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(71) Applicants: GUNZE LIMITED [JP/JP]; 1, Zeze, Aono-cho, Ayabe-shi, Kyoto 6238511 (JP). GUNZE MEDICAL DEVICES (SHENZHEN) LIMITED [CN/CN]; Room 802, Kerry Centre, 2008 Renminnan Rd., Shenzhen, Guangdong 518001 (CN).

(72) Inventors: TANAKA, Chiaki; c/o GUNZE LIMITED, 1, Ishiburo, Inokurashinmachi, Ayabe-shi, Kyoto 6238512 (JP). YUL, Yoshinari; c/o GUNZE LIMITED, 1, Ishiburo, Inokurashinmachi, Ayabe-shi, Kyoto 6238512 (JP). MATSUDA, Shojiro; c/o GUNZE MEDICAL DEVICES (SHENZHEN) LIMITED, Room 802, Kerry Centre, 2008 Renminnan Rd., Shenzhen, Guangdong 518001 (CN). TAKAMORI, Hideki; c/o GUNZE MEDICAL DEVICES (SHENZHEN) LIMITED, Room 802, Kerry Centre, 2008 Renminnan Rd., Shenzhen, Guangdong 518001 (CN).

(74) Agent: SHANGCHENG & PARTNERS; 18th Floor, Ever Bright World Center Building No. 28 West Ping An Li Avenue, Xicheng District, Beijing 100034 (CN).

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(54) Title: MEDICAL FIBER STRUCTURE AND MEDICAL LAMINATE

(57) Abstract: The medical fiber structure and the medical laminate provided herein are capable of sufficiently adhering to damaged tissue to stop bleeding and more reliably reinforcing weakened tissue by preventing air leakage or fluid leakage. The medical fiber structure includes a fiber structure made of cellulose which is produced through etherification and carboxylation of hydroxy groups of cellulose.



WO 2017/206131 A1

MEDICAL FIBER STRUCTURE AND MEDICAL LAMINATE

DESCRIPTION

5 TECHNICAL FIELD

[0001]

The present invention relates to a medical fiber structure and a medical laminate, which are capable of sufficiently adhering to damaged tissue to stop bleeding and more reliably reinforcing weakened tissue by preventing air leakage or fluid leakage.

BACKGROUND ART

[0002]

15 The most fundamental issue in the field of surgery is to stop bleeding of a damaged or weakened organ or tissue and repair it. 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 stop bleeding of damaged tissue and reinforce weakened tissue. However, hemostasis may be insufficient or air leakage or fluid leakage may occur 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.

[0006]

Absorbable hemostatic agents prepared from regenerated oxidized cellulose are commercially available as hemostatic agents excellent in bioabsorbability. The absorbable hemostatic agents prepared from regenerated oxidized cellulose are considered to be highly safe as they are originated from plants and provide a hemostatic effect by forming a salt together with erythrocyte. The absorbable hemostatic agents prepared from regenerated oxidized cellulose are, however, highly acidic, which may inhibit wound healing. Moreover, even in the case of using an absorbable hemostatic agent prepared from regenerated oxidized cellulose, hemostasis may be insufficient or air leakage or fluid leakage may occur at a reinforced area.

CITATION LIST

- Non-Patent Literature

[0007]

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

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

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)

SUMMARY OF INVENTION

- Technical Problem

[0008]

In consideration of the state of the art, the present invention aims to provide a medical fiber structure and a medical laminate, which are capable of sufficiently adhering to damaged tissue to stop bleeding and more reliably reinforcing weakened tissue by preventing air leakage or fluid leakage.

- Solution to problem

[0009]

The present invention relates to a medical fiber structure including a fiber structure made of cellulose that is produced through etherification and carboxylation of hydroxy groups of cellulose.

The present invention is specifically described in the followings.

[0010]

The present inventors have researched the cause of insufficient hemostasis or air leakage or fluid leakage from a reinforced area of wounded tissue subjected to hemostasis or reinforcement 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 it has almost no adhesiveness. Air leakage or fluid leakage presumably occurs at such a separation area.

[0011]

The present inventors have also researched the cause of insufficient hemostasis or air leakage or fluid leakage from a reinforced area of wounded tissue subjected to hemostasis or

reinforcement using a conventional absorbable hemostatic agent prepared from regenerated oxidized cellulose, and found out that the absorbable hemostatic agent prepared from regenerated oxidized cellulose is less likely to adhere to wounded tissue if the wounded part has significant surface roughness.
[0012]

As a result of further intensive studies, the present inventors have found that a fiber structure including cellulose produced through etherification and carboxylation of hydroxy groups of cellulose can sufficiently adhere to wounded tissue even if the wounded part has significant surface roughness to surely stop bleeding. Moreover, such a fiber structure causes neither cohesive failure nor interfacial peeling even under a high pressure, which allows more reliable reinforcement of weakened tissue to prevent air leakage or fluid leakage. The present invention was thus completed.
[0013]

The medical fiber structure of the present invention includes a fiber structure made of cellulose that is produced through etherification and carboxylation of hydroxy groups of cellulose (hereafter, also simply referred to as "etherified and carboxylated cellulose").

Etherified and carboxylated cellulose is a compound proven to be highly safe, and gels in a short time like fibrin glue to be attached to biological tissue. In a case where the medical fiber structure of the present invention including a fiber structure made of such etherified and carboxylated cellulose is attached to wounded tissue, the medical fiber structure can sufficiently adhere to the wounded tissue to surely stop bleeding even if the wounded part has significant surface roughness. Further, since gelled etherified and carboxylated cellulose has a certain level of adhesive force, even if cohesive failure or interfacial peeling occurs due to high pressure, the etherified and carboxylated cellulose can

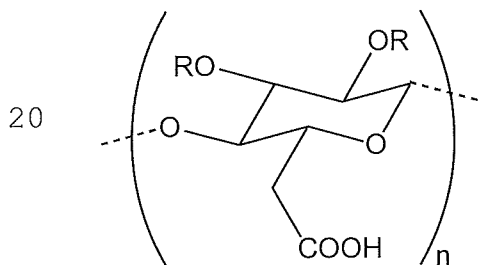
adhere again to the wounded tissue to prevent air leakage or fluid leakage.

[0014]

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 cellulose are replaced with hydroxyethyl groups and carboxyl groups, and hydroxypropylated and carboxylated cellulose in which hydroxy groups of cellulose are replaced with hydroxypropyl groups and carboxyl groups. Particularly preferred is hydroxyethylated and carboxylated cellulose because it is proven to be highly safe.

Preferred hydroxyalkylated and carboxylated cellulose is, for example, represented by the following formula (1).

[0015]



[0016]

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

[0017]

In cases where the etherification for producing the etherified and carboxylated cellulose is hydroxyethylation, the molar ratio of a diethylene glycol group and 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 and 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 one anhydroglucose unit is preferably 1.0, and the upper limit thereof is preferably 4.0. The lower limit of the average
5 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
10 glycol groups, diethylene glycol groups, and triethylene glycol groups can be measured, for example, by NMR or thermal decomposition GC-MS.

[0018]

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

The cellulose may be carboxylated as follows, for example. In the reaction with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as an oxidant and sodium hypochlorite, hydroxy groups of the cellulose is oxidized to produce aldehyde (TEMPO
20 oxidation step). Then, in the reaction with sodium chlorite, the aldehyde is carboxylated (carboxylation step).

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

In hydroxyethylated and carboxylated cellulose obtained
30 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.

[0019]

The lower limit of a water absorption rate of the fiber
35 structure made of the etherified and carboxylated cellulose is

preferably 200%, and the upper limit thereof is preferably 1000%. The fiber structure made of the etherified and carboxylated cellulose having a water absorption rate within such a range can gel in a short time with high gel strength, and tightly adhere to damaged tissue to stop bleeding. 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 be lowered. 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 as used 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 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 further added dropwise to the sample, excess water leaks) is determined as a maximum water absorption weight. 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.

[0020]

The lower limit of a moisture absorption rate of the fiber structure made of the etherified and carboxylated cellulose is preferably 7%, and the upper limit thereof is preferably 50%. The fiber structure made of the etherified and carboxylated cellulose having the moisture absorption rate within such a range can gel in a short time with high gel strength, and tightly adhere to damaged tissue to stop bleeding. 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 be lowered. 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 two 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 environment at 20°C and 65%Rh for seven hours to control the moisture content thereof. The weight of the resulting sample is determined as a weight after moisture control. A moisture absorption rate can be calculated from the following equation using the obtained absolute dry weight and the weight after moisture control:

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

[0021]

The fiber structure made of the etherified and carboxylated 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.

[0022]

In cases where the fiber structure made of the etherified and carboxylated 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 lower limit is preferably 20 g/m², and the upper limit is preferably 700 g/m². If the non-woven fabric has a weight per unit area of less than 20 g/m², the fiber structure may fail to sufficiently adhere to damaged tissue. If the non-woven fabric has the weight per unit area of more than 700 g/m², gelation of etherified and carboxylated cellulose may need a long time. The lower limit of the weight per unit area of the non-woven fabric is more preferably 50 g/m², and the upper limit thereof is more preferably 500 g/m².

[0023]

The thickness of the fiber structure made of the etherified and carboxylated cellulose is not particularly limited, and the lower limit is preferably 50 μm , and the upper limit is preferably 10 mm. If the fiber structure made of the etherified and carboxylated cellulose has a thickness of less than 50 μm , the fiber structure may fail to sufficiently adhere to damaged tissue. If the fiber structure made of the etherified and carboxylated cellulose has a thickness of more than 10 mm, the fiber structure is less likely to absorb water to have an impaired texture, and have poor handleability. The lower limit of the thickness of the fiber structure made of the etherified and carboxylated cellulose is more preferably 50 μm , and the upper limit thereof is more preferably 5 mm.

[0024]

The medical fiber structure of the present invention can sufficiently adhere to damaged tissue to stop bleeding, without containing fibrin glue that is a blood product, and more reliably reinforce weakened tissue by preventing air leakage or fluid leakage. The medical fiber structure of the present invention is almost neutral and therefore does not disturb wound healing.

The medical fiber structure of the present invention can be used for hemostasis of damaged or wounded organs or tissues and for prevention of air leakage or fluid leakage therefrom in the field of surgery.

[0025]

The medical fiber structure of the present invention may be used alone or in the form of a laminate in combination with other film(s) or fiber structure(s) made of bioabsorbable polymer(s). In the case of such a laminate, while the film(s) or fiber structure(s) made of bioabsorbable polymer(s) enable(s) more certain hemostasis and reinforcement of tissue, the medical fiber structure of the present invention serves as

an adhesive between the film(s) or fiber structure(s) made of bioabsorbable polymers and damaged tissue.

The present invention also encompasses a laminate including the medical fiber structure of the present invention and the film(s) or fiber structure(s) made of bioabsorbable polymer(s).

[0026]

In the medical laminate of the present invention, the medical fiber structure of the present invention and the film(s) or fiber structure(s) of bioabsorbable polymer(s) are preferably integrated. An integrated structure shows more enhanced handleability.

The integration may be performed by any method, and examples of the method include needle punch entanglement, hydroentanglement, air entanglement, interknitting, weaving, and spray spinning (melt blowing, electrospinning).

The phrase "integrated" as used herein means a state where the laminate of the medical fiber structure of the present invention and the film(s) or fiber structure(s) of bioabsorbable polymer(s) can be treated as one structure, and are not easily separated.

[0027]

The bioabsorbable polymer is not particularly limited, and examples thereof include synthetic absorbable polymers such as α -hydroxy acid polymers (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), glycolide-lactide (D, L, DL isomer)- ϵ -caprolactone copolymers) and natural absorbable polymers such as collagen, gelatin, chitosan, and chitin. These may be used alone, or in combination of two or more thereof. For example, in cases where the synthetic absorbable polymer is used as the bioabsorbable polymer, a natural absorbable polymer may be used together. In particular, preferred is a α -hydroxy acid polymer that is a

homopolymer or copolymer prepared by polymerizing at least one monomer selected from the group consisting of glycolide, lactide, ϵ -caprolactone, dioxanone, and trimethylene carbonate because of its high strength. More preferred is a
5 α -hydroxy acid polymer that is a homopolymer or copolymer prepared by polymerizing a monomer containing glycolide because the polymer shows appropriate decomposition behavior.

[0028]

If polyglycolide (homopolymer or copolymer of glycolide)
10 is used as the bioabsorbable polymer, the lower limit of the weight average molecular weight of the polyglycolide is preferably 30,000, and the upper limit thereof is preferably 1,000,000. Polyglycolide having a weight average molecular weight of less than 30,000 is poor in strength and may not impart
15 a sufficient tissue reinforcement effect. Polyglycolide having a weight average molecular weight of more than 1,000,000 slowly decomposes in the body and therefore may lead to a foreign-body reaction. The lower limit of the weight average molecular weight of the polyglycolide is more preferably 50,000,
20 and the upper limit thereof is more preferably 300,000.

[0029]

The film(s) or fiber structure(s) made of bioabsorbable polymer(s) may be in any form, and may be a nonwoven fabric, a knitted fabric, a woven fabric, gauze, or yarn. Moreover,
25 these forms may be combined.

[0030]

The film(s) or fiber structure(s) made of bioabsorbable polymer(s) may be subjected to hydrophilization.

The hydrophilization may be performed by any method, and
30 examples thereof include plasma treatment, glow discharge treatment, corona discharge treatment, ozone treatment, surface graft treatment, and irradiation with ultraviolet light. In particular, plasma treatment is preferred for significant improvement of the water absorption rate without changing the
35 external appearance of the nonwoven fabric.

- Advantageous Effects of Invention

[0031]

The present invention can provide a medical fiber
5 structure and a medical laminate, which are capable of
sufficiently adhering to damaged tissue to stop bleeding and
more reliably reinforcing weakened tissue by preventing air
leakage or fluid leakage.

10 BRIEF DESCRIPTION OF DRAWINGS

[0032]

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

15 DESCRIPTION OF EMBODIMENTS

[0033]

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
20 examples.

[0034]

(Example 1)

(1) Preparation of fiber structure made of hydroxyethylated and
carboxylated cellulose

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

The bleached knit was immersed in a TEMPO oxidation
solution (TEMPO concentration: 20%owf, 5% sodium hypochlorite
30 concentration: 180%owf, sodiumbromide: 17.5%owf, pH 10 aqueous
solution) at 25°C for 10 minutes at a bath ratio of 1:30 to be
oxidized. The oxidized knit was washed with water three times,
and then immersed in a sodium chlorite solution (25% sodium
chlorite concentration: 20%owf, CG1000 concentration: 1.0 g/L,
35 pH 3.8 aqueous solution) at 80°C for 90 minutes at a bath ratio

of 1:15 to be carboxylated. The resulting knit was washed with hot water and then with water, and immersed in a hydrogen peroxide/sodium borohydride solution (30% hydrogen peroxide concentration: 1%owf, sodium borohydride concentration: 5%owf, PCL7000 concentration: 0.4 g/L, pH 10.5 aqueous solution) at 70°C for 20 minutes at a bath ratio of 1:20 for dechlorination treatment and treatment of reducing partially formed ketone to hydroxy groups. The obtained knit was further washed with hot water, neutralized, and washed with water. A carboxylated knit was thus prepared.

[0035]

The obtained carboxylated knit was immersed in a 20% sodium hydroxide aqueous solution at 15°C for 30 minutes at a bath ratio of 1:40 to be alkalized. To the resulting knit was applied a load of 2.5 to 3.0 kg for padding. The knit after padding was immersed in a 0.8 mol/L solution of ethylene oxide in hexane at 50°C for 30 minutes at a bath ratio of 1:15 to be hydroxyethylated. The knit after the reaction was immersed in 70 mL of a mixture of methanol and methyl isobutyl ketone (methanol:methyl isobutyl ketone = 35:35) at 25°C for five minutes at a bath ratio of 1:30 to be washed, and then immersed in a mixture of methanol, methyl isobutyl ketone, and acetic acid (methanol:methyl isobutyl ketone:acetic acid = 35:35:2.6) at 25°C for 10 minutes at a bath ratio of 1:30 to be neutralized. The neutralized knit was immersed (twice) in a mixture of isopropyl alcohol and water (isopropyl alcohol:water = 63:7) at 25°C for three minutes at a bath ratio of 1:30, then immersed in acetone at 25°C for five minutes at a bath ratio of 1:60, and dried at 40°C for 24 hours to give a medical fiber structure including a fiber structure made of hydroxyethylated and carboxylated cellulose.

As a result of analysis of the hydroxyethylated and carboxylated cellulose of the resulting fiber structure using a thermal decomposition GC-MS, the molar ratio of a diethylene glycol group and an ethylene glycol group (diethylene glycol

group/ethylene glycol group) was 0.18, and the molar ratio of a triethylene glycol group and an ethylene glycol group (triethylene glycol group/ethylene glycol group) was 0.15. [0036]

5 (2) Evaluation of adhesion to damaged tissue

A grilled chicken liver was used as a model of damaged tissue. To the surface of the obtained medical fiber structure, purified water was dropped. The medical fiber structure was then placed on the center of the damaged-tissue model in such
10 a manner that the surface on which purified water was dropped was in contact with the liver. After standing for 15 minutes, the state of the medical fiber structure was evaluated based on the following criteria.

"oo (excellent)": The fiber structure pulled by a hand was not
15 at all peeled.

"o (good)": The fiber structure pulled strongly by a hand was peeled.

"Δ (not good)": The fiber structure was seemed to tightly adhere to the model but easily peeled when pulled by a hand.

20 "× (poor)": The fiber structure was not seemed to tightly adhere to the model and was easily peeled when pulled by a hand.

Table 1 shows the results.

[0037]

(3) Preparation of medical laminate and pressure test

25 A 150-μm-thick nonwoven fabric made of polyglycolide (NEOVEIL Type NV-M015G, Gunze Limited) was prepared as a fiber structure made of a bioabsorbable polymer.

Two sheets of the obtained fiber structure made of hydroxyethylated and carboxylated cellulose, a nonwoven fabric
30 made of polyglycolide, and one sheet of the fiber structure made of hydroxyethylated and carboxylated cellulose were stacked in the stated order and integrated to one another by needle punch entanglement to give a medical laminate. A 9-mm circle piece was punched out from the obtained medical laminate and used as
35 a test sample.

[0038]

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

A 24-mm circle piece was punched out from a collagen film (about 130 μm in thickness, Nippi. Inc.), washed with 70% ethanol, wiped to remove moisture, and set on a filter holder 2 (EMD Millipore Corporation, Swinnex(®)25). A 3-mm hole was punched at the center of the collagen film set on the filter holder 2. At a downstream side of the filter holder, a 20-ml syringe 3 (Terumo syringe SS-20ESZ, Terumo Corporation) and a pressure gauge 5 (Digital Manometer FUSO-8230, Fusorika Co., Ltd.) were set through a three-way cock 4. A pressure tester was thus prepared.

[0039]

Purified water was dropped onto a surface of the obtained test sample on the side where two sheets of the fiber structure made of hydroxyethylated and carboxylated cellulose were positioned. The test sample was then placed on the center of the collagen film set on the filter holder in such a manner that the surface where purified water was dropped was in contact with the collagen film. After standing for 15 minutes, air was delivered from the syringe until the test sample was peeled. The maximum pressure before the test sample was peeled was measured with the pressure gauge for evaluation of the pressure resistance (initial pressure resistance).

After evaluation of the initial pressure resistance, air was delivered from the syringe five times every five minutes for measurement of the maximum pressure before the test sample was peeled with the pressure gauge. Based on the results, the repeated pressure resistance was evaluated.

Table 2 shows the results.

[0040]

(Example 2)

Preparation of a medical fiber structure and a medical laminate, evaluation of the adhesion to damaged tissue, and the

pressure test were performed in the same manner as in Example 1, except that the TEMPO oxidation solution used in the TEMPO oxidation step was a TEMPO oxidation solution (TEMPO concentration: 20%owf, 5% sodium hypochlorite concentration: 350%owf, sodium bromide: 17.5%owf, pH 10 aqueous solution).

Tables 1 and 2 show the results.

[0041]

(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 9-mm circle piece was punched out from a 150- μ m-thick nonwoven fabric made of polyglycolide (NEOVEIL TypeNV-M015G, Gunze Limited).

A collagen film was set on the filter holder of the pressure tester prepared in Example 1. Then, 20 μ L of liquid A of fibrin glue (CSL Behring K.K., Beriplast P) was dropped onto the center of the collagen film in such a manner as to avoid the hole in the collagen film and spread in an approximately 9-mm-diameter shape. Next, the nonwoven fabric in the shape of a 9-mm circle was placed on the spread liquid A, and was impregnated with the liquid A. Then, 40 μ L of the liquid A was dropped onto the nonwoven fabric, and the nonwoven fabric was sufficiently impregnated with the liquid A. Then, 40 μ L of liquid B was dropped onto the nonwoven fabric.

After 15 minutes from dropping of the liquid B, air was delivered through the syringe, and the maximum pressure before the test sample was peeled was measured with the pressure gauge for evaluation of the pressure resistance (initial pressure resistance).

After evaluation of the initial pressure resistance, air was delivered through the syringe four times every five minutes, and the maximum pressure before the test sample was peeled was measured with the pressure gauge for evaluation of the repeated pressure resistance.

Table 1 shows the results.

[0042]

(Comparative Example 2)

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

10 The bleached knit was immersed in a TEMPO oxidation solution (TEMPO concentration: 20%owf, 5% sodium hypochlorite concentration: 180%owf, sodiumbromide: 17.5%owf, pH 10 aqueous solution) at 25°C for 10 minutes at a bath ratio of 1:30 to be oxidized. The oxidized knit was washed with water three times, and then immersed in a sodium chlorite solution (25% sodium chlorite concentration: 20%owf, CG1000 concentration: 1.0 g/L, pH 3.8 aqueous solution) at 80°C for 90 minutes at a bath ratio
15 of 1:15 to be carboxylated. The resulting knit was washed with hot water and then with water, and immersed in a hydrogen peroxide/sodium borohydride solution (30% hydrogen peroxide concentration: 1%owf, sodium borohydride concentration: 5%owf, PCL7000 concentration: 0.4 g/L, pH 10.5 aqueous solution) at
20 70°C for 20 minutes at a bath ratio of 1:20 for dechlorination treatment and treatment of reducing partially formed ketone to hydroxy groups. The obtained knit was further washed with hot water, neutralized, and washed with water. A medical fiber structure including a fiber structure made of carboxylated
25 cellulose was thus prepared.

The evaluation of the adhesion to damaged tissue, production of a medical laminate, and the pressure test were performed in the same manner as in Example 1, except that the obtained medical fiber structure was used.

30 Tables 1 and 2 show the results.

[0043]

(Comparative Example 3)

The evaluation of the adhesion to damaged tissue, production of a medical laminate, and the pressure test were
35 performed in the same manner as in Example 1, except that the

fiber structure used was a commercially available absorbable hemostatic agent prepared from regenerated oxidized cellulose (Johnson & Johnson K.K., Surgicel).

Tables 1 and 2 show the results.

5 [0044]

(Comparative Example 4)

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

10 An amount of 3.55 g of the bleached knit was immersed in 140 mL of a 10% sodium hydroxide aqueous solution at 15°C for 30 minutes so that the cellulose was alkalized. To the alkalized knit was applied a load of 2.5 to 3.0 kg for padding.

Next, 12.25 g of the obtained knit made of alkali cellulose
15 was immersed in 50 mL of a 0.8 mol/L solution of ethylene oxide in hexane at 25°C, and then reacted at 50°C for three hours. The reacted knit was immersed in 70 mL of a mixture of methanol and methyl isobutyl ketone (methanol:methyl isobutyl ketone = 35:35) at 25°C for five minutes to be washed, and then immersed
20 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 25°C for 10 minutes to be neutralized. 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
25 three minutes, and then in 70 mL of acetone at 25°C for five minutes. The resulting knit was then dried at 40°C for 24 hours to prepare a fiber structure made of hydroxyethylated cellulose.

As a result of analysis of the hydroxyethylated cellulose
30 of the resulting fiber structure using a thermal decomposition GC-MS, the molar ratio of a diethylene glycol group and an ethylene glycol group (diethylene glycol group/ethylene glycol group) was 0.20, and the molar ratio of a triethylene glycol group and an ethylene glycol group (triethylene glycol
35 group/ethylene glycol group) was 0.21.

[0045]

[Table 1]

	Adhesion to damaged tissue
Example 1	○○
Example 2	○
Comparative Example 1	○
Comparative Example 2	△
Comparative Example 3	×
Comparative Example 4	△

[0046]

5 [Table 2]

	Pressure resistance (mmHg)				
	First time (Initial pressure resistance)	Second time	Third time	Fourth time	Fifth time
Example 1	44.6	43.8	39.1	36.7	55.9
Example 2	45.6	45.3	37.5	50.8	43.3
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
Comparative Example 3	2.3	2.3	2.2	2.1	2.2
Comparative Example 4	59.3	56.3	55.1	62.4	65.3

INDUSTRIAL APPLICABILITY

[0047]

10 The present invention can provide a medical fiber structure and a medical laminate, which are capable of sufficiently adhering to damaged tissue to stop bleeding and more reliably reinforcing weakened tissue by preventing air leakage or fluid leakage.

15

REFERENCE SIGNS LIST

[0048]

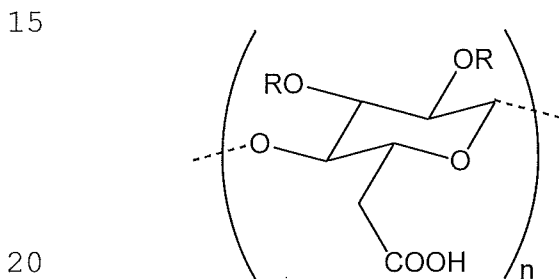
1. Pressure tester
2. Filter holder
3. Syringe
- 5 4. Three-way cock
5. Pressure gauge
6. Collagen film with a hole

CLAIMS

Claim 1. A medical fiber structure comprising
a fiber structure made of cellulose that is produced
5 through etherification and carboxylation of hydroxy groups of
cellulose.

Claim 2. The medical fiber structure according to claim
1,

10 wherein the cellulose that is produced through
etherification and carboxylation of hydroxy groups of cellulose
is cellulose that is produced through hydroxyalkylation and
carboxylation of hydroxy groups of cellulose, represented by
the following formula (1):



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

Claim 3. The medical fiber structure according to claim
25 1 or 2,

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

30

Claim 4. A medical laminate comprising
a laminate that includes the medical fiber structure
according to claim 1, 2, or 3 and a film or a fiber structure
made of a bioabsorbable polymer.

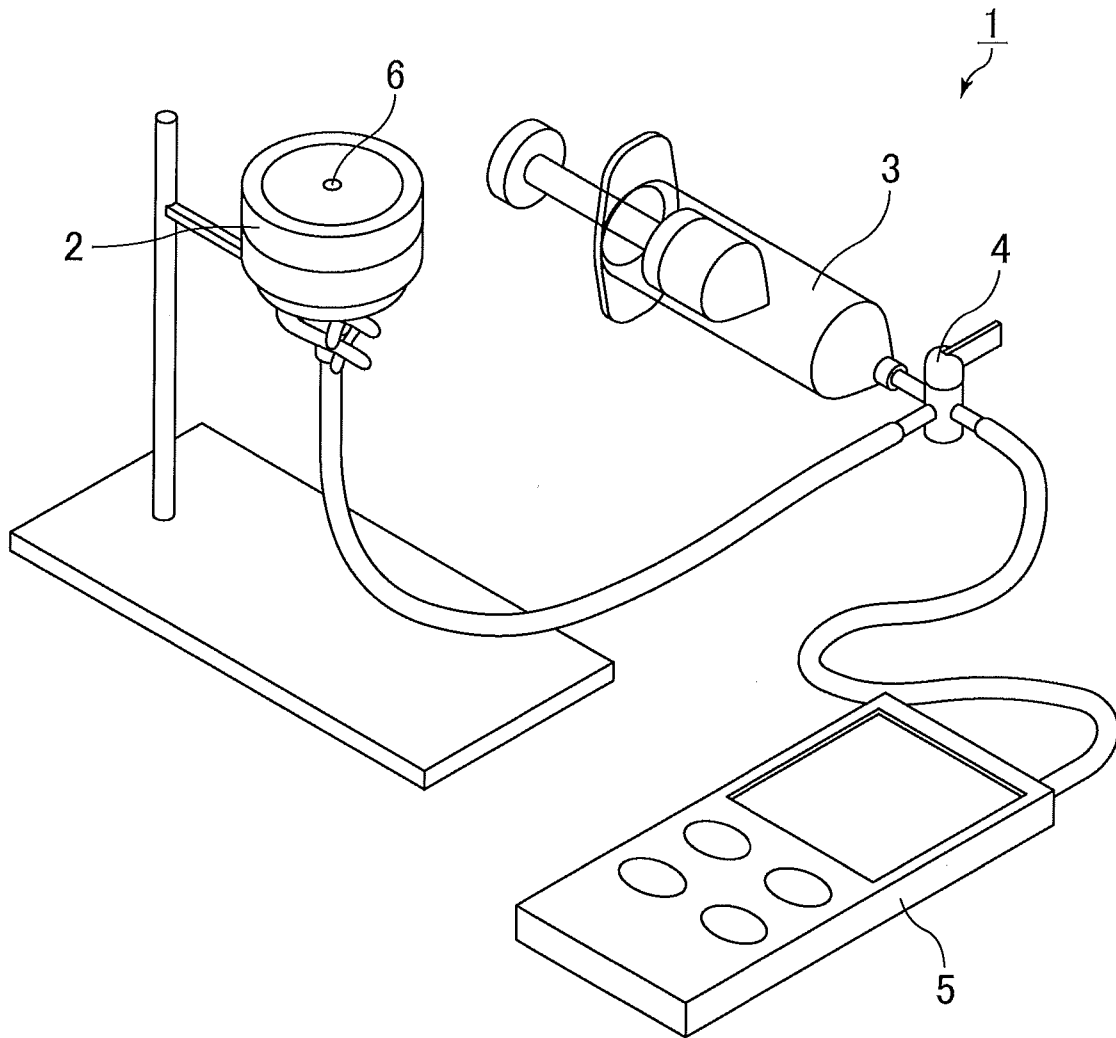
35

Claim 5. The medical laminate according to claim 4,
wherein the bioabsorbable polymer is a α -hydroxy acid
polymer.

5 Claim 6. The medical laminate according to claim 5,
 wherein the α -hydroxy acid polymer is a homopolymer or
 a copolymer prepared by polymerization of at least one monomer
 selected from the group consisting of glycolide, lactide,
10 ϵ -caprolactone, dioxanone, and trimethylene carbonate.

1/1

FIG.1



INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/084448**A. CLASSIFICATION OF SUBJECT MATTER**

C08B 15/04(2006.01)i; C08B 11/08(2006.01)i; A61L 15/28(2006.01)i; D06M 13/355(2006.01)i; D06M 13/11(2006.01)i;
D06M 11/80(2006.01)i; D06M 11/50(2006.01)i; D06M 11/30(2006.01)i; D06M 101/06(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)

C08B; A61L; D06M

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; cellulose, carboxylation, etherification, hydroxyalkyl, medical, fiber, laminate, bleeding, blood, hemostatic, stanch

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 104208742 A (BEIJING NATONG TECHNOLOGY GROUP CO LTD) 17 December 2014 (2014-12-17) claims 1-20	1, 3-6
X	CN 101890179 A (HUZHOU FORYOU MEDICAL DEVICES CO LTD) 24 November 2010 (2010-11-24) claims 1-15	1, 3-6
X	CN 103429622 A (MITSUBISHI CHEM CORP ET AL.) 04 December 2013 (2013-12-04) paragraphs [0024], [0046]-[0052], [0120]-[0136], [0283]-[0285]	1, 3-6
A	CN 104805723 A (UNIV DONGHUA) 29 July 2015 (2015-07-29) the whole document	1-6
A	US 2005/0028292 A1 (WEYERHAEUSER COMPANY) 10 February 2005 (2005-02-10) the whole document	1-6

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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“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

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“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

13 February 2017

Date of mailing of the international search report

03 March 2017

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P.R.CHINA
6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing
100088
China**

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Authorized officer

LING,Hui

Telephone No. (86-10)82246914

INTERNATIONAL SEARCH REPORT

International application No.

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/29309 A1 (WEYERHAEUSER COMPANY) 26 April 2001 (2001-04-26) the whole document	1-6

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2016/084448

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