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Reconstruction of Upper Extremity Peripheral Nerve Injuries Using an Epineurial-Like Collagen Device—A Prospective Clinical Study

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Abstract

Background Epineurium acts as a barrier to protect nerves from injury and maintains its structural and functional integrity. A device was developed to mimic the native structure of epineurium. The aim of this study was to evaluate its biological characteristics and clinical performance in the reconstruction of upper extremity peripheral nerves.

Methods Scanning electron microscopy, transmission electron microscopy, and enhanced microcomputed tomography were used to examine the ultrastructural characteristics of the device. A prospective case series with 2-year follow-up was undertaken and reported. Patients who required nerve reconstruction in the upper extremities were included and underwent single or multiple nerve reconstructions in one or both upper limbs.

Results The device mimics the structural and biological properties of epineurium. During surgical use, it can form compression-free and self-engaged wrapping around the repaired nerves. A total of 36 peripheral nerve reconstructions were performed using either nerve transfer or nerve grafting in 19 patients. Of these, 14 patients had upper limb nerve injuries and 5 had C5 to C8 spinal cord injuries resulting in tetraplegia. Nerve reconstruction using the device restored peripheral nerve function, with functional motor recovery (FMR) observed in 76% of the most proximal target muscle at 12 months and 85% of most proximal muscles at 24 months post-treatment. FMR was observed in 61% of all target muscles at 12 months and 75% at 24 months post-treatment.

Keywords
- nerve reconstruction
- epineurium
- nerve transfer
- upper extremity

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Conclusion The device restored FMR in the upper extremities in patients with peripheral nerve or spinal cord injuries.
Level of Evidence Therapeutic IV

Peripheral nerve injuries, caused by trauma, surgical procedures, and degenerative disorders, are a common clinical problem worldwide.[1–4] Peripheral nerve injuries most commonly affect the upper limb and can result in intractable neuropathic pain, disability, and a lifelong impact on patients' quality of life.[5,6] For patients who have suffered neurotmesis, current practice suggests that surgical management to re-establish nerve continuity, combined with functional rehabilitation, remains the best option.[7–9] However, the outcome of surgical treatment often depends on patient factors (age, comorbidities, and severity of injury), surgical factors (timing of surgery and surgical technique), and compliance with rehabilitation.[10]

Autografts such as adipofascial/muscle flaps and autologous vein wraps have been tested for nerve repair. However, limited clinical evidence is available to support their efficacy.[11] Several nerve conduit devices have been developed as barriers, to mimic epineurium, to minimize epineural scarring, and support nerve regeneration.[4,11–13] Conduit designs utilize methods inherited from historical nerve repairs which used bone and vein for rigidity and strength to protect the nerve from compression or tension forces during repair.[14] Many of these conduits are composed of polymers or reconstituted/natural collagen and are commonly fashioned into a hollow tube or cuff, which is placed around the coaptation site.[15–19] Processed acellular nerve allografts (PNA), similar to the hollow tube of collagen conduits, are biodegradable and have been tested for nerve repair.[20] In a recent study, the use of PNA showed meaningful motor recovery in up to 82% of upper extremity nerve reconstructions.[20] However, PNA still have issues of potential disease transmission, and there are several issues in general regarding the use of nerve conduits for nerve reconstruction. Most currently available conduits are rigid and difficult to shape, with specific diameters not always appropriate for the coaptation site. Precise diameter of the conduits matching to both proximal and distal ends of the nerve is crucial to the clinical outcome of nerve reconstruction.[21] Prevention of epineural scar formation and minimizing the chances of ischemia of nerve are also critical for successful nerve reconstruction.[11]

Epineurium, the outermost layer that surrounds and encloses the peripheral nerve, acts as a protective barrier and provides mechanical and biological support to nerve axons.[22,23] Epineurium, containing dense irregular connective tissue composed of collagen-rich extracellular matrix, also provides an undulation to nerve and free of soft tissue adhesion, enabling longitudinal mobility of nerve within subcutaneous spaces. The epineural sheath has two distinct layers, consisting primarily of type I collagen, a small amount of type III collagen, and elastin fibers. The outer layer consists of relatively dense, large collagen fibers, and associated blood vessels, while the inner layer contains smaller collagen fibers and is in contact with the nerve itself.[24] Human epineurium constitutes up to 70% of the cross-sectional area of the peripheral nerve and its thickness ranges between 100 and 200 µm depending on the anatomical location.[25] Under normal physiological conditions, the epineurium has several functions. It acts as an anatomical and electrical barrier, protects the nerve from stretch injury, maintains the structural integrity of the nerve, and facilitates motion between the fascicles within the nerve and provides nutrients for nerve homeostasis.

Several animal studies have demonstrated that biological scaffolds mimicking the structure of the epineurium can act as protective barrier and provide a neurotrophic microenvironment for nerve regeneration. One study used epineurial allograft as an alternative to autografts, and others have produced epineurial sheath tubes.[26,27] The results have shown that the use of an epineurial-like structure decreases fibrosis around the repair sites, with similar nerve healing properties and reduced numbers of sutures required for tension free nerve repair. In addition, a biofabrication method has been developed to create a composite of chitosan, collagen, and hyaluronic acid that mimics the biological characteristics of epineurium.[28,29] While these studies have shown great promise for epineurium-mimicking constructs for nerve regeneration, none of these studies were able to proceed to human clinical studies.

Here, we have used a rollable bilayer collagen sheet designed to mimic the native structure and biological performance of epineurium. The device can act as a barrier structure to protect peripheral nerves and provides a favorable microenvironment to retain nutrients and neurotrophic factors required for axon regeneration. In a preclinical rat sciatic nerve repair model study, it was shown to form an epineurial-like structure at the coaptation site with induction of Schwann cell migration and axon outgrowth demonstrated distal to the coaptation site.[30] The purpose of this study was to evaluate the biological characteristics and clinical performance of the device in the reconstruction of upper extremity peripheral nerve injuries.

Methods

The collagen device, named Remplir, which recently received regulatory approval in Australia for peripheral nerve reconstruction, was supplied by Orthocell Ltd.

Structural Characterization

Scanning electron microscopy (SEM), transmission electron microscopy (TEM), and enhanced microcomputed tomography

(micro-CT) were used to examine the ultrastructural characteristics of the device. All analyses were performed at the Centre for Microscopy, Characterization and Analysis at The University of Western Australia. For SEM assessment, 1 cm squares of the device were mounted on a stub and sputter coated with a layer of platinum (Pt). Samples were analyzed using a Zeiss 1555 VP-FESEM (a high-resolution, field-emission variable-pressure scanning electron microscope; Carl Zeiss, Germany). For TEM, 2 mm squares of the device were cut and immersed in 2.5% glutaraldehyde fixative in 0.1M phosphate buffer. Samples were then embedded and sectioned for viewing under a JEOL JEM 2100 analytical transmission electron microscope (JEOL Ltd, Japan). For micro-CT assessment, the device was first stained with 0.3% potassium iodine solution as a contrast agent for viewing of soft tissues under micro-CT and 3D image reconstruction was performed using XM Reconstructor software, v10.7.3679.13921. These staining techniques provided a high-resolution image without damage to the samples.

Clinical Study Design and Participants

Adult patients aged between 18 and 50 years old with long segmental nerve damage, injury, or defect that required nerve transfer surgery were recruited for the study. Written informed consent was obtained from all participants prior to any study-related procedures being performed. All participants were given adequate time to review the approved informed consent form and ask the investigator any questions about the study. Patients who had confirmed tetraplegia with a preoperative motor level of injury at C5 or below and met the criteria of nerve transfer were also recruited for the study. We excluded patients with active infection or systemic pathology including inflammatory joint disease, human immunodeficiency virus, uncontrolled or poorly controlled diabetes, hepatitis, neoplastic disorders, known hypersensitivity to the study treatment or its excipients, known relevant medication allergy, known substance abuse, or concurrent medical condition which precludes the administration of the study treatment from the study. In total, 35 patients were screened and 19 were treated in the study. The requirement for use of the device (or appropriateness of the planned nerve repair procedure in general) was not able to be confirmed until assessment during surgery. The majority of exclusions occurred following this assessment. The study received approval from the Human Research Ethics Committee of St John of God Health Care and was registered with the Australian and New Zealand Clinical Trials Registry.

Surgical Intervention

Nerve reconstructions were conducted for patients who required nerve transfers or grafts. Participants underwent single or multiple nerve reconstructions in one or both upper limbs. The major reconstructive procedures were radial nerve (branch to triceps) transferred to axillary nerve for shoulder function: posterior axillary nerve to radial nerve (triceps function), nerve to supinator transferred to posterior interosseous nerve (finger and thumb extension), and musculocutaneous nerve (branch to brachialis) transferred to anterior interosseous or median nerve (finger and thumb flexion). All surgical procedures were performed by a single surgeon (A.O.B.). Surgeries were conducted under general anesthesia with the patient positioned as required for the most suitable surgical approach.

Donor and recipient nerves were identified with the use of a nerve stimulator and locator device and dissected away from surrounding fascia. Nerve stumps were coaptated with two anchored sutures using 8-0 nylon. The device was placed under the coaptation site with the rough (inner) side facing up and in direct contact with nerve epineurium (►**Fig. 1A–D**). The device was then wrapped around the coaptation site, with at least 1.5 cm coverage across proximal and distal stumps of the nerve, and then wrapped with minimum 30% overlay to create a self-engaged contact between the two surfaces of the device. After wrapping, the device forms a compression-free interface with the repaired nerves. As a result, the number of sutures required to stabilize the coaptation is reduced, thereby significantly reducing complexity of the microsurgical technique and operative time. The operated limb(s) were protected in a sling for 1 to 2 weeks postoperatively to protect the coaptation site. Standard postoperative therapy was done in an outpatient setting by an experienced occupational therapist (J.C.).

Outcome Assessments

A physical examination of the affected limb was conducted at baseline and at each postoperative clinic visit by an occupational therapist (J.C.). Efficacy endpoints including functional assessment and patient reported outcomes were described using the following criteria.

Motor Function

The British Medical Research Council (MRC) grading system is used for grading of muscle power as an assessment of motor function via manual muscle testing.[31,32] An MRC score of 3 or greater represents functional recovery in this patient population.[32] The MRC scale has been demonstrated to have substantial inter- and intrarater reliability for the upper limb and is suitable for use even where extreme muscle weakness exists.[33]

Sensory Function

Tactile gnosis is the ability to recognize the properties of objects through touch (e.g., texture) and is a key indicator of sensory function. Static two-point discrimination (s2PD) and moving two-point discrimination (m2PD) testing was used for determination of sensory function. s2PD and m2PD is an assessment tool that tests the ability of the patient to discern the shortest distance between two points that can be perceived as being separate.[34] Normal values for the fingers are less than 6 mm for static 2PD and 2 to 3 mm for moving 2PD. The static test measures the innervation density of slowly-adapting nerve receptors, while the moving test measures quickly-adapting nerve receptors.

Visual Analog Scale

Pain is a common outcome after peripheral nerve injury and contributes significantly to disability.[35–37] Paradoxically, both reduction and increase in pain can be associated with

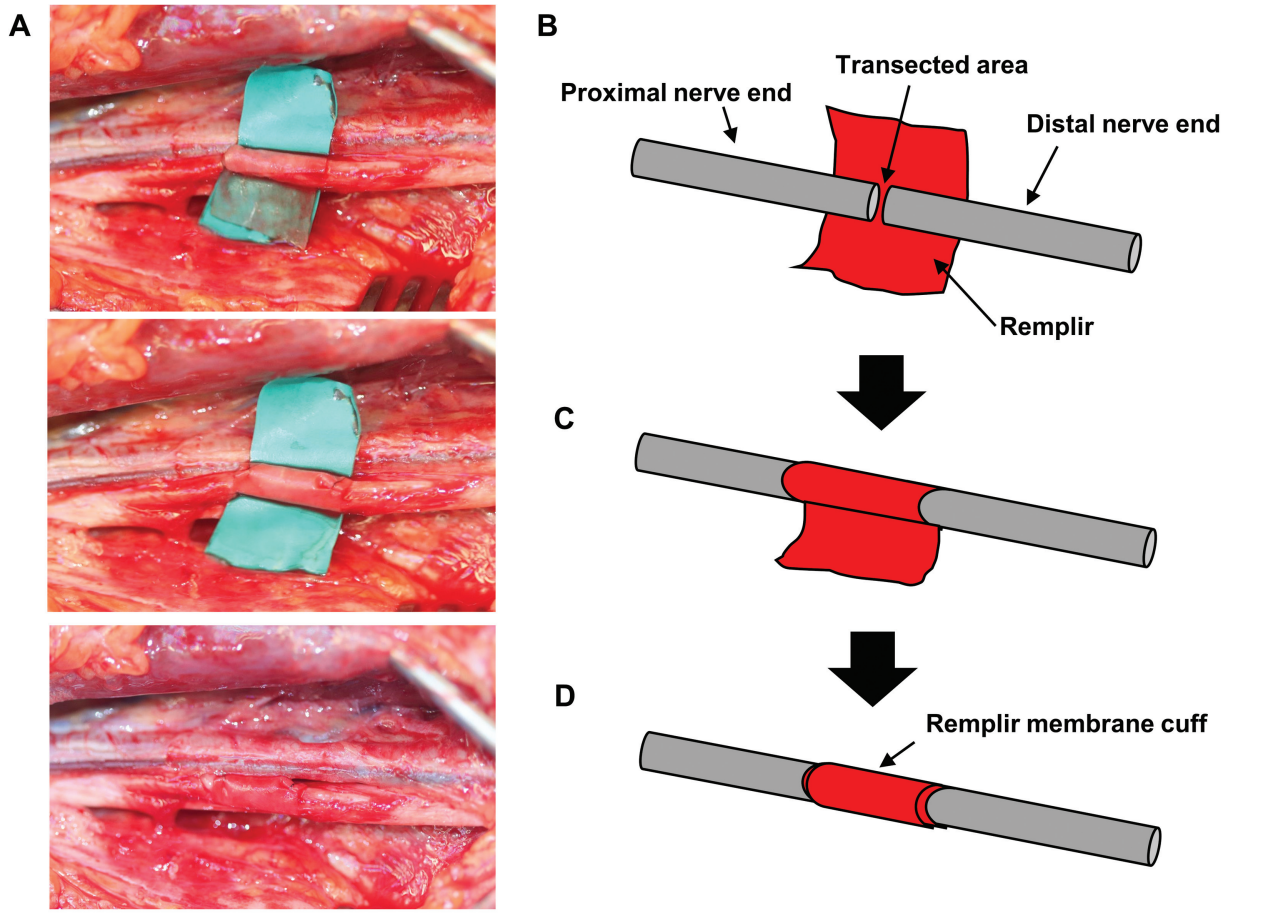

Fig. 1 Surgical procedure of nerve reconstruction using the device. (**A**) Surgical procedure of wrapping the device at the coaptation site. Note that the device forms a compression-free, self-engaged interface around the nerve. (**B–D**) Schematic diagram of laying and wrapping the device around the donor and recipient nerves at the coaptation site. Note that the device forms a compression-free, self-engaged interface around the nerve.

nerve regeneration after surgical repair. Participants rated worst pain at rest, at night and activity-related (lifting heavy object and performing repetitive task) on a standardized visual analog scale (VAS) from 0 (no pain) to 10 (worst pain ever).

Adverse Events

Information on adverse events and complications associated with study treatment or procedures was collected from visit 1, through to the final study visit.

Data Management and Analysis

The study was conducted in accordance with the approved protocol, Good Clinical Practice (GCP) and all applicable regulatory requirements. Assessments were recorded on paper-based case report forms for each participant.

Data from the VAS pain outcome measures were entered into SPSS (v27) for statistical analysis. One-way repeated measure analysis of variance was performed using time point as the within-subjects factor, with Greenhouse–Geisser correction applied to data that returned significant results for Mauchly's test of sphericity. Post-hoc testing was performed (where applicable) using Bonferroni correction. MRC scores were reported as median and interquartile range (IQR)

Results

Structural Characterization of Nerve Device

Enhanced micro-CT showed that the device consists of two distinct layers, an outer layer containing dense and transversely distributed collagen bundles and an inner layer containing most longitudinally distributed collagen bundles (►**Fig. 2A**). Characteristic D-spacing, a structural element of native collagen fibrils, was also observed (►**Fig. 2B**). The thickness was approximately 150 µm (►**Fig. 2A**), with a mean diameter of collagen fibrils of 90 ± 20 nm measured based on the cross-sectional view of the device (►**Fig. 2C, D**).

Patient Demographics

In total, 19 patients (2 females) with 2-year follow-up were reported in accordance with the PROCESS guidelines (►**Table 1** and ►**Fig. 3**). Five participants had a cervical spinal cord injury. Eight patients had traumatic injury to the brachial plexus. Six patients had upper limb peripheral nerve

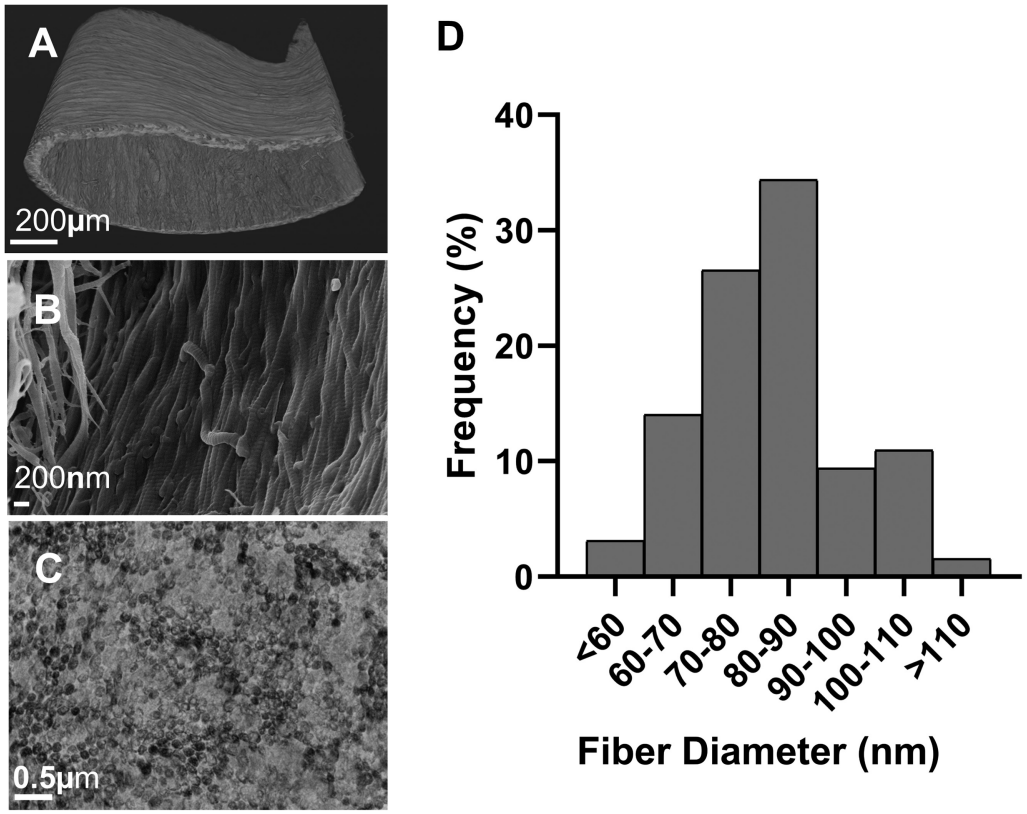

Fig. 2 Morphological characteristics of the device. (**A**) Enhanced micro-CT showed that outer layer containing dense and transversely distributed collagen bundles and an inner layer containing longitudinally distributed collagen bundles along the scaffold. (**B**) Surface view of inner layer by SEM. (**C**) Cross-sectional view of collagen fibrils by TEM. (**D**) Histogram distribution of collagen fibril diameters.

Table 1 Baseline patient demographics

Age	^36 (12.6)
Sex (M/F)	17/2
Number of limbs (L/R)	22 (11/11)
Time since injury (months)	^18.72 (43.03)
Mechanism of Injury	
Motor vehicle	10 (52.6%)
Sport/recreation	5 (26.3%)
Fall	2 (10.5%)
Other	2 (10.5%)
^Mean (SD)	

injuries. One patient with cervical spinal injury died 14 months postoperatively due to pneumonia and two patients were lost to follow-up after 6 months.

Evaluation of Outcomes

A total of 36 surgical procedures were conducted, 35 for the restoration of motor function and 1 to restore sensory function (►**Table 2**). Individual MRC grades for target muscles at 12 and 24-month follow-up are provided in ►**Supplementary Table S1** (available in the online version). The median overall MRC score for all nerve transfer at baseline was 0 (IQR 0; $n = 60$). At 6 months, the median MRC score improved to 1 (IQR 2; $n = 60$), with further improvement observed at 12 months (median MRC score $= 3$, IQR 2; $n = 59$) and 24 months (median MRC score $= 4$, IQR 1.25; $n = 48$) after surgery. A summary of outcomes of functional motor recovery (FMR) after surgery is provided in ►**Table 2**. As shown, FMR (MRC ≥ 3) was achieved in 61 and 75% of all target muscles at 12 and 24 months, while FMR was achieved in 76 and 85% of the most proximal target muscles at 12 and 24 months, respectively. ►**Fig. 4A–D** shows representative improvement in hand function of a 19-year-old male participant with C6 incomplete tetraplegia. In this participant, the nerve supplying the brachialis was transferred to the median nerve (left and right side), and the nerve supplying the supinator was transferred to the posterior interosseous nerve (right side only).

One participant received nerve transfer to restore sensory function to the ulnar nerve with no significant improvement of MRC. However, Semmes–Weinstein monofilament testing performed demonstrated an improvement from red (6.65) to purple (4.31) in the ring finger and blue (3.61) in the little finger.

Assessment of mean VAS pain scores was not significantly different between baseline and at 12 or 24 months after nerve reconstruction (►**Fig. 5**), suggesting that no participants experienced an increase in musculoskeletal or neuropathic pain after nerve reconstruction. Participants' use of

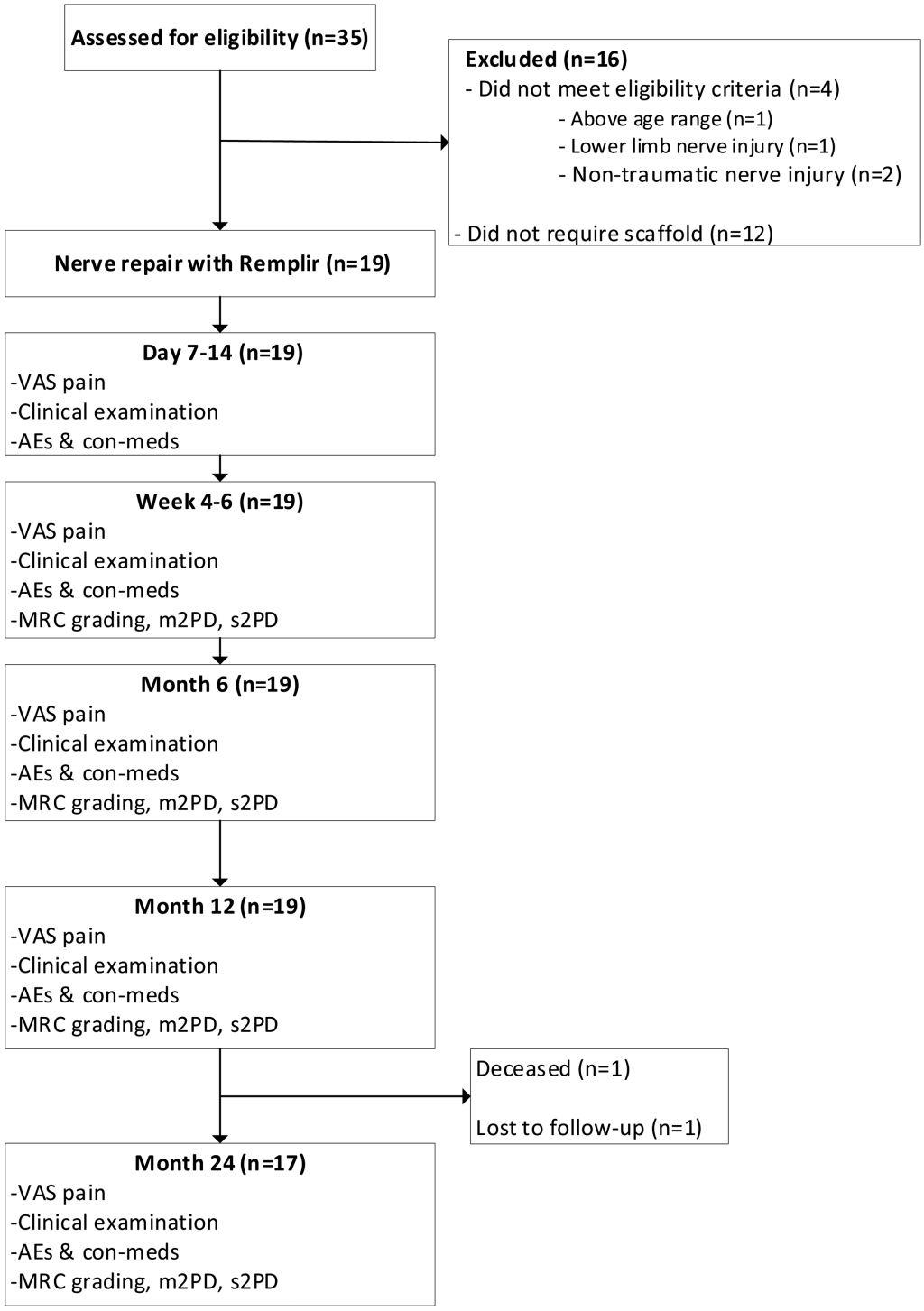

Fig. 3 The CONSORT flow diagram.

medication for chronic pain before and after study treatment is shown in ►**Table 3**. At baseline, 14 participants were prescribed more than one (mean 1.8 ± 1.56) medication of neuroleptics, antidepressants, opioids, and/or nonopioid analgesics. By month 24, 9/10 participants had ceased taking pain medication, and the remaining patient was taking a reduced dose. Of the four participants who required opiates at baseline, two reduced their dose and two ceased taking it.

Discussion

There is a long history of using nerve conduits for nerve reconstruction but, currently, there is not an "ideal nerve conduit" available. Dy et al hypothesized that an ideal conduct would be one that can act as a barrier to protect nerve axon growth and to minimize the chances of ischemia and scar formation.[11] However, the technical and

Table 2 Posttreatment MRC scores and functional motor recovery (FMR, MRC score of 3 or better) for all target muscles and most proximal target muscle to site of repair

Time point		MRC score					FMR
		0	1	2	3	4	
Baseline	Most proximal target	31/34 (91%)	1/34 (3%)	2/34 (6%)	0/34 (0%)	0/34 (0%)	n/a
	All targets	57/60 (95%)	1/60 (2%)	2/60 (3%)	0/60 (0%)	0/60 (0%)	n/a
Month 6	Most proximal target	7/34 (21%)	4/34 (12%)	12/34 (35%)	7/34 (21%)	4/34 (12%)	11 /34 (32%)
	All targets	24/60 (40%)	8/60 (13%)	15/60 (25%)	8/60 (13%)	5/60 (8%)	13 /60 (22%)
Month 12	Most proximal target	0/33 (0%)	1/33 (3%)	7 /33 (21%)	9/33 (27%)	16 /33 (48%)	25 /33 (76%)
	All targets	4/59 (7%)	7/59 (12%)	12 /59 (20%)	17 /59 (29%)	19 /59 (32%)	36/59 (61%)
Month 24	Most proximal target	0/27 (0%)	2/27 (7%)	2/27 (7%)	6 /27 (22%)	17 /27 (63%)	23/27 (85%)
	All targets	6/48 (13%)	3/48 (6%)	3/48 (6%)	10/48 (21%)	26 /48 (54%)	36 /48 (75%)

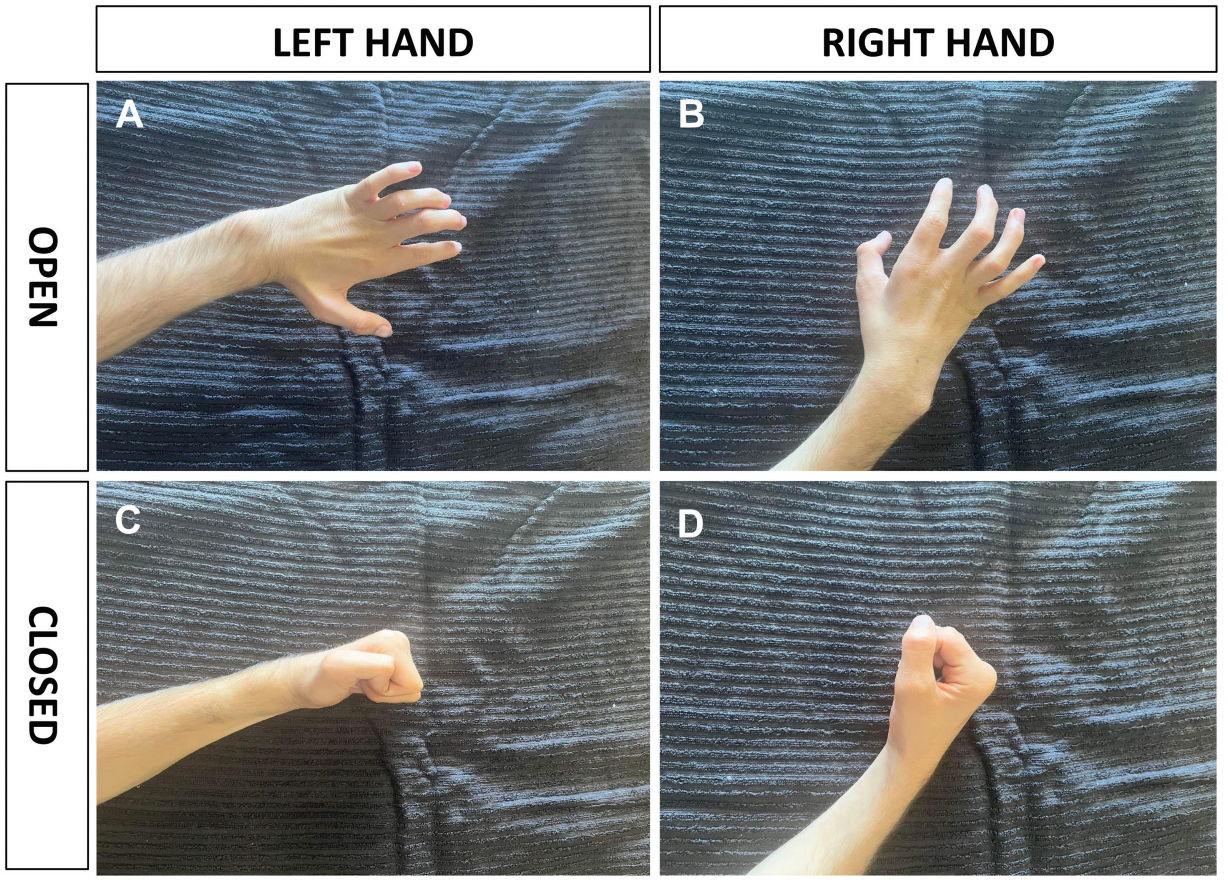

Fig. 4 Hand function at 24 months after transfer of the nerve supplying brachialis to the median nerve (left and right side) and transfer of the nerve supplying the supinator to the posterior interosseous nerve (right side only). Clockwise from top left: (**A**) left-hand open, dorsal view; (**B**) right-hand open, dorsal view; (**C**) left-hand closed, lateral view; and (**D**) right-hand closed, lateral view.

biological features of current nerve conduit devices regulated under 21 CFR 882.5275 (product code JXI) appear not to meet the ideal design criteria and have shown unfavorable biological responses in situ and variable clinical outcomes. Here, we have shown that a rollable bilayer collagen scaffold device mimics the native structure of nerve epineurium. Morphological characterization demonstrated that it displays similar structural and biological properties to epineurium. The thickness of 100µm is within the range of epineurial thickness of most human peripheral nerves. Similarly, the diameter of collagen fibrils in the device, at approximately 90 nm, is also very similar to that of epineurium.[25] The topographical features of the inner layer showed collagen fibrils in a longitudinal arrangement, resembling the inner layer structure of epineurium. Preclinical studies in rat sciatic nerve models demonstrated that nerve repair using the device preserved 97% of myelinated axons distally at 4 weeks (Pletikosa and Zheng et al

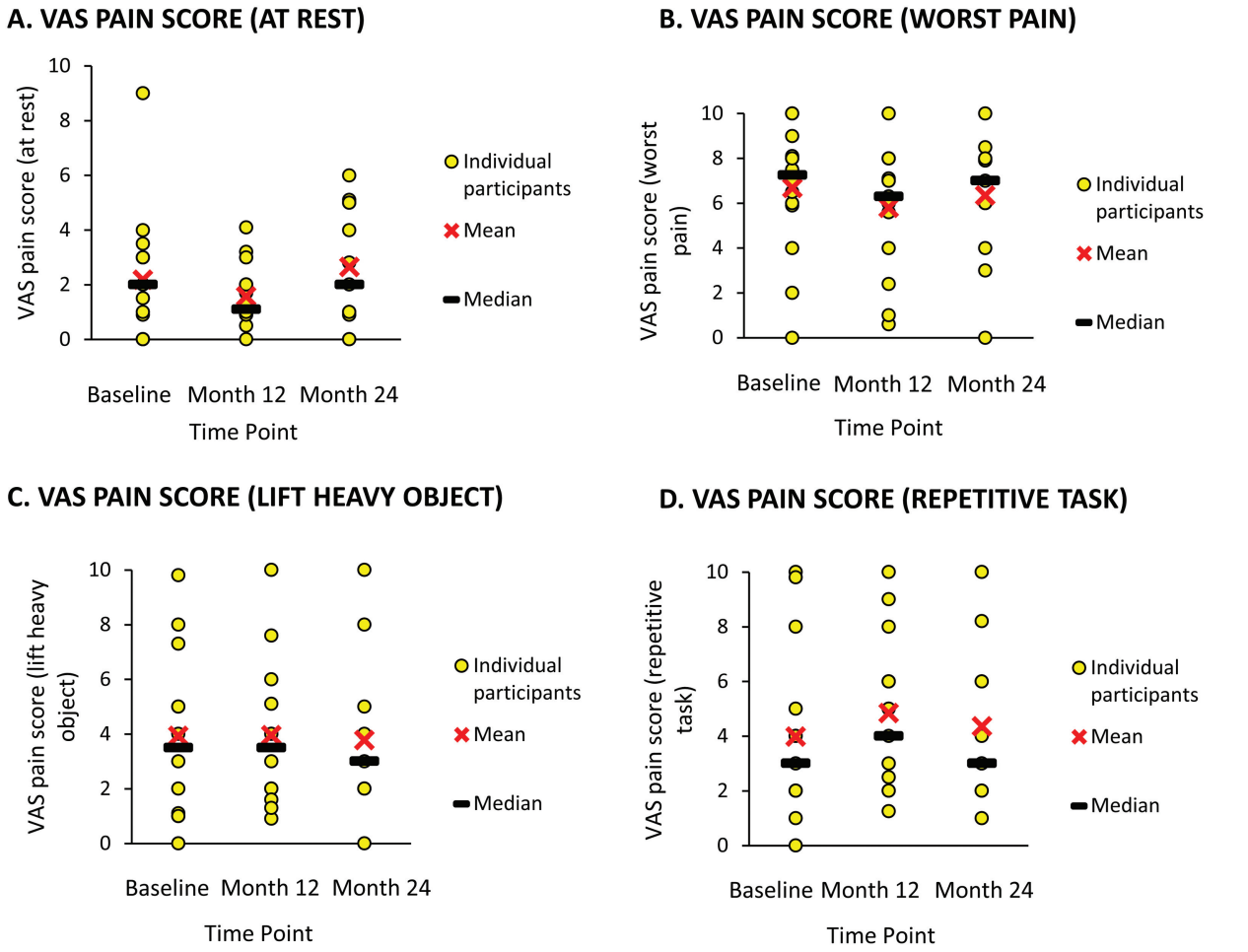

Fig. 5 VAS pain score at (**A**) rest, (**B**) worst, (**C**) lifting heavy object, and (**D**) repetitive tasks. There are no significant difference between baseline and at 12 or 24 months after nerve reconstruction.

unpublished data). To our knowledge, this device is the first collagen scaffold that mimics nerve epineurium and has regulatory approval for clinical use in humans for peripheral nerve reconstruction.

Peripheral nerve reconstruction applies a range of procedures including nerve repair with sutures, nerve conduit, nerve grafting, and nerve transfer.[38] In general, nerve repairs using sutures or devices can yield reasonable outcomes, especially where the repair is performed close to the end organ target.[39,40] Nerve graft, in particular autograft, can yield superior results compared to other nerve repair techniques.[39–41] However, the use of nerve autograft has limitation if the graft length reaches a critical interval over 6 cm.[39,40] After this point, nerve transfer is indicated when tensionless coaptation of the severed nerve ends cannot be achieved, where there is a long distance between the injury and target organs or when the injury is proximal to the spinal cord (i.e., high peripheral nerve or brachial plexus injury).[42] Increasing evidence has shown that nerve transfer is a paradigm shift in nerve reconstruction.[41] While both nerve graft and nerve transfer result in functional loss of the donor nerve, it is possible in nerve transfer to split out some of the nerve fascicles to reroute to the recipient nerve, ensuring that some donor nerve function is retained. In support of this current literature, it has been shown that nerve transfer results in better functional recovery as compared to autologous nerve graft.[38,43–45] In our study, we have shown that a functional donor nerve joined to an inactive recipient nerve in nerve transfer, using a device that mimics epineurial structure with reduced sutures, appears to achieve excellent outcomes in functional recovery. To our knowledge, this may be first time reporting of the use of a nerve device for nerve transfer.

In our proof-of-concept clinical study using the device for nerve reconstruction, we successfully performed 36 nerve transfers in 19 participants with upper-extremity paralysis due to long segmental damage, injury, or defect of the peripheral nerve. Clinical assessment showed that FMR of all target muscles was achieved in 61 and 75% of muscles at 12 and 24 months postsurgery, while FMR of the most proximal target muscles was achieved in 76 and 85% of muscles at 12 and 24 months, respectively. Assessment of VAS pain scores showed that no participants experienced an increase in musculoskeletal or neuropathic pain, and there was a dramatic reduction in the use of pain medication, such as opioids, neuroleptics, and/or nonopioid analgesics after nerve reconstruction.

Table 3 Chronic pain medications of the participants (note: does not include transient medications, e.g., postoperative pain relief)

Participant	Medication	Total daily dose			
		Baseline	Month 6	Month 12	Month 24
Participant 1	Tapentadol Oxycodone	Nil Nil	1 tablet 10 mg	Nil Nil	Nil Nil
Participant 2	No chronic pain medication	Nil	Nil	Nil	Nil
Participant 3	Amitriptyline Paracetamol Pregabalin Tapentadol	50 mg 2 g 600 mg 300 mg	Nil Nil 200 mg Nil	Nil Nil Nil Nil	Nil Nil Nil Nil
Participant 6	Duloxetine Paracetamol Pregabalin	90 mg 2 g 325 mg	90 mg 2 g 350 mg	Nil Nil 100 mg	Nil 2.66 g Nil
Participant 8	No chronic pain medication	Nil	Nil	[a]	[a]
Participant 11	Duloxetine Nortriptyline Pregabalin	240 mg 25 mg 600mg	240 mg 25 mg 600mg	60 mg 50 mg Nil	60 mg 50 mg Nil
Participant 12	Duloxetine Paracetamol Pregabalin	90 mg 2g 325 mg	Nil Nil 100 mg	Nil 2 g Nil	Nil Nil Nil
Participant 13	Oxycodone Paracetamol Pregabalin Tramadol	Nil 3 g 600 mg 200 mg	10 mg 2 g 200 mg 50 mg	Nil 1.33 g Nil Nil	Nil 1.33 g Nil 150 mg
Participant 14	Paracetamol Pregabalin Tapentadol Tramadol	3 g 600 mg 400 mg 200 mg	2 g 200 mg Nil 50 mg	1.33 g Nil Nil Nil	1.33 g Nil 100 mg 150 mg
Participant 15	Duloxetine Pregabalin	60 mg 600 mg	60 mg 150 mg	60mg Nil	[b]
Participant 16	No chronic pain medication	Nil	Nil	Nil	Nil
Participant 17	Amitriptyline Pregabalin Norspan Targin	20 mg 600 mg Nil Nil	25 mg 600 mg Nil Nil	50 mg 150 mg 15 mg 5/2.5 mg	50 mg 150 mg 15 mg 5/2.5 mg
Participant 19	Tapentadol Pregabalin	400 mg 200 mg	Nil 500 mg	Nil 400 mg	Nil Nil
Participant 20	Amitriptyline Pregabalin Norspan Targin	20 mg 600 mg Nil Nil	25 mg 600 mg Nil Nil	25 mg 75 mg 15 mg/wk 5/2.5 mg	25 mg 75 mg 15 mg/wk 5/2.5 mg
Participant 21	No chronic pain medication	Nil	Nil	Nil	Nil
Participant 24	No chronic pain medication	Nil	Nil	Nil	Nil
Participant 25	Amitriptyline Paracetamol	25 mg Nil	100 mg 3.99 g	100 mg 3.99 g	100 mg 3.99 g
Participant 27	Pregabalin	75 mg	75 mg	75mg	Nil

[a]Participant withdrew from study after month 6 visit.
[b]Participant deceased.

Notably, five patients in the study had C5 to C8 spinal cord injuries resulting in tetraplegia. The result showed that the use of the device for nerve transfers to restore upper limb function in these patients is encouraging, with all nerve transfers aimed at restoring triceps function achieving FMR at 12 months. The improvement in triceps function allowed participants to perform daily activities that were not possible before the surgery, such as being able to roll over in bed, use a manual wheelchair, and independently transfer from bed to wheelchair using a slide board. These results compare favorably to those reported in van Zyl et al who reported a median MRC score of 3, 24 months after surgery.[46]

There are limitations to the current study. This was a prospective case series study conducted by a single surgeon.

The study findings may not be generalizable. A patient selection bias may exist, and the patient cohort is heterogeneous with mixed peripheral nerve, brachial plexus or spinal cord injuries. There are multiple factors affecting the functional outcome of nerve reconstruction. These include age, gender, injured nerve, time between injury, and surgery. The outcome assessments may also be influenced by these confounding factors. While our study has shown the use of the device appears to provide better patient outcomes, it warrants a randomized, controlled clinical trial to compare current strategies to the use of the device as epineurium-like substitute.

In conclusion, this device is an epineurial-like substitute that supports and guides nerve regeneration. This human clinical study of the use of the device in nerve reconstruction shows promising improvements in muscle function of the upper extremity.

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Conflict of Interest
MHZ, MZ and CL hold shares in Orthocell Ltd.

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