Optimal Axon Counts for Brachial Plexus Nerve Transfers to Restore Elbow Flexion

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Background: Nerve transfer surgery has revolutionized the management of traumatic brachial plexus injures. However, the optimal size ratio of donor to recipient nerve has yet to be elucidated. The authors investigated the axon count ratios of ulnar and median fascicular transfers to restore elbow flexion. The authors hypothesized that donor nerve axon counts would be correlated with historical success of various nerve transfers used to restore elbow flexion.
Methods: Ten cadaveric specimens were used for a histomorphologic analysis of fascicular nerve transfers. Review of previously published axon counts and clinical results following transfer to the musculocutaneous nerve to restore elbow flexion was performed for the following donor nerves: medial pectoral, spinal accessory, intercostal, thoracodorsal, ulnar, and median fascicular.
Results: The average number of fascicles identified was 7.9 in the ulnar nerve and 8.0 in the median nerve. The mean fascicular axon count was 1318 for the ulnar nerve and 1860 for the median nerve. Mean recipient nerve axon count was 1826 for the musculocutaneous biceps branch and 1840 for the brachialis branch. A significant correlation between axon count and clinical results of transfers to restore elbow flexion was observed. Donor-to-recipient nerve axon count ratios below 0.7:1 were associated with a decreased likelihood of a successful outcome.
Conclusions: In nerve transfers to restore elbow flexion, an appropriate size match between donor and recipient nerves appears to be a factor affecting clinical success. These data support a donor-to-recipient axon count ratio greater than 0.7:1 as the goal for brachial plexus nerve transfers to restore elbow flexion. (*Plast. Reconstr. Surg.* 135: 135e, 2015.)

The transfer of functioning motor fascicles to reinnervate denervated muscles has revolutionized the treatment of traumatic brachial plexus injuries. Multiple nerve transfers to the musculocutaneous nerve have been described to restore elbow flexion, including the spinal accessory, thoracodorsal, medial pectoral, and intercostal nerves.[1] In 1994, Oberlin et al. described a transfer to the biceps that uses one or two fascicles, or up to 20 percent of the cross-sectional area, of the ulnar nerve.[2] This fascicular transfer has been widely used, with outcomes exceeding those of other described transfers,[2–8] and the concept has been expanded to the median nerve with similar success.[9]

Although many factors affect outcomes following nerve transfer surgery, an appropriate size match is universally considered an important criterion.[10,11] However, the ideal size ratio of donor to recipient nerve for optimizing muscular recovery remains undefined. Despite the wealth of publications with reports on donor and recipient nerve axon counts[12–19] (Table 1), none has reported the axon counts of this widely used and highly successful nerve transfer.[2–8]

Given the success of the ulnar fascicular transfer, we propose that this transfer can be used as a model to investigate the threshold of axon counts for successfully restoring elbow flexion. We hypothesized that donor nerve axon counts would be correlated with historical success of various nerve transfers used to restore elbow flexion.

MATERIALS AND METHODS

Anatomical Dissection

After obtaining Institutional Review Board of the Hospital for Special Surgery exemption, the

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Table 1. Relevant Published Axon Counts

Nerve	Mean Axon Count	Reference
Extraplexal		
Spinal accessory	1603	Pruksakorn et al., 2007[15]
Spinal accessory	1054	Vathana et al., 2007[18]
Intercostal III (total axons)	742	Malungpaishrope et al., 2007[13]
Intercostal IV (total axons)	830	Malungpaishrope et al., 2007[13]
Intercostal V (total axons)	1353	Malungpaishrope et al., 2007[13]
Intercostal II–IV (motor axons)	520–720	Samardzic et al., 1986[17]
Intraplexal		
Thoracodorsal, lateral branch	1843	Raksakulkiat et al., 2009[16]
Thoracodorsal, medial branch	974	Raksakulkiat et al., 2009[16]
Thoracodorsal	1530–2470	Samardzic et al., 1986[17]
Medial pectoral	1170–2140	Samardzic et al., 1986[17]
Medial pectoral	500	Norkus et al., 2005[14]
Ulnar	16,412	Bonnel, 1980[12]
Median	18,288	Bonnel et al., 1980[12]
Musculocutaneous	6061	Bonnel et al., 1980[12]
Musculocutaneous	14,004	Brandt and Mackinnon, 1993[19]

brachial plexus of 10 fresh frozen cadaveric upper extremities were dissected under loupe magnification. The number chosen was based on historical models for axon count studies.[14,17,19] The musculocutaneous nerve was dissected along its intermuscular course, and branches to the biceps and brachialis were identified and harvested at their most proximal site of divergence from the continuing lateral antebrachial cutaneous nerve. The distalmost portion of the nerve harvest was just proximal to arborization into the biceps and brachialis muscles, with sufficient additional "swing distance" (2 cm) to reach the ulnar or median nerve, respectively.

The ulnar and median nerves were identified along their intermuscular courses, and internal neurolysis was performed under loupe magnification to identify individual fascicles. The individual fascicular locations within the trunk were noted and recorded. Fascicles of the ulnar nerve were harvested at the level of the biceps branch of the musculocutaneous nerve, and fascicles of the median nerve were harvested at the level of the brachialis branch of the musculocutaneous nerve.

Histomorphologic Evaluation

Once all nerves were identified and measured, a 5-mm sample of each nerve was obtained by means of biopsy at the aforementioned locations for axon counting. The nerves were processed for histologic evaluation in the following manner: after fixation for 18 hours in 10% formalin, the samples were postfixed using 2% aqueous osmium tetroxide for 36 hours and washed thoroughly. Using a Tissue Tek VIP (Sakura Finetek USA, Inc., Torrance, Calif.), the samples were dehydrated through a graded alcohol series and cleared with two xylene rinses. They were then processed and embedded in paraffin. The samples were embedded perpendicular to the block, and sections of 7 μm were cut on a microtome (Reichert 2030; Reichert-Jung, Depew, N.Y.) from the center of each specimen. Sections were deparaffinized through two rinses of xylene and a graded alcohol series. Viewings were performed with a light microscope, and histomorphometric measurements of the sections were made using image analysis software (BIOQUANT Osteo II; BIOQUANT Image Analysis Corp., Nashville, Tenn.). Sections were stained with a 0.5% aqueous solution of toluidine blue before image analysis. The protocol identifies myelinated axons, and axon counts were performed manually with computer assistance. All axon count results were reported as means.

Literature Review

A series of MEDLINE searches and cross-referencing were performed to identify previously published studies reporting human axon counts pertinent to brachial plexus reconstructions (Table 1). The nerves were divided into extraplexal, intraplexal, and distal nerves by anatomical site. A review of published literature on outcomes of the following nerve transfers used to restore elbow flexion was also performed: ulnar fascicular, median fascicular, spinal accessory, thoracodorsal, medial pectoral, and intercostal (two and three) nerves. Because of the markedly improved results using modern intraplexal transfers for elbow flexion, we defined a successful outcome as a British Medical Research Council grade of M4 or greater, which represents useful elbow flexion function, and all identified studies that reported this metric were included.

Statistical Analysis

The proportion of successful clinical results (British Medical Research Council grade $\geq$ 4) for each transfer was calculated as a frequency weighted average of individual studies. The correlation between axon count and clinical success was assessed with a two-tailed Pearson r analysis. Odd ratios of a successful outcome, defined as motor strength greater than or equal to 4, were calculated for each transfer to evaluate the contribution of axon count to clinical success.

RESULTS

We identified an average of 7.9 fascicles in the ulnar nerve and 8.0 in the median nerve. The mean myelinated axon count within donor fascicles was 1318 ($n = 79$) per fascicle for the ulnar nerve and 1860 ($n = 80$) per fascicle for the median nerve. Mean recipient nerve axon count was 1826 ($n = 10$) for the musculocutaneous biceps branch and 1840 ($n = 10$) for the brachialis branch. Using published guidelines of transferring 20 percent of the ulnar[3,9] and a single fascicle of the median nerve[9,20] would result in an average of 2082 axons from the ulnar nerve and 1860 axons from the median nerve. The resulting axon count ratio of donor to recipient nerve was 1.1:1 for the ulnar to biceps nerve transfer and 1:1 for the median to brachialis transfer.

Seven outcome studies ($n = 132$) on the ulnar fascicular transfer had an aggregate successful outcome (British Medical Research Council grade ≥ 4) rate of 78 percent; other published outcomes included median fascicular transfer [one study, $n = 40$ (90 percent success rate)], thoracodorsal [six studies, $n = 37$ (78 percent)], medial pectoral (four studies, $n = 69$ (54 percent)], spinal accessory [seven studies, $n = 220$ (37 percent)], double intercostal [15 studies, $n = 372$ (36 percent)], and triple intercostal transfers [nine studies, $n = 213$ (44 percent)]. Results are summarized in Table 2.[2–8,20–52]

Mean myelinated axon counts from previously published studies were 2409 for the thoracodorsal nerve,[16,17] 1329 for the spinal accessory nerve,[15,18] and 1078 for the medial pectoral nerve.[14,17] Given that a single intercostal nerve is composed of 30 percent motor axons,[17] the mean published motor axon count of a single intercostal nerve is 375 (Fig. 1).[14,53]

Pearson r analysis between axon count and clinical success found a significant correlation (Fig. 2) ($r^2 = 0.72$, $p = 0.016$). Donor nerve axon counts below 1329 (ratio of 0.7:1) were associated with a decreased likelihood of a successful outcome ($p < 0.001$) (Table 3).

DISCUSSION

Transferring ulnar or median nerve fascicles to restore elbow flexion following brachial plexus injuries has resulted in reliable and reproducible outcomes,[2–8,20] with a dramatic improvement in reported strength parameters compared with previously described extraplexal nerve transfers (intercostal, spinal accessory). In this investigation, we report the axon counts of donor nerves that have been used to restore elbow flexion and correlate this with clinical success. Our findings suggest that a minimum donor-to-recipient axon count ratio of greater than 0.7:1 may be the goal for nerve transfers in brachial plexus reconstructions.

Multiple previous studies have looked at axon counts in anatomical studies for both feasibility and compatibility evaluations (Table 1).[11–19,53–55] However, despite the prolific success of using ulnar and median nerve fascicles for reinnervating the biceps and brachialis muscles and restoring elbow flexion, to the best of our knowledge, the axon counts and ratios of the involved nerves have not yet been published.

The principles for successful nerve transfer surgery have been described to include the following: (1) selecting a donor nerve with many axons and with a good size match with the recipient nerve, (2) using a purely motor donor nerve, (3) using a donor nerve in proximity to the neuromuscular junction of the recipient muscle, (4) choosing an expendable donor nerve, and (5) selecting a donor muscle that is synergistic with the target muscle.[10,11] Although size match is universally considered an important criterion, the acceptable ratio and range have not been defined. The observed correlation between axon count and clinical results is intuitive, as others have shown that the number of active motoneurons within a donor fascicle has an impact on postoperative contraction strength.[56,57]

Animal studies of partial nerve sectioning have shown that remaining motor units (as little as 20 percent) display an impressive ability to compensate through terminal sprouting to partially restore contractility.[58] Although interesting, the applicability of these data to human nerve transfer surgery is not directly apparent. Furthermore, the degree to which terminal collateral sprouting versus new nascent motor units affect muscle strength has not been definitively analyzed. In addition, in an animal nerve repair model, using a donor-to-recipient axon count ratio of 0.5:1 was found to result in significantly inferior clinical results compared with a 1:1 ratio.[59] The results of the present study not only corroborate that finding but more precisely define the optimal ratio.

Several nerve transfer combinations have been used to restore elbow flexion that can be generally divided into extraplexal and intraplexal transfers. Intraplexal transfers, such as the ulnar and median fascicular transfer, have generally outperformed extraplexal donor nerves (e.g., spinal accessory nerve and intercostal nerves) (Table 2). Although several factors may play a role in the

Table 2. Published Outcomes of Nerve Transfers to the Musculocutaneous Nerve for Restoring Elbow Flexion

Donor Nerve	Total No. of Cases	MRC ≥ 4 (n)	MRC ≥ 4 (%)	Reference
Intraplexal nerves				
Median ulnar fascicular	40	36	90	Nath et al., 2006[20]
Ulnar fascicular	32	30	94	Leechavengvongs et al., 1998[8]
Ulnar fascicular	4	3	75	Oberlin et al.,1994 [2]
Ulnar fascicular	18	6	33	Socolovsky et al., 2012[3]
Ulnar fascicular	36	30	83	Sungpet et al., 2000[4]
Ulnar fascicular	8	6	75	Suzuki et al., 2011[5]
Ulnar fascicular	32	26	81	Teboul et al., 2004[6]
Ulnar fascicular	2	2	100	Estrella, 2011[7]
Totals	132	103	78	
Thoracodorsal	1	1	100	Dai et al., 1990[21]
Thoracodorsal	6	5	83	Novak et al., 2002[22]
Thoracodorsal	4	3	75	Richardson, 1997[23]
Thoracodorsal	9	8	89	Samardzic et al., 2012[24]
Thoracodorsal	10	6	60	Samardzic et al., 2002[25]
Thoracodorsal	7	6	86	Samardzic et al., 2000[26]
Totals	37	29	78	
Medial pectoral	5	3	60	Brandt and Mackinnon,1993 [19]
Medial pectoral	17	10	59	Samardzic et al., 2012[24]
Medial pectoral	6	2	33	Samardzic et al., 2000[26]
Medial pectoral	41	22	54	Sulaiman et al., 2009[27]
Totals	69	37	54	
Extraplexal nerves				
Spinal accessory	15	2	13	Allieu and Cenac, 1988[28]
Spinal accessory	9	4	44	Kawai et al., 1988[29]
Spinal accessory	6	1	17	Samardzic et al., 1990[30]
Spinal accessory	20	7	35	Samardzic et al., 2000[26]
Spinal accessory	39	11	28	Samii et al., 2003[31]
Spinal accessory	130	56	43	Waikakul et al., 1999[32]
Spinal accessory	1	0	0	Chuang et al., 1993[33]
Totals	220	81	37	
Intercostal (2)	156	45	29	Nagano et al., 1989[34]
Intercostal (2)	2	0	0	Celli et al., 1988[35]
Intercostal (2)	19	3	16	Chalidapong et al., 2004[36]
Intercostal (2)	29	17	59	Chuang et al., 1992[37]
Intercostal (2)	8	4	50	Krakauer and Wood, 1994[38]
Intercostal (2)	2	1	50	Malessy and Thomeer, 1998[39]
Intercostal (2)	17	12	71	Minami and Ishii, 1987[40]
Intercostal (2)	64	23	36	Nagano et al., 1992[41]
Intercostal (2)	21	5	24	Ochiai et al., 1993[42]
Intercostal (2)	9	7	78	Ogino and Naito, 1995[43]
Intercostal (2)	11	7	64	Okinaga and Nagano, 1999[44]
Intercostal (2)	4	0	0	Simensen and Haase, 1985[45]
Intercostal (2)	9	0	0	Sulaiman et al., 2009[27]
Intercostal (2)	17	8	0	Tonkin et al., 1996[46]
Intercostal (2)	4	2	50	Ruch et al., 1995[47]
Totals	372	134	36	
Intercostal (3)	10	7	70	Merrell et al., 2001[48]
Intercostal (3)	13	6	46	Ruch et al., 1995[47]
Intercostal (3)	4	1	25	Bhandari et al., 2009[49]
Intercostal (3)	37	27	73	Chuang et al., 1992[37]
Intercostal (3)	17	10	59	Coulet et al., 2010[50]
Intercostal (3)	20	9	45	El Gammal and Fathi, 2002[51]
Intercostal (3)	16	7	44	Friedman et al., 1990[52]
Intercostal (3)	21	11	52	Malessy and Thomeer, 1998[39]
Intercostal (3)	75	15	20	Waikakul et al., 1999[32]
Totals	213	93	44	

differences in outcomes, the extraplexal donors have lower axon counts (Fig. 1). Proximity and reinnervation distance along with anatomical location and surgical difficulty likely contribute to the success rate, but the inadequate axon count match may be an additional factor contributing to their inferior clinical performance.

This study is not without limitations. Given the cadaveric nature of this study, it was not possible to electrically stimulate individual fascicles and identify individual fascicular function and axon counts based on distal innervation. In addition, the standard histomorphologic techniques used do not allow for differentiation of motor and sensory

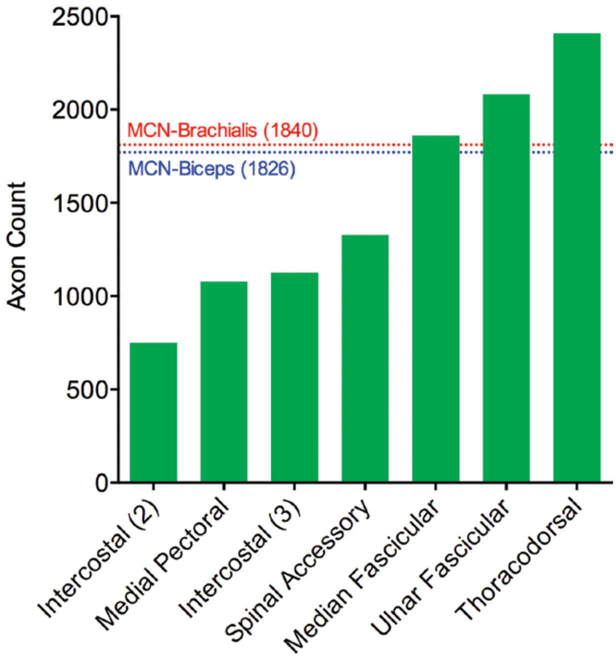

Fig. 1. Mean published axon counts of donor nerves used to restore elbow flexion. *MCN*, musculocutaneous nerve.

axons. Early reports on the Oberlin transfer did not differentiate which ulnar nerve fascicle was used.[2,8] Subsequent reports used electrical nerve stimulation to specifically select fascicles supplying wrist flexors.[4,6] This was recommended to minimize the possibility of a donor deficit.[4,6,9,60] Anatomically, these ulnar fascicles tend to lie along the anterolateral aspect of the ulnar nerve.[60] The location of expendable fascicles within the median nerve has also been described, as the redundant components lie within the anteromedial portion of the nerve.[61] Given that postoperative sensory loss is exceedingly rare,[1] we feel that these donor fascicles (e.g., to the flexor carpi ulnaris for an ulnar fascicular transfer and to the pronator teres in the case of a median fascicular transfer) contain predominantly motor axons, and that the axon count ratios reported are accurate. In our dissection, we did specify these fascicles anatomically in each specimen, and found that they were not significantly different in size from the remaining ulnar fascicles.

Another limitation is the heterogeneity in reporting outcomes observed in our literature analysis, and we limited our study to including those investigations that specified British Medical Research Council grade greater than or equal to 4 outcomes, as this is universally considered clinically useful elbow function. In addition, the correlation investigated only axon counts, but there are other potential confounding variables that we cannot account for in a historical comparative analysis, including patient factors, time from injury to surgery, and differences in reinnervation distance between the transfers investigated.[1] This may explain slight variability in the correlation observed in Figure 2.

CONCLUSIONS

In summary, these data demonstrate a correlation between donor nerve axon counts and

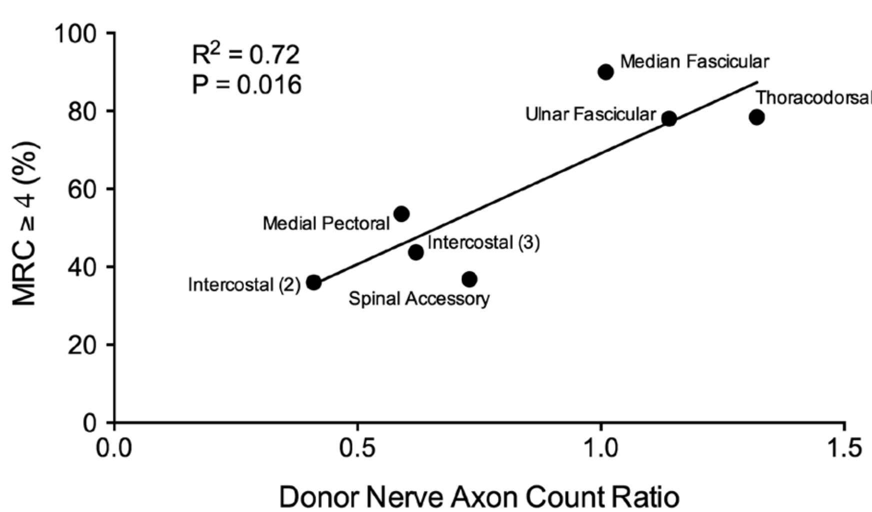

Fig. 2. Aggregate clinical success rates (British Medical Research Council grade ≥4) from Table 2 as a function of donor nerve axon count ratio. Axon count ratio is the donor nerve axon count relative to the recipient nerve (musculocutaneous branch to biceps for all transfers other than median fascicular, which is relative to musculocutaneous branch to brachialis). A significant correlation was observed between axon count and likelihood of successful (British Medical Research Council grade ≥4) outcome ($p = 0.016$).

Table 3. Odds Ratios and 95 Percent Confidence Intervals of Successful Outcomes of Selected Nerve Transfers Used to Restore Elbow Flexion

Donor Nerve	Successful Outcome % (MRC ≥ 4)	Axon Count Ratio	OR (95% CI)	*p*
Thoracodorsal	78	1.3	1.02 (0.42–2.47)	0.96
Ulnar fascicular	78	1.1	1.00 (1.00–1.00)	1.0
Median fascicular	90	1.0	2.53 (0.83–7.71)	0.14
Spinal accessory	37	0.7*	0.16 (0.10–0.27)	<0.001†
Medial pectoral	54	0.6*	0.33 (0.17–0.61)	<0.001†
Intercostal (3)	44	0.6*	0.22 (0.13–0.36)	<0.001†
Intercostal (2)	36	0.4*	0.16 (0.10–0.25)	<0.001†

MRC, British Medical Research Council grade.
*The ulnar fascicular transfer and its donor-to-recipient axon count ratio was used as the reference. Axon count ratios of 0.7:1 and lower were associated with an increased likelihood of unsuccessful outcome.
†Statistically significant.

success of nerve transfers to restore elbow flexion. Based on the excellent clinical outcomes of ulnar and median fascicular transfers, we recommend a donor-to-recipient axon count ratio exceeding 0.7:1 to optimize strength of elbow flexion for nerve transfers. Future studies are necessary to identify the ideal ratio and range of acceptable axon counts in other commonly used transfers.

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