RESEARCH ARTICLE

Comparison between direct repair and human acellular nerve allografting during contralateral C7 transfer to the upper trunk for restoration of shoulder abduction and elbow flexion

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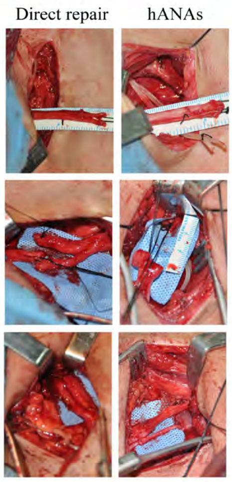
Graphical Abstract

Comparison between direct repair and human acellular nerve allografts (hANAs) in contralateral C7 (CC7) transfer to upper trunk



Harvesting CC7 nerve root and length measurement

Assessment of the gap length between the harvested CC7 nerve root and the upper trunk for making the operation plan

Direct repairing or human acellular nerve allografting based on the gap length between the harvested CC7 nerve root and the upper trunk

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Abstract

Direct coaptation of contralateral C7 to the upper trunk could avoid the interposition of nerve grafts. We have successfully shortened the gap and graft lengths, and even achieved direct coaptation. However, direct repair can only be performed in some selected cases, and partial procedures still require autografts, which are the gold standard for repairing neurologic defects. As symptoms often occur after autografting, human acellular nerve allografts have been used to avoid concomitant symptoms. This study investigated the quality of shoulder abduction and elbow flexion following direct repair and acellular allografting to evaluate issues requiring attention for brachial plexus injury repair. Fifty-one brachial plexus injury patients in the surgical database were eligible for this retrospective study. Patients were divided into two groups according to different surgical methods. Direct repair was performed in 27 patients, while acellular nerve allografts were used to bridge the gap between the contralateral C7 nerve root and upper trunk in 24 patients. The length of the harvested contralateral C7 nerve root was measured intraoperatively. Deltoid and biceps muscle strength, and degrees of shoulder abduction and elbow flexion were examined according to the British Medical Research Council scoring system; meaningful recovery was defined as M3–M5. Lengths of anterior and posterior divisions of the contralateral C7 in the direct repair group were 7.64 ± 0.69 mm and 7.55 ± 0.69 mm, respectively, and in the acellular nerve allografts group were 6.46 ± 0.58 mm and 6.43 ± 0.59 mm, respectively. After a minimum of 4-year follow-up, meaningful recoveries of deltoid and biceps muscles in the direct repair group were 88.89% and 85.19%, respectively, while they were 70.83% and 66.67% in the acellular nerve allografts group. Time to C5/C6 reinnervation was shorter in the direct repair group compared with the acellular nerve allografts group. Direct repair facilitated the restoration of shoulder abduction and elbow flexion. Thus, if direct coaptation is not possible, use of acellular nerve allografts is a suitable option. This study was approved by the Medical Ethical Committee of the First Affiliated Hospital of Sun Yat-sen University, China (Application ID: [2017] 290) on November 14, 2017.

Key Words: *nerve regeneration; contralateral C7 nerve root transfer; nerve graft; brachial plexus avulsion injury; direct repair; human acellular nerve allograft; shoulder function; elbow function; nerve transfer; phrenic nerve; accessary nerve; neural regeneration*

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Introduction

Brachial plexus avulsion injuries are devastating events for the upper extremity (Kovachevich et al., 2010; Yu et al., 2017; Gao et al., 2018a, b; Jiang et al., 2018). Nerve transfer is a major advancement for treating such injuries (Yang et al., 2015). Shoulder abduction and elbow flexion are the top priorities of nerve reconstruction (Baltzer et al., 2017); however, the number of donor nerves remains insufficient, especially when brachial plexus avulsion injuries are combined with phrenic nerve and accessory nerve injuries (Huan et al., 2017). Contralateral C7 (CC7) nerve transfer was introduced by Gu et al. (1992) in 1986. It was an innovative solution that provided a substantial number of axons for motor and sensory restoration of the paralyzed limb without greatly affecting function of the donor limb (Chuang et al., 1998; Gu et al., 2002; Zheng et al., 2018). Motor function of the C7 nerve root greatly overlaps with that of other nerve roots that give rise to the brachial plexus (Zheng et al., 2018). Generally, a gap remains between donor and recipient nerves when performing CC7 transfer to repair the upper trunk. Although autografts have commonly been used to bridge this gap, their primary drawback has always been that growing axons are required to cross two anastomotic sites to reach target muscles (Bhatia et al., 2017). Therefore, techniques to shorten the tunnels or length of the autograft, or even achieve direct repair are desirable.

McGuiness and Kay (2016) first created a prespinal retropharyngeal route for shorter nerve grafts. In 2008, Xu et al. (2008) modified the McGuiness-Kay technique by transecting the scalenus anterior muscle on both sides, and reduced the graft length. The prespinal passage described by Wang et al. (2012) created the shortest tunnel, making direct coaptation of the CC7 nerve root to the upper trunk possible. In a previous study, we adopted a strategy similar to that described by Wang et al. (2012) for the treatment of brachial plexus avulsion injury. Patients underwent CC7 nerve transfer *via* the prespinal route and direct neurorrhaphy of the CC7 nerve with the upper trunk or C5/C6 nerve roots. This study confirmed the success of the procedure through the dissection of fifteen cadaveric specimens under a microscope, consistent with a previous study (Qin et al., 2016). We successfully shortened the gap and graft lengths, and even achieved direct coaptation. However, direct repair can only be performed in some selected cases, and partial procedures still require autografts, which are the gold standard for repairing neurologic defects. Moreover, symptoms often occur after autografting, such as the sacrifice of donor nerves, need for additional surgeries (and their inherent risks), pain, infection, and size mismatching (Jiang et al., 2016). Our study team created an alternative graft material, human acellular nerve allografts (hANAs), which have been available for clinical use since 2012 (He et al., 2015; Zhu et al., 2017; Li et al., 2019). The present study aimed to retrospectively investigate the quality of shoulder abduction and elbow flexion after direct repair and human acellular nerve allografting to evaluate issues that require attention during different procedures.

Patients and Methods

Patients

This retrospective study was approved by the Medical Ethical Committee of the First Affiliated Hospital of Sun Yat-sen University, China (Application ID: [2017] 290) on November 14, 2017. All patients signed informed consent. Patients who refused to participate in this study were excluded. From January 2010 to June 2014, sixty-four patients suffered from total or near total brachial plexus avulsion injuries and underwent CC7 nerve transfer to innervate the injured upper trunk or C5/C6 nerve roots using the prespinal route.

Inclusion criteria

Patients presenting with all of the following criteria were considered for study inclusion:

(1) C5–8 or total brachial plexus injury (Wang et al., 2013);
(2) postoperative interval ≥ 4 years;
(3) all procedures were performed by the same medical team;
(4) CC7 nerve root transfer to repair the upper trunk was the only reconstruction method.

Exclusion criteria

Patients were excluded from the study if one of the following exclusion criteria applied (**Figures 1–3**):

(1) diabetes;
(2) fracture in the affected upper extremity;
(3) peripheral neuropathy;
(4) refusal to participate;
(5) lost to follow-up.

Fifty-one patients qualified for this study, including 27 patients undergoing a direct repair (direct repair group) and 24 patients undergoing human acellular nerve allografting to bridge the gap between the CC7 nerve root and upper trunk [hANAs group; Guangzhou Zhongda Medical Devices Company, Guangzhou, Guangdong Province, China; approval No. (2012) 3460641].

The demographic characteristics of patients in the two groups are presented in **Table 1**. Two patients were female (both were in the direct repair group). The median age for the direct repair group was greater than that of the hANAs group. Heights and weights were measured at primary admission. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). BMI was also categorized for analysis using World Health Organization criteria: underweight (< 18.5), normal weight (18.5 to < 25.0), and overweight (25.0 to < 30.0) (Galloway et al., 2018; Hole et al., 2018; Chung, 2019). Mean height and weight were higher, but BMI was lower in the direct repair group compared with the hANAs group. The direct repair group included 12 cases of four nerve root avulsions (C5–8) and 15 cases of five nerve root avulsions (C5–T1). The hANAs group included 10 cases of C5–8 and 14 cases of C5–T1. Types of lesions were confirmed by physical examination, electromyography, magnetic resonance imaging, and intraoperative exploration (Gao et al., 2018a, b; Wang et

Table 1 Patient characteristics

Item	Direct repair (n = 27)	hANAs (n = 24)	P-value
Gender			0.174
Male [n(%)]	25 (92.0)	24 (100.0)	
Female [n(%)]	2 (8.0)	0	
Age (year)	31.07±11.34	26.00±8.18	0.076
Height (cm)	171.56±4.40	168.67±3.77	0.016*
Weight (kg)	66.30±5.17	65.88±9.77	0.846
Body mass index (kg/m^2)	22.51±1.36	23.10±2.81	0.338
Interval between injury to surgery (day)	123.89±91.86	145.00±126.68	0.496
Follow-up time (month)	66.19±16.10	56.54±4.15	0.006#
Causes of injury [n(%)]			0.205
Motorcycle accident	15 (55.6)	19 (79.2)	
Car accident	8 (29.6)	3 (12.5)	
Dropping from height	2 (7.4)	2 (8.3)	
Bicycle accident	2 (7.4)	0	
Type of lesion [n(%)]			0.842
C5–8	12 (44.4)	10 (41.7)	
C5–T1	15 (55.6)	14 (58.3)	
Side [n(%)]			$P < 0.01$#
Right	26 (96.2)	13 (54.2)	
Left	1 (3.9)	11 (45.8)	

Data are expressed as the mean ± SD or n(%). Comparisons were performed using chi square tests or Student's t-test. #$P < 0.01$. hANAs: Human acellular nerve allografts.

al., 2018). Preoperative chest X-rays and pulmonary function tests were conducted to exclude pulmonary diseases and in preparation for phrenic nerve transfer (Socolovsky et al., 2018; Li et al., 2019).

Surgical techniques

All procedures were performed by a senior physician the author LQG as previously described (Li et al., 2016). The patient was placed in a supine position with the neck extended (a sandbag was placed under the scapulae). The injured brachial plexus was explored first to confirm the condition of brachial plexus avulsion injury, and then the entire upper trunk, C5/C6 nerve roots, C7, and lower trunk were carefully dissected. Next, the distal stump of the upper trunk was carefully inspected and trimmed until a healthy nerve was identified. The removed neuroma was sent for pathological examination to determine the healthy nerve end. On the healthy side, a similar supraclavicular transverse incision was adopted; the CC7 nerve root was dissected and transected as distal as possible to the anterior and posterior division of the middle trunk under a microscope (Qin et al., 2016). The length of the CC7 nerve was measured (**Figure 4A** and **D**). When transecting the posterior division of CC7, special attention is required to avoid injuring the posterior division of the lower trunk. Thus, particular attention should be paid while separating the posterior division of the middle trunk from that of the lower trunk. A prevertebral tunnel was created by blunt dissection. The sternocleidomastoid muscle on the healthy side was separated bluntly along its medial border and retracted laterally. The omohyoid was then exposed, the deep cervical fascia was divided, and the carotid sheath was retracted laterally. The esophagus was retracted medially to expose the anterior vertebrae. After creating a posterior tunnel to the scalenus anterior muscle, the harvested CC7 root was placed to pass to the injured side. The length of the remaining gap, if one existed, between recipient and donor nerves was measured (**Figure 4B** and **E**). Direct repair (**Figure 4C**) was more commonly performed in earlier cases. If the reach appeared adequate within 2 cm, the utility of shortening the ipsilateral clavicle by 2 cm to achieve that reach was considered. We began to favor bridging the remaining gap using hANAs when the allograft was introduced in 2012. Generally, if the distal ends of C5/C6 were available, the anterior division of CC7 was connected to the C6 nerve root through hANA bridging (**Figure 4F**), while the posterior division of CC7 was connected to C5. End-to-end coaptation with 8-0 Prolene sutures was adopted. Shortening of the ipsilateral clavicle was performed in only one case in the direct repair group. A segment of the shaft was excised from the middle part; the length of the excised segment was 2 cm. The bone ends were held together, and fixation was performed using a seven-holed reconstruction plate.

The suprascapular nerve was additionally reinnervated by the phrenic nerve (**Figure 4F**) if the patient was not found to have concomitant phrenic nerve palsy. The phrenic nerve was separated at the lateral edge of the anterior scalene muscle, and the functional status of the phrenic nerve was confirmed by intraoperative electrical stimulation to elicit potent diaphragm contraction. The phrenic nerve was dissected and transected as distally as possible. The suprascapular nerve, located in the suprascapular notch under the transverse ligament of the scapula, was then identified and isolated. The suprascapular nerve was divided as proximally as possible for transfer, and the proximal end of the phrenic nerve was coapted to the distal end of the suprascapular nerve.

After the operation, a custom cast was adopted to hold the head in a neutral position, and the injured upper extremity was immobilized in the position of shoulder abduction and elbow flexion for 6 weeks. The follow-up plan was explained to subjects. Postoperative evaluations were performed every 3 months (Socolovsky et al., 2017), and an intense rehabilitation program was started 6 weeks postoperatively. After CC7 nerve root transfer, patients were encouraged to carry out more exercises of the healthy upper limb, especially shoulder adduction and elbow extension, to stimulate regeneration from CC7 toward the injured side along the nerve allograft. Physical therapy with passive range of motion, acupuncture, moxibustion, and slow-pulse electrical stimulation was conducted in the Department of Rehabilitation Medicine. Neurotrophic drug administration was performed throughout the patient's early treatment process (1–3 months). The rehabilitation program was the same for all patients.

Clinical evaluation

Motor function assessment

Recovery of motor and sensory functions was evaluated based on the British Medical Research Council grading system (Terzis et al., 2010) at 6 weeks postoperatively and during regular outpatient follow-ups; the follow-up period was at least 4 years. Motor function assessment included the angle of shoulder abduction and elbow flexion, as well as muscle strength of the deltoid and biceps. Shoulder abduction and elbow flexion were evaluated with the patient standing.

The range of motion achieved was measured against gravity. Shoulder range of motion was measured as the angle between the thorax and humerus with a manual goniometer (Weidu electronic, Wenzhou, Zhejiang Province, China). Elbow range of motion was defined as the angle of elbow flexion when the ipsilateral upper limb was adducted. Meaningful functional recovery was defined as M3–M5 based on the British Medical Research Council scoring system (Terzis et al., 2010).

Tinel's sign assessment

Assessment of Tinel's sign was carried out 6 weeks postoperatively and during regular monthly follow-ups to evaluate the time of C5/C6 reinnervation by lightly percussing a percussion hammer over the site of nerve coaptation to elicit a sensation of tingling or "pins and needles" in the nerve distribution. The injured upper extremity was classified into the following twelve areas (**Figure 5A**) based on the neural pathway and distribution of C5/C6: 1, greater supraclavicular fossa; 2, subclavian fossa; 3, clavicular part of the pectoralis major; 4, proximal upper arm (deltoid); 5, middle upper arm; 6, distal upper arm; 7, elbow; 8, proximal forearm; 9, middle forearm; 10, distal forearm; 11, wrist; and 12, palm (Professor Li-Qiang Gu routinely assesses Tinel's sign in outpatient clinics. According to the C5/C6 innervation area, the dominating area was divided into 12 parts on average, which are self-made follow-up methods). Tinel's sign was assessed in every patient at each follow-up, and all patients were advised to pay close attention to the positive Tinel's sign elicited by themselves and document the locations of "tingling" feelings in the injured upper extremity monthly; this ensured that a positive Tinel's sign was not present prior to being elicited at follow-up.

Statistical analysis

The data are normally distributed. Categorical numbers are provided as absolutes with relative percentages in parentheses. Continuous numbers are provided as mean ± standard deviation. Statistical Package for Social Sciences (SPSS) 20.0 software (IBM SPSS, Armonk, NY, USA) was used for statistical analysis of explorative data. Descriptive statistics were used to describe clinical characteristics and outcomes. Bivariate comparisons were performed using a chi-square test for dichotomic data. Means were compared using Student's *t*-test. For analysis of C5/C6 reinnervation time, a scatter plot, regression line, and Pearson product-moment correlation coefficient (*r*) were used to estimate criterion validity. *P* values < 0.05 were considered statistically significant.

Results

Fifty-one subjects completed follow-up and no one withdrew from the follow-up (**Figure 1**).

Outcome characteristics of patients

Outcome characteristics of the two groups are listed in **Table 2**. Lengths of the anterior and posterior divisions of CC7 in the direct repair group were greater than in the hANAs group. In the direct repair group, CC7 nerve roots were applied to innervate the injured upper trunk in 8 cases and to innervate C5/C6 nerve roots in 19 cases; additional phrenic nerve transfer to innervate the suprascapular nerve occurred in 12 cases. In the hANAs group, CC7 nerve roots were transferred to repair the upper trunk in five cases and to C5/C6 nerve roots in 19 cases; additional suprascapular nerve reinnervation occurred in nine cases. Thirty patients among the two groups did not undergo additional suprascapular nerve innervation due to palsy of the diaphragm.

Comparison of neural functional outcomes

Patients regained active shoulder abduction and the mean angle of shoulder abduction and elbow flexion was larger in the direct repair group compared with the hANAs group (*P* = 0.283 and 0.002, respectively). In patients who received additional suprascapular nerve reinnervation with the phrenic nerve, mean angle of shoulder abduction was 76.25° ± 20.35°, which was greater than observed in the hANAs group (*P* = 0.366); similarly, mean angle of elbow flexion was greater in the direct repair group compared with the hANAs group (*P* = 0.007).

Table 2 Outcome characteristics

Item	Direct repair (*n* = 27)	hANAs (*n* = 24)	*P*-value
PN-SSN			
Number [*n*(%)]	12 (44.44%)	9 (37.50%)	0.615
Shoulder abduction (degree)	76.25±20.35	67.78±21.23	0.366
Length of CC7			
Anterior division (cm)	7.64±0.69	6.46±0.58	$P < 0.01^\#$
Posterior division (cm)	7.55±0.69	6.43±0.59	$P < 0.01^\#$
Range of motion			
Shoulder abduction (degree)	63.33±23.78	56.25±22.71	0.283
Elbow flexion (degree)	89.44±39.23	55.63±33.34	0.002#
Shoulder abduction (PN-SSN) (degree)	76.25±20.35	67.78±21.23	0.366
Elbow flexion (PN-SSN) (degree)	110.83±31.10	67.22±35.10	0.007#
Muscle strength (grade)			
Deltoid	3.56±0.96	3.04±0.91	0.057
Biceps	3.46±1.02	3.02±1.27	0.087
Time of C5/C6 reinnervation (months after surgery)	12.48±1.22	17.13±1.39	$P < 0.01^\#$

Data are expressed as the mean ± SD or *n*(%). Comparisons were performed using chi square tests or Student's *t*-test. #$P < 0.01$. CC7: Contralateral cervical 7 nerve root; PN: phrenic nerve; SSN: suprascapular nerve; PN-SSN: phrenic nerve transfer to repair suprascapular nerve.

Comparison of C5/C6 reinnervation time

A comparison of time to C5/C6 reinnervation among the two groups is shown in **Table 2**. Mean time to C5/C6 reinnervation was shorter in the direct repair group compared with the hANAs group ($P < 0.01$). We subjected the scatter plot to a linear regression analysis (**Figure 5B**), which had values of $r = 0.8989$ and $r = 0.9534$, where $r \geq 0.7$ was classified as good (Song et al., 2018). These result suggest that time to C5/C6 reinnervation was shorter in the direct repair group than in the hANAs group.

Comparison of muscle strengths

Mean muscle strengths of the deltoid and biceps were not significantly different between the two groups ($P = 0.190$ and 0.071, respectively). Muscle strengths in the deltoid and biceps were increased in the direct repair group compared with the hANAs group. A comparison of shoulder abduction and elbow flexion outcomes between the two groups is shown in **Table 2**. Muscle strengths of M3–M4 in the deltoid and biceps of the direct repair group were 88.89% and

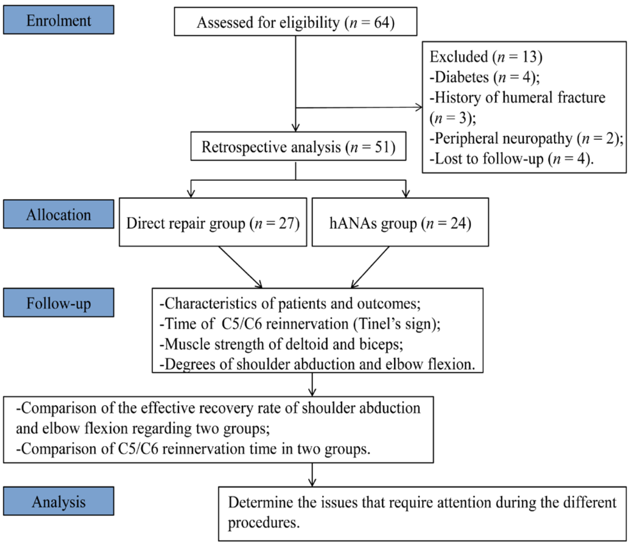

Figure 1 Flow chart of the study.
hANAs: Human acellular nerve allografts.

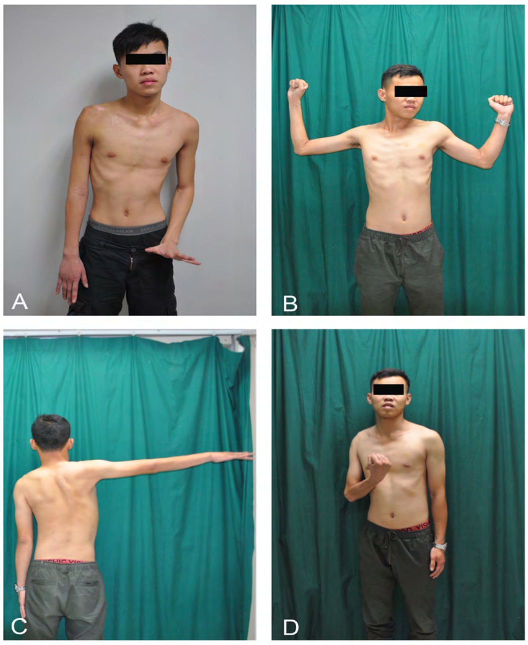

Figure 2 An 18-year-old male with an injury to the right C5–8 nerve roots.
The patient underwent direct coaptation of CC7 nerve transfer to the ipsilateral upper trunk via the prespinal route with additional suprascapular nerve innervation 90 days after brachial plexus avulsion injury. (A) Preoperative view of the right upper limb, which lost the functions of shoulder abduction, elbow flexion, and partial finger flexion and extension. (B) The patient showed excellent right shoulder external rotation. (C) The patient showed excellent right shoulder abduction at the 48-month follow-up. Muscle strength in the deltoid was M4. (D) The patient had excellent right elbow flexion independent of synchronous shoulder adduction and contralateral shoulder adduction at the 48-month follow-up. Muscle strength in the biceps was M4. CC7: Contralateral cervical 7 nerve root.

Figure 3 A 35-year-old male with an injury to the left C5–8 nerve roots.
The patient underwent CC7 nerve transfer combined with human acellular nerve allograft reconstruction to reinnervate the injured upper trunk via the prespinal route with additional suprascapular nerve innervation 60 days after injury. (A, B) Preoperative view of the left upper limb, which lost the functions of shoulder abduction, elbow flexion, and partial finger flexion and extension. (C) The patient showed excellent left shoulder abduction during the 52-month follow-up. Muscle strength in the deltoid was M4. (D) The patient had excellent left elbow flexion independent of synchronous shoulder adduction and contralateral shoulder adduction during the 52-month follow-up. Muscle strength in the biceps was M4. CC7: Contralateral cervical 7 nerve root.

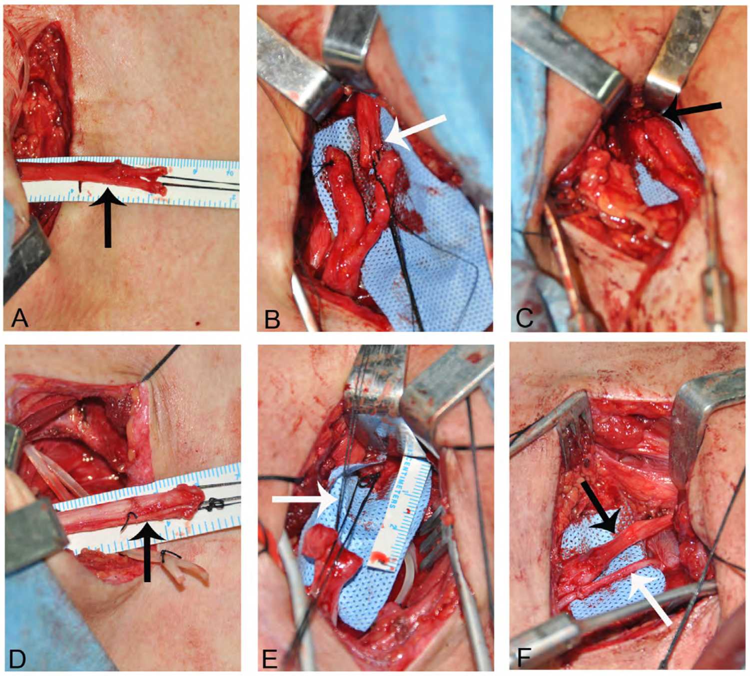

Figure 4 Surgical procedure in the two groups.
(A–C) Direct repair group: (A) The CC7 nerve root (black arrow) was identified and transected as distally as possible, and then the length of the harvested CC7 nerve root was measured. (B) The reach appeared adequate between CC7 and C5/C6 nerve roots (white arrow). (C) Direct repair (black arrow) was performed without tension to avoid interposing the graft. (D–F) Surgical procedure in the hANAs group: (D) The CC7 nerve root (black arrow) was identified and transected as distally as possible, and then the length of the harvested CC7 nerve root was measured. (E) Measurement of the length of the gap (white arrow) between the CC7 nerve root and upper trunk. (F) hANAs (black arrow) were applied to bridge the gap between the end of the CC7 nerve root and the upper trunk, and end-to-end coaptation was adopted with 8-0 Prolene sutures. Additional suprascapular nerve (white arrow) reinnervation was simultaneously undertaken. CC7: Contralateral cervical 7 nerve root; hANAs: human acellular nerve allografts.

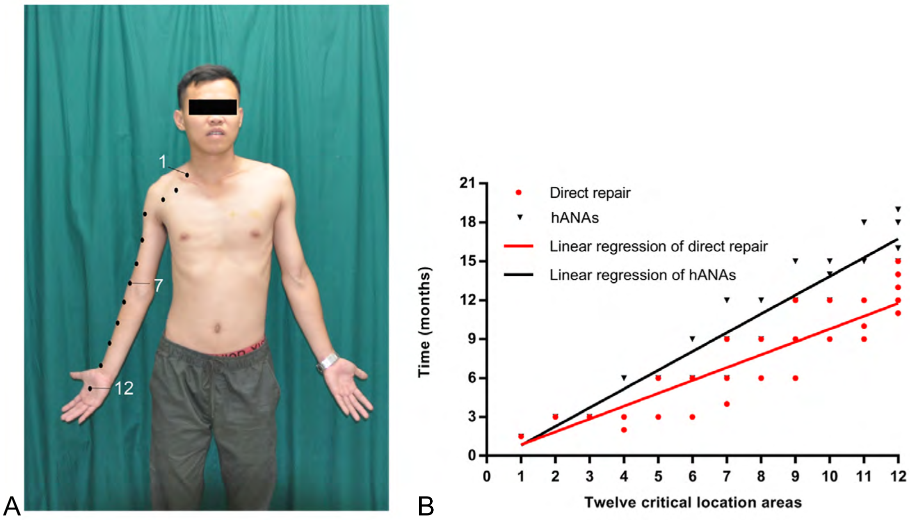

Figure 5 An 18-year-old male with an injury to the right C5–8 nerve roots.
The patient underwent direct coaptation of CC7 nerve transfer to the ipsilateral upper trunk via the prespinal route with additional suprascapular nerve innervation 90 days after brachial plexus avulsion injury. In the follow-up period, Tinel's sign assessment was performed monthly. (A) The 12 critical location areas on the recipient-side upper extremity for Tinel's sign assessment: 1, greater supraclavicular fossa; 2, subclavian fossa; 3, clavicular part of the pectoralis major; 4, proximal upper arm (deltoid); 5, middle upper arm; 6, distal upper arm; 7, elbow; 8, proximal forearm; 9, middle forearm; 10, distal forearm; 11, wrist; and 12, palm. Comparisons were performed using Student's *t*-test. (B) Comparison of C5/C6 reinnervation times in the two groups. Plots are evenly distributed on both sides of the regression line. CC7: Contralateral cervical 7 nerve root; hANAs: human acellular nerve allografts.

85.19%, respectively, and in the hANAs group were 70.83% and 66.67%, respectively.

Complications

No adverse events related to the use of hANAs were reported. Moreover, there were no complications related to injury of the esophagus, phrenic nerve, recurrent laryngeal nerve, or major cervical blood vessels. All patients complained of paresthesia in the distribution area of the CC7; hyperalgesia was reported in 33 cases, while hypoalgesia was found in 18 cases. Complaints about neuropathic pain symptoms were most commonly associated with the thumb and index finger, and sometimes in the ring finger and along the lateral side of the dorsal hand. In 36 patients, the aforementioned symptoms disappeared within 12 weeks after surgery, while for others, this occurred within 3 to 6 months. Few patients among the two groups complained of "tingling" or "pain caused by light touch". However, the contralateral upper limb of some patients affected numbness and tingling when a physical examination of the injured limb was performed. Most muscle strengths of the extensors and grip strength on the donor side were within the normal range at 1 year after the operation. No complete deficits were encountered.

One patient in the direct repair group encountered transient lymphatic drainage from the wound on the injured side (left side) of the neck. A sandbag was placed on the wound, and the patient had to abstain from food and water intake, which was replaced with intravenous nutrition for 3 days. The wound did not fully heal until 2 weeks later.

Four of the 21 patients who underwent additional suprascapular nerve reinnervation suffered from postoperative dyspnea on the ward. These symptoms lasted for 2 weeks and were alleviated by low-flow oxygen inhalation. No patient had obvious breathing problems at rest or during daily activities 1 year postoperatively (Bertelli and Ghizoni 2016; Li et al., 2018).

Discussion

CC7 nerve transfer has been adopted and modified by other surgeons to shorten the gap between donor and recipient nerves (Xu et al., 2008; Wang et al., 2012; Vanaclocha et al., 2015; Jiang et al., 2016; Leblebicioglu et al., 2016). In our previous study, the proximal end of CC7 was separated from the intervertebral foramen, while the distal part was dissected as distally as possible under a microscope. Subsequently, the proximal end was passed through the prespinal passage and beneath the anterior scalene and longus colli muscles. This technique facilitated prolongation of the mean length of the harvested C7 nerve root, greatly shortened the gap, and allowed direct coaptation of the CC7 nerve to the upper trunk. Xu et al. (2008) modified the McGuiness-Kay technique; in their procedure, a nerve graft of 6.25 ± 0.35 cm in length was used to repair the supraclavicular brachial plexus, and a graft 8.56 ± 0.45 cm long was used to repair the infraclavicular brachial plexus. These two cases achieved direct suture to the C5/C6 nerve roots. Muscle strengths were graded M3 for the deltoid and M4 for the biceps in some patients at less than 12 months of follow-up. Wang et al. (2012) used CC7 nerve transfer with nerve autografting through a modified prespinal route to repair the upper trunk in 41 brachial plexus avulsion injury patients. Only one case achieved direct repair. Mean length of the dissected CC7 nerve root was 6.56 ± 0.7 cm, while mean length of the autograft was 6.86 ± 1.9 cm. Muscle strengths were graded as M3–M4 for the deltoid in 82.9% of patients, and for the biceps in 85.4% of patients. Our results showed that rates of M3–M4 for the deltoid and biceps in the direct repair group were 88.89% and 85.19%, respectively, and in the hANAs group were 70.83% and 66.67%, respectively. These results indicated that the effects of autografting were inferior to those of direct repair, but superior to those of hANAs alone.

Bridging of nerve gaps has puzzled surgeons, not only because of disappointing functional recovery, but also because of the difficulty in selecting a suitable nerve graft. Autografting is the gold standard for reconstruction of a peripheral nerve gap. However, this technique has some major drawbacks, including scant donor nerves and the sacrifice of donor nerves (Moore et al., 2009; Ray and Mackinnon 2010; Boyd et al., 2011). Clinical nerve allografting was attempted in 1885, but it was limited by the need to mitigate the host immune response (Mackinnon et al., 2001). Nerve conduits have been explored as an option for nerve reconstruction for many years. Their drawbacks include limited use for segmental nerve defects < 30 mm and unacceptable functional outcomes for the reconstruction of motor and mixed nerves (Meek and Coert, 2008; Deal et al., 2012). The hANAs used in our study are the second form of allografts that have been put into clinical application (Cho et al., 2012; He et al., 2015). The safety and efficacy of hANAs has been demonstrated in primate studies (Hu et al., 2007; Wang et al., 2008) and multicenter clinical trials (Zhu et al., 2017). In our previous study, hANA transplantation had favorable outcomes, with gap lengths of ≤ 30 mm in sensory, motor, and mixed nerves. The results of allografting for gap lengths of 30–50 mm were comparable to the results of autografting for reconstruction. However, the previous study mainly applied hANAs to digital nerve reconstruction; the scope was expanded to the brachial plexus, which includes great, mixed, and high-level nerves. Our results were encouraging. In addition, we examined the performance of additional suprascapular nerve reinnervation for the two groups and found that rates were similar between the two groups. Increasing evidence suggests that additional suprascapular nerve reinnervation increases the stability of the shoulder joint, and a stable shoulder is a prerequisite for optimal elbow flexion (Ray et al., 2016). We did not use the accessory nerve to reinnervate the suprascapular nerve to preserve its function for free gracilis transfer, which can be used to reconstruct elbow flexion or finger extension/flexion during a second-stage operation (Hou et al., 2015), if necessary.

Our current study provided us the opportunity to evaluate the quality of shoulder abduction and elbow flexion after direct repair of the CC7 nerve to the upper trunk, with or without the utilization of hANAs. By creating a prespinal passage for CC7 nerve transfer or performing clavicular shortening, even by means of reliable microsurgical techniques, it might be possible to weaken the demand for nerve grafts. Gu et al. (2002) hypothesized that reducing the distance of nerve regeneration could also promote functional recovery of the nerve; however, they were concerned about whether the distance was sufficiently shortened and the safety of the new route. Our present study demonstrated that direct repair did have benefits for the restoration of shoulder abduction and elbow flexion. Except for one patient who encountered transient lymphatic drainage, the remaining operations were uncomplicated, without damage to the esophagus, major blood vessels, phrenic nerve, pleura, or thoracic duct during or after the operation. In addition, we found that heights were greater, BMIs were lower, and separable lengths of the CC7 nerve root and its divisions were longer for patients in the direct repair group compared with the hANAs group. These results indicated that patient height and BMI may have a relationship with the available length of the C7 nerve root and length of passage required for the CC7. Xu et al. (2008) reported that direct neurorrhaphy with the residual C5/C6 roots was possible because of the slim stature of patients. In our study, increased heights and lower BMIs enabled direct coaptation of the CC7 nerve transfer to the upper trunk via a modified prespinal tunnel. These characteristics could provide references for further clinical strategies when planning surgery in brachial plexus avulsion injury cases.

At present, Tinel's sign is widely used to evaluate regenerating injured peripheral nerves (Davis and Chung, 2004; Lee and Dellon, 2004). Tinel's sign is the "tingling" feeling elicited when an injured nerve trunk is percussed at or distal to the lesioned site of the nerve (Hoffmann et al., 1993). A positive sign can indicate the level of regeneration or localize the level of damage to a nerve (Davis and Chung, 2004). To determine the regeneration time of axons across the dominant area of the C5/C6, the upper extremity was classified into 12 areas from the ipsilateral greater supraclavicular fossa to the palm, based on the neural pathway and distribution of C5/C6. This method is very simple and facilitates the evaluation of axonal regeneration rates in follow-up. The scatter plot shown in **Figure 5B** revealed that axonal regeneration time was longer in the hANAs group compared with the direct repair group. This result likely occurred because vascularization of the acellular allograft required time (Zhu et al., 2015), and the new growing axons must cross two neurorrhaphy sites, further delaying recovery and impoverishing the results. Generally, electromyography examination is a precise assessment tool for assessing the quality of nerve regeneration and speed of axonal growth (Chin et al., 2018). However, it is not easy to widely apply this technique at each follow-up, as it is costly and time-consuming. Thus, not all patients underwent long-term and fixed-period electromyography examinations in our clinical practice.

This study was limited by its retrospective nature and small size. In addition, the gold standard for bridging the nerve gap is autografting; thus, we should also examine data regarding autograft transplantation during brachial plexus reconstruction as a control group. However, as only five patients have undergone autografting for upper trunk repair in our clinic, the small number of cases severely limited their use as a control group. Moreover, our results were only compared with those of autografting in CC7 nerve root transfer to the upper trunk; results reported in Xu et al. (2008) could also be set as control groups. Furthermore, partial data regarding Tinel's sign as reported by patients or their family members, as well as differences in examiners, may return different results. We advocated using light pressure when performing the test because a normal intact nerve can be stimulated with a higher percussion (Hoffmann et al., 1993). Despite the retrospective nature of our study, we observed homogeneity among our comparison groups. All patients underwent CC7 nerve transfer to repair the upper trunk, and patient characteristics were similar between the two groups.

The current study was performed to validate this challenging technique and show that direct repair during CC7 transfer to the upper trunk can benefit shoulder abduction and elbow flexion. This procedure should be undertaken by an experienced surgeon for selected patients. In addition, the patient's height and BMI should be considered when planning surgery. Our results provide sufficient evidence to demonstrate that every effort to achieve a direct repair of the CC7 nerve root with the ipsilateral upper trunk should be taken. However, if such a coaptation is not possible, use of hANAs is a suitable option.

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