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(54) Title: BIOLOGICAL TISSUE-REINFORCING MATERIAL

(57) Abstract: Provided is a biological tissue-reinforcing material capable of more reliably reinforcing weakened tissue while preventing air leakage and fluid leakage without using fibrin glue, which is a blood product. Provided is a biological tissue-reinforcing material comprising a laminated structure, the laminated structure comprising: a fiber structure made of a bioabsorbable polymer; and a fiber structure made of etherified cellulose that is produced through etherification of hydroxyl groups of cellulose.



DESCRIPTION

BIOLOGICAL TISSUE-REINFORCING MATERIAL

5 TECHNICAL FIELD

[0001]

The present invention relates to a biological tissue-reinforcing material capable of more reliably reinforcing weakened tissue while preventing air leakage or fluid leakage without using fibrin glue, which is a blood product.

BACKGROUND ART

[0002]

15 The most fundamental issue in the field of surgery is to repair a damaged or weakened organ or tissue. For example, bleeding of a damaged organ is still treated by stopping bleeding and suturing the wound, which is the most commonly used surgical procedure to stop bleeding even now. Furthermore, another important issue in the surgical treatment is to prevent fluid leakage or air leakage from weakened or damaged tissue. Particularly in the field of chest surgery, it is important to prevent air leakage due to pneumothorax or after resection of lung cancer. In particular, pneumothorax is a disease that is difficult to treat because the recurrence rate is increased without appropriate treatment.

[0003]

Pneumothorax often occurs due to air leakage into a thoracic cavity from a stump or suture site of the lung after resection, a site of the lung after partial resection to remove lung cancer, or a damaged site of lung tissue due to injury; or air leakage into a thoracic cavity from a tear of cysts (referred to bullae) which are transformed from some alveoli. Such leakage has been treated by pleurodesis in which lung tissue is allowed to adhere to pleura with drugs or by artificial

chemical burns. Pleurodesis can prevent recurrence of pneumothorax to some extent. However, if lung tissue does not tightly adhere to pleura, the recurrence rate is increased. If further surgery is needed, adhesion between lung tissue and parietal pleura needs to be removed, which prolongs a surgical time or causes bleeding during removal of the adhesion. Therefore, new treatment alternative to pleurodesis has been investigated.

Furthermore, an important issue in the field of digestive surgery is to prevent leakage of pancreatic juice from a stump of the pancreas after partial pancreatectomy. Pancreatic juice dissolves granulation tissue that is responsible for wound healing, and prevents the growth of the tissue, leading to difficulty in regeneration of pancreatic tissue.

Furthermore, it is concerned that leakage of pancreatic juice digests blood vessels to possibly cause postoperative hemorrhage, which is a life-threatening complication.

[0004]

For such a situation, fibrin glue and a fiber structure made of a bioabsorbable polymer have been used in combination to reinforce lung tissue and seal the surface of the lung. Non-Patent Literatures 1 to 4 suggest that this method more reduces the recurrence rate of pneumothorax than usual pleurodesis. Non-Patent Literature 5 suggests that such a method is also used to prevent bleeding after liver resection in the field of digestive surgery.

[0005]

Use of fibrin glue and a fiber structure made of a bioabsorbable polymer in combination is remarkably effective to reinforce weakened tissue. However, air leakage or fluid leakage may occur even at a reinforced area, which may give rise to the need of further surgery. The incidence of such a case is not high, but leakage may become a risk factor to cause severe symptoms. Therefore, a reliable method of reinforcement has been needed. Further, fibrin glue, which is a blood product,

may lead to unknown viral infection.

CITATION LIST

- Non-Patent Literature

5 [0006]

Non-Patent Literature 1: J. Pediatric Surg, 42, 1225-1230
(2007)

Non-Patent Literature 2: Interact. Cardiovasc. Thorac. Surg,
6, 12-15 (2007)

10 Non-Patent Literature 3: The Journal of the Japanese
Association for Chest Surgery, 19(4), 628-630 (2005)

Non-Patent Literature 4: The Journal of the Japanese
Association for Chest Surgery, 22(2), 142-145 (2008)

15 Non-Patent Literature 5: The Japanese Journal of Clinical and
Experimental Medicine, 84, 148 (2007)

SUMMARY OF INVENTION

- Technical Problem

[0007]

20 It is an object of the present invention to provide a
biological tissue-reinforcing material capable of more
reliably reinforcing weakened tissue while preventing air
leakage and fluid leakage without using fibrin glue, which is
a blood product.

25

- Solution to Problem

[0008]

The present invention is a biological tissue-reinforcing
material comprising a laminated structure, the laminated
30 structure comprising: a fiber structure made of a bioabsorbable
polymer; and a fiber structure made of etherified cellulose that
is produced through etherification of hydroxy groups of
cellulose.

The present invention is described in detail below.

35 [0009]

The present inventors have researched the cause of air leakage or fluid leakage from a reinforced area of biological tissue reinforced using fibrin glue and a fiber structure made of a bioabsorbable polymer in combination, and found that the cause of the leakage is in an adhesion area with fibrin glue. Fibrin glue, which gels in a short time, is very useful as biological glue. However, since fibrin glue in the form of a gel is relatively hard, cohesive failure or interfacial peeling is likely to occur due to impact. In particular, in cases where fibrin glue is used to reinforce lung tissue, cohesive failure or interfacial peeling presumably occurs by a very high pressure applied to lung tissue by coughing or sneezing. Gelled fibrin glue once separated cannot adhere again because of its less adhesion. Air leakage or fluid leakage presumably occurs at such a separation area.

[0010]

The present inventors have further made various studies, and have found that use of etherified cellulose produced through etherification of hydroxy groups of cellulose (hereinafter, also referred to as "etherified cellulose") instead of fibrin glue allows more reliable reinforcement of weakened tissue, and gives a biological tissue-reinforcing material that causes no air leakage or fluid leakage. As a result, the present invention has been completed.

Etherified cellulose is a compound proven to be highly safe, and gels in a short time like fibrin glue to act as glue to attach a fiber structure made of a bioabsorbable polymer to biological tissue. Further, since gelled etherified cellulose has a certain level of adhesive force, even if cohesive failure or interfacial peeling occurs due to high pressure, the etherified cellulose can adhere again to prevent air leakage or fluid leakage. Further, since etherified cellulose can be processed into fiber, a laminated structure preliminary made by laminating a fiber structure made of such etherified cellulose on a fiber structure made of a bioabsorbable polymer

can provide a biological tissue-reinforcing material remarkably easy to use.

[0011]

The biological tissue-reinforcing material of the present invention has a laminated structure that includes a fiber structure made of a bioabsorbable polymer and a fiber structure made of etherified cellulose.

The fiber structure made of a bioabsorbable polymer is designed to show a tissue reinforcement effect, an air leakage prevention effect, and a fluid leakage prevention effect when it is attached to a damaged or weakened organ. The fiber structure made of etherified cellulose absorbs moisture to gel, and acts as glue to attach the fiber structure made of a bioabsorbable polymer to biological tissue.

[0012]

Examples of the bioabsorbable polymers include, but are not particularly limited to, synthetic absorbable polymers such as a α -hydroxy acid polymer (e.g. polyglycolide, polylactide (D, L, DL isomer), glycolide-lactide (D, L, DL isomer) copolymers, glycolide- ϵ -caprolactone copolymers, lactide (D, L, DL isomer)- ϵ -caprolactone copolymers, poly(p-dioxanone), and glycolide-lactide (D, L, DL isomer)- ϵ -caprolactone copolymers); and natural absorbable polymers such as collagen, gelatin, chitosan, or chitin. Any of these may be used alone, or two or more of these may be used in combination. For example, in cases where the synthetic absorbable polymer is used as the bioabsorbable material, a natural absorbable polymer may be used together therewith. In particular, a α -hydroxy acid polymer which is a homopolymer or copolymer of at least one monomer selected from the group consisting of glycolide, lactide, ϵ -caprolactone, dioxanone, and trimethylene carbonate is preferred because of its high strength. A α -hydroxy acid polymer which is a homopolymer or copolymer of a monomer containing glycolide is more preferred because the polymer shows appropriate decomposition behavior.

[0013]

In cases where polyglycolide (homopolymer or copolymer of glycolide) is used as the bioabsorbable material, the preferable lower limit of a weight average molecular weight of the polyglycolide is 30000, and the preferable upper limit thereof is 1000000. Polyglycolide having the weight average molecular weight of less than 30000 is poor in strength and may not impart a sufficient tissue reinforcement effect.

Polyglycolide having the weight average molecular weight of more than 1000000 slowly decomposes in the body and therefore may lead to a foreign-body reaction. The more preferable lower limit of the weight average molecular weight of the polyglycolide is 50000, and the more preferable upper limit thereof is 300000.

15 [0014]

The fiber structure made of the bioabsorbable polymer may be in any form, and may be in the form of a non-woven fabric, a knitted fabric, a woven fabric, gauze, or yarn. In addition, these forms may be combined one another. In particular, a non-woven fabric is preferred.

[0015]

In cases where the fiber structure made of the bioabsorbable polymer is in the form of a non-woven fabric, the weight per unit area of the non-woven fabric is not particularly limited, and the preferable lower limit is 5 g/m², and the preferable upper limit is 300 g/m². A non-woven fabric having a weight per unit area of less than 5 g/m² has strength not enough for a biological tissue-reinforcing material, and may not reinforce weakened tissue. A non-woven fabric having a weight per unit area of more than 300 g/m² may poorly adhere to tissue. The more preferable lower limit of the weight per unit area of the non-woven fabric is 10 g/m², and the more preferable upper limit thereof is 100 g/m².

[0016]

35 The non-woven fabric may be produced by any method, and

examples of the method include conventionally known methods such as electro spinning deposition, melt blowing, needle punching, spun bonding, flash spinning, hydroentanglement, air laying, thermal bonding, resin bonding, or wet processing.

5 [0017]

The fiber structure made of the bioabsorbable polymer may be subjected to hydrophilization. The fiber structure subjected to hydrophilization rapidly absorbs moisture such as normal saline in contact with the structure, and is therefore
10 easily used.

Examples of the hydrophilization include, but are not particularly limited to, plasma treatment, glow discharge treatment, corona discharge treatment, ozone treatment, surface graft treatment, ultraviolet irradiation treatment,
15 and the like. In particular, plasma treatment is preferred because it remarkably increases the water absorption rate without changing the outward appearance of the non-woven fabric.

[0018]

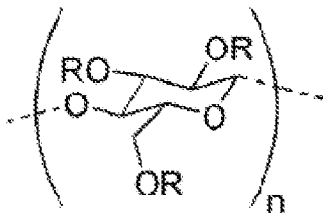
20 The thickness of the fiber structure made of the bioabsorbable polymer is not particularly limited, and the preferable lower limit is 5 μm , and the preferable upper limit is 1.0 mm. A fiber structure made of the bioabsorbable polymer having a thickness of less than 5 μm is poor in strength and
25 may not impart a sufficient tissue reinforcement effect. A fiber structure made of the bioabsorbable polymer having a thickness of more than 1.0 mm may not sufficiently adhere to and fix tissue. The more preferable lower limit of the thickness of the fiber structure made of the bioabsorbable
30 polymer is 10 μm , and the more preferable upper limit thereof is 0.5 mm.

[0019]

The etherified cellulose is produced through etherification of hydroxy groups of cellulose. Specific
35 examples thereof include hydroxyalkylated cellulose

represented by the formula (1) such as hydroxyethylated cellulose in which hydroxy groups of cellulose are replaced with hydroxyethyl groups, and hydroxypropylated cellulose in which hydroxy groups of cellulose are replaced with hydroxypropyl groups. In particular, hydroxyethylated cellulose, which is proven to be highly safe, is preferred.

[0020]



[0021]

In the formula (1), n represents an integer, and R represents hydrogen or $-R'OH$ in which R' represents an alkylene group.

[0022]

In cases where the etherified cellulose is hydroxyethylated cellulose, in the hydroxyethylated cellulose, the molar ratio of a diethylene glycol group to an ethylene glycol group (diethylene glycol group/ethylene glycol group) is preferably 0.1 to 1.0, and the molar ratio of a triethylene glycol group to an ethylene glycol group (triethylene glycol group/ethylene glycol group) is preferably 0.1 to 0.5. The etherified cellulose having molar ratios within such ranges imparts excellent initial adhesive force when the fiber structure made of the bioabsorbable polymer adheres to biological tissue through the fiber structure made of the etherified cellulose, and the high adhesive force is maintained even after adhesion. Even if cohesive failure or interfacial peeling occurs due to high pressure, the etherified cellulose can adhere again to prevent air leakage or fluid leakage.

The numbers of moles of ethylene glycol groups, diethylene glycol groups, and triethylene glycol groups can be measured, for example, by NMR or thermal decomposition GC-MS.

[0023]

In cases where the etherified cellulose is hydroxyethylated cellulose, the preferable lower limit of the average number of molecules (Molar Substitution, MS) of alkylene oxides bonded to one anhydroglucose unit is 1.0, and the preferable upper limit thereof is 4.0. The etherified cellulose having a MS within such a range can gel in a short time with high gel strength, and closely adhere to and fix tissue. If the MS is less than 1.0, gelled hydroxyethylated cellulose tends to be less viscous. If the MS is more than 4.0, gelation tends to need a long time. The more preferable lower limit of the MS is 1.3, and the more preferable upper limit thereof is 3.0.

[0024]

In cases where the etherified cellulose is hydroxyethylated cellulose, the preferable lower limit of the average degree of substitution (DS) of alkylene oxides to hydroxyl groups at positions 2, 3, and 6 of an anhydroglucose unit is 0.2, and the preferable upper limit thereof is 2.5. The etherified cellulose having a DS within such a range can gel in a short time with high gel strength, and closely adhere to and fix tissue. Furthermore, the strength due to the fiber structure is likely to be imparted, and fibers are likely to retain moisture therein. If the DS is less than 0.2, gelation may need a long time. If the DS is more than 2.5, the strength due to the fiber structure in a wet condition may reduce. The more preferable lower limit of the DS is 0.3, and the more preferable upper limit thereof is 1.5.

[0025]

The MS and DS can be calculated from the measurement of NMR spectrum of an aqueous solution of hydroxyethylated cellulose, and the quantification of the intensities of signals belonging to carbon atoms of an anhydroglucose ring and carbon atoms of a substituent group in the spectrum (see for example JP-H6-41926 B).

Specifically, for example, 0.2 g of a sample, 30 mg of an enzyme (cellulase), and an internal standard material are dissolved in 3 ml of heavy water. The resulting solution is subjected to ultrasonication for 4 hours, and its NMR spectrum is determined using an NMR measuring device (e.g. JNM-ECX400P produced by JEOL) under the conditions of the number of scanning of 700, pulse width of 45°, and observed frequency of 31500 Hz. [0026]

The hydroxyethylated cellulose can be produced, for example, by the reaction of an ethylene oxide with alkali cellulose produced by treating cellulose with an aqueous solution of an alkali.

Specifically, for example, alkali cellulose is produced from a fiber structure made of cellulose as a raw material by treating the fiber structure with an aqueous solution of an alkali such as sodium hydroxide. Then, to the resulting alkali cellulose are added a certain amount of an ethylene oxide and a reaction solvent, and a reaction is performed. [0027]

The preferable lower limit of a water absorption rate of the fiber structure made of the etherified cellulose is 200%, and the preferable upper limit thereof is 1000%. The fiber structure made of the etherified cellulose having the water absorption rate within such a range can gel in a short time with high gel strength, and closely adhere to and fix tissue. If the water absorption rate is lower than 200%, gelation may need a long time. If the water absorption rate is higher than 1000%, gel strength tends to reduce. The more preferable lower limit of the water absorption rate is 400%, and the more preferable upper limit thereof is 800%.

The water absorption rate herein can be measured by the following method.

Specifically, the initial weight of a sample is measured, and it is placed in a petri dish. Distilled water is slowly added dropwise to the sample. The weight of the sample

containing absorbed distilled water to the maximum (the sample in a condition that any more distilled water cannot be absorbed, and if distilled water is added dropwise to the sample, excess water leaks) is determined as a maximum water absorption weight.

5 The water absorption rate can be determined from the following equation using the resulting initial weight and the maximum water absorption weight.

Water absorption rate (%) = (maximum water absorption weight - initial weight)/initial weight × 100

10 [0028]

The preferable lower limit of a moisture absorption rate of the fiber structure made of the etherified cellulose is 7%, and the preferable upper limit thereof is 50%. The fiber structure made of the etherified cellulose having the moisture
15 absorption rate within such a range can gel in a short time with high gel strength, and closely adhere to and fix tissue. If the moisture absorption rate is lower than 7%, gelation may need a long time. If the moisture absorption rate is higher than 50%, the gel strength tends to reduce. The more preferable
20 lower limit of the moisture absorption rate is 10%, and the more preferable upper limit thereof is 35%.

The moisture absorption rate used herein can be measured by the following method.

Specifically, a sample is heated at 105°C for 2 hours.
25 The weight of the resulting sample is determined as an absolute dry weight. Next, the absolute dry sample is allowed to stand in an atmosphere at 20°C and 65%Rh for 7 hours to control the moisture content of the sample. The weight of the sample is determined as a weight after moisture control. A moisture
30 absorption rate can be calculated from the following equation using the resulting absolute dry weight and the weight after moisture control.

Moisture absorption rate (%) = (weight after moisture control - absolute dry weight)/absolute dry weight × 100

35 [0029]

The fiber structure made of the etherified cellulose may be in any form, and may be in the form of a non-woven fabric, a knitted fabric, a woven fabric, gauze, or yarn. In addition, the fiber structures having such forms may be combined one another. In particular, a non-woven fabric is preferred.
[0030]

In cases where the fiber structure made of the etherified cellulose is in the form of a non-woven fabric, the weight per unit area of the non-woven fabric is not particularly limited, and the preferable lower limit is 20 g/m^2 , and the preferable upper limit is 700 g/m^2 . If the non-woven fabric has a weight per unit area of less than 20 g/m^2 , the biological tissue-reinforcing material cannot be attached to biological tissue with sufficient adhesive force. If the non-woven fabric has the weight per unit area of more than 700 g/m^2 , gelation of etherified cellulose may need a long time. The more preferable lower limit of the weight per unit area of the non-woven fabric is 50 g/m^2 , and the more preferable upper limit thereof is 500 g/m^2 .
[0031]

The thickness of the fiber structure made of the etherified cellulose is not particularly limited, and the preferable lower limit is $50 \mu\text{m}$, and the preferable upper limit is 10 mm . A fiber structure made of the etherified cellulose having a thickness of less than $50 \mu\text{m}$ may not allow adhesion of the biological tissue-reinforcing material to biological tissue with sufficient adhesive force. Alternatively, a fiber structure made of the etherified cellulose having a thickness of more than 10 mm is less likely to absorb water, has an impaired texture, and may be poorly operatable. The more preferable lower limit of the thickness of the fiber structure made of the etherified cellulose is $50 \mu\text{m}$, and the more preferable upper limit thereof is 5 mm .
[0032]

The fiber structure made of the bioabsorbable polymer and

the fiber structure made of the etherified cellulose are preferably integrally combined. A structure integrally combined shows more enhanced easiness of use.

The method of integrally combining may be any method, and
5 examples of the method include needle punching, hydroentanglement, air entanglement, knitting, and weaving or spray spinning (melt blowing, electrospinning).

The phrase "integrally combined" used herein means a state where two fiber structures laminated to each other can
10 be treated as one structure, and are not easily separated.
[0033]

The biological tissue-reinforcing material of the present invention is used to stop bleeding from a damaged or weakened organ or tissue, or to prevent air leakage or fluid
15 leakage in the field of surgery. In particular, the biological tissue-reinforcing material is favorably used to prevent air leakage due to pneumothorax or after resection of lung cancer in the field of chest surgery.

The biological tissue-reinforcing material of the present invention can be easily attached to an affected area
20 just by placing, at the affected area, the material preliminary immersed into normal saline. Further, the biological tissue-reinforcing material absorbs blood or fluid from an affected area to show adhesive force.

25

BRIEF DESCRIPTION OF DRAWINGS

[0034]

Fig. 1 is a view schematically illustrating pressure test equipment used in the pressure test performed in examples.

30

- Advantageous Effects of Invention

[0035]

The present invention can provide a biological tissue-reinforcing material capable of more reliably
35 reinforcing weakened tissue while preventing air leakage or

fluid leakage without using fibrin glue, which is a blood product.

DESCRIPTION OF EMBODIMENTS

5 [0036]

The following describes examples to more specifically illustrate embodiments of the present invention. It should be noted that the present invention is not limited only to these examples.

10 [0037]

(Example 1)

(1) Preparation of fiber structure made of hydroxyethylated cellulose

15 A 280- μ m-thick single knit made of No. 80 count cellulose yarn as a raw material was bleached by hydrogen peroxide bleaching.

20 Then, 3.55 g of the bleached knit was immersed in 140 mL of an aqueous solution of 10% sodium hydroxide at 15°C for 30 minutes to alkalize cellulose. The alkalized knit was padded by applying a load of 2.5 to 3.0 kg.

25 Next, 12.25 g of the resulting knit made of alkali cellulose was immersed in 50 mL of a 0.8 mol/L solution of ethylene oxide in hexane at 25°C, and was then reacted at 50°C for 3 hours. The reacted knit was washed by immersing in 70 mL of a mixture of methanol and methyl isobutyl ketone (methanol:methyl isobutyl ketone = 35:35) at 25°C for 5 minutes, and then neutralized by immersing in 72.6 mL of a mixture of methanol, methyl isobutyl ketone, and acetic acid (methanol:methyl isobutyl ketone:acetic acid = 35:35:2.6) at 30 25°C for 10 minutes. Further, the neutralized knit was immersed in 70 mL of a mixture of isopropyl alcohol and water (isopropyl alcohol:water = 63:7) at 25°C for 3 minutes, and immersed in 70 mL of acetone at 25°C for 5 minutes, and dried at 40°C for 24 hours. In this manner, a fiber structure made of 35 hydroxyethylated cellulose was obtained.

Analysis of the hydroxyethylated cellulose of the resulting fiber structure using a thermal decomposition GC-MS shows that the molar ratio of a diethylene glycol group to an ethylene glycol group (diethylene glycol group/ethylene glycol group) was 0.20, and the molar ratio of a triethylene glycol group to an ethylene glycol group (triethylene glycol group/ethylene glycol group) was 0.21.

[0038]

(2) Production of biological tissue-reinforcing material

A 150- μ m-thick non-woven fabric (NEOVEIL Type NV-M015G produced by GUNZE LIMITED) made of polyglycolide was prepared as a fiber structure made of a bioabsorbable polymer.

A biological tissue-reinforcing material was obtained in such a way that a combination of two fiber structures made of hydroxyethylated cellulose/a non-woven fabric made of polyglycolide/one fiber structure made of hydroxyethylated cellulose were laminated in the stated order, and they were integrally combined by needle punching.

The resulting biological tissue-reinforcing material was cut into a 9-mm-diameter circular shape to give a test sample for measurement.

[0039]

(3) Pressure test

A pressure test was performed using pressure test equipment 1 illustrated in Fig. 1.

An about 130- μ m-thick collagen film (produced by Nippi. Inc.) was cut into a 24-mm-diameter circular shape, and the cut film was washed with 70% ethanol, and liquid was wiped off. The cut film was set in a filter holder 2 (Swinnex (registered trademark) 25 produced by Merck Millipore.) A 3-mm-diameter hole was formed in the center of the collagen film that was set in the filter holder 2 using a punch. A 20-ml syringe 3 (Terumo Syringe SS-20ESZ produced by TERUMO CORPORATION) and a pressure gauge 5 (digital manometer FUSO-8230 produced by FUSORIKI Co., Ltd.) were placed at the downstream of the filter holder through

a three way cock 4. In this manner, pressure test equipment was fabricated.

[0040]

Purified water was added dropwise to the surface on the
5 side of the combination of two fiber structures made of
hydroxyethylated cellulose of the test sample. The resulting
test sample was placed at the center of the collagen film that
was set in the filter holder such that the surface on the side
of the combination of two fiber structures was in contact with
10 the collagen film. After the test sample was allowed to stand
for 15 minutes, air was delivered to the test sample through
a syringe. The maximum pressure that does not cause peeling
of the test sample was measured using a pressure gauge, and the
pressure resistance (initial pressure resistance) was
15 evaluated. After evaluation of the initial pressure
resistance, air was delivered through a syringe every five
minutes five times and at each time, the maximum pressure of
the air for peeling the test sample was measured using a pressure
gauge, and the repeatability of the pressure resistance was
20 evaluated.

Table 1 shows the results.

[0041]

(Example 2)

A biological tissue-reinforcing material made of was
25 obtained in the same manner as in Example 1, except that a fiber
structure made of hydroxyethylated cellulose was prepared from
a 200- μ m-thick single knit made of No. 160 count cellulose yarn
as a raw material, and a combination of three fiber structures
made of hydroxyethylated cellulose/a non-woven fabric made of
30 polyglycolide/a combination of two fiber structures made of
hydroxyethylated cellulose were laminated in the stated order.
The biological tissue-reinforcing material was subjected to a
pressure test. In the pressure test, the resulting test sample
was placed at the center of the collagen film that was set in
35 the filter holder such that the surface on the side of the

combination of the three fiber structures made of hydroxyethylated cellulose was in contact with the collagen film.

Table 1 shows the results of the pressure test.

5 [0042]

(Comparative Example 1)

Pressure resistance in the case of using fibrin glue and a fiber structure made of a bioabsorbable polymer in combination was evaluated by the following method.

10 A 150- μ m-thick non-woven fabric made of polyglycolide (NEOVEIL Type NV-M015G produced by GUNZE LIMITED) was cut into a 9-mm-diameter circular shape.

A collagen film was set in the filter holder of the pressure test equipment prepared in Example 1. Then, 20 μ L of
15 liquid A of fibrin glue (Beriplast P produced by CSL Behring K.K.) was added dropwise to the center of the collagen film so as to avoid hole of the collagen film and spread in an approximately 9-mm-diameter shape. Next, the non-woven fabric cut into a 9-mm-diameter circular shape was placed on the spread
20 liquid A, and was impregnated with the liquid A. Then, 40 μ L of the liquid A was added dropwise to the non-woven fabric, and the non-woven fabric was sufficiently impregnated with the liquid A. Then, 40 μ L of liquid B was added dropwise to the non-woven fabric. After 15 minutes have passed from the end
25 of dropping of the liquid B, air was delivered through a syringe, and the maximum pressure that does not cause peeling the test sample was measured using a pressure gauge, and the pressure resistance (initial pressure resistance) was evaluated.

After evaluation of the initial pressure resistance, air
30 was delivered through a syringe every five minutes four times and at each time, the maximum pressure that does not cause peeling the test sample was measured using a pressure gauge, and the repeatability of the pressure resistance was evaluated.

Table 1 shows the results.

35 [0043]

(Comparative Example 2)

A biological tissue-reinforcing material was obtained in the same manner as in Example 1, except that a fiber structure made of oxidized cellulose (SURGICEL produced by Johnson & Johnson K.K.) was used instead of the fiber structure made of hydroxyethylated cellulose. The biological tissue-reinforcing material was subjected to a pressure test.

Table 1 shows the results of the pressure test.

[0044]

10 [Table 1]

	Pressure resistance (mmHG)				
	First (Initial pressure resistance)	Second	Third	Fourth	Fifth
Example 1	59.3	56.3	55.1	62.4	65.3
Example 2	52.1	52.3	66.1	59.5	55.3
Comparative Example 1	34.7	11.3	13.2	11.5	11.5
Comparative Example 2	20.7	16.7	14.3	15.6	15.7

[0045]

Table 1 shows that in the case of using fibrin glue and a fiber structure made of a bioabsorbable polymer in combination, the initial pressure resistance was relatively high, as high as 34.7 mmHg, but remarkable reduction in pressure resistance was observed in the test sample once separated by pressure (from the second measurement). The pressure resistance did not return to the original level. On the other hand, in the case of using biological tissue-reinforcing materials of Examples 1 and 2, the initial pressure resistances were high (59.3 mmHg and 52.1 mmHg). In addition, little reduction in pressure resistance was observed in the test samples once separated by pressure (from the second measurement). It is considered that this is because the test samples adhere again during a 5-minute interval. In Comparative Example 2, a case of using a fiber structure made of oxidized cellulose, which was known as an

absorbable hemostat, was tested. As a result, the initial pressure resistance was as low as 20.7 mmHg, and reduction in pressure resistance was observed in each measurement from the second measurement.

5

INDUSTRIAL APPLICABILITY

[0046]

The present invention can provide a biological tissue-reinforcing material capable of more reliably reinforcing weakened tissue while preventing air leakage and fluid leakage without using fibrin glue, which is a blood product. The biological tissue-reinforcing material of the present invention can also be used for a dura mater, an oral mucosa, adhesion preventive materials, and the like.

15

REFERENCE SIGNS LIST

[0047]

- 1 Pressure test equipment
- 2 Filter holder
- 20 3 Syringe
- 4 Three way cock
- 5 Pressure gauge
- 6 Collagen film with hole

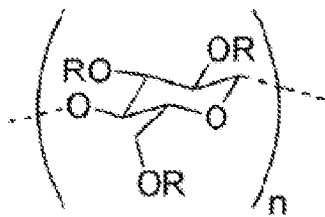
CLAIMS

Claim 1. A biological tissue-reinforcing material comprising a laminated structure, the laminated structure
 5 comprising:

a fiber structure made of a bioabsorbable polymer; and
 a fiber structure made of etherified cellulose that is produced through etherification of hydroxy groups of cellulose.

10 Claim 2. The biological tissue-reinforcing material according to claim 1,

wherein the etherified cellulose that is produced through etherification of hydroxy groups of cellulose is hydroxyalkylated cellulose represented by the following
 15 formula (1):



wherein n represents an integer, and R represents hydrogen or -R'OH, wherein R' represents an alkylene group.

20 Claim 3. The biological tissue-reinforcing material according to claim 1,

wherein the etherified cellulose that is produced through etherification of hydroxy groups of cellulose is hydroxyethylated cellulose.

25

Claim 4. The biological tissue-reinforcing material according to claim 1, 2, or 3,

wherein the fiber structure made of the etherified cellulose that is produced through etherification of hydroxy groups of cellulose is in the form of a non-woven fabric, a
 30 knitted fabric, a woven fabric, gauze, or yarn.

Claim 5. The biological tissue-reinforcing material according to claim 1, 2, 3, or 4,

5 wherein the bioabsorbable polymer is a α -hydroxy acid polymer.

Claim 6. The biological tissue-reinforcing material according to claim 5,

10 wherein the α -hydroxy acid polymer is a homopolymer or copolymer of at least one monomer selected from the group consisting glycolide, lactide, ϵ -caprolactone, dioxanone, and trimethylene carbonate.

Claim 7. The biological tissue-reinforcing material according to claim 1, 2, 3, 4, 5, or 6,

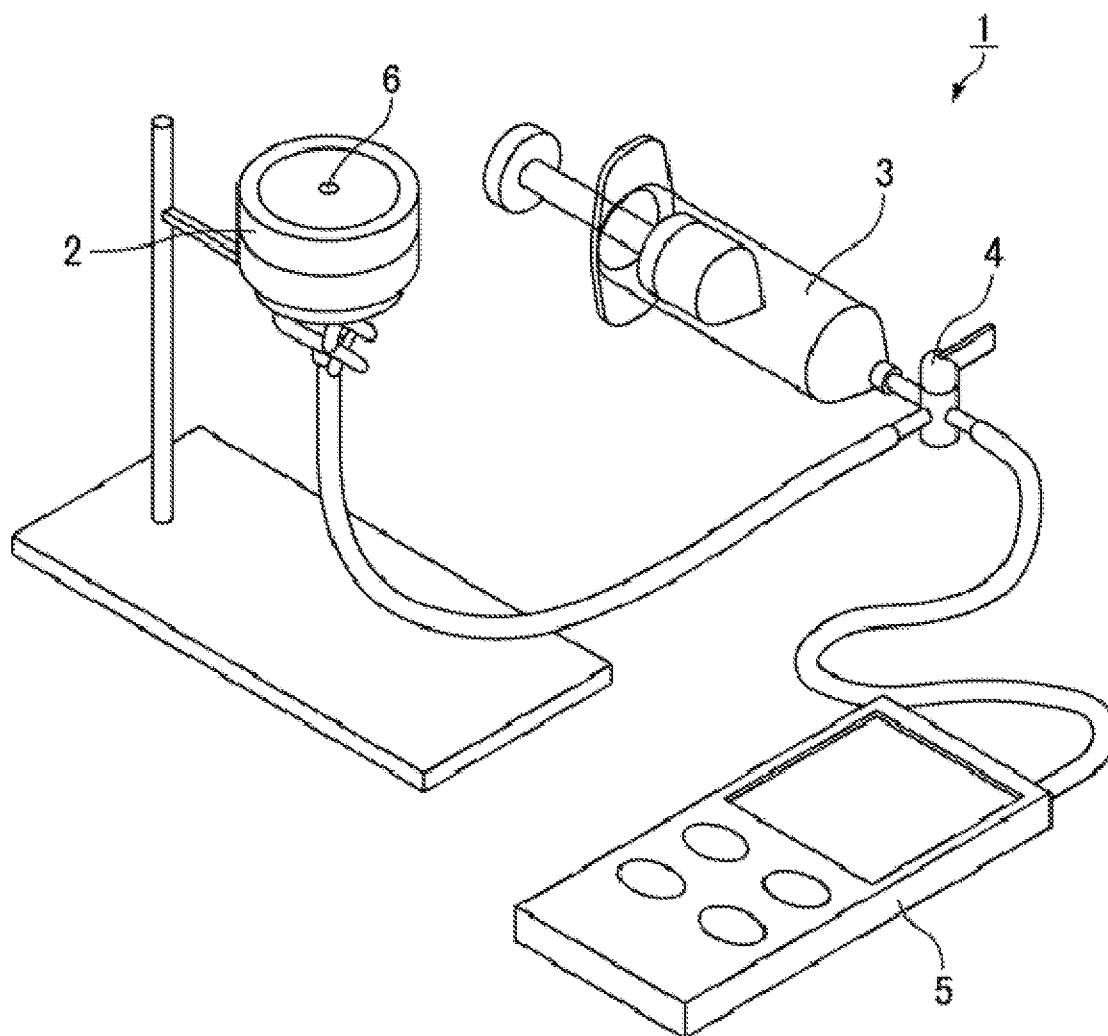
15 wherein the fiber structure made of the bioabsorbable polymer is in the form of a non-woven fabric, a knitted fabric, a woven fabric, gauze, or yarn.

20 Claim 8. The biological tissue-reinforcing material according to claim 1, 2, 3, 4, 5, 6, or 7,

25 wherein the fiber structure made of the bioabsorbable polymer and the fiber structure made of the etherified cellulose that is produced through etherification of hydroxy groups of cellulose are combined by needle punching, hydroentanglement, air entanglement, knitting, weaving, or spray spinning (melt blowing, electrospinning).

1/1

FIG.1



INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/077342

A. CLASSIFICATION OF SUBJECT MATTER

A61F 13/53(2006.01)i; A61F 13/511(2006.01)i; D21H 27/38(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61F13/--;D21H27/--

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI,EPODOC,CNPAT,CNKI:tissue,+absorb+,cellulose,fiber?,+reinforc+,laminat+

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 102600013 A (SUZHOU BOCHUANG TONGKANG BIOENGINEERING CO.) 25 July 2012 (2012-07-25) description, paragraphs [0006] to [0010], [0016], [0028] and [0031]	1-8
A	CN 1799649 A (TSINGHUA UNIVERSITY) 12 July 2006 (2006-07-12) description, page 2 line 21 to page 4 line 5	1-8
A	CN 104207879 A (TIANJIN FAMO WEST PHARM TECHNOLOGY CO.) 17 December 2014 (2014-12-17) description, paragraphs [0003] to [0005], [0008] to [0010]	1-8
A	CN 101137402 A (ETHICON INC.) 05 March 2008 (2008-03-05) description, page 2 line 24 to page 4 line 7	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

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“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

05 January 2016

Date of mailing of the international search report

26 January 2016

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2015/077342

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				JP	5437419	B2	12 March 2014
				CA	2626683	A1	27 April 2006
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				EP	1802358	B1	25 February 2015
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