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REVIEW ARTICLE

New Perspectives in Peripheral Nerve Surgery for Neuropathic Pain

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Abstract

Background and Aims: Neuropathic pain can occur following intentional or unintentional peripheral nerve injury. The purpose of this review was to determine in patients who have post-traumatic trigeminal neuropathic pain or required ablative mandibular operations with transection of the nerve, do those who undergo immediate or early surgical interventions, when compared to those whose nerves are not repaired or delayed, have a decreased or increased risk for resolving neuropathic pain?

Methods: Two single-site and one multi-site retrospective observatory studies of patients who had neuropathic pain prior to operative treatment of the injured nerve and in patients who underwent resection of the mandible for benign or malignant disease with either no repair or immediate repair were analyzed for the presence or absence of neuropathic pain at 6 months post-surgery. The primary predictor variable in the surgical treatment of neuropathic pain pre-existing surgery was the time from injury to repair and the preoperative pain intensity rated by Visual Analogue Scale (VAS). The primary predictor variable in the study of intentional transected nerve was the immediate repair or no repair of the nerve at the time of resection.

Results: There was statistically significant difference in the primary outcome based on time from injury to repair. When the time to surgery was less than 200 days, the percentage of patients with no neuropathic pain was greater than 60%. There was a significant difference in mean VAS between those who had no neuropathic pain (6.4,SD 2.68) and those with recurrence (7.75,SD 1.95). Following mandibular resection there was statistically significant difference between the immediate repair and no repair group. Post-hoc logistic regression modeling showed an inverse relationship between the immediate repair and the incidence of chronic postoperative pain and neuropathic pain with an odd ratio <1.

Conclusions: In patients with neuropathic pain, earlier diagnosis and treatment, including peripheral nerve surgery, should be considered with the best outcomes when operative interventions occur within 200 days of the injury and pain intensity are mild or moderate on VAS scales.

The immediate repair of an intentionally transected trigeminal nerve appears to reduce and possibly eliminate the development of neuropathic and chronic postoperative pain compared to avoiding nerve repair.

Introduction

Neuropathic pain is defined as pain due to a lesion or disease affecting the somatosensory system¹. Post-traumatic peripheral neuropathic pain occurs after a peripheral sensory nerve injury and is characterized by abnormal hypersensitivity to non-painful stimulus (allodynia), painful stimulus (hyperalgesia) and repetitive stimuli (hyperpathia) within and sometimes outside the distribution of the somatosensory nervous system injured. Post-traumatic peripheral neuropathic pain is reported to occur in 50% to 85% after limb amputation², 5%-10% following thoracotomy, breast surgery, 4% after c-section, 2%-4% after herniorrhaphy³. Surveys of patients with post-traumatic neuropathic pain show 84.7% report significantly high negative impact on quality of life while 97.6% have at least moderate negative impact by their nerve injury and pain⁴. The dysfunction due to post-traumatic peripheral neuropathic pain has been a treatment challenge for clinicians and patients. Bates et al (2019) advocated an evidence base non-surgical algorithm with six lines of treatment, including pharmacological, non-pharmacologic, operative, neuromodulatory and behavioral based care with recommended time to intervention at each line of therapy from the 1st to 6th levels⁵. Unfortunately, the long-term outcome of non-surgical interventions provided benefit to only 25% of patients seen in tertiary care centers with 92.1% reporting at least 1 adverse effect⁶. Operative therapies of the peripheral nerves include neuroma resection, neurolysis, neurorrhaphy with or without auto- or allo-grafts with reported benefits ranging from 40% with >50% relief of

pain⁷, 80% with reduction of 2 points on VAS (only 11% had pain resolved)⁸, and 48.8% rating complete satisfaction⁴ with different surgical methods. Identification of surgical outcome variables have been challenging due, in part, to the variability in pain characteristic, various types of nerve injury, age, locations, and durations.

Of the twelve cranial nerves, the trigeminal nerve provides the majority of somatosensation and special sense function for the head and neck. Injury to any of the three divisions of the trigeminal nerve occurs inadvertently during common surgical procedures (approximate 1% of all wisdom teeth extractions, via trauma (50% of body and angle fractures of the mandible and 35% of maxillary fractures) or intentionally (100% of hemi- and total mandibulectomy for benign and malignant pathology). Post-traumatic trigeminal neuropathic pain (PTTNp) may result from injury to the sensory division of the trigeminal nerve. The branches of the trigeminal nerve most commonly affected are the inferior alveolar nerve (IAN) and the lingual nerve (LN)^{9,10}. The exact etiology is still not completely understood. However, several animal studies have suggested certain biological processes as underlying contributors such as inflammation, enhanced neuropeptide-mediated pain signal transmission, endothelin receptor activity, and glial cell dysfunction causing trigeminal hyperexcitability¹¹⁻¹⁵.

Like non-trigeminal peripheral neuropathies, Meewis et al (2020) showed that neurosensory deficits with PTTNp had lower quality of life

values when compared to patients with neurosensory deficits without PTTNp¹⁶. Van der Cruyssen (2021) reported that after 20 weeks of pharmacologic, behavioral, topical or any non-surgical treatment there was no significant correlation with improvement or resolution of PTTNp¹⁷. In case series and cohort studies the resolution of PTTNp using neurolysis, neurorrhaphy direct, autograft or allograft were reported in 11% (2/14 cases)¹⁸, 20% (8/10 cases)¹⁹, 9% (1/11 cases)²⁰, and 25% (7/28 cases)²¹. Thus, the general consensus was that peripheral trigeminal nerve surgery had limited benefit (20% resolution, 40% reduction and 40% recurrence with enhancement of PTTNp) in the resolution of PTTNp. Like non-trigeminal neuropathic pain, the identification of surgical outcome variables was challenging, however, two studies of PTTNp patients treated with surgery that had resolution or recurrence postoperatively, the time from injury to surgery and the visual analog scaling of the preoperative pain intensity was correlated with the resolution, but was not statistically significant^{20,21}.

The purpose of this review was to present the results of three observatory studies on the effects of peripheral trigeminal nerve surgery on the resolution of PTTNp. Specifically, the time from injury to surgery of the trigeminal nerve in patients with PTTNp, the preoperative pain intensity level as measured by Visual Analogue Score (VAS) in patients with PTTNp and the intentional transection of the IAN or LN with immediate repair using long span nerve allografts. The investigative hypotheses were that the time from injury to

surgery and the preoperative pain intensity has no effect on the resolution of PTTNp and the occurrence and incidence of PTTNp are not affected by the immediate repair of an intentionally transected trigeminal nerve. The 3 independent variables listed above were used to determine the dependent variable in these studies as the presence or absence of PTTNp in patients 6 months post-surgery.

Patients and Methods

Two retrospective cohort studies were conducted with the approval of the UT Southwestern (UTSW, Dallas, Texas) institutional review board (STU-2021-1163). A third was conducted at 7 sites in the USA with the approvals of institutional review boards at UT Southwestern, University of Illinois at Chicago, University of Texas Health Sciences Center at Houston, Tufts University School of Dental Medicine, University of Texas Medical Branch at Galveston, John Peter Smith Health Network, and Oregon Health Sciences Center including reciprocal data transfer and use agreements. To test the hypothesis of the single institute studies, the investigation recruited patients with PTTNp who elected trigeminal nerve surgery. In the multi-site study, patients were included who had undergone resection of the mandible for benign or malignant disease, including the intentional transection of the IAN or LN and had immediate repair of the nerve (compared to a no repair arm).

The Inclusion criteria of the patients in the single site studies were similar and included: 1. neurosensory complaints in the IAN or LN distributions following third molar extraction,

endodontic treatment, orthognathic surgery, dental implant placement, or mandibular trauma; 2. clinical neurosensory nerve test (NST) and/or magnetic resonance neurography (MRN) findings of a Sunderland Class II to V injury; 3. Clinical neurosensory test based diagnosis of neuropathic pain that resolved with local anesthetic blocks to the injured nerve preoperatively; and, 4. Any age, gender or race. Patients were excluded if they had any of the following: 1. acute infection at the time of surgery; 2. history of radiation therapy to the head and neck; 3. current or previous malignancy of the head and neck; 4. medication-induced osteonecrosis of the jaw; 5. demonstrated persistent PTTNp after peripheral trigeminal nerve blocks or in response to control nerve blocks; and 6. did not have postsurgical neurosensory and neuropathic testing.

Post-traumatic trigeminal neuropathic pain was the primary outcome value that was recorded as present or absent using a previously described classification system²². The primary predictive variables were time to surgery in four groups (group 1= 0 to 100 days; group 2 = 101 to 200 days; group 3 = 201 to 300 days; group 4 = >300days) and visual analog scale pain intensity rating presurgical in three groups (group 1= VAS score 1-3; group 2 = VAS score 4-6; group 3 = 7 -10). In the multi-site study, the primary predictive value was the immediate repair of the trigeminal nerve or no repair.

Each patient underwent microneurosurgery of the involved IAN or LN as previously described²³. One of the 4 following classifications of Sunderland based on the

surgical findings was assigned: 1. Normal and intact (Class II); 2. Compressed and intact (Class III); 3. Partial transection (Class IV); or 4. Complete transection (Class V). The type of repair was assigned to one of 3 categories: 1. Neurolysis; 2. Direct neurorrhaphy; 3. neurorrhaphy with allograft (AVANCE, AxoGen Inc. Alchua, FL). For every patient, preoperative non-surgical management(s) of their PTTNp (medical, behavioral, physical or other) were held postoperatively to eliminate confounding effects. Non-surgical treatment was held indefinitely or until the recurrence of PTTNP was confirmed.

The following data were collected for each patient: 1. Age; 2. Gender; 3. Subcategory of neuropathic pain (allodynia, hyperpathia, hyperalgesia, combinations); 4. Branch of nerve injured (IAN and LN); 5. Sunderland Classification (Class II, III, IV, V determined at the time of surgery); 6. Form of nerve repair performed (Neurolysis, direct neurorrhaphy, neurorrhaphy with allograft); 7. Duration of follow up (in months); 8. Medical Research Council Somatosensory (MRCs) grading at 6 months postsurgery; 9. Presence (weighted value = 1) or absence (weighted value = 2) of neuropathic pain at 6 months postsurgery; and, 10. The time from injury to repair (in months).

The explanatory values were placed in mutually exclusive and internally equivalent subgroups (ordinal data points) using assigned and weighted values. The demographic and injury characteristics of the 4 cohorts of time to surgery and 3 cohorts of VAS pain intensity were compared to assess whether the 4 groups were similar using

Wilcoxon signed rank analysis. Repeated measures analysis of variance (ANOVA) with a confidence level of 0.05 was used to assess whether there was significant difference in the presence or absence of PTTNp. If a statistical difference was found in ANOVA testing, a post hoc Tukey-Kramer test was performed, with a p -value of 0.05 considered significant to determine whether the presence or absence of PTTNp found at 6 months was affected by any or all of the covariate variables.

Linear and logistic regression models were performed to determine the relationship between the primary predictor, the primary outcome variable and the explanatory covariate variables.

The inclusion criteria for the multi-site study was the following: 1. patients who had undergone the resection of the mandible for benign or malignant disease including the inferior alveolar nerve (IAN) or lingual nerve (LN) of any age, gender, race or socioeconomic background at the 7 study sites between 2012 and 2022; 2. Had either a nerve allograft reconstruction of the IAN or LN (4 to 7cm) performed immediately with reconstruction of the mandible; 3. No reconstruction of the IAN or LN performed with reconstruction of the mandible; 4. Data regarding pain presence or absence at least 6 months postoperatively; and 5. No evidence of sensory disorder or neuropathic pain prior to surgery. Patient data was excluded for the following: 1. History of sensory abnormality (numbness, paresthesia, dysesthesia, etc) prior to surgery; 2. History of peripheral neuropathy; 3. History of additional surgeries required on affected side(s) within 6 months

from initial surgery; and 4. Inadequate pain information at least 6 months postoperatively.

The data collected was the same as the single-site studies with the addition of the following: 1. classification of the pathology treated, benign or malignant; 2. use of either radiation or chemotherapy; and 3. Postoperative pain (CPSP) at 6 months and/or post-traumatic trigeminal neuropathic pain (PTTNp). Two-tailed independent Student's- t -test or independent Welch's t -test were performed and, a post hoc logistic and simple linear regression model were performed to determine the relationship between the primary predictor, the primary outcome variables and the explanatory covariate variables.

Results

Three retrospective observational studies were conducted. In the single institution studies there were 60 patients in the time to surgery and 48 in the VAS pain intensity analyses that met inclusion and exclusion criteria. The mean age was 43 and 42 respectively (median – 44, range 16-82, std.dev. 15.98). Twenty-three % to 27% males and 73% to 77% females. Thirty-three % to 37% lingual and 62% to 67% inferior alveolar nerves. Every patient had PTTNp preoperatively with distributions of characteristics as follows: allodynia (50%-58%), hyperpathia (10%-23%), and hyperalgesia (23%-33%) with 9% having combinations. The Sunderland Classification found at surgery included the following classes: Class II (13%-15%), Class III (35%-40%), Class IV (29%-31%), and Class V (16%-

20%) injuries. No patients underwent internal neurolysis, with surgical procedures characterized as the following: external neurolysis with placement of a nerve wrap (40%-42% , AXOGUARD, AxoGen Inc., Alchua, Florida), direct neurorrhaphy (10%-17%), and neurorrhaphy with allograft (40%-42%, AVANCE, AxoGen Inc., Alchua, Florida). The mean follow-up in months from surgery was 14.66 months (median- 12, range 6 -86, std dev -16.57). The MRCS grading at the 6-month postsurgical follow up included the following ranges: S2 (16%-17%), S2+ (13%), S3 (33%), S3+ (20%), and S4 (16%).

Time to Surgery

Table 1 presents the distribution of the presence or absence of PTTNp at the 6-month postsurgical follow up within and between the 4 cohorts based on time from injury to surgery. The weighted mean PTTNp score in Group 1 was 1.6±0.32; Group 2 was 1.61±0.18; Group 3 was 1.3±0.29; and Group 4 was 1±0.0. There was a statistically significant difference between the cohorts, p

= 0.0002 and no statistically significant difference within the cohorts. Post hoc analysis of the between-group differences showed statistically significant differences, p < 0.01, in the following distributions: 1. between Group 1 and Groups 3 and 4; 2. between Group 2 and Groups 3 and 4. Post hoc analysis of the between-group differences showed no statistically significant differences in the following distributions: 1. between Group 1 and Group 2; 2. between group 3 and group 4. Within the 4 cohorts, the percentage of patients with PTTNp before surgery with no neuropathic pain at the 6-month follow up was 41.6%. However, between the 4 cohorts, when the time to surgery was 200 days or less, the percentage of patients with PTTNp before surgery with no neuropathic pain at the 6-month follow up was greater than 60% with statistically significant differences when the time to surgery was greater than 200 days. Figure 1 shows the presence and absence of PTTNp within each of the 4 cohorts at the 6-month postsurgical follow up.

Table 1. Overall 6 month post-traumatic trigeminal neuropathic pain weighted scores per group based on time to surgery in days from injury

Cohort (days)	Mean	Standard Deviation	95% CI
Group 1 (0-100)	1.6	0.32	[1.27-1.92]
Group 2 (101-200)	1.61	0.18	[1.42-1.8]
Group 3 (201-300)	1.3	0.29	[1.0-1.59]
Group 4 (>300)	1.0	0.01	[0.99-1.0]

Between Groups ANOVA p value= 0.0002

Tukey Post-hoc HSD test p value

Group 1,2; Group 3,4 = NS

Group 1,3; 1,4; 2,3; 2,4 = <0.01

Figure 1

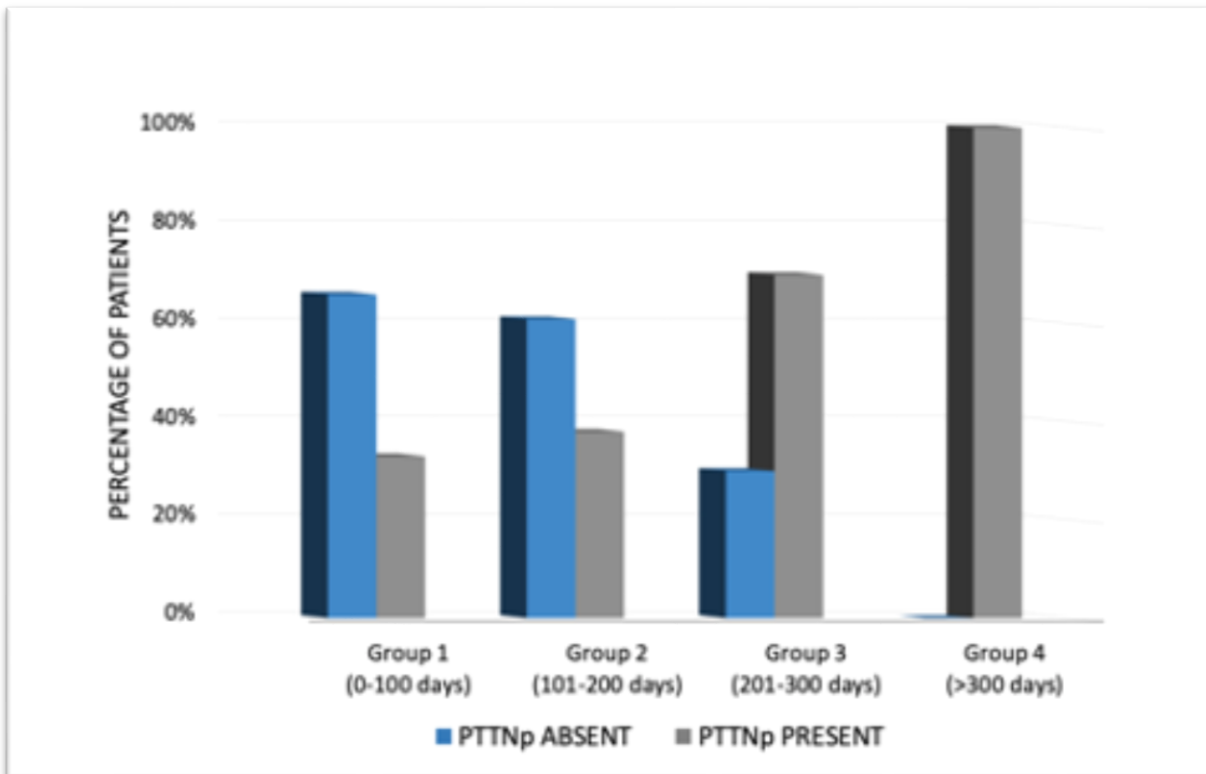


Figure 1: Absence and presence of post-traumatic trigeminal neuropathic pain at 6 months postsurgical follow up. When the time to surgery was 200 days or less, the percentage of patients with neuropathic pain before surgery with no neuropathic pain at the 6-month follow up was greater than 60%.

Preoperative pain intensity

Two cohort groups were established to determine the relation of preoperative pain intensity as measured by the VAS to postoperative recurrence of PTTNp. All patients had preoperative PTTNp, and the cohorts were divided by presence or absence of PTTNp at the 6 month postoperative visit. In the patients who had no PTTNp at 6 months, the average VAS score was 6.4 (range 1-10, std dev 2.68). In patients who had recurrence of PTTNp at 6 months, the average VAS score was 7.75 (range 4-10, std dev 1.95). There was a statistically significant difference between the two groups ($p= 0.0412$). Figure 2

shows the percentage of patients who had recurrence of PTTNp at 6 months based on the level of preoperative pain intensity from group 1 (1-3), group 2 (4-6) and group 3 (7-10).

Figure 2

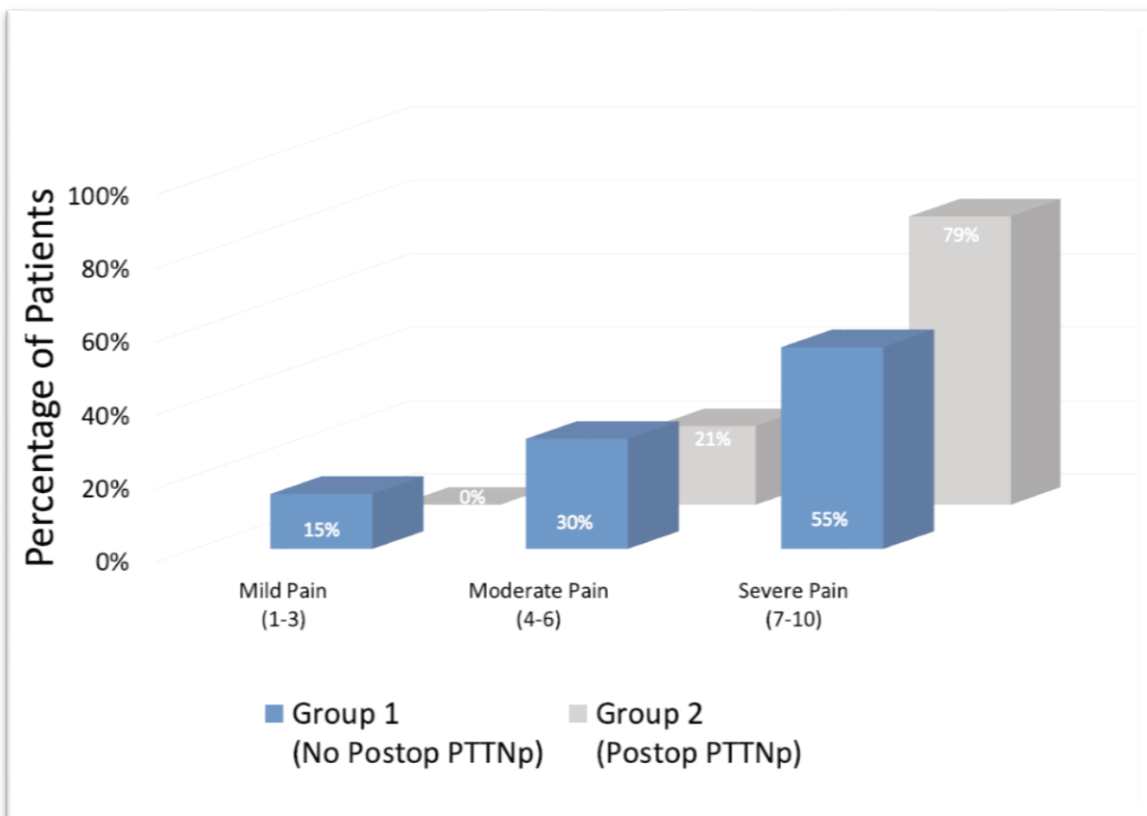


Figure 2: Percentage of patients with no post-traumatic trigeminal neuropathic pain at the six month postoperative visit compared to those with post-traumatic trigeminal neuropathic pain at that time with preoperative mild, moderate or severe pain measured by the Visual Analog Scale score.

Immediate repair of intentionally transected nerve

In the multi-site observational study, 197 patients met inclusion and exclusion criteria. Of the 197, 103 had immediate reconstruction of the intentionally transected nerve with a long-span nerve allograft between 4 to 7 cm (AVANCE, AxoGen Inc, Alchuala, FL). One hundred and forty-seven (74.6%) mandibular resections were for benign pathology and fifty (25.4%) mandibular resections were for malignant pathologies. Radiation or chemotherapy was provided to 60 patients (30.5%).

There was a statistical difference in age ($p < 0.00001$), type of pathology ($p < 0.00005$), chemo/radiation treatment ($p < 0.00001$) and postoperative pain and PTTNp ($p < 0.00008$) between the immediate and no repair groups. Patients were older, more likely having malignant mandibular pathology that required chemo/radiation treatment in the no repair group than the immediate repair group. Table 2 shows the mean, standard deviation and 95% confidence intervals of the primary outcome variable per primary predictor variable (immediate repair and no repair). A statistically significant difference was found

between the predictor variables ($p=0.00009$) and post-hoc logistic regression modeling confirmed statistical significance ($p=0.05$) with an inverse relationship between immediate repair and the presence of pain and PTTNp at 6 months (less pain present with immediate repair and no PTTNp). In the immediate repair group, 4 had CPSP and none had PTTNp for an incidence of 3.8% and 0% respectively

while the no repair group had an incidence of 22.3% and 2.12% respectively. An odd ratio of 0.43 points out that the immediate repair group has 43% lower odds of developing and reporting chronic postoperative pain or PTTNp when the nerve is immediately repaired compared to the no repair group.

Table 2: Primary Outcome Variable (pain at 6 months) per Primary Predictor Variable (immediate repair and no immediate repair) of the resected mandible for benign or malignant disease

Cohort	Mean	Standard Deviation	95% Confidence Interval
Immediate Repair	1.97	0.17	[1.94 – 2.00]
No Immediate Repair	1.76	0.42	[1.60 – 1.84]

Welch's independent t-test P value = 0.000092

Linear Regression R square = 0.077, $p<0.001$, goodness of fit $F(1,182) = 16.035$ with $p= 0.000088$

Logistic Regression coefficient = -0.85, $p\text{-value}=0.05$, Odds Ratio=-0.43, 95% CI = 0.18, 1.01

Discussion

This review presents two retrospective single-site and one multi-site observatory studies on the effect of trigeminal nerve surgery on the presence or absence of PTTNp. In patients who had developed PTTNp prior to surgery due to documented trigeminal nerve injuries we found that time from injury to surgery effects the recurrence of PTTNp and surgery performed within 200 days had greater than 60% chance for resolution of PTTN pain without affecting the level of sensory recovery. Surgical delay after 200 days, approximating 6 months, negatively impacts the resolution of PTTNp and when delayed after 300 days, approximating 1 year, PTTNp was not resolved at all²⁴. We also showed that preoperative VAS pain level was related to

surgical outcome in the treatment of PTTNp. Lower presurgical pain score was related to relief of PTTNp after surgery with mild pain scores (15% of the patients) presurgically had 0% recurrence of PTTNp after surgery while severe pain scores (55% of the patients) presurgically had nearly 80% of the PTTNp recurrence after surgery²⁵. Finally, in the multi-site study in patients without PTTNp prior to the intentional transection of the IAN and LN during resection of the mandible for benign and malignant disease, the immediate repair of the transected IAN or LN demonstrated no cases of PTTNp compared to no repair group with 2.12%.

In the existing literature, including our own clinical trials, the benefit of trigeminal nerve surgery was questioned due to high

recurrence rates and possibility of exacerbation of the levels of PTTNp when it was present before surgery in the trigeminal^{18-21,26} and non-trigeminal peripheral nerves⁶⁻⁸.

The literature has also pointed out that greater neuropathic pain scores preoperatively predicted greater neuropathic pain scores at 6 months post thoractomy ($p < 0.001$)²⁷. In a large multicenter study assessing neuropathic pain following 13 different types of surgical procedures, acute pain levels higher than 4 in the immediate postoperative period predicted neuropathic pain at 2 months²⁸. In two studies of PTTNp patients treated with surgery that had resolution or recurrence postoperatively, the time interval from injury to surgery and VAS pain intensity score was correlated with the resolution, but was not statistically significant^{20,21}. Several studies have reported that resection of the mandible for benign pathology, including the trigeminal nerve, can be reconstructed immediately with long span nerve allograft with functional sensory recovery in 92% of adult patients in a prospective, multicenter, controlled study^{29,30} and 100% of pediatric patients in a retrospective, controlled study³¹. Recently an ambispective, non-controlled study reported functional sensory recovery was achieved with immediate reconstruction of the mandible for malignant disease with or without radiation and chemotherapy postsurgical treatment³². Another retrospective, controlled study showed that functional sensory recovery was present in 70% of patients an average of 4 to 5 years postresection without immediate repair using a nerve allograft³³. None of these

studies reported an incidence of PTTNp. It is likely that previous studies for PTTNp were not able to detect differences due to low power in the post TNI PTTNp groups and both immediate and no repair groups reported following mandibular resection surgery.

This review points out that peripheral nerve (trigeminal) surgery should be revisited as a positive modality in the prevention of and treatment for post-traumatic neuropathic pain when a nerve will be intentionally injured or after the development of neuropathic pain as a consequence of an injury. In patients who have developed post-traumatic neuropathic pain, at least for trigeminal, the time from injury to surgery has an effect on the recurrence of PTTNp. Best outcomes occur when operative interventions occur within 200 days of the injury. The reason why early intervention is emphasized is that the current recommendations for the management of neuropathic pain is pharmacologic therapy as the 1st and 2nd lines, each for 4 to 6 weeks, before moving to operative, neuromodulatory or central nervous system interventions. Given an early and immediate post-injury diagnosis of PTTNp and exhaustion of the 1st and 2nd line treatments, the time to consider operative management is now 60 to 90 days which would be within the 100 day margin found to have better than chance for resolution of PTTNp. However, if the diagnosis is delayed beyond 90 days and certainly after 120 days, and the treatment has failed after an additional 60 to 90 days, then the chance for resolution of PTTNp using operative interventions drops to 30% . Pain intensity

provides additional support for surgical intervention outcome. Providers should consider earlier surgical intervention if mild or moderate pain intensity (range 1 to 6 of 10) is reported in the first 200 days from the PNI. In our study, the cohort with pain at 6 months follow up had higher mean preoperative VAS scores. This cohort also had a longer mean time interval from injury to surgery. Some point out that post-traumatic neuropathic pain continues to increase in intensity over time when corrective interventions are not provided^{6,34}. Furthermore, patients with PTTNp who report moderate to severe pain and high VAS scores have lower quality of life and depression scores which affect outcome of treatment^{16,17}. Our two studies suggest that earlier operative intervention in patients who report mild to moderate pain intensity will have the best outcomes so that intentional delay by pharmacologic means or chronic management may not be justifiable unless operative risks are present.

To address the preventive role of operative peripheral nerve surgery on the development of PNI neuropathic pain, we must consider the concept of the neuromatrix modulating input from sensory and/or motor nerves when their input is removed by injury or surgery on phantom limb and pain development post-amputation introduced by Melzack³⁵. This sensitization concept was extended to include neuroplastic changes in the peripheral and central nervous systems response to persistent nociceptive stimuli which can also be due to amputation neuroma formation at the proximal end of the transected, unrepaired peripheral nerve³⁶⁻³⁸. By repairing

the nerve, the noxious input can be eliminated so there can be a significant reduction or even prevention of sensitization in either or both peripheral and central nervous systems^{36,38}. A recent study reported that prophylactic regenerative peripheral nerve interface (RPNI) surgery at the time of limb amputation had a statistically significant difference in the resolution of both neuroma pain and phantom pain (97% in both) compared to treatment of patients with pre-existing postamputation pain (<50% in both groups)³⁹. Our findings support the concept that early/immediate re-establishment of sensory input to peripheral and central sites prevents or even can reverse the peripheral driver responsible for the development of PTTNp. However, the possibility that central changes at higher levels may not be affected exists.

This review of the outcomes of three retrospective observational studies of the effect of nerve surgery on neuropathic pain suggests that peripheral nerve surgery should be reconsidered as an early and effective intervention in the treatment and/or prevention of neuropathic pain. Future studies should determine if the positive effects of surgery on neuropathic pain are more profound when operative care is provided in the acute (within 4 days) and subacute (between 5 and 21 days) phases that parallel our findings in the immediate repair condition when compared to the delayed conditions.

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Conflicts of Interest statement

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