Research Article

Safety and efficacy of a nerve matrix membrane as a collagen nerve wrapping: a randomized, single-blind, multicenter clinical trial

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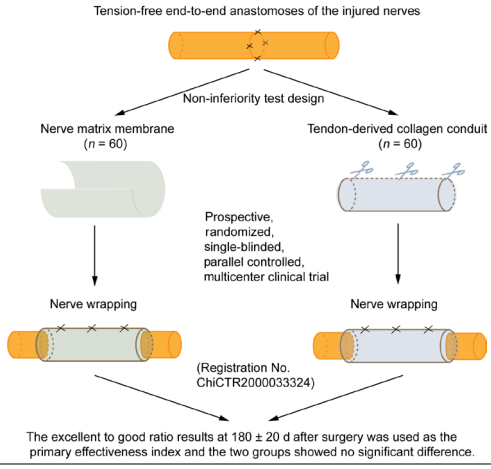
Graphical Abstract *The novel nerve matrix membrane may be considered an alternative treatment to the commercial bovine-derived collagen membrane*



Abstract

A new nerve matrix membrane derived from decellularized porcine nerves has been shown to retain the major extracellular matrix components, and to be effective in preventing adhesion between the nerve anastomosis sites and the surrounding tissues in a rat sciatic nerve transection model, thereby enhancing regeneration of the nerve. The effectiveness of the membrane may be attributed to its various bioactive components. In this prospective, randomized, single-blind, parallel-controlled multicenter clinical trial, we compared the safety and efficacy of the new nerve matrix membrane with a previously approved bovine tendon-derived type I collagen nerve wrapping. A total of 120 patients with peripheral nerve injury were recruited from Beijing Jishuitan Hospital, The First Bethune Hospital of Jilin University, and Yantai Yuhuangding Hospital, China. The patients were randomly assigned to undergo end-to-end and tension-free neurorrhaphy with nerve matrix membrane (n = 60, 52 male, 8 female, mean age 41.34 years, experimental group) or tendon-derived collagen nerve wrapping (n = 60, 42 male, 18 female, mean age 40.17 years, control group). Patients were followed-up at 14 ± 5, 30 ± 7, 90 ± 10 and 180 ± 20 days after the operation. Safety evaluation included analyses of local and systemic reactions, related laboratory tests, and adverse reactions. Efficacy evaluation included a static 2-point discrimination test, a moving 2-point discrimination test, and a Semmes–Weinstein monofilament examination. Sensory nerve function was evaluated with the British Medical Research Council Scale and Semmes–Weinstein monofilament examination. The ratio (percentage) of patients with excellent to good results in sensory nerve recovery 180 ± 20 days after the treatment was used as the primary effectiveness index. The percentages of patients with excellent to good results in the experimental and control groups were 98.00% and 94.44%, respectively, with no significant difference between the two groups. There were no significant differences in the results of routine blood tests, liver and renal function tests, coagulation function tests, or immunoglobulin tests at 14 and 180 days postoperatively between the two groups. These findings suggest that the novel nerve matrix membrane is similar in efficacy to the commercially-available bovine-derived collagen membrane in the repair of peripheral nerve injury, and it may therefore serve as an alternative in the clinical setting. The clinical trial was approved by the Institutional Ethics Committee of Beijing Jishuitan Hospital, China (approval No. 20160902) on October 8, 2016, the Institutional Ethics Committee of the First Bethune Hospital of Jilin University, China (approval No. 160518-088) on December 14, 2016, and the Institutional Ethics Committee of Yantai Yuhuangding Hospital, China (approval No. 2016-10-01) on December 9, 2016. The clinical trial was registered with the Chinese Clinical Trial Registry (registration number: ChiCTR2000033324) on May 28, 2020.

Key Words: clinical trial; extracellular matrix; nerve conduit; nerve matrix; nerve repair; neural regeneration; neurorrhaphy; peripheral nerve injury; sensory nerve recovery

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Introduction

Despite the progress in our understanding of the pathophysiology of peripheral nervous system injury and regeneration, the clinical techniques for repairing these injuries are still not optimal. End-to-end and tension-free neurorrhaphy, described by Sunderland (1951) more than 60 years ago, is still the gold standard for repairing complete nerve rupture without significant defects (Neubrech et al., 2016; Dahlin and Wiberg, 2017; Dunlop et al., 2019). Wrapping the anastomotic site is one of the few advances in this field because the use of a soft tissue envelope appears to minimize ischemia and scar formation, which can impede neural regeneration (Dy et al., 2018). Autologous vein for wrapping was the first material to be used in the clinical setting (Dy et al., 2018). However, the use of vein wrapping is limited by donor site morbidity and increased operative time. Accordingly, various commercially-available nerve wrapping materials have been developed, such as those that contain allogenic veins, collagen wraps, degradable polymer material film, and human amniotic membrane.

Type I collagen is an appealing material to use as a nerve wrap because it is known to have biocompatibility and selective permeability (Chowdhury et al., 2018; Yen et al., 2019). The most commonly-used source of type I collagen wraps is the bovine tendon (Dy et al., 2018). In a retrospective cohort study that included 41 patients with 42 lingual nerve injuries who underwent surgical repair by the same surgeon, patients treated with the type I collagen membrane demonstrated a greater level of functional sensory recovery compared with those treated without the membrane (Erakat et al., 2013). Lee et al. (2014) also evaluated the effects of wrapping material around a primary suture repair on motor nerve regeneration in a randomized controlled study of a rat model. They found that wrapping a bioabsorbable nerve conduit around a primary nerve repair offers advantages by decreasing perineural scar tissue formation (Lee et al., 2014).

Because each tissue has a unique extracellular matrix that possesses a distinct set of optimal substrates for specific cell types to attach and grow *in vivo* (Zhang et al., 2009), the nerve-derived extracellular matrix may contain a large amount of biological information that influences gene expression in regenerating nerve cells. However, the bovine-derived type I collagen membrane only contains a portion of the extracellular matrix, and the effect of this material on the regeneration of nerve cells may not be as great as that of nerve-derived materials. A new nerve matrix membrane derived from decellularized porcine nerves has been shown to retain the main extracellular matrix components, and to be effective in preventing adhesion between the nerve anastomosis sites and the surrounding tissues, thereby enhancing nerve regeneration in a rat sciatic nerve transection model, which could be attributed to its various bioactive components (Li et al., 2020). The purpose of this study is to compare the safety and efficacy of the new nerve matrix membrane with bovine tendon-derived nerve wrapping in the clinical setting.

Subjects and Methods

This clinical trial was approved by the Institutional Ethics Committee of Beijing Jishuitan Hospital, Beijing, China (approval No. 20160902) on October 8, 2016, approved by the Institutional Ethics Committee of the First Bethune Hospital of Jilin University, Changchun, Jilin Province, China (approval No. 160518-088) on December 14, 2016, and approved by the Institutional Ethics Committee of Yantai Yuhuangding Hospital, Yantai, Shandong Province, China (approval No. 2016-10-01) on December 9, 2016 (**Additional file 1**). We designed this study as a prospective, randomized, single-blind, parallel-controlled multicenter clinical trial (registration number: ChiCTR2000033324 at Chinese Clinical Trial Registry) on May 28, 2020. A nerve matrix membrane from Shandong Junxiu Biotechnology Co., Ltd. was used in the experimental group, and a tendon-derived collagen conduit (Tianxinfu Medical Appliance, Beijing, China), which is the only product approved by China Food and Drug Administration (licence No. 20163462399), was used in the control group. There were no changes to methods after trial commencement. We provided a detailed informed consent form to the subjects, which described the protocols of the trial, possible risks, and rights of patients. All patients in the trial signed the informed consent form (**Additional file 2**). The writing and editing of the article were performed in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) statement (**Additional file 3**).

Patient recruitment

Patients were included if they met the following criteria: 1) 18–70 years of age; 2) suffered from acute or subacute peripheral nerve injury; and 3) direct nerve anastomosis could be performed. The exclusion criteria were as follows: 1) neurological and other diseases such as diabetes that could potentially affect the nervous system; 2) autoimmune diseases or other severe physical diseases that could affect the research; 3) mental disease; 4) pregnant or breast-feeding women; 5) severe multiple nerve injury; 6) participants engaged in other research within a 3-month period; 7) patients who could not tolerate surgery; and 8) other serious conditions assessed by researchers. Patients were recruited by surgeons (the sixth to tenth authors) and signed informed consent in the emergency room. The flowchart of the study is shown in **Figure 1**.

Sample size calculation and randomization methods

The calculation formula for sample size is as follows:

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 [P_1(1-P_1) + P_2(1-P_2)]}{(\varepsilon - \delta)^2}$$

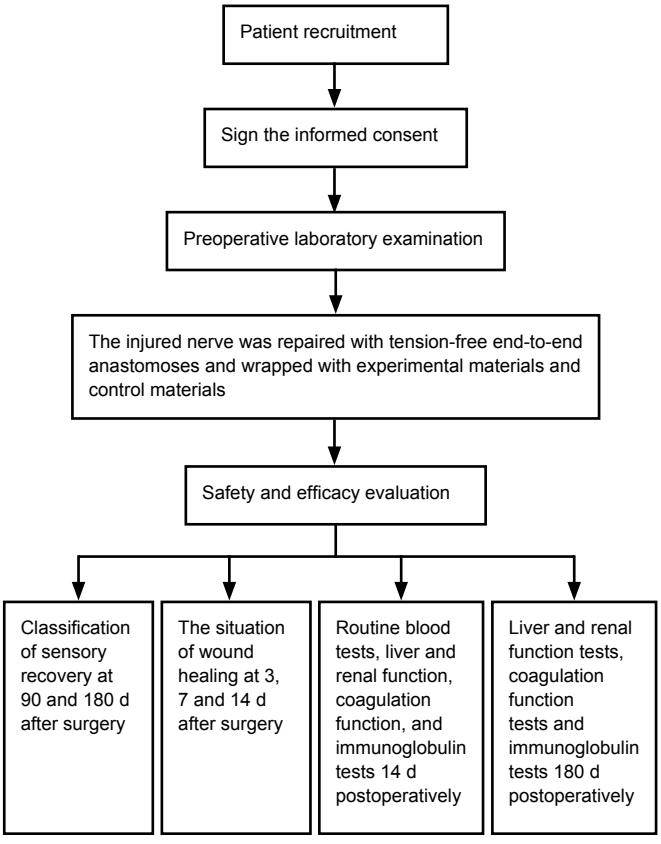

Figure 1 | **Flowchart of the study.**

where N is sample size; $Z_{1-\alpha/2}$ and $Z_{1-\beta}$ are Z-scores from the Z-table; P_1 is the probability for the experimental group; P_2 is the probability for the control group; δ represents the clinically significant limiting value; and ε is the true difference value between the two groups (Fang, 1997). Sample size calculation and randomized grouping were done by Beijing Chenger Medical Technology Co., Ltd., Beijing, China.

In this study, a non-inferiority test design was used. The ratio (percentage) of patients with excellent to good results 180 ± 20 days after treatment was taken as the primary effectiveness indicator. If the ratio in the experimental group was 97%, the non-inferiority standard was 10% compared with the control group (Altissimi et al., 1991; Wang et al., 1996; Segalman et al., 2001; Bulut et al., 2016; Fakin et al., 2016; Oruç et al., 2016). Forty-eight pairs of samples were calculated. Taking a maximum possible loss of 20% over the course of the study, we recruited 60 pairs of subjects, 120 subjects in total. When α = 0.025, there is more than 80% confidence (1 – β), which proves that the experimental group was not inferior to the control group. Using block randomization, all subjects were randomly divided into two equal-proportion groups; the size of the block was set to 4. SAS®9.4 software (SAS, Cary, NC, USA) was used for the procedure. According to the time sequence of the patients in each center, envelopes with sequential numbering were obtained. The number of patients admitted to each center was a multiple of 4. Each envelope contained a random code and grouping information, which were blinded before operation.

Nerve matrix membrane preparation

Fresh sciatic nerves were harvested from slaughtered 6-month-old Duroc-Landrace-Yorkshire swines (Yantai Guolian Food Processing Company; licence No. 20171003). Adipose tissue around the nerve and partial epineurium was removed, and the nerve was agitated and rinsed with purified water for 2 hours. Then, the nerve was subjected to a chemical decellularization process in a 0.5% trypsin solution and 3.0% Triton X-100. After rinsing with purified water, the porcine decellularized nerve matrix scaffold was lyophilized, crushed into powder, and treated with hydrochloric acid solution (1 mg/mL) containing pepsin at 37°C, with agitation, until completely dissolved. The solution was then freeze-dried as a film. The film was rinsed with purified water until the pH was neutral, freeze-dried again, and sterilized with cobalt-60.

Surgical procedure

The injured nerve was exposed and repaired with tension-free end-to-end anastomoses (Sunderland, 1951). The sites of nerve anastomoses in the experimental group were wrapped with the nerve matrix membrane, which was cut to a size appropriate for the diameter of the nerve. The wrap was closed with 8-0 nylon interrupted sutures (**Figure 2**). In the control group, the tendon-derived collagen nerve conduit was cut open longitudinally, and the anastomotic site was wrapped and then sutured as in the experimental group (**Figure 3**).

Follow-up

Patients were followed-up at 14 ± 5, 30 ± 7, 90 ± 10 and 180 ± 20 days after the operation. Follow-ups were conducted by senior surgeons (the first to fourth authors) who were blind to whether patients were in the control or experimental group. Efficacy evaluations included static 2-point discrimination (s2PD) tests, moving 2-point discrimination (m2PD) tests, and Semmes-Weinstein (SW) monofilament examination by Touch-Test™ Sensory Evaluators (North Coast Medical, Inc., Camino Arroyo, CA, USA; specifications (/10 mm): 6.65, 4.56, 4.31, 3.61 and 2.83), which was done at 90 ± 10 days and 180 ± 20 days after the operation. Sensory nerve function was evaluated with the British Medical Research Council Scale and SW monofilament examination (**Tables 1** and **2**). The primary indicator was the excellent to good ratio results at 180 ± 20 days after surgery.

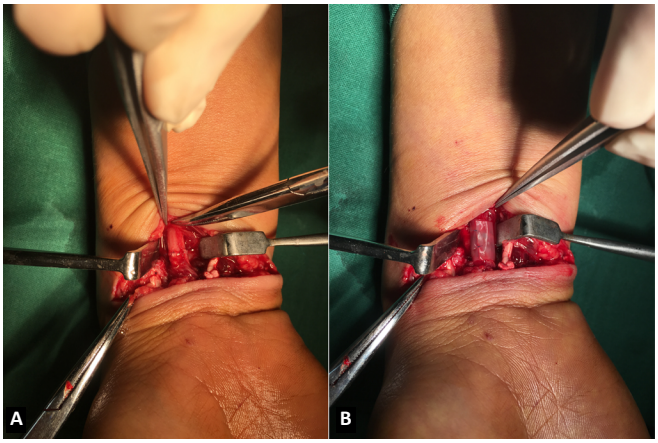

Figure 2 | **A nerve matrix membrane was used in injured nerve.**
(A) The injured nerve was repaired with tension-free end-to-end anastomoses. (B) The sites of nerve anastomoses were wrapped with the nerve matrix membrane, and the wrap was closed with 8-0 nylon interrupted sutures.

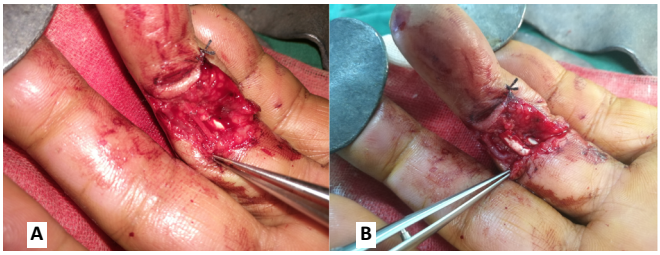

Figure 3 | **A tendon-derived collagen nerve wrapping was used in the injured nerve.**
(A) The injured nerve was repaired. (B) The sites of nerve anastomoses were wrapped with the nerve conduit which was cut open longitudinally.

Table 1 | **British Medical Research Council Scale Assessments**

Scale	Recovery	s2PD (mm)	m2PD (mm)
S0	No recovery of sensation in the autonomous zone of the nerve	–	–
S1	Recovery of deep cutaneous pain sensation within the autonomous zone of the nerve	–	–
S2	Recovery of superficial pain and some touch sensation	–	–
S3	Recovery of pain and touch sensation with disappearance of over-response	> 15	> 7
S3+	As S3, but localization of the stimulus is good and there is imperfect recovery of 2-point discrimination (7–12 mm)	7–15	4–7
S4	Complete recovery	2–6	2–3

m2PD: Moving 2-point discrimination; s2PD: static 2-point discrimination.

Table 2 | **Classification of sensory recovery**

Classification	British Medical Research Council Scale	Semmes-Weinstein monofilament examination
Excellent	S3+, S4	Normal or diminished light touch (2.83 or 3.61)
Good	S3	Diminished protective sensation (4.31 or 4.56)
Moderate	S2	Loss of protective sensation (6.65)
Poor	S0, S1	Anesthetic (cannot feel 6.65)

The safety evaluation included assessments of local and systemic reactions. Evaluation of local reactions included duration and extent of wound swelling and persistent pain, and volume and color of exudates. Evaluation of the systemic reactions included routine blood tests, liver and renal

function, coagulation function, and immunoglobulin tests at 14 ± 5 days postoperatively, and liver and renal function tests, coagulation function tests and immunoglobulin tests at 180 ± 20 days postoperatively. Related adverse events were also recorded.

Statistical analysis

Data were statistically analyzed by an independent data management service (Beijing Chenger Medical Technology Co., Ltd.).

Analysis sets

For the full analysis set (FAS), the intention-to-treat principle was used to establish the full set of subjects. The per-protocol set (PPS) was made up of the sub-group remaining after exclusion for breach of protocol according to the exclusion criteria. The safety set (SS) included all subjects with at least one safety evaluation. The efficacy analysis was based on the PPS, and the safety analysis was based on the SS.

Data analysis and evaluation

All statistical analyses were two-tailed and evaluated at a significance level of $P \leq 0.05$. SAS®9.4 software was used for statistical analysis. PASS®13.0 software (NCSS, LLC, Kaysville, UT, USA) was used to calculate the sample size.

Enrolment at each center was identified, and all subjects from each set were analyzed. The demographic characteristics (such as age and sex) and medical history of the patients were logged, and the age, sex, distribution of the injured nerves, time to repair and operation time were compared between the two groups. Nonparametric distribution data were expressed as median value and interquartile range, and analyzed with the Wilcoxon rank-sum test. Chi-square test or Fisher's exact test were used for categorical variables.

The last observation carried forward principle (Hamer and Simpson, 2009) was used for missing data transfer.

Results

Basic data of the peripheral nerve injury patients

In this study, 120 subjects were enrolled, and 16 (13.33%) were rejected because of inappropriate inclusion (5 patients), failing to complete the experiment (2 patients), being lost to follow-up (8 patients), or because of incorrect use of testing materials (1 patient). Overall, 120 cases (n = 60 per group) were included in the FAS, 104 were included in the PPS, 50 in the experimental group, 54 in the control group, and 119 were included as part of the SS. The only case excluded from the SS was subject 45, who was in the experimental group. Subject 45 presented with two injured nerves, and the researchers first repaired one nerve using the experimental group products, and then repaired another using the control group products.

The mean age of the patients in the experimental group was 41.34 ± 15.33 years (range 16.16–71.48 years) and the mean age in the control group was 40.17 ± 11.88 years (range 18.50–64.03 years). There was no significant difference between the two groups (P = 0.879). There were 52 male (86.67%) and 8 female (13.33%) patients in the experimental group, and 42 male (70%) and 18 female (30%) patients in the control group. There was a significant difference in sex distribution between the groups (P = 0.027).

Distribution of the injured nerves

Distribution of the injured nerves is shown in **Table 3**. Fisher's exact probability method was used to compare the injured nerves, revealing no significant difference between the groups (P = 0.649).

Time from injury to repair

The time from injury to repair data are shown in **Table 4**. Wilcoxon rank sum test was used to compare the time between injury and treatment. The statistical analysis showed that there was no significant difference between the two groups (P = 0.25).

Operation time

The operation times are shown in **Table 5**. Wilcoxon's rank sum test was used to compare the operation time between the groups, revealing no significant difference between the two groups (P = 0.237 in FAS, P = 0.357 in PPS).

Efficacy of nerve matrix membrane and tendon-derived collagen conduits on peripheral nerve injury

Results of the SW monofilament tests, s2PD and m2PD at 90 ± 10 days and 180 ± 20 days after surgery are shown in **Tables 6–8**. A rank sum test was used to compare the groups. There were no significant differences between the groups.

Classifications of sensory recovery at 90 ± 10 days and 180 ± 20 days after surgery are shown in **Tables 9** and **10**. A rank sum test was used to compare the results, revealing no significant difference between the two groups.

The excellent to good ratio results at 180 ± 20 days after surgery are shown in **Table 11**. There was no significant difference in excellent to good results between the

Table 3 | **Distribution of the injured nerves in peripheral nerve injury patients treated with nerve matrix membrane or tendon-derived collagen conduit**

Injured nerves	Experimental group	Control group
Median nerve	10(16.67)	6(10.00)
Digital nerve	37(61.67)	38(63.33)
Radial nerve	6(10.00)	9(15.00)
Ulnar nerve	7(11.67)	6(10.00)
Peroneal nerve	0	1(1.67)

Data are expressed as number (percentage), and were analyzed by Fisher's exact probability method. There were no significant differences between the experimental and control groups (P = 0.649).

Table 4 | **Time (h) from injury to repair of peripheral nerve injury patients treated with nerve matrix membrane or tendon-derived collagen conduit**

	Experimental group	Control group
n	50	50
Mean±SD	55.53±175.31	85.62±363.36
Median	3.00	4.00
Q1, Q3	2.00, 7.13	2.00, 8.63
Min, Max	0.25, 720.00	1.00, 2160.00

Data were analyzed with the Wilcoxon rank sum test. There were no significant differences between the experimental and control groups (P = 0.25).

Table 5 | **Operation time (min) in peripheral nerve injury patients treated with nerve matrix membrane or tendon-derived collagen conduit**

	FAS		PPS	
	Experimental group (n = 60)	Control group (n = 60)	Experimental group (n = 50)	Control group (n = 54)
Mean±SD	138.05±105.52	118.17±89.68	135.06±101.00	115.93±78.55
Median	118.5	92.5	118.5	95
Q1, Q3	60.00, 175.00	60.00, 167.00	60.00, 165.00	60.00, 164.00
Min, Max	30.00, 610.00	20.00, 470.00	30.00, 610.00	20.00, 470.00

Data were analyzed with Wilcoxon's rank sum test. There were no significant differences between the experimental and control groups (P = 0.237 in FAS, P = 0.357 in PPS).

Table 6 | Semmes-Weinstein monofilament test results among peripheral nerve injury patients treated with nerve matrix membrane or tendon-derived collagen conduit

	Experimental group (*n* = 50)	Control group (*n* = 54)	*P*-value
90±10 d			0.237
Cannot feel 6.65	2(4.00)	1(1.85)	
6.65	11(22.00)	16(29.63)	
4.31+4.56	35(70.00)	28(51.85)	
2.83+3.61	2(4.00)	9(16.67)	
180±20 d			0.357
Cannot feel 6.65	0	1(1.85)	
6.65	1(2.00)	2(3.70)	
4.31+4.56	23(46.00)	22(40.74)	
2.83+3.61	26(52.00)	29(53.70)	

Data are expressed as number (percentage), and were analyzed by rank sum test.

Table 7 | Static 2-point discrimination test results in peripheral nerve injury patients treated with nerve matrix membrane or tendon-derived collagen conduit

	Experimental group (*n* = 50)	Control group (*n* = 54)	*P*-value
90±10 d			0.762
2–6 mm	1(2.00)	2(3.70)	
7–15 mm	21(42.00)	23(42.59)	
> 15 mm	28(56.00)	29(53.70)	
180±20 d			0.799
2–6 mm	11(22.00)	13(24.07)	
7–15 mm	36(72.00)	38(70.37)	
> 15 mm	3(6.00)	3(5.56)	

Data are expressed as number (percentage), and were analyzed by rank sum test.

Table 8 | Moving 2-point discrimination test results among peripheral nerve injury patients treated with nerve matrix membrane or tendon-derived collagen conduit

	Experimental group (*n* = 50)	Control group (*n* = 54)	*P*-value
90±10 d			0.855
2–3 mm	0	0	
4–7 mm	5(10.00)	6(11.11)	
> 7 mm	45(90.00)	48(88.89)	
180±20 d			0.294
2–3 mm	3(6.00)	2(3.70)	
4–7 mm	26(52.00)	24(44.44)	
> 7 mm	21(42.00)	28(51.85)	

Data are expressed as number (percentage), and were analyzed by rank sum test.

Table 9 | Classification of sensory recovery at 90 ± 10 days in peripheral nerve injury patients treated with nerve matrix membrane or tendon-derived collagen conduit

	FAS		PPS	
	Experimental group (*n* = 60)	Control group (*n* = 60)	Experimental group (*n* = 50)	Control group (*n* = 54)
Excellent	1(1.67)	4(6.67)	1(2.00)	4(7.41)
Good	33(55.00)	30(50.00)	28(56.00)	28(51.85)
Moderate	20(33.33)	19(31.67)	19(38.00)	19(35.19)
Poor	6(10.00)	7(11.67)	2(4.00)	3(5.56)

The classification of sensory recovery is shown in Table 2. Data are expressed as number (percentage), and were analyzed by rank sum test. There were no significant differences between the two groups (P = 0.826 in FAS, P = 0.718 in PPS). FAS: Full analysis set; PPS: per-protocol set.

Table 10 | Classification of sensory recovery at 180 ± 20 days among peripheral nerve injury patients treated with nerve matrix membrane or tendon-derived collagen conduit

	FAS		PPS	
	Experimental group (*n* = 60)	Control group (*n* = 60)	Experimental group (*n* = 50)	Control group (*n* = 54)
Excellent	25(41.67)	22(36.67)	22(44.00)	21(38.89)
Good	29(48.33)	31(51.67)	27(54.00)	30(55.56)
Moderate	2(3.33)	2(3.33)	1(2.00)	2(3.70)
Poor	4(6.67)	5(8.33)	0	1(1.85)

The classification of sensory recovery is shown in Table 2. Data are expressed as number (percentage), and were analyzed by rank sum test. There were no significant differences between the two groups (P = 0.595 in FAS, P = 0.620 in PPS). FAS: Full analysis set; PPS: per-protocol set.

Table 11 | The ratio (percentage) of excellent to good results at 180 ± 20 days among peripheral nerve injury patients treated with nerve matrix membrane or tendon-derived collagen conduit

	FAS		PPS	
	Experimental group (n = 60)	Control group (*n* = 60)	Experimental group (n = 50)	Control group (*n* = 54)
Excellent to good	54(90.00)	53(88.33)	49(98.00)	51(94.44)
Moderate to poor	6(10.00)	7(11.67)	1(2.00)	3(5.56)
Moderate	2(3.33)	2(3.33)	1(2.00)	2(3.70)
Poor	4(6.67)	5(8.33)	0	1(1.85)

The classification of sensory recovery is shown in Table 2. Data are expressed as number (percentage), and were analyzed by rank sum test. There were no significant differences between the two groups (P = 0.768 in FAS, P = 0.411 in PPS). FAS: Full analysis set; PPS: per-protocol set.

experimental and control groups in the FAS or PPS. The sensitivity analysis showed that the non-inferiority conclusion was credible (**Table 12**).

Safety, complications and adverse events associated with the nerve matrix membrane or tendon-derived collagen conduit on peripheral nerve injury

Subject 53 in the experimental group underwent replantation of the hand, which had been amputated. This was done with experimental material 10 days after the replantation surgery because of necrosis. The wound healed 1 month following the procedure. Subject 71 in the control group had crush injuries in the hand and forearm, and subsequently underwent three operations; eventually he had his middle finger amputated. The wound healed after skin grafting by the 3-month follow-up. These two patients were excluded from PPS. The other patients healed well with no complications 14 days after the operation.

Subject 21 in the experimental group suffered from pompholyx 7 days after the operation, which resolved 13 days later. The routine blood tests and immunoglobulin tests 14 days postoperatively in this patient were normal. Subject 44 in the control group suffered from a slight fever 3 days after the operation, which lasted for 1 day. There were no material-related adverse events such as local infection, synovitis or allergic maculopapular rash in either group.

Routine blood tests, liver and renal function, coagulation function, and immunoglobulin tests 14 days postoperatively

Changes in routine blood tests, liver and renal function tests, coagulation tests, and immunoglobulin tests between the

screening period and 14 days after the operation are shown in **Table 13**. Chi-square test or Fisher's exact test was used for qualitative index comparisons. These tests revealed no significant difference between the two groups.

Liver and renal function tests, coagulation function tests and immunoglobulin tests 180 days postoperatively

Changes in liver and renal function tests, coagulation tests and immunoglobulin tests between the screening period and 180 days following the surgery are shown in **Table 14**. Chi-square test or Fisher's exact test was used for qualitative index comparisons, which indicated no significant difference between the two groups.

Discussion

Nerve wrapping at the anastomotic site is an effective treatment option for the following reasons. First, the anastomotic site is separated from the surrounding tissues that supply a relatively closed chamber for nerve regeneration and growth maintenance. Second, a mechanical chamber can prevent the surrounding scar tissue from invading the nerve anastomotic site and allow room for sprouting axons to be well-aligned within the chamber. Third, it reduces neuroma formation by isolating the nerve from the inflammatory cascade and neurotrophic factor production triggered by nerve trauma in the surrounding tissues (Leuzzi et al., 2014).

Several types of wrapping films composed of different materials have been effective in animal models and clinical trials (Neubrech et al., 2018; Ren et al., 2018; Zhu et al., 2018; Colonna et al., 2019; Lopez et al., 2019; Sarhane et al., 2019; Zhang et al., 2019; Dietzmeyer et al., 2020; Wang et al., 2020).

Table 12 | **Non inferiority evaluation of sensory recovery at 180 ± 20 days in peripheral nerve injury patients treated with nerve matrix membrane or tendon-derived collagen conduit (sensitivity analysis)**

Set	REG (EG, %)	REG (CG, %)	Difference between 2 groups (%)	*P*-value	Non-inferiority Margin (%)	95% CI (%)
FAS	90.00	88.33	1.67	0.020	–10.00	–9.45, 12.78
PPS	98.00	94.44	3.56	< 0.001	–10.00	–3.68, 10.79

CG: Control group; CI: confidence interval; EG: experimental group; FAS: full analysis set; PPS: per-protocol set; REG: the ratio of excellent to good.

Table 13 | **Comparison of routine blood tests, liver and renal function tests, coagulation tests and immunoglobulin tests among peripheral nerve injury patients treated with nerve matrix membrane or tendon-derived collagen conduit between the screening period and 14 days after operation**

	Experimental group (*n* = 59)				Control group (*n* = 60)				
	Normal-normal	Normal-abnormal	Abnormal-normal	Abnormal-abnormal	Normal-normal	Normal-abnormal	Abnormal-normal	Abnormal-abnormal	*P*-value
Hgb	36(78.26)	3(6.52)	4(8.70)	3(6.52)	42(82.35)	3(5.88)	2(3.92)	4(7.84)	0.85
RBC	32(69.57)	2(4.35)	5(10.87)	7(15.22)	35(68.63)	3(5.88)	7(13.73)	6(11.76)	0.93
WBC	26(56.52)	3(6.52)	15(32.61)	2(4.35)	29(56.86)	0(0.00)	19(37.25)	3(5.88)	0.36
Platelet	34(73.91)	8(17.39)	3(6.52)	1(2.17)	44(86.27)	4(7.84)	1(1.96)	2(3.92)	0.3
Neutrophils	20(43.48)	3(6.52)	20(43.48)	3(6.52)	22(43.14)	2(3.92)	22(43.14)	5(9.80)	0.9
Lymphocyte	36(78.26)	3(6.52)	7(15.22)	0(0.00)	36(70.59)	2(3.92)	10(19.61)	3(5.88)	0.41
ALT	33(78.57)	6(14.29)	3(7.14)	0(0.00)	37(82.22)	3(6.67)	3(6.67)	2(4.44)	0.44
AST	28(66.67)	11(26.19)	0(0.00)	3(7.14)	34(73.91)	7(15.22)	1(2.17)	4(8.70)	0.51
BUN	37(90.24)	1(2.44)	2(4.88)	1(2.44)	37(78.72)	1(2.13)	8(17.02)	1(2.13)	0.25
Cr	35(85.37)	1(2.44)	3(7.32)	2(4.88)	35(76.09)	1(2.17)	8(17.39)	2(4.35)	0.59
PT	39(95.12)	0(0.00)	1(2.44)	1(2.44)	46(100.00)	0(0.00)	0(0.00)	0(0.00)	0.22
APTT	32(80.00)	2(5.00)	4(10.00)	2(5.00)	40(86.96)	1(2.17)	4(8.70)	1(2.17)	0.76
IgG	28(75.68)	3(8.11)	5(13.51)	1(2.70)	40(86.96)	1(2.17)	3(6.52)	2(4.35)	0.41
IgA	35(97.22)	0(0.00)	1(2.78)	0(0.00)	40(88.89)	3(6.67)	0(0.00)	2(4.44)	0.12
IgM	31(83.78)	0(0.00)	5(13.51)	1(2.70)	39(82.98)	1(2.13)	4(8.51)	3(6.38)	0.76

Screening period is the preoperative examination point. This time point may be 1 day before operation, 2 days before operation, or immediately before operation. Data are expressed as number (percentage), and were analyzed by chi-square test or Fisher's exact test. ALT: Alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Cr: creatinine; Hgb: hemoglobin; PT: prothrombin time; RBC: red blood cell; WBC: white blood cell.

Table 14 | **Comparison of liver and renal function tests, coagulation tests and immunoglobulin tests among peripheral nerve injury patients treated with nerve matrix membrane or tendon-derived collagen conduit at the screening period and 180 days after operation**

	Experimental group (*n* = 59)				Control group (*n* = 60)				
	Normal-normal	Normal-abnormal	Abnormal-normal	Abnormal-abnormal	Normal-normal	Normal-abnormal	Abnormal-normal	Abnormal-abnormal	*P*-value
ALT	41(87.23)	3(6.38)	3(6.38)	0(0.00)	37(78.72)	5(10.64)	3(6.38)	2(4.26)	0.59
AST	37(78.72)	6(12.77)	2(4.26)	2(4.26)	35((72.92)	7(14.58)	3(6.25)	3(6.25)	0.93
BUN	40(83.33)	3(6.25)	3(6.25)	2(4.17)	38(77.55)	2(4.08)	9(18.37)	0(0.00)	0.15
Cr	39(81.25)	2(4.17)	6(12.50)	1(2.08)	36(75.00)	3(6.25)	8(16.67)	1(2.08)	0.86
PT	47(97.92)	0(0.00)	1(2.08))	0(0.00)	53(100.00)	0(0.00)	0(0.00)	0(0.00)	0.22
APTT	41(85.42)	0(0.00)	6(12.50)	1(2.08)	48(90.57)	1(1.89)	2(3.77)	2(3.77)	0.31
IgG	35(81.40)	2(4.65)	5(11.63)	1(2.33)	41(82.00)	4(8.00)	5(10.00)	0(0.00)	0.77
IgA	41(95.35)	0(0.00)	2(4.65)	0(0.00)	46(93.88)	2(4.08)	0(0.00)	1(2.04)	0.17
IgM	35(81.40)	0(0.00)	6(13.95)	2(4.65)	42(85.71)	0(0.00)	6(12.24)	1(2.04)	0.81

Screening period is the preoperative examination point. This time point may be 1 day before operation, 2 days before operation, or immediately before operation. Data are expressed as number (percentage), and were analyzed by chi-square test or Fisher's exact test. ALT: Alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Cr: creatinine; PT: prothrombin time.

The membrane used in the control group was the only nerve wrap approved by the China Food and Drug Administration, and was composed of type I collagen. Type I collagen wraps have been used for the treatment of compressive neuropathy and the repair of nerve rupture in the clinical setting (Soltani et al., 2014; Kokkalis et al., 2016; Zhu et al., 2018). In the current study, we did not include a no-wrapping control group, because according to previous studies, almost all subjects given nerve wrapping had better outcomes compared with those who did not (Chowdhury et al., 2018; Dy et al., 2018; Lopez et al., 2019; Mukai et al., 2019).

In addition to acting as a physical barrier, extracellular matrix molecules, such as laminin, fibronectin and collagen, have been shown to play a significant role in axonal development and regeneration (Amado et al., 2010). Porcine nerve fascicles contain collagen, glycosaminoglycans, laminin and fibronectin, together with Schwann cells, all of which play critical roles in nerve regeneration (Zilic et al., 2015). Lin et al. (2018) used a hydrogel derived from porcine decellularized nerve matrix, with a preserved extracellular matrix composition and nanofibrous structure, and found that it supported Schwann cell proliferation and peripheral nerve regeneration. However, our findings suggest that multi-component membranes are not better than single component membranes *in vivo*. In the current study, membranes in the experimental group derived from porcine decellularized nerve matrix consisted mostly of extracellular matrix proteins, including fibronectin and collagens I and IV. These membranes were not more effective in promoting nerve recovery following end-to-end neurorrhaphy compared with bovine-derived type I collagen membranes. The SW monofilament tests, s2PD tests and m2PD tests at 3 and 6 months after surgery did not show any significant differences between the two groups. The percentages of patients with excellent to good results (the primary effectiveness index) in the experimental and control groups in the PPS were 98.00% and 94.44%, respectively, with no significant difference between the two groups. We therefore conclude that endogenous factors from the injured axons play a more important role than exogenous factors from the nerve wraps after direct neurorrhaphy. Nerve wrapping mainly functions as a physical barrier that blocks the overflow of nerve growth factors, reduces axonal escape, and prevents the extraneural scar tissue from growing into the anastomotic site. Thus, the development of new nerve wrapping materials may cease to be the focus of upcoming research. Increasing endogenous or exogenous growth factors in the chamber formed by the nerve wrapping membrane at the anastomotic site is more likely to improve functional recovery of the nerve. Indeed, Mukai et al. (2019) found that a collagen sheet wrap impregnated with basic fibroblast growth factor was superior to one without basic fibroblast growth factor and a no wrapping control in a rat model of sciatic nerve injury.

Only a few studies have compared two types of nerve wraps in animal experiments. Mathieu et al. (2012) studied the effects of a collagen membrane and a technique of autologous vein wrapping on scar formation after peripheral nerve repair, and found adhesions in the surrounding tissues and intraneural fibrosis were significantly less in the collagen membrane group than in the autologous vein wrapping group. Stocco et al. (2019) assessed the efficacy of two biodegradable wraps made of a synthetic 1% oxidized polyvinyl alcohol and a natural leukocyte-fibrin-platelet membrane versus the bovine-derived type I collagen membrane. The oxidized polyvinyl alcohol and leukocyte-fibrin-platelet membrane wraps were both effective in preserving nerve integrity, thereby representing an alternative to the commercial collagen membrane (Stocco et al., 2019). To our knowledge, there are no clinical reports comparing different nerve wraps for nerve repair or the treatment of compressive neuropathy. Our present study provides much needed insight into the clinical effectiveness of these two different nerve wrapping materials.

Nerve recovery outcomes following repair have been variable in the literature. In a systematic review and meta-analysis, Dunlop et al. (2019) reported the surgical repair outcomes of adult digital nerve injuries. The range of normal sensibility achieved was between 8% and 60% following nerve repair, while almost all (94%) gained protective sensation, which is considered a good result, 6 months following surgery (Dunlop et al., 2019). It is reasonable to suggest that the percentage of excellent to good results was 97%, considering the improvement after nerve wrapping. The inclusion criteria were not limited to sensory nerve injury, and only evaluation of sensory function recovery was used in the study, which may have influenced the results; however, was no significant difference in the distribution of the injured nerves between the two groups, which may have helped mitigate its impact.

We assumed a maximum possible loss of 20% in the study process; however, the actual loss rate was 13.33%. For efficacy, we assumed a satisfaction rate of a non-inferiority standard of ±10%. As the rate was 1.67% in the FAS group versus 3.56% in the PPS group, the non-inferiority hypothesis was valid.

Various porcine decellularized materials have been shown to be safe for human use (Yanagawa et al., 2013; Wang et al., 2019). However, there are no reports on porcine decellularized nerve matrix material used in humans to the best of our knowledge. In the current study, the results of routine blood tests, liver and renal function tests, coagulation function tests, and immunoglobulin tests 14 and 180 days postoperatively revealed that there was no significant difference between the two materials. There were no material-related adverse events in either group. Therefore, we consider the porcine-derived neurogenic matrix membrane material to be as safe as type I collagen wraps for human use.

In addition, the cost of porcine-derived materials may be lower than that of bovine-derived materials; the market price of the neurogenic matrix membrane may be lower than that of the tendon-derived collagen conduit. Therefore, if the new nerve wrap is approved by the China Food and Drug Administration, it may reduce the financial burden on patients. Because of the subjectivity of sensory examination, the results of the SW monofilament test and the s2PD and m2PD tests may be affected by the patient's mental state, temperature and surrounding environment of the examination room. This may account for the difference in the ratio of excellent to good results of peripheral nerve recovery among published studies. Accordingly, during the follow-up after operation, we arranged for the same doctors to check the four patients from the same randomized block to reduce the effect of this systematic error on the results.

In conclusion, the porcine-derived neurogenic matrix membrane is not inferior to bovine-derived collagen membranes for the treatment of peripheral nerve injuries, and it may therefore be a suitable alternative to the commercial bovine-derived collagen membrane.

Author contributions: *Study conception and design: YBG, SC; Technical operation in experiment: LC, BTH, YBY, CY, LYS, YBR; data acquisition: YBG, ZGL, GDL, YG; data analysis and interpretation: YBG; manuscript writing: YBG; manuscript review: SC. All authors approved the final version of the manuscript.*
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No. 20160902) on October 8, 2016, approved by the Ethics Committee of the First Bethune Hospital of Jilin University, Changchun, Jilin Province, China (approval No. 160518-088) on December 14, 2016, and approved by the Ethics Committee of Yantai Yuhuangding Hospital, Yantai, Shandong Province, China (approval No. 2016-10-01) on December 9, 2016. This study was registered in the Chinese Clinical Trials Registry (Registration No. ChiCTR2000033324) on May 28, 2020.

Declaration of patient consent: *The authors certify that they have obtained the consent forms from patients. In the form, patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published.*

Reporting statement: *The writing and editing of the article were performed in accordance with the CONsolidated Standards Of Reporting Trials (CONSORT) statement.*

Biostatistics statement: *The statistical methods of this study were reviewed by the epidemiologist of Beijing Institute of Traumatology and Orthopaedics, China.*

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Data sharing statement: *Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices). Study protocol and informed consent form will be available immediately following publication, without end date. Results will be disseminated through presentations at scientific meetings and/or by publication in a peer-reviewed journal.*

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Additional files:

Additional file 1: *Hospital Ethics Approval (Chinese).*

Additional file 2: *Informed consent form (Chinese).*

Additional file 3: *CONSORT checklist.*

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Page
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	3-4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4-5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	5
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	8-7
Sample size	7a	How sample size was determined	5-6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	5-6
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5-6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5-6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5-6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5-6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5-6

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	6-7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8-9
	14b	Why the trial ended or was stopped	None
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	8,16-17
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8-9,17-19
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	9-10, 18-19
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	19
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	9
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12-13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10-12
Other information			
Registration	23	Registration number and name of trial registry	4-5,13
Protocol	24	Where the full trial protocol can be accessed, if available	4-5,13
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1,13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.