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(54) Title: BIOLOGICAL TISSUE-REINFORCING MATERIAL

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



BIOLOGICAL TISSUE-REINFORCING MATERIAL

DESCRIPTION

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 even now the most common surgical technique to treat bleeding. Another
20 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
25 difficult to treat because of the high recurrence rate unless properly treated.

[0003]

Pneumothorax often occurs due to air leakage into a thoracic cavity from a stump or suture site of the lung after
30 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 (called bullae) which are transformed from some alveoli. Such leakage has been treated by pleurodesis in which lung tissue is allowed
35 to adhere to pleura using drugs or through 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 increases. If further surgery is necessary, the adhesion between lung tissue and parietal
5 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 sought.

Meanwhile, an important issue in the field of digestive surgery is to prevent leakage of pancreatic juice from a stump
10 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 leaked pancreatic juice
15 digests blood vessels to possibly cause postoperative hemorrhage, 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
20 to reinforce lung tissue and seal the surface of the lung. Non-Patent Literatures 1 to 4 suggest that this method reduces the recurrence rate of pneumothorax more 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
25 digestive surgery.

[0005]

Use of a combination of fibrin glue and a fiber structure made of a bioabsorbable polymer is remarkably effective to reinforce weakened tissue. However, air leakage or fluid
30 leakage may occur even at a reinforced area, leading to the need of further surgery. Although the incidence of such a condition is not high, leakage may become a risk factor to cause severe symptoms. Therefore, a reliable method of reinforcement has been needed. Furthermore, fibrin glue, which is a blood product,
35 unfortunately may lead to unknown viral infection.

CITATION LIST

- Non-Patent Literature

[0006]

5 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)

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

15

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

25 - Solution to Problem

[0008]

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

The present invention is described in detail below.

[0009]

35 The present inventors have investigated the cause of air

leakage or fluid leakage from a reinforced area of biological tissue having been reinforced using fibrin glue and a fiber structure or the like made of a bioabsorbable polymer in combination, and found that the problem occurs at an adhesion area attached 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 due to a very high pressure applied to lung tissue when the patient coughs or sneezes. Since gelled fibrin glue has almost no adhesion, once separated, it cannot adhere again. Air leakage or fluid leakage presumably occurs at such a separation area. [0010]

As a result of further various studies, the present inventors have found that weakened tissue can be more reliably reinforced by a film made of etherified cellulose that is produced through etherification of hydroxy groups of cellulose (hereinafter, also referred to as "etherified cellulose") than fibrin glue, and the use of such a film gives a biological tissue-reinforcing material causing no air leakage or fluid leakage. Accordingly, the inventors completed the present invention.

Etherified cellulose is a compound proven to be very 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. In particular, a film made of etherified cellulose absorb moisture to gel, and very strongly adheres to biological tissue. Thus, even when an extremely high pressure caused by coughing or sneezing is applied to such a film, cohesive failure or interfacial peeling of the film can be prevented from occurring. Further, since such a film has a certain level of adhesion even after it gels, if cohesive failure or interfacial

peeling occurs due to high pressure, the film can adhere again to prevent air leakage or fluid leakage. Furthermore, a laminated structure prepared by stacking a film made of etherified cellulose on a fiber structure, sponge body, or film made of a bioabsorbable polymer can be used as a biological tissue-reinforcing material remarkably easy to use.

[0011]

The biological tissue-reinforcing material of the present invention includes a laminated structure that includes a fiber structure, sponge body, or film made of a bioabsorbable polymer and a film made of etherified cellulose.

The fiber structure, sponge body, or film made of a bioabsorbable polymer is designed to exhibit a tissue-reinforcing effect, an air leakage prevention effect, and a fluid leakage prevention effect when it is attached to a damaged or weakened organ. The film made of etherified cellulose absorbs moisture to gel, and acts as glue to attach the fiber structure or the like made of a bioabsorbable polymer to biological tissue. The film made of etherified cellulose may be stacked on only one surface of the fiber structure, sponge body, or film made of a bioabsorbable polymer or may be stacked on both surfaces of the fiber structure, sponge body, or film made of a bioabsorbable polymer. The biological tissue-reinforcing material in which the films made of etherified cellulose are stacked on the respective surfaces of the fiber structure, sponge body, or film made of a bioabsorbable polymer can very strongly adhere to biological tissue.

[0012]

Non-limiting examples of the bioabsorbable polymer include synthetic absorbable polymers such as α -hydroxy acid polymers, for example, 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), or

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,
5 in cases where the synthetic absorbable polymer is used as the bioabsorbable polymer, a natural absorbable polymer may be used together therewith. In particular, an α -hydroxy acid polymer which is a homopolymer or copolymer of at least one monomer selected from the group consisting of glycolide, lactide,
10 ϵ -caprolactone, dioxanone, and trimethylene carbonate is preferably used because of its high strength. An α -hydroxy acid polymer which is a homopolymer or copolymer of a monomer containing glycolide is more preferably used because the polymer shows appropriate decomposition behavior.

15 [0013]

In cases where polyglycolide (homopolymer or copolymer of glycolide) is used as the bioabsorbable polymer, the preferable lower limit of the weight average molecular weight of the polyglycolide is 30,000, and the preferable upper limit thereof is 1,000,000. Polyglycolide having a weight average
20 molecular weight of less than 30,000 is poor in strength and may not impart a sufficient tissue-reinforcing effect. Polyglycolide having a weight average molecular weight of more than 1,000,000 slowly decomposes in the body and therefore may
25 cause a foreign-body reaction. The more preferable lower limit of the weight average molecular weight of the polyglycolide is 50,000, and the more preferable upper limit thereof is 300,000.

[0014]

The fiber structure made of the bioabsorbable polymer may
30 be in any form, including the form of a non-woven fabric, a knitted fabric, a woven fabric, gauze, or yarn, or a combination of these forms. In particular, the form of a non-woven fabric is preferred.

[0015]

35 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/m^2 , and the preferable upper limit is 300 g/m^2 . A non-woven fabric having a weight per unit area of less than 5 g/m^2 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/m^2 may result in poor adhesion to tissue. The more preferable lower limit of the weight per unit area of the non-woven fabric is 10 g/m^2 , and the more preferable upper limit thereof is 100 g/m^2 .

[0016]

The non-woven fabric may be produced by any method, and examples of the method include conventionally known methods such as electrospinning deposition, melt blowing, needle punching, spun bonding, flash spinning, hydroentanglement, air laying, thermal bonding, resin bonding, or wet processing.

[0017]

The weight per unit area of the sponge body made of the bioabsorbable polymer is not particularly limited, and the preferable lower limit is 5 g/m^2 , and the preferable upper limit is $1,000 \text{ g/m}^2$. A sponge body having a weight per unit area of less than 5 g/m^2 has strength not enough for a biological tissue-reinforcing material, and may not reinforce weakened tissue. A sponge body having a weight per unit area of more than $1,000 \text{ g/m}^2$ may result in poor adhesion to tissue. The more preferable lower limit of the weight per unit area of the sponge body is 30 g/m^2 , and the more preferable upper limit thereof is 500 g/m^2 .

[0018]

The thickness of the fiber structure or sponge body made of the bioabsorbable polymer is not particularly limited, and the preferable lower limit is $5 \text{ }\mu\text{m}$, and the preferable upper limit is $1 \text{ }\mu\text{m}$. A fiber structure or sponge body made of the bioabsorbable polymer having a thickness of less than $5 \text{ }\mu\text{m}$ is

poor in strength and may not impart a sufficient tissue-reinforcing effect. A fiber structure or sponge body made of the bioabsorbable polymer having a thickness of more than 1 mm may not sufficiently adhere to and fix tissue. The more preferable lower limit of the thickness of the fiber structure or sponge body made of the bioabsorbable polymer is 10 μm , and the more preferable upper limit thereof is 0.5 mm. [0019]

The thickness of the film made of the bioabsorbable polymer is not particularly limited, and the preferable lower limit is 10 μm , and the preferable upper limit is 800 μm . A film made of the bioabsorbable polymer having a thickness of less than 10 μm is poor in strength and may not impart a sufficient tissue-reinforcing effect. A film made of the bioabsorbable polymer having a thickness of more than 800 μm may not sufficiently adhere to and fix tissue. The more preferable lower limit of the thickness of the film made of the bioabsorbable polymer is 20 μm , and the more preferable upper limit thereof is 300 μm . [0020]

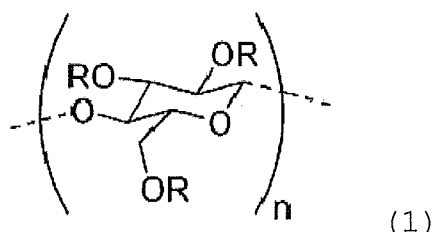
The fiber structure, sponge body, or film made of the bioabsorbable polymer may be subjected to hydrophilization. The fiber structure subjected to hydrophilization rapidly absorbs moisture such as physiological saline upon contact, and is therefore readily handled.

Non-limiting examples of the hydrophilization include plasma treatment, glow discharge treatment, corona discharge treatment, ozone treatment, surface graft treatment, and ultraviolet irradiation treatment. In particular, plasma treatment is preferred because this treatment markedly increases the water absorption rate without changing the outward appearance of the non-woven fabric. [0021]

The etherified cellulose is produced through etherification of hydroxy groups of cellulose. Specific

examples thereof include: hydroxyalkylated cellulose represented by the formula (1) below such as hydroxyethylated cellulose in which hydroxy groups of the cellulose have been replaced with hydroxyethyl groups or hydroxypropylated cellulose in which hydroxy groups of the cellulose have been replaced with hydroxypropyl groups; and carboxyalkylated cellulose such as carboxymethylated cellulose in which hydroxy groups of the cellulose have been replaced with carboxymethyl groups. In particular, hydroxyethylated cellulose, which is proven to be very safe, is preferred.

[0022]



[0023]

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

[0024]

In cases where the etherified cellulose is 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 in the hydroxyethylated cellulose. The etherified cellulose having molar ratios within such ranges imparts excellent initial adhesion when the fiber structure, sponge body, or film made of the bioabsorbable polymer adheres to biological tissue through the film made of the etherified cellulose, and the high adhesion is maintained after adhesion. Even if cohesive failure or interfacial peeling occurs due to

high pressure, the fiber structure, sponge body, or film 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. [0025]

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 an 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. When the MS is less than 1.0, gelled hydroxyethylated cellulose tends to be less viscous. When the MS is more than 4.0, gelation tends to take a long time. The more preferable lower limit of the MS is 1.3, and the more preferable upper limit thereof is 3.0. [0026]

In cases where the etherified cellulose is hydroxyethylated cellulose, the preferable lower limit of the average degree of substitution (DS) of alkylene oxides to hydroxy 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. When the DS is less than 0.2, gelation may take a long time. When the DS is more than 2.5, the strength may decrease. The more preferable lower limit of the DS is 0.3, and the more preferable upper limit thereof is 1.5. [0027]

The MS and DS can be calculated by determining the NMR spectrum of an aqueous solution of the hydroxyethylated cellulose, and measuring 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 available from JEOL) under the conditions of the number of scanning of 700, pulse width of 45°, and observed frequency of 31,500 Hz.

[0028]

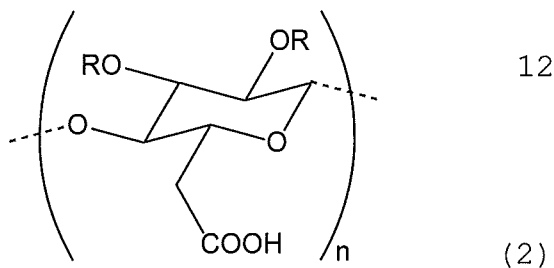
The etherified cellulose may be cellulose that is produced through etherification and carboxylation of hydroxy groups of cellulose so that part of unetherified hydroxy groups are carboxylated (hereinafter, also referred to as "etherified and carboxylated cellulose"). The use of etherified and carboxylated cellulose enables strong adhesion to damaged sites with particularly large surface irregularities.

[0029]

The etherified and carboxylated cellulose is produced through etherification and carboxylation of hydroxy groups of cellulose. Specific examples thereof include hydroxyalkylated and carboxylated cellulose such as hydroxyethylated and carboxylated cellulose in which hydroxy groups of the cellulose have been replaced with hydroxyethyl groups and carboxyl groups, or hydroxypropylated and carboxylated cellulose in which hydroxy groups of the cellulose have been replaced with hydroxypropyl groups and carboxyl groups. Particularly preferred is hydroxyethylated and carboxylated cellulose because it is proven to be very safe.

Preferred is, for example, hydroxyalkylated and carboxylated cellulose represented by the following formula (2):

[0030]



5 [0031]

wherein n represents an integer, R represents hydrogen or $-R'OH$ in which R' represents an alkylene group.

[0032]

In cases where the etherification for producing the etherified and carboxylated cellulose is hydroxyethylation, the molar ratio of a diethylene glycol group to an ethylene glycol group (diethylene glycol group/ethylene glycol group) in the hydroxyethylated and carboxylated cellulose is preferably 0.1 to 1.5, 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 1.0.

The lower limit of the average number of molecules (molar substitution, MS) of alkylene oxide bonded to an anhydroglucose unit is preferably 1.0, and the upper limit thereof is preferably 4.0. The lower limit of the average degree of substitution (DS) of alkylene oxides to hydroxy groups at positions 2, 3, and 6 of an anhydroglucose unit is preferably 0.2, and the upper limit thereof is preferably 2.5.

The average number of molecules (MS), the average degree of substitution (DS), and the numbers of moles of ethylene glycol groups, diethylene glycol groups, and triethylene glycol groups in the hydroxyethylated and carboxylated cellulose can be measured, for example, by NMR or thermal decomposition GC-MS.

[0033]

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. To the resulting alkali cellulose are added a certain amount of an ethylene oxide and a reaction solvent, and a reaction is performed.

5 [0034]

The etherified and carboxylated cellulose can be produced by, for example, carboxylating and then etherifying cellulose.

The cellulose may be carboxylated as follows, for example. Through a reaction with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as an oxidant and sodium hypochlorite, hydroxy groups of the cellulose are oxidized to aldehyde (TEMPO oxidation step). Subsequently, the cellulose is reacted with sodium chlorite so that the aldehyde is carboxylated (carboxylation step).

15 The resulting carboxylated cellulose is treated with an aqueous solution of an alkali such as sodium hydroxide (alkali treatment step) and is then reacted with ethylene oxide to be etherified (hydroxyethylated) (hydroxyethylation step). In this manner, etherified and carboxylated cellulose (hydroxyethylated and carboxylated cellulose) can be prepared.

In hydroxyethylated and carboxylated cellulose obtained by such a method, carboxyl groups are mainly introduced to position 6 of cellulose, and hydroxyethyl groups are mainly introduced to position 2 or 6.

25 [0035]

The preferable lower limit of the water absorption rate of the film made of the etherified cellulose is 200%, and the preferable upper limit thereof is 1,000%. The film made of the etherified cellulose having a water absorption rate within such a range can gel in a short time with high gel strength, and closely adhere to and fix tissue. When the water absorption rate is lower than 200%, gelation may take a long time. When the water absorption rate is higher than 1,000%, gel strength tends to be low. 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 the sample is placed in a petri dish. Distilled water is slowly dropped onto the sample. The weight of the sample having absorbed distilled water to the maximum (in a condition the sample absorbs no more distilled water, and excess distilled water leaks from the sample if distilled water is further dropped) is determined as a maximum water absorption weight. The water absorption rate can be calculated based on the following equation from the initial weight and the maximum water absorption weight.

Water absorption rate (%) = (maximum water absorption weight - initial weight)/initial weight × 100
[0036]

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

absorption rate can be calculated based on the following equation from the absolute dry weight and the weight after moisture control.

Moisture absorption rate (%) = (weight after moisture control
5 - absolute dry weight)/absolute dry weight × 100
[0037]

The thickness of the film made of the etherified cellulose is not particularly limited, and the preferable lower limit is 10 μm, and the preferable upper limit is 1,500 μm. A film made
10 of the etherified cellulose having a thickness of less than 10 μm may fail to attach the biological tissue-reinforcing material to biological tissue with sufficient adhesion. A film made of the etherified cellulose having a thickness of more than 1,500 μm is less likely to absorb water, takes a long time to
15 gel, and may not be readily handled. The more preferable lower limit of the thickness of the film made of the etherified cellulose is 20 μm, and the more preferable upper limit thereof is 1,000 μm.
[0038]

20 The fiber structure, sponge body, or film made of the bioabsorbable polymer and the film made of the etherified cellulose are preferably integrated to improve the handleability.

The expression "integrated" herein means a state where
25 two structures laminated to each other can be treated as one structure, and are not easily separated.

Non-limiting example of the mode of the integration include a mode in which a part of the fiber structure or sponge body made of the bioabsorbable polymer has entered a part of
30 the film made of etherified cellulose.
[0039]

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
35 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 readily attached to an affected area just by applying the material preliminary immersed into physiological saline to the affected area. Furthermore, the biological tissue-reinforcing material absorbs blood or fluid from an affected area so that it can exhibit adhesion.

BRIEF DESCRIPTION OF DRAWINGS

[0040]

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

- Advantageous Effects of Invention

[0041]

The present invention can provide 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.

DESCRIPTION OF EMBODIMENTS

[0042]

The following describes examples to more specifically illustrate embodiments of the present invention. The present invention is not limited only to these examples.

[0043]

(Example 1)

(1) Production of biological tissue-reinforcing material

A sol solution of hydroxyethylated cellulose was prepared by dissolving a commercial hydroxyethylated cellulose

(available from Wako Pure Chemical Industries, Ltd., the molar ratio of a diethylene glycol group to an ethylene glycol group

(diethylene glycol group/ethylene glycol group): 1.06, the molar ratio of a triethylene glycol group to an ethylene glycol group (triethylene glycol group/ethylene glycol group): 4.01) in distilled water so that the solution had a solid content of 7.5% by weight.
[0044]

A 150- μ m-thick non-woven fabric (NEOVEIL Type NV-M015G available from GUNZE LIMITED) made of polyglycolide was cut to have a length of 5.0 cm and a width of 5.0 cm to prepare a fiber structure made of a bioabsorbable polymer.

A small amount of a 70% ethanol solution was sprayed to one surface of the non-woven fabric made of polyglycolide using a spray to wet the surface of the non-woven fabric. On the surface of the fabric made of polyglycolide was casted 6.8 g of the sol solution of hydroxyethylated cellulose. Air bubbles formed after the casting were eliminated as much as possible by poking them with a needle wetted with ethanol.

The resulting fabric was dried at 60°C for two hours, thereby providing a biological tissue-reinforcing material including a laminated structure in which a film made of hydroxyethylated cellulose was stacked on one surface of the fabric made of polyglycolide.

The biological tissue-reinforcing material was punched into a 11-mm-diameter circular shape to give a test sample for measurement.
[0045]

(2) Pressure test

A pressure test was performed using a pressure tester 1 illustrated in Fig. 1.

An about 130- μ m-thick collagen film (available from Nippi. Inc.) was punched into a rectangular shape with a length of 5.5 cm and a width of 5.0 cm, and the film was washed with 70% ethanol, and liquid was wiped off. The resulting film was set in a filter holder 2 (Swinnex (registered trademark) 25 available from Merck Millipore). A 3-mm-diameter hole was formed with a punch

in the center of the collagen film that was set in the filter holder 2. A 20-mL syringe 3 (Terumo Syringe SS-20ESZ available from Terumo Corporation) and a pressure gauge 5 (digital manometer FUSO-8230 available from Fusorika Co., Ltd.) were placed at the downstream of the filter holder via a three way cock 4. In this manner, the pressure tester was fabricated. [0046]

An amount of 20 μ L of phosphate buffer was dropped onto a surface of the test sample on the side of the combination of two fiber structures made of hydroxyethylated cellulose. The resulting test sample was placed at the center of the collagen film set in the filter holder such that the surface was in contact with the collagen film. After the test sample was allowed to stand for 5 minutes, air was delivered to the test sample through the syringe. The maximum pressure before the test sample for measurement was peeled was measured with a pressure gauge for evaluation of the pressure resistance.

Table 1 shows the result.

[0047]

(Example 2)

A 150- μ m-thick non-woven fabric (NEOVEIL Type NV-M015G available from GUNZE LIMITED) made of polyglycolide was cut to have a length of 5.0 cm and a width of 5.0 cm to prepare a fiber structure made of a bioabsorbable polymer.

A small amount of a 70% ethanol solution was sprayed to one surface of the non-woven fabric made of polyglycolide using a spray to wet the surface of the non-woven fabric. On the surface of the fabric made of polyglycolide was casted 3.4 g of a sol solution of hydroxyethylated cellulose prepared as in Example 1. Air bubbles formed after the casting were eliminated as much as possible by poking them with a needle wetted with ethanol, followed by drying at 60°C for two hours.

Subsequently, a small amount of a 70% ethanol solution was sprayed to the other surface of the non-woven fabric made of polyglycolide using a spray to wet the surface of the

non-woven fabric. On this surface of the non-woven fabric made of polyglycolide was casted 3.4 g of a sol solution of hydroxyethylated cellulose prepared as in Example 1. Air bubbles formed after the casting were eliminated as much as possible by poking them with a needle wetted with ethanol, followed by drying at 60°C for two hours.

In this manner, a biological tissue-reinforcing material including a laminated structure in which films made of hydroxyethylated cellulose were stacked on the respective surfaces of the fabric made of polyglycolide was obtained.

The biological tissue-reinforcing material was subjected to a pressure test as in Example 1. Table 1 shows the result. [0048]

(Example 3)

A sol solution of carboxymethylated cellulose was prepared by dissolving a commercial carboxymethylated cellulose (available from Wako Pure Chemical Industries, Ltd.) in distilled water so that the solution had a solid content of 7.5% by weight.

A 150- μ m-thick non-woven fabric (NEOVEIL Type NV-M015G available from GUNZE LIMITED) made of polyglycolide was cut to have a length of 5.0 cm and a width of 5.0 cm to prepare a fiber structure made of a bioabsorbable polymer.

A small amount of a 70% ethanol solution was sprayed to one surface of the non-woven fabric made of polyglycolide using a spray to wet the surface of the non-woven fabric. On the surface of the fabric made of polyglycolide was casted 3.4 g of the sol solution of carboxymethylated cellulose. Air bubbles formed after the casting were eliminated as much as possible by poking them with a needle wetted with ethanol, followed by drying at 60°C for two hours.

Subsequently, a small amount of a 70% ethanol solution was sprayed to the other surface of the non-woven fabric made of polyglycolide using a spray to wet the surface of the non-woven fabric. On this surface of the non-woven fabric made

of polyglycolide was casted 3.4 g of the sol solution of carboxymethylated cellulose. Air babbles formed after the casting were eliminated as much as possible by poking them with a needle wetted with ethanol, followed by drying at 60°C for two hours.

In this manner, a biological tissue-reinforcing material including a laminated structure in which films made of carboxymethylated cellulose were stacked on the respective surfaces of the fabric made of polyglycolide was obtained.

The biological tissue-reinforcing material was subjected to a pressure test as in Example 1. Table 1 shows the result. [0049]

(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.

A 11-mm-diameter circular piece was punched out from a 150- μ m-thick nonwoven fabric made of polyglycolide (NEOVEIL Type NV-M015G, GUNZE LIMITED).

A collagen film was set on a filter holder of the pressure tester prepared in Example 1. Then, 20 μ L of a solution A of fibrin glue (Beriplast P consisting of a solution A (mixture of fibrinogen powder and an aprotinin solution) and a solution B (mixture of thrombin powder and a calcium chloride solution), available from CSL Behring K.K.) was dropped onto the center of the collagen film in such a manner as to avoid the hole in the collagen film, and was spread into a shape with a diameter of approximately 11 mm. Next, the nonwoven fabric punched into a 11-mm-diameter circle was placed on the spread solution A and impregnated with the solution A. Subsequently, 20 μ L of the solution A was dropped onto the nonwoven fabric, and the nonwoven fabric was sufficiently impregnated with the solution A. Thereafter, 20 μ L of a solution B was dropped onto the nonwoven fabric.

Five minutes after the dropping of the solution B, air was delivered through the syringe. The maximum pressure before the test sample for measurement was peeled was measured with a pressure gauge for evaluation of the pressure resistance.

5 Table 1 shows the result.

[0050]

(Comparative Example 2)

A 150- μ m-thick non-woven fabric (NEOVEIL Type NV-M015G available from GUNZE LIMITED) made of polyglycolide was cut to
10 have a length of 5.0 cm and a width of 5.0 cm to prepare a fiber structure made of a bioabsorbable polymer.

Separately, a 320- μ m-thick fiber structure made of oxidized cellulose (available from Johnson & Johnson K.K., Surgicel) was cut to have a length of 5.0 cm and a width of 5.0
15 cm.

The fiber structure made of oxidized cellulose, the non-woven fabric made of polyglycolide, and the fiber structure made of oxidized cellulose were stacked in the stated order, and they were integrated by needle punching, thereby providing
20 a biological tissue-reinforcing material.

The biological tissue-reinforcing material was subjected to a pressure test as in Example 1. Table 1 shows the result.
[0051]

(Comparative Example 3)

25 A sol solution of oxidized cellulose was prepared by dissolving a commercial oxidized cellulose (available from Wako Pure Chemical Industries, Ltd.) in distilled water so that the solution had a solid content of 7.5% by weight.

A 150- μ m-thick non-woven fabric (NEOVEIL Type NV-M015G available from GUNZE LIMITED) made of polyglycolide was cut to
30 have a length of 5.0 cm and a width of 5.0 cm to prepare a fiber structure made of a bioabsorbable polymer.

A small amount of a 70% ethanol solution was sprayed to one surface of the non-woven fabric made of polyglycolide using
35 a spray to wet the surface of the non-woven fabric. On the

surface of the fabric made of polyglycolide was casted 3.4 g of the sol solution of oxidized cellulose. Air babbles formed after the casting were eliminated as much as possible by poking them with a needle wetted with ethanol, followed by drying at 60°C for two hours.

Subsequently, a small amount of a 70% ethanol solution was sprayed to the other surface of the non-woven fabric made of polyglycolide using a spray to wet the surface of the non-woven fabric. On this surface of the non-woven fabric made of polyglycolide was casted 3.4 g of the sol solution of oxidized cellulose. Air babbles formed after the casting were eliminated as much as possible by poking them with a needle wetted with ethanol, followed by drying at 60°C for two hours.

In this manner, a biological tissue-reinforcing material including a laminated structure in which films made of oxidized cellulose were stacked on the respective surfaces of the fabric made of polyglycolide was obtained.

The biological tissue-reinforcing material was subjected to a pressure test as in Example 1. Table 1 shows the result.

[0052]

[Table 1]

	Pressure resistance (mmHg)
Example 1	189.3
Example 2	251.1
Example 3	172.3
Comparative Example 1	34.7
Comparative Example 2	59.3
Comparative Example 3	3.9

INDUSTRIAL APPLICABILITY

[0053]

The present invention provides 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.

REFERENCE SIGNS LIST

- 5 [0054]
 - 1 Pressure tester
 - 2 Filter holder
 - 3 Syringe
 - 4 Three way cock
- 10 5 Pressure gauge
- 6 Collagen film with hole

CLAIMS

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

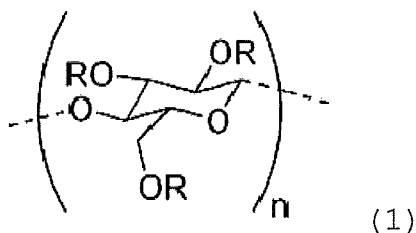
a fiber structure, sponge body, or film made of a bioabsorbable polymer; and

a film made of etherified cellulose that is produced through etherification of hydroxy groups of cellulose.

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 formula (1):



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

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.

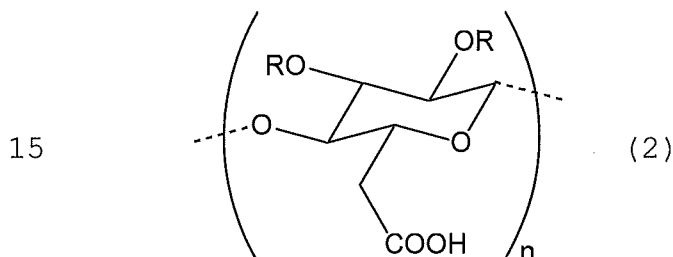
Claim 4. The biological tissue-reinforcing material according to claim 1, 2, or 3,

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

is produced through etherification and carboxylation of hydroxy groups of cellulose so that part of unetherified hydroxy groups are carboxylated.

5 Claim 5. The biological tissue-reinforcing material according to claim 4,

wherein the cellulose that is produced through etherification and carboxylation of hydroxy groups of cellulose is cellulose that is produced through hydroxyalkylation and
10 carboxylation of hydroxy groups of cellulose, represented by the following formula (2):



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

20

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

wherein the bioabsorbable polymer is an α -hydroxy acid polymer.

25

Claim 7. The biological tissue-reinforcing material according to claim 6,

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
30 trimethylene carbonate.

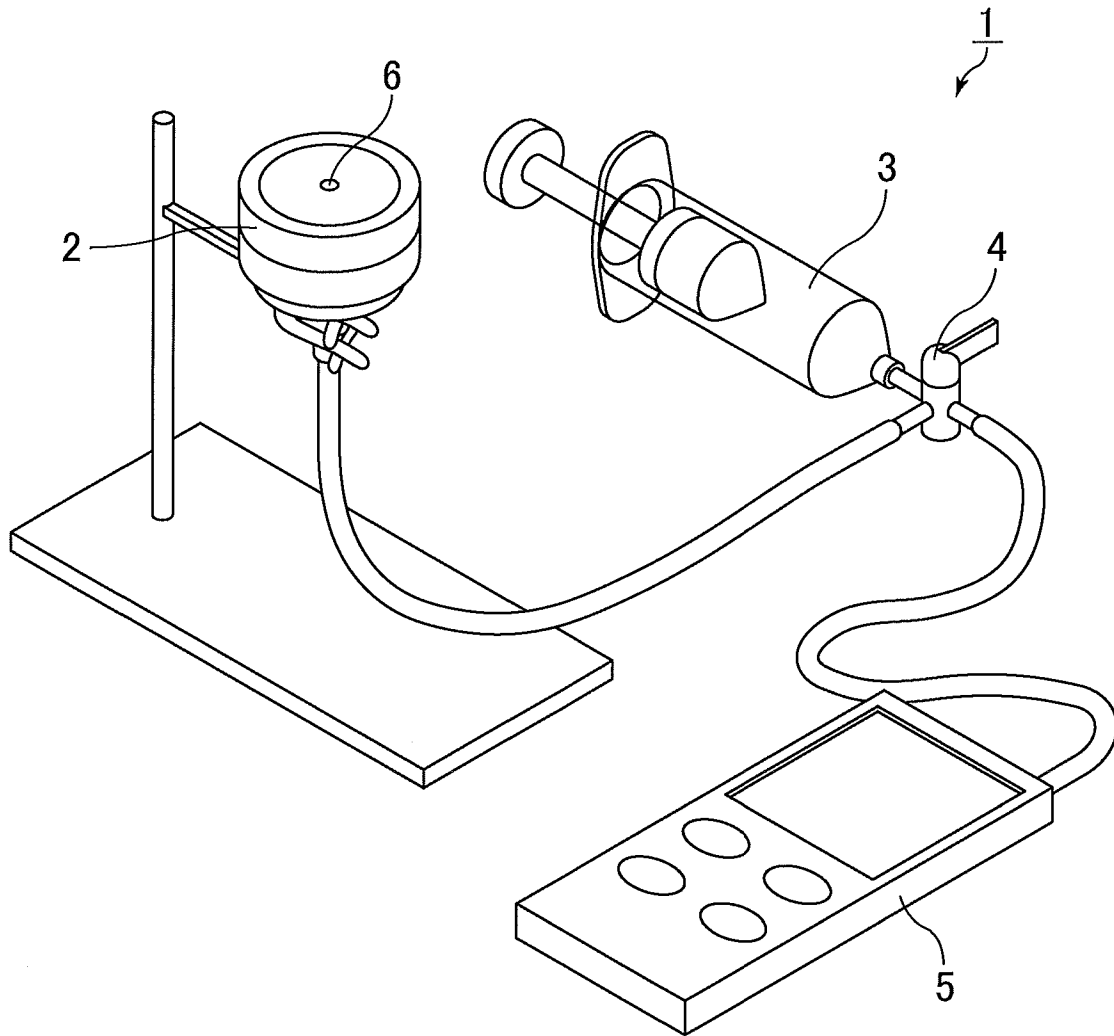
Claim 8. The biological tissue-reinforcing material according to claim 1, 2, 3, 4, 5, 6, or 7,

35 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.

1/1

FIG. 1



INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/104881

A. CLASSIFICATION OF SUBJECT MATTER

A61L 15/28(2006.01)i; A61L 31/12(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)

A61L 15/- A61L 31/-

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)

CNPAT;WPI;EPODOC;ISI Web of Knowledge;CNKI:Gunze Limited, biological tissue, reinforce+, fibrin glue, fiber, sponge, film, bioabsorbable, etherifi+, cellulose, hydroxy+, carboxy+

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	CN 1181979 A (JOHNSON & JOHNSON MEDICAL INC.) 20 May 1998 (1998-05-20) claims 1-4	1-8
X	CN 104941011 A (YANTAI SENSEN ENVIRONMENTAL PROTECTION SCIENCE AND TECHNOLOGY CO., LTD.) 30 September 2015 (2015-09-30) paragraph [0008]	1-8
A	CN 105963769 A (XING MENGQIU) 28 September 2016 (2016-09-28) whole document	1-8
A	CN 101530353 A (BEIJING TRANSEASY MEDICAL TECHNOLOGY CO., LTD.) 16 September 2009 (2009-09-16) whole document	1-8
A	CN 101773689 A (YUAN GUOZHONG) 14 July 2010 (2010-07-14) whole document	1-8
A	US 2006116696 A1 (ODERMATT ERIC K. ET AL.) 01 June 2006 (2006-06-01) whole document	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

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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

30 June 2017

Date of mailing of the international search report

20 July 2017

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/104881

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2016/104881

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