



Oral Presentation Abstracts

1. Anatomical Study Of The Axillary Nerve: Description Of A Surgical Blind Zone

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Introduction: The aim of this study is to quantify the length of the axillary nerve (AN) that is able to be dissected through a standard anterior (deltopectoral) and posterior approach. We hypothesize that a segment of the AN cannot be reached using both approaches simultaneously.

Material and Methods: ANs of 5 frozen cadavers were dissected using an anterior and posterior approach. A first surgical clip marked the most visible distal part of the nerve from the deltopectoral approach; a second surgical clip marked the most proximal part from the posterior approach. The two surgical clips were localized with a shoulder radiograph. We performed measurements of the different AN segments.

Results: In all specimens there were three zones of the AN. Zone A (anterior): nerve segment from the origin of the AN to the first surgical clip, located at the level of the triangle formed by the subscapularis muscle (medial), conjoined tendon (lateral) and axillary fat (inferior). Zone B (blind – nerve segment not reachable through both approaches): from the first to the second surgical clip. Zone C (circumflex): nerve segment from the second surgical clip (located at the level of the quadrilateral space) to entry into the deltoid muscle. The mean length of the blind zone was 1.6 cm. This blind zone was found 1-2 cm. to the glenohumeral joint.

Conclusions: We have described a segment of the AN that cannot be evaluated through anterior (deltopectoral) and posterior combined approaches. An AN classification is presented based on the possible injured segment. We believe that this finding is important for the surgical evaluation of AN injuries around the quadrilateral space.

2. Cadaveric Study of Levator Scapulae Nerve as a Potential Donor in Brachial Plexus Reconstruction

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Introduction: Complete brachial plexus palsies represent a surgical dilemma given the paucity of available donor nerves for transfer. The spinal accessory nerve (SAN) is commonly transferred to the suprascapular nerve (SSN) to help with shoulder abduction and stabilization; however, other donors must be identified for additional reconstruction options. We hypothesize that the levator scapulae nerve (LSN) is a potential nerve donor in brachial plexus nerve reconstruction with tension free neuroorrhaphy and appropriate donor to recipient axon count ratio.

Methods: Bilateral cervical and brachial plexus dissections were performed on six adult cadavers. Demographic data was recorded for each specimen. The SAN was identified on the anterior border of the trapezius. The phrenic nerve was identified and then was traced proximally to find contributions from C3, C4, and C5 nerve roots. We identified separate C3 and C4 branches to the LSN. The long thoracic nerve (LTN) was identified piercing the middle scalene. Each nerve (SAN, SSN, LTN, and LSN) was neurolysed to obtain maximum length. Nerve transfers were performed from the donor LSN and SAN to the recipient SSN and LTN. Overlap between donor and target nerves was measured. Finally, each nerve was cut and sent to histology lab for axon counts.

Results: The mean fascicular axon counts for examined nerves were as follows: LSN (mean = 841.8, SD = 198.3), SAN (mean = 1323.4, SD = 171.4), SSN (mean = 3361.7, SD = 627.4), and LTN (mean = 1737.7, SD = 332.4). The resulting axon count donor-to-recipient ratio was as follows: LSN to SSN 1: 4.0, LSN to LTN 1: 2.1, SAN to SSN 1: 2.5, and SAN to LTN 1: 1.3. The mean overlap distance from the LSN to SSN was 1.7 cm (SD = 3.1) and from LSN to LTN it was 2.9 cm (SD = 2.8). The mean overlap from the SAN to SSN was 4.5 cm (SD = 0.7) and from SAN to LTN it was 0.75 cm (SD = 1.0).

Conclusions: Levator scapulae nerve is a potential donor nerve for nerve transfers with target recipient nerves such as the SSN, LTN, and other nerves with the addition of a graft such as the nerve to triceps. Future studies are required to investigate the clinical outcomes for these potential nerve transfers.

Table 1. Characteristics of Cervical Plexus Nerves

Variable		
<u>Cervical Plexus Nerve</u>		
	<u>Axon Count</u>	
Levator Scapulae Nerve	841.8 ± 198.3	-
Spinal Accessory Nerve	1323.4 ± 171.4	-
Suprascapular Nerve	3361.7 ± 627.4	-
Long Thoracic Nerve	1746.3 ± 332.4	-
<u>Axon Count Ratio</u>		
Donor Nerve	Recipient Nerve	Ratio
Levator Scapulae Nerve	Suprascapular Nerve	1 : 4.0
Levator Scapulae Nerve	Long Thoracic Nerve	1 : 2.1
Spinal Accessory Nerve	Suprascapular Nerve	1 : 2.5
Spinal Accessory Nerve	Long Thoracic Nerve	1 : 1.3
<u>Nerve Overlap</u>		
Donor Nerve	Recipient Nerve	Overlap (cm)
Levator Scapulae Nerve	Suprascapular Nerve	1.7 ± 3.1
Levator Scapulae Nerve	Long Thoracic Nerve	2.9 ± 2.8
Spinal Accessory Nerve	Suprascapular Nerve	4.5 ± 0.7
Spinal Accessory Nerve	Long Thoracic Nerve	0.75 ± 1.0

3. Investigation into the Optimal Number of Intercostal Nerve Transfers for Musculocutaneous Nerve Re-Innervation

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Introduction: Intercostal nerve transfer is one approach to neurotize the musculocutaneous nerve in brachial plexus injury. This study investigates outcomes following intercostal nerve transfer with a primary focus on the number of nerve transfers required to achieve optimal return of elbow flexion.

Methods: A systematic review of the literature was performed in accordance with PRISMA guidelines searching the MEDLINE/Pubmed and Google Scholar databases. Studies investigating intercostal nerve transfer for musculocutaneous innervation following brachial plexus injury in adults were included. Citations were cross-referenced and relevant studies included for analysis. All studies evaluated return of motor function based on the British Medical Research Council scale for muscle strength. Statistics were calculated using weighted means and the student's t test with $\alpha \leq 0.05$. With $\beta = 20\%$, power calculations demonstrated a minimum of 25 patients per study arm.

Results: Nine studies were included for analysis. A total of 641 patients were analyzed with average age 24.9 ± 5.4 years and 93% male population. The average time to surgery was 4.0 ± 1.5 months with average follow up of 41.3 ± 3.7 months. One study reported a single intercostal transfer resulting in restoration of M3 strength elbow flexion. Eight studies reported transfer of 2 intercostals in 414 patients with 76.6% of patients achieving $\geq M3$ flexion. Six studies reported transfer of 3 intercostals in 218 patients with 62.4% of patients achieving $\geq M3$ flexion. Finally, 6 (87.5%) of the 8 patients who underwent 4 intercostal nerve transfers achieved $\geq M3$ flexion.

There was no statistically significant difference in return of $\geq M3$ function between 2 vs. 3 transfers ($p = 0.4$), 2 vs. 4 transfers ($p = 0.4$), and 3 vs. 4 transfers ($p = 0.07$). When comparing return of M4 vs. M3 function, more patients developed M4 function when transferring 2 intercostal nerves ($p = 0.05$), but there was no difference when transferring 3 intercostals ($p = 0.2$).

Conclusion: Intercostal nerve transfer to the musculocutaneous nerve is an operation largely performed in 25-year-old males around 4 months after brachial plexus injury. No significant difference in return of $\geq M3$ elbow flexion was demonstrated with increased transfer of intercostal nerves. Based on equivalent outcomes, transfer of 2 intercostal nerves is recommended.

Fig. 1 Intercostal Nerve Transfer to the Musculocutaneous Nerve

# Intercostals	n	Age	Male	Interval to surgery (mo)	Follow up (mo)	Return of M4	Return of $\geq M3$	Return of $< M3$
1	1	1	nr	nr	42	nr	100%	0
2	414	24.1 ± 4.6	$94.6 \pm 2.2\%$	3.8 ± 1.6	41.4 ± 3.4	50%	77%	23%
3	218	27.9 ± 4.9	$87.2 \pm 11.4\%$	4.6 ± 1.2	41.0 ± 4.0	29.40%	62.40%	37.60%
4	8	33.6 ± 9.8	100%	1.7 ± 0.2	45.6 ± 3.3	62.50%	87.50%	12.50%
Weighted mean		24.9 ± 5.4	$93.0 \pm 7.0\%$	4.0 ± 1.5	41.3 ± 3.7	44.10%	71.70%	28.30%
p-value 2 vs. 3		0.6	0.5	0.5	0.7	0.3	0.4	0.9

4. Role of Electromyography and Intraoperative Nerve Stimulation in Isolated Long Thoracic Nerve Palsy

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Introduction: Electromyography is unreliable in guiding the management of isolated long thoracic nerve palsy. Optimal management depends on history, physical examination, and intraoperative nerve stimulation of the long thoracic nerve.

Materials & Methods: 19 patients who required surgery for an isolated long thoracic nerve palsy were reviewed retrospectively. Preoperative demographics, electromyography, and physical examinations were reviewed. Intraoperative nerve stimulation, surgical decision-making, and postoperative outcomes were reviewed.

Results: 19 patients with an average age of 32 were included in the study. All patients had an isolated long thoracic nerve palsy cause by either an injury (58%), Parsonage-Turner syndrome (32%), or shoulder surgery (10%). 18 patients (95%) underwent preoperative electromyography, 10 with evidence of denervation (56%). 13 patients had motor unit potentials in the serratus anterior (72%). Intraoperative nerve stimulation was performed on all patients and intervention was based upon these results. The preoperative EMG did not correlate with intraoperative nerve stimulation in 13 patients (72%) and did correlate in 5 patients (28%). 3 patients had a nerve transfer (3 thoracodorsal to long thoracic at lateral chest, 1 pec to long thoracic at supraclavicular incision). In the 15 patients who had decompression alone, there was return of full forward flexion of the shoulder in 11 patients (73%) at average of 3.3 weeks. In the 3 patients who had a nerve transfer, there was return of full forward flexion of the shoulder at average of 2.5 months.

Conclusions: The preoperative EMG is unreliable in determining whether there is a conduction block in patients with isolated long thoracic palsy. A treatment algorithm based on intraoperative nerve stimulation will help guide surgeons in their clinical decision making in patients with isolated long thoracic nerve palsy (Figure 1). Intraoperative nerve stimulation is the gold standard in the management of isolated long thoracic nerve palsy.

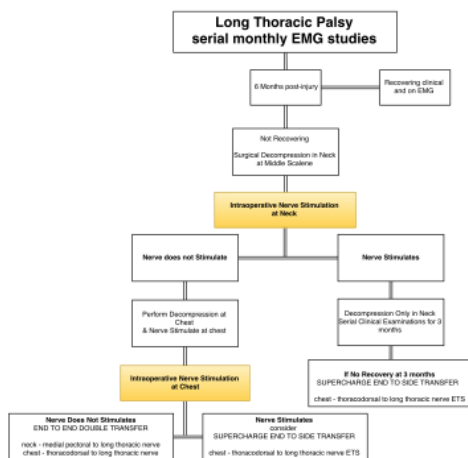


Figure 1. Surgical decision-making algorithm in isolated long thoracic nerve palsy.

5. Reinterpretation of Electrodiagnostic Studies and MRIs in Patients with Non-Traumatic “Isolated” Anterior Interosseous Nerve Palsy

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Introduction: Different hypotheses have been proposed for the pathophysiology of anterior interosseous nerve (AIN) palsy: compression, fascicular constriction or nerve inflammation (Parsonage-Turner Syndrome). We hypothesized that critical reinterpretation of electrodiagnostic studies (EDX) and MRIs of patients with a diagnosis of AIN palsy could provide insight into the pathophysiology and treatment.

Materials and Methods: A retrospective review was performed of all patients with a diagnosis of non-traumatic AIN palsy and an upper extremity MRI performed at our institution. The original EDX and MRI reports were re-interpreted by a neuromuscular neurologist and musculoskeletal radiologist respectively, both blinded to our hypothesis.

Results: One hundred and twenty-three patients were identified with non-traumatic AIN palsy. Of these, 16 patients met the inclusion criteria as having “isolated” AIN palsy. Physical examination revealed weakness in muscles not innervated by the AIN in 5 cases (31%) and EDX abnormalities not related to the AIN were found in 9 cases (60%). The initial MRI report described atrophy in muscles not innervated by the AIN or nerve enlargement different from the AIN in 8 cases (50%). In all cases, reinterpretation of the MRIs demonstrated atrophy in at least one muscle not innervated by the AIN and did not reveal any evidence of compression of the AIN.

Conclusion: All patients in our series with presumed isolated AIN palsy had MRI evidence of a more diffuse muscle involvement pattern, without any radiologic signs of nerve compression of the AIN branch itself. These data strongly support an inflammatory pathophysiology.

6. A Clinical and Radiographic Score to Assess Malignant Potential in Peripheral Nerve Sheath Tumors

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Introduction: The differentiation of malignant peripheral nerve sheath tumors (MPNST) from benign nerve sheath tumors is critical, as the treatments of these two lesions differs drastically. While histopathological diagnosis remains the gold standard, clinical and radiographic assessments are key for lesions that present with diagnostic uncertainty, such as benign appearing lesions with progressive neurologic symptoms. Previous studies have attempted to distinguish lesions based on these criteria but have been limited by low sensitivity and specificity. Here, we describe scoring system based on clinical presentation, neurological examination, and contrast enhanced MRI and apply it retrospectively to a single surgeon series of peripheral nerve sheath tumors.

Methods: Clinical characteristics common to the presentation of patients with peripheral nerve sheath tumors were identified by the surgeon, which includes pain, neurologic deficits, schwannomatosis, and entrapment. Further, salient imaging characteristics, such as contrast enhancement, tissue edema, and border irregularity were noted. The degree of the presenting characteristic was assigned a score of -1 or +1, whether it suggested for or against malignancy, respectively, and with 0 assigned for an absence of the characteristic. This scoring system was retrospectively assigned to peripheral nerve sheath lesions diagnosed from 2004-2015 and treated by the senior author. All patients have had pathologic studies. Statistics were performed with two-tailed t-test and ROC analysis.

Results: A total of 50 nerve sheath tumors were identified, of which 8 were MPNST. The average malignancy score of benign lesions were 0.1(range -1 to 1, sd=0.58) was significantly different from the average score of MPNST were 4.38(range 3 to 5, sd=0.58) ($p<0.0001$). Furthermore, a ROC analysis reveals an AUC of 1.0, with a score of >2 having 100% sensitivity and specificity for malignancy.

Conclusions: Obtaining histopathologic diagnosis is critical for the diagnosis of MPNST, however the decision to operate may be difficult in cases with features suggestive of both benign and malignant pathologies. A score that can be quickly calculated based on clinical characteristics and radiographic imaging, with adequate sensitivity and specificity, is a valuable tool during the initial consultation with these patients. We demonstrate an example of such a scoring criteria, though prospective validation with multiple surgeons and patients would be required.

7. Introduction of Adipose-Derived Stem Cells In Decellularized Nerve Allografts: An In-Vitro Analysis of the Gene Expression and Growth Factors

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Objective: Successful repair of segmental peripheral nerve defects remains a clinical challenge. The gold standard, an autologous nerve graft, creates donor site morbidity with loss of sensation and potential scarring. Processed nerve allografts have been used to bridge segmental nerve gaps. However, in large nerve defects, functional outcomes are not comparable to autograft reconstruction yet. Since all cellular material including Schwann cells and axons are removed after processing, the addition of supporting cells has been proposed to improve the allograft. Adipose-Derived Mesenchymal Stem Cells (AMSC) can potentially provide the necessary support for nerve regeneration due to local production of essential growth factors. While the mechanisms underlying the neurotrophic potential of AMSC remains unknown, it is postulated that the remaining extracellular matrix (ECM) still has biological activity that influences the AMSC and their differentiation. Therefore, the purpose of this study was to quantitate the changes in gene expression profiles of the cells and quantify the actual produced growth factors after seeding the allograft with AMSC in vitro.

Method: A total of 35 human nerve allografts were decellularized and seeded with human AMSC. At each time point (1, 3, 14, 21 and 28 days), total RNA was extracted, reverse transcribed into cDNA and qRT-PCR was performed in combination with gene specific assays for genes essential for nerve regeneration including: NGF, BDNF, PTN, VEGF and GAP43. Additional genes were analyzed to map AMSC characteristics. Growth factor production was evaluated and quantified using Enzyme-Linked Immunosorbent Assay (ELISA).

Results: Semi-quantitative RT-PCR analysis showed that the interaction of the allograft and AMSC enhanced the expression of neurotrophic factors NGF, BDNF and GAP43. The expression of the angiogenic molecule, VEGF-a was also increased and remained significantly elevated at 28 days post seeding. Analysis of ECM-related gene expression showed that LAMB2, COL1A1, COL3A1, FBLN1 were significantly elevated until 21 days. Angiogenic factor CD31 and neurotrophic factor PTN were down regulated in the seeded cells. ELISA analysis showed an upregulation of NGF and VEGF-a growth factor levels.

Conclusion: This study demonstrates that the remaining ECM of decellularized nerve allografts has a stimulating effect on AMSC. Upon the seeding, secretion of neurotrophic and angiogenic factors were triggered; the cells cultured on the allograft showed enhanced levels of neurotrophic genes and growth factors. The combination of patient's own easily accessible, abundant supply of AMSC's and the readily available processed nerve allograft is potentially a promising method for individualized peripheral nerve repair.

8. Stem Cell-Derived Exosomes: A New Option in the Treatment of Peripheral Nerve Injury?

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Introduction: Aiming to develop new treatment strategies that could speed up regeneration and guide axons across nerve gaps, we have explored the effect that exosomes from adipose-derived stem cells (ASC) have on neurite outgrowth. Functional recovery following a significant peripheral nerve injury continues to be inadequate. This impacts considerably on both patients and society as sufferers are commonly young workers. Poor outcomes often are due to the proximity of the injury and subsequent length to regenerate, or secondary to a nerve gap injury. We propose exosomes (nanovesicles involved in intercellular communication) could contribute to the management of such injuries.

Materials and Methods: Rat ASCs were differentiated into Schwann cell-like cells (dASCs). Exosomes from both Schwann cells (SCs) and dASCs were isolated and applied to neurons *in vitro*. Computerised image analysis assessed neurite outgrowth after 24 hours for comparison against a control group. The exosome cargo was also investigated for RNAs involved in nerve regeneration through RT-PCR techniques.

Results: Neurons incubated with either SC or dASC exosomes showed significantly longer neurites after 24 hours than the control group (Figure 1). SC and dASC exosomes both transport microRNA and mRNA cargo that has a role in nerve regeneration, and these neurons were shown to internalise this RNA carried.

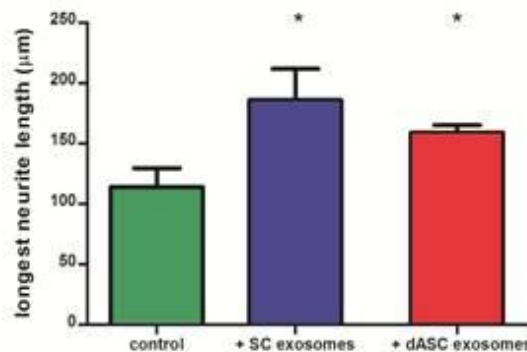


Fig.1: Neurons incubated with either SC or dASC exosomes produced longer neurites compared to control ($p < 0.05$).

Conclusions: dASC exosomes increase neurite outgrowth *in vitro*, mirroring the proven success of their SC counterparts. The RNAs within these exosomes likely coordinate this regenerative enhancement. Potential applications of this for clinical use could include direct injections of dASC exosomes to primary repairs of simple injuries, or in combination with synthetic conduits for nerve gaps. Such methods could overcome the concerns of harvesting a functioning nerve for an autologous graft, and avoid the numerous problems associated with using stem cells themselves.

9. An Effective Way to Track Amniotic Fluid Derived Stem Cells on Acellular Nerve Graft in a Rat Model

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Introduction: Traumatic transections of peripheral nerves are associated with poor nerve regeneration. The use of nerve grafts with stem cells provides an alternative to autograft for nerve repair. The purpose of this study was to track the fate of amniotic fluid derived stem (AFS) cells that are seeded into nerve allografts and to elucidate the mechanism of their impact on the regenerating nerve.

Methods: AFS cells were labeled using supraparamagnetic micron sized iron oxide (MPIO) coated with fluorescent dye. Labeled cells were plated and viability was assessed. Next, cells were cultured in neurogenic induction media; the conditioned media was collected to evaluate the neurogenic growth factors. Differentiated cells were confirmed with real-time PCR for neurogenic lineage markers.

Viable MPIO labeled AFS cells were injected into an acellular nerve allograft (ANA) used to repair a 1.5 cm sciatic nerve defect in 10 rats. Labeled AFS cells were evaluated by MRI at 1, 2, and 4 weeks post-surgery. Intensity of the MPIO regions was quantified using ImageJ. Contiguous frozen sections were stained for iron to identify the labeled AFS cells incorporated into the nerve graft. Co-localization of transplanted cells was confirmed using human specific nuclear antibody (Anti-NuMA).

Results: Labeled AFS cells were viable *in vitro* (Figure 1). Proliferation rate and morphology between the control and labeled cells demonstrated no significant differences ($p=0.58$). Cells differentiated towards Schwann-like cells after being cultured in neurogenic induction media. NGF and NEFL gene expression were elevated by fold change of 202.60 ± 1.89 and 30.62 ± 1.99 , respectively ($p < 0.005$) compared to control. Cytokine quantification analysis of AFS cells showed significantly increased BDNF, β -NGF, β -FGF, GDNF, NGF R, NT-4 and TGF- β production. (Fold change compared to undifferentiated control: 10.25 ± 1.96 , 383.06 ± 12.93 , 3.95 ± 1.06 , 5.78 ± 1.33 , 46.84 ± 3.67 , 2.69 ± 0.77 , 25.39 ± 3.74 , $p < 0.001$ respectively).

7T MRI demonstrated MPIO labeling with a strong decrease in signal, appearing as fuzzy dark spots in T2-weighted images at 4 weeks post-surgery. There was no significant difference in average normalized hypointense region volume between 2 and 4 weeks post-injury (0.47 ± 0.06 and 0.52 ± 0.12 , respectively, Figure 2). Cell integration was confirmed by iron and Anti-NuMA staining.

Conclusions: AFS cells remained viable after labeling and can be used to augment nerve repair by seeding onto ANAs. Cytokine analysis suggests a paracrine-mediated effect on nerve repair. MRI can effectively track the AFS cells longitudinally in the rat model, demonstrating the potential to monitor AFS cell delivery strategies for nerve regeneration.

Figure 1.

Figure 1.

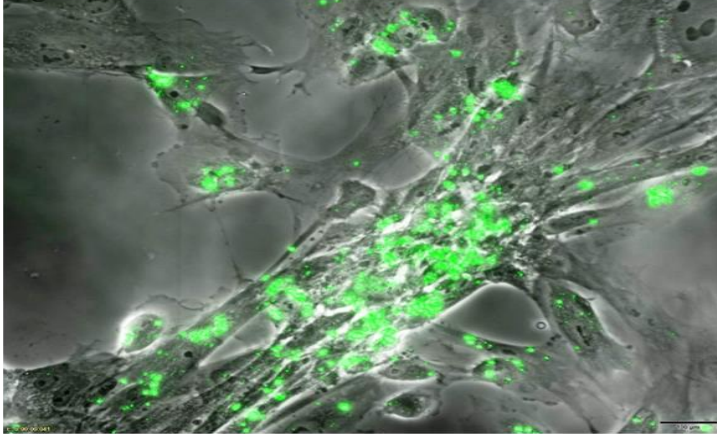


Figure 1. AFS cells infused with MPIO at 14 days *in vitro*.

Figure 2.

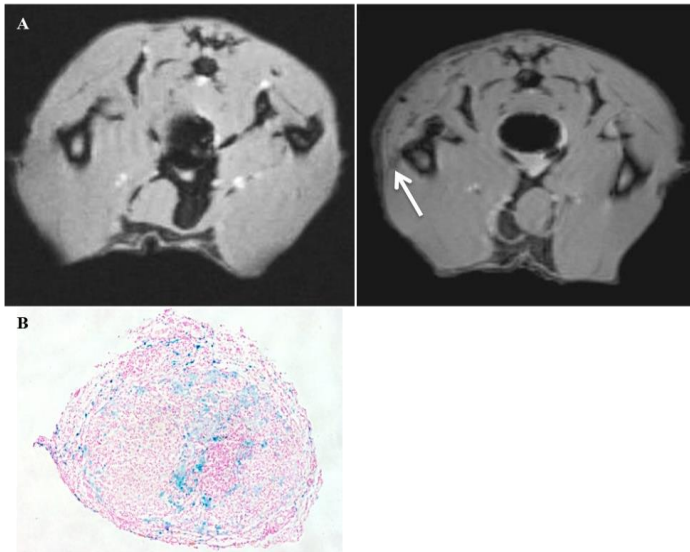


Figure 2. A. Longitudinal images of the same animal before injury (left) and 4 weeks post-surgery (right). AFS cells were labeled with MPIO and seeded into ANA graft and implanted to the left sciatic site of the rat for 4 weeks. The MPIO signals on the graft side (white arrow) suggest MRI effectively tracks the temporal location of cells. B. Prussian blue staining for iron indicated AFS cells co-localize with the hypointense region.

10. In-Vivo Survivability of Stem Cells After Peripheral Nerve Reconstruction Using Decellularized Nerve Allografts

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Objective: Successful repair of segmental peripheral nerve defects remains a clinical challenge. Processed nerve allografts have been used to bridge segmental nerve gaps. However, in large nerve defects, functional outcomes are not comparable to autograft reconstruction yet; the longer the nerve gap, the poorer the outcome. Nerve architecture and the extracellular matrix are preserved after processing, while all cellular material including Schwann cells and axons are removed. Therefore the addition of supporting cells has been proposed to improve the allograft. Adipose-Derived Mesenchymal Stem Cells (AMSC) can potentially provide the necessary support for nerve regeneration due to local production of essential growth factors. While the mechanisms underlying the neurotrophic potential of AMSC remains unknown, it is postulated that the remaining extracellular matrix (ECM) still has biological activity that influences the AMSC and their differentiation. Therefore, the purpose of this study was to 1) evaluate the in-vivo survivability of the AMSC after seeding in a rat sciatic nerve model, 2) quantitate the fate and differentiation potential of the cells and 3) evaluate the neurotrophic factors produced.

Method: A total of 27 rat nerve allografts were decellularized and seeded with autologous AMSC. Seeded allografts were implanted to reconstruct a 10-mm sciatic nerve defect and results were compared to autograft and allograft reconstruction. Prior to transplantation, cells were labelled with a lentiviral Luciferase vector to detect living cells by Bioluminescence imaging at different time points. To study the early regeneration, semi-quantitative RT-PCR was performed after 14 days in combination with gene specific assays for genes that are associated with nerve regeneration. To determine the fate of the implanted AMSC, immunohistochemical staining was obtained for the surface markers S100, PGP9.5, RECA-1, NGF and Luciferase.

Results: In-vivo Bioluminescence imaging showed a stem cell survival up to 31 days. Immunohistochemical stains and q-PCR results are currently being analyzed. Based on pilot data, we anticipate differences in growth factor levels released by the seeded allograft compared to the control groups.

Conclusion: This study demonstrates that it is feasible to seed AMSC's on a decellularized allograft and that the cells survive for a maximum period of 31 days after transplantation. Upon the seeding, secretion of neurotrophic and angiogenic factors are expected to be triggered. The combination of patient's own easily accessible, abundant supply of stem cells harvested from adipose tissue and the readily available processed nerve allograft is potentially a promising method for individualized peripheral nerve repair.

11. Knockout Of Toll-Like Receptors Delay The Nerve Regeneration In Sciatic Nerve Crushing Injury Of Mice

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Purpose: Toll-like receptors (TLRs) can recognize specific endogenous molecules associated to danger signals that are released from damaged cells or tissues after injury and trigger an innate immune response. TLRs had been suggested to be crucial in Wallerian degeneration after peripheral nerve injury. This study was designed to explore the effect of TLRs knockout on the nerve regeneration in a mice sciatic nerve crushing injury model.

Materials and Methods: The right sciatic nerve at the mid-thigh level was crushed by a No.5 Jeweler forcep for 30 seconds in C57BL/6, Tlr2^{-/-}, Tlr3^{-/-}, Tlr4^{-/-}, Tlr5^{-/-}, and Tlr7^{-/-} mice. At 1, 3, 7, 14 d after nerve crush injury, one cm nerve segment distal to the crush site were harvested and detected by PCRarray to detect the change mRNAs regarding to demyelination and remyelination factors including myelination protein (Mal, Mbp, Plp, Pmp22), myelination promoting factors (Bdnf, Brn2, Gdnf, Igf, Krox20, Nrg1, Oct6, Sox10, Hdac1, Ndr1), and myelination inhibiting factors (Jun, Notch1, Ntf3, Pax3, Sox2, Tgfb). Four mice in each group at indicated postoperative days were harvested for Western blotting of the myelin protein MPZ as well as re-myelination transcription factors Oct6 and Sox10. Sciatic nerve segments 5 mm distal to the crushed site were harvested at postoperative day 10 (n=6) and fixed in 3% EM grade glutaraldehyde at 4°C and stained with 1% toluidine blue dye for a quantitative assessment of the regenerated nerve fibers with the Leco IA32 Image Analysis System.

Results: Analysis of the histomorphometric image of the nerve specimens from these Tlr^{-/-} mice presented prominent debris and less percentage nerve tissue with less fiber count, fiber width, fiber area, total fiber area, myelin area, axon area and axon width than those from the C57BL/6 mice. PCRarray experiments demonstrate that TLR knockout changed the expression profile of the myelination-promoting and -inhibiting factors from the nerve segment after the crush injury. In addition, delayed re-myelination of the distal nerve stump in Tlr2^{-/-} and Tlr4^{-/-} mice with an average 4-day delayed expression of the myelin protein MPZ was observed with delayed occurrence of Oct6 and Sox10 for 4 and 7 days, respectively.

Conclusion: This study using a mouse model of sciatic nerve crushing injury demonstrated that the knockout of toll-like receptors deter the nerve regeneration with change of the balance between the expression of myelination promoting and inhibiting factors in the distal nerve segment. 1

12. Controlling Axonal Regeneration Following Rat Sciatic Nerve Transection Reduces Neuroma Formation

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Introduction: The treatment of neuroma is a challenging clinical problem despite existing management approaches. Investigation of acellular nerve allografts (ANAs) as a tool to bridge nerve gaps has shown an unintentional, controlled termination of axonal regrowth within long (>3cm) ANAs. We hypothesized that long ANAs can be beneficially utilized to “cap” injured nerve and guide regenerating axons to a gradual termination effectively minimizing neuroma formation.

Materials & Methods: Thy1-GFP and Lewis rats were randomized to eight groups which received: 1) nerve transection alone, 2) traction neurectomy, 3) transection and 0.5 cm closed end silicone conduit, 4) transection and 0.5 cm ANA, 5) transection and 2.5 cm ANA, 6) transection and 5.0 cm ANA, 7) transection and proximal nerve crush, or 8) transection, proximal nerve crush and 5.0 cm ANA. In all groups, the distal nerve stump was ligated and the distal nerve turned from the proximal end to remove any trophic influence. The Thy1-GFP rat nerves were serially imaged for 20 weeks to provide a visual history of regeneration. Lewis rats were sacrificed at 5 and 20 weeks for quantitative nerve histology and IHC. ANOVA with post hoc analysis were performed to evaluate significance ($p < 0.05$).

Results: GFP animals that received transection alone, traction neurectomy, or transection and crush showed signs of neuroma with chaotic nerve regeneration (multidirectional axonal regrowth) extending from the proximal stump as early as 4 weeks confirmed with histology. At 5 weeks, axons grew through the entirety of the 0.5 cm ANAs, with neuroma formation extending beyond the grafts. In the 2.5 and 5.0 cm ANAs, robust axonal regeneration was demonstrated in the proximal portions of the grafts with a gradual tapering of regeneration as it moved distally, and axons failed to grow beyond the grafts. At 20 weeks, gross visualization of Thy1-GFP labeled axons demonstrates that regeneration dwindles and terminates within 5.0 cm ANAs by 5 months without neuroma formation. Further histological analysis is ongoing, as are additional 20 week experiments to evaluate controlled termination.

Conclusions: Following nerve transection, long ANA “caps” can be used to control aberrant axonal growth, the hallmark of neuroma formation. Therefore, the “capping” of a transected nerve with a long ANA is a potential surgical tool in the future of neuroma management.

13. Gpr126 Contributes to Terminal Schwann Cell Function after Nerve Injury

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Introduction: Terminal Schwann cells (tSCs), non-myelinating glia cells at the neuromuscular junction (NMJ), contribute to NMJ reinnervation after injury, and represent an excellent potential cell type to target to improve functional recovery. After nerve injury and NMJ denervation, tSCs extend cytoplasmic processes away from the NMJ in search of nearby axons. *Gpr126*, an adhesion G-protein coupled receptor, is essential for the development and function of myelinating Schwann cells (SCs). The function of *Gpr126* in tSC biology, however, is unknown. We hypothesize that *Gpr126* is essential for tSC contributions to NMJ reinnervation after peripheral nerve injury.

Method: The spinal accessory nerve (SAN) was unilaterally transected and immediately repaired in *Dhh^{Cre};Gpr126^{fl/fl}* conditional knockout (*cGpr126*-KO) mice, in which *Gpr126* is deleted in mature SCs, and was compared to sibling controls for the study. The NMJs in the sternomastoid (SM) muscle were evaluated at 1, 2, and 3 weeks following nerve injury via immunofluorescence and confocal microscopy.

Results: Three weeks after injury, control mice showed extensive NMJ regeneration. In contrast, NMJ reinnervation was compromised in SM from *cGpr126*-KO mice compared to the uninjured contralateral side or to sibling controls. In the *cGpr126*-KO mice, acetylcholine receptors (AChRs) were partially fragmented. Nerve terminals partially colocalized with AChRs or were absent in some NMJs, but showed collateral sprouting in others. Lower tSC numbers were noted in the *cGpr126*-KO mice without injury, but thicker and more numerous tSC processes were noted after nerve injury in the *cGpr126*-KO mice compared to controls. In addition, significantly higher numbers of macrophages were observed at the NMJs.

Conclusion: *cGpr126*-KO mice showed delayed NMJ reinnervation 3 weeks following peripheral nerve injury. These data support a model in which *Gpr126* is required for tSC contributions to NMJ reinnervation after peripheral nerve injury. The information gained from this research has important implications regarding development, injury, and repair of the NMJ, which may lead to translational research to improve recovery following peripheral nerve injury.

14. Biomechanical Dynamics of Rapid-Stretch Nerve Injury Model

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Objective: While the majority of adult brachial plexus injuries result from high speed mechanisms, no laboratory model has been created to model rapid-stretch nerve injuries. Furthermore, prior research on nerve biomechanics is conflicted. Understanding the biomechanical response of nerves to rapid stretch, including failure location, is essential to developing models that mimic the clinical scenario.

Methods: The sciatic nerves of 103 freshly euthanized Sprague-Dawley rats were dissected and subjected to rapid- and slow-stretch methods. Rapid-stretch injury involved fixed direction strain produced via constrained weight drop applied to an intact nerve. Slow-stretch techniques included fixed direction strain produced by slowly progressive force and formal material testing instrumentation, both to an intact nerve. Maximal nerve strain, persistent length deformation, regional strain variation and location of nerve failure were recorded.

Results: Both rapidly- and slowly-stretch sciatic nerves failed at similar strain deformation values, which depended upon the vector of force (antero-posterior vector: rapid = 61.6%, slow = 56.6%; longitudinal vector: rapid = 14.4%, slow = 20.1%). The regional strain variation varied in association with periarticular regions, with maximal compliance at the knee (69.1%,) and at the hip (64.6%), and least at the mid portion of the sciatic nerve (10.1%). Rupture location of stretched sciatic nerves was dependent upon vector more than the rate of stretch and was associated with the differing regional compliance or branch location (antero-posterior vector associated with rupture at the hip/hamstrings branch in 70.1%; longitudinal vector associated with rupture at spinal (17%), middle (43%) and at trifurcation (30%). Velocity of stretch was positively associated with maximal strain and odds of rupture increased when sciatic nerves were stretched above 6 m/s. Elastic deformation (with return to within 15% of baseline value) occurred below 50% maximal strain ($37\% \pm 12\%$ stdev), whereas plastic deformation (persistent length change) occurred above 50% maximal strain ($59\% \pm 17\%$ stdev).

Conclusions: Effects of rapid-stretch nerve injury can reliably be predicted upon the vector and the rate of injury. Rupture of the sciatic nerve was predominantly predicted by rate of stretch. The location of nerve rupture was correlated with loading, with longitudinal tension on the nerve associated with avulsions and strain accumulation at non-compliant regions. In contrast, antero-posterior tension led to rupture at proximal branch points. Elastic-to-plastic deformation predictably followed the maximal strain occurred during stretching

15. Delayed Nerve Repair is Affected by Irreversible Changes Occurring in Long-term Denervated Schwann Cells

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Introduction: The complete recovery after peripheral nerve injury does not always occur and can be influenced by many factors including patient age, lesion site, injury severity, size of the gap between damaged nerve stumps and time interval that elapses before performing surgical repair.

The poor outcome occurring after a long delay can be due to loss of the neuron ability to regenerate, loss of the Schwann cell ability to support regeneration and, of course, progressive muscle atrophy.

The aim of this study was to investigate the nerve regeneration after delayed repair and to study the degenerative processes of the denervated distal nerve stump.

Materials and methods: A rat surgical model of delayed nerve repair consisting of a cross suture between the chronically degenerated median nerve distal stump (3 and 6 months) and the freshly axotomized ulnar proximal stump was used. Functional, morphological, morphometrical and biomolecular analyses were carried out on regenerated distal nerve stumps 6 months after nerve repair.

Results: Morphological and biomolecular analyses carried out on degenerated nerves show atrophic Schwann cells, several collagen fibers and fibroblasts and a significant reduction of soluble Neuregulin 1 (NRG1, an important factor for the survival and activity of Schwann cells) already after 3 months of degeneration.

Functional recovery analysis performed after nerve repair shows that only the group repaired immediately and not the two delayed-repaired groups, recovered partially. Moreover, quantitative analysis shows that the delayed groups have fewer and smaller myelinated fibers compared to the immediate repair group. Finally, biomolecular analysis performed on the 6-months delayed group shows that soluble NRG1 maintains a low expression also after 6 months of regeneration.

Conclusions: These results demonstrate that, despite a delay of 3 or 6 months, the fibers are still able to regenerate, even if they are fewer and smaller than the immediate repaired group. Moreover, the analysis of the NRG1/ErbB system shows a significant decrease of soluble NRG1 in both degenerating and delayed-repaired nerves.

Our results suggest that NRG1 plays an important role in Schwann cell activity after denervation, therefore its manipulation could be a good strategy to improve the outcome after delayed nerve repair.

16. Histologic Evaluation of Rapid-Stretch Nerve Injury Model

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Objective: While the majority of adult brachial plexus injuries result from high speed mechanisms, no laboratory model has been created to model rapid-stretch nerve injuries. Importantly, the microanatomical injury of rapid-stretch has not be qualitatively nor quantitatively described. Elucidating the patterns of injury is essential to developing models that mimic the clinical scenario.

Methods: The sciatic nerves of 28 freshly euthanized Sprague-Dawley rats were dissected and subjected to rapid-stretch nerve injury, utilizing fixed direction strain produced via constrained weight drop applied to an intact nerve. Biomechanical parameters, including maximal nerve strain, persistent length deformation, regional strain variation and location of nerve failure were recorded to categorize nerve injury patterns. Sciatic nerves were then histologically evaluated with modified Lillie's trichrome staining, osmium tetroxide, and immunofluorescent techniques. Serial longitudinal sectioning was performed to volumetrically quantify nerve injury patterns.

Results: Five injury grades were produced: control, sham, elastic (stretch with return to within 15% of pre-stretch length), plastic (persistent length change) and rupture. Two patterns of injury were noted on histologic examination: loss of fiber undulation (straight fibers) and microruptures of fibers. Epineurial tissue remained associated with the stretched sciatic nerve, except at rupture, partial rupture sites or segments with severe fiber disruption. No cases of intact epineurium and complete internal disruption were found (Sunderland grade 4). Serial longitudinal sectioning demonstrated a predilection for microruptures at the hamstring branch in elastic and plastic grade injuries, and incidence of microruptures demonstrated distinct levels based upon injury grade ($p < 0.05$, Two-way ANOVA with posthoc tests). Loss of fiber undulation, similarly, was found to correlate with progressively severe injury ($p < 0.05$, Two-way ANOVA with posthoc tests). Laminin immunofluorescence demonstrated that endoneurial tubes were intact in sciatic nerves stretched within elastic limits, but ruptured in plastic grade injuries.

Conclusions: The microarchitecture of peripheral nerves is altered in predictable patterns that primarily affect the fibers of the nerve, not external structural elements. The internal architecture is injured in graded fashion that reflects the tissue biomechanics. Nerve fibers are more resistant to rapid stretch than epineurium. This study suggests a new consideration for producing graded nerve injuries with a rapid-stretch nerve injury model.

17. The Quality of Systematic Reviews Addressing Peripheral Nerve Repair and Reconstruction

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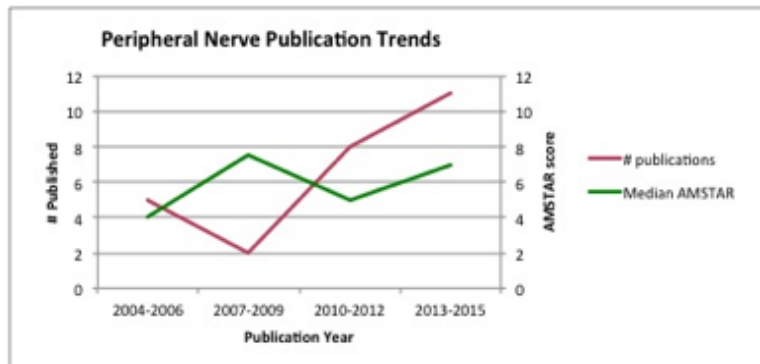
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Introduction: While systematic reviews are regarded as the strongest level of medical evidence, not all systematic reviews are equally reliable. Inconsistency in the quality and rigor of systematic reviews raises concerns about their use as a tool in guiding quality delivery in evidence-based clinical practice. The objective of this present study was to assess methodological soundness of systematic reviews with a particular focus on peripheral nerve repair and reconstruction.

Materials & Methods: We performed a comprehensive search using PubMed and Scopus to identify all systematic reviews published on peripheral nerve reconstruction in 9 high-impact surgical journals. Literature searches, abstract screening, and data extraction were independently performed by two separate authors. Discrepancies were resolved by consensus. The quality of systematic reviews was assessed using AMSTAR criteria.

Results: Initial search retrieved 184 articles. Forty-six duplicates were removed, leaving 138 for review. After screening titles, abstracts, and conducting full text reviews, 26 studies met inclusion criteria. Of those, 18 (65%) were published by Plastic Surgery, 7 (27%) by Orthopedic Surgery, and 1 (4%) by Occupational Therapy. The vast majority (20; 77%) focused on upper extremity nerves only, whereas 4 (15%) focused on lower extremity nerves only, 1 (4%) addressed both upper and lower extremity nerves, and 1 (4%) focused on nerves of the trunk. The total number of systematic reviews published on peripheral nerves each year has shown an increasing trend from 2004 through 2015. Overall median AMSTAR score was 5, reflecting a "fair" quality. There was no evidence of AMSTAR score improvement over time.

Conclusion: Although the number of systematic reviews published on peripheral nerve repair has risen over the last decade, their quality has unfortunately not exhibited the same increase. This highlights the necessity to increase familiarity with and conform to methodological quality criteria to improve the integrity of evidence-based medicine in peripheral nerve repair and reconstruction.



18. Early Postoperative Complications and Healthcare Utilization Following Thoracic Outlet Decompression for Thoracic Outlet Syndrome

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Introduction: Surgical intervention for Thoracic Outlet Syndrome (TOS) follows failure of conservative management and involves resection of the anterior scalene +/- resection of the cervical rib. We reviewed the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database for all cases of TOS and hypothesized that rib resection would be associated with increased 30-day complications and healthcare utilization.

Methods: The NSQIP database for 2005-2013 was queried to identify patients with TOS based on ICD-9-CM code 353.0. The TOS patients were separated into two groups based on whether they were treated with cervical rib resection. Normality was assessed and Mann-Whitney U tests were conducted to compare differences in outcomes between groups ($p < 0.05$ significance).

Results: 312 patients were identified: males=34.6%; average age=37.02y (+/-12.5); BMI \geq 30=26.9%. There were no mortalities, but 12 (3.8%) patients had early complications, including 10 (3.2%) surgical complications, 7 (2.2%) major complications, 7 (2.2%) adverse events, and 1 (0.32%) infection. In total, 205 (65.7%) patients had cervical rib resection, of which 116 (37.2% of all patients) also had anterior scalenectomy.

Of the 12 patients with early complications, 7 (58.3%) had cervical rib resection; of the 10 patients with surgical complications, 7 (70%) had rib resection; of the 7 patients with major complications, 5 (71.4%) had rib resection; and of the 7 patients with adverse events, 5 had rib resection (71.4%). The only patient with infection also had rib resection. However, these complication and adverse event rates did not achieve statistical significance. However, rib resection was associated with significantly longer hospital stays (average=4.22 days) than no rib resection (average=2.85 days) ($p=0.000$), and as well with longer operative-time than no rib resection (average=221.66 minutes vs. 169.38 minutes, $p=0.000$). Lastly, there were 7 patients that required re-operation, 5 (71.4%) of whom had rib resection. Furthermore, 10 were re-admitted ($n=95$ reported), out of whom 9 (90%) had rib resection.

Conclusions: Early postoperative complications are relatively rare after decompression of the thoracic outlet. There may be a relationship between cervical rib resection, and complications and increased health care utilization. These data suggest that, when appropriate, cervical rib resection should be avoided to reduce the risk of early postoperative complications, thus highlighting the importance of preoperative evaluation in determining the location of brachial plexus compression to direct surgical management that reduces morbidity for patients and utilization of limited healthcare resource.

19. Letters of Recommendation for Integrated Plastic Surgery Residency Highlight Unconscious Gender Bias

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Introduction: Letters of recommendation may be the most important component of a residency application. We hypothesize that letters of recommendation are significantly affected by unconscious gender bias.

Methods: A retrospective, IRB-exempt review of standardized letters of recommendation (SLOR) for all medical student applicants to our integrated plastic surgery residency program for the last two years, 2014-2015 (n=177) and 2015-2016 (n=182) was performed. Synonymous strengths and weaknesses were combined, and their use was recorded for each applicant.

Results: Female medical students comprise 37% (134/359) of applicants to our integrated plastic surgery residency program. Only 9.5% (128/1346) of letters were written by women. Women were nearly twice as likely (OR 1.8, 1.2-2.8) to be described as quiet, reserved, or shy and more than three times as likely to be described as a pleasure to teach (OR 3.2, 1.3-7.8). However, women were only half as likely as their male counterparts to be praised for their knowledge base (OR 0.6, 0.3-0.97). Some adjectives were exclusively used to describe female applicants, such as “strikingly beautiful,” “chatty,” and “enjoyable.” Terminology aside, women were slightly more likely to successfully match than their male counterparts.

Conclusions: Letters of recommendation are powerful tools in resident selection. Understanding subtle biases in how letter writers describe male and female applicants will help to more fairly and successfully promote and recruit resident physicians.

20. Thirty-Day Perioperative Adverse Outcomes Following Peripheral Nerve Surgery

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Background: As the growth in peripheral nerve surgery volume, the demand for health care safety and cost effectiveness has increased in recent years. Given our limited understanding, we evaluated prospectively identified and randomly sampled patients who underwent peripheral nerve surgery from 2005 to 2014 through the American College of Surgeons National Surgical Quality Improvement Program database.

Methods: We used bivariate testing and multivariate logistic regression analysis to identify patient- and surgery-related risk factors for postoperative complication and unplanned readmission in peripheral nerve surgery patients, and especially estimate the impact of nerve grafting procedure.

Results: Overall, 2351 patients underwent peripheral nerve surgery, 120 complications were identified in 100 patients (4.25%), 103 patients (4.38%) received nerve grafting. Thirty-one (1.95%) Of 1593 patients were unplanned readmitted. Nerve grafting procedures had no association with postoperative complications and unplanned readmission rates. Patients who experienced inpatient procedure (OR= 2.54, P<0.001), longer operative time (OR= 1.00, P<0.001) and had worse wound classifications (OR= 1.83, P<0.001) increased odds of postoperative complication. Inpatient procedure (OR= 2.74, P=0.014) and any complications (OR= 24.43, P<0.001) were significantly associated with unplanned readmission.

Conclusions: Our study confirms that peripheral nerve surgery and nerve graft procedure can safely be performed after the proper patient selection was made, and appropriate and timely surgery was executed. We also identified risks associated with perioperative adverse outcomes, these data may be used as an adjunct for risk stratification for patients being considered for peripheral nerve surgery, which allow better targeting of the most costly and harmful complications of preventive measures.

21. Conducting Polymer Nanostructures Facilitate Peripheral Nerve Regeneration

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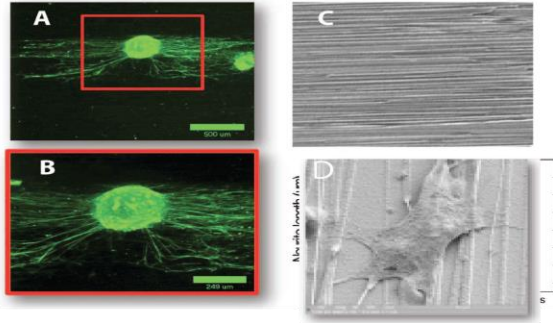
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Introduction: Autografts are the clinical "gold standard" for bridging peripheral nerve gaps and have been widely used for reconstruction, however, they have some disadvantages such as painful dysesthesias. Biomaterials have been utilized for design of nerve conduits, but regeneration of functional axons in long nerve gap remains challenging due to the lack of biomaterials that can provide both biochemical and biophysical growth cues. Conducting polymers (CPs) have been considered neural interfaces due to their unique physical, chemical, and electrical properties. We hypothesized that nanostructured CPs can facilitate axonal regeneration by providing guidance cues. To access this hypothesis, we developed a novel method for fabrication of (1) aligned conducting polymer nanotubes (ACPNTs) and (2) hybrid conducting polymer-hydrogel conduits for axonal regeneration.

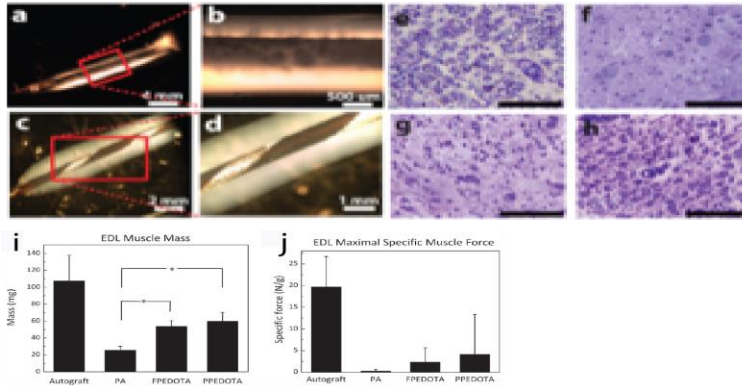
Materials & Methods: The fabrication process involves the electrospinning of aligned nanofibers into which nerve growth factor (NGF) have been incorporated followed by electrochemical deposition of conducting polymer poly(3,4-ethylenedioxythiophene) (PEDOT) around the nanofibers. Dorsal root ganglion explants, and PC12 cells were cultured on these ACPNTs. Scanning electron and fluorescence microscopy examined the topography and neurite outgrowth. We fabricated hybrid conduit consisting PEDOT and agarose hydrogel. PEDOT was electrodeposited inside the lumen to create a fully coated-PEDOT agarose (FPEDOTA) conduit and a partially coated-PEDOT agarose (PPEDOTA) conduit. These conduits were compared with autograft controls: animals that received plain agarose (PA), FPEDOTA, and PPEDOTA conduits. These conduits were implanted in 10 mm peroneal nerve gaps in rats and compared with autograft after 12 weeks postoperatively. The outcome measures utilized included extensor digitorum longus muscle contractile force measurements, a muscle innervated by the peroneal nerve, and nerve histomorphometry.

Results: In vitro results revealed that neurites were preferentially guided in the direction of the ACPNTs. The Cell culture experiments confirmed retained bioactivity of NGF during the fabrication process. We demonstrated that FPEDOTA and PPEDOTA conduits supported superior neural regeneration as compared to the PA conduit. PEDOT polymerization within a hydrogel has been shown to mechanically strengthen the combination.

Conclusions: This study paves the way for the design of a three-dimensional conductive hydrogel scaffold for accelerated, directional, and controlled axonal growth in the peripheral nervous systems. The PEDOT lining may be used to facilitate future studies using electrical stimulation and/or controlled release of neurotrophins.



(A), (B) Optical images of DRG cells on ACPNTs (C) SEM image of ACPNTs (D) SEM image of PC12 cells on ACPNTs



PEDOT-agarose nerve conduit. Optical micrographs: (a, b) fully coated PEDOT (FPEDOTA) (c, d) partially coated PEDOT (PPEDOTA) inside the lumen of agarose nerve conduits. Cross section of nerve midgraft after 14 weeks of implanting conduits: (e) autograft, (f) plan agarose, (g) FPEDOTA, (h) PPEDOTA. (i) Bar graph EDL muscle mass. (j) Bar graph maximal specific muscle force. Column height represents the mean while error bars reflect the standard deviation of the mean (n = 5). Scale bars are 50 μm

22. Resorbable Electronics for Peripheral Nerve Interfacing

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Introduction: Functional electrical stimulation of peripheral nerve tissue has been demonstrated to restore sensorimotor function and accelerate axonal regeneration in vivo. Yet, existing methods of applying electrical stimulation to peripheral nerve tissue have presented significant barriers to clinical translation. The present study describes the implementation of a fully-resorbable wireless nerve stimulator capable of delivering functional, therapeutic, and diagnostic electrical stimulation of injured and un-injured peripheral nerve tissue.

Methods: Fully-resorbable electronic implants were fabricated and subcutaneously implanted into Lewis rats. Implanted devices were utilized to deliver functional and brief electrical stimulation (0-20Hz) to sciatic nerves following nerve crush, nerve transection/repair, and sham surgery. Following initial electrical stimulation, implanted wireless devices were utilized to serially assess functional recovery over 3 months post-operatively.

Results: Fully-resorbable wireless nerve stimulators were shown to successfully stimulate peripheral nerve tissue in vivo for over 2 weeks prior to dissolution. Brief electrical stimulation delivered by the implants was observed to increase both the rate of functional recovery and maximal capacity for functional recovery following nerve transection and repair. Fully-resorbable stimulators successfully facilitated both therapeutic stimulation of peripheral nerve tissue as well as serial assessment of nerve and muscle function following nerve crush and nerve transection injury.

Discussion: The present study highlights the ability of a new class of fully-resorbable implantable electronics to successfully interface and therapeutically stimulate peripheral nerve tissue. Fully-resorbable wireless nerve stimulators may therefore serve as a novel means of facilitating therapeutic electrical stimulation and neuromodulation in a variety of clinical settings.

23. A Novel Conduit-Based Nerve Repair Improves Early Outcomes

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Introduction: Conduit-based nerve repairs are commonly used for small nerve gaps, whereas primary repair may be performed if there is no tension on nerve endings. However, primary nerve repairs require sutures at the neuroorrhaphy site, which can be traumatic to the repair. We hypothesize a conduit-based nerve coaptation device will improve nerve repair outcomes by avoiding sutures at the nerve repair site and utilizing the advantages of a conduit-based repair.

Methods: The left sciatic nerves of female Sprague-Dawley rats (n=18) were transected and repaired using a novel conduit-based device. The novel conduit-based device is a pulley system that coapts nerve endings without requiring sutures at the coaptation site. The conduit-based device group was compared to a control group of rats that underwent a standard end-to-end microsurgical repair of the sciatic nerve. Animals underwent behavioral assessments at weekly intervals post-operatively using the Sciatic Functional Index (SFI) test. Animals were sacrificed at 4 weeks to obtain motor axon counts from immunohistochemistry. A sub-group of animals were sacrificed immediately post repair to obtain MRI images (4.7 T) of the nerve to demonstrate nerve coaptation.

Results: SFI scores were superior in rats which received conduit based repairs at 7 days, 14 days, 21 days, and 28 day postoperatively compared to the control group (**Figure 1**). As expected, motor axon counts were similar between the control and device groups proximal to the injury site. Motor axon counts distal to the injury in the device group at 4 weeks were statistically superior to the control group (**Figure 2**). **Figure 3** shows MRI tractography of two nerves after repair using the novel conduit device. The repaired tracts appear continuous, and this finding indicates good alignment with our device.

Conclusion: A conduit-based nerve coaptation device avoids sutures at the nerve repair site and leads to improved outcomes in a rat model. Conduit-based nerve repair devices have the potential to standardize nerve repairs while improving outcomes.

Figure 1

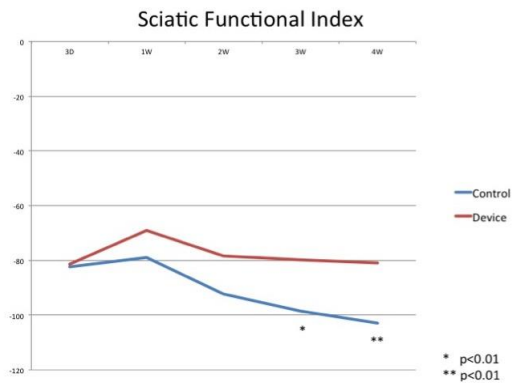


Figure 2

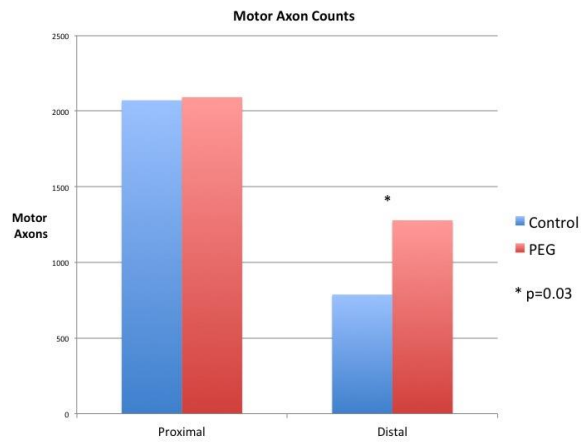
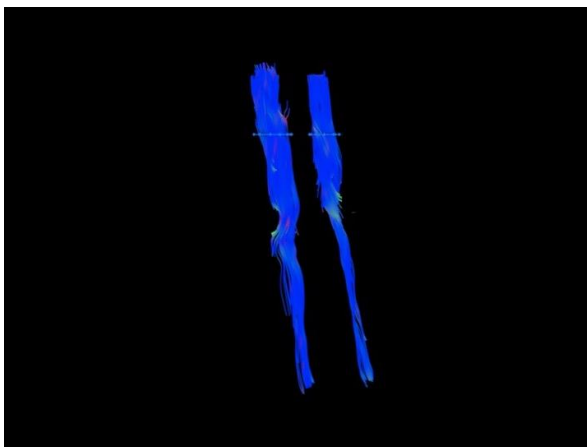


Figure 3



24. Proteome of the Distal Nerve: Its Implication in Delayed Repair and Poor Functional Recovery

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Introduction: Nerve regeneration and functional recovery is poorer when nerve repair is delayed. Among the many contributing factors, chronic denervation mainly affects Schwann cell function and axon outgrowth. After losing axonal contact, Schwann cells proliferate and secrete neurotrophic factors to provide a growth-supportive environment. With chronic denervation the permissive factors progressively decline. Those factors/proteins were individually studied. To better understand the global protein expression profiles, proteomics analysis of chronically denervated nerves was carried out in this study to delineate proteins that were contributory to this detrimental effect.

Methods: Rat sciatic nerve repair model was used. In 4 rats nerve repair was done immediately after transection, while in the other 4 rats repair was done after a 12 week delay. After 16 weeks, nerve samples distal to the repair site were harvested. Proteins were individually extracted using bead mill homogenizer containing SDS lysis buffer. 25 ug of protein from each sample was fractionated by SDS-PAGE gels. Gels were stained, excised, digested, and peptides extracted for analysis by nanoLC-MS/MS. Individual protein expression level of the surgery side was compared to that of the control side using label-free analysis (MaxQuant software). Any protein with a P value less than 0.05 and a fold change of ≥ 4 was considered as differentially expressed. Ingenuity Pathway Analysis (IPA) and Cytoscape softwares were used for pathway/network analysis.

Results: The distal nerve stump proteome contained 5754 detectable proteins. Differential expression analysis showed significant increase of immune and inflammatory response related proteins and decrease of proteins related to axon regeneration and lipid metabolism process in the delayed repair model. Proteins related to Schwann cell function and axonal outgrowth that were down-regulated included CBL, MPZ, PTGDS, MADD, IGDF1R, DHH, HSPB8, GJB1, SHH, MAPK11, ADGRG6, LGALS8, PAK3, CNTF, CAMKK1, TNPV1 and ARPP19. Proteins associated with inflammatory response and apoptosis that were up-regulated were S100A8, S100A9, PLA2G4A, CASP6, CASP3, IGFBP5 and C6. IPA revealed that protective pathways involved in LXR/RXR activation, RAC signaling, ERK/MAPK signaling, CNTF signaling, IL-6 signaling, and FGF signaling were inhibited in the delayed repair group, while 3 detrimental pathways including complement system, PTEN signaling and apoptosis signaling were activated.

Conclusions: The poorer regeneration in delayed repair may be attributed to down-regulation of beneficial proteins and up-regulation of detrimental proteins. The proteins and pathways identified in this study can be potential therapeutic targets.

25. A Systems Biology Approach to Peripheral Nerve Regeneration

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Introduction: Most peripheral nerve research focuses on short gaps (<3 cm in humans). The most urgent clinical need is the treatment of large gaps (5-15 cm). This challenge requires coordinated integration of multiple components, to address: nerve gap; distal effects of axonotmesis and Wallerian degeneration; functional deficits at motor/sensory targets. True clinical solution requires combining state-of-the-art technologies to provide a comprehensive nerve regeneration treatment.

Methods: We have developed: (1) A neurotrophic, guiding conduit across the defect: Nerve guidance wraps (NGWs) were braided from tyrosine-derived polycarbonate microfibers, with optimized wall porosity and hyaluronic acid (HA) coating. They have been used for rapid screening of fillers and biologically active mimetics for driving preferential motor reinnervation (assessed by retrograde labeling of rat/rabbit spinal cord motoneurons). Cell-selective hydrogels are being developed, that are permissive to axons and Schwann cells (SCs) but resist fibroblasts. (2) A neuro-biologically active, structurally-aligned filler across the defect and for maintaining neuromuscular junctions (NMJs): Tissue-engineered nerve graft (TENG) “living scaffolds” are 3D constructs embedded in collagen, comprising highly aligned axonal tracts developed by stretching motor/sensory axons spanning discrete neuronal populations. (3) Electrical stimulation of the proximal repair, NMJs, and denervated muscles, to facilitate regeneration and maintain viability: Stretchable microelectrode arrays (sMEAs) were manufactured using multistep microfabrication patterning of gold electrodes (in space-filling/Peano curve manner to increase flexibility) onto flexible polydimethylsiloxane backing.

Results: (1) NGWs were found to be (a) neurotrophic (improved regeneration vs. non-porous conduits in 1.5 cm rat model; and vs. commercial conduits in 5 cm pig model with TENGs); (b) kink- and compression-resistant; (c) a barrier to scar infiltration while facilitating mass exchange (due to microporous, HA-coated walls); (d) bioresorbable over tunable periods. (2) TENGs were found to accelerate axonal regeneration and functional recovery in rats and pigs across 1-5 cm gaps (“axon-mediated axonal regeneration”); and to promote SC infiltration from stumps to maintain distal structures. (3) sMEAs are capable of stimulating denervated muscles to prevent atrophy, while providing real-time muscle/nerve health assessment through telemetry of neural recordings. Initial biocompatibility testing showed no significant changes in host response when compared to unmodified polydimethylsiloxane controls.

Conclusions: To our knowledge, this is the first proposed application of a systems biology approach to nerve regeneration: a truly comprehensive approach from spinal cord roots to target organs. The current status of each technology will be presented, with plans for their integration.

26. Recovery of Hand Function After Surgical Reconstruction of Brachial Plexus in OBPP

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Introduction: Obstetric brachial plexus palsy (OBPP) is an injury with deleterious medical, psychological and socioeconomic sequelae both for the patient and his or family. The loss of feeling or the simplest God-given skills such as muscle control in an infant's arm and hand can affect families for an entire lifetime.

Patients and methods: 43 patients with total obstetric brachial plexus palsy underwent brachial plexus exploration and reconstruction. The distribution of the patients between the two genders was almost equal, with 22/43 males (51.1%) and 21 females (48.9%). The right side was affected in 27 (62.7%) cases and left side in 15 (35.3%) cases. Bilateral affection was noticed in 1 (2.3%) case in which the left side was treated conservatively and the other side was explored surgically. The Mean age at surgery was 15.8 months (3-96 months). The mean follow-up period was 3.7 years.

Surgical procedures included neurolysis; neuroma excision and interposition nerve grafting and neurotization, using spinal accessory nerve, intercostal nerves and cross neck C7 root. Nerve suture was done in all cases using 10/0 Nylon suture.

Evaluation of hand function using the Toronto scale, Raimondi grading system and Limb integration into the normal daily activities

Results: Satisfactory recovery was obtained in 61.1% for finger flexion; 31.4% for wrist extension and 45.8% for fingers extension. Using the Raimondi scoring system, out of 32 cases 16 achieved a score of 3 or more (functional hand), 16 cases had a score of 2 or less. As regards limb integration into the normal daily activities 3 cases were poor, 8 cases were fair, 14 were good and 8 were excellent. Limb integration did not significantly correlate with any of the regained upper limb functions except a positive significant correlation with shoulder external rotation.

Summary and conclusion: Supra and infra clavicular explorations should be conducted in every case for possible existence of double level lesion. In total palsy the earlier the intervention the better the results. Apparently intact C8 and T 1 root should be left alone if the patient has partial recovery, no horner sign and was operated early enough (3 or 4 month age). An apparently intact non functioning root with no positive response to electrical stimulation and especially in the presence of Horner syndrome should be neurotized with the best available intraplexal donor.

27. Oberlin Nerve Transfer Confers Early Elbow flexion and Forearm Supination in Neonatal Brachial Plexus Palsy

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Introduction: The use of nerve transfers for Neonatal Brachial Plexus Palsy (NBPP) remains controversial. However, supportive evidence for nerve transfers includes potential early reinnervation and improved functional outcomes, potentially via earlier cortical reorganization. The Oberlin nerve transfer (ulnar nerve fascicle to biceps branch of the musculocutaneous nerve) results in excellent restoration of elbow flexion in adults. Infants lacking upper trunk function require restoration of not only active elbow flexion but also supination to avoid muscle contractures and consequent pronation deformity -- both of which can yield significant physical and psychosocial detriments in children. We report the functional results from a series of infants with NBPP who have undergone the Oberlin transfer.

Materials and Methods: This case series reviewed 19 patients who underwent the Oberlin transfer by one neurosurgeon at a single institution, from ages 5 to 11 months (mean age 7 months). Patients' demographics, NBPP involved side, Narakas scale, lesion type, and operative descriptions were reported. Post-operative active range of motion in elbow flexion (in adduction and abduction), forearm supination and pronation were assessed by 1 of 2 certified occupational therapists pre-operatively and post-operatively at Time A (3-5 months), Time B (6-9 months), and Time C (10-12 months). Biceps muscle strength was evaluated via Medical Research Council (MRC) muscle grading scale. Paired T-Test was used to report pre- and post-operative comparisons for elbow and forearm functions.

Results: Elbow flexion in adduction showed significant improvement post-operatively at Time B ($72^{\circ} \pm 40^{\circ}$, $P=0.001$) and C ($82^{\circ} \pm 37^{\circ}$, $P=0.001$), when compared to pre-operative measures ($28^{\circ} \pm 35^{\circ}$). A similar trend was presented in elbow flexions in abduction (pre-op= $51^{\circ} \pm 45^{\circ}$ vs. Time B= $95^{\circ} \pm 54^{\circ}$, $P=0.007$; Time C= $108^{\circ} \pm 39^{\circ}$, $P < 0.0001$). MRC strength of biceps increased from grade 2 to grade 3 by Time C. On interest, forearm supination improved from $-67^{\circ} \pm 38^{\circ}$ to $-26^{\circ} \pm 65^{\circ}$ at Time A ($P=0.041$), $-12^{\circ} \pm 66^{\circ}$ at Time B ($P=0.029$), and $31^{\circ} \pm 39^{\circ}$ at Time C ($P < 0.0001$) while forearm pronation remained 90° pre-and post-operatively.

Conclusions: We demonstrate that the use of Oberlin transfer in infants with NBPP demonstrates advantageous early recoveries in both elbow flexion and forearm supination. As use of nerve transfers increases among surgeons (for reasons including decreased operative time, avoidance of the injured/scarred region, etc.), more studies are needed to establish the comparative outcomes after nerve transfer vs graft and to establish the indications for these procedures.

28. Sensory Outcome in Children with Total Brachial Plexus Palsy Following Microsurgical Reconstruction

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Introduction: Children with total brachial plexus palsy (C5-T1) have long-term sequelae that include sensory impairment in the affected limb. Early microsurgical intervention is indicated for these children. The sensory outcome of children with total plexus palsy following microsurgical reconstruction that prioritizes reconstruction of the lower trunk (C8, T1) with nerve grafting or neurotisation has not been well studied.

Purpose: The purpose of this study was to first describe the sensory thresholds of children with total brachial plexus palsy who had reconstruction of the entire plexus including the lower trunk. Second, to determine the benefit of microsurgical reconstruction of the lower trunk on sensory outcome by comparing the outcomes between those with upper versus total plexus palsy.

Materials and Methods: A prospective case series of children between 6 to 18 years with a diagnosis of obstetrical brachial plexus palsy who had microsurgery at less than 12 months of age with nerve grafting or neurotisation was conducted. The sensory thresholds of children with upper and total plexus palsy were evaluated with the Weinstein Enhanced Sensory Test (WEST). Five sites on the affected and unaffected hands were tested. Results: Sixty children were evaluated. Deficits in the sensory threshold at the C6 (thenar eminence) distribution and the superficial branch of the radial nerve were statistically significant in the affected hands of children with total plexus palsy (n=34) compared to the unaffected hands. The sensory thresholds in the other 3 areas tested were not statistically different. Twelve of the children with upper plexus (46.2%) and 12 (35.3%) of the children with total plexus palsy had abnormal sensory thresholds. The proportion of children with and without sensory impairment was not statistically different between children with upper versus total plexus palsy.

Conclusions: Children with total plexus palsy had excellent recovery in their sensory thresholds in their hand following microsurgical reconstruction of the lower trunk of the brachial plexus.

29. Pain in Infants with Obstetrical Brachial Plexus Palsy Following Primary Microsurgical Reconstruction

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Purpose. Pain in children with obstetrical brachial plexus palsy (OBPP) is under-appreciated and not well understood. Objective evaluation of pain in infants with OBPP is needed to better understand longitudinal trajectories of pain experienced by this population. The purpose of this study was to evaluate postoperative pain in infants with OBPP undergoing microsurgical reconstruction.

Methods. A retrospective cohort study was conducted of infants with OBPP undergoing microsurgical reconstruction of the brachial plexus between 2001 and 2015. Postoperative pain was evaluated using the well-validated Face, Legs, Activity, Cry, Consolability (FLACC) scale, as well as opioid requirements. FLACC scores and opioid requirements were compared in patients with upper plexus palsy versus total plexus palsy.

Results. 159 infants were evaluated: 60 (38%) with upper plexus and 99 (62%) with total plexus palsy. Mean age at the time of surgery was 6.8 ± 3.1 months. The overall mean and median of the FLACC scores were 0.8 ± 1.9 and 0 for all observations ($n=3213$ scores). Both the median and the distribution of FLACC scores did not statistically differ between postoperative days 1 through 8. The proportion of FLACC scores > 0 was not statistically different between infants with total versus upper plexus palsy. The overall mean and median of opioid requirements from the post-anaesthesia care unit to postoperative day 2 were 4.5 ± 1.9 mg and 4.2 mg, respectively. After adjusting for patient weight, there was no significant difference in opioid requirements between patients with total versus upper plexus palsy.

Conclusions. Objective assessment of infants with OBPP who had microsurgical reconstruction indicated that these infants have minimal to no pain in the immediate postoperative period. There was no difference in pain experienced by infants with upper versus total plexus palsy.

30. Outcome Analysis of Medial Triceps Motor Nerve Transfer to Axillary Nerve in Isolated and Brachial Plexus-associated Axillary Nerve Palsy

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Introduction: Originally described using the branch to long head of triceps¹, our institution has performed the triceps to axillary nerve transfer using the medial triceps branch since 2007 to reconstruct axillary nerve function in both brachial plexus and isolated axillary nerve palsies. The choice of donor was based on its longer length for transfer, two distal branches, and larger cross-sectional area, leading to the hypothesis of more neural input for transfer. This is the first large series assessing strength and functional outcomes from medial triceps to axillary nerve transfer from our center.

Materials & Methods: A retrospective chart review of patients treated with a medial triceps to axillary nerve transfer for complete axillary nerve palsy was performed. Patient demographics, injury mechanism, associated injuries, electrodiagnostic studies (EMG) and time to surgery were analyzed. Pre- and post-operative function was assessed using the modified MRC muscle strength grading and the DASH questionnaire. Subgroup analysis for brachial plexus and isolated axillary nerve injuries was performed using the Mann-Whitney U test.

Results: Fifty-eight (58) patients were treated with medial triceps to axillary nerve transfer. Sixteen (16) patients were excluded for insufficient follow-up (< 5 months). Median time to surgical intervention was 6 months (IQR 4-8). Median pre- and post-operative DASH scores were 57.73 (N=28, IQR 22.2-70.9) and 28.3 at final follow-up (N=27, range 9.2-60.0). Only 4 patients had no re-innervation in deltoid muscle after transfer. MRC grade 3 or greater was achieved in 69.0% of patients, 28.6% achieved near perfect results (MRC \geq 4). No patients achieved normal function. Isolated Axillary Nerve Palsy had significantly greater deltoid recovery compared to transfer performed for brachial plexus -associated axillary nerve palsy (3+ vs 3, p=0.048). There was no significant difference in postoperative deltoid strength or DASH scores between patients with axillary nerve transfer versus axillary nerve transfer plus suprascapular nerve reconstruction.

Conclusions: Medial triceps nerve branch is a strong donor for triceps to axillary nerve transfer; however, injury factors may limit the motor recovery in this complex patient population, particularly in brachial plexus-associated axillary nerve palsy.

31. Reliability of Various Predictors for Preoperatively Accurate Diagnosis of Infraclavicular (Level IV) Adult Brachial Plexus Injury When Combined Paralysis of Shoulder and Elbow Encountered

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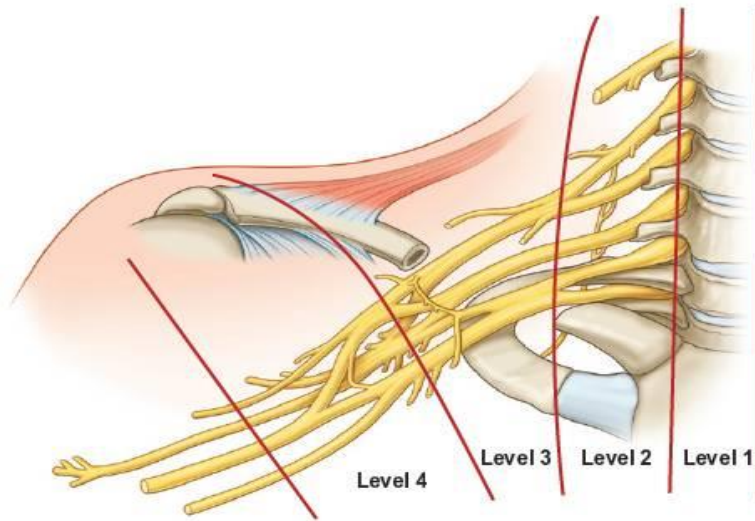
Introduction: Patients presenting with elbow and shoulder paralysis but are misdiagnosed preoperatively as supraclavicular or infraclavicular BPI are rare but can occur (Figure 1). In order to avoid big incision (from upper medial arm to neck) and unnecessary dissections by accurately diagnosing the correct level of injury, our goal was to evaluate the reliability of various predictors including trauma history, clinical motor and sensory examination, tinel sign, electrodiagnosis and radiologic studies.

Material and method: A retrospective study of 75 brachial plexus injuries from 2004 to 2013 with shoulder and elbow paralysis was performed. Clinical symptoms and signs neurological motor and sensory examinations, electrodiagnosis with EMG and NCV, radiology examination (plain X-ray, and/or imaging studies) which were routinely performed were recorded. A preoperative diagnosis was made first. The patients underwent surgical exploration and any discrepancies between preoperative and intraoperative findings were recorded. The reliability of different preoperative predictors were made for their accuracy in predicting the level of injury.

Results: 46 of those patients presented supraclavicular BPI, while 29 patients were diagnosed with infraclavicular BPI. In terms of history taking and preoperative examination, infraclavicular tinel sign was the most accurate predictor (OR 11.738), with scapular fracture being the next most reliable. With the assistance of EMG/NCV, an innervated clavicular head of pectoralis major (OR36.562) , biceps, teres major, serratus anterior and latissimus dorsi muscles would significantly differentiate level IV infraclavicular BPI from supraclavicular BPI (Figure 2 to 4).

Conclusion: This study has proven that certain pre-operative predictors are more reliable in differentiating diagnosis of level IV from level I to level III BPI.

Figure 01



- Level 1** Preganglionic root injury
- Level 2** Postganglionic spinal nerve injury
- Level 3** Pre- and retroclavicular injury (trunks and divisions injury)
- Level 4** Infraclavicular injury (cords and terminal branches injury)

Figure 02

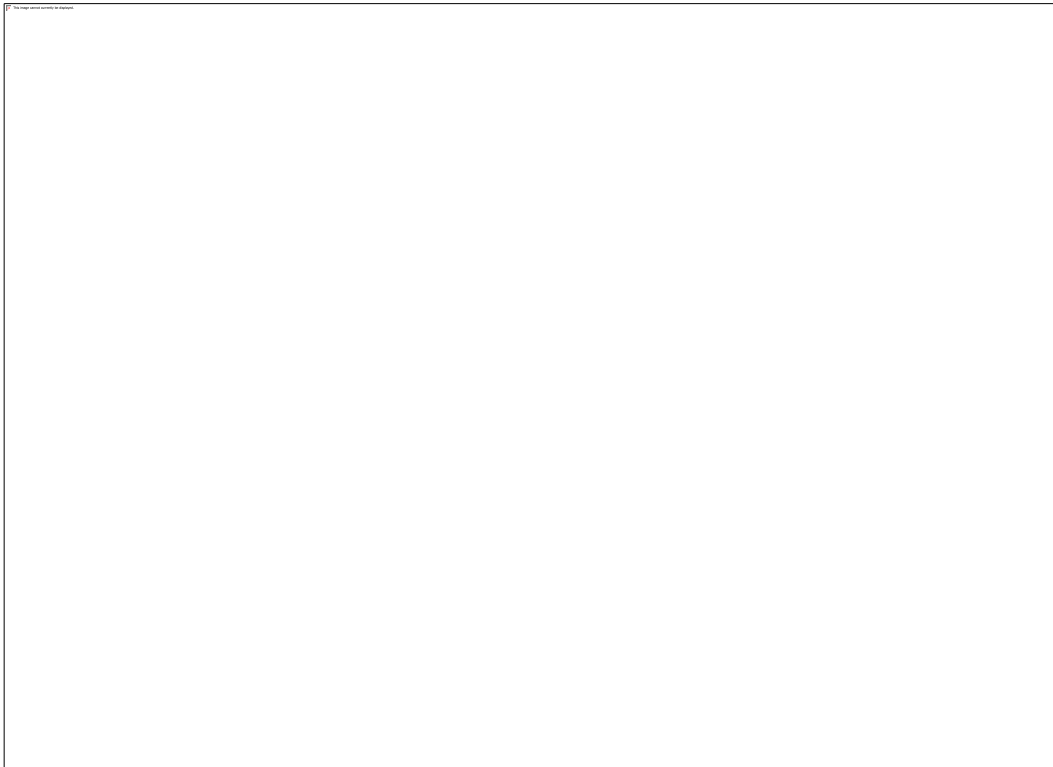


Figure 3

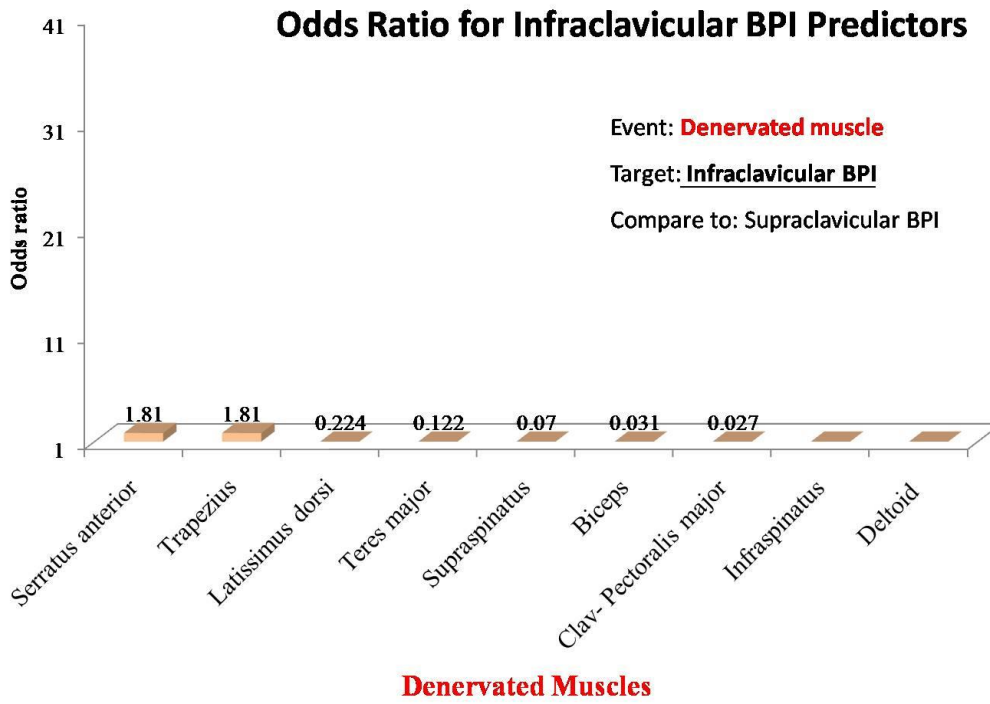
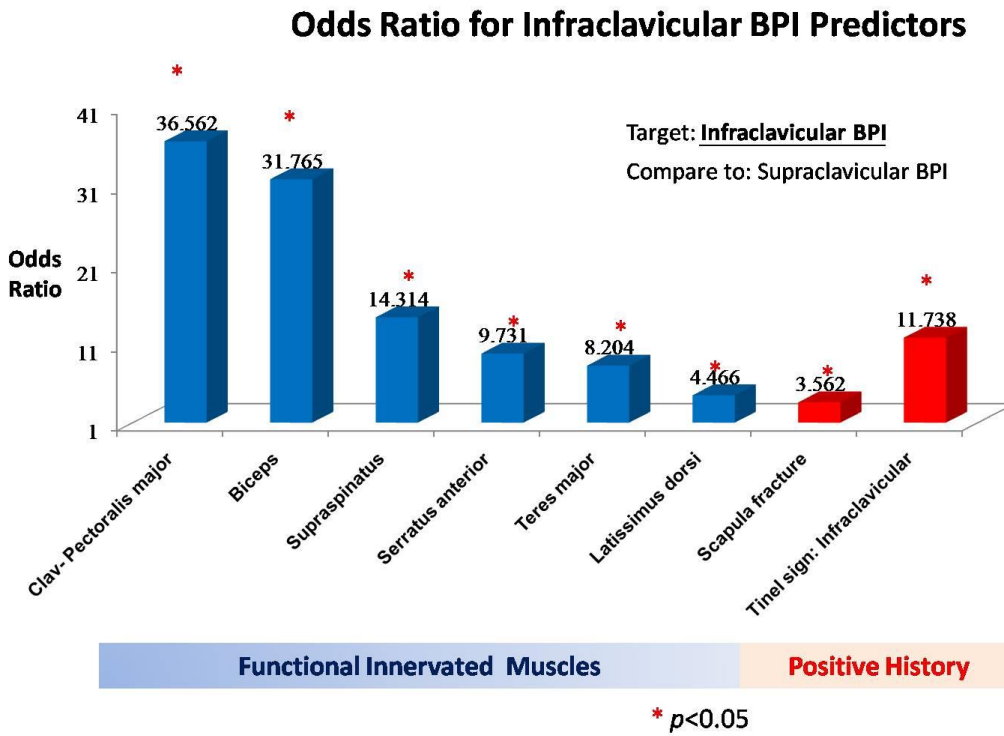


Figure 4



32. Transfer of the Rhomboid Nerve to the Suprascapular Nerve in Partial Brachial Plexus Palsies: a New Nerve Transfer

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Recovery of shoulder function is a real challenge in partial brachial plexus palsies. Currently in C5 C6 root injuries, transfer of the long head of the triceps branch is proposed to reanimate the deltoid muscle. Spinal accessory nerve transfer is usual to reanimate the suprascapular nerve. We have proposed an alternative technique using the nerve of the rhomboid muscles transferred to the suprascapular nerve.

Two patients, 27 and 33 year-old males, with a C5 C6 root rupture with shoulder and elbow flexion palsy underwent surgery 7 months after injury. The rhomboid nerve was transferred to the suprascapular nerve and the long head of the triceps branch to the axillary nerve for shoulder reanimation. A double transfer of fascicles was performed, from the ulnar and median nerve to the biceps branch and the brachialis branch, respectively, for elbow flexion. At the 14-month follow-up, elbow flexion was rated at M4. Shoulder elevation was 85 degrees and rated M4, and external rotation was 80 degrees and rated M4. No complications were noted.

In an anatomical study previously published, we showed that the transfer of the rhomboid nerve to the suprascapular nerve is technically possible. The rhomboid nerve comes from the C5, and sometimes C3 and C4 roots, therefore, it may be used in case of C5 rupture. These two first cases prove that this transfer is clinically possible and gives some positive results. Obviously, these results should be confirmed in a larger series with longer follow-up. This transfer could be an alternative to the spinal accessory nerve transfer to the suprascapular nerve, especially in cases of supraclavicular scarring, spinal accessory nerve injuries, or in order to use the spinal accessory nerve for another target.

33. Improvement in Functional Elbow Movement with a Myoelectric Orthotic Device: A Novel Application of a Post-CVA Assistive Rehabilitation Orthotic Device

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Introduction: Nerve grafting, nerve transfers and free functioning muscle transfers (FFMTs) have lead to improved functional outcomes in brachial plexus injury (BPI) patients. Reports have shown that 41% of nerve transfers and 79% of the FFMTs for elbow flexion achieve \geq M4 elbow flexion strength. However, there remains a substantial minority of patients with less favorable functional outcomes that need to be addressed further.

The MyoPro (Myomo Inc., Cambridge, MA, USA) is an FDA-cleared myoelectric elbow-wrist-hand orthosis that uses surface EMG signals from affected muscle groups to control a powered orthosis to assist with the movement of a paretic upper limb. This device was originally designed for the treatment of post-CVA upper extremity paresis, in patients who had incomplete recovery of muscle strength but preserved voluntary EMG signals. We describe the application of this orthosis for enhancement of elbow flexion and extension in patients with incomplete recovery from BPI with poor voluntary elbow movement.

Materials and Methods: Two patients from a single-surgeon practice have been evaluated for the suitability of the myoelectric functional orthotic device. Both patients are 37 year-old men who were involved in motor vehicle accidents, 14 and 17 years ago, that resulted in left and right brachial plexus injuries. Patient 1 initially had brachial plexus reconstruction by nerve transfers and secondarily a free functioning muscle transfer for restoration of elbow flexion and finger extension. Patient 2 underwent brachial plexus exploration and neurolysis only. Both patients failed to regain voluntary elbow movement. Evaluation showed 0 –130 degree elbow passive range of motion in flail arms. Both patients had detectable EMG signals in the biceps or gracilis, and triceps muscles. Both patients underwent 30 minutes of training with the device, which provides powered assistance for elbow flexion and extension via motors attached to the exterior of the orthosis. After the training, patients were asked to perform voluntary assisted elbow flexion and extension.

Results: Both patients demonstrated voluntary active elbow flexion and extension from 0 to 115 degrees using EMG control signals from the gracilis and triceps in Patient 1, and from the biceps and triceps muscles in Patient 2.

Conclusion: Given the limited options available after definitive reconstruction, this myoelectric orthosis is a valuable option to improve the functional outcome in patients with BPI and poor return of voluntary elbow movement following reconstruction.

34. Experimental Validation of a New Rabbit Model of Brachial Plexus Injury

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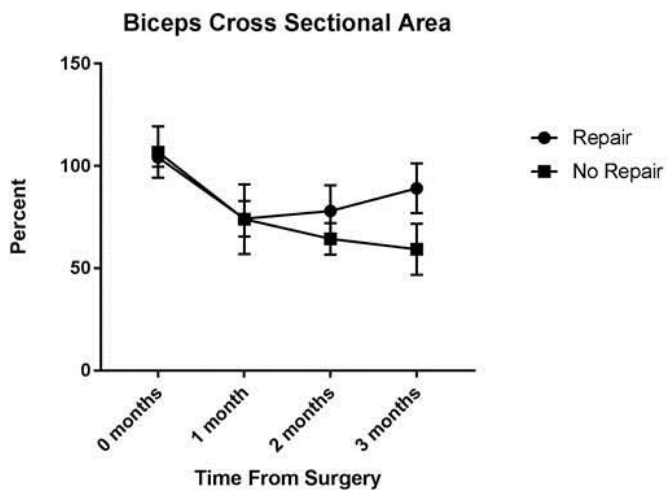
Introduction: Though the rat sciatic nerve has frequently been used to model peripheral nerve injury, it is not suitable for study of the brachial plexus. We describe a true brachial plexus injury model in the rabbit upper extremity. We have found the biceps to be reliably innervated by the middle trunk (formed by the C6 and C7 nerve roots). We aim to demonstrate both long-term biceps paralysis when this trunk is severed, and recovery after nerve repair. We hypothesized that middle trunk repair would result in significantly larger muscle cross-sectional area (CSA), biceps isometric tetanic force (ITF), wet muscle weight (WMW) and compound muscle action potentials (CMAP) than those left unrepaired.

Methods: 22 rabbits underwent bilateral ultrasound measurement of biceps CSA prior to unilateral surgical division of the middle trunk. Five rabbits were randomized to the “no repair” group. The remaining 17 rabbits underwent direct coaptation. CSA was measured at 4 weeks, 8 weeks and 12 weeks post-operatively. At 12 weeks, rabbits were sacrificed and bilateral CMAP and ITF were measured. Biceps WMW was recorded, and its motor nerve analyzed for total nerve area, myelinated area, axon area, axon count and N-ratio (myelinated area/total nerve area). Results from the operative side were expressed as a percentage of the non-operated side, and groups compared across outcomes.

Results: By 8 weeks post-operatively, the CSA of the no repair biceps measured 64.4% of the non-operated side while the repair group measured 78.0% ($p=0.05$). By 12 weeks CSA fell to 59.3% for the unrepaired group and increased to 89.1% for the repair group ($p=0.008$, Figure 1).

At sacrifice, biceps WMW was significantly higher in the repair group ($65.8\% \pm 19.4\%$) as compared to the no repair group ($52.0\% \pm 9.6\%$, $p=0.047$). The repair group rabbits exhibited significantly higher CMAP ($23.3\% \pm 29.3\%$, $p=0.0048$) and ITF ($25.6\% \pm 37.4\%$, $p=0.012$) as compared to the no repair group, which exhibited no recovery.

Conclusions: The middle trunk is the main source of innervation to the rabbit biceps muscle. This model can be successfully used for evaluation of reinnervation of the biceps muscle. Ultrasound can be used as a non-invasive measure to monitor recovery of biceps muscle function over time. Based on our findings, a survival time longer than 12 weeks is recommended for future investigations.



35. Anatomic Variations of Brachial and Lumbosacral Plexus Models in Different Rat Strains.

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Purpose: The selection of an appropriate model for preclinical assessment of new methods of peripheral nerve injury management should consider parameters, such as nerve course, diameter, length and type. This report presents anatomic variations within brachial and lumbosacral plexuses in three selected rat strains of Sprague Dawley (Hsd:Sprague Dawley®SD®), Athymic Nude (Hsd:RH-Foxn1^{tmu}) and Lewis (LEW/SsNHsd) rats.

Methods: Eighteen cadaver rats were divided into three groups, based on their strain. The rats' mean age was 17.1±0.8 weeks (Sprague Dawley), 17.8±0.8 weeks (Lewis) and 16.6±0.8 weeks (Athymic Nude). A total of 90 brachial plexus nerves (axillary, musculocutaneous, median, ulnar, and radial nerves) and 72 lumbosacral plexus nerves (sciatic, tibial, common peroneal and sural nerves) were analyzed for the length, diameter and correlation with the animals body weight. A detailed anatomic course of each nerve within the brachial and lumbosacral plexuses was outlined.

Results: The sural nerve was the longest nerve in all studied rat strains (Sprague Dawley-38.61±0.82mm, Athymic Nude-42.31±1.5mm, Lewis-34.94±1mm), whereas the sciatic nerve had the largest diameter (Sprague Dawley-1.64±0.1mm, Athymic Nude-1.63±0.05mm, Lewis-1.59±0.07mm). Comparison of all the nerves' length demonstrated that the Lewis rat sciatic and sural nerves were significantly shorter ($p<0.05$). The ulnar nerve remained the longest measured nerve within the brachial plexus in all tested strains (Sprague Dawley - 25.6±1.03mm, Lewis - 26.43±1.05mm and Athymic Nude rats - 25.83±1.63mm). No significant differences in nerve diameters were found among the analyzed rat strain groups. Significant correlation was revealed between the length of sciatic nerve and the rats' weight, which is irrelevant to the rats' genetic background. However, there was no correlation found in any of the experimental groups between nerve diameter and body weight.

Conclusions: To the best of our knowledge, this study is the first to compare the anatomic variations of nerves within the brachial and lumbosacral plexuses in different rat strains. Similar results of length values for respective nerves among tested strains confirmed that nerve length within rat's brachial and lumbosacral plexus depends on the inter-individual variations within the rat strains rather than on the differences in the peripheral nerve development, which is inherent to the specific rat strain. Correlation between the nerve length and body weight suggests that bigger rats should be considered for studies requiring access to long nerves. This study will facilitate the optimal selection of the rat strain and nerve model for researchers in the field of novel nerve conduits, biopolymers, or nerve grafts materials.

36. Proximal versus Distal Nerve Transfer for Biceps Reinnervation – A Comparative Study in the Rat Model for Brachial Plexus Injury

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Background: Debate persists between proponents of proximal and distal nerve transfers for brachial plexus reconstruction. The best role for each method has not yet been defined. Here, we use a rat model to compare proximal versus distal nerve reconstruction strategies.

Methods: Male Sprague-Dawley rats were used. C6 spinal nerve with nerve graft (proximal transfer model, n=42) and 50% of ulnar nerve (distal transfer model, n=42) were used as the donor nerves (Figure 1). The target for reinnervation was the musculocutaneous nerve (MCN). Outcomes were recorded at 4, 8, 12, and 16 weeks. Outcome parameters were grooming test, biceps muscle weight, compound muscle action potentials, tetanic contraction force, and axonal morphology of the MCN.

Results: The axonal morphology revealed no significant difference between groups. Ultimately, the proximal transfer model produced superior outcomes at 16 weeks compared to the distal transfer model (Figure 2 to 5). The proximal transfer group's time interval analysis showed a peak in axonal counts at 12 weeks with trend of improvement in all functional and physiologic parameters across all time points. In contrast, the distal transfer group reached its peak performance at 8 weeks and plateaued from 8 to 16 weeks. Also, its axonal counts were highest at the initial 4 week time point with some axonal loss occurring thereafter.

Conclusion: Proximal nerve transfer outcomes are superior to distal nerve transfer in our experimental model. The distal nerve transfer group reaches an early peak performance plateau, but the proximal nerve transfer group progressively improves and eventually surpasses the distal nerve transfer group.

Figure 1

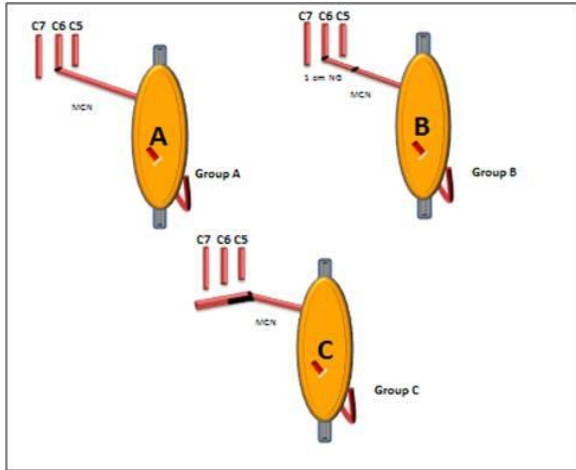


Figure 2



Figure 3

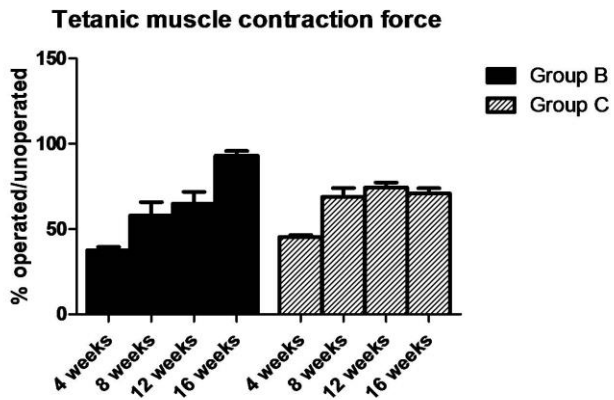


Figure 4

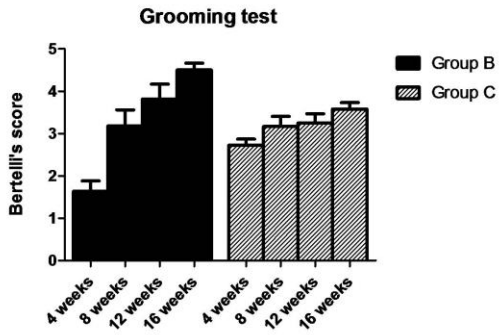
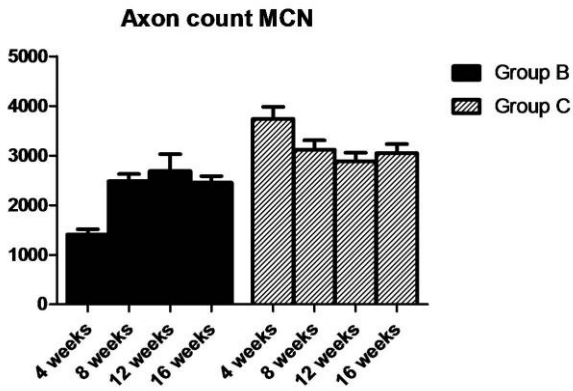


Figure 5



37. UTE-MRI Strategies for Imaging Peripheral Nerve Injury

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Introduction: Functional recovery following peripheral nerve damage is often poor. The structural environment of a regenerating nerve, including progressive changes to the extracellular matrix and basal lamina, can profoundly influence recovery. Current non-invasive imaging approaches are limited in their ability to characterize distal nerve stump quality.

Materials and Methods: We have developed novel 3D-ultrashort-time-to-echo with cones readout (3D-UTE-Cones) magnetic resonance imaging (MRI) strategies to provide rapid, noninvasive, and high-resolution quantitative assessment of nerve architecture. These strategies exploit the properties of nerve collagen and myelin, which have much shorter T2s than nerve fibers, and are not well characterized using conventional MRI. In particular, we applied 3D-UTE-Cones strategies to a Lewis rat sciatic nerve injury model. Using both 11.7T high-resolution and 3T clinical MRI scanners, 3D-UTE-Cones-DWI (diffusion weighted imaging), 3D-UTE-Cones bi-component analysis, and 3D-UTE-Cones-MT (magnetization-transfer) sequences were applied to the proximal and distal stumps of uninjured control nerves and nerves injured and capped without repair for 1, 3, and 12 weeks, corresponding to different phases of degeneration. Several MRI biomarkers, including diffusion parameters, bound/free water T2*s and fractions, water/macromolecule fractions and exchange rates were correlated with structural features of the stumps, including connective tissue area fractions, axon density, and myelination, which were assessed using immunohistochemistry (IHC; trichrome labeling, beta3-tubulin, laminin, and myelin basic protein antibodies). Imaging and analyses were also piloted on human cadaveric nerves and in vivo.

Results: Consistent with IHC outcomes, scanned control rat nerves showed well-defined differences between epineurial, perineurial, and endoneurial/nerve fiber compartments, and subtraction images selectively showed the external and internal epineurium. Diffusion imaging also showed well-defined differences between nerve compartments, providing a baseline for changes that may occur with neuropathy. After injury, IHC revealed that the near distal stump (close to the injury site) lost integrity at 3 weeks, and was unanalyzable at 2 months, while the far distal stump (away from injury site) maintained its integrity at 3 weeks, but lost its integrity by 2 months. 3D-UTE-Cones outcomes also showed differences in nerves injured for 2 months, compared to uninjured controls. Consistent with increased fibrotic infiltration into the nerve, bicomponent analysis revealed an increase in short component (collagen content) from 33% to 55% in the stump margin compared to control. MT modeling indicated fewer macromolecule-bound protons after injury, likely reflecting fewer neurofilaments and/or reduced myelin.

Conclusions: We successfully deployed novel methods to image nerves, which may have significant clinical impact on surgical decision making.

38. Three-Dimensional Wet-Mount Imaging of Peripheral Nerves by Two-Photon Microscopy: A Transgenic Murine Model with High-Throughput Automated Histomorphometric Assessment

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Background: Traditional resin-embedded bright-field microscopy approaches to neural histomorphometric assessment are time consuming, necessitate a high-level of technical skill, and are fraught with bias due to sampling errors and limited resolution. Herein is described a high-resolution wet-mount model of peripheral nerve regeneration.

Method & Materials: Transgenic mice expressing yellow-fluorescent protein at high-levels uniquely in motor and sensory neurons (B6.Cg-Tg(Thy1-YFP)16Jrs/J, Joshua R. Sanes, The Jackson Laboratory) underwent unilateral transection and suture repair of the buccal branch of the facial nerve. Control- and injured-side nerves were harvested at 1, 3, 5, 7, 14, and 21 days, formalin-fixed, and three-dimensionally imaged using two-photon microscopy with broadband excitation between 1 and 1.04 μm and a long-pass dichroic mirror at 525 nm. An algorithm was developed using Imaris software (v 8.0, Bitplane Inc.) for automated calculation of histomorphometric parameters including axon counts, axon diameters, myelin thickness, and axon volumetric density.

Results: Three-dimensional reconstructions with sub-micron resolution capable of resolving small and large fiber axons were obtained in high-throughput fashion. Histomorphometric outcomes were calculated in automated fashion using the entire neural volume over the region of interest to eliminate sampling bias.

Conclusions: A high-throughput, label-free transgenic murine model of neural regeneration that allows for automated histomorphometric assessment at high resolution in three-dimensions with minimal bias has been described.

39. Macrophage Activation to Skeletal Muscle After Nerve Injury

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Introduction: The skeletal muscle is a unique immunologic tissue that is particularly dynamic following muscle injury. Immune cells such as macrophages, normally few in number during physiologic conditions, are quickly recruited to the muscle following injury to assist in inflammatory and reparative processes. In response to their microenvironment, macrophages are able to change their phenotypes during these processes. Although macrophage recruitment and activation have been demonstrated in direct muscle injury models, this dynamic process has not been described in muscle after nerve injury. The goal of this study was to determine if acute nerve injury resulted in the recruitment of macrophages to the distal muscle target, and to characterize the phenotype of these activated macrophages.

Materials & Methods: Eight (n=4 per time point) adult wildtype C57BL/6 mice underwent right sciatic nerve transection without repair. At one or five days after nerve injury, the animal was sacrificed, and all muscles of the hindlimb innervated by the sciatic nerve were harvested from the right injured and left uninjured sides. Following muscle digestion, total cells present in muscle after sciatic nerve injury were isolated for flow cytometry.

Results: Overall, there was a higher number of CD45⁺ hematopoietic cells isolated from denervated muscle than uninjured controls. Moreover, preliminary data demonstrate that there were significantly more Ly6C⁺F480⁻ cells, a classic marker for monocytes, and CD206⁺MerTK⁺ cells, specific markers for macrophages, recruited to the muscle following acute nerve injury. At postoperative day 5, CD206⁺MerTK⁺ macrophages had decreased CD11c expression, suggesting activation of these immune cells.

Conclusions: Our studies demonstrate that acute nerve injury induces recruitment of macrophages to the distal target muscle. Moreover, recruited macrophages have an altered phenotype, which may suggest a functional transformation of these important inflammatory and regenerative immune cells. Further studies are ongoing to determine the functional impact of this macrophage phenotypic change on reinnervation of the muscle following acute nerve injury. Knowledge of this process may allow new therapeutic targets to improve functional recovery following nerve injury.

40. Spatial Analysis of Rat Motoneurons that Regenerate their Axons Following Nerve Transection and Coaptation Demonstrates that Chronic Electrical Muscle Stimulation (EMS) Does Not Prevent Random Reinnervation of Target Muscles

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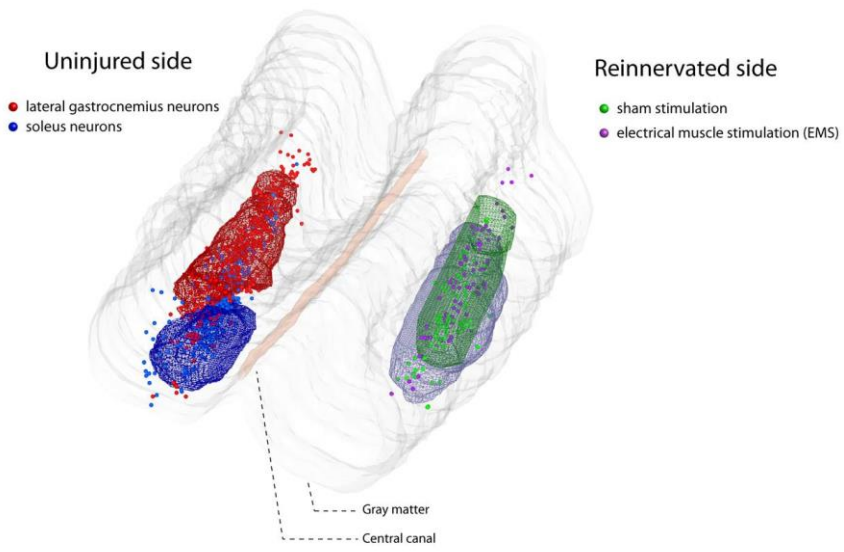
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Introduction: Regenerating motor nerves randomly reinnervate target muscles resulting in synkinesis. Previous studies in a canine model of laryngeal nerve injury demonstrated through functional measurements that EMS promoted selective reinnervation of muscles. In this study, we examine directly through retrograde labelling and spatial analysis whether or not EMS increases preferential muscle reinnervation.

Methods: The soleus and lateral gastrocnemius (LG) muscles in rats (n=13) were used as the target muscles. The normal soleus motoneuron pool was labelled unilaterally by intramuscular injection of TB. One week later, the lateral gastrocnemius soleus (LGS) nerve was transected and coapted using one epineurial suture and electrodes were implanted into the muscle for EMS. The soleus muscle in one group of rats was subjected to daily EMS, 12 hrs at 20 Hz (10 sec on, 20 sec off, 400 μ s pulse width) followed by 12 hrs of intermittent stimulation (10 sec on, 1 hr off). Two months later, the regenerated soleus nerves were retrogradely labelled with Fluoro-Ruby (FR). The contralateral soleus and LG nerves were labelled to determine the distribution of normal motoneuron pools. Labelled motoneurons were counted, and where possible, spatially normalized models were created to analyze and compare the spatial distributions between groups.

Results: Numbers of double labelled soleus motoneurons (TB and FR) were the same in EMS treated and untreated rats demonstrating that EMS did not promote preferential reinnervation of the muscle. Figure 1 shows a 3D representation of all labelled motoneurons. On the uninjured left side, soleus and LG motoneuron distributions that differed significantly are indicated by the red mesh (LG) and blue mesh (soleus). On the reinnervated right side, areas where 80% of reinnervated soleus motoneurons were located are highlighted by a green mesh (sham EMS) and purple mesh (EMS). The distributions of the reinnervated soleus motoneuron pools on the right side were the same whether or not the muscle was subjected to EMS.

Conclusions: Our spatial analysis of retrogradely labelled motoneurons that regenerate their axons after surgical transection and repair of the LGS nerve demonstrate that the motoneuron pools become intermingled randomly irrespective on whether the soleus muscle was subjected to daily EMS. Our results confirm original findings that reinnervation is random and they demonstrate that EMS does not influence this random reinnervation. Importantly, EMS does not prevent muscles from being reinnervated by regenerating nerves.



41. Botulinum Toxin Injection in the Contralateral Gastrocnemius Muscle After Tibial Nerve Repair in Rats: Improvement of Functional Recovery

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Introduction: there is evidence that transient paralysis of the contralateral nonlesioned hemiface with botulinum toxin has positive effects on the functional recovery of the paralyzed side^{1,2}. In an attempt to reproduce this phenomenon, we created an experimental model to study the effects of botulinum toxin injection in the contralateral gastrocnemius muscle on tibial nerve regeneration in rats.

Materials & Methods: 50 rats were divided into 5 groups of 10, according to the procedure performed: I, control, II: tibial nerve sectioned and not repaired, III: tibial nerve sectioned followed by immediate neurorrhaphy, IV: tibial nerve sectioned, immediate neurorrhaphy performed and botulinum toxin injected in the contralateral gastrocnemius muscle, and V: botulinum toxin injected in the gastrocnemius muscle without surgery. The assessment methods used were: walking track, electromyography, gastrocnemius muscle weight ratio and histological analysis of the nerve.

Results: the paralysis in the group submitted to botulinum toxin injection in the gastrocnemius muscle without surgery (V) was transient and the function results returned to normal values after 8 weeks. In the 12th week of assessment, the group submitted to neurorrhaphy and botulinum toxin injection (IV) showed higher functional outcomes in walking track than the group submitted only to neurorrhaphy (III) ($p = 0.001$).

Conclusions: transient paralysis of the contralateral gastrocnemius muscle by botulinum toxin had positive effects on the functional recovery of rats submitted to section and repair of the tibial nerve.

42. Extended Sensory Blockade Using Hydrogel Encapsulated Bupivacaine

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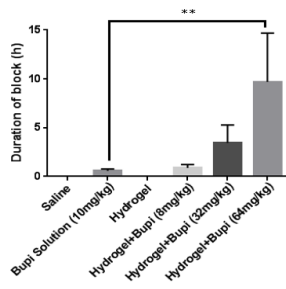
Introduction: Nerve blocks or wound infiltration with local anesthetics relieve postsurgical pain for a few hours but a longer duration is needed. Given the side effects and dependency associated with opioid use, a reduction in their use would be beneficial. Extending the duration of action of local anesthetics could aid in this endeavor. Using a rat sciatic nerve block model, we investigated the efficacy of a novel hydrogel combined with bupivacaine.

Methods: Rats received an injection of either a control bupivacaine solution or hydrogel encapsulated bupivacaine around the sciatic nerve. Assessment of the nerve block included the Von Frey monofilament test, a noxious pinch test, and cold plantar assay.

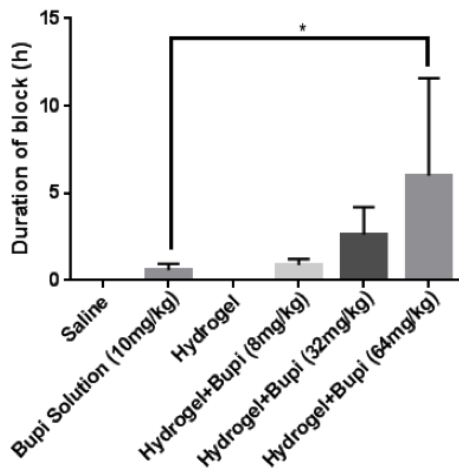
Results: In a sample of 62 male Sprague Dawley rats, the hydrogel encapsulated bupivacaine resulted in a significantly ($p < 0.001$) longer nerve block of 21.4 ± 4.4 hours as measured by the Von Frey test; this block lasted 13 times the duration of the control nerve block. The hydrogel encapsulated bupivacaine also yielded a significantly longer nerve block as measured by the noxious pinch test ($p < 0.001$) and cold plantar assay ($p < 0.01$).

Conclusion: This hydrogel encapsulated bupivacaine yields a significantly longer nerve block than bupivacaine alone. We suspect that this formulation may greatly extend the duration regional anesthesia in humans. Given the potential morbidities associated with opiate use and the fact that pain is the primary reason for readmission after any type of surgical procedure, our findings may have major clinical implications.

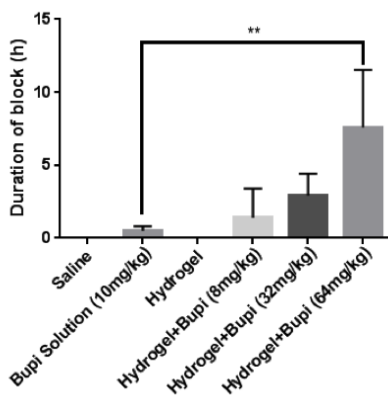
Mean Nerve Block Duration – Von Frey



Mean Nerve Block Duration – Pinch Test



Mean Nerve Block Duration – Cold Plantar Assay



43. Corneal Neurotization: An Update After Five Years Of Experience

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Introduction: Corneal anesthesia leaves patients susceptible to occult corneal injury, scarring and progressive vision loss. We have previously reported a novel surgical technique, termed corneal neurotization, to reinnervate the insensate cornea using sural nerve grafts and host trigeminal sensory nerves in 4 patients, all of whom had improved corneal sensation at 8 months follow-up. We now report outcomes of corneal neurotization in 15 patients.

Methods: Fifteen patients that underwent corneal neurotization at the Hospital for Sick Children, Toronto were included in this study. Data on visual acuity, ocular surface integrity and corneal sensation (measured with Cochet-Bonnet esthesiometry) were collected. In the 3 patients who received corneal transplants after corneal neurotization, the explanted corneal tissue was examined histologically to assess the degree of corneal nerve regrowth after the neurotization procedure. Statistical analysis was performed with the Mann-Whitney U test, with $p < 0.05$ being statistically significant.

Results: 19 eyes in 15 patients underwent corneal neurotization between November 2012 and April 2016. Seven patients were male, and median age at surgery was 9.3 years (range: 1.9 – 34.3). Pre-operatively, median visual acuity was 0.65LogMAR (range: 0.3 – 2.7), and median central corneal sensation was 0mm (range: 0 – 20). All patients presented with persistent corneal epithelial defect (PED), with 3 patients suffering corneal perforation and 4 others with abnormal corneal vascularization. Postoperatively, median central corneal sensation improved to 60mm (range: 0-60, $N=12$, $P < 0.001$). After a median of 16.4 months (range 1.5 – 43.0), median visual acuity was unchanged (range: 0.1 – 2.7). Three patients underwent corneal transplantation at a median of 30 months post-operatively (range: 24 – 33 mo). All corneal transplants remain clear and regained full sensation without any complications. Immunohistochemical analysis of the explanted corneas identified neurofilament-positive axons, indicating corneal reinnervation after initial neurotization surgery.

Conclusions: Corneal neurotization significantly improved corneal sensation, preserved vision, and enhanced ocular surface health. Corneal transplantation was also made possible after reinnervation was established, giving visually-impaired patients a new opportunity to regain their sight.

44. Imaging A Smile: A Novel Approach To Measuring Brain Activity Accompanying Facial Expressions And Its Application In Facial Nerve Palsy

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Purpose: Facial nerve palsy can have a profound impact on physical and social aspects impacting social communication and normal psychological development. Surgical treatment to restore facial motor control for these children improves their self-esteem and sociability. Successful motor rehabilitation following surgery is critical for positive outcomes. Understanding neuroplasticity and functional reorganization of the sensorimotor cortex will allow for tailored surgical approaches and post-operative therapies. Changes with facial and oromotor movements remain unstudied. Functional MRI produces artifacts with orofacial movements, requires specific scan sequences and has low temporal resolution of the signal. Measurements obtained do not separate pre-movement activity, primary motor cortex, post-central cortex and are difficult to carry in young children. The aims of this study are the following: Aim#1 To use a novel imaging technique (MASK-MEG) for measurements of neuroplastic changes in children. Aim #2 To outline functional and structural mapping in a control group of healthy children. Aim #3 To measure changes in sensory and motor cortex in patients undergoing reanimation surgery. Methodology: Aim#1: 4 healthy participants were tested in the MASK-MEG system. Aim #2: Six healthy participants; 3 adults; 3 children (8, 10, 16 yo) underwent tasks in a 151-Channel MEG system with two electromyography (EMG) electrodes on left/right masseter muscles. These tasks included 50-100 cued facial movements, Left and right unilateral smiles, natural bilateral smiles and speech. Aim#3: Control and clinical patients underwent neuroplasticity mapping of their smile centre in a MASK-MEG system. Results: The MASK-MEG system is able to determine location of smile in the precentral gyrus in both adults and children. EMG is too noisy in children and non-specific to smile. In children with facial nerve palsy, responses locations and trajectories are comparable to child control, but with less strong (and noisier) results. Motion differences can be seen between control and clinical participants.

Conclusions: We have demonstrated successful use of a novel MEG-compatible motion tracking device to measure brain activity of subtle facial expressions in children. EMG is highly non-specific for facial muscles due to the number of muscles within a small surface area and lacks ability to determine movement direction or amplitudes. The MASK system coils provide greater movement specificity and are small and light-weight enough not to impede on natural movements. MASK-MEG is a useful tool to assess location of smile in controls and patients with facial nerve palsy.

45. Combined Nerve Transfers for Facial Paralysis

Nobutaka Yoshioka, MD

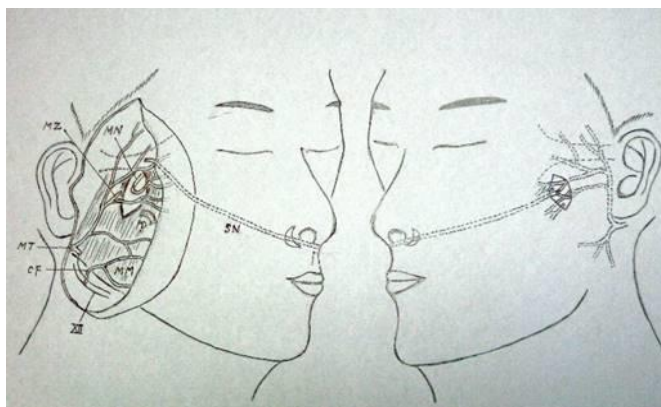
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Background: Although various nerve transfers have been reported as the treatment for the patients with facial paralysis who still have vital facial musculature without available proximal facial nerve stumps, an ideal nerve transfer for reanimating the face has not yet been established. The author has performed combined nerve transfers to the separate distal facial nerve branches with concomitant staged cross-face nerve graft for the patients with reversible facial paralysis with aim of acquiring symmetry at rest, minimizing synkinesis, and spontaneous smile.

Patients and Methods: From May 2013 to October 2015, seven patients with unilateral facial paralysis were treated with this technique. The ages of the patients ranged from 14 to 71 years (mean: 48 years). Five patients had modified House-Brackmann grade 6 facial nerve function and two had grade 5 preoperatively. The etiology of facial paralysis was extirpation of the brain tumor in six patients and Hunt syndrome in one. Duration of paralysis was between 4 months and 27 months (median: 9). All patients underwent masseteric nerve transfer to the main zygomatic branch of the facial nerve and direct or indirect mini-hypoglossal nerve transfer to the lower trunk of the facial nerve. Concomitant staged cross-face nerve graft between the both zygomatic branches was intended to reconstruct smiling (Figure 1). Secondary neurorrhaphy between the cross-face nerve graft and distal branches of the main zygomatic branch in the affected side was performed with the previously performed masseteric to the main zygomatic branch coaptation being left intact.

Results: The follow-up period after the secondary neurorrhaphy was between 3 and 24 months (mean: 12months). Five patients had modified House-Brackmann grade 4 function and two patients had grade 3 function. Every patient achieved nearly symmetrical resting symmetry and voluntary elevation of the corner of the mouth with minimal synkinesis. No spontaneous smile was acquired in every patient during the follow-up period.

Conclusions: Among various nerve transfer techniques, combined masseteric and mini-hypoglossal nerve transfers to the separate distal facial nerve branches provide reliable dynamic facial reanimation, resting symmetry, and minimal synkinesis. Further follow-up is necessary to evaluate the synchronized movement of the corners of the mouth and spontaneous smiling.



(Figure 1) MN: masseteric nerve, MZ: main zygomatic branch, PD: parotid duct, MT: main trunk, CF: cervicofacial trunk, MM: masseter muscle, SN: sural nerve

46. Cervical Branch Nerve Transfer for Restoring Marginal Mandibular Nerve Function

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Background: Injuries of the marginal mandibular branch (MM) of the facial nerve results in paralysis of lower lip muscle depressors and asymmetrical smile. Nerve reconstruction when possible is the method of choice, however in the presence of long nerve gaps or delayed nerve reconstruction, conventional nerve repairs maybe difficult to perform or provide suboptimal outcomes. Herein we investigate the anatomical technical feasibility of the nerve transfer of the cervical branch of the facial nerve (CB) to the MM for restoration of lower lip function. In addition we present a clinical case where this nerve transfer was successfully performed.

Methods: Ten adult fresh cadavers were dissected. Measurements included the number of MM and CB branches, maximal length of dissection of the CB from the parotid and the distance from anterior border of parotid to the facial artery. CB reach for direct coaptation to the MM at the level of the crossing with the facial artery was assessed. We also performed histomorphometric analysis of the MM and CB branches. We present a clinical case of a 66 years-old man with a soft tissue sarcoma in the face that needed resection of skin, submandibular gland and sacrifice of the MM, reconstructed with CB to MM nerve transfer and a free flap for soft tissue coverage.

Results: The anatomy of the MM and CB was consistent in all dissections, with an average number of sub branches of 1.5 for the MM and 1.2 for the CB. The average maximal length of dissection of the CB was of 46.5 mm and in every case tension-free coaptation with the MM was possible at the level of crossing with the facial artery. The histomorphometric analysis demonstrated that the MM nerve contained an average of 3856 myelinated fiber counts per mm and of 5015 for the CB . After 3-years follow-up of the clinical case, complete recovery of MM function was observed without need of central relearning and without functional or aesthetic impairment resulting from the denervation of the platysma muscle.

Conclusion: The CB to the MM nerve transfer is an anatomically feasible procedure for reconstruction of isolated MM nerve injuries being a valid alternative to conventional nerve grafts. In our patient, by direct nerve coaptation fully recovery of lower lip muscle depressors was achieved without the need of central relearning due to the synergistic functions of the CB and MM functions and with minimal donor site morbidity.

47. Surgical Approach to Injuries of the Cervical Plexus and its Peripheral Nerve Branches

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Introduction: Located in the neck beneath the sternocleidomastoid muscle, the cervical plexus comprises a coalition of nerve fibers from C1 through C4, which ultimately provides input to four cutaneous, seven motor and three cranial nerves, as well as the sympathetic trunk. Diagnosis and treatment of painful neuromas of the cervical plexus remain under-appreciated and incompletely described.

Methods: A retrospective cohort of eleven patients with painful cervical plexus neuromas is described. There were combinations of injury to the Lesser Occipital, Greater Auricular, Transverse Cervical and Supraclavicular nerves. Inciting events included prior facelift, migraine and thoracic outlet procedures, as well as traumatic events including seatbelt trauma during a motor vehicle crash, a fall, and a clavicular fracture. Diagnoses were confirmed with nerve blocks. Neurectomy with intramuscular transposition into the sternocleidomastoid muscle was performed for three nerve branches in one patient, two branches in two patients, and one branch in the remaining eight patients.

Results: Nine of the eleven patients had complete relief of their cervical plexus-related pain following neuroma(s) resection and muscle implantation. There was no pain at the site of muscle implantation and no pain with head movement. The two failures were in patients with pain after previous face lift surgery. In each of these patients residual perception of neck tightness and “choking” sensation persisted despite relief of cheek and ear pain.

Conclusion: Knowledge of the anatomy of the cervical plexus and its branches is crucial for any surgeon operating in this area to minimize iatrogenic nerve injury. Proper diagnosis and surgical intervention can help 90% of patients with these debilitating pain problems.

48. Intraoperative Brief Electrical Stimulation For Prevention Of Shoulder Dysfunction After Oncologic Neck Dissection: A Double-Blinded Randomized Controlled Trial

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Introduction: Shoulder pain and dysfunction are common after head and neck cancer (HNC) surgery due to traction or compression injuries to the spinal accessory nerve (SAN). In addition to hindering postoperative rehabilitation and hygiene, this can negatively impact activities of daily living (ADLs) and return to work. Therefore, methods to accelerate recovery are much needed. Recently brief post surgical electrical stimulation (BES) was shown to enhance neuronal regeneration in patients with carpal tunnel syndrome and digital nerve laceration. The objective of this study is to test the hypothesis that post-surgical BES is effective in accelerating spinal accessory nerve regeneration and restoring shoulder function after oncologic neck dissection in HNC patients.

Methods & Methods: In this double blinded randomized controlled trial, adult participants with a new diagnosis of HNC undergoing surgery with neck dissection including Level IIb or V were enrolled. Patients were randomized to "BES" or "sham" in 1:1 allocation scheme. BES group participants underwent post-surgical BES after completion of neck dissection for 60 min at 20 Hz, 3-5 V of 0.1msec duration pulses to the spinal accessory nerve on the side with the most extensive nodal burden. Pre- and postoperatively, participants were evaluated by a blinded physiotherapist using the Constant-Murley Shoulder score (CMS). Secondary outcomes included nerve conduction studies (NCS) performed by a blinded neurophysiologist. Post-surgical outcomes were assessed at 6 and 12 months. Mann-Whitney and Chi-squared analyses were used for continuous and dichotomous values, respectively.

Results: Fifty-four patients were recruited. No differences in demographics, tumor characteristics, or neck dissection types were observed between groups. A significantly smaller change in CMS scores from baseline was observed in the BES group at 12 months, indicating better clinical preservation of shoulder function ($p=0.022$). Change in NCS values were significantly smaller in the BES group at 12 months ($p=0.048$), indicating better neurophysiologic preservation of SAN function in the BES group.

Conclusion: Application of BES to the SAN after oncologic neck dissection objectively improves shoulder dysfunction after surgery. BES may be considered as a useful adjunct to postoperative shoulder rehabilitation in patients with HNC.

49. A Novel Local FK506 Delivery System Results in Excellent Nerve Regeneration in Rats

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Purpose: Many challenges exist in improving outcomes following peripheral nerve injuries, specifically in cases with delayed nerve repair and with large nerve defects. This study focused on investigating a new method to improve axon regeneration after surgical repair of a severely injured nerve. FK506, an FDA approved immunosuppressant, promotes functional recovery and reinnervation following peripheral nerve injury. However, FK506 has not been widely adopted for treating nerve injuries because the systemically delivered drug causes undesirable immunosuppression. We investigated a novel local delivery system for FK506 which utilizes fibrin gel as a biodegradable drug reservoir that could be placed at a site of nerve injury and surgical repair.

Methods: FK506 was incorporated into fibrin gel in solubilized, particulated and poly(lactic-co-glycolic) acid (PLGA) microspheres-encapsulated forms. In order to analyze the effectiveness of the delivery systems in enhancing nerve regeneration, a rat nerve transection model was used, where the proximal tibial nerve stump was cross-sutured to the distal stump of a cut common peroneal nerve. Rats in the negative control groups either did not receive any delivery system treatment or received fibrin gel with empty microspheres (without any FK506). The experimental groups included rats treated with fibrin gel loaded with solubilized, particulated, or PLGA microspheres encapsulated FK506. Three weeks after repair, nerve regeneration was assessed using retrograde labeling and collecting nerve samples 7 mm distal to the repair site for histomorphometric analysis.

Results: Rats in experimental groups receiving FK506-loaded microspheres and the particulate form of FK506 doubled the number of motoneurons regenerating their axons after injury and allowing *all* the tibial motoneurons to regenerate their axons successfully. The numbers of the motor and sensory neurons that regenerated their axons in the FK506 microspheres treated group and the particulated FK506 treated group were significantly higher than the numbers in all the groups, including the solubilized FK506 treated group and negative control groups. Histomorphometric analysis indicated increased number of myelinated axons following particulated FK506 and FK506 microspheres treatment compared to the negative control groups.

Conclusion: The local application of FK506 via our proposed delivery systems resulted in excellent axon regeneration while eliminating the toxicity of systemic FK506 that has prevented clinicians from using FK506 routinely for treating severe cases of peripheral nerve injuries.

50. A Rat Model Of Corneal Denervation And Neurotization Using the Thy1-GFP+ Rat

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Introduction: Corneal neurotization significantly improves corneal sensation in patients with corneal anesthesia, using nerve grafts and donors from the contralateral face to reinnervate the denervated cornea. Important questions remain, including whether donor sensory nerves, foreign to the cornea, maintain corneal clarity and how the cornea regulates nerve ingrowth after neurotization. In this study, we developed an experimental animal model of corneal neurotization where experimental factors can be manipulated and tissue harvested, in order to investigate these questions.

Methods: Our model of corneal neurotization was designed using the *thy1*-GFP+ rat, which expresses green fluorescent protein (GFP) in axons. First, stereotactic surgery was performed to electrosurgically ablate the ophthalmic nerve (V1), which innervates the cornea, using a 21G insulated needle. Multiple stereotactic variables, including the stereotactic coordinates, number of lesion sites, and the amount and duration of energy stimulus were investigated (n = 75). The cornea was examined 1, 2 and 4 weeks later for effective denervation with whole-mount confocal microscopy. Once corneal denervation was established, a second group of rats (n = 12) was used to establish a method of corneal neurotization. Common peroneal (CP) and sural nerve grafts were coapted to the contralateral inferior orbital nerve (ION) and then sutured to the corneal limbus for corneal neurotization. Corneal reinnervation was examined and compared to non-neurotized controls 2 and 4 weeks later with the same microscopic method.

Results: Optimal stereotactic corneal denervation was achieved by ablating two locations of the intracranial ophthalmic nerve at the coordinates 2.1, 1.5, 11 and 2.3, 0, 11 mm with electrosurgical parameters of a 390 kHz sinusoid waveform and 3 W administered for 30 s at each coordinate. The cornea remained denervated for 2 weeks with minimal reinnervation at 4 weeks (Fig 1B). ION reinnervation of the cornea through CP and sural autografts occurred within 4 weeks of denervation (Fig 1C).

Conclusions: We have established a rat model of corneal neurotization by optimizing stereotactic parameters to ablate the corneal innervation intracranially and successfully neurotizing the corneal using nerve grafts from the ION. This provides an excellent model to study corneal neurotization and in turn, optimize clinical corneal reinnervation.

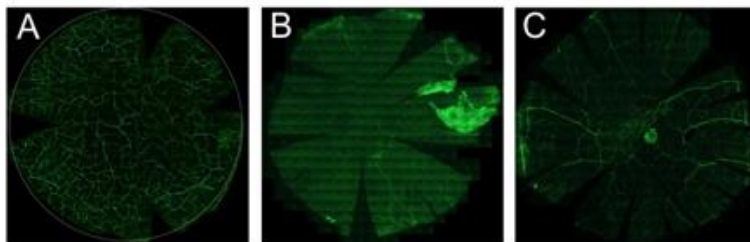


Figure 1. *Thy1*-GFP+ axons in the uninjured cornea (A) are absent 4 weeks after denervation (B). Significant corneal reinnervation occurs 4 weeks after corneal neurotization (C).

51. In Vivo FK506 Transport from a Novel Local Delivery System in Rats

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Purpose: Administration of FK506, an FDA approved immunosuppressant, has shown to enhance nerve regeneration following peripheral nerve injuries. However, the severe side effects of the systemically delivered FK506 has prevented clinicians from using this drug routinely. Therefore, we have developed a novel fibrin gel based local delivery system for FK506. In this study, for the first time, we analyzed FK506 transport to the surrounding tissues and the nervous system, *in vivo*, from the local delivery system placed at the nerve injury site.

Methods: FK506 was incorporated into fibrin gel in solubilized, particulated and poly(lactic-co-glycolic) acid (PLGA) microspheres-encapsulated forms. A nerve transection model was used in which the rat common peroneal nerve was immediately coapted after transection. Three experimental groups received the three forms of the FK506 delivery system. Rats in a negative control group did not receive any delivery system. Using mass spectrometry, FK506 tissue concentrations were analyzed at the site of the injury, in sciatic nerve, dorsal root ganglia (DRGs), spinal cord, brain, heart, liver, kidney, and plasma at 7, 14, and 28 days post repair.

Results: The duration of FK506 release was the shortest in the solubilized form for 7-days, then the particulate form for 14-days. The most prolonged release period was seen with the PLGA microsphere-encapsulated form for 28-days. FK506 was detectable within the injured sciatic nerve, DRGs (L4, L5), the entire spinal cord, and the muscles surrounding the nerve repair site, decreasing in concentration over time. The highest FK506 tissue concentration was detected within the entire spinal cord at day 7 regardless of the delivery system formulation. Kidney tissues had low FK506 levels only during the first week in the solubilized FK506 treated rats. No FK506 was detected in plasma, brain, liver, and heart during the study period in all rats. Twenty-eight days post repair, all rats had below the detectable level of FK506 in the examined tissues, except at the site of nerve injury and the surrounding muscles. Most importantly, the treated rats did not show any side effects during the entire study.

Conclusions: We have demonstrated effective release of FK506 from the novel fibrin gel based delivery system *in vivo*. For the first time, this study shows the *in vivo* transport of the locally released FK506. The findings from this study are necessary to engineer a local FK506 delivery system that provides the optimal concentration of the drug within the targeted tissues.

52. Injury to the Perineal Branch of the Pudendal Nerve in Women: Outcomes from Surgical Resection of the Perineal Branches and Implantation of Proximal End into the Obturator Internus Muscle

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Background: The traditional transgluteal approach for the surgical treatment of “pudendal neuralgia” has been disappointing for those patients with “anterior” pudendal nerve symptoms, such a pain in the labia, vestibule, and perineum. In this study, we describe outcomes from a new surgical approach to resect the perineal branches of the pudendal nerve (PBPN).

Materials & Methods: An IRB-approved prospective study enrolled 16 consecutive female patients from 2012 through 2015 who did not have rectal symptoms. Each woman had a successful, diagnostic, pudendal nerve block. The surgical procedure was resection of the PBPN and implantation of the nerve into the obturator internus muscle through a para-labial incision. Mean age at surgery was 49.5 years (SD = 11.6 years). Mechanism of injury was episiotomy in 31%, athletic injury in 25%, vestibulectomy in 31%, and falls in 13%. Four women (25%) had urethral symptoms. Outcomes were the Female Sexual Function Index (FSFI), the Vulvar Pain Functional Questionnaire (VQ), and the Numeric Pain Rating Scale (NPRS). 14 patients completed these questionnaires, reporting on their condition before surgery and currently.

Results: The mean post-operative length of follow-up was 15 months (range: 6 to 43 months). Post-operative significant bruising was the only complication, occurring in 10% of the patients. The overall FSFI significantly improved after surgery ($p < 0.05$). The specific domains that showed significant improvement were those for arousal, lubrication, orgasm, satisfaction, and pain ($p < 0.05$). The VQ also significantly improved after surgery ($p < 0.001$) in 13 of 14 (93%) patients. The NPRS score decreased, on average, from an 8 to a 3 out of 10 ($p < 0.0001$). Each of the 4 women with urethral symptoms had relief of these symptoms post-operatively.

Conclusions: Resection of the perineal branch of the pudendal nerve with implantation of the nerve into the obturator internus muscle significantly improved the sexual function, vulva function, and pain of women who sustained injury to the perineal branches of the pudendal nerve.

53. Does Duration of Neuropathy, Duration of Diabetes, or HbA1c Affect the Response to Nerve Decompression in Diabetic Neuropathy: Conclusions from the DNND (Diabetic Neuropathy Nerve Decompression) Study – a Prospective, Randomized, Controlled Trial

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Introduction: The DNND study - a level one prospective, randomized, double blinded, sham-procedure controlled trial, was designed to evaluate the effects of nerve decompression on pain reduction in patients suffering from painful diabetic neuropathy (PDN). In an average 54.5-month follow-up, the seven-year study revealed a statistical reduction in pain in the surgical vs. non-surgical group (SD=2.54;p<0.0001) and surgical versus sham group (7.47+2.09 vs. 5.97+2.43, p=0.0002). Yet, the effect of HbA1c, duration of diabetes, and duration of neuropathy on pain reduction after nerve decompression has not been elucidated. This study aims to analyze if these three variables affect the pain reduction over time in patients after nerve decompression.

Methods: Of the 2987 screened patients in the DNND study, statistics were based on the 138 enrolled patients, with 92 randomized to surgery and 46 as controls. At average follow-up period of 54.5 months, 36 surgical patients (each having a side randomized to nerve decompression or sham-procedure), and 14 control patients had full completion data. The significant reductions in pain scores at the 1 and 4-year follow-ups in the surgical and sham-procedure legs when compared to the non-surgical legs had previously been established. The variables: 1) duration of diabetes, 2) duration of neuropathy, and 3) HbA1c level were modeled with the pain scores, and analysis was completed via Analysis of Variance (ANOVA) models by the UT Southwestern Department of Biostatistics.

Results: There was no statistically significant impact on the pain scores at baseline, 1-year, or 54.5 month follow-ups by HbA1c levels (F-value=. 15, P< .69), the duration of neuropathy (F-Value=.02, P<.88), nor the duration of diabetes (F-Value= .45, p<.71) in the 50 patients who had full 54.5 month follow-up data.

Conclusion: The seven-year clinical trial on which this analysis has been completed has substantial implications on the treatment and management of lower extremity diabetic neuropathy. However, it is crucial to first stratify which patients will have the best chance for benefit from surgical decompression. These results indicate that the efficacy of lower extremity nerve decompression for painful diabetic neuropathy is applicable across the broad spectrum of patients with varying severities and durations of diabetes.

54. Highly Variable Phenotype of LZTR1 Schwannomatosis Includes Neurofibromas

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Introduction: Schwannomatosis is a hereditary disorder defined by the presence of 2 or more peripheral or cranial (non vestibular) nerve schwannomas. Schwannomatosis is genetically heterogeneous; two known causative genes are *SMARCB1* and the more recently identified *LZTR1*. The *LZTR1* schwannomatosis phenotype has been expanded to include unilateral vestibular schwannoma (UVS). To date, neurofibromas have never been described in patients with schwannomatosis. Herein we describe a family with schwannomatosis due to a *LZTR1* gene mutation, in which one family member has a severe early-onset phenotype encompassing both schwannomas and pathologically confirmed neurofibromas.

Materials & Methods: Whole exome sequencing was performed in the proband. Mutation and cosegregation was confirmed using Sanger sequencing.

Results: A 55 year old male (proband) suffered a severe phenotype including multiple cutaneous schwannomas, unilateral trigeminal schwannoma and pathologically confirmed subcutaneous and multiple intraneural neurofibromas. Age of disease onset was 16yo. His sister showed a mild phenotype with late onset schwannomas. Both parents were not available for examination or testing. Whole exome sequencing identified a mutation in the *LZTR1* gene (c.2324dup, p.Ile776fs) in both proband, also present in affected sister. Exome sequencing did not show any mutations in *SMARCB1*, *NF1* en *NF2*.

Conclusions: We describe the presence of neurofibromas as a part of the *LZTR1* phenotype, implying loss of *LZTR1* function could predispose to the development of neurofibromas, as well as schwannomas and UVS. This finding suggests a role of *LZTR1* in Ras/MAPK pathway, in parallel with *NF1*, a GTPase activating protein that is a negative regulator of Ras.

#91 Partial Radial Nerve Transfers for Patients with Isolated Traumatic Axillary Nerve Injuries

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Hypothesis:

Isolated axillary nerve injuries can occur subsequent to trauma or as a direct complication from shoulder procedures. While partial radial to axillary nerve transfers have previously been described, there has been a lack of information related to patient selection, surgical methodology, and outcomes. We hypothesize that partial radial to axillary nerve transfers is an under-utilized, promising treatment option for patients with this devastating injury.

Methods:

We performed a retrospective analysis of all partial radial nerve transfers for isolated axillary nerve injuries (n=7) performed by a single surgeon over the past four years. All patients had nerve conduction studies verifying a complete axillary nerve lesion with no reinnervation as detailed by fibrillation potentials without evidence of nascent potentials. The surgery consisted of (1) using a direct posterior approach to the arm, (2) isolating one fascicle of the radial nerve responsible for only elbow flexion as confirmed by intra-operative monitoring, and (3) coapting this branch to the proximal portion of the axillary nerve in the quadrilateral space. All patients were protected in a shoulder sling for three weeks until the nerve repair healed.

Results:

There was no donor nerve deficit for any patient. Four of the seven patients had undergone previous shoulder surgery and had received a preoperative nerve block. One patient had the nerve transfer performed within four months of injury and regained functional motion with forward elevation to 160 degrees and M4 strength. The other patients had surgery after the initial 7 months after the injury and did not have any meaningful improvement in function after the nerve transfer. The other three patients had an axillary nerve injury related to a traumatic injury and had nerve transfer performed within the initial 6 month time period. One patient has subsequent restoration of his deltoid muscle; however, his range of motion was limited due to an underlying proximal humerus nonunion. The other two patients have forward elevation to 160 degrees with M4 strength.

Conclusion:

For patients with axillary nerve injuries, a partial radial to axillary nerve transfer is a safe procedure without donor deficit that can provide functional recovery with early intervention. While the expanded use of regional anesthesia may cloud the initial post operative exam for patients undergoing shoulder surgery, the surgeon should be suspicious of patients who do not demonstrate recovery and refer patients early for intervention rather than prolonged observation in order to maximize the chances of recovery.

#92 Recovery of Elbow Flexion After Delayed Nerve Reconstruction versus Free Functional Muscle Transfer for Traumatic Brachial Plexus Palsy: A Systematic Review

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Purpose:

In delayed presentation of brachial plexus trauma, the question arises as to whether donor nerves should be devoted to nerve reconstruction or reserved for free functional muscle transfer (FFMT). The purpose of this study was to systematically review recovery of elbow flexion after delayed nerve reconstruction versus FFMT for traumatic brachial plexus palsy.

Methods:

A systematic review was performed using the PUBMED, SCOPUS, and Cochrane databases in order to identify all cases of traumatic brachial plexus palsy in patients 18 years or older. Patients who underwent delayed (≥ 12 months) nerve reconstruction or FFMT for elbow flexion were included. Demographics were recorded, including age, time to operation, and level of brachial plexus injury. Functional outcomes were evaluated, including British MRC strength and range of motion for elbow flexion.

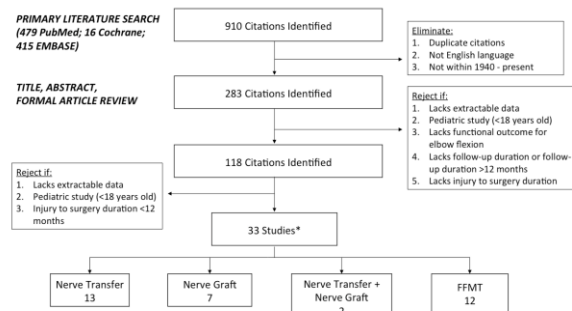
Results:

Thirty-three studies met criteria (**Figure 1**) for a total of 103 patients (53 delayed nerve reconstruction, 50 FFMT). The methodological quality of included studies (MINORS) ranged from 50-92%, with a median MINORS criteria score of 54% (IQR 54-71%) for nerve reconstruction and 54% (IQR 54-56%) for FFMT articles ($p=0.72$). Surgical age and preoperative elbow flexion were no different across the groups, whereas time to surgery and follow-up time were significantly longer in the FFMT group (**Table 1**). For upper trunk injuries, 53% of nerve reconstruction patients versus 100% of FFMT patients achieved M3 or greater strength ($p<0.01$) and 43% of nerve reconstruction patients versus 70% of FFMT patients achieved M4 or greater strength ($p=0.17$). In total brachial plexus injuries, 37% of nerve reconstruction patients versus 78% of FFMT patients achieved M3 or greater strength ($p<0.01$) and 16% of nerve reconstruction patients versus 46% of FFMT patients achieved M4 or greater strength ($p<0.04$).

Conclusion:

In delayed presentation of traumatic brachial plexus injuries, donor nerves should be reserved for free functional muscle transfer rather than for nerve reconstruction to restore elbow flexion.

Figure 1. Attrition diagram for systematic review



*One study had three different procedures. The patients we included from this study were segregated into their respective cohorts.

	Upper Trunk			Total BPP			Overall			
	Nerve Reconstruction	FFMT	P-value	Nerve Reconstruction	FFMT	P-value	Nerve Reconstruction	FFMT	P-value	
Overall Sample Size (n)	34	30		39	40		53	50		
Age	27.5	28.7		25	29.5		27	28.9		
[median years (range)]	(18-54)	(23-32)	0.86	(18-47)	(18-56)	0.38	(18-54)	(18-56)	0.47	
Pre-op MRC =1	100%	100%		100%	100%		100%	100%		
% (n)	(25/25)	(5/5)	1	(2/2)	(20/20)	1	100%	(27/27)	(26/26)	0.92
Time to Operation	13	32.7		12	23.5		13.0	24.0		
[median months (range)]	(12-75)	(13-74)	<0.01	(12-24)	(12-156)	<0.01	(12-75)	(12-156)	<0.01	
Length of Follow-Up	22.5	34.2		24	36		24.0	35.5		
[median months (range)]	(10-74)	(14-260)	<0.01	(12-120)	(12-180)	0.76	(10-120)	(12-260)	0.02	
Post-op MRC =3	53%	100%		37%	28%		43%	28%		
% (n)	(16/30)	(10/10)	<0.01	(7/19)	(9/37)	<0.01	(23/49)	(9/47)	<0.01	
Post-op MRC =4	43%	70%		16%	46%		16%	46%		
% (n)	(15/30)	(7/10)	0.17	(3/19)	(17/37)	<0.04	(16/49)	(24/47)	<0.02	

Individual data points were extracted from qualifying studies, and analyzed to identify differences between delayed nerve reconstruction or free functional muscle transfer. (BPP = brachial plexus palsy; MRC = Medical Research Council)

#93 Molecular Basis for the Utilization of a Novel Anti-fibrotic Agent to Minimize Perineural Fibrosis Following Nerve Repair

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Introduction:

Neural scar formation constitutes a major barrier to peripheral nerve regeneration following repair or injury. Extra-neural scarring occurs through myofibroblastic collagen deposition that leads to fibrosis. These adhesions compromise nerve gliding and result in poor function. In contrast, intra-neural scarring results in diversion or blockade of regenerating axons. The goals of this study were to evaluate the pathophysiology of neural fibrosis.

Methodology:

We utilized 4 White New Zealand rabbits to create a peripheral nerve injury model. Crush and 50% partial transection injuries were performed to replicate Seddon Grade 2 and 3 nerve injuries.

In Phase 1 of the study, we histologically compared the partially transected and crushed nerves two week time intervals and evaluated changes in the healing nerve. We measured the extent of fibrosis by analyzing the expression of Heat Shock Protein (HSP) 47, a collagen-specific chaperone and alpha smooth muscle actin. The percent positivity of HSP47 was calculated in regions of interest.

Results:

Fibrotic tissue was heterogeneously concentrated in the epineurium and at the site of injury in the partial transection injury (Figure 1 B). Fibrotic tissue was concentrated homogeneously in the epineurium and endoneurium in the crush injury model (Figure 1 C). The epineurium of both the transection and crush nerve injury models yielded comparable positivity for HSP47 (Graph 1). There was a significant increase in HSP47-positive cells in the crushed nerve injury endoneurium compared to the transection nerve injury endoneurium distant to the site of injury ($p < 0.001$) (Graph 1). Finally, while aSMA-positive cells were clearly apparent in epineurium of cut and crushed nerves, this marker, except in pericytes, was absent in the endoneurium (Figure 2).

Conclusions:

Increased number of HSP47-positive cells suggests that a pro-fibrotic response in peripheral nerves includes activation of a mechanism that controls increased collagen production. The absence of aSMA-positive cells in endoneurium of injured nerves suggests an independent intra-neural fibrotic pathway that may exist outside the myofibroblastic cascade.

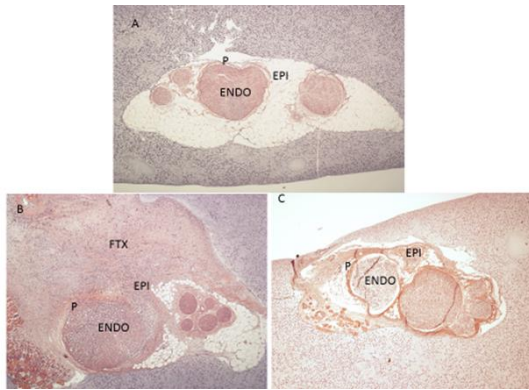


FIGURE 1:

A.) Uninjured nerve on Hematoxylin and Eosin Stain (H&E) **B.)** 50% Partial Transection Injury at 2 weeks on H&E **C.)** Crush injury at 2 weeks on H&E

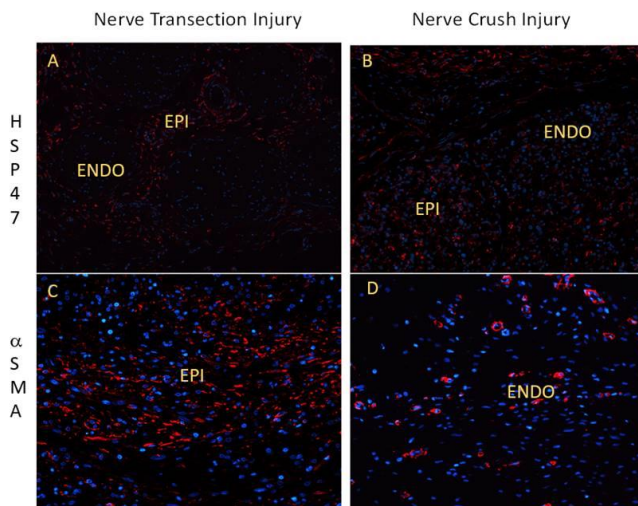
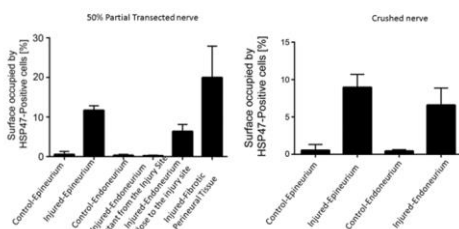


Figure 2:

A.) Transection injury at 2 weeks staining for HSP47 **B.)** Crush injury at 2 weeks staining for HSP47 **C.)** Transection Injury at 2 weeks staining for alpha SMA **D.)** Crush Injury at 2 weeks staining alpha SMA

LEGEND: ENDO (Endoneurium), EPI (Epineurium), P (Perineurium), FTX (Fibrotic Tissue)



#94 Outcomes of Digital Nerve Reconstruction Using Posterior Interosseous Nerve Autografts

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Introduction:

Nerve autografts are considered the “gold standard” for reconstructing digital nerve injuries with segmental loss, but are associated with donor site morbidity. The terminal branch of the posterior interosseous nerve (PIN) is easy to harvest, is usually of sufficient caliber for digital nerve reconstruction, and its harvest yields no known donor deficit. Despite this, the PIN is not routinely used as a source of autograft, and there is minimal outcome data in the literature.

Materials & Methods:

A retrospective review was conducted of all patients who underwent reconstruction of a digital nerve gap with a PIN autograft by a single surgeon between 2004 and 2014. Demographics, medical history, location and mechanism of injury, interval between injury and repair, concomitant injuries, gap length were recorded. Clinic and therapy charts were accessed to obtain sensory recovery data and identify complications. Recovery was graded according to the Medical Research Council Classification for sensory function, with meaningful recovery defined as \geq S3. Outcomes were compared to historical data for autograft reconstructions using other donor nerves.

Results:

37 digital nerve repairs in 34 subjects were included. In 5 additional patients the PIN was deemed of insufficient caliber. There were 28 males and 6 females (mean 35). Two patients gave a prior history of diabetes, and there were 13 smokers. The most commonly reported mechanisms of injury were saw injuries (n=10), glass lacerations (n=7), and knife injuries (n=5). The average gap length was 10.7 ± 3.1 mm (range 5-18 mm). Objective outcomes data were recorded for 22 patients at three months postop, and for 17 patients at 6 months. Recovery to the \geq S3 level was reported in 88% of repairs at 6 months. Mean s2PD was 10.1 ± 3.3 mm at 3 months, and 8.1 ± 2.7 mm at 6 months. Mean m2PD was 9.1 ± 3.9 mm at 3 months, and 7.8 ± 3.1 mm at 6 months. These data compared favorably to historical data for nerve autograft repairs, with reported levels of meaningful recovery of 60-88%. Two patients had delayed healing, and three patients had mild local cellulitis. No patient required reoperation or readmission.

Conclusions:

The caliber of the PIN varies, but it was sufficient for use in 87% of patients. The PIN is a suitable donor for digital nerve reconstruction in gaps up to 18 mm, and high rates of meaningful recovery can be achieved, without significant donor sensory loss.

#95 The "TouchSurgery" Surgical Simulation App: A Comparative Analysis of Efficacy Using a Carpal Tunnel Release Module

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INTRODUCTION:

The need and utilization for surgical simulation training in medical school and residency programs continue to grow. The "TouchSurgery" application is a new interactive virtual reality smartphone or tablet-based application that offers a step-by-step tutorial and simulation for the execution of various operations. The purpose of this study was to compare the efficacy and validity of the application versus traditional teaching modalities utilizing the "Carpal Tunnel Surgery" module.

METHODS:

A total 100 medical students were recruited to participate. The control group (n=50) consisted of medical students learning about carpal tunnel release surgery using the "traditional" medium consisting of a video lecture on powerpoint. The study group (n=50) consisted of students learning the procedure through the application. Each group was blinded to the other. The content covered was identical in both groups but delivered through the different mediums. Outcome measures included comparison of standardized test scores and overall application satisfaction.

RESULTS:

The study group using the "TouchSurgery" application significantly outperformed the control group with the given assessment by 14.2%. The average grade on the assessment for the application study group was 89.3 % with a Stdev of 6.05%. The average grade for the control group was 75.6% with a Stdev of 8.71%. A Two-tailed T-test was conducted and demonstrated that the difference was statistically significant ($p < 0.001$). The students rated the overall quality of the application including content validity, quality of graphics, and ease of use as (Median: 5, Mean 4.81 ± 0.38), Usefulness for surgical training (Median: 5, Mean: 4.74 ± 0.41), Willingness to use the app to learn more procedures (Median: 5, Mean: 4.83 ± 0.33), and willingness to add this application as a part of their training curriculum (Median: 5, Mean: 4.85 ± 0.35).

CONCLUSION:

The results of the study demonstrated that the use of the "TouchSurgery" application was superior than the traditional teaching methods for preparing medical students about the steps of a carpal tunnel release surgery. With regards to secondary objective regarding content validity, usefulness, and willingness to include this simulation as a part of the surgical education curriculum, students strongly agreed in the study group that this should be implemented within the curriculum and preferred to use it to learn other surgical procedures. The study findings lend support for the use of the application for medical students to prepare for and learn the steps for various surgical procedures.

#96 Epineural Sheath Jacket Prevents Neuroma Formation in the Rat Sciatic Nerve Model

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Background:

Recent data of modern war conflicts, natural disasters and traffic accidents show an increase in the number of patients suffering from severe peripheral nerve injuries. Persistent stump pain is reported in 74% limb amputees. Furthermore, it is estimated that up to 25% of patients after limb amputation develop painful end-bulb neuromas. This study investigates the efficacy of epineural sheath jacket (ESJ) as a novel technique to prevent neuroma formation in the rat sciatic nerve model.

Methods:

Eighteen Lewis rats were divided into three experimental groups (n=6): Group I– 20mm sciatic nerve segment was resected and proximal nerve stump was left without protection (positive control), Group II- nerve stump was buried into the adjacent muscle (standard for neuroma management), Group III- nerve stump protected by ESJ. The ESJ was created from the resected 20mm segment of sciatic nerve by removal of the fascicles and ligation of its distal end. Next, the ESJ was applied over the proximal sciatic nerve stump as a cap. The presence of neuropathic pain was assessed weekly up to 24 weeks post-surgery by autotomy, pinprick test and Tinel sign. At 24 weeks end-point, macroscopic evaluation, histomorphometry and neural/connective tissue ratio (N/C) were assessed. Retrograde labeling (RNL) of sensory neurons was used to evaluate Dorsal Root Ganglions (DRGs) viability.

Results:

ESJ application significantly reduced neuroma formation, which was associated with decreased autotomy (16.7%, $p < 0.05$) and Tinel sign (16.7%, $p < 0.05$) compared to the nerve stump control. Moreover, ESJ reduced axonal sprouting, bulb–shape nerve ending formation and perineural adhesions as confirmed by macroscopic evaluation. Histological staining showed that nerve stumps protected by ESJ were less fibrotic and presented well-organized axonal architecture and lower number of inflammatory cells. N/C ratio and RNL analysis revealed significantly better results in the ESJ group compared to the stump group ($p = 0.032$ and $p = 0.042$, respectively).

Conclusion:

The protective effect of ESJ against neuroma formation was confirmed by behavioral and histological analysis showing outcomes comparable to the muscle burying – the standard for neuroma management. ESJ inhibits neuroma development by creating a physical barrier for nerve fascicle outgrowth and limits inflammation, fibrosis and scar tissue formation around the nerve stump. The surgical technique for ESJ creation is straightforward and can be easily transferred to the clinic by applying the same principles of ESJ creation from human cadaver donor nerves. ESJ may become an off-the-shelf product, readily available for both the civilian and military patients.

#97 Fibrin Glue Increases the Tensile Strength of Conduit-Assisted Primary Digital Nerve Repair

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Purpose

Evaluate the tensile strength of conduit-assisted primary digital nerve repairs with varying suture number and location with and without fibrin glue.

Methods

Ninety cadaveric digital nerves were harvested and divided equally into the following repair groups: A (4/4), B (2/2), C (0/2), D (0/1), E (0/0) with the first number referring to the number of sutures at the coaptation and the second number referring to the number at each proximal and distal end of the nerve-conduit junction. Fibrin glue (Tisseel, Baxter, Deerfield, IL) was added to half of each group. The nerve specimens were transected and then repaired with 8-0 nylon suture and conduit (AxoGuard Nerve Protector, Axogen, Alchua, FL). The tensile strength of the repairs was tested at a rate of 0.33 mm/s and maximum failure load was determined. The results were analyzed with a two-way and one-way ANOVA (Minitab 17, Minitab Inc., State College, PA). Tukey's Post Hoc Test with a 95% confidence interval compared repair groups if the two-way ANOVA showed a significant difference between the groups.

Results

Both suture group and glue presence significantly affected the maximum failure load. Increasing the number of sutures increased the maximum failure load and the presence of fibrin glue also increased the failure load. Groups B' and B were not statistically different from Group A, the second strongest repair, but contains half the suture (6 vs 12).

Conclusion

This is the first study to demonstrate that fibrin glue is of any benefit to increase the tensile strength of conduit-assisted primary digital nerve repair. Also, strength of the repairs can be maintained despite less suture, which may be most important at the primary coaptation to improve nerve regeneration.

#98 In Vivo Tracking Of Amniotic Fluid Derived Stem Cells on Acellular Nerve Graft

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Introduction:

Traumatic transections of peripheral nerves are associated with poor nerve regeneration. The use of nerve grafts with stem cells provides an alternative to autograft for nerve repair. The purpose of this study was to track the fate of amniotic fluid derived stem (AFS) cells that are seeded into nerve allografts and to elucidate the mechanism of their impact on the regenerating nerve.

Methods:

AFS cells were labeled using supraparamagnetic micron sized iron oxide (MPIO) coated with fluorescent dye. Labeled cells were plated and viability was assessed. Next, cells were cultured in neurogenic induction media; the conditioned media was collected to evaluate the neurogenic growth factors. Differentiated cells were confirmed with real-time PCR for neurogenic lineage markers. Viable MPIO labeled AFS cells were injected into an acellular nerve allograft (ANA) used to repair a 1.5 cm sciatic nerve defect in 10 rats. Labeled AFS cells were evaluated by MRI at 1, 2, and 4 weeks post-surgery. Intensity of the MPIO regions was quantified using ImageJ. Contiguous frozen sections were stained for iron to identify the labeled AFS cells incorporated into the nerve graft. Co-localization of transplanted cells was confirmed using human specific nuclear antibody (Anti-NuMA).

Results:

Labeled AFS cells were viable *in vitro* (Figure 1). Proliferation rate and morphology between the control and labeled cells demonstrated no significant differences ($p=0.58$). Cells differentiated towards Schwann-like cells after being cultured in neurogenic induction media. NGF and NEFL gene expression were elevated by fold change of 202.60 ± 1.89 and 30.62 ± 1.99 , respectively ($p < 0.005$) compared to control. Cytokine quantification analysis of AFS cells showed significantly increased BDNF, β -NGF, β -FGF, GDNF, NGF R, NT-4 and TGF- β production. (Fold change compared to undifferentiated control: 10.25 ± 1.96 , 383.06 ± 12.93 , 3.95 ± 1.06 , 5.78 ± 1.33 , 46.84 ± 3.67 , 2.69 ± 0.77 , 25.39 ± 3.74 , $p < 0.001$ respectively). 7T MRI demonstrated MPIO labeling with a strong decrease in signal, appearing as fuzzy dark spots in T2-weighted images at 4 weeks post-surgery. There was no significant difference in average normalized hypointense region volume between 2 and 4 weeks post-injury (0.47 ± 0.06 and 0.52 ± 0.12 , respectively, Figure 2). Cell integration was confirmed by iron and Anti-NuMA staining.

Conclusions:

AFS cells remained viable after labeling and can be used to augment nerve repair by seeding onto ANAs. Cytokine analysis suggests a paracrine-mediated effect on nerve repair. MRI can effectively track the AFS cells longitudinally in the rat model, demonstrating the potential to monitor AFS cell delivery strategies for nerve regeneration.

#99 Comparison Between Two Collagen Nerve Conduits and Nerve Autograft for Motor Nerve Regeneration in a Rat Model

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Introduction:

Current synthetic conduits fail to provide equivalent motor recovery compared to autologous nerve repairs of peripheral nerve injuries. Autograft repairs are additionally associated with donor site morbidity and are limited by tissue availability. A synthetic conduit that enables equivalent motor recovery would thus provide an ideal graft alternative. A novel polyglycolic acid conduit (Nerbridge, Toyobo Co., Ltd., Osaka, Japan), uniquely contains collagen fibers within the tube to provide support and guidance for regenerating peripheral nerves through the transected site. We hypothesized that this collagen-filled conduit would generate motor recovery equivalent to that of autograft, and superior to a hollow collagen conduit (NeuraGen *nerve guide*, Integra, Plainsboro, NJ) as a result of its internal scaffold.

Methods:

72 Lewis rats were randomized into 3 experimental groups, in which a unilateral 10-mm sciatic defect was repaired using nerve autograft, collagen-filled conduit, or hollow collagen conduit. Outcomes were measured at twelve and sixteen weeks postoperatively, and included bilateral tibialis anterior muscle weight, voltage and force maximal contractility, assessment of ankle contracture, and nerve histology. Results were expressed as a percentage of recovery from the contralateral side. Kruskal-Wallis analysis was utilized with an alpha level of $p < 0.05$ to determine significance, and post-hoc Bonferroni-correction was used for multiple comparisons.

Results:

At twelve weeks, mean muscle force compared to that of the contralateral control side was 50% ± 21 for autograft, 9% ± 6 for the collagen filled conduit, and 32% ± 21 for the hollow collagen conduit. After sixteen weeks, the mean muscle force was 72.4% ± 22.5 for autograft, 58.0% ± 19.3 for collagen-filled conduit, and 61.1% ± 24.8 for collagen hollow conduit. Autograft was statistically superior to both conduits for all outcomes except histology (Fig 1). The conduits demonstrated equivalence to each other across outcomes. Although all three groups experienced improved outcomes from twelve to sixteen weeks, the collagen filled conduit demonstrated the greatest rate of recovery in axonal density over this period.

Conclusion:

Autograft repair provided superior motor recovery than the use of two distinct collagen conduits for a 10-mm nerve gap in a rat model. Nevertheless, the collagen filled conduit demonstrated encouraging improvement in muscle force and axon density between 3 and 4 months postoperatively, highlighting its utility in spanning nerve gaps, particularly when autograft is unavailable.

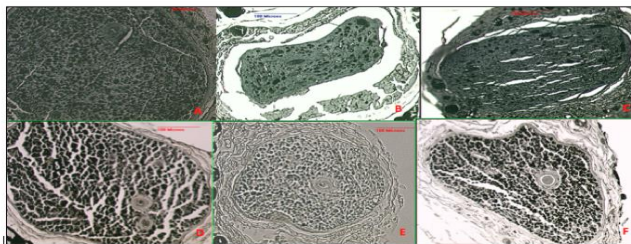


Fig 1. Transverse sections of rat tibial nerve (100 microns): autograft group (A), collagen-filled conduit group (B), and hollow collagen conduit group (C) at 12 weeks. Autograft group (D), collagen-filled conduit group (E), and hollow collagen conduit group (F) at 16 weeks.

#100 Study of Nerve Regeneration in Peripheral Nerve of Spontaneously Hypertensive Rats (SHR) Using Nerve Graft Covered with Vein Tube and Enriched with Platelet Rich Fibrin (PRF)

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Introduction:

The treatment of peripheral nerve injuries has quite varied results. The search for new treatment methods allowed the knowledge of Platelet Rich Fibrin (PRF) and vein tubes, which release growth factors with potential for tissue regeneration. This study aims to determine if the addition of an adjuvant (vein tube with or without PRF) improve nerve regeneration rate, measured by functional score and histomorphometric analysis.

Methods:

We used SHR rats divided into 4 groups: nerve graft covered with vein (NGCV) (n = 10); nerve graft covered with vein filled with PRF (NGCVP) (n = 10); nerve graft (NG) (n = 10) and the SHAM control group (n = 10). The repair results of sciatic nerve damage through nerve grafts, nerve grafts enriched vein tubes with or without PFR obtained from centrifugation of blood were evaluated by sciatic functional index (SFI) at 0, 30 60 and 90 days, morphological and morphometric analysis of nerve distal to the lesion, and quantitative histological analysis of neurons labeled by the dye-Fluoro Gold® the anterior horn of the spinal cord.

Results:

The graft groups covered with vein (NGCV) and graft covered with vein filled with PRF (NGCVP) had lower SFI values than the control group (SHAM) throughout the study period. The NGCV group showed improvement in the sciatic functional index at day 90, a statistically significant when compared to the nerve graft group (NG). The diameter of the fiber and the axon of NGCV and NGCVP groups were similar to each other, and were lower statistically significant, the SHAM and NG groups.

Conclusion:

All experimental groups obtained parameters decreased in relation to statistically significant SHAM. Functional improvement of the sciatic functional index at day 90, in NGCV group compared to NG, can be explained due to factors released by vein or vein itself as a conduit to reorient axonal. Further studies are needed to evaluate the role of adjuncts to nerve graft in repair of peripheral nerve injuries

101. Anatomic and Histologic Evaluation of Brachialis to Anterior Interosseous Nerve Transfer

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Introduction: Brachialis to anterior interosseous nerve (AIN) transfer offers patients improved hand function with the ability to pinch. The AIN fascicle has previously been described topographically within the postero-medial region of the median nerve. We present a new description of the AIN fascicle based on anatomic terms seen intra-operatively to improve fascicular identification. We hypothesize that this nerve transfer can be performed with reliable anatomy, tension free neurorrhaphy, and appropriate donor-to-recipient axon count ratio.

Methods: Six cadaveric specimens were dissected. The median and musculocutaneous nerves were identified in the mid upper arm. The epineurium overlying the median nerve was incised to expose three fascicles (Figure 1). The fascicle location was described in anatomic terms seen intra-operatively with the arm in the abducted position (ventral, dorsal, cranial, and caudal)(Figure 2). The dorso-caudal fascicle was marked. The AIN was then identified in the proximal forearm as it branched from the median nerve and dissected proximally to confirm that the initial prediction of the AIN fascicle was correct. The AIN branching pattern, length, and fascicle location were recorded. All distances were measured from the medial epicondyle (ME). Brachialis branching pattern and length were also measured from the ME. The brachialis nerve was transferred to the AIN and overlap was measured. Each nerve was then sectioned and sent to histology lab for axon counts.

Results: The AIN fascicle was correctly predicted in all six specimens and was identified in the dorso-caudal portion of the median nerve. The AIN exited the median nerve 6.9 cm (SD 1.04) distal to the ME. Total neurolysable distance of the AIN was 13.9 cm (SD 1.46) proximal to the ME. The brachialis nerve branched from the musculocutaneous nerve 14.7 cm (SD 1.15) proximal to the ME. Length of brachialis nerve prior to branching was 5.2 cm (SD 1.15). Total neurolysable distance of the brachialis was 5.1 cm (SD 1.31). All nerve anastomoses overlapped by average of 1.8 cm (SD 0.49). AIN axon counts averaged 2661.2 while brachialis axon counts averaged 1452.5 (donor-to-recipient ratio 1:1.8).

Conclusions: Identifying the AIN fascicle in the median nerve is predictable based on topographic mappings of the median nerve. Describing the AIN fascicle as dorso-caudal, instead of previously described postero-medial, helps identify AIN fascicle with arm in abducted surgical position. Brachialis to AIN transfer is a tension free transfer with appropriate axon count ratio.

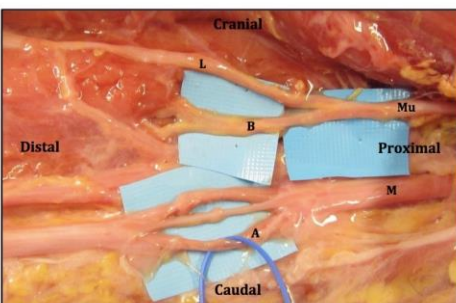


Figure 1 – L: Lateral antebrachial cutaneous nerve; B: Brachialis nerve; Mu: Musculocutaneous nerve; M: Median nerve; A: AIN fascicle.

102. Bionic Hand Reconstruction Successfully Reduces Deafferentation Pain in Patients with Brachial Plexus Avulsion Injury

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Medical University of Vienna, Vienna, Austria

Introduction: Root avulsions of the brachial plexus represent one of the most severe nerve injuries. Next to apparent sensorimotor deficits, the avulsion injury often leads to unbearable pain in the arm and hand, frequently referred to as deafferentation pain. In avulsion injuries of the inferior trunk the burden of pain is most intense and hand function that can be expected by reconstructive surgery (intra-/extraplexual nerve transfers) is less than poor. Here, we report of seven patients with global brachial plexopathies with multiple root avulsions, who have approached our specialist center of extremity reconstruction in the years of 2011 to 2016. The impact of bionic hand reconstruction on hand function, deafferentation pain and quality of life is presented.

Materials & Methods: In all seven patients selective nerve transfers (and muscle transfers in selected cases) were performed but in some did not avail sufficient hand function. However, thereby generated electromyographic signals could be used for the control of a prosthetic device. After intense rehabilitative training and consequent intuitive signal control, the functionless hand was electively amputated and replaced by a prosthetic hand, a procedure now defined as "bionic reconstruction". Pain was assessed with the Visual Analogue Scale (VAS). Additionally pre- and post-interventional pain medication was documented and quality of life as well as general health were assessed on a regular basis (Health Survey SF-36). Patients were evaluated pre-interventionally, during the rehabilitative process and after amputation as well as after final prosthetic fitting.

Results: Bionic hand reconstruction led to significant pain reduction compared against pre-interventional pain conditions. Pain medication intake could be reduced in all patients after the prosthetic hand had been incorporated into the user's activities of daily living. Quality of life, subjectively perceived health state, and psychological role functioning also improved significantly.

Conclusion: The functional and cognitive re-integration of the extremity into the patient's body image led to major pain relief as well as markedly improved quality of life in all so far treated patients. In some patients even a re-entry into working life was permitted by the functional gain of the prosthetic hand, which also came along with social and economic benefits.

103. Use of Processed Nerve Allografts to Repair Nerve Gap Injuries Greater than 25mm in the Hand

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Introduction: Recent research has shown that processed nerve allografts (PNA) have improved clinical results compared to hollow conduits for reconstruction of digital nerve gaps less than 25 mm. However, the utility of PNAs as a nerve autograft alternative in injuries involving longer gaps warrants further clinical investigation. Long nerve gaps have been traditionally hard to study due to low incidence. We queried a large national registry to examine the efficacy of PNA in the reconstruction of long gaps.

Materials & Methods: The RANGER registry is an IRB approved, active database for PNA (Avance® Nerve Graft, AxoGen, Inc). The database was queried for digital nerve repairs ≥ 25 mm. Demographics, injury, treatment, and functional outcomes were recorded on standardized forms. Patients younger than 18, and those lacking quantitative follow-up data were excluded. Recovery was graded according to the Medical Research Council Classification (MRCC) for sensory function, with meaningful recovery defined as \geq S3. Outcomes were compared to historical data for nerve autograft reconstructions.

Results: Fifty digital nerve injuries in 28 subjects were included. There were 22 males and 6 females, and the mean age was 45. Three patients gave a prior history of diabetes, and there were six active smokers. The most commonly reported mechanisms of injury were saw injuries (n=13), crushing injuries (n=9), resection of neuroma (n=9), amputation/avulsions (n=8), sharp lacerations (n=7), and blast/gunshots (n=4). The average gap length was 35 ± 8 mm (range 25-50 mm). Recovery to the S3 or greater level was reported in 86% of repairs. Static two point discrimination (s2PD) and Semmes-Weinstein monofilament (SMF) were the most common completed assessments. Mean s2PD in 24 repairs reporting 2PD data was 9 ± 4 mm. For the 38 repairs with SWF data, protective sensation was reported in 33 repairs, deep pressure in 2, and no recovery in 3. These data compared favorably to historical data for nerve autograft repairs, with reported levels of meaningful recovery of 60-88%. There were no reported adverse effects.

Conclusions: Processed nerve allograft can be used to reconstruct long gap nerve defects in the hand with consistently high rates of meaningful recovery. Results for PNA repairs of digital nerve injuries with gaps longer than 25 mm compare favorably to historical reports for nerve autograft repair, but without donor site morbidity.

104. Anterior Subcutaneous Transposition for persistent Ulnar Neuropathy after Neurolysis

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Introduction: The standard for surgical treatment of ulnar neuropathy at the elbow is neurolysis. Success rates of this procedure vary between 75 and 90%. Little is known about optimal treatment if neurolysis fails. Anterior subcutaneous transposition is than one of the treatment options.

Materials & Methods: A consecutive series of 26 patients treated by a single surgeon between 2009-2014 was retrospectively analysed. All patients had anterior subcutaneous transposition to treat persistent ulnaropathy after neurolysis. Pre- and postoperative differences in three clinical modalities were compared: pain and tingling, weakness and numbness. A 6-point satisfaction score was obtained using a telephonic systematic survey.

Results: At presentation, 88% of patients experienced pain and tingling, 46% had weakness and 50% had numbness of the forth and fifth finger. The mean age was 55 years (range 28-79). The mean duration of complaints until transposition was 32 months (range 4-49) with a mean interval of 12 months between the two surgeries. After transposition, pain and tingling improved in 35%, motor function in 23% and sensory disturbances in 19% of all patients. Improvement in at least one of the three clinical modalities was found in 58% of patients of which two symptoms improved in 15%. However, a deterioration in one of the three modalities was noted in 46% of patients. On the patient satisfaction scale, 61% reported good or excellent outcome. Patient satisfaction was correlated with pain (Pearson correlation coefficient 0.62), more than weakness (0.40) or numbness (0.22). Patients with good/excellent outcome were on average 10.3 years younger than patients with a poor outcome. No other factors were significantly related to satisfaction score.

Conclusions: Symptoms that persist after neurolysis employed to treat sulcus ulnaropathy are difficult to treat. Subcutaneous transposition is a viable surgical option. The majority of patient is satisfied after this second surgery, however, only part of the initial symptoms resolve. In some patients, symptoms even deteriorate. The reason why some patients do not fair well remains unknown. The total outcome of treatment of all patients that present with ulnar neuropathy can still be improved. Patient selection, timing of intervention and choice of surgical technique need to be considered.

105. The Dorsal Cutaneous Branch of the Ulnar Nerve as a Donor for Median Nerve Sensory Reconstruction: A Cadaveric Study

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Introduction: Hand sensibility is extremely important but most difficult to achieve in upper extremity reconstruction. Loss of median nerve (MN) distribution sensation disables hand function after upper brachial plexus injury and failed MN repair. Motor fascicular and/or tendon transfers are commonly used strategies for motor restoration. However, options for sensory reconstruction are limited. The common digital nerve (CDN) to ring and small of the ulnar nerve may be used for first web space sensory restoration, but it further sacrifices ring and small finger sensation. The current study describes anatomical considerations and feasibility of transferring the dorsal cutaneous branch of ulnar nerve (DCBUN) to the MN for sensory restoration. We hypothesize the DCBUN is a feasible donor nerve and provides more than one branch for transfer without sacrificing existing volar sensation.

Methods & Methods: Seven fresh cadaveric upper limb specimens were used for this study. The DCBUN was identified proximally and dissected distally identifying and preserving all branches. The MN was dissected within the carpal tunnel; CDNs were identified. The DCBUN was isolated from the ulnar nerve proximally. Nerve transfer was performed after transecting the branches of the DCBUN distally. The DCBUN was transferred volar for coaptation with the MN CDNs. The branching point, length, isolation point, and transfer length were measured utilizing the wrist crease as a reference point. Samples of each branch from the MN and DCBUN were analyzed histologically.

Results: The DCBUN had 2-4 branches. The longest branch consistently innervated the dorsal 4th web space (7.6 ± 0.82 cm). The 2nd, 3rd, and 4th longest had lengths of 4.7 ± 2.01 , 3.8 ± 3.89 , and 2.7 ± 1.19 cm, respectively. After transfer to the palm, the DCBUN branch lengths were 7.9 ± 0.90 , 6.2 ± 1.33 , 5.1 ± 3.71 , and 2.4 ± 1.28 cm distal to the wrist crease, respectively. The DCBUN could be isolated from the ulnar nerve proper 10.5 ± 2.7 cm and 17.8 ± 5.45 cm proximal to the wrist crease before and after internal neurolysis, respectively. On histology, the MN CDNs and DCBUN branches had mean nerve surface areas of 1.44 ± 1.14 and 0.40 ± 0.34 mm², respectively, and mean axon counts of 10.4 ± 4.57 and 4.05 ± 2.48 , respectively.

Conclusion: The DCBUN reliably provides 2 or more branches suitable for transfer to the MN CDNs. It has the potential to reconstruct all 3 CDNs of the MN without sacrificing function of the 4th CDN.

106. Does Partial Muscle Reinnervation Preserve Future Reinnervation Potential?

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Virginia Commonwealth University, Richmond, VA

Introduction: Inadequate recovery following nerve injury or repair offers a difficult treatment dilemma. Partial innervation may have a “baby sitting” or muscle preservation effect. Alternatively, partial reinnervation may only protect a limited percentage of muscle fibers and once a critical time period has passed, revision nerve repair may not improve final motor recovery. Therefore, our purpose was to evaluate final muscle recovery following partial denervation and with and without delayed repair.

Materials & Methods: Sixty (three months old) Sprague-Dawley rats underwent the following tibial nerve manipulations (n=15/group): Group A (partial denervation of tibial nerve - 2/3rds of nerve resected and remaining 1/3rd crushed; revision repair after 8 months with 1cm autograft, and testing at 11 months), Group B (partial denervation and testing at 11 months), Group C (full denervation and immediate reconstruction with 1cm autograft followed by testing at 11 months), Group D (full denervation, delayed reconstruction with 1cm autograft at 8 months, and testing at 11 months). Final testing included functional and morphological assessment.

Results: Muscle weight was significantly ($p < 0.01$) different between all groups (from highest to lowest: B > C > A > D), with the delayed reconstruction groups (A and D) having the lowest weights. Group A and Group D also had significantly smaller muscle areas than Groups B and C ($p < 0.05$). Group A and Group D were not significantly different in muscle area when compared to each other. Developed muscle force were not different between groups ($p > 0.05$).

Conclusions: Partial reinnervation with subsequent delayed reconstruction did not preserve muscle over a long period of denervation compared to partial denervation without repair or full denervation with immediate repair. However, partial reinnervation over a prolonged period in a rat model did result in increased muscle size when compared to delayed repair without partial reinnervation.

AAHS #1 Simple Assessment of Global Bone Density and Osteoporosis Screening Utilizing Standard Radiographs of the Hand

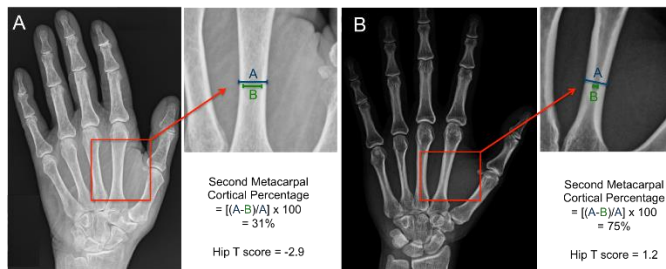
Joseph J. Schreiber, MD; Robin N Kamal, MD; Jeffrey Yao, MD
Stanford University Medical Center, Redwood City, CA

Background:

Osteoporosis and resultant fragility fractures have vast consequences at both the individual level and to the overall health care system. Screening rates remain low, and our current system tends to be more reactive than preventative. While dual-energy x-ray absorptiometry (DXA) is the gold standard for assessing bone mineral density (BMD), other simpler tools may be able to provisionally screen bone quality and signal the need for intervention. We hypothesized that the second metacarpal cortical percentage (2MCP) that is calculated from standard radiographs of the hand or wrist would correlate with hip BMD derived from DXA, and could provide a novel simple screening tool for osteoporosis.

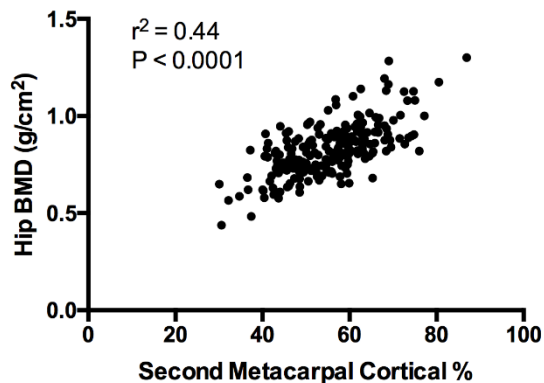
Methods:

200 consecutive patients who had hand or wrist radiographs and hip DXA scans within one year of another were included in this retrospective diagnostic series. Mid-diaphyseal 2MCP was calculated as a ratio of the cortical diameter to the total diameter (Figure 1). The correlation between 2MCP and total hip BMD was assessed. Subjects were stratified into normal, osteopenic, and osteoporotic cohorts based on hip t-scores, and thresholds were identified to optimize screening sensitivity and specificity.



Results:

Second metacarpal cortical percentage (2MCP) correlated significantly with BMD and t-scores from the hip (Figure 2, $r^2 = 0.44$, $P < 0.001$). A 2MCP threshold of $< 60\%$ optimized sensitivity (88%) and specificity (60%) for discerning osteopenic subjects from normal subjects, whereas a threshold of $< 50\%$ optimized sensitivity (100%) and specificity (91%) for differentiating osteoporotic from normal subjects.



Conclusions:

By demonstrating that global BMD may be assessed from 2MCP, our data suggests that radiographs of the hand and wrist can play a roll in accurately screening for osteopenia and osteoporosis. This simple screening tool that is already ubiquitously utilized for patients with hand or wrist problems may help identify patients at risk for fragility fractures. This would thereby prompt additional studies, appropriate referral, or initiation of treatment. Routine use could be valuable for decreasing morbidity on an individual level and improving financial efficiency on a systems level.

AAHS #2 Are Opioids Necessary to Manage Post-Operative Pain after Carpal Tunnel Release? A Prospective Cohort Evaluation

Andrew Miller, MD; Asif Ilyas, MD; Jonas Matzon, MD
Thomas Jefferson University Hospital, Philadelphia, PA

INTRODUCTION:

Managing postoperative pain in hand surgery is important for both patients and surgeons. However, there is growing concern over prescription opioid abuse. We hypothesized (1) that pain medications after carpal tunnel release (CTR) surgery are over-prescribed and (2) that opioids are unnecessary in the majority of patients.

METHODS:

We prospectively studied two demographically similar patient cohorts receiving either opioid or tramadol for CTR performed by two hand surgery fellowship-trained orthopaedic surgeons over a 1 year period. The first cohort of patients undergoing CTR received opioid pills postoperatively. The second cohort of patients received a standard prescription of 10 tramadol pills postoperatively. Student t-tests were performed to evaluate statistically significant differences between the tramadol and opioid cohorts in total pill consumption and number of postoperative days the medication was used.

RESULTS:

The opioid cohort consisted of 159 patients with a mean opioid consumption of 4.9 pills for 2.3 days. Eleven of these patients declined the use of opioids postoperatively and instead substituted for NSAIDs and/or acetaminophen. The tramadol cohort consisted of 110 patients with a mean tramadol consumption of 3.3 pills for 1.8 days. Seven of these patients requested opioids postoperatively, and 14 substituted for NSAIDs and/or acetaminophen. When comparing the postoperative consumption of opioids and tramadol for CTR, there was a statistically significant difference in total pill consumption based on both intention to treat as well as the medication ultimately prescribed. There was no difference in the duration of postoperative utilization.

CONCLUSION:

Following CTR, pain medications are being over-prescribed, with patients receiving more than double the amount of pills than they consume. Tramadol appears to be equally effective in managing post-operative pain compared to opioids. Based on our findings, we recommend prescribing less than 10 pills of either tramadol or an opioid to manage post-operative pain after primary CTR.

ASPN #1 The DNND (Diabetic Neuropathy Nerve Decompression) Study: A Controlled Randomized Double Blinded Prospective Study on The Effect Lower Extremity Nerve Decompression on Pain and Quality of Life in Patients with Painful Diabetic Neuropathy

Shai Michael Rozen, MD¹; Gil Wolfe, MD²; Philip Raskin, MD¹; Steven Vernino, MD¹; Geetha Pandian, MD¹; Kathleen Wyne, MD³; Shiv Sharma, MD¹; Joan Reisch, PhD¹; Linda Hynan, PhD¹; Rita Fulmer, RN¹; Annamaria Salvadore, BS¹

¹University of Texas Southwestern Medical Center, Dallas, TX, ²University of Buffalo, Buffalo, NY, ³The Ohio State University Wexner Medical Center, Columbus, OH

Purpose:

An estimated fifty-percent of 74.8 million pre-and diabetic patients in the USA suffer from Painful Diabetic Neuropathy (PDN), of which approximately one-third are prone to nerve compression. Previous studies suggest surgical decompression alleviates pain, however the American Neurological Association considers available evidence level U (Unproven). We present a seven-year NIH and institutionally funded, prospective, controlled, randomized double-blinded study to determine the long-term effect of nerve decompression in patients with PDN on pain and quality of life.

Methods:

A multidisciplinary neurology, endocrinology, PM&R, pain, and surgery group performed baseline pain examinations (Likert 0-10, Neuropathy-scores) and SF-36 quality of life exams. Patients were randomized into surgical and non-surgical-control groups (2:1 ratio, respectively). Surgical patients underwent surgery bilaterally with each side randomized to nerve decompression or sham surgery. Patient and final evaluators were blinded to side. Quarterly, final one-year, and four-year evaluations were performed. A 2 way repeated measures ANOVA statistical analysis on pain was performed on all groups at one year and 54.5 month follow-up.

Results:

Of 2987-screened patients, 138 enrolled: 92 randomized to surgery and 46 as controls. 40 surgical and 27 controls completed the study. At one year the surgical group experienced a mean pain reduction of 5.70 in the surgical leg (SD=2.54;p<0.0001) and 5.25 (SD=2.79;p<0.0001) in the sham leg while the control group had no statistically significant reduction of pain. A 54.5-month follow-up of 36 surgical patients revealed a mean pain reduction of 7.47 in the surgical leg (SD=2.09;p<0.0001) and 5.97 (SD=2.43;p<0.0001) in the sham leg, while the control group revealed no reduction in pain. The SF-36 General Health component score revealed a significant interaction for group by time, p=.0010; while group means at baseline, 3mo, and 6months (p=0.53, 0.24, and 0.10, respectively) were not significantly different, means at 9 months and 1 year were significant (p=0.01 and 0.02, respectively).

Conclusion:

Surgical decompression in patients with PDN unequivocally reduces bilateral pain with statistical significance at one year and continued bilateral improvement at four years, yet demonstrates more statistically significant pain reduction in the decompressed side at four years. In addition, quality of life is significantly improved at 1-year follow up.

ASPN #2 Macaques Implanted with Regenerative Peripheral Nerve Interfaces (RPNIs) Control Prosthesis Finger Movements

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INTRODUCTION: Regenerative Peripheral Nerve Interfaces (RPNIs) are promising for interfacing human intentions to myoelectric prostheses. Rat studies led to proof of RPNI long-term function and high signal to noise ratio with no adverse biological effects. However, true voluntary fine control of fingers and hand prostheses would be more convincing with macaque implanted RPNIs.

METHODS: Two macaques had Regenerative Peripheral Nerve Interfaces (RPNIs) implanted (n=3/macaque) in the forearm. The RPNI consists of a free muscle graft implanted on the end of a transected nerve fascicle. Intramuscular EMG electrodes were implanted in each RPNI. Macaques were trained to perform index finger movements to acquire virtual targets on a computer screen. Finger position was recorded via a flex sensor on the index finger.

RESULTS: At harvest RPNIs were well vascularized but smaller in size than when implanted (Fig 1). For the continuous EMG decode using 10-fold cross-validation, the resulting predicted finger position had a correlation coefficient $\rho=0.82$ between predicted and true finger positions. The EMG decode correctly classified 97.7% of movements (out of 261 total movements). RPNI muscle fibers were continuing to regenerate after implantation for 1 year (Fig 2).

CONCLUSIONS: Macaques voluntarily controlled virtual finger movements with signals transferred through implanted RPNIs.

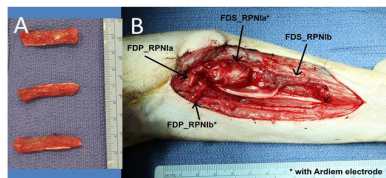


Figure 1. A, muscle cut for RPNI prior to RPNI implantation. B, RPNIs at post implantation of ~ 1 year.

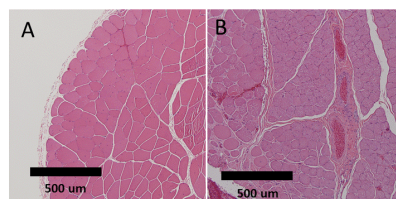


Figure 2. Cross sections of Macaque muscle stained with H&E. A, normal flexor digitorum superficialis muscle. B, RPNI with radial nerve branch that innervates the Extensor Digitorum Communis Muscle. Arrows indicate regenerating muscle fibers with central nuclei. RPNI muscle fibers are slightly smaller in diameter than normal muscle fibers.

ASPN #1 Outcomes from a Pilot Study on the Technical Feasibility of Robotic Assisted Laparoscopic Interpositioning of Processed Nerve Allograft for Reconstruction of the Neurovascular Bundle, with a Twenty-four Month Follow-up Term to Assess Efficacy

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Introduction: In the United States, prostate cancer is the most common form of cancer and the second-leading cause of cancer death in males. In a radical prostatectomy procedure the goal is to remove the prostate and often times surrounding tissues in order to attain a negative surgical margin. In high grade disease the cavernous neurovascular bundle surrounding the prostate may be damaged or removed resulting in loss of erectile function and urinary continence. Historical norms for potency following unilateral resection of the cavernous nerve without reconstruction range from 33-53%, with similar trends observed with incontinence. Reconstruction of these nerves may provide improvements in functional outcomes, however poses a surgical challenge due to a difficult field of view and location. Robot-assisted radical prostatectomy (RARP) has been accepted as the procedure of choice at many centers worldwide since its first introduction in 2000 and provides advancements that could overcome the challenges of reconstructing these nerves. This pilot study was conducted to explore the feasibility of robotic assisted reconstruction of the cavernous nerves using processed nerve allograft.

Methods: Twelve prostate cancer patients with normal pre-operative erectile and urinary function were enrolled to receive robot-assisted radical prostatectomy with unilateral cavernous nerve reconstruction using processed nerve graft. Patients were followed up to 24 months after surgery for erectile and urinary function recovery and any possible adverse event related to nerve graft implantation.

Results: RARP with unilateral cavernous nerve reconstruction was performed following standard procedure, with the steps to implant processed nerve graft incorporated immediately after complete resection of the prostate gland and affected adjacent tissue. All surgeries were successfully performed without any complication and adverse events. The implantation procedure extended operation time by 16 ± 4.3 minutes without significant increase of blood loss. Recovery of erectile function (IIEF-6 ≥ 13) was seen in 50% and 70% of patients 12 and 24 months after surgery respectively. Recovery of potency (erection firm enough for intercourse, IIEF ≥ 22) was achieved in 50% of patients 24 months after surgery. Urinary continence (0-1 pad used per day) was restored in 75%, 83.3% and 91.7% of patients by 6, 12 and 24 months after surgery respectively.

Conclusions: Cavernous nerve reconstruction using processed nerve graft during robot-assisted radical prostatectomy is technically feasible and shows promise of desirable functional outcomes. The preliminary efficacy data from this study could be useful in supporting the development of future randomized controlled trials.

ASPN #2 Perfusion to the Ulnar Nerve as Affected by Three Surgical Conditions: In Situ Decompression, Subcutaneous Transposition, and Submuscular Transposition: Preliminary Results

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Introduction: Currently, there is conflicting data that fails to support one surgical treatment for ulnar neuropathy at the elbow over other. One possible reason may be a lack of understanding of how these procedures change the perfusion to the ulnar nerve. Although many theories have been proposed, no studies have demonstrated how these procedures actually affect the perfusion to the ulnar nerve. The purpose of this study is to compare the perfusion of the ulnar nerve in vivo during different surgical conditions.

Materials and Methods: All patients who met criteria of being diagnosed with recalcitrant ulnar neuropathy failing nonoperative management were enrolled prospectively in this study during September 2015 to April 2016. Exclusion criterion was previous ulnar nerve surgery involving transposition. Using intraoperative fluorescence scanning angiography, the perfusion of the ulnar nerve in each patient was measured at four conditions: native nerve exposure, in situ decompression, subcutaneous transposition, and submuscular decompression. Perfusion measurements were taken in five locations on each nerve: 8 cm proximal to the medial epicondyle (Area 1); 4 cm proximal to medial epicondyle (Area 2); at medial epicondyle (Area 3); 4cm distal of medial epicondyle (Area 4); and 8cm distal to medial epicondyle (Area 5).

Results: 14 patients were enrolled which included 10 males and 4 females. 5 had diabetes and 4 were smokers. 3 patients had previous ulnar nerve decompression. 4 patients underwent concomitant surgery which included carpal tunnel release, radial head excision, and lateral epicondylar debridement. Overall, nerve perfusion increased 30% with in situ decompression. Perfusion, however, decreased 16% after subcutaneous transposition as compared to decompression with Areas 4 and 5 demonstrating the most substantial drops (12% and 15% respectively). With submuscular transposition, perfusion returned to decompression values, with Areas 2 and 4 demonstrating the most substantial improvements (10% and 8%, respectively).

Conclusions: All three surgical treatments evaluated improved ulnar nerve perfusion, but subcutaneous transposition did not allow as much perfusion as either in situ decompression or submuscular transposition. Given the segments of the nerve affected after subcutaneous transposition, it is possible that the nerve's contact against the adjacent muscle distal to the medial epicondyle may have caused excessive intraneural tension. In situ decompression appears to be a preferred choice for the purpose of maximizing the perfusion to the nerve. When transposition is indicated, however, submuscular may be preferred to subcutaneous, particularly in patients who may have predisposed compromised vascularity such as smokers or diabetics.

ASPN #3 InVivo Optical Microscopy to Investigate Revascularization and Regeneration Following Peripheral Nerve Repair

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Introduction. Re-establishment of blood supply to the injured nerve has been postulated as a necessary component to neural recovery. The process by which this occurs and the impact of graft revascularization on the regenerative process remains poorly understood.

The objective of this study was to image the process of neural revascularization in conjunction with regeneration and remyelination using optical frequency domain imaging (OFDI). OFDI is a non-invasive, optical imaging modality that uses low-power infrared light to visualize tissue microstructure. Functional extensions of OFDI, such as angiography and polarization-sensitive platforms are used to simultaneously acquire data regarding tissue vascularization and myelination with spatial registration of tissue microanatomy.

Methods. The rodent sciatic nerve model was utilized for the following experimental groups: 1) crush injury, 2) repair with 5 mm nerve autograft, and 3) repair with 5 mm acellular nerve allograft. OFDI was used to perform intravital imaging at baseline, post-operative days 7, 14, and 28. Angiographic-OFDI was used to detect microvascular networks in the surrounding nerve bed and epineurium. Polarization Sensitive-OFDI was used to assess axonal myelination as it correlated to nerve birefringence. Auto-fluorescence detection was used to measure axonal regeneration in these thy1-GFP rats. Experimental groups were then compared regarding blood vessel formation, axonal myelination, axonal regeneration, and histomorphometry.

Results. In vivo imaging showed a robust neovascularization stemming from the surrounding tissues to the site of injury at day 7 and subsequent remodeling as evidenced by the presence of epineural vessels by day 28 (Image 1). On post-operative day 7, notable loss of fluorescence (axonal) and birefringence (myelin) at the site of injury and distally had occurred. Marginal recovery was visualized by day 28; crush>autograft>allograft. Correlating histomorphometry is in progress.

Conclusions. OFDI has sufficient spatial resolution to permit clear visualization of neural microvasculature and allows for quantitative measurements of neural birefringence enabling the examination of spatial and temporal reestablishment of blood supply and myelination following nerve repair. Based on preliminary imaging results, there is a significant increase in vascularity originating from the surrounding tissue with a development of epineural vessels in crush, autograft and even allograft groups, albeit slowest in the allograft group. This non-invasive technology provides greater insight into the role of neovascularization in peripheral nerve regeneration, particularly in the setting of autografts and allografts.

