COMPARISON OF AUTOGRAFTS VS. ALLOGRAFTS IN THE SURGICAL REPAIR OF PEDIATRIC OBSTETRICAL BRACHIAL PLEXUS INJURIES

A thesis submitted to the University of Arizona College of Medicine – Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine

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Class of 2019

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Abstract

Background: For patients with Obstetrical Brachial Plexus Injury (OBPI) that do not obtain a functional recovery, treatment is primarily surgical in nature. Surgical treatment involves removal of scar tissue, neurolysis, and then bridging the nerve discontinuity or block with a nerve graft. Standardly, nerve graft was autograft using sural nerve. More recently, a decellularized processed cadaveric nerve allograft (Axogen) has been utilized in numerous peripheral nerve injury repairs but has not been used in pediatric OBPI. Both types of nerve graft potentially provide a three-dimensional extracellular matrix that promotes Schwann cell migration and axon regeneration.

Object: To determine the functional efficacy of acellular processed nerve allografts (Axogen) as compared to sural nerve autografts taken at time of surgery.

Methods: This is a retrospective case cohort of patients who underwent surgical repair of an OBPI at Barrow Neurological Institute at Phoenix Children's Hospital using either a sural nerve autograft or a decellularized processed cadaveric nerve allograft (Axogen). There were 50 patients total, 22 in the autograft (control) and 30 in the allograft (intervention) groups. The primary outcome measures were motor strength and functionality measured by the British motor strength score and Mallet score, respectively. Secondary outcomes included surgical time, rate of complications, and future surgeries. Means and standard deviations (SD) of our outcomes were analyzed and are reported pre- and post-surgery.

Results: There was no significant difference in the motor strength and functional outcomes between the sural nerve autografts and allografts in follow-up to the surgery. Mean follow up was 614 days (SD = 547). The BRMC Motor Strength Score was statistically significant for each muscle group we measured except for elbow extension and each component of the Mallet Score showed statistically significant increases. Allografts had shorter operative time (Beta (95% CI): -30.7 minutes (-62.7, 1.31)) but the same rate of future surgeries although this association only trended toward significance with a $p = 0.06$. Two patients had superficial infections with stitch abscesses in the autograft group at the sural nerve harvest site and no infections in the

allograft group (9% vs. 0%) (p=0.17). All patients with the autograft had anesthesia in the sural nerve distribution on the dorsum of the foot.

Conclusions: These data would suggest that nerve allografts can be utilized in OBPI repair as they have comparable outcomes to autograft but are less invasive, requiring only one surgical site, decreased surgical time, and decreased risk of complications.

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Introduction

Brachial Plexus Injury

The brachial plexus refers to the nerve roots from C5 to T1 and provides the motor and sensory innervation for the upper extremity. Injury to the brachial plexus disrupts this innervation and can result in a number of different pathologies based on the extent of injury. Sunderland classifies peripheral nerve injuries into five classes from least to most severe. First degree (neurapraxia) is demyelination of the nerve. Second degree (axonotmesis) involves Wallerian degeneration of the distal portion of the nerve and proximal nerve degeneration. Third degree is similar to second degree but also involves damage to the endoneurial tubes. Fourth degree also includes an area of scar that prevents axon regeneration, called a neuroma. Fifth degree (neurotmesis) is complete transection of a nerve. Avulsion is a type of fifth degree injury where the nerve root is separated from the spinal cord. Injury to all of the nerves of the brachial plexus results in a flail upper limb with no motor or sensory function. More commonly, an upper plexus injury (C5, C6, and sometimes C7) occurs and is referred to as Erb's Palsy. In these injuries, typically, the patient has a "waiter's tip" positioning of the arm due to loss of function of the deltoid, infraspinatous, and biceps muscles. Less common are lower plexus injuries, called Klumpke's palsy, which most often involves the lower trunk (C8, T1, and sometimes C7). Lower plexus injuries result in isolated hand muscle dysfunction. If the injury or damage is proximal to the separation of the sympathetic fibers, the neurological findings include a Horner Syndrome, which is characterized by ptosis, miosis, anhidrosis, and pseudoenophthalmos.[10]

Obstetrical Brachial Plexus Injuries (OBPI) refers to a brachial plexus injury during delivery. The incidence of OBPI ranges globally from 0.2- 4% of live births. Factors that are associated with OBPI include large birth weight (>4000 g), prolonged labor course, breech delivery, and shoulder dystocia.[10] Shoulder dystocia is associated with a 100-fold increased risk of brachial plexus injury, which is noted in 11% of shoulder dystocia cases.[10] Mothers with diabetes, obesity, or preeclampsia, as well as mothers who are multiparous and previously had large babies are at higher risk for their children to have OBPI.[10] The mechanism for OBPI is thought to be a result of an increase in the angle from the infant's neck to shoulder during birth, creating

traction stretch injury of the brachial plexus. Shoulder dystocia increases the angle of deviation of the fetal head during delivery and may cause an increased traction injury on the brachial plexus.[10] However, some OBPI can occur in utero from increased intrauterine pressure, compression of the fetal shoulder on the symphysis pubis, intrauterine maladaptation, failure of the shoulders to rotate, and impaction of the posterior shoulder behind the sacral promontory.[10] Other mechanisms of brachial plexus injury include traumatic injuries causing downward or upward traction on the shoulder, penetrating traumatic injury, nerve compression, ischemia, neoplastic, radiation induced, thoracic outlet syndrome, hereditary brachial plexopathy, and neuralgic amyotrophy.[2]

Sufficient injury to the nerves of the BP can result in a wide range of injury severity from mild injury to complete nerve root avulsion depending on the extent of stretch, force, and over time. Favorable prognosis is associated with early clinical improvement, elbow flexion at 3 to 6 months of age, normal or near-normal strength in multiple muscle groups.[21] Generally, prognosis is good and spontaneous complete recovery rates have been reported in up to 95% of patients.[13] Poor prognostic indicators include Horner Syndrome, no neurologic recovery by 4 months, and flail upper limb.[21]

Physical therapy is the mainstay of treatment to retain passive range of motion, improve strengthening, and increase function. For those patients that do not recover adequate function, treatment is primarily surgical in nature. It is recommended that those patients with poor prognostic indicators proceed with surgical management. Absence of elbow flexion by three to four months of age has historically been used as a predictor of patient benefit from surgical management.[21]

Surgical treatment is recommended for these patients when they have not recovered function by four months. Surgery usually consists of Neurolysis and potential nerve grafting.[21] Classically, sural nerve graft is harvested from the lower extremity(ies) of the patient to provide sufficient material for grafting. This requires a separate incision(s) as well as morbidity (numbness in the sural nerve distribution, dorsum of the foot.) Acellular deproteinized sural nerve allografts provide the matrix for axonal outgrowth without the necessity to sacrifice a function. Similarly,

without need for harvest of the nerve, there is the potential for decreased operative time, anesthesia, and complications, leading to better overall outcomes. What is unclear is the efficacy in children and in children with OBPI.

The aim of this study is to determine if using nerve allografts (Axogen) will have similar functional outcomes as compared to sural nerve autografts in reconstruction of the brachial plexus after OBPI. We hypothesize that sural nerve autografts and Axogen allografts will have similar outcomes in motor strength and functional outcome following surgery. We further hypothesize that utilizing allograft will have the same rate of complications, rate of future surgeries but shorter operative time.

Methods

Approval

This study was approved by the Phoenix Children's Hospital Institutional Review Board (#15-002) as an expedited review.

Population

A retrospective chart review included patients who underwent brachial plexus repair after OBPI with either an autograft or an Axogen allograft at Barrow Neurological Institute at Phoenix Children's Hospital between 2008-2015 at Phoenix Children's Hospital by a single surgeon (PDA). Patients before August 2012 were given an autograft and after were given an allograft. Patients were included in the study if they experienced a lack of functional recovery (Mallet 3 on hand to mouth testing) of the ipsilateral brachial plexus by 4 months post injury and then underwent surgical repair of at Phoenix Children's Hospital. Patients who suffered mechanisms of Injury other than OBPI or other peripheral nerve injuries were excluded.

Surgical Approach

If an autograft is being used, the first step in surgical management is to harvest a nerve graft, most commonly a sural nerve. Incision is carried out at the posterolateral aspect of the malleolus and identified followed by extending the incision or through cross hatch or stair step incisions were performed to provide sufficient length. Sometimes, this is done bilateral. Harvest of the sural nerve creates a permanent insensate patch on the lateral foot that most patients do not notice.

The brachial plexus exploration, neurophysiologic testing, neuroplasty, and nerve grafting were the same for autografts and allografts. The supraclavicular approach to the brachial plexus begins posterior to the sternocleidomastoid muscle with a linear incision parallel to the clavicle approximately 1 finger breadth superior in the posterior triangle. Undermining of the surrounding tissues allows for adequate mobilization and flexibility of the approach. The platysma is taken down from clavicle and then parallel to the sternocleidomastoid muscle in an

"L" shape and the muscle and underlying fat pad are reflected posterosuperiorly. Dissection is then deepened to identify each root of the brachial plexus. To determine the extent and location of the injury (pre or post ganglionic), electrophysiological studies including somatosensory evoked potentials (SSEP) and electromyography (EMG)/ nerve conduction studies are performed intraoperatively to determine the function of the neuromuscular unit and connection to the spinal cord. If there is no conduction proximally indicating an avulsion, then grafting from that nerve root is avoided. If there is no conduction distally, then the area is resected, and an end-to-end "cable" inter-positional nerve graft is fashioned. However, if there is conduction across the damaged segment, a neurolysis is first performed and an end-to-side "jump" graft is performed, bypassing the neuroma but allowing for new connectivity to form.[15] The autografts are variable in size and condition depending on each individual patient's anatomy. Allograft consistency was notable for diameter 1-2 mm and using 2- 2.5 cm lengths.

Primary Outcomes

Following surgery, the patients undergo physical and or occupational therapy (OT) at least once a week with instructions and family teaching to perform range of motion and a full battery of exercises multiple times per day. The children are then followed routinely in our brachial plexus clinic every three to six months postoperatively throughout the next two years. They undergo a full neurologic exam and OT assessment at each visit by the senior author/ primary surgeon (PDA) and an occupational therapist.

For this study, the primary outcome measure was the British Medical Research Council (BMRC) motor strength scale (converted pediatric motor scale) and functional strength (Mallet score) in the pre-operative and post-operative follow up visits. BMRC Motor Strength Scale utilizes a 0 - 5 scale where 0 is no muscle contraction and 5 is normal/full contraction (Figure 1). Typically, this scale is used in specific ranges of motions to elicit a numeric score for each muscle or muscle group.[14] This scale has substantial inter- and intra-rater reliability for the upper extremity.[16]

Figure 1: British Medical Research Council (BMRC) Motor Strength Scale

Score	Definition
0	No contraction
1	Flicker/trace contraction
2	Active movement with gravity eliminated
3	Active movement against gravity
4-	Slight movement against resistance
4	Moderate movement against resistance
4+	Strong movement against resistance
5	Normal/full power

Figure 1: BMRC Motor Strength Scale utilizes a 0- 5 scale where 0 is no muscle contraction and 5 is normal/full contraction.[3]

For functionality, the Mallet Score is a reliable method for assessing upper extremity function utilizing a 1 - 5 score where 1 is no function and 5 is normal function (Figure 2). Seven specific functions are tested including lifting the hand to the neck (elevation and external rotation), hand to the mouth, placing the hand on the spine (internal rotation), global supination, global external rotation, global abduction, and the position of the arm at rest. The Mallet score has been shown to be reliable across pediatric age groups.[5,21]

The Toronto Score was also recorded for each patient, which is a way to classify functional status. The score is 0 - 2, where a 0 is no function, a 1 is decreased function, and a 2 is normal function that is symmetrical to the unaffected side. Specific movements that are measured are elbow flexion, elbow extension, wrist extension, digit extension, and thumb extension. These five movements rated from 0 - 2 are added together to get a score with a maximum of 10.[21]

The process of nerve regeneration takes months[4]; therefore, these assessments would not show recovery of function until months after surgery. The endpoint for each patient was last clinic visit up to August 2017.

Figure 2: Mallet Score

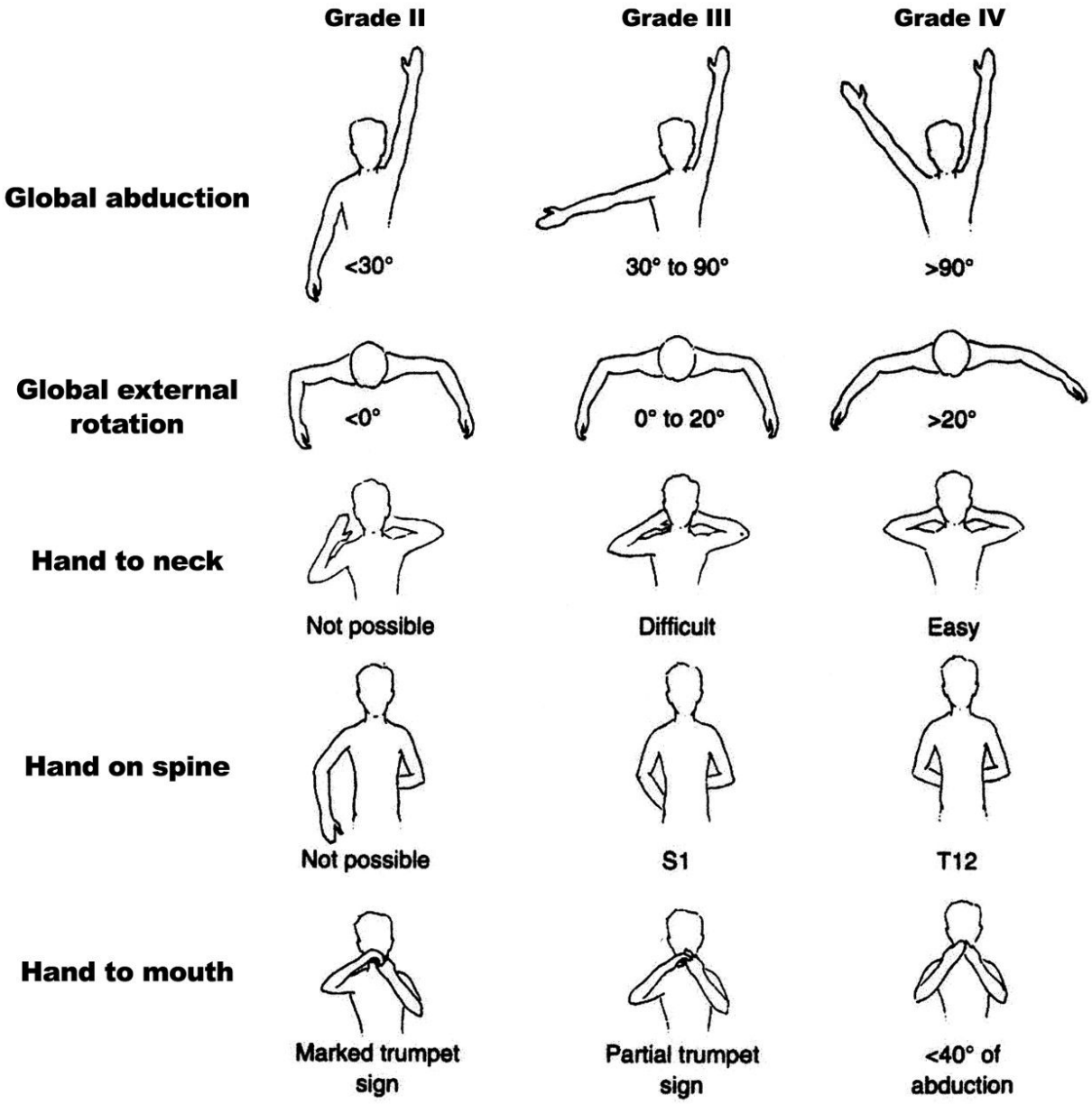

Figure 2: Representation of the modified Mallet Classification for assessing upper trunk function. Grade I is no movement. Grade V is normal function, which is symmetric to the unaffected side. Grades II, III, and IV are depicted. Scores 1-5 are assigned and correspond to the grade.[5,14]

Secondary Outcome Measures

Secondary outcome measures comparing the autograft and allograft groups included surgical length of time, rate of complications, and rate of future need of other surgeries. We hypothesized that surgical time would be decreased with allograft use because it does not require separate incisions for nerve graft harvesting as part of surgical management. Increased surgical time correlates with increased anesthesia, increased blood loss, increased length of stay and consequently increased costs incurred for the patient and the hospital.[6,7] As with any surgery, complications may arise during or after surgical repair of the brachial plexus. Common complications that we followed were infection, neuroma, and painful scar at the repair sites. Some patients require additional surgeries to improve function. Typical surgeries after a brachial plexus nerve reconstruction that we followed are tendon transfers, muscle transfers, tendon releases, muscle releases, humeral osteotomies, and musculotendinous lengthening.

Data Collection

Independent variables that were collected to determine if there were any confounding factors included gender, side of injury, birth history, comorbidities, associated injuries, and type of surgical repair. Since all the patients were evaluated and surgically managed by the primary surgeon (PDA), the data came from a single rater. However, one study found intra-rater reliability to be substantial to excellent in the context of medical records[12], which we expect to be consistent with our medical record data.

Power and Sample

The primary outcome of this power and sample size calculation is the mean difference in the change in motor strength and the functional Mallet score from pre-surgery to post-op. Our sample size estimate was 50 patients of approximately equal number in the control group (autograft) and in the intervention group (allograft). A clinically significant difference of 0.8 between the two groups would render a statistical power of 80% with an alpha of 0.05. Since our hypothesis states no statistically significant differences in our outcomes (null hypothesis), we expected the score differences to be less than 0.8 between the two groups.

Statistical Analysis

Demographic and clinical characteristics of patients who underwent the autograft and allograft interventions were evaluated using descriptive statistics including means and standard deviations (SD) for continuous variables, frequencies and proportions for categorical variables. The Wilcoxon Rank Sum was used to assess the difference in mean scores between patients who underwent the autograft and allograft interventions. The Fisher's exact test was used to compare proportions between the same groups. The means and standard deviations of our outcomes were measured at baseline and post-surgery. The Wilcoxon Signed Rank was used to compare differences between pre-surgery and follow up. Multiple linear regression was used to ascertain the estimated mean difference of the length of surgery between the two types of surgeries utilizing allograft and autograft with the autograft group as the reference group.

Multiple logistic regression was used to ascertain the likelihood of subsequent surgeries between the allograft and autograft groups using the autograft group as a reference group. To compare the complication rate between groups, Fisher's exact test was used. All p values were two sided and p less than 0.05 was considered statistically significant. All data analyses were conducted using STATA Version 14 (College Station, Texas).

Results

In total, we identified 52 patients, 22 (42.3%) in the autograft group and 30 (57.7%) in the allograft group. The only significant difference in demographics between groups was that the autograft group had a greater prevalence of patients with multiparous mothers (64% vs 33%). Otherwise, there were no statistically significant differences in demographic and clinical characteristics between the groups (Table 1). With respect to injury type, a noticeable difference in the prevalence of right limb injuries was observed between the two groups. Right limb injuries were present in 72% of autograft patients and 47% of the allograft patients. However, this difference only showed trends toward significance ($p=0.06$) (Table 2). Otherwise there were no differences between the two groups as to age at surgery, gender or any other demographic or clinical characteristic. Of note, the mean time from surgery through last follow-up was 614 days ($\pm$ 547).

The pre-operative motor assessments compared to the post-operative motor assessments for the combined groups (autograft and allograft), showed statistically significant improvements for specific muscle groups (Table 3). The BRMC Motor Strength Score was statistically significant for each muscle group we measured except for elbow extension. With regards to functionality, each component of the Mallet Score showed statistically significant increases. The largest increases within the Mallet Score components were the mean global abduction scores (pre-score: 2.23 (0.89) vs post-scores: 3.46 (1.05); $p<0.001$) and the hand to mouth scores (pre-score: 1.88 (0.71) vs post-scores: 3.09 (1.06); $p<0.001$). In terms of the Toronto Score, the majority of patients did not have thumb extension recorded in the medical record. Therefore, we were unable to calculate the difference in thumb extension or use the complete score. Similar to the BRMC and Mallet score, the Toronto Score showed statistically significant improvements for the combined groups in every range of motion except for elbow extension. This is evidence that overall, patients improved from the surgical procedure pre-operative to post-operative and gained functionality.

Table 1: Demographics and Clinical Characteristics

Variables	Autograft N=22	Allograft N=30	P-value
Gender (male, %)	8 (36.4)	17 (56.7)	0.15
Maternal Medical History			
Maternal Musculoskeletal Disorders (yes, %)	0 (0.0)	1 (3.3)	1.0
Maternal Gestational Diabetes (yes, %)	4 (18.2)	1 (3.3)	0.15
Maternal Hypertension (yes, %)	5 (22.7)	3 (10.0)	0.26
Maternal Immune-compromised (yes, %)	0 (0.0)	0 (0.0)	N/A
Maternal Difficult Healing (yes, %)	0 (0.0)	1 (3.33)	1.0
Maternal Peripheral Neuropathy (yes, %)	0 (0.0)	0 (0.0)	N/A
Maternal Excessive Weight Gain in Pregnancy (yes, %)	1 (4.55)	0 (0.0)	0.42
Other Maternal history (yes, %)	12 (54.6)	18 (60.0)	0.69
Mother's Occupation (Office Admin, %)	7 (31.8)	13 (43.3)	0.24
Smoking History (Non-Smoker, %)	14 (63.6)	19 (63.3)	0.98
Mother's Pregnancy Number (Gravida, n, %)			0.20
1	8 (36.4)	12 (40.0)	
2	2 (9.09)	8 (26.7)	
$\geq$3	12 (54.6)	10 (33.3)	
Number of Live Children Delivered (>1, %)	14 (63.6)	10 (33.3)	0.03
Child's Medical History			
Delivery (Cesarean-Section, %)	3 (13.6)	1 (3.57)	0.30
Shoulder Dystocia (yes, %)	17 (77.3)	17 (56.7)	0.15
Vacuum (yes, %)	4 (18.2)	4 (13.3)	0.70
Forceps (yes, %)	3 (13.6)	4 (13.3)	1.0
Need for Neonatal Intensive Care (yes, %)	4 (18.2)	2 (6.67)	0.38
Sibling with OBPI (yes, %)	0 (0.0)	0 (0.0)	N/A
Neurological Disorder (yes, %)	2 (9.09)	1 (3.33)	0.56
Peripheral Neuropathy (yes, %)	0 (0.0)	0 (0.0)	N/A
Musculoskeletal Disorder (yes, %)	0 (0.0)	2 (6.67)	0.50
Diabetes (yes, %)	0 (0.0)	0 (0.0)	N/A
Hypertension (yes, %)	0 (0.0)	0 (0.0)	N/A
Immuno-compromised (yes, %)	0 (0.0)	0 (0.0)	N/A
Difficulty Healing (yes, %)	0 (0.0)	0 (0.0)	N/A

Chi-Squared/Fisher's Exact to compare categorical variables.

Table 2: Characteristics of Nerve Injury

Variables	Autograft N=22	Allograft N=30	P-value
Mechanism of injury (OBPI, %)	21 (95.5)	29 (96.7)	1.0
Affected Limb (right, %)	16 (72.7)	14 (46.7)	0.06
C5 (post-ganglionic, %)	19 (86.4)	23 (76.7)	0.48
C6 (post-ganglionic, %)	19 (86.4)	24 (80.0)	0.71
C7 (post-ganglionic, %)	15 (68.2)	21 (70.0)	0.88
C8 (post-ganglionic, %)	3 (13.6)	4 (13.3)	1.0
T1 (post-ganglionic, %)	2 (9.09)	3 (10.0)	1.0
Fracture to Clavicle (yes, %)	0 (0.0)	3 (10.0)	0.25
Fracture to Humerus (yes, %)	0 (0.0)	1 (3.33)	1.0
Phrenic Nerve Injury (yes, %)	0 (0.0)	0 (0.0)	N/A
Anoxic Brain Injury (yes, %)	0 (0.0)	1 (3.33)	1.0
Horner's Syndrome (yes, %)	2 (9.09)	2 (6.67)	1.0

Chi-Squared/Fisher's Exact to compare categorical variables.

Table 3: Mean Pre- and Post-Operative for Groups Combined

Variables	Pre Mean, SD	Post Mean, SD	P-value
BMRC Motor Score			
Shoulder Flexion AMS	2.07 (1.24)	3.36 (1.09)	<0.001
Shoulder Abduction AMS	2.80 (3.49)	3.61 (1.16)	<0.001
Shoulder External Rotation AMS	0.77 (0.92)	2.48 (1.50)	<0.001
Elbow Flexion AMS	2.22 (1.29)	3.61 (1.12)	<0.001
Elbow Extension AMS	3.45 (1.35)	3.70 (1.26)	0.23
Forearm Pronation AMS	3.37 (1.23)	4.09 (0.81)	<0.001
Forearm Supination AMS	1.22 (1.09)	2.57 (1.44)	<0.001
Wrist Flexion AMS	3.26 (1.63)	4.08 (1.31)	<0.001
Wrist Extension AMS	2.78 (1.70)	3.67 (1.51)	<0.001
Digit Flexion AMS	3.67 (1.58)	4.15 (1.00)	0.005
Digit Extension AMS	3.27 (1.55)	4.00 (1.19)	<0.001
Mallet Score			
Arm at Rest	2.20 (0.90)	3.02 (0.98)	<0.001
Global Abduction	2.23 (0.89)	3.46 (1.05)	<0.001
Global External Rotation	2.11 (0.79)	3.00 (0.84)	<0.001
Head and Neck	1.81 (0.62)	2.81 (1.29)	<0.001
Head and Spine	1.93 (0.66)	2.90 (0.89)	<0.001
Head to Mouth	1.88 (0.71)	3.09 (1.06)	<0.001
Supination	1.93 (0.75)	2.92 (0.84)	<0.001
Toronto Score			
Elbow Flexion	0.86 (0.34)	1.11 (0.32)	0.001
Elbow Extension	1.00 (0.30)	1.07 (0.34)	0.31
Wrist Extension	0.86 (0.48)	1.32 (0.53)	0.011
Digit Extension	1.03 (0.47)	1.28 (0.45)	0.018
Scapular Elevation	2.38 (0.77)	2.20 (0.76)	0.53

Wilcoxon Signed Rank to compare Pre- to Post-Op.

When the study groups were separated, they each showed an improvement in scores (Table 4). In fact, every component we measured had an average improvement, as shown by the positive numbers in Table 4, except for elbow extension and scapular elevation in the autograft group. However, the change in scores showed no statistically significant difference between the autograft and allograft groups ($p>0.05$). Ultimately, the autograft and allograft groups had similar increases in scores, meaning that neither one was superior in this study, a finding consistent with our initial hypothesis.

The length of surgery time showed that there was a decrease of 30.7 minutes (Coef (95% CI): -30.7 (.62.7, 1.31): $p=0.06$) in the allograft group as compared to autograft. There were secondary predictors that showed trends towards significance with regards to decreasing surgical times (Maternal Diabetes ($p=0.07$) and multiparous mothers $p=0.08$). The primary covariate that was associated with a statistically significant increase in surgery length was if the patient had a comorbid neurological disorder, which was associated with an increase of surgical length of 82.3 minutes (Coef (95% CI): 82.3 (6.82, 157.8); $p=0.03$) (Table 5).

The rate of subsequent surgeries was not statistically different between groups. In the allograft group, patients were 2.69 times more likely to have a subsequent surgery (such as a tendon or muscle release or transfer), however this was not statistically significant and had a large confidence interval (OR (95% CI) = 2.69 (0.30, 23.9); $p = 0.37$) (Table 6). There were no complications reported for the allograft group. There were two patients that had superficial infections with stitch abscesses in the autograft group in the incisions for the sural nerve harvest. There were no infections in the primary supraclavicular surgical site in either group. The complication rate was therefore not significantly different for autografts 9% and for allografts 0% ($p=0.17$).

Table 4: Change in Mean between Groups

Variables	Autograft N=22	Allograft N=30	P-value
	Δ Mean, SD	Δ Mean, SD	
BMRC Motor Score			
Shoulder Flexion AMS	1.17 (0.41)	1.46 (1.12)	0.83
Shoulder Abduction AMS	1.42 (0.79)	0.58 (4.52)	0.97
Shoulder External Rotation AMS	1.87 (1.35)	2.11 (1.49)	0.64
Elbow Flexion AMS	1.43 (1.34)	1.40 (1.24)	0.51
Elbow Extension AMS	-0.14 (1.23)	0.41 (1.08)	0.22
Forearm Pronation AMS	0.50 (0.55)	0.95 (1.19)	0.55
Forearm Supination AMS	1.45 (1.21)	1.40 (1.31)	0.89
Wrist Flexion AMS	1.13 (1.64)	0.73 (1.16)	0.49
Wrist Extension AMS	0.13 (1.72)	1.19 (1.46)	0.35
Digit Flexion AMS	0.23 (1.01)	0.67 (1.20)	0.50
Digit Extension AMS	0.40 (0.69)	1.04 (1.25)	0.17
Mallet Score			
Arm at Rest	0.71 (0.72)	0.78 (0.95)	0.79
Global Abduction	1.07 (1.11)	1.25 (0.75)	0.66
Global External Rotation	1.00 (0.78)	0.78 (0.75)	0.37
Head and Neck	1.07 (1.03)	0.93 (1.29)	0.56
Head and Spine	1.00 (0.84)	1.00 (0.87)	0.94
Head to Mouth	1.31 (0.94)	1.11 (1.18)	0.54
Supination	0.71 (0.82)	1.11 (0.99)	0.23
Toronto Score			
Elbow Flexion	0.21 (0.42)	0.25 (0.45)	0.75
Elbow Extension	0.14 (0.53)	0.04 (0.44)	0.49
Wrist Extension	0.17 (0.93)	0.41 (0.50)	0.63
Digit Extension	0.17 (0.71)	0.34 (0.64)	0.46
Scapular Elevation	-0.71 (1.49)	0 (0.89)	0.14

Wilcoxon Rank Sum to compare continuous variables.

Figure 3: Change in Mean from Pre- to Post-Op

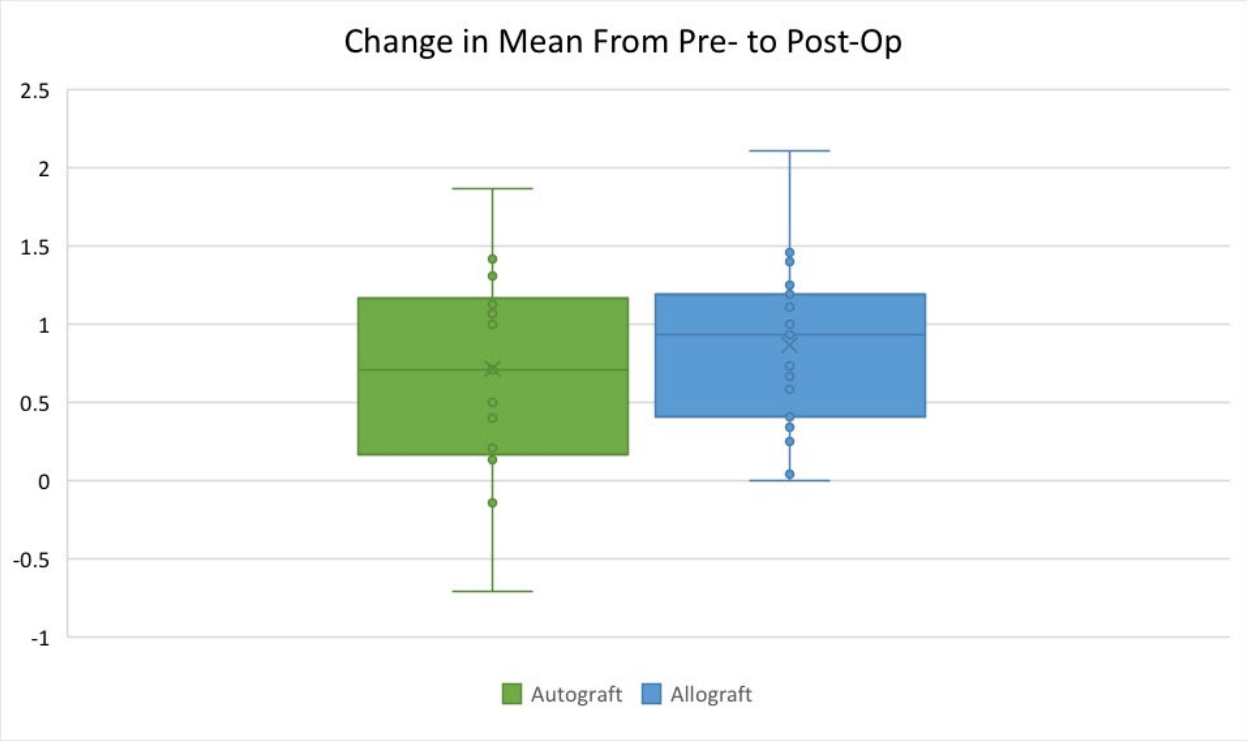

Figure 3: Graph showing Table 4 in pictorial format. The change in mean from pre- to post-op in the autograft and allograft groups is not statistically significant.

Table 5: Association between Group and Length of Surgery

Variables	Beta (95% CI)	P-value
Graft		
Autograft	REF	
Allograft	-30.7 (-62.7, 1.31)	0.06
Gender		
Female	REF	
Male	-1.85 (-35.2, 31.5)	0.91
Maternal Musculoskeletal Disorder		
No	REF	
Yes	76.84 (-18.0, 171.7)	0.11
Maternal Diabetes		
No	REF	
Yes	-57.7 (-122.5, 7.14)	0.07
Maternal Hypertension		
No	REF	
Yes	-24.1 (-66.6, 18.5)	0.25
Number of Children		
≤ 1	REF	
>1	-27.1 (-60.4, 4.44)	0.08
Delivery		
Vaginal	REF	
C-Section	-2.34 (-56.6, 51.9)	0.93
NICU Stay		
No	REF	
Yes	11.6 (-37.9, 61.1)	0.63
Patient Neurological Disorder		
No	REF	
Yes	82.3 (6.82, 157.8)	0.03
Affected Limb		
Left	REF	
Right	-1.47 (-29.8, 26.8)	0.81
C5 Injury		
No	REF	
Yes	-13.8 (-57.8, 30.2)	0.52
C6 Injury		
No	REF	
Yes	-23.0 (-68.9, 22.9)	0.31
Clavicle Fracture		
No	REF	
Yes	49.1 (-8.10, 106.2)	0.09

Beta (95% CI) calculated using Multiple Linear Regression adjusting for all other variables in the model.

Table 6: Association between Graft and Subsequent Surgery

Variables	OR (95% CI)	P-value
Graft		
Autograft	REF	
Allograft	2.69 (0.30, 23.9)	0.37
Gender		
Female	REF	
Male	0.27 (0.04, 2.01)	0.21
Maternal Diabetes		
No	REF	
Yes	0.11 (0.002, 6.01)	0.28
Occupation		
Other	REF	
Office Assistant	4.16 (1.10, 15.6)	0.04
Number of Children		
≤ 1	REF	
>1	0.19 (0.02, 2.05)	0.17
Delivery		
Vaginal	REF	
C-Section	0.20 (0.0001, 246.7)	0.66
NICU Stay		
No	REF	
Yes	13.8 (0.53, 359.1)	0.11
Affected Limb		
Left	REF	
Right	4.92 (0.79, 31.4)	0.08
C5 Injury		
No	REF	
Yes	0.07 (0.006, 0.93)	0.04
Clavicle Fracture		
No	REF	
Yes	12.0 (0.56, 256.7)	0.11

OR (95% CI) calculated using Multiple Logistic Regression adjusting for all other variables in the model.

Discussion

Our study has found that the utilization of autograft and allograft for the treatment of OBPI during the primary surgery to repair the brachial plexus were found to be equally efficacious with regards to functional outcomes as measured by the BRMC Motor Strength Score, Mallet score, and Toronto Score. Importantly, all of the children who underwent surgical intervention utilizing these grafting materials were found to improve and most were able to gain functionality (i.e.) ability to get their hand to mouth to feed themselves. The surgical time was shorter in the utilization of allograft although this only showed a trend toward significance. Our analysis showed no difference in the rate of subsequent surgeries or complications.

Nerve grafting

Peripheral nerve allograft safety and functionality in animal models has been well established.[1] However, there is still controversy about the efficacy of allografts in comparison to autografts in animal models. In one study there was a significant decrease in nerve fibers and muscle mass in the acellular nerve allograft group.[22] In another study, there was no difference between autograft and allograft groups in terms of electrophysiologic or histomorphologic outcomes.[20] In yet another study, acellular nerve allografts were superior to cabled nerve autografts in normalized maximum isometric tetanic force.[19]

However, not many studies have attempted to determine the efficacy of decellularized cadaveric nerve allografts for return of strength and functionality in humans, especially in comparison to autografts in a pediatric population. Reports and case series show mixed efficacy of allografts and there is no current consensus on the optimal use of autografts as compared to allografts though for generally long segments (> 5 cm), autografts may be better.[11,18] Our study compared autografts to decellularized cadaveric nerve allografts in children with multiple outcome measures that have not previously been compared. In our study, allograft efficacy may be tied to the short segment and methodology for their utilization though this would need further study to better understand the electrophysiologic and histomorphologic outcomes in

this patient population. The graft segments tended to be short (< 2.5 cm) and may have contributed to the equal efficacy between the groups.

Allograft (Avance®) Nerve Grafts are processed cadaveric human nerves that are sterilized, decellularized, and deproteinized. The structure of the extracellular matrix of the nerve is retained and provides a three-dimensional scaffold for axon regeneration across a peripheral nerve discontinuation.[4] Histologic examinations have concluded that decellularized nerve allografts have a suitable scaffold for bridging nerve discontinuities.[20] A large benefit of using Axogen allografts is the lack of co-morbidities associated with harvesting an autograft, most commonly the sural nerve. The allografts are flexible enough to be used across joints and come in diameters up to 5mm and lengths up to 70 mm.[4] In this study 1-2 mm diameter grafts were used with generally < 2.5 cm lengths to perform the jump grafts.

Allografts help the peripheral nerve to repair itself using the extracellular matrix scaffold to aid in axon regeneration. The first step in the process of repair is for the matrix to be vascularized, which happens within hours of the surgical repair. In a few days post operatively, Schwann cells migrate into the matrix and form tube-like structures that subsequently guide the axon regeneration. Within weeks, many of these tubes formed by Schwann cells have regenerating axons within them. Within months, these regenerating axons grow the full length of the allograft and with axon maturation, become thicker and myelinated.[4]

Safety of acellular nerve allografts in humans has been well established.[8,9,18,23] In humans, limited studies have been done to determine efficacy differences between autografts and allografts. In an adult population, it has been shown that autografts and allograft sensory outcomes were similar in digital nerve reconstruction.[17] When comparing historical autograft data to peripheral nerve reconstruction using processed nerve allografts in an adult population, studies suggest that efficacy is similar.[8,9] Through an extensive literature search, we have not found any studies that compared allografts to autografts in a pediatric population. Our study would seem to indicate that use of the allografts is safe and with potentially less complications than the use of autografts.

Limitations

The largest limitation of this study is the small sample size. The multiple inclusion criteria for this project limited the sample size to one mechanism of injury in one hospital. The Mallet score is on a scale of 0 to 5 and the change in mean score was relatively small, between 0.71 to 1.31 for the autograft group and 0.75 to 1.25 for the allograft group. The standard deviations were large in comparison to the change in mean, as seen in Table 4. This study was powered to detect a difference of score of 0.8, to be able to detect a significant difference pre-operative to post-operative motor and functional outcome but was not able to detect any small possible difference between groups.

Other limitations were non-randomized patient population, possibly allowing for unknown factors between the two groups. As the data was collected from the electronic medical record, the medical staff was not blinded to the surgery the patient received.

One possible future direction would be a cost analysis. In order to quantify the amount that could be saved, a cost analysis could be done to consider the cost of the operative time saved with using allografts vs. the cost of the allografts themselves. This could provide not only a clinical rational to use allografts but a cost savings rationale as well. Cost but also cost effectiveness is always a consideration in this ever expanding and unsustainable healthcare environment.

Conclusions

Our analysis showed that autografts and allografts are equally efficacious in the treatment of the primary injury in children with OBPI. With two equally efficacious methods, the less invasive method would seem to be preferable. We suggest that this is the case with allografts.

Allograft use only requires one surgical site and inherently has a lack of comorbidities associated with a second surgical site. In our population, although not statistically significant, there were fewer infections in the allograft group. In the autograft group, there were two infections due to the incisions in the leg from the nerve harvest.

In addition, the use of allografts has the potential for better repair for extensive lesions. Nerve autografts can only provide a certain length of graft, whereas the amount of allograft is not limited to what can be harvested. For patients with large discontinuities or multiple levels of the brachial plexus, allografts have the potential to provide repair for all nerves involved instead of just a few.

Allograft surgery length was shorter in our cohort. Decreased surgical time implies decreased time under anesthesia and decreased risks associated with anesthesia. Considering many of these surgeries are multiple hours long in young children, decreased anesthetic exposure would be favored as long-term effects of exposure to anesthesia in pediatric patients is unknown. It also has the potential to decrease the complications associated with prolonged anesthetic usage.

For these reasons, nerve allografts are the preferable route for surgical management.

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