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# Nerve transfer helps repair brachial plexus injury by increasing cerebral cortical plasticity

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## Abstract
In the treatment of brachial plexus injury, nerves that are functionally less important are transferred onto the distal ends of damaged crucial nerves to help recover neuromuscular function in the target region. For example, intercostal nerves are transferred onto axillary nerves, and accessory nerves are transferred onto suprascapular nerves, the phrenic nerve is transferred onto the musculocutaneous nerves, and the contralateral $C_7$ nerve is transferred onto the median or radial nerves. Nerve transfer has become a major method for reconstructing the brachial plexus after avulsion injury. Many experiments have shown that nerve transfers for treatment of brachial plexus injury can help reconstruct cerebral cortical function and increase cortical plasticity. In this review article, we summarize the recent progress in the use of diverse nerve transfer methods for the repair of brachial plexus injury, and we discuss the impact of nerve transfer on cerebral cortical plasticity after brachial plexus injury.

***Key Words:*** *nerve regeneration; brachial plexus injury; nerve transfer; cortical plasticity; intercostal nerve; phrenic nerve; radial nerve; cerebral functional reconstruction; review; neural regeneration*

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## Introduction
The brachial plexus consists of nerve roots $C_5$–$T_1$, which mainly innervate the muscles of the upper arm, and control the normal activities of these muscles. Brachial plexus injury, particularly total root avulsion, is one of the most serious disabilities of the extremities. It has an unfavorable prognosis and may cause paralysis of part of or even the entire upper arm. Therefore, treatment of brachial plexus injury is a major topic of study in the field of peripheral nerve injury. Nerve transfer is currently the optimal clinic strategy for the treatment of brachial plexus injury. To achieve good results from treatment, early nerve repair is essential. One major goal of this literature review is to provide a comprehensive survey on the numerous intra and extra-plexal nerves that have been used in transfer procedures, both within China and overseas, to repair brachial plexus injury. The other goal is to discuss the role of candidate nerves for transfer in the surgical management of common severe brachial plexus problems encountered clinically.

Nerve transfer involves the reconstruction of a distal de-innervated nerve by using a proximal foreign nerve as the donor of neurons and axons to re-innervate the distal targets (Chen et al., 1994). This can be regarded as "neurotinzation" or "nerve crossing". Two types of nerves can be used: extra-plexal donor nerves and intra-plexal donor nerves (Addas and Midha, 2009). Extra-plexal donor nerves include the intercostal nerve (ICN), spinal accessory nerve, cervical plexus, phrenic nerve and contralateral $C_7$ root. Intra-plexal donor nerves include the ipsilateral nerve trunk and the bundle branch of the medial or ulnar nerves.

Nerve transfer is indicated in the following situations (Hems, 2011): (1) brachial plexus root avulsion or proximal intra-foraminal injury close to the spinal cord with no, or poor, nerve stump available for nerve grafting; (2) proximal injury with a long distance to the target muscle; (3) significant vascular or bony injuries in the region of the brachial plexus; (4) previously failed attempts at brachial plexus or proximal nerve repair.

A review of the historical precedents as well as the anatomical basis and rationale for nerve transfers in brachial plexus surgery was clearly presented 30 years ago (Gu, 2005). Since then, nerve transfer procedures have been increasingly performed to treat severe brachial plexus injury, and the methods of treatment for total brachial plexus root avulsion have continued to improve (McGuiness and Kay, 2002; Bertelli and Ghizoni, 2003). According to the site of injury, lesions of the brachial plexus are classified as either preganglionic or postganglionic. For a postganglionic lesion, conservative treatment or nerve grafting, including nerve suture or neurolysis, can often achieve good results. But for a preganglionic lesion, no recovery can be expected using these methods. Extra-plexal or intra-plexal donor nerve transfer or an alternative reconstructive procedure should be considered without delay. The former involves the following nerve transfers: ICN transfer to the axillary nerves, and accessory nerve transfer to the suprascapular nerves, phrenic nerve transfer to the musculocutaneous nerves, and contralateral $C_7$ nerve transfer to the median nerves or radial nerves. In intra-plexal nerve transfer, part of the bundle branch of the ulnar or median nerves is transferred to the musculocutaneous nerves, or the branch of the radial nerve supplying the long head of the triceps brachii is transferred to the axillary nerves.

There are several important principles to follow to optimize the outcome of nerve transfers. The first is to re-innervate the recipient nerve as closely as possible to the target organ. The second is to perform a direct repair without intervening grafts. The third is to use combinations of similarly behaving neuromuscular units. The outcome of nerve transfers is enhanced when the donor and recipient are properly selected, as cortical re-adaptation is the physiological basis of functional recovery.

## Treatment Options for Brachial Plexus Injury

### Intercostal nerves

The concept of ICN transfer for repairing brachial plexus injury can be credited to Seddon, Tsuyama and Nagano. Seddon first used ICNs for nerve transfer in 1963. He used the ulnar nerve as a nerve graft to connect the ICNs to the musculocutaneous nerve. However, this achieved poor results. Six years later, Tsuyama improved Seddon's method by directly splicing ICNs to the musculocutaneous nerve, thus achieving satisfactory results. After reviewing 159 cases, Nagano et al. (1989) concluded that using the fish-mouth technique during suturing achieved the highest efficacy in nerve transfer procedures. Based on these principles, Gu (2005) made the following conclusions based on his own clinical practice: (1) when cutting out ICNs, the fourth ICN should be used as the center; (2) when transferring to the musculocutaneous nerve, at least two ICNs should be sutured; (3) when cutting out three ICNs, transverse incisions should be made along the intercostal spaces; (4) while cutting out at least four ICNs, a longitudinal incision should be made along the anterior axillary line. With innovations based on these principles, the efficacy of nerve transfer has increased to 67.39%. Since then, ICNs have been commonly used as extra-plexal donor nerves. They are commonly transferred to the thoracodorsal nerves and the branch of the radial nerve supplying the long head of the triceps brachii to restore shoulder abduction and external rotation (Terzis and Kokkalis, 2008). This is of great significance for patients who have severe brachial plexus injury involving the $C_5$–$T_1$ roots, where the sources of the donor nerves are limited (Midha, 2004). Better results can be achieved in patients younger than 30 years old who receive the operation within 6 months of injury (Nagona, 1998).

### Spinal accessory nerve (SAN)

Classified as an extra-plexal nerve, SANs are rarely injured in patients who have brachial plexus injury (Samardzić et al., 2000). When they were first used in 1972, SANs produced satisfactory outcomes. Since then, SANs have been transferred to suprascapular and musculocutaneous nerves to restore shoulder abduction and elbow flexion, respectively. Brunelli and Brunelli (1991) showed that SAN transfer to the suprascapular nerves was the best solution because the supraspinatus and infraspinatus muscles are supplied by similar nerves. In 1987, Gu proved that the efficacy of directly suturing SANs to suprascapular nerves was higher than that of using a nerve graft. Nerve transfers involve the donor nerve being brought closer to the end organ. The closer the transfer is to the target muscle, the shorter the distance the regenerating axons have to travel and the better the functional re-innervation (Addas and Midha, 2009).

Traditionally, accessory to suprascapular nerve transfer has been accomplished through an anterior supraclavicular approach. However, there are some disadvantages of this method, such as scarring, nerve retraction or displacement, and nerve tumor. Each of these complications may cause difficulties when searching for the suprascapular and accessory nerves. Consequently, clinicians have started to use a posterior approach, particularly when transfer of the triceps branch of the axillary nerve is considered in combination to accessory nerve transfer (Rui et al., 2013). Colbert and Mackinnon (2006) used the posterior approach, and achieved better protection to the nerves supplying the trapezius as well as better recovery of shoulder abduction in comparison to the anterior approach. Plate et al. (2011) came to the same conclusion after treating nine patients using combined nerve transfer. The posterior approach offers the following advantages: (1) it is better for functional recovery as the anastomosis lies next to the target muscles; (2) anatomically, the scapular nerve and accessory nerve can be easily tracked, maintaining a fixed location when descending to shoulder level; (3) this operation relieves nerve compression syndrome of the suprascapular nerve caused by the transverse ligament. A larger number of cases will be needed to evaluate its efficacy compared with the traditional method, because the number of distal fibers of the accessory nerve is substantially low (Lao, 2010).

### Phrenic nerve

The phrenic nerve originates mainly from the fourth cervical root, while both $C_3$ and $C_5$ roots contribute to and augment the nerve. As a result, it contains more pure motor axons than other nerves, allowing for the possibility of partial or complete nerve transfer with great success (Viterbo et al., 1995). For a complete phrenic nerve, $C_4$ and $C_5$ must remain intact. Injury to both $C_4$ and $C_5$ is uncommon as both nerve roots are strongly bound by fibrous tissue forming a chute-like structure.

Liu et al. (2014) compared the vascularized phrenic nerve transfers of 14 patients with the non-vascularized phrenic nerve transfers of 19 patients. No statistically significant difference was found between the two groups after a 3-year follow up. This is most likely because the nerve itself has a small diameter and a well-vascularized bed.

In recent years, the thoracoscope has been widely used in cutting out the phrenic nerve. In 1999, Gu and Shi (1999) first carried out a study of this procedure. Preliminary results showed that this method was used to transfer the phrenic nerve to the ulnar nerve, successfully restoring thumb flexion in 20 patients. Compared with traditional methods used in cutting out the phrenic nerve, the length of the excised nerve can be increased by using a thoracoscope. In 2002, Xu et al. (2002) successfully cut out the full length of the phrenic nerve with the aid of a thoracoscope and transferred it to the musculocutaneous nerve. This method reduced the recovery time for elbow flexion to an average of just 5 months.

The greatest concern in phrenic nerve transfer is the impairment of lung function. Giddins et al. (1995) showed that the lower ICNs of rats also participated in the innervation of the diaphragm. When the phrenic nerve is sacrificed for nerve transfer, respiratory function decreases by an average of 10% (Luedemann et al., 2002). This can produce symptoms in high oxygen demand situations, particularly in infants and children with respiratory infections. In 2006, Jiang et al. (2006) found a statistically significant drop in vital capacity when using the right phrenic nerve compared with the left. He demonstrated that transposition of the left phrenic nerve does not lead to severe respiratory dysfunction. Consequently, clinicians should be cautious when using the right phrenic nerve if maximal inspiratory pressure is low preoperatively. Until a long-term follow-up study is completed, it will remain unclear whether respiratory function will be maintained as patients age. Therefore, at the present, transfer of the phrenic nerve should be avoided.

**Contralateral $C_7$ nerve**

The contralateral $C_7$ root has a large number of nerve fibers (approximately 420,00), and it was first used for nerve transfer in 1986 (Gu et al., 1992). Since then, many clinical cases and experiments have demonstrated that transfer using this root can achieve very good outcomes (Kim et al., 2003). Also, there is little risk to function by harvesting the $C_7$ spinal nerve, providing additional sources of donor nerves (Gu et al., 2003). Contralateral $C_7$ nerve transfer has been widely used, both within China and overseas, for shoulder and elbow restoration. This method returns grasp function and achieves sensory recovery, and is considered a major breakthrough in the treatment of brachial plexus injury. Contralateral $C_7$ nerve transfer is an optimal strategy for treating brachial plexus injury (Dubuisson and Kline, 2002; Friedman et al., 1990), especially when root avulsion and phrenic and accessory nerve damage is encountered simultaneously. In this situation, contralateral $C_7$ transfer is the only solution (Terzis and Kokkalis, 2010).

The procedure for contralateral $C_7$ nerve transfer can be divided into two stages; stage I and stage II (Gu et al, 1992). In stage I, the contralateral $C_7$ root is transferred to the nerve graft (ulnar nerve with vessel pedicle is frequently used), and in stage II, the other part of the nerve graft is transferred to the recipient nerve, including the median nerve and radial nerve. There are numerous follow-up patient reports, providing evidence of the importance of such a division. Waikakul et al. (1999) reported that only 20% of the 96 patients who underwent contralateral $C_7$ nerve root transfer regained forearm and hand flexor muscle strength to grade 3 or 4, measured using the modified MRC scale, within period I. Lao (2010) concluded that different methods contributed to the large disparity in the proportion of patients who achieved strength recovery during periods I and II—36% and 63%, respectively.

Cortical plasticity appears to play an important physiological role in the functional recovery of the re-innervated muscles. Recently, an increasing number of investigators have focused their attention on cerebral plasticity following contralateral cervical nerve transfer in humans. Many animal and clinical experiments (Bao et al., 2001) have shown that the brain is capable of extensive reorganization after the peripheral nervous system is injured (Wang et al., 2010). Contralateral $C_7$ nerve transfer provides an ideal opportunity to study the relationship between brachial plexus injury and cortical reorganization (Florence et al., 1996). Peripheral nerve conduction testing shows that degeneration and regeneration after peripheral nerve injury are complex processes. Physiological changes occur not only at the site of injury, but also upstream (brain and spinal cord) and downstream (muscles and effectors) of the damage (Kemp et al., 2010). Peripheral nerve injuries block the flow of output from the motor cortex to the denervated muscles, thereby resulting in paralysis. However, with the gradual maturation of regenerating axons, the dominant functions of the muscles eventually recover (Muñetón-Gómez et al., 2004; Anastakis et al., 2008).

Li et al. (2004, 2005) showed that plastic changes indeed take place in the contralateral motor cortex of adult rats with total brachial plexus root avulsion. Feng et al. (2005) demonstrated changes within the primary motor cortex of patients who underwent contralateral $C_7$ nerve translocation following brachial plexus injury using functional MRI. He also proposed that earlier rehabilitation of the affected limb results in better and more extensive cortical reorganization. In 2012, Liu et al. (2012) used contralateral $C_7$ nerve transfer to treat six patients with central spastic hemiplegia. After a 2-year follow-up, they concluded that functional recovery of the affected limb, particularly of the wrist and elbow, was satisfactory.

**Combined application**

In patients with total root avulsion of the brachial plexus, elbow flexion is restored by ICN transfer, and shoulder function is restored by shoulder arthrodesis. Hand function is restored by an ICN transfer for the median nerve, or by free muscle transplantation in combination with nerve transfer (Nagano, 1998). Different neural transplantation approaches for the treatment of brachial plexus injury provide differential outcomes, but direct transplantation of collateral branches are associated with better outcome compared with the use of other nerve plexuses, especially in patients with delayed treatment (Bertelli and Ghizoni, 2010).

## Expectations

The use of nerve transfers has been a major advancement in the field of brachial plexus nerve reconstructive surgery. Many different and ingenious transfer strategies have been developed and have helped enhance functional recovery. Root avulsion of the brachial plexus should be treated with comprehensive treatment and rehabilitation (Korak et al., 2004). The efficacy of treatment is strongly impacted by the following factors: (1) type of involved roots; (2) time period between injury and operation; (3) degree of damage; (4) restorative exercises post-operation; and (5) co-therapy of the central nerves. A large number of clinical and animal experiments have shown that a combined treatment approach involving the brain, spinal cord and effectors that control muscle movement is required to obtain satisfactory clinical results in the rehabilitation of brachial plexus root avulsion.

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