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One-stage human acellular nerve allograft reconstruction for digital nerve defects

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Abstract

Human acellular nerve allografts have a wide range of donor origin and can effectively avoid nerve injury in the donor area. Very little is known about one-stage reconstruction of digital nerve defects. The present study observed the feasibility and effectiveness of human acellular nerve allograft in the reconstruction of < 5-cm digital nerve defects within 6 hours after injury. A total of 15 cases of nerve injury, combined with nerve defects in 18 digits from the Department of Emergency were enrolled in this study. After debridement, digital nerves were reconstructed using human acellular nerve allografts. The patients were followed up for 6–24 months after reconstruction. Mackinnon-Dellon static two-point discrimination results showed excellent and good rates of 89%. Semmes-Weinstein monofilament test demonstrated that light touch was normal, with an obvious improvement rate of 78%. These findings confirmed that human acellular nerve allograft for one-stage reconstruction of digital nerve defect after hand injury is feasible, which provides a novel trend for peripheral nerve reconstruction.

***Key Words:** nerve regeneration; peripheral nerve; allograft; digital nerve; nerve conduit; nerve reconstruction; nerve defect; sensory nerve; neural regeneration*

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Introduction

Autologous nerve graft repair has become a gold standard for treatment of peripheral nerve injury combined with defects(Dellon and Mackinnon, 1988). However, a variety of biological conduits and nerve allografts have played increasingly important roles in the repair of nerve defects (Meek and Coert, 2002; Ducic et al., 2012). Human acellular nerves have become the most promising substitute for autologous nerve grafts (Yang et al., 2011). Compared with traditional methods, human acellular nerves do not induce damage to affected areas of the donor, and there is a wide variety of sources. Mackinnon and Hudson (1992) confirmed that nerve allograft without special treatment might cause rejection, even with administration of immunosuppressive drugs. With developments in medical technology, nerve allografts after acellular treatment have been shown to retain the original structure and reduce immunogenicity (Hudson et al., 2004). Moreover, patients do not have to take medicine following surgery. The clinical use of nerve allografts is still in the early stages, but studies have shown positive clincial repair outcomes of digital nerve defects (Cho et al., 2012; Taras et al., 2013). In previous studies, nerve graft reconstruction was conducted at 1 week or several weeks after injury, resulting in wound stability and reduced incidence rate of postoperative inflammation. The disadvantage of this method is that patients require two surgeries, which increased hospitalization and recovery time. According to our experience with emergency trauma, class-I clean wounds and class-II mildly contaminated wounds rarely suffer from infection after timely debridement and prophylactic use of antibiotics. Thus, since 2012, human acellular nerve allografts have been used to treat one-stage reconstruction of digital nerve defects in patients admitted to the emergency department.

Subjects and Methods

Subjects

A total of 15 patients with acute (6 hours after injury) digital nerve defects, including 11 males and 4 females between the age of 17–57 years old and averaging 36 years, were enrolled from Ningbo City and the surrounding area in China. A total of 18 digits with nerve injury and nerve defects were involved. The average defect length was 19 mm (5–50 mm). Of them, four cases were > 30 mm. Nine digits involved a fracture. Eight digits involved tendon and blood vessel damage. One digit combined with simple nerve defects. There were 5 cases of emergency class-I clean wounds and 10 cases of class-II mildly contaminated wounds. Patients older than 60 years, and those with diabetes or other immune deficiencies, were excluded. Experiments were approved by the Ethics Committee of Ningbo No. 6 Hospital in China. All patients and families signed informed consent. The causes of injury and location are shown in **Table 1**.

Table 2 Clinical data and postoperative functional recovery in emergency one-stage digital nerve defect patients repaired by nerve allograft

No.	Gender	Age	Digit	Contamination degree	Position	Length (mm)	Follow-up (month)	Two-point discrimination (mm)	Monofilament test (gm)
1	Male	34	Forefinger	Clean	Proximal	20	7	10	3.64
			Middle finger		Proximal	20	7	10	3.64
2	Male	50	Thumb	Light	Middle	21	8	6	3.64
3	Female	49	Middle finger	Light	Middle	20	19	12	3.64
4	Male	53	Little finger	Light	Middle	15	18	6	3.64
5	Male	17	Middle finger	Light	Distal	15	6	6	0.068
6	Male	28	Forefinger	Light	Middle	35	24	12	448
7	Male	41	Ring finger	Clean	Proximal	50	22	10	3.64
8	Female	40	Little finger	Light	Proximal	20	6	12	0.068
9	Male	24	Ring finger	Clean	Proximal	40	15	>15	448
10	Male	18	Thumb	Light	Distal	30	24	>15	448
			Forefinger		Proximal	10	24	5	0.068
11	Female	23	Forefinger	Light	Proximal	25	12	>15	126
12	Male	57	Ring finger	Light	Middle	10	18	6	0.068
13	Male	25	Ring finger	Clean	Middle	15	11	6	3.64
14	Male	51	Middle finger	Clean	Proximal	5	6	5	0.068
15	Female	30	Ring finger	Light	Middle	8	8	6	0.068
			Little finger		Proximal	8	8	6	0.068

In static two-point discrimination and Semmes-Weinstein monofilament tests, the small value that the patient can perceive represents sensitive touch.

Table 1 The causes and location of injury in patients with digital nerve defect

	Number of digits
Side of injury	
Left limb	5
Right limb	10
Finger	
Thumb	2
Index	4
Long	4
Ring	5
Little	3
Cause of injury	
Knife	3
Glove avulsion	2
Sheet metal	1
Table saw	5
Punching machine	2
Belt conveyor	3
Glass	2

Nerve allograft

Acellular nerve repair materials (Guangzhou Zhongda Medical Devices Company, Guangzhou, Guangdong Province, China; Approval No. (2012)3460641) were obtained from natural nerve after acellular treatment. The materials were made from extracellular matrix. They did not contain cells, but retained the structure of a natural nerve, including tunnels with basilar membrane, perineurium, and epineurium (**Figure 1A**).

Repair was performed within 6 hours after injury. After brachial plexus block, a pneumatic tourniquet with 250 mmHg pressure was used on the upper arm. Antibiotics were intravenously administered at 30 minutes before surgery to prevent infection. After careful debridement, reduction and internal fixation were initially performed for fractures and for repairing tendon and blood vessel damage. Under a 10-fold microscope, the nerve stump was trimmed to reveal the papilla visible to the naked eye. When fingers were straight and the digital nerve was in tension-free status, the length of the nerve defects was measured. If the defects were between 5 and 50 mm, nerve allografts with corresponding diameters were selected in accordance with the donor area diameter of digital nerve defects. Under the microscope, samples were epineurial and perineurial sutured with 2–4 stitches using a 9-0 nylon suture. Electric coagulation hemostasis was used. The wound was closed with 5-0 esthetic suture (**Figure 1B**).

Postoperative treatment

A splint was used to inhibit wrist flexion, metacarpophalangeal joint flexion, and interphalangeal joint extension for 4–6 weeks. Antibiotics were also used. Vitamin B1, B6, and mecobalamin were used for neurotrophy for 3–6 months. The dressing was replaced every other day. The occurrence of wound infection or immunological rejection was observed, including delayed wound healing, increased wound exudate, and local skin rashes. After movement inhibition for 3 weeks, the affected finger was allowed limited flexion and extension. At 6 weeks later, the splint was removed. The finger was allowed to extend to a neutral position. None of the patients took immunosuppressants.

Follow-up observation

Recovery of sensory function was observed from 3 months

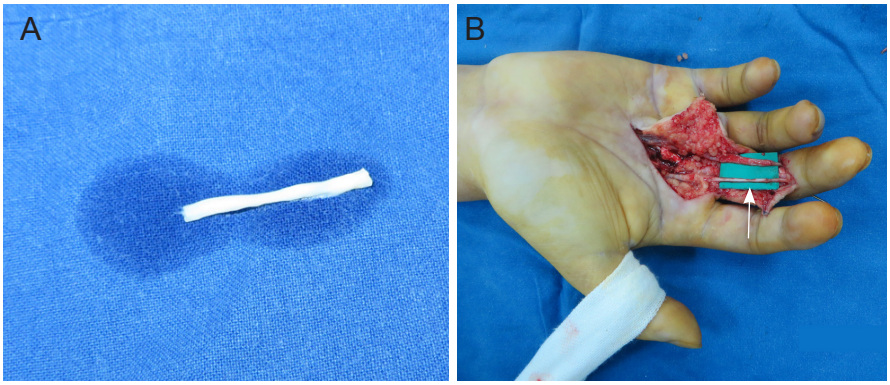

Figure 1 Acellular nerve repair material (A) and its application for the repair of 2 cm radial nerve defect in the right middle finger (B).
(A) Nerve allograft: 1.5 mm × 2.0 cm. (B) Nerve allograft (arrow): 1.5 mm × 2.0 cm.

after the surgery. Final recovery of sensory function was recorded. Modified Mackinnon-Dellon static two-point discrimination (S2PD) (Weber et al., 2000) was used: excellent (S2PD ≤ 6 mm), good (S2PD 7–15 mm), and poor (S2PD > 15 mm). Semmes-Weinstein monofilament test (Bell-Krotoski and Tomancik, 1987) was applied to evaluate recovery of touch sensation: normal light touch (0.026–0.068 gm) and reduced light touch (0.166–3.64 gm). Semmes-Weinstein monofilament test results showed slightly light touch (5.51–126 gm) in two digits; one light touch was poor, with no positioning (126–448 gm). Normal light touch and reduced light touch were considered to be a recovery status of excellent and good status. The smaller the value that the patient perceived, the more sensitive their touch was. A normal individual can perceive 0.026–0.068 gm.

Results

A total of 15 patients were followed up for 6 months to 2 years, averaging 12.1 months. Local infection occurred in 1 case at 3 days after surgery, and improved after anti-infection treatment. The remaining patients did not exhibit apparent rashes, exudation, or delayed healing in the local wound. After debridement, measurement results demonstrated that there were 14 digits with < 30 mm digital nerve defects and 4 digits with 30–50 mm defects. Mackinnon-Dellon static two-point discrimination results were excellent in 9 digits, good in 7 digits, and poor in 2 digits, showing an excellent and good rate of 89%. The excellent and good rate of discrimination was 78% in 9 cases of digital nerve defects in the proximal phalanx, which was significantly less than the overall level. The Semmes-Weinstein monofilament test demonstrated that there were seven digits with normal light touch, seven digits with reduced light touch, two digits with slight light touch, and two digits with poor light touch and unable to position, resulting in an excellent and good rate of 78% (**Table 2**). The excellent and good rate of light touch was 78% in 9 cases of digital nerve defects in the proximal phalanx. In the four digits with 30–50 mm defects, the excellent and good rate of discrimination was 50%, and that of light touch was 25%.

Discussion

Repair materials of peripheral nerve defects consist of autologous nerves, artificial nerves, biological conduit, and nerve allograft. Autologous nerve grafts best meet transplant needs, but the donor area will inevitably result in over sensory dysfunction, the appearance of scars, and prolonged surgery. Even in autologous nerve grafts, it is difficult to completely restore function in the post-traumatic limb. Peripheral nerve regeneration mechanisms are complex, and post-traumatic cerebral cortex function also needs remodeling, which is partly responsible for adverse neurological function after reconstruction (Lundborg, 2000).

Artificial conduits for the repair of peripheral nerve defects has been reported (Zhang et al., 2014), but there are great differences in results from both animal experiments and clinical studies (Isaacs and Browne, 2014; Owusu et al., 2014). In particular, silicone tubes and other non-absorbent materials result in foreign body sensation after surgery and have, therefore, rarely been used in the clinic. Biofilms and biological conduits have been widely applied in the clinic and have received good clinical results (Whitlock et al., 2009). Johnson et al. (2011) compared nerve allografts and neurobiological conduits, and verified that the density of regenerating nerve fibers in the middle segment of sciatic nerve defects were decreased and centralized. In acellular nerve allografts, the regenerating nerve fiber is uniformly distributed. From three-dimensional space structures, artificial nerves or conduits do not have the specific anatomical framework of a nerve allograft. Indeed, the nerve regeneration mode is changed within the conduit. However, because of the same three-dimensional structure, nerve allografts maintain a uniform distribution of the regenerating nerve fibers. Johnson et al. (2011) confirmed that the clinical outcomes were poorer in nerve conduits use to reconstruct > 30 mm defects compared with nerve allograft. As an ideal substitute, nerve allografts are obviously better than nerve conduits with respect to anatomical structure and acellular three-dimensional structure.

Sensory and motor nerve regeneration after nerve allograft has been verified by animal experiments (Whitlock et al., 2009; Moore et al., 2011; Giusti et al., 2012). The application of nerve allografts in the repair of pure sensory nerves, particularly neural defects, is most widely used, and the clinical effects are the most satisfactory. No evident immunological rejection occurred, and the incidence of adverse reaction was very low (Siemionow and Sonmez, 2007). In repair of upper extremity peripheral nerve defects, the recovery of sensory

and motor nerve was also satisfactory (Brooks et al., 2012; Taras et al., 2013). Nevertheless, Berrocal et al. (2013) reported that there was no evidence of nerve regeneration at 8 months after nerve allograft in 1 case of ulnar nerve defects. Although the present study used a different sensory evaluation system, the excellent and good rate of static two-point discrimination was similar to results from previous studies (Cho et al., 2012; Taras et al., 2013), especially in patients with 30–50 mm digital nerve defects. To accurately assess functional recovery of touch sensation on the affected side, the Semmes-Weinstein monofilament test was used. At 6 months after surgery, nine digits recovered to a value of 3.64. In patients with > 30 mm defect, light touch was slight in 2 cases, and poor in 2 cases. These findings indicated that the factors affecting sensory recovery included length of nerve defects, as well as site of nerve defects.

We initially used human acellular nerve grafts produced by Guangzhou Zhongda Medical Devices Company in China. There were no rejections, and sensory recovery was good, which was consistent with a previous study (Ding et al., 2006). On this basis, we first used nerve allografts in emergency hand trauma surgeries. A clean wound or light contaminated wound was selected. After strict debridement and povidone liquid immersion, one-stage nerve allograft reconstruction for digital nerve defects was conducted. Results confirmed that the surgery was safe and effective, and reduced the number of operations, as well as the financial burden of patients. Among 15 patients, only 1 case experienced slight reddish swelling around the wound. The reddish swelling subsided completely after preventive antibiotic treatment. No patients were administered immunosuppressive drugs. During follow-up, adverse reactions, such as immune rejection, also did not occur.

Author contributions: *HLH was responsible for data processing. HC had full access to all data and participated in analysis and manuscript correction. XYL had full access to all data and participated in analysis and manuscript preparation. HLH and JRF participated in most of the surgery part and statistics. TBW, PXZ and XW were responsible for study design, study supervision. All authors approved the final version of the paper.*
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