

Nerve allograft transplantation for functional restoration of the upper extremity: case series

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Background: Major trauma to the spinal cord or upper extremity often results in severe sensory and motor disturbances from injuries to the brachial plexus and its insertion into the spinal cord. Functional restoration with nerve grafting neurotization and tendon transfers is the mainstay of treatment. Results may be incomplete due to a limited supply of autologous material for nerve grafts. The factors deemed most integral for success are early surgical intervention, reconstruction of all levels of injury, and maximization of the number of axonal conduits per nerve repair.

Objective: To report the second series of nerve allograft transplantation using cadaveric nerve graft and our experience with living-related nerve transplants.

Participants: Eight patients, seven men and one woman, average age 23 years (range 18–34), with multi-level brachial plexus injuries were selected for transplantation using either cadaveric allografts or living-related donors.

Methods: Grafts were harvested and preserved in the University of Wisconsin Cold Storage Solution at 5°C for up to 7 days. The immunosuppressive protocol was initiated at the time of surgery and was discontinued at approximately 1 year, or when signs of regeneration were evident. Parameters for assessment included mechanism of injury, interval between injury and treatment, level(s) of deficit, post-operative return of function, pain relief, need for revision surgery, complications, and improvement in quality of life.

Results: Surgery was performed using living-related donor grafts in six patients, and cadaveric grafts in two patients. Immunosuppression was tolerated for the duration of treatment in all but one patient in whom early termination occurred due to non-compliance. There were no cases of graft rejection as of most recent follow-up. Seven patients showed signs of regeneration, demonstrated by return of sensory and motor function and/or a migrating Tinel's sign. One patient was non-compliant with the post-operative regimen and experienced minimal return of function despite a reduction in pain.

Conclusions: Despite the small number of subjects, it appears that nerve allograft transplantation may be performed safely, permitting non-prioritized repair of long-segment peripheral nerve defects and maximizing the number of axonal conduits per nerve repair. For patients with long, multi-level brachial plexus injuries or combined upper and lower extremity nerve deficits, the use of nerve allograft allows a more complete repair that may translate into greater functional restoration than autografting alone.

Keywords: Brachial plexus, Nerve transplantation, Nerve allograft

Introduction

Injuries to the spinal cord and brachial plexus are debilitating consequences of severe trauma.¹ Patients with chronic spinal cord injury (SCI) may ultimately benefit from procedures that bypass their clinical deficit through neurotization from more intact proximal

(cranial) sources to establish more distal function. Patients with chronic SCI who have upper extremity dysfunction may be candidates for techniques developed to treat bilateral brachial plexus injuries. Allograft can provide an abundant supply of donor nerves; however, consideration of potential infectious complications from allograft immunosuppression is prudent in patients with SCI.

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Early and aggressive surgical treatment is the optimal approach for restoration of function. Present methods of treatment include autologous nerve grafting, neurotization, tendon transfer, and arthrodesis. Nerve grafting is usually first attempted as this technique attempts to repair the deficit anatomically with the aim of achieving the highest level of function. A significant limitation to maximal functional recovery is the paucity of autologous donor nerve for grafting. There are limited sources of donor nerve that will provide long segments for grafting without significant sensory losses.

The mainstay of donor nerve is the sural nerve. Other potential sources for nerve grafting include the ulnar, medial/lateral, antebrachial, saphenous, and cutaneous femoral nerves, but they are short and of poor caliber. When there are long, multi-level defects each requiring multiple axonal conduits, there is a prioritization of procedures to provide recovery of those functions deemed most necessary for daily activities. For example, arm abduction, elbow extension, and flexion are considered the most important functional targets of restoration. There is also a growing body of literature that shows that axonal density contributes to muscle strength. Having a large supply of donor nerve enables multiple cable grafting and hopefully increases axonal density. In this context, the use of allograft can be helpful in providing maximal axonal density when, as often is the case, there is not enough autograft. Unfortunately, the result is incomplete return of function due to unrepaired injuries.

There is an ongoing search for alternative methods of reconstruction in order to provide a more complete return of function in patients with long, multi-level defects. MacKinnon *et al.* reported the first series using interpositional peripheral nerve allografts for traumatic injuries to the upper and lower extremities.¹ The purpose of the current study is to report additional cases of cadaveric peripheral nerve allografts and to report our experience using living-related sources of donor nerve for functional restoration of the upper and lower extremities.

Brachial plexus injuries may be caused by closed injuries (traction, compression, combined lesion), open injuries (sharp, gunshot), and radiation. Traction injury is the most common brachial plexus injury representing nearly 95% of adult injuries.² Mild cases usually resolve with time; however, moderate-to-severe cases require surgical intervention. Surgical treatments include neurolysis, direct neurotomy, nerve grafting to bridge the defect (free and vascularized), neurotization/nerve transfers, arthrodesis, tenodesis, transfer of regenerated muscles, and adding new muscles via microvascular muscle transplantation.²

Long-segment, multi-level complex palsies prove to be a formidable challenge. The plexus reconstruction goals in complete palsy are obtaining brachial thoracic pinch, elbow flexion, and basic hand function (thumb/index sensation, wrist extension, finger flexion), and, in certain cases, to alleviate or improve pain.

Within the literature, current standard outcomes with nerve transfers are as follows: with C5–T1 avulsion injuries, reconstruction leads to 75% improvement representing greater than or equal to M3 muscle function in thoracobrachial grip and elbow flexion. With C5 rupture and C6–T1 avulsion, there is a 60% recovery with greater than or equal to M3 function in thoracobrachial grip and elbow flexion. With C5–C6 rupture and C7–T1 avulsion, we see a 70% recovery with reconstruction in thoracobrachial grip and elbow flexion; however, we see less than 25% recovery with hand function. In C5, C6, and C7 rupture and C8–T1 avulsion, the literature shows 75% recovery in thoracobrachial grip and elbow function with reconstruction and less than 30% recovery in hand function. Finally, with C5–T1 ruptures, which represent a limited series, the literature shows 75% recovery in thoracobrachial grip and elbow function, but less than 5% recovery in hand function.²

Methods

Eight patients with major trauma to the upper extremity were offered reconstruction using nerve autografts and allografts from 2003 through 2006. These patients were selected from a much larger cohort who were not surgical candidates or who could be successfully treated using only autologous tissue or other methods of reconstruction. All patients underwent an extensive preoperative evaluation, including history and physical examination, plain films, chest X-ray, MRA/MRI, CT myelography, electrodiagnostic testing (EMG), blood chemistry/hematology, urinalysis, viral titers (hepatitis (B, C), human immunodeficiency virus, Epstein–Barr virus, rapid plasma reagin, cytomegalovirus), ABO typing, and dental clearance. Inclusion criteria for nerve transplantation were long, multi-level nerve deficits exceeding the length that could be reconstructed using autologous tissue alone, or injuries requiring multiple axonal conduits to optimize functional return to denervated muscles. Patients were excluded if their medical history precluded the use of immunosuppressive therapy. The source of nerve allograft, either cadaveric or living related, was based upon the availability and a suitable donor match. Informed consent was obtained in accordance with the research review board at our institution. Cadaveric nerve donors and living-related donors were screened and ABO blood type-matched

according to protocol for solid organ donors – as well as testing for communicable disease.

Nerve allograft harvests from living-related donors for six patients were performed prior to, or simultaneously with, transplant procedures. Bilateral sural nerves were harvested using an endoscopic or limited incision technique when possible. Most donor nerves were harvested with two to three 2 cm incisions. Cadaveric donor harvests in two patients included removal of bilateral sural, tibial, median, ulnar, and/or radial nerves. Upon harvest, grafts were preserved in University of Wisconsin Cold Storage Solution at 5°C for up to 7 days, as per MacKinnon protocol. All nerve reconstructions were performed by the first author (AI Elkwood) as primary surgeon.

The immunosuppressive protocol was initiated by the consulting transplant nephrologist at the time of surgery and was discontinued at approximately 1 year or when the migrating Tinel's sign passed the distal anastomosis. The standard regimen consisted of basiliximab (Simulect)/(IL-2 receptor) (days 0 and 5), tacrolimus (FK506), azathioprine (Imuran), and co-trimoxazole (Bactrim), whereas prednisone reserve was not required in any of the patients. The surgical procedures were performed under general anesthesia and consisted of nerve exploration with intraoperative electrophysiological testing, harvesting of bilateral autologous sural nerves when feasible, and nerve grafting using both autologous and allograft sources. When appropriate, cable grafting was used to maximize axonal density. As autologous grafting still represents the gold standard, where possible, all cables represented at least a single strand of autologous nerve. A short segment of allograft was implanted in the volar forearm of the recipient extremity as a satellite marker in order to monitor for objective signs of rejection. Of the eight patients enrolled, six underwent transplantation using living-related donors and cadaveric transplants were performed in the remaining two patients. Parameters for assessment included mechanism of injury, timing of injury, level(s) of deficit, post-operative return of function, pain relief, need for revision surgery, and complications and improvement of quality of life. Muscle strength was graded on a standard scale: 0 – no contraction; 1 – slight contraction, no movement; 2 – full range of motion gravity neutral; 3 – active movement against gravity; 4 – active movement against gravity and resistance; and 5 – normal.³

Results

This series included seven men and one woman with an average age of 23 years (range 18–34). All patients had

multi-level brachial plexus injuries, including one patient with a combined upper extremity and sciatic deficit. Mechanisms of injury included accidents on motorcycles (four), automobiles (two), or motorboats (one), or as a result of gunshot wounds (one).

Surgery was performed using living-related donor grafts in six patients, and cadaveric grafts in two patients. Although there were no operative or peri-operative complications, one patient developed a post-operative cellulitis 6 months after termination of the immunosuppressive regimen that was managed successfully with antibiotic therapy.

Immunosuppression was tolerated for the duration of treatment in all but one patient in whom early termination was due to non-compliance. There were no cases of graft rejection as of most recent follow-up. Function was assessed through pre- and post-operative video, and pain based on the patient's subjective post-operative decreased use of narcotics.

Seven patients experienced either recovery of sensory and motor function (4/7) and/or a migrating Tinel's sign (4/7). One patient was non-compliant with the post-operative regimen and experienced minimal return of function despite a reduction in pain (see Table 1). Sensation recovery was assessed via two-point discrimination and muscle function via the currently accepted muscle grading system (*M* value) by the British Medical Research Council.³

There was no unanticipated donor site morbidity among the nerve graft donors. All nerve donors experienced paresthesias of the lateral ankle in the distribution of the sural nerve; however, there were no cases of symptomatic neuroma or wound infection. Individual case details are illustrated in Table 1. The following two patients from the series (patients 3 and 7) are described in detail to review patient demographics, injuries, treatment, and outcome.

Patient No. 3

A 19-year-old woman who was ejected from a car received living-related nerve transplant approximately 5 months after her injury. She initially presented with pan-brachiolexopathy. Pre- and intra-operative studies, as well as physical examination, revealed multi-level rupture of the posterior cord and axillary nerve. Patient had pan-neurolysis of the brachiolexus with allograft and autograft from C7 to the axillary nerve and allograft and autograft from C7 to the posterior cord. Patient initially presented with no arm abduction, minimal latissimus, no tricep function, and minimal bicep function. She also had minimal wrist extension and finger extension. Post-operatively, she

Table 1 Patient demographics, injuries, treatment, and outcome

Patient no.	Age/gender	Mechanism/type of injury	Interval between injury and grafting G (months)	Injured structures	Nerve grafting	Results
1	33 male	GSW	13	Medial cord (ulnar and medial nerve palsies)	Allograft to medial cord, ulnar nerve, median nerve	M4 pain free
2	26 male	Motorcycle accident	9	C5–C6 avulsions, partial C7 rupture, axillary and suprascapular nerve injuries	Cadaveric allograft to spinal accessory, musculocutaneous, middle trunk, lateral cord	Initial improvement then lost due to follow-up
3	19 female	Motor vehicle accident	5	Multi-level rupture of posterior cord and axillary nerve	Allograft and autograft from C7 at axially nerve and posterior cord	M5 – deltoid, lat dorsi, tricep, bicep, wrist (finger extensors)
4	19 male	Motorcycle accident	6	Median, ulnar, radial nerves	Allograft and autograft to median, ulnar, radial nerves	Minimal motor recovery due to extensive soft tissue loss
5	21 male	Motor vehicle accident	17	C5–C7 avulsions	Allograft and autograft SA-posterior cord/cross-chest C7 and C6 SA-C5,C6/cross-chest C7 and upper trunk	M5 – lat dorsi, M4 – pectoralis, M3 – tricep, M1 – bicep, M1 – deltoid pain free
6	27 male	Motorcycle accident	4	C5–T1 avulsions	Autografts to MCN, axillary, C7 cross-chest to median and radial nerves	M4 – supraspinatus, M3 – pectoralis, M2 – bicep, tricep pain free
7	17 male	Motorcycle accident	5	C5–C7 avulsions	Autograft C7 to radial, allograft to MCN, autograft to axillary, allograft to medial MCN	M5 – deltoid, M4 – bicep, M5 – tricep, M4–5 – extensors pain free
8	39 male	Motorcycle accident	7	C5–T1 avulsions	Autograft to median MCN, allograft to MCN, axillary, radial nerves	Pending tinels

M1–M5, muscle grading system, British Medical Research Council; GSW, gunshot wound; MCN, musculocutaneous nerve; lat. dorsi, latissimus dorsi muscle; SA, spinal accessory nerve

had 5 out of 5 strength of her deltoid, latissimus, tricep, bicep, wrist extensors, and finger extensors. This patient has done very well clinically and showed good response to cable nerve grafts. It is difficult to tell whether the spinal accessory donor to C7 donor was influential in improving her arm abduction, but this case does indicate that mixed nerve grafting may result in restored function.

Patient No. 7

A 17-year-old boy who was operated on 5 months status post-avulsion injuries to C5, C6, and C7. Pre-operatively, he had significant pain and no function of the deltoid, bicep, supinator, tricep, pectoralis, latissimus, or extensor digitorum communis (EDC). He had cross-chest autograft from C7 to his radial nerve, allograft from his median pectoral nerve to his musculocutaneous nerve, autograft spinal accessory to axillary

nerve, allograft ulnar nerve to median nerve, and allograft from his levator scapula nerve to his musculocutaneous nerve. Post-operatively, he developed M5 strength to his deltoid, M4 strength to his bicep, M5 strength to his tricep, and M4–M5 strength to his extensors. The patient was pain free. This case demonstrated an excellent response based on both his autograft and allograft.

Discussion

In the early 1900s the surgical treatment of brachial plexus injuries provided little return of function and subjected patients to significant morbidity.^{4–6} In the last 50 years, the development of microsurgical techniques and a greater understanding of peripheral nerve physiology contributed to improved surgical results with autologous grafts. The current philosophy regarding management of peripheral nerve injuries is early and aggressive surgical intervention for maximal functional restoration.

Functional restoration of brachial plexus injuries typically involves multiple steps. Initially, the algorithm begins with operative exploration. EMG mapping as well as visual inspection is usually performed and the details of the injury are mapped. Rupture (injury within the peripheral nerves) is typically treated with nerve grafting, whereas root avulsion (injury to the spinal cord/plexus juncture) is treated with neurotization with or without nerve grafts. Next, after about a year or so (enough time for healing to take place and for axons to regenerate), the injuries are reassessed and secondary methods are utilized to treat residual injuries. Techniques such as muscle/tendon transfer, arthrodesis, tenodesis, and splinting are typically utilized.

Terzis and Papakonstantinou published a comprehensive review of the surgical treatment of brachial plexus injuries in adults.⁷ The reconstructive algorithm outlined by these authors is based upon a prioritization of goals, aiming at restoring function to those muscle groups deemed most important for daily function. In this scheme, shoulder and elbow functions should be restored first by providing the supraspinatus, deltoid, triceps, and biceps muscles with the best motor donor nerves. Restoration of the median nerve by grafting from sensory intercostals or supraclavicular sensory nerves should be the next priority to recover protective sensitization. These authors also emphasize the importance of axonal density, citing improved results when multiple axonal conduits (i.e. multiple grafts) are used in parallel for each nerve repair. The number of axons tends to correlate with the strength of reinnervated muscle. In patients with extensive brachial plexus injuries, it becomes clear to reconstruct multiple motor nerves. To accomplish this, it is necessary to have an abundance of nerve graft. The primary surgeon did modify the technique in successive cases adopting MacKinnon's emphasis on axonal density via multiple parallel grafts.

The first attempts at peripheral nerve allografting were performed more than 100 years ago;^{8,9} however, the results were disappointing. Renewed interest in this technique was not seen until investigators began to understand the immunological responses to nerve allografts and developed techniques to combat antigenicity, such as pre-treatment with irradiation and lyophilization.¹⁰ Ultimately, clinical success with peripheral nerve allografts has paralleled the development of modern immunosuppressive regimens.^{1,11} The neuroregenerative properties of tacrolimus (FK506) have been well established and appear to be associated with improved functional outcomes, especially when combined with cold preservation of nerve grafts in

University of Wisconsin Cold Storage Solution that may be maintained without detriment for periods of 1 week.^{12,13} Based on the favorable experience with FK506 in nerve allografting, these authors have promoted its use for purely autologous reconstructions as well. Unique to nerve transplantation is that immunosuppression may be terminated in transplanted patients when there is clinical evidence of regeneration. This was determined after experimental investigations elucidated the mechanism by which allografts provide a conduit for regeneration – the grafts act as conduits for host axons to grow, supported by allogeneic cells, and with time are completely replaced by host tissue.^{14–16}

Treatment of long, multi-level brachial plexus injuries requires all of the available grafting techniques to maximize functional results. The use of autologous nerve and cadaveric nerve allograft may significantly enhance our ability to optimize results in these patients. Living-related nerve donor allograft is another option for patients and families who are committed to functional restoration of the extremity. We have learned a great deal from our colleagues devoted to solid organ transplantation and, accordingly, can extrapolate their protocols for identifying suitable transplant donor candidates. The results in this small series support both sources of donor nerve allograft for these major injuries and increase the possibility for maximal functional restoration. It also expands the options for patients who have injuries of multiple extremities that otherwise require grafting. In addition, nerve reconstruction has two theoretical additional benefits. Firstly, additional grafting material will allow for cable grafting, minimizing caliber mismatch between donor nerves and recipient nerves. This will minimize 'wasting' of any potential donor nerve – with the assumption that the surgeon can make use of more donor axons. Finally, when devising a nerve reconstructive protocol, the surgeon needs to prioritize function targeted for recovery (i.e. a typical hierarchy is shoulder abduction, elbow extension, elbow flexion, wrist extension, finger flexion, etc.) with alternative sources of nerve graft available – one can proceed further down the functional hierarchy targeting finer motor function that may have previously been avoided due to lack of nerve graft material. In sum, nerve allografting clearly affords opportunity to attempt reconstruction in multi-level and multi-limb reconstruction that otherwise is simply not available with autografting alone. Allografting, at least in theory, may provide an opportunity for a more elegant return of function with greater *M* value. Certainly, a small clinical study as the authors have outlined cannot prove or disprove these notions. This work

rather presents a variety of patients and injuries and their outcomes. While no statistical significance can be attributed to these cases, it is clear that in several instances functions relying solely on allografts returned with M4–M5 strength. This group of patients illustrates that when allograft and autograft are cabled together, M4 and M5 strength may also be achieved. Clearly, there is significant room for further laboratory and clinical study of this technique as an option for individuals with paralysis.

From our assessment of the results in this small series it is not possible to draw conclusions about favorable prognosticators. However, as we continue to monitor the long-term progress of these patients it appears that the best functional return occurs in younger patients treated within the first 6 months after injury and who are committed to functional restoration. This is in line with the preponderance of operative procedures regarding autografting techniques. For example, although patient 5 was not a pan-plexus injury, she did have a severe injury and essentially presented with a flail arm. Our early and aggressive intervention in this young patient and her absolute dedication to rehabilitation likely correlated with her excellent outcome. If the benefits of early intervention are ultimately confirmed, then the advantages of using living-related donors cannot be overstated. The delays associated with cadaveric allografts can be reduced significantly when the patient can enlist multiple family members or friends as potential nerve donors.

Conversely, a poor outcome may be expected in patients who are not committed to the immunosuppression and/or post-operative rehabilitation. Patient 2 in our series was non-compliant with both the immunosuppressive regimen and the post-operative rehabilitation protocols. He experienced a less than optimal return of function despite an early and aggressive surgical approach. It is of great importance to appropriately screen patients pre-operatively and we have begun enlisting the help of a mental health professional to help us wean out patients who may not be committed to this kind of undertaking.

This study has also shown that reinnervated muscles may be later used for muscle/tendon transfer for more important functions, as demonstrated in one of our patients, depending upon a reconstructive scheme designed for a specific patient.

Finally, this technology may be applied to patients with central nervous system processes, such as stroke or SCI, by providing donor nerve material to allow bypassing their clinical deficit by neurotization from functioning nerve. For example, caudal SCIs can be

neurotized from more cranial sources, and hemiparetic stroke deficits can be grafted to/from contralateral sources. Brunelli and Brunelli via a non-human primate model demonstrate that upper central nervous system (CNS) motorneurons may be connected with skeletal muscles through peripheral nervous system (PNS) segments bypassing a lesion of the spinal cord.^{17,18} This work suggests that upper CNS motor neurons may reach peripheral nerves to restore functional return by axonal migration through a connecting graft. Brachial plexus surgeons should consider the use of allografts with a period of immunosuppression for major nerve injuries.

In this series, immunosuppression was not associated with complications and probably having additional nerve grafts led to increased numbers of proximal axons reaching distal targets, although there is no easy way to confirm this hypothesis. Having more nerve grafts available for reconstruction certainly does permit more extensive nerve grafting than could be accomplished with only autografts. This is particularly important as more brachial plexus surgeons are employing long grafts from viable roots to specific motor branches, in contrast to the traditional methods of multiple grafts between root and division or cord. An abundance of grafts would permit very specific targeting.

Conclusion

Complex brachial plexus injuries are consequences of trauma that can result in severe functional disturbances. Early and aggressive surgery is the appropriate treatment philosophy. The limited supply of autologous graft often restricts the number of axonal conduits that may be used for each nerve repair, and even prevent complete repair in the setting of multi-level nerve injuries. Cadaveric and living-related nerve allotransplantation has been performed successfully and safely in this small series, without the need for prioritization. We were able to augment functional recovery without graft rejection using only a limited duration of immunosuppression.

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