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Efficacy and safety of novel collagen conduits filled with collagen filaments to treat patients with peripheral nerve injury: A multicenter, controlled, open-label clinical trial

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ABSTRACT

Introduction: The safety and efficacy of using artificial collagen nerve conduits filled with collagen filaments to treat nerve defects has not been fully studied in humans. We conducted a multicenter, controlled, open-label study to compare the safety and efficacy of artificial nerve conduit grafts with those of autologous nerve grafts.

Methods: We included patients with a sensory nerve defect of ≤30 mm, at the level of the wrist or a more distal location, with the first-line surgical methods selected according to a patient's preference. We compared sensory recovery using static two-point discrimination and adverse events between the artificial collagen nerve conduit and autologous nerve grafting.

Results: The artificial nerve conduit group included 49 patients, with a mean age of 42 years and nerve defect of 12.6 mm. The autologous nerve graft group included 7 patients, with historical data of an additional 31 patients, with a mean age of 36 years and nerve defect of 18.7 mm. The rate of recovery of sensory function at 12 months was 75% (36/49) for the artificial nerve conduit group and 73.7% (28/38) in the autologous nerve group. No serious adverse events directly associated with use of the artificial nerve conduit were identified.

Conclusions: The treatment of nerve defects ≤30 mm using artificial collagen nerve conduits was not inferior to treatment using autologous nerve grafts. Based on our data, the new artificial collagen nerve conduit can provide an alternative to autologous nerve for the treatment of peripheral nerve defects.

Introduction

Trauma and surgery, such as tumor resection, can cause peripheral nerve injury, with end-to-end nerve suturing or autologous nerve grafting performed to treat these injuries. If the nerve defect is too large for end-to-end suturing, an autologous nerve graft is selected. However, autologous nerve grafting requires that a normal nerve is sacrificed at a donor site. In order to avoid this, the feasibility of bridging the nerve defect with an artificial nerve conduit has been investigated.

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The first artificial nerve conduits were generated using non-biodegradable materials, such as silicon. Although these nerve conduits do support peripheral nerve regeneration, there is a risk of entrapment between the silicon conduit and the regenerating nerve [1]. As such, the development and use of nerve conduits constructed with biodegradable materials have been investigated.

Artificial nerve conduits constructed using polyglycolic acid (PGA) have been successfully used in humans to bridge a digital nerve defect [2,3]. Artificial nerve conduits constructed using collagen and poly-L-lactic acid (PLLA) have also been used, with outcomes comparable to those of the standard reconstruction techniques [4,5].

Nerve regeneration can be enhanced by filling the nerve conduit with certain substances, rather than using a hollow conduit [6,7]. PGA–collagen conduits filled with laminin-coated collagen fibers have been investigated in animal models, with peripheral nerve regeneration confirmed by clinical observation, electrophysiologic testing, and histological evaluation at 12 months post-surgery [8]. Furthermore, a clinical study using artificial PGA–collagen conduits filled with collagen sponges was performed in humans, with good recovery of sensory function and improvement of pain having been reported [9].

As collagen possesses a higher biocompatibility and cellular affinity than synthetic polymers [10], Nipro (United States patent US 6953482 B2) has developed an artificial nerve conduit that is constructed using only collagen, consisting an outer collagen cylinder and longitudinal collagen filaments (Fig. 1). A study of these collagen nerve conduits in female Beagle dogs provided a detailed assessment of the process of morphological, electrophysiological and functional recovery of the regenerated nerves [11]. Although the efficacy and safety of artificial collagen nerve conduits have been confirmed in animal experiments, the efficacy and safety in humans remain uncertain. Therefore, we conducted a multicenter, controlled, open-label clinical study to investigate the efficacy and safety of artificial collagen nerve conduits in patients with sensory nerve injury, at the level of the wrist or more distal location, and compared outcomes to those obtained for patients who underwent autologous nerve grafting.

Materials and methods

Collagen conduits filled with collagen filaments

Enzyme-solubilized collagen (a mixture of collagen types I and III) was dissolved in water to prepare an aqueous solution and extruded in a coagulating liquid to produce the collagen filaments used to fill the conduits. The outer cylinder of the conduit was formed by wrapping collagen fiber around a mandrel, with the cylinder subsequently filled with the aqueous solution containing longitudinally aligned collagen fibers. The constructs were frozen and then lyophilized in vacuo. The construct contained 10% v/v of collagen filaments under dry conditions. The product was sterilized with gamma ray irradiation.

The artificial collagen nerve conduit has passed several tests for safety, including: genotoxicity, carcinogenicity, and reproductive toxicity tests (ISO10993-3); in vitro tests of cytotoxicity (ISO10993-5) and effect after implantation (ISO10993-6); as well as testing for irritation, skin sensitization(ISO10993-10), and systemic toxicity (ISO10993-11).

Study design and patient population

A multi-center, controlled, open-label study was performed in 9 facilities in Japan, between February 2010 and September 2014. This study was approved by the institutional review board of each institution. Patients with open or closed traumatic injuries involving sensory nerves at the level of the wrist, or more distal lesions, were candidates for inclusion in this study, according to the following inclusion criteria: age, 20–64 years at the time of surgery; provision of written informed consent, including a statement that they agreed to participate in this clinical study at their own will; injuries consisting of a completely divided peripheral nerve, classified as a neurotmesis according to Seddon's

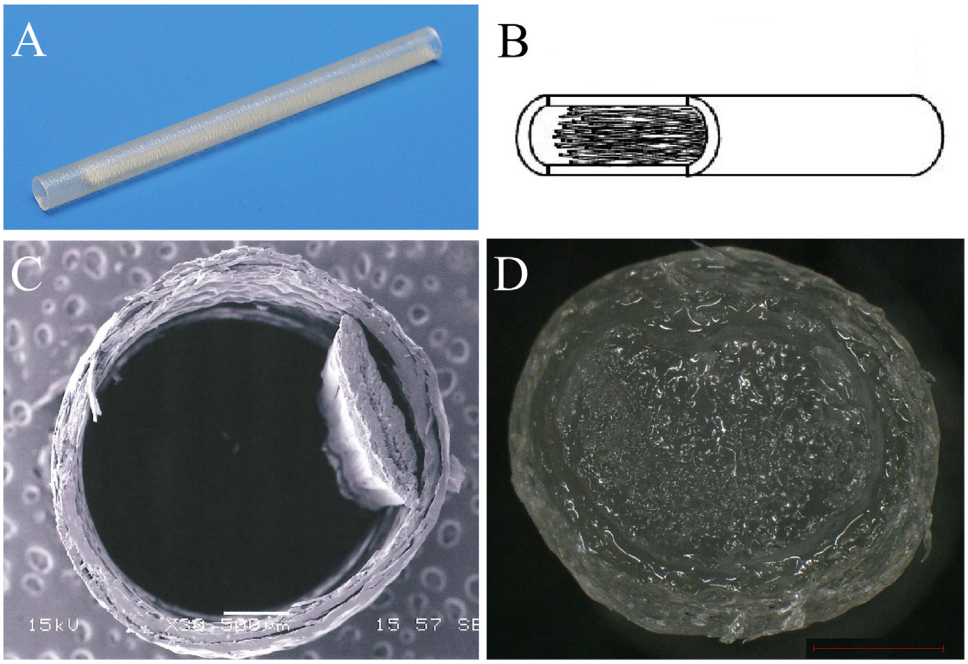

Fig. 1. The artificial nerve conduit.
A: Gross view of the artificial collagen nerve conduit filled with collagen filaments. B: Schema of the artificial collagen nerve conduit and collagen filaments. C: Electron microscope image of the collagen outer cylinder and collagen filaments (Dry state). Scale bar = 500 μm. D: Optical microscope image of the collagen outer cylinder and collagen filaments (Wet state). The outer cylinder was filled with the expanded wet filaments. Scale bar = 1 mm.

classification, an injury with nerve continuity but without any sign of clinical recovery or with continuous paresthesia, classified as an axonotmesis or neurotmesis; a peripheral nerve defect, 2–30 mm in length, measured after releasing the nerve or if the stumps could not withstand the tension required for suturing using an 8-0 nylon; and involvement of peripheral nerves with a diameter ≤3.7 mm to fit within the inner diameters of the conduits available, namely 1.0 mm, 1.3 mm, 2.0 mm, 2.3 mm, 2.8 mm, and 3.7 mm under wet condition. We also included patients with multiple finger injuries if one or more of the fingers met the criteria for nerve defects. Exclusion criteria included the following: inability to discriminate a 20 mm distance during a static two-point discrimination (s2PD) test; administration of anesthesia on the unaffected side; chronic peripheral nerve injuries (≥12 months after injury); presence of a central nervous system disorder that hindered assessment of the peripheral nerve treatment; severe crush injuries or soft tissue damage that were not amenable to reconstructive surgery; severely septic wounds; diabetic neuropathy or another peripheral neuropathy; current use of selected drugs known to affect sensation (cyclosporine, tacrolimus, nelarabine, docetaxel hydrate, paclitaxel, vincristine sulfate, bortezomib, sanilvudine, lamivudine, recombinant adsorbed hepatitis B vaccine (yeast origin), interferon alfa (NAMALWA), interferon alfacon-1 (genetic recombination), or metronidazole); lactating or pregnant women; and participation in concurrent clinical trial (including a drug clinical trial). Patients judged to be inappropriate for inclusion by the principal or co-investigators were also excluded.

Procedures

Surgeries were performed by surgeons with >10 years of hand and microsurgery. Patients were selected by the principal investigator or co-investigators according to the inclusion and exclusion criteria. At the time of consent to participate, the surgical method was confirmed with the patient, with the first-line surgical method selected according to each patients' preference.

The s2PD and Semmes-Weinstein test were measured using a two-point discriminator and an esthesiometer (Kono Seisakusho Co, Ltd., Chiba, Japan), on the palmar side of the hand and distal joint of the treated finger; measures were also obtained on the contralateral side as a control for comparison. The s2PD and Semmes-Weinstein test were assessed prior to surgery, as well as at 3, 6, 9, and 12 months post-surgery. Moreover, for patients with a neuroma in continuity, the s2PD and Semmes-Weinstein test were also performed at 1-week post-surgery to evaluate the regeneration of the repaired nerve. The primary investigator, co-investigators or study coordinators assessed each patient at all time points. Anesthesia was defined as a discrimination distance ≥16 mm, with a loss of protective sensation defined by an inability to detect a 447 g weight (red Semmes-Weinstein monofilament). The sensory function score, based on s2PD, was defined using the criteria of the Japanese Society for Surgery of the Hand [12] (Table 1). Recovery of sensory function was judged according to the classification criteria (Table 2). If multiple fingers had sensory disturbance due to one peripheral nerve injury, the finger that was farthest from the treated lesion was selected. Safety was assessed during and after surgery by the principal investigator or co-investigators.

Surgical treatment

The injured or damaged peripheral nerve was exposed, and both nerve ends were refreshed, as needed, if the nerve was completely divided or the damaged part of nerve was resected, despite presence of a continuity. The size of the artificial nerve conduit suitable for the nerve was selected and soaked in saline for >3 min, until complete expansion. The direction of the artificial nerve conduit was confirmed. The outer cylinder and filaments were aligned and attached to each other distally to ensure that there would be no slippage prior to cutting of the conduit. Proximally, there is a hollow space as the inner filaments are shorter than the outer cylinder. The artificial nerve conduit was then cut to the length of the nerve defect plus the length of the inserted nerve stump. The length of the nerve stump inserted into the conduit was recommended to be equivalent to the length of the inner diameter of the conduit. After the distal end of the artificial nerve conduit was cut, the attached portion was cut, creating a hollow space distally for inserting the nerve by pushing the filaments in a proximal direction (Fig. 2). The proximal nerve stump was positioned into the conduit and sutured with an epineurium (the nylon suture size was between 8 and 0 and 12-0). The epineurium of the proximal nerve was sutured to the collagen conduit with more than one suture, and fixed so that it did not emerge from the conduit. The distal nerve stump was then sutured into the artificial nerve conduit in the same way as for the proximal end, again to prevent the nerve from emerging from the conduit (Fig. 3).

Efficacy and safety assessment

The primary assessment of efficacy targeted the wrist or the more distal sensory nerve lesions. In cases of multiple nerve injuries ≤30 mm, the longest injury was targeted for evaluation. In cases with multiple nerve injuries of the same length, the most ulnar injury was targeted for evaluation. Recovery of sensory function was defined as 'Good or Excellent' according to the classification criteria based on the s2PD distance.

The primary endpoint of efficacy was recovery of sensory function for the targeted lesion at 12 months post-surgery, compared between the artificial nerve conduit and the autologous nerve graft group. The secondary endpoints of efficacy were the time until recovery of sensory function and the operative time.

Adverse events (AEs) were monitored to ascertain the safety of inserting the artificial nerve conduits in the patients. AEs were defined as any unfavorable event occurring after insertion of the artificial nerve conduits or autologous nerves, without concern of a causal relationship between the AE and the type of surgical repair. The investigators or co-investigators determined the severity of AEs using the following criteria: mild, the AE resulted in minor symptoms which allowed the patient to continue with the trial

Table 1
Evaluation criteria for sensory function score.

Score	Classification criteria
S0	Incapable of discriminating 20 mm distance or anesthesia
S1	Capable of discriminating 16 or 20 mm distance and having deep sensation
S2	Capable of discriminating 11 or 15 mm distance
S3	Capable of discriminating 6 or 10 mm distance
S4	Capable of discriminating 5 mm distance

Table 2
Classification criteria for sensory recovery.

s2PD score and s2PD distance (unaffected side)		s2PD score and s2PD distance(affected side)							
		S0	S1		S2		S3		S4
		Indiscernible	20 mm	16 mm	15 mm	11 mm	10 mm	6 mm	5 mm
S1	20 mm	Poor	Good	Good	Good	Good	Good	Excellent	Excellent
	16 mm	Poor	Good	Good	Good	Good	Good	Excellent	Excellent
S2	15 mm	Poor	Poor	Good	Good	Good	Good	Excellent	Excellent
	11 mm	Poor	Poor	Poor	Good	Good	Good	Excellent	Excellent
S3	10 mm	Poor	Poor	Poor	Good	Good	Good	Excellent	Excellent
	6 mm	Poor	Poor	Poor	Good	Good	Good	Excellent	Excellent
S4	5 mm	Poor	Poor	Poor	Good	Good	Good	Excellent	Excellent

s2PD, static two-point discrimination.

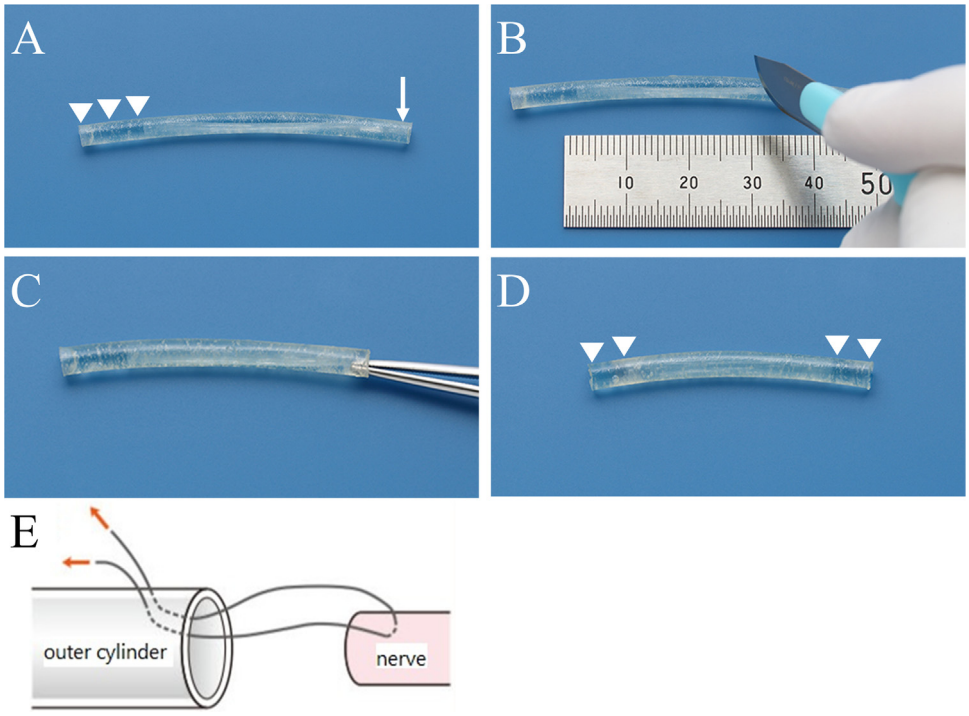

Fig. 2. Instructions when using the artificial nerve conduit.
A: The artificial collagen conduit (wet state). The outer cylinder and filaments were aligned and fixed to each other at distal side (arrow), with a hollow space available proximally of insertion of the nerve (arrowheads). B: The distal side of the conduit was cut to the length of the nerve defect plus the length of the inserted nerve. C: Pushing the filaments proximally. D: Hollow spaces were created at both sides of the conduit (arrowheads). E: The suture of nerve to the collagen conduit, with the nerve stump drawn by the suture and positioned into the collagen conduit.

without intervention; moderate, the AE required intervention but the patient was able to continue with the trial; severe, the AE caused serious problems, with considerable limitation in the performance of activities of daily living. The AEs were evaluated by third-party investigators, who had no conflicts of interest with the study. It is these objective evaluators who made a decision regarding the causal relationship between the AEs and the use of either the artificial nerve conduit or autologous nerves, using the following classification: related, probably related, possibly related, unrelated, and unknown relation.

Statistical analyses

The recovery of 80% of sensory function was deemed to be clinically meaningful. To compare recovery for the artificial nerve conduit to the autologous graft, taking into consideration that peripheral nerve injuries have varying clinical treatment outcomes, a target value of −25% between the sensory recovery for the artificial nerve conduit compared to the autologous nerve graft was used as a criterion of non-inferiority. Therefore, treatment of the lesion was deemed to be successful if the lower limit of the 95% confidence interval (CI) exceeded −25%, with 41 patients in each group needed to achieve a statistical power of 80%. Anticipating a 10% dropout rate, we set our target recruitment for each group to 46 patients. Between-group differences for continuous variables were evaluated using a *t*-test, with Fisher's exact test to compare the proportions of categorical variables between groups.

Results

Patients

Forty-nine patients who underwent artificial nerve conduit grafting and 7 patients who underwent autologous nerve grafting were enrolled in this study. In the artificial nerve grafting group, 25 patients had sustained a sharp injury and 24 a blunt or

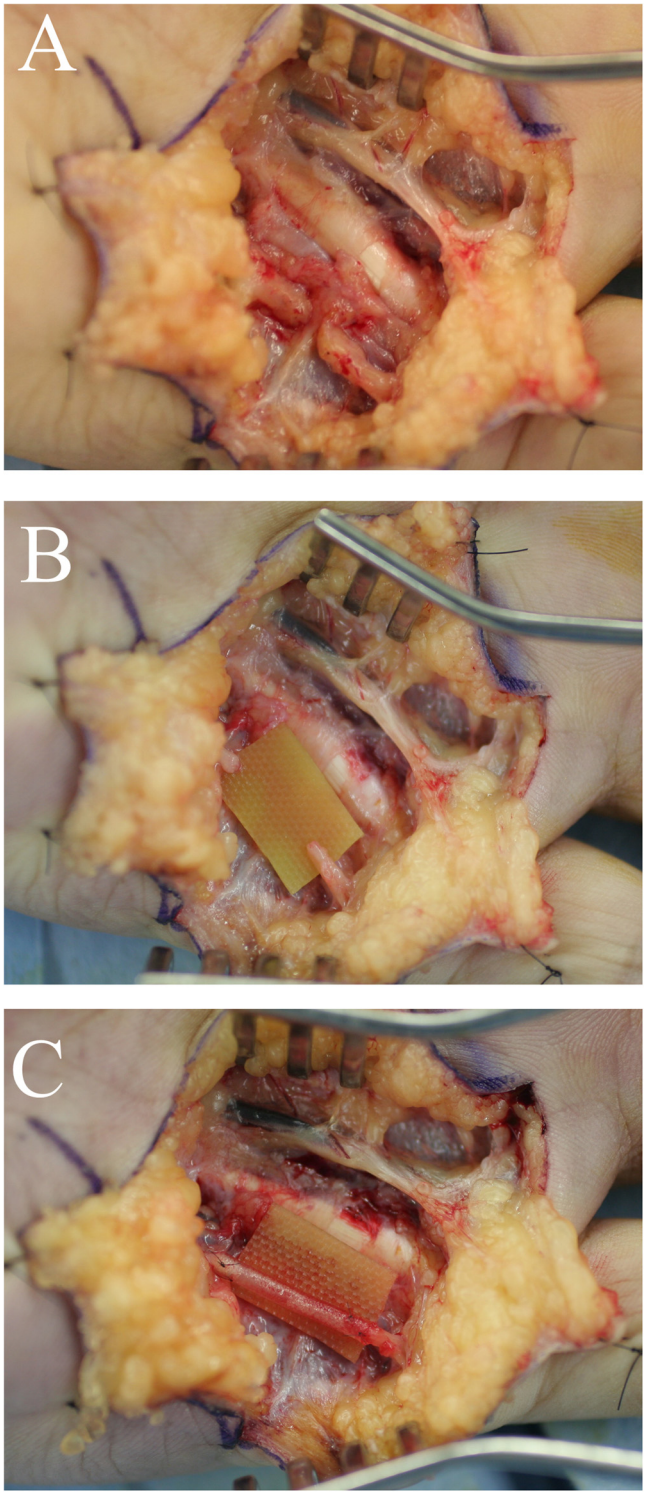

Fig. 3. Intraoperative photographs.
A: Injured digital nerve on the ulnar side of the left little finger (arrows). B: After refreshing both nerve ends. C: The digital nerve (arrows) was reconstructed using an artificial collagen nerve conduit.

crushing injury. In the autologous nerve group, 1 patient had sustained a sharp injury and 6 a blunt or crushing injury, with soft tissue reconstruction being possible. As only 7 patients opted to undergo nerve repair using an autologous graft during our trial, we added historical data from 31 patients who had undergone an autologous graft repair and for whom data on sensory recovery at 12 months post-surgery were available. Of these 31 patients, data for 6 patients were obtained from clinical records of affiliated hospitals; for the remaining 25 patients, we used previously published data [13–15]. Three articles were selected from the book by Mackinnon and Dellon for use as historical data [16]. We excluded cases of war trauma because the condition of the lesion was expected to be worse than for the lesions in our study. We included articles that had individual data on the length of the nerve defect and s2PD scores to compare to our dataset. For all data obtained from previous publications and for 4 of the 6 patients for whom data was obtained from the clinical records of the affiliated hospitals, the recovery of sensory function was evaluated based on the assumption of normal sensory function on the unaffected side.

The primary endpoints of efficacy and the proportion of all treated lesions in which sensory function recovered by 12 months after surgery were determined for both groups. One of the 48 patients in the artificial nerve conduit group was excluded from this assessment as the conduit needed to be removed for treatment of a wound infection. For the 31 patients with historical data, s2PD was measured only once after surgery and there were no data regarding AEs.

The mean age of patients in the artificial nerve conduit group was 42 years and 36 years in the autologous nerve group. The mean defect of the targeted nerve was 12.6 mm in the artificial nerve conduit group and 18.7 mm in the autologous nerve group (Tables 3A and 3B). Seven of the 48 patients in the artificial nerve grafting group and 2 of the 7 patients who underwent repair using an autologous graft presented with multiple nerve injuries.

The mean delay from the time of injury to surgery was 85 days (range, 2–331 days) for the artificial nerve conduit group, and 39 days (range, 4–113 days) for the 7 patients who underwent repair with an autologous nerve graft during this trial, and 4.4 months for 19 patients in the historical data group. A delay of 6 to 12 months between the injury and surgery was reported in another 12 patients in the historical data group.

Primary efficacy endpoint

Thirty-six patients in the artificial nerve conduit group and 28 patients in the autologous nerve group (5 of 7 were from this study, 23 of 31 were from historical data group) recovered sensory function based on the s2PD distance at 12 months post-surgery, for a sensory recovery rate of 75.0% (95% CI: 60%–86%) for the artificial conduit and 73.7% (95% CI: 57%–87%) for the autologous nerve graft. The difference in the recovery rate of sensory function between the two groups was 1.3% (95% CI: −20%–22%). In the artificial nerve conduit group, the distribution of recovery on the s2PD test, reported in Tables 4A and 4B, was as follows: S4 recovery, 13 patients; S3 recovery, 19 patients; S2 recovery, 4 patients; and S1 recovery, 5 patients. Among the 7 patients from this study in the autologous nerve graft group, 1 patient achieved an S4 recovery and 4 an S3 recovery. For patients in the historical data group, 3 achieved an S4 recovery; 16 an S3 recovery; and 4 an S2 recovery. For the Semmes-Weinstein Monofilaments test, 1 patient could not feel the red monofilament (447 g) in the artificial conduit group. Otherwise, at 12 months post-surgery, 5 felt the red monofilament; 15, the yellow (2.0 g); 15, the blue (0.4 g); and 12, the green (0.07 g) in the artificial nerve conduit group. In the autologous nerve graft group, 1 patient felt the red monofilament; 3, the yellow; 2, the blue; and 1, the green (Table 5).

Secondary endpoints of efficacy

Recovery of sensory function at 3 months post-surgery was identified in 21 patients (44%) in the artificial nerve conduit group

Table 3A
Patient demographics.

	Artificial nerve conduit (n = 48)	Autologous nerve (n = 38)	P-value
Mean age (SD)	42 (11.7)	36 (14.0)	0.032*
Range	20–63	14–67	
Mean size of the nerve defect, mm (SD)	12.6 (7.03)	18.7 (6.46)	<.0001**
Range	4.0–30.0	5.0–30.0	

SD: standard deviation.

and 4 (57%) in the autologous nerve group, with no significant difference in recovery time between the two groups (Table 6). The mean operative time was also comparable for the two methods (P = 0.06), with a mean of 124 min for the artificial nerve conduit group and 177 min for the autologous nerve graft group.

Safety

AEs were noted in 70% of patients in the artificial nerve conduit group and 86% of the patients in the autologous nerve graft group. The majority of AEs were mild-to-moderate in terms of severity, with a serious AE identified in 10 patients in the artificial nerve conduit grafting group and 2 patients in the autologous nerve grafting group. Serious AEs included: flexor tendon rupture, re-rupture or adhesion, wound infection, wound pain, anterior interosseous nerve palsy, perianal abscess, hemorrhoids, triangular fibrocartilage complex injuries, and joint contracture after tendon injury in the artificial nerve conduit group; and skin defect, purulent tendosynovitis, and bite wound at the operation site in the autologous nerve graft group. A causal relationship between the serious AE and artificial nerve conduits or autologous nerve grafts was ruled out in each case.

Wound infection occurred in 3 patients whose nerve defects were bridged using an artificial nerve conduit. One patient underwent removal of the artificial conduit because of wound infection related to poor care by the patient; this patient was subsequently excluded from the analysis. In the other two cases, the infection was mild and effectively treated with antibiotics. There was no causal relationship between the infection and the artificial nerve conduit graft in 1 of these patients, although a causal relationship could not be excluded in the other. Donor site pain was reported in 1 patient who underwent autologous nerve grafting. Damage to the collagen outer cylinder at the time of suturing was reported in 2 patients. Complex regional pain syndrome, type II and stump neuralgia were not reported.

Discussion

The effectiveness of artificial collagen conduits for the treatment of nerve defects has previously been demonstrated in a canine model [11], with the findings of effectiveness and safety being supported by our data for nerve defects of ≤30 mm at the level of the wrist (or more distal location) in humans. We provide evidence that the clinical outcomes for these injuries are not inferior when treated with a collagen artificial nerve conduit compared to an autologous nerve graft.

Collagen, which forms the epineural and perineural sheaths, plays an important role in the formation of the nerve tissue matrix and, therefore, in the nerve regeneration process [17]. Even in the absence of a conduit, collagen fibers can effectively guide axon regeneration [18]. A collagen conduit filled with collagen filaments provided a suitable environment for nerve regeneration comparatively with an autologous nerve graft.

In our study, the mean age of patients whose nerve defects were bridged using the artificial nerve conduits was statistically higher than for patients who underwent autologous nerve grafting. Previous retrospective studies reported that older age was associated with disability after a peripheral nerve injury [19]. However, the significant difference in mean age did not change our determination that the artificial nerve conduit graft was not inferior to an autologous nerve graft in the recovery of sensory function at 12 months post-surgery. Of note, however, the mean length of the nerve defect to be bridged was smaller in the artificial nerve conduits than in the autologous nerve graft group. This difference may have influenced our determination of the non-inferiority of the artificial nerve conduits to autologous nerve grafts. However, there was no significant difference in sensory recovery at 12 months between the two groups, indicative of the efficacy of the artificial nerve conduit graft as an alternative to autologous nerve grafting to bridge nerve defects ≤30 mm.

The majority of patients recovered sensory function at 3 months post-surgery in both groups, with no evidence of a relationship between the average length of the artificial nerve conduit used to bridge the nerve defects and the time until recovery of sensory function.

The mean operative time for artificial nerve conduit grafting was shorter than that of autologous nerve grafting, although this finding should be interpreted with caution due to the small number of patients in the autologous nerve group. The longer operative time when using an autologous graft likely reflects the additional time required to harvest the nerve graft.

No serious AEs were identified, regardless of the type of graft used. However, wound infection occurred in 3 patients whose nerve defects were bridged using an artificial nerve conduit, and the possibility of a causal relationship between infection and the artificial nerve conduit could not be denied in 1 patient. However, the previous study on artificial nerve conduit grafting in beagle dogs did not report any incidence of infection [11]. Similarly, no cases of infection associated with nerve repair were reported in the study using hollow PGA conduits in humans and PGA collagen conduits filled with collagen fibers in Beagle dogs [3,20]. Damage of the collagen's outer cylinder at the time of suturing was reported in 2 patients, with the damaged site removed in 1, while a suture repair was successfully performed in the other. These damages did not adversely influence the strength of the outer cylinders. As well, we did not identify any case of compression neuropathy, which reflects the minimal inflammatory response and scarring associated with the use of an artificial nerve conduit [4]. Therefore, entrapment of the anastomotic site due to scarring is less likely to occur [21].

The limitations of this study should be acknowledged. Data of 31 patients were added as historical data to the autologous nerve group to provide a comparator group against which to assess the efficacy and safety of an artificial nerve conduit. In adherence to the ethics of clinical practice, the first-line surgical method was selected based on patients' preference. In all patients from the previous studies and for 4 patients for whom data were obtained from the clinical records of affiliated hospitals, sensory function recovery was evaluated with the assumption of normal sensory function on the contralateral (unaffected) side. In all patients whose data were added as historical data, the s2PD score was measured not at 12 months but between 7 and 38 months after surgery. The difference of the timing of measurement may affect the s2PD scores and the judgment of the recovery of sensory function.

Table 3B
Characteristics of patients in the artificial or autologous nerve grafting groups.

Patient	Age (years)	Site of Injury	Type of Injury	Seddon's classification	Nerve defects (mm)	Time to surgery (d: day, m: month)	s2PD distance (mm)	Sensory recovery
Artificial nerve conduit								
1	39	Digital	Sharp	Neurotmesis	14	71 d	Indiscernible	Poor
2	41	Digital	Sharp	Neurotmesis	7	74 d	11	Good
3	28	Digital	Sharp	Neurotmesis	13	12 d	5	Excellent
4	37	Digital	Blunt	Neurotmesis	30	64 d	5	Excellent
5	62	Digital	Crush	Neurotmesis	30	110 d	16	Poor
6	59	Digital	Crush	Axonotmesis	8	65 d	Indiscernible	Poor
7	31	Digital	Crush	Neurotmesis	15	102 d	Indiscernible	Poor
8	35	Digital	Crush	Neurotmesis	7	2 d	20	Poor
9	43	Digital	Sharp	Neurotmesis	8	234 d	10	Excellent
10	51	Median	Crush	Neurotmesis	12	10 d	5	Excellent
11	55	Digital	Blunt	Neurotmesis	6	3 d	15	Good
12	25	Digital	Sharp	Neurotmesis	7	15 d	10	Good
13	41	Digital	Blunt	Neurotmesis	15	9 d	16	Poor
14	50	Digital	Sharp	Neurotmesis	8	6 d	10	Good
15	38	Digital	Blunt	Neurotmesis	6	90 d	6	Excellent
16	33	Digital	Crush	Neurotmesis	10	10 d	5	Excellent
17	58	Digital	Sharp	Axonotmesis	20	90 d	6	Excellent
18	20	Digital	Crush	Neurotmesis	17	238 d	Indiscernible	Poor
19	51	Digital	Sharp	Neurotmesis	8	30 d	cessation	cessation
20	33	Digital	Sharp	Neurotmesis	13	71 d	15	Good
21	29	Digital	Sharp	Neurotmesis	4	102 d	5	Excellent
22	38	Radial	Crush	Neurotmesis	30	115 d	6	Excellent
23	58	Ulnar	Sharp	Neurotmesis	10	29 d	10	Good
24	47	Digital	Sharp	Neurotmesis	7	38 d	6	Excellent
25	63	Digital	Sharp	Neurotmesis	8	165 d	10	Good
26	33	Ulnar	Sharp	Neurotmesis	8	83 d	5	Excellent
27	45	Digital	Sharp	Neurotmesis	7	25 d	5	Excellent
28	30	Digital	Sharp	Neurotmesis	7	9 d	10	Good
29	51	Radial	Blunt	Neurotmesis	22	98 d	10	Good
30	51	Digital	Sharp	Neurotmesis	15	90 d	5	Excellent
31	39	Digital	Sharp	Neurotmesis	12	76 d	10	Good
32	60	Digital	Sharp	Neurotmesis	7	34 d	5	Excellent
33	41	Digital	Blunt	Axonotmesis	21	170 d	5	Excellent
34	52	Digital	Sharp	Neurotmesis	5	10 d	5	Excellent
35	23	Digital	Sharp	Neurotmesis	12	73 d	10	Good
36	37	Radial	Blunt	Axonotmesis	10	293 d	5	Excellent
37	36	Digital	Sharp	Neurotmesis	9	15 d	10	Good
38	56	Digital	Sharp	Neurotmesis	15	34 d	10	Good
39	42	Digital	Sharp	Neurotmesis	11	95 d	Indiscernible	Poor
40	32	Ulnar	Blunt	Neurotmesis	20	87 d	5	Excellent
41	29	Radial	Blunt	Axonotmesis	10	178 d	16	Poor
42	58	Digital	Blunt	Neurotmesis	20	160 d	10	Good
43	55	Digital	Blunt	Neurotmesis	15	111 d	10	Good
44	25	Digital	Blunt	Neurotmesis	5	62 d	10	Good
45	52	Digital	Blunt	Neurotmesis	15	65 d	15	Good
46	60	Digital	Blunt	Neurotmesis	5	77 d	20	Poor
47	40	Digital	Sharp	Neurotmesis	10	331 d	6	Excellent
48	36	Digital	Blunt	Neurotmesis	8	45 d	Indiscernible	Poor
49	36	Digital	Crush	Neurotmesis	30	204 d	Indiscernible	Poor
Autologous nerve								
1	37	Digital	Blunt	Neurotmesis	25	12 d	Indiscernible	Poor
2	45	Digital	Blunt	Neurotmesis	8	78 d	5	Excellent
3	22	Digital	Crush	Neurotmesis	12	37 d	10	Good
4	30	Digital	Blunt	Neurotmesis	11	20 d	10	Good
5	30	Digital	Sharp	Neurotmesis	11	4 d	10	Good
6	52	Median	Blunt	Neurotmesis	26	113 d	Indiscernible	Poor
7	27	Digital	Crush	Neurotmesis	5	6 d	10	Good
8	39	Digital			20	92 d	10	Good
9	62	Digital			15	136 d	8	Good
10	62	Digital			13	12 d	3	Excellent
11	67	Digital			15	0 d	14	Good
12	14	Digital			20	0 d	Indiscernible	Poor
13	37	Digital			30	0 d	Indiscernible	Poor
14[12]	20	Digital			20	4 m	20	Poor
15[12]	22	Digital			30	4 m	20	Poor
16[12]	22	Digital			20	5 m	7	Good
17[12]	26	Digital			20	8 m	10	Good
18[12]	32	Digital			15	5 m	Indiscernible	Poor
19[12]	32	Digital			25	5 m	20	Poor
20[12]	41	Digital			30	2 m	15	Good
21[12]	44	Digital			15	6 m	20	Poor
22[12]	44	Digital			15	6 m	20	Poor
23[12]	45	Digital			30	7 m	15	Good

Table 3B (*Continued*)

Patient	Age (years)	Site of Injury	Type of Injury	Seddon's classification	Nerve defects (mm)	Time to surgery (d: day, m: month)	s2PD distance (mm)	Sensory recovery
24[12]	53	Digital			15	10 m	7	Good
25[12]	53	Digital			20	10 m	10	Good
26[13]	27	Digital			25	6 m<	6	Excellent
27[13]	17	Digital			20	6 m<	6	Excellent
28[13]	20	Digital			15	6 m<	8	Good
29[13]	18	Digital			20	6 m<	6	Excellent
30[13]	19	Digital			20	6 m<	4	Excellent
31[13]	53	Digital			10	6 m<	6	Excellent
32[13]	34	Digital			15	6 m<	5	Excellent
33[13]	54	Digital			20	6 m<	6	Excellent
34[13]	46	Digital			20	6 m<	6	Excellent
35[13]	40	Digital			15	6 m<	8	Good
36[13]	32	Digital			15	6 m<	10	Good
37[14]	28	Digital			25	4 m	10	Good
38[14]	36	Digital			20	4 m	14	Good

Data in gray-shaded cells are historical; s2PD, static two-point discrimination.

Table 4A
Number of patients with sensory recovery.

	Artificial nerve conduit (n = 48)	Autologous nerve (n = 38)	Between-group difference	P-value
Number of patients with sensory recovery (%) (95% CI)	36 (75.0) (60–86)	28 (73.7) (57–87)	(1.3) (−20–22)	0.9

CI: confidence interval.

Table 4B
Details of sensory recovery.

s2PD score and s2PD distance unaffected side		s2PD score and s2PD distance (affected side) Artificial nerve conduit group/Autologous nerve group							
		S0	S1		S2		S3		S4
		Indiscernible	20 mm	16 mm	15 mm	11 mm	10 mm	6 mm	5 mm
S1	20 mm								
	16 mm								
S2	15 mm				1/0				
	11 mm								
S3	10 mm							1/0	
	6 mm					1/0	1/0	1/0	
S4	5 mm	7/2	2/0	3/0	2/0		13/4	3/0	13/1

s2PD, static two-point discrimination.

Table 5
Results of the Semmes-Weinstein Monofilaments test.

Color	Force (gram)	Artificial nerve conduit n (%)	Autologous nerve n (%)
Green	0.07	12 (25)	1 (14)
Blue	0.4	15 (31)	2 (29)
Yellow	2.0	15 (31)	3 (43)
Red	447	5 (10)	1 (14)
No response for Red		1 (2)	0 (0)

Table 6
Number of patients with sensory recovery by time.

	Artificial nerve conduit (%)	Autologous nerve (%)	P-value
3 months	21/48 (44)	4/7 (57)	0.51
6 months	27/48 (57)	4/7 (57)	0.96
9 months	33/48 (70)	5/7 (71)	0.9
12 months	38/48 (80)	5/7 (71)	0.64

Conclusions

This study provides evidence that good treatment results can be achieved using an artificial nerve conduit to bridge defects ≤30 mm in length. To the best of our knowledge, this is the first study to have evaluated the effectiveness of artificial collagen nerve conduits filled with collagen filaments in humans. Based on our data, artificial collagen nerve conduit grafting could provide a suitable alternative treatment to autologous nerve grafting for the repair of peripheral nerve defects.

Conflict of interest

The authors declare the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: H. Hirata is a medical expert remunerated by Nipro. R. Nakamura is a consultant remunerated

by the study sponsor. The remaining authors have no conflicts of interest.

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Informed consent

Written consent was obtained from all patients before the start of the study.

Ethical publication statement

The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice, and followed the protocol approved by the institutional review board of each institution. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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