratio of Elastic Deformation Rate to Maximum Tensile Elongation	Single-suture Tensile Force
Colon, Ileum	14.8-44.6%	13.7-39.1%	39-89%	15.6-54.1 N
Rectum	14.8-44.6%	14.6-39.1%	50-89%	15.6-54.1 N
Duodenum	14.8-44.6%	13.7-39.1%	50-89%	15.6-54.1 N
Stomach	14.8-44.6%	14.6-39.1%	56-89%	19.7-54.1 N
General for All Sites	14.8-44.6%	14.6-39.1%	56-89%	19.7-54.1 N

[0154] Based on the above clinical trial results, the biological patch prepared with maximum tensile elongation of 14.8-44.6%, elastic deformation rate of 14.6-39.1%, ratio of elastic deformation rate to maximum tensile elongation of 56-89%, and single-suture tensile force of 19.7-54.1 N is suitable for digestive surgery including colon, rectum, ileum, duodenum and stomach.

[0155] VI. Clinical Trial II

[0156] (1) Biological patches with the following parameters were obtained by adjusting the preparation method:

Table 14: Biomechanical Parameters of Examples 18-20

Group	Maximum Tensile Elongation	Elastic Deformation Rate	Ratio of Elastic Deformation Rate to Maximum Tensile Elongation	Single-suture Tensile Force
Example 18	43.4±0.3%	16.5±0.1%	38%	26.3±0.1 N
Example 19	43.6±0.1%	15.9±0.4%	36%	21.8±0.3 N
Example 20	35.1±0.5%	16.7±0.1%	48%	34.5±0.1 N

Table 15: Main Differences in Preparation Methods of Examples 18-20

Condition/Group	First Water Bath Shaking Condition	10% $NaHCO_3$ Concentration and pH Increase Unit	Second Water Bath Shaking Condition	Normal Saline Rinsing Time	Glutaraldehyde Solution Concentration and Soaking Time
Example 18	42°C, 4 h	0.5 pH	46°C, 110 min	120 min	0.5%, 3.5 h
Example 19	41°C, 4 h	0.3 pH	45°C, 100 min	90 min	0.9%, 3.5 h
Example 20	42°C, 4 h	0.4 pH	44°C, 110 min	80 min	0.9%, 3.5 h

[0157] On the basis of Clinical Trial I, 88 more patients were enrolled to further verify the influence of

the ratio of elastic deformation rate to maximum tensile elongation on the clinical application effect.

Table 16: Trial Results of Clinical Trial II

Group	Colon Surgery	Rectal Surgery	Ileal Surgery	Duodenal Surgery	Gastric Surgery	Total Cases
Example 18	1/2	2/2	1/1	4/5	7/10	15/20
Example 19	6/7	3/4	3/5	2/3	8/10	22/29
Example 20	0/10	3/5	0/8	4/6	7/10	14/39

[0158] Note: The number before "/" is the number of cases with bleeding points requiring clinical hemostasis treatment or pulsatile bleeding points > 5. If the number of bleeding points requiring clinical hemostasis treatment and pulsatile bleeding points in the same patient are both > 5, it is counted as 1 case; the number after "/" is the total number of patients.

[0159] The ratios of elastic deformation rate to maximum tensile elongation of the biological patches obtained in Examples 18 and 19 are lower than the requirements obtained in Clinical Trial I. It can be seen that the number of cases with bleeding points requiring clinical hemostasis treatment or pulsatile bleeding points > 5 in digestive surgery at different sites is large. The ratio of elastic deformation rate to maximum tensile elongation of the biological patch obtained in Example 20 only meets the requirements of colon and ileum surgery. It can be seen that the number of cases with bleeding points requiring clinical hemostasis treatment or pulsatile bleeding points > 5 in patients undergoing colon and ileum surgery is significantly reduced, while the number of such cases in patients undergoing rectal, duodenal and gastric surgery is large.

[0160] Table 16 further proves that the ratio of elastic deformation rate to maximum tensile elongation is indeed related to the bleeding or fluid exudation of the biological patch. Too small elastic deformation rate and maximum tensile elongation will increase the incidence of complications such as anastomotic bleeding and fluid exudation.

[0161] The preferred specific embodiments of the present invention are described in detail above. It should be understood that those skilled in the art can make many modifications and changes according to the concept of the present invention without creative work. Therefore, all technical solutions obtained by those skilled in the art through logical analysis, reasoning or limited experiments based on the concept of the present invention and the prior art shall fall within the protection scope determined by the claims.

CLAIMS

What is claimed is:

1. A biological patch for digestive surgery, characterized in that a maximum tensile elongation of the biological patch is not less than 14.8%, an elastic deformation rate is not less than 13.7%, and a single-suture tensile force is greater than 15.6 N.

2. The biological patch for digestive surgery according to claim 1, characterized in that the biological patch has a maximum tensile elongation of 14.8-44.6%, an elastic deformation rate of 13.7-39.1%, a single-suture tensile force of 15.6-54.1 N, and a ratio of the elastic deformation rate to the maximum tensile elongation is 39-89%.

3. The biological patch for digestive surgery according to claim 1, characterized in that the biological patch has a maximum tensile elongation of 14.8-44.6%, an elastic deformation rate of 14.6-39.1%, a single-suture tensile force of 15.6-54.1 N, and a ratio of the elastic deformation rate to the maximum tensile elongation is 50-89%.

4. The biological patch for digestive surgery according to claim 1, characterized in that the biological patch has a maximum tensile elongation of 14.8-44.6%, an elastic deformation rate of 13.7-39.1%, a single-suture tensile force of 15.6-54.1 N, and a ratio of the elastic deformation rate to the maximum tensile elongation is 50-89%.

5. The biological patch for digestive surgery according to claim 1, characterized in that the biological patch has a maximum tensile elongation of 14.8-44.6%, an elastic deformation rate of 14.6-39.1%, a single-suture tensile force of 19.7-54.1 N, and a ratio of the elastic deformation rate to the maximum tensile elongation is 56-89%.

6. The biological patch for digestive surgery according to claim 2, characterized in that the biological patch for digestive surgery is a biological patch for colon or ileum surgery.

7. The biological patch for digestive surgery according to claim 3, characterized in that the biological patch for digestive surgery is a biological patch for rectal surgery.

8. The biological patch for digestive surgery according to claim 4, characterized in that the biological patch for digestive surgery is a biological patch for duodenal surgery.

9. The biological patch for digestive surgery according to claim 5, characterized in that the biological patch for digestive surgery is a biological patch for gastric surgery.

10. The biological patch for digestive surgery according to any one of claims 1-9, characterized in that the biological patch for digestive surgery is a bovine pericardium-derived biological patch.

11. The biological patch for digestive surgery according to any one of claims 1-9, characterized in that the biological patch for digestive surgery is provided with two perforations, and the two perforations are located at opposite ends of the biological patch.

12. An anastomosis device kit comprising the biological patch for digestive surgery according to any one of claims 1-9.

13. A method for preparing the biological patch for digestive surgery according to any one of claims 1-9, characterized by comprising the following steps:

(1) Soaking healthy bovine pericardium sheet tissue in hypotonic Hank's solution, and rinsing repeatedly with fresh hypotonic Hank's solution for multiple times to fully swell and break various cells present in the tissue;

(2) Rinsing the treated tissue sheet repeatedly with normal saline for 60-120 minutes each time, replacing the normal saline each time, until no visible cells, cell components or cell debris are observed under a microscope, and quantitative determination of proteins and nucleic acids shows no detectable soluble proteins and nucleic acids;

(3) Removing phospholipids, non-structural proteins and immunogenic molecules such as hyaluronic acid, chondroitin sulfates and mucopolysaccharides in the tissue sheet with Tween 80 surfactant solution;

(4) Soaking in 0.5-1.5% glutaraldehyde solution for 3-3.5 hours; and

(5) Placing the pretreated tissue material in a chromium hydroxide solution with a Cr^{3+} ion

concentration of 0.0625 mol/dm³ and an OH/Cr ratio of 0.5, and shaking in a water bath at 35-42°C for 3.5-5 hours; detecting the pH of the material treatment solution and raising the pH by 0.3-0.5 units with 10% $NaHCO_3$, then shaking in a water bath at 40-46°C for 60 minutes.