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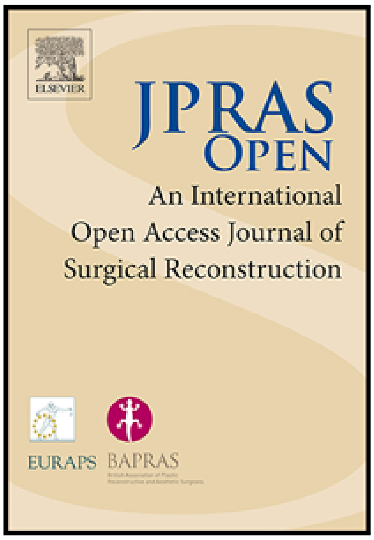

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Timing and Predictors of Upper Extremity Peripheral Nerve Reconstruction

Kelsey M Gray, MD[1], Andrzej J Burkat, MD[1], Lucas A Arney, BS[2], Nicholas J Peterman, MD[3], Sahith R Mandala, MD[1], Anthony E Capito, MD, FACS[1]

1. Virgina Tech Carilion School of Medicine, Section of Plastic and Reconstructive Surgery, Roanoke, Virginia
2. Virginia Tech Carilion School of Medicine, Roanoke, Virginia
3. Virginia Tech Carilion School of Medicine, Department of Orthopaedics, Roanoke, Virginia

Work attributable to:

Department of Surgery, Section of Plastic and Reconstructive Surgery
1906 Belleview Ave SE, Roanoke, VA 24014

Correspondence:

Kelsey Gray, MD
Department of Surgery, Section of Plastic and Reconstructive Surgery
1906 Belleview Ave SE
Roanoke, VA 24014
f: 540.981.8681
t: 540.750.3642
e: kmgray2@carilionclinic.org

Partial data on digital nerve repair timing presentation at AAHS 2022

SUMMARY/ABSTRACT

Primary neurorrhaphy is the preferred reconstruction modality over nerve grafting, especially for motor nerves. The main limitation to primary repair is often dictated by tension secondary to increased nerve defect length. A retrospective review was conducted of sharp transections of mixed motor and purely sensory nerves in the upper extremity to assess factors influencing defect length. Two groups of either primary repair or nerve graft/conduit were created for comparison. 71 injured mixed motor nerves and 224 injured sensory nerves were included for analysis. There were no significant differences in patient demographics between groups. The primary repair group had a significantly shorter time interval between injury and surgical fixation when compared to the conduit/graft group. Conduit or graft technique was associated with a significantly larger tissue gap after preparation of the nerve ends. Our data suggest the best chance of primary repair is within 3 days for mixed nerves and within 7 days for purely sensory. A total of 167 nerve reconstructions were included in a random forest plot, which demonstrated nerve defect size to be influenced by days from injury, type of nerve injured, age, and hypertension. A publicly available 4-feature calculator, NERVE (Nerve Evaluation and Retraction Variability Estimator), was developed from the forest plot to predict a patient's nerve deficit ± 3.78 mm on average, R^2 = 0.89. This calculator could aid surgeons with surgical planning for the potential need of grafts or conduits for reconstruction.

Keywords: peripheral nerve repair, nerve repair timing, nerve calculator, nerve grafting, nerve primary repair, nerve defect

INTRODUCTION

Peripheral nerve injury has been noted to occur in 2.8% of trauma patients referred to Level I centers, while a review of United States private insurer encounter and claims data reveals associated nerve injury in 1.6% of limb trauma patients.[1,2] Although the incidence is relatively low, the results of traumatic upper extremity motor nerve dysfunction can be disastrous, with less than 50% of patients achieving functional recovery and up to 30% of patients seeking long-term disability.[3,4] Sensory nerve disruption can also lead to impaired hand function, most noticeable when the thumb or index fingers are involved, while also contributing to neuropathic pain resulting in reduced quality of life and socioeconomic burden. [3,5–8] Optimizing outcomes and recovery becomes more imperative when the dominant extremity is involved, as patients continue to prefer to use the injured dominant hand even when the other is relatively more functional.[9]

There are several established principles meant to maximize outcomes. Coaptation of healthy nerve fascicles in a tension-free manner remains the gold standard for repair of sharply transected nerves.[4,10,11] A tension-free neurorrhaphy may prove to not be feasible when the tissue preparation phase of repair results in a resection defect measuring over 1 cm.[5,10] Attempting to primarily reapproximate such a gap over 1 cm results in tension on the nerve intolerable to axon regeneration due to ischemia and promotes further scarring, which is where neural tube conduits and nerve grafts are available to alleviate tension in these gaps, though still inferior to that of direct primary repair.[12]

It has long been established that prolonged axotomy results in inferior functional outcomes; however, the exact timing of repair has not been elucidated.[13,14] Multiple time tables have been suggested as the critical timing cutoff.[5,15–17] Classic studies have suggested repair within 72 hours; this was generalized from studies of facial nerve transections, which showed depletion of factors from the injured nerve stumps, making identification of the distal stump challenging.[18,19] This is not as relevant in upper extremity nerve injuries, as the transected ends are readily identifiable. Subsequent studies have suggested critical periods ranging from several weeks up to 3 months.[5,17]

Following nerve transection, histologic changes mediated by Schwann cells and other inflammatory cells occur in the proximal and distal nerve stumps.[11,17] These culminate in axonal and myelin breakdown, with the distal stump undergoing Wallerian degeneration. The proximal stump undergoes degenerative changes as well that may extend several millimeters to even centimeters from the injury site.[5] With increasing time from injury, the proximal stump undergoes fibrosis and consequent reduction in endoneurial tube diameter.[5,20] Recovery from these changes following repair relies on re-establishment of functional connections, which may take weeks to months.[21]

The aim of our study is to address the paucity of information relating to how the timing of surgical intervention impacts the method utilized for repair. We hypothesize that a delay in repair of sharp lacerating nerve injuries of the upper extremity correlates with an increased amount of nerve resection and therefore results in a decreased ability to achieve primary repair.

METHODS

Institutional Review Board approval was obtained to create a database of peripheral nerve repairs performed by eight board-certified hand surgeons at a level I tertiary medical center over a course of ten years. The Current Procedural Terminology (CPT) codes corresponding to neurorrhaphy (64830-64837), nerve grafting (64890-64898), and conduit repair (64911, 64912) were used to populate the database.

Individual chart review was conducted to identify the mechanism of injury, site, and specific nerve involved. For the purpose of this study, we focused on transecting upper extremity injuries to purely sensory and mixed-motor nerves distal to the elbow joint. It is our assertion that sharp lacerating injuries with no significant tissue loss have a more clear zone of injury and are acutely amenable to primary repair at presentation. Injuries sustained by an avulsion, crush, or ballistic mechanism were excluded since the zone of injury and the length of segmental nerve loss could not be standardized. Patients presenting for initial evaluation in a delayed fashion, peripheral nerve repairs at sites proximal to the elbow joint, or those noting a traumatic loss of native tissue were also excluded from this study for similar reasons of standardization on injury day one.

The charts were subsequently placed into two cohort groups based on repair method utilized: primary repair versus conduit or graft repair. The day interval elapsed between the time of injury and surgical repair, as well as, the nerve defect length after tissue preparation were recorded and compared between groups. Demographic (age and sex) and comorbidity (diabetes, hypertension, and smoking history) information was also recorded and compared between groups.

A Student's t-test was utilized for continuous variables and Fisher's exact test for categorical variables with a significance set at p=0.05. This collected data was then filtered to include only defect lengths greater than 0 mm and analyzed in a random forest plot model to assess factors that were predictive of nerve deficit length. Random forest modeling allowed for the successful creation of a publicly available 4-feature calculator, NERVE (Nerve Evaluation and Retraction Variability Estimator), that is able to predict a patient's expected nerve deficit. (Figure 1)

RESULTS

The database created based on the CPT codes provided 760 patient charts. Implementation of our criteria resulted in a dataset of 71 injured mixed motor nerves (Table 1) and 224 injured sensory nerves (Table 2). There was no difference between groups regarding age, presence of hypertension, diabetes, smoking status, or complications (Tables 1 and 2).

For mixed motor nerves, the primary repair group had an average of 3.2 days from time of injury to surgical repair compared to 8.7 days for the graft/conduit group, which was statistically significant ($p<0.01$, Table 1). The graft/conduit group also had a larger average defect size, 26.8 mm compared to 3.5 mm for the primary repair group ($p<0.001$, Table 1).

For sensory nerves, the primary repair group had an average of 6.6 days from time of injury to surgical repair compared to 8.5 days for the graft/conduit group, which was statistically significant ($p= 0.02$, Table 2). The graft/conduit group also had a larger average defect size 9.8 mm compared to 0.1 mm for the primary repair group ($p<0.001$, Table 2).

A random forest model was then created to assess which factors were predictive of nerve defect size. After excluding defects of 0 mm, a total of 167 nerve repairs were included and the associated variable distributions are represented in Table 3. Size of defect was most influenced by type of nerve injured (39%), followed by age (28%) and days from injury (23%), and finally by the comorbidity of hypertension (11%). Smoking, sex, and diabetes were initially included, but were found to have an importance of influence of less than 2% and therefore were not included in the predictive calculator (Table 4). Ultimately, the above allowed for the creation of a 4-feature calculator, NERVE, to predict a patient's nerve deficit ± 3.78 mm on average, $R^2 = 0.89$ (Figure 1).

DISCUSSION

Open nerve injuries should always be explored. The traditional recommendation is that nerve injuries ideally be repaired within 72 hours of the injury. This has been based on studies by Gilliatt et. al and Chaudhry et. al., which have shown a significantly decreased response of the distal stump to nerve stimulation after a period of 3 to 5 days.[18,19] After this delay, neurotransmitters disappear from the distal nerve stump and further intraoperative identification of fascicles is no longer possible.[22] This time period is critical for repair of small caliber nerve injuries, where identification of the distal target may require the use of a nerve stimulator, such as in facial nerve injuries. However, it is less relevant in the extremity, where the course of motor and sensory nerves are well defined. Dvali and Mackinnon have expanded the period for optimal repair of peripheral nerve injury to 7 days.[15] This is in line with our data showing primary repair was most often achieved within 6.6 days of injury for sensory nerve injuries; however, the best chance of primary repair for a mixed motor nerve occurred within the first 72 hours from injury. The critical window is bound by the progressive loss of motor nerve plate viability, as well as, the desire to optimize motor recovery and ease the surgical approach in a relatively less scarred surgical bed regardless of nerve type.[16]

Although several well-established surgical techniques exist for repair of nerve injuries, primary repair remains the gold standard when appropriate tension is feasible.[10,23] In injuries with a resulting nerve gap of less than 1 cm, end-to-end neurorrhaphy has been found to offer superior results compared to other nerve repair modalities.[24,25] Using the NERVE calculator with the average demographics of our cohort, a 1 cm defect would be predicted at 9 days from injury.

In the case of nerve gaps longer than 1 cm, primary repair results in undue tension on the repair site with consequently inferior outcomes.[26] Recent digital sensory nerve meta-analysis demonstrated similar outcomes for nerve autograft and allograft, with allograft comparable to primary repair, leading to some surgeons adopting this treatment for all injuries and lowering the threshold for digital nerve resection.[27] The increased use of grafting or conduits can be seen in the majority of our studies patient population, 70% in the mixed motor group and 64% in the sensory nerve repair group. However, meaningful recovery of function with grafts is not as high in motor or mixed nerve injuries compared to sensory nerve injuries, where primary neurorrhaphy remains superior.[25,28] Additionally, there also appears to be limited regeneration of nerves with grafts longer than 2 cm.[5,29,30] Therefore repair prior to development of gap greater than 2 cm is recommended, which we found this time point to be 12 days from sharp injury, although this estimate is limited by low number of patients in our cohort found to have a 2 cm defect (n=16).

Several studies demonstrate a progressive loss of neural tissue elasticity and nerve diameter in relation to time passed since the initial insult.[5,15,20] One expects this to result in an increased extent of tissue resection required to reach viable nerve ends, which may decrease or even preclude the possibility of a successful primary neurorrhaphy. Our study offers evidence to this expected trend, revealing that each day passed since the time of injury until the definitive surgical repair correlates with an increase of tissue resected to reach healthy and viable nerve ends appropriate for suture repair (Figure 1).

Functional outcomes were not assessed following performed repairs, which is a limitation of our study. The graft or conduit group were included as a single group for this reason, as functional outcome was not the area of interest for this investigation. Future studies may be designed to follow patient outcomes on a longitudinal basis utilizing The British Medical Research Council muscle strength grading system, 2 point discrimination testing, or other comparable paradigm.

Other limitations of the study are inherent to its retrospective design, as the cohorts were not randomized. Selection bias precludes the generalization of the results to all populations and only reflects the outcomes of the patients included in this study. We excluded delayed presentations (greater than 30 days), as this does not correlate with the question at hand with the optimal timing of repair from a nerve injury presenting acutely to our institution. We attempted to address the question of whether these cases should be done at immediate presentation to a hospital system, or if they are appropriate for outpatient care that would delay surgical timing. We also excluded ballistic injury cases, which result in a mixed injury pattern rather than nerve transection and are often associated with soft tissue loss where one can assume there could be segmental loss of neural tissue negating the option of primary repair based on mechanism of injury.[16] An additional limitation was that the nerve reconstruction modality was based on eight different hand surgeons. Individual preference for neural tissue preparation could have altered the results and was not controlled for in this study.

When considering both the technical and temporal aspects of repair, in order to ensure the best possible result, one must acknowledge that the outcome is ultimately multifactorial. Other factors aside from the utilized repair modality have been identified. These include age, sex, medical comorbidities, proximal or distal site of injury, as well as, the specific nerve involved.[31,32] Our study and NERVE calculator in particular found age, hypertension, and type of nerve involved to be predictive for final defect size along with time from injury. Our findings related to age, are also suggestive that the elastin found in peripheral nerve perineurium and epineurium could degenerate with age, as is similarly seen in skin, resulting in decreased retraction and therefore decreased nerve defect length after transection with older age.[33,34]

In conclusion, surgeons should consider early exploration of sharp lacerating peripheral nerve injuries of the upper extremity, especially in patients with hypertension, younger age, and mixed motor injuries, in order to maximize the chances of a tension-free primary nerve repair. This study demonstrated that timing does effect nerve defect size with best chance of primary repair within 3 days for mixed nerves and within 7 days for purely sensory. Defect size increased from time of injury, and the NERVE calculator could aid surgeons with surgical planning for the potential need of grafts or conduits for reconstruction.

Conflict of interest statement:

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Statement of Human and Animal Rights Procedures:

This retrospective article was in accordance with the ethical standards of the responsible committee on human experimentation (Institutional Review Board 21-1357).

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Figure 1. Calculation App User Interface. App available for public use at https://nervecalc.streamlit.app/

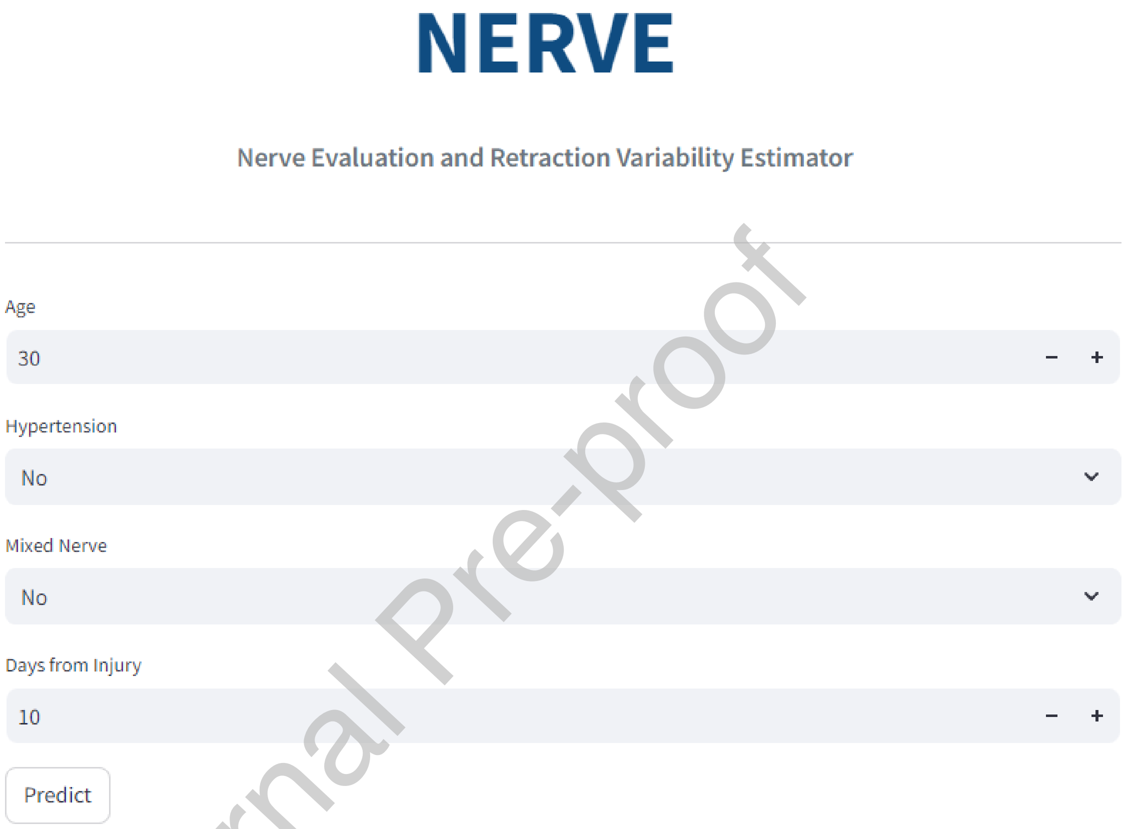

Table 1: Mixed Motor Nerve

	Primary (n=21)	Graft/conduit (n=50)	p value
Mean Prepared Defect Size (mm)	3.52	26.76	<0.001
Mean Days to Intervention	3.23	8.68	0.006
Mean Age in Years	39.71	41.14	0.384
Sex Distribution (F/M)	7/14	16/34	>0.999
Complications			
Reoperation	1 (5%)	6 (12%)	0.638
Wound dehiscence	0	2 (4%)	0.797
Neuroma	1 (5%)	5 (10%)	0.734
Infection	0	1 (2%)	0.517
Comorbidities			
Smoking	11(52%)	29 (58%)	0.716
DM	1 (5%)	4 (8%)	0.836
HTN	2 (10%)	11 (22%)	0.414

Millimeters (mm), Diabetes Mellitus (DM), Hypertension (HTN)

Table 2: Sensory Nerve

	Primary (n=81)	Graft/conduit (n=143)	p value
Mean Prepared Defect Size (mm)	0.06	9.82	<0.001
Mean Days to Intervention	6.63	8.45	0.029
Mean Age in Years	39.91	38.51	0.539
Sex Distribution (F/M)	27/54	52/91	0.756
Complications			
Reoperation	0	0	0.997
Wound dehiscence	0	0	0.997
Neuroma	1 (1%)	3 (2%)	0.915
Infection	0	0	0.997
Comorbidities			
Smoking	35 (43%)	62 (43%)	0.986
DM	9 (11%)	7 (5%)	0.441
HTN	13 (16%)	27 (19%)	0.726

Millimeters (mm), Diabetes Mellitus (DM), Hypertension (HTN)

Table 3: Variable distributions

Variable	Summary n = 167
Age, mean (SD)	39.2 (15.8)
Sex, n (%)	
Male	105 (63)
Female	62 (37)
Diabetes, n (%)	
Yes	12 (7)
No	155 (93)
Hypertension, n (%)	
Yes	33 (20)
No	134 (80)
Smoking, n (%)	
Yes	81 (49)
No	86 (51)
Nerve Type, n (%)	
Mixed	40 (24)
Sensory	127 (76)
Days From Injury, median (IQR)	7.0 (9.0)
Defect Distance (mm), median (IQR)	10.0 (12.0)

Standard Deviation(SD), Interquartile Range (IQR), Millimeters (mm)

Table 4: Random Forest Model Feature Importance

Feature	Model Importance (%)
Mixed Nerve Status	39
Age in Years	27
Days from Injury	23
Hypertension	11
Root Mean Squared Error: 3.777 mm, R^2: 0.8915	