Review

Considerations in the Diagnosis and Treatment of Post-Traumatic Neuropathic Pain: A Narrative Review

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Review

Considerations in the Diagnosis and Treatment of Post-Traumatic Neuropathic Pain: A Narrative Review

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Abstract: This study aims to provide an updated overview of the systematic evaluation and management of Post-Traumatic trigeminal neuropathic pain (PTTN) resulting from dental procedures or trauma. PTTN arises following an injury to the trigeminal nerve, which is responsible for sensory and motor functions in the maxillofacial region. The etiology encompasses various dental procedures and craniofacial trauma, leading to a spectrum of symptoms, from tingling to severe pain. Diagnostic challenges stem from the absence of standardized criteria and the overlap with focal neuralgia, necessitating comprehensive evaluation. Misdiagnosis can result in prolonged suffering and unnecessary procedures. Successful management hinges on prompt diagnosis and interdisciplinary collaboration, with early intervention crucial in mitigating chronicity. While nerve recovery post-trauma is challenging, preventive measures through accurate evaluation and treatment are paramount. Management for PTTN includes non-invasive and surgical interventions. Non-invasive intervention includes systematic and local pharmacological management. This review enhances uniformity in PTTN evaluation and treatment approaches despite standardized study limitations.

Keywords: management; neuropathic pain; post-trauma; trigeminal nerve

1. Introduction

This study aims to provide a comprehensive overview of the current understanding and management strategies concerning Post-Traumatic Neuropathic Pain (PTTN) arising from dental procedures or traumatic events. PTTN refers explicitly to neuropathic pain arising after injury to the trigeminal nerve, the fifth cranial nerve governing sensory and motor functions across the maxillofacial region through its divisions: V1, V2, and V3 [1]. It serves as the conduit for sensory input related to temperature, pain, and tactile sensations in the facial region while also contributing significantly to motor control of masticatory muscles [1]. When these nerves sustain an injury, the pain persists beyond the typical healing period. This persistence manifests in a spectrum of symptoms, ranging from the absence of pain to sensations of tingling and severe discomfort [1,2].

Various factors can contribute to its onset, including dental procedures and significant craniofacial interventions such as extracting mandibular third molars, placing implants, performing root canal therapy, and administering local anesthesia [3]. The extent of damage can vary greatly, ranging from mild to severe cases [1]. Prevalence rates of PTTN fluctuate across studies, primarily due to the absence of clearly defined diagnostic criteria [4]. Nevertheless, PTTN appears to have a relatively low incidence in the oral and maxillofacial regions compared to other systemic neuropathic pains [5].

PTTN relies predominantly on clinical signs and symptoms, occasionally supplemented by a patient's medical history and evidence of structural damage or trauma [3]. Clinicians navigate challenges in diagnosis due to potential overlap with focal neuralgia, necessitating a meticulous examination to distinguish PTTN from other sources of oral cavity pain, including odontogenic pain and referred pain [2]. Misdiagnosis risks prolonging patient suffering and may lead to unnecessary, costly, and potentially harmful interventions such as root canals or surgeries [6]. The diagnostic

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process entails comprehensive medical and dental history assessments and thorough intra-oral and extra-oral examinations, occasionally augmented by supplementary diagnostic tests [7]. Standardized diagnostic tools for PTTN are lacking, underscoring the importance of demonstrating trigeminal nerve dysfunction to meet diagnostic criteria [7]. While evident sensory deficits may facilitate diagnosis in significant trigeminal nerve damage cases, subtler deficits may necessitate extensive somatosensory testing to confirm lesions [7].

The rising demand for dental care correlates with an increase in trigeminal nerve injuries, adding to the global healthcare burden as neuropathic pain tends to persist chronically [8]. Moreover, chronic pain often precipitates adverse social and psychological outcomes, including depression, anxiety, and post-traumatic stress disorder, further complicating patient management [9].

Effective management of neuropathic pain necessitates timely diagnosis and intervention. Early initiation of appropriate treatment can mitigate the progression towards chronic pain in some instances [6]. However, preventing the progression of chronic neuropathic pain is often challenging, necessitating collaboration among specialists, including neurologists. Moreover, when pain management is complicated by psychosomatic factors, collaborative consultation with a psychiatrist becomes essential [6].

Nerve recovery following injury is frequently constrained, underscoring the critical need for precise evaluation and intervention to avert such injuries. This study seeks to thoroughly examine the pathological features, systematic evaluation, and management of PTTN, utilizing insights from the latest research. Despite recognizing the challenges in offering definitive assessments and solutions, this study aims to contribute to partially standardizing evaluation and treatment practices.

2. Characteristics, Etiology, and Pathophysiology of PTTN

2.1. Characteristics of PTTN

The clinical characteristics of PTTN demonstrates considerable heterogeneity, attributable to an interplay of environmental, psychosocial, and genetic factors [9,10]. The clinical phenotype may include spontaneous and evoked pain, positive symptoms (e.g., paresthesias), and negative symptoms (e.g., numbness) [9,10]. PTTN typically manifests at the injury site or within the dermatomes corresponding to the affected nerves [9.10]. It can be confined to the injury site, extend throughout the dermatome, or present as either localized or diffuse pain [9,10]. The intensity of pain experienced can range from mild to severe [9,10].

In instances of significant nerve branch damage, patients may experience severe allodynia [9,10]. Over time, some patients may develop hyperalgesia and other sensory alterations in regions beyond the trigeminal nerve, indicating more extensive changes in central somatosensory processing [9,10]. PTTN pain is unilateral and rarely extends beyond the midline [9,10]. In some cases, PTTN becomes more diffuse over time [9,10]. Symptoms of PTTN come in many forms: persistent pain usually lasts all day and is present most days, while paroxysmal pain is spontaneous or initiated by touch or function [9–11]. Patients may experience clinically unexplained swelling, foreign body sensation, heat or cold, and localized pain [9–11].

This chronic pain frequently leads to psychological issues such as sleep disturbances, depression, and anxiety, consequently diminishing the quality of life [12.13].

2.2. Etiology of PTTN

PTTN can result from various types of trauma, and its prevalence varies significantly across studies [1,2,5,6,14]. According to a survey by Benoliel et al., the prevalence of PTTN ranges from approximately 3% to 5% in patients undergoing root canal treatment, and around 3% following major trauma such as facial fractures, extraction of mandibular third molars, or implant treatment [2]. The association between the severity of trauma and the outcome was found to be insufficiently robust [2].

Olga et al. reported that, unlike traumatic injuries in other parts of the spinal cord, those in the maxillofacial region have a significantly lower incidence of developing painful neuropathic pain [15]. Specifically, they found that about 3.3% of facial fracture patients, approximately 8% of patients after

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implant treatment, 3-13% of patients undergoing general/non-surgical root canal treatment, and around 5% of those undergoing surgical root canal treatment developed chronic neuropathic pain [15].

The incidence of neuropathic pain appears to be higher in women than in men [2,6,14]. Ajay et al. reported a PTTN prevalence of 1.55%. In the age group of 41 to 60 years, sensory impairment related to PTTN was significantly higher in men (60.4%) than in women (39.5%), which contrasts with findings from other studies [14]. The distribution of PTTN showed a higher involvement of the right quadrant (upper/lower) of the jaw (67.4%) compared to the left quadrant (32.5%) [14].

In a study by Kumar et al., the prevalence of PTTN was found to be 2.11%, with a higher incidence in women than in men in the 40 to 60 age group [5]. Out of the PTTN cases, 85.7% occurred in the lower jaw, with the right quadrant involvement at 57.1%, slightly higher than the left quadrant [5]. This could be attributed to anatomical variations, such as a smaller opening on the right side of the skull through which branches of the mandibular nerve pass [5].

Klazen et al. conducted a study on 53 cases of iatrogenic trigeminal nerve injury, reviewing patient records for PTTN associated with nerve injuries during implant surgery, root canal treatment, local anesthesia, tooth extraction, or third molar removal [16]. The patient cohort ranged from 15 to 80 years of age (mean age, 42.1 years), with a predominance of females (68%) [16]. The inferior alveolar nerve (IAN) was the most frequently injured (53%), followed by the lingual nerve (LN) (40%) [16]. Nerve injuries predominantly occurred during third molar removal (45%), implant placement (17%), and local anesthesia administration (17%) [16]. Pain symptoms were reported in 54% of patients with IAN injuries, compared to 10% of those with LN injuries, and persistent neurosensory impairment was observed in 60% of the cases [16].

Penarrocha et al. found that in 63 patients with trigeminal neuropathy of traumatic origin, 54% of all cases were diagnosed after mandibular third molar surgery [17]. Sensory deficits were attributed to the mental and lingual nerves in 37 and 19 patients, respectively, affecting the areas these nerves dominate [17]. Pain was reported in 57% of cases, especially in elderly patients [17]. Regarding the impact on quality of life, no changes were observed in 3 cases, mild changes in 25 cases, and serious changes in 8 cases [17]. Partial or complete recovery was seen in 25 cases after 6 months and in 32 cases after one year, with minimal recovery beyond that period [17]. The youngest patients with the least pain recovered the fastest [17].

2.3. Pathophysiology of PTTN

Iatrogenic trauma leading to PTTN is frequently caused by dental interventions such as endodontic treatments, tooth extractions, oral surgeries, dental implants, orthognathic surgeries, and other invasive procedures [2,6]. Notably, even relatively minor procedures, like local anesthetic injections, can provoke neuropathic pain within the trigeminal nerve's territory [2,6]. Local anesthetic-induced neuropathy may result from direct physical trauma and/or the neurotoxic effects of the anesthetic agent [2,6].

Animal studies have been instrumental in elucidating the pathophysiology of PTTN [2,6,15,18,19]. These studies highlight the pivotal role of inflammatory responses in the injured nerve system [15,18,19]. Numerous inflammatory mediators contribute to peripheral and central sensitization over time, which includes modifications in the functional, biochemical, and physical properties of glial cells and neurons against the backdrop of their genetic makeup [15,18,19].

Nerve injury disrupts neuronal electrical activity, leading to peripheral sensitization and nociceptor activation [15,18,19]. This process involves the release of inflammatory mediators, which lower the thresholds and increase the excitability of the peripheral terminal membrane [15,18,19]. The resultant inflammatory response causes blood vessel dilation, white blood cell recruitment, and mast cell degranulation, further reducing the threshold [15,18,19]. Peripheral sensitization intensifies rapidly due to inflammation associated with the activation or sensitization of nociceptors, potentially manifesting early clinical signs of hyperalgesia and allodynia [15,18,19].

Multiple studies have demonstrated altered firing properties of Aβ, Aδ, and C fibers during the spontaneous activity associated with painful neuropathies [15,18,19]. Spontaneous activity in C and

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Aδ fibers is likely responsible for spontaneous burning or sharp pain, while spontaneous activity in Aβ fibers is typically associated with paresthesia and dysesthesia commonly observed in neuropathies [15,18,19]. Following trauma, damaged neurons can form neuromas that act as ectopic centers for neurophysiological activity, amplifying nociceptive input during certain stages of the healing process [15,18,19]. Additionally, Aβ fibers, which usually transmit only innocuous stimuli, can undergo phenotypic changes and produce substance P, thereby eliciting pain sensations in response to peripheral stimulation, potentially explaining the phenomenon of allodynia [15,18,19].

Central changes arise from the persistent activity of afferent nerves transmitted to the central nervous system (CNS), leading to increased CNS sensitivity and amplified responses in the context of central sensitization [15,18,19].

3. Assessment and Diagnosis of PTTN

The diagnostic criteria for Post-Traumatic Trigeminal Neuropathy (PTTN) as outlined in the International Headache Society's ICHD-3rd edition are as follows [20]:

Table 1. Diagnostic criteria of PTTN in the International Headache Society's ICHD-3rd edition.

Diagnostic criteria
A. Facial and/or oral pain in the distribution(s) of one or both trigeminal nerve(s) and fulfilling criterion C
B. History of an identifiable traumatic event[1] to the trigeminal nerve(s), with clinically evident positive (hyperalgesia, allodynia) and/or negative (hypaesthesia, hypalgesia) signs of trigeminal nerve dysfunction
C. Evidence of causation demonstrated by both of the following:
1. pain is localized to the distribution(s) of the trigeminal nerve(s) affected by the traumatic event
2. pain has developed <6 months after the traumatic event
D. Not better accounted for by another ICHD-3 diagnosis.

When these criteria are met, a diagnosis of PTTN can be made.

Another international standard, the first edition of the International Classification of Orofacial Pain (ICOP), defines post-traumatic trigeminal neuropathic pain (PTNP) as unilateral or bilateral facial or oral pain and other symptoms secondary to trigeminal nerve trauma, with clinical signs of functional impairment persisting for more than 3 months or recurring [21].

Unlike other neuropathic pain conditions, there is no consensus on the diagnostic criteria for PTTN, but evidence of trigeminal nerve dysfunction is essential for diagnosis [1,4]. Diagnosis is straightforward when evaluation reveals direct damage to the trigeminal nerve with clear sensory deficits related to neuroanatomy [4]. In cases where sensory impairment is less pronounced, extensive evaluation of somatosensory function may be necessary to demonstrate lesions [4].

Dental imaging is crucial to confirm whether trauma has affected the nerves [4,7,22]. Panoramic radiography can evaluate if trauma directly affected the nerve [7,22]. For a more accurate assessment of bony structure, Cone Beam Computed Tomography (CBCT) is required [22]. Magnetic resonance imaging (MRI), due to metal artifacts, has limited diagnostic value for intraoral PTTN but may provide important information for surgical planning [23].

Various qualitative and quantitative sensory tests have been proposed to evaluate orofacial somatosensory functions [22,24]. Reliable and accurate methods require repeated stimulation, making the choice of technique time-dependent [22,24]. Standardized screening and comprehensive psychophysical testing are essential to improve diagnostic accuracy and understanding of neural mechanisms and somatosensory changes in orofacial pain conditions [22,24]. Quantitative sensory testing (QST), using advanced techniques to assess sensory thresholds and deficits, is effective but expensive and time-consuming [24].

Qualitative Sensory Testing (QualST), performed with simple tools such as thermal (ice, hot tools) and mechanical (pinprick, cotton wool, calibrated monofilament) stimuli, can be done next to

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a dental chair [4,7,22,24,25]. However, factors such as patient instructions, age, gender, mood, cognitive function, ongoing litigation, psychological distress, and patient cooperation can affect outcomes [22,24,25]. More systematic studies are needed to accurately distinguish pain conditions through psychosocial test comparisons [9,12,13,22,24].

Neurophysiological tests, such as brainstem reflexes that assess cranial nerve pathways, are useful for demonstrating somatosensory dysfunction and should be included in a comprehensive work-up with QST and sensory nerve action potential (SNAP) assessments, even though they do not directly measure somatosensory function [2].

Studies have evaluated methods for diagnosing PTTN[2,4,18]. Devine et al. systematically reviewed diagnostic and evaluation methods for neuropathic pain, analyzing 25 out of 28 papers that used various methods such as questionnaires, mechanical sensory evaluation (e.g., von Frey), QST, and psychological evaluation [4]. This review aimed to develop a comprehensive evaluation protocol for PTTN diagnosis, highlighting the need for consensus on systematic evaluation standards due to inconsistencies in diagnostic criteria [4].

Peñarrocha et al. demonstrated that clinical neurophysiological tests and QST are sensitive, quantitative, and objective methods for diagnosing and localizing trigeminal neuropathy [18]. Baad-Hansen and Benoliel found that QST could detect various somatosensory abnormalities in PTTN patients, indicating both loss and gain of function, although no specific QST profile exists [2]. Intraoral PTTN often goes unnoticed due to the small affected area, and few studies have mapped these impairments [2]. Approximately 7% of patients showed both trigeminal and extratrigeminal dysfunction, suggesting broader pain issues potentially linked to primary chronic pain, neuroplasticity, or functional pain rather than neuropathic pain [2].

PTTN is a chronic pain disorder often associated with psychosocial distress and sleep disorders, which can exacerbate chronic conditions. Evaluating these factors is crucial, typically using the Pittsburgh Sleep Quality Index (PSQI), a self-report questionnaire assessing sleep quality, latency, duration, efficiency, disturbances, use of sleeping pills, and daytime dysfunction. The SCL-90-R is also useful for assessing various psychosocial conditions [9,12,13,22,24].

4. Considerations for the Treatment of PTTN

Once a nerve has been damaged, recovery is very difficult [26,27]. Therefore, for successful treatment of PTTN, a rapid and accurate diagnosis must first be performed using a comprehensive evaluation method [26,27]. When appropriate treatment is administered quickly, further worsening of symptoms or complications can be reduced [26,27]. Above all else, it is essential to prevent such damage from occurring by conducting a thorough evaluation in advance. Early intervention is generally considered necessary in the management of all types of pain to avoid or reduce the risk of chronicity [2,4,26,27]. Many studies have shown that in managing PTTN, it is essential to surgically remove any causative factors, such as invaded implant into IAN or lingual plate fracture affecting LN in the early stages [28,29]. In a systematic review and meta-analysis, Kushnerev and Yates discussed the management of patients with PTTN. It was explained that it is necessary to remove the causative factors of the lesion within 12 hours if possible [30]. If this is not possible, it should be removed within a maximum of 30 to 48 hours after injury to avoid lasting nerve damage [30].

After the causative factors are removed, drug treatment is considered a priority because it is noninvasive and usually produces a good treatment response [28,29]. Early management of nerve damage aims to control the associated inflammation, considered one of the initiating factors of neuropathic pain [25,28,29]. Steroids are considered (prednisone 40 to 60 mg initially, gradually tapered over 7 to 10 days; dexamethasone, 12 to 16 mg initially and then similarly tapered) [25]. Tapering aims to reduce side effects from continuously high doses, but it is not always necessary [25,29,31]. Supporting this, animal studies have shown that early treatment with dexamethasone alleviates neuropathic pain, although no evidence from clinical studies currently exists [25,29,31].

If the larger nerve trunk is damaged, it may be suitable for surgical repair of the defect [25,31–34]. Early intervention may offer the best chance of restoring lost sensation [31]. However, It is currently unknown whether early surgical treatment affects the risk of developing PTTN [32.33]. It is

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unclear how quickly healing and function can be restored for nerve injuries that are not amenable to surgical treatment [31–33]. However, A study by Ziccardi and Steinberg recommends that surgery be performed within 90 days and reports that surgery performed after that is not very effective [34].

In patients with permanent neurological deficits, some may remain with painless neuropathy, while others may develop PTTN [32]. In such cases, further management first requires an accurate explanation of the patient's current condition and education on treatment directions, including the fact that additional invasive procedures aimed at relieving PTTN pain are not helpful and carry the risk of worsening the pain [32]. In the case of PTTN that occurs chronically, drug treatment is usually performed, and the most commonly used drugs are gabapentin and tricyclic antidepressants (TCAs) [26–30]. If there are side effects or pain is not controlled well with these drug treatments, selective noradrenaline reuptake inhibitors (SNRIs), pregabalin, and other drugs can be applied [26–30,35]. Compared to other neuropathic pain conditions such as postherpetic neuralgia, painful diabetic neuropathy, and painful spinal traumatic neuropathy, which have drug response rates of 20 to 40%, the response rate for PTTN is reported to be lower at approximately 11% [2]. Additionally, about one in three patients discontinue drug treatment, primarily due to side effects [2].

When systemic drug treatment cannot be used due to drug side effects or any other reason, local anesthetics or capsaicin can be a topical application [28,36]. Topical drug action helps reduce drug interactions by delivering high concentrations of drugs locally to the painful area while minimizing systemic effects [28,36]. It may be especially beneficial for patients taking multiple medications [28]. At this time, avoiding contact with areas other than the mouth is essential [28]. Commercially available LA and capsaicin patches are convenient to apply [28]. For topical application within the oral cavity, it is advisable to manufacture a device, such as a custom stent, designed to cover the painful area, as this allows the treatment to be applied only to the local area without damaging other tissues [28]. There are currently no official recommendations on the concentration of LA or capsaicin for oral use, but for capsaicin, the maximum concentration to avoid too much pain upon application is usually 0.1% [28]. For local anesthetic, commercially available lidocaine gel or cream can be used [28].

Botulinum toxin (BTX) injection therapy can help control PTTN pain when existing pharmacological treatments are ineffective [37,38]. BTX inhibits the release of various nociceptive mediators such as substance P, glutamate, and Calcitonin Gene-Related Peptide (CGRP) and expresses TRPV1, justifying its use in peripheral neuropathic pain [37,38].

Ranoux et al. conducted a randomized, double-blind, placebo-controlled study involving 8 patients with post-traumatic neuralgia, 17 patients with post-operative neuralgia, and 4 patients with post-herpetic neuralgia [39]. The study found that BTX injections were effective in reducing neuropathic pain. Patients were assessed at baseline and 4, 12, and 24 weeks post-injection, showing significant reductions in swelling allodynia, spontaneous pain, and cold allodynia, although no changes were observed in thermal or mechanical pain responses [39]. The therapeutic effects typically began 2 weeks after the BTX injection and lasted up to 24 weeks [38].

Various administration protocols for botulinum toxin in treating neuropathic pain have been reported, but there is no consensus on the optimal dosage for achieving an adequate therapeutic effect [37–39]. A recent systematic review reported that 25 to 100 units for trigeminal neuralgia are administered divided into 1 to 20 injections [37]. However, it needs to be used cautiously because it is still lacking to evaluate the effectiveness and safety of single or repeated injections of botulinum toxin [37–39].

Chronic pain, especially neuropathic pain that persists for a long time and is difficult to treat, has a significant impact on human health and well-being and often causes significant emotional distress in the form of anxiety and depression [40]. Psychological intervention may also be helpful in these cases, but studies evaluating the long-term prognosis of PTTN are lacking [27].

If prior non-invasive treatments are failed, surgical intervention may be condsidered such as neuroma resection, neurolysis, neurorrhaphy [27,28]. Identifying surgical outcome variables is crucial to guide the surgical treatment of PTTN [27,28,41]. The variability in pain nature, nerve damage severity, location, and time from injury to surgery contributes to the complexity of treatment

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[34]. In patients with preoperative neuropathic pain, 67% experienced neuropathic pain post-microsurgery [34]. The reasons for the variable effectiveness of nerve repair surgery in resolving neuropathic pain are unclear [34]. Chronic posttraumatic neuropathic pain can occur after surgery, with psychological, medical, and age-related factors as risk factors [34]. Recently, impaired surgical time and preoperative visual analog scale scores have been identified as influencing surgical outcomes for PTTN, highlighting the importance of timely intervention [34]. Delayed surgical intervention negatively impacts PTTN treatment, and patients with pain recurrence at six months often had more severe preoperative pain and a longer period between injury and surgery [34]. This suggests that persistent PTTN may lead to increased pain intensity over time [34]. Despite these findings, some patients with PTTN recover spontaneously or through non-surgical treatments after nerve injury [34].

With this surgical approach, a minimally invasive surgical technique using peripheral nerve stimulation, similar to the treatment of trigeminal neuralgia, is being introduced [41,42]. This may help treat PTTN when other treatment modalities have failed [41]. Although there are no papers documenting the complication rate for this technique, they say that smaller incisions can minimize the potential risks associated with nerve stimulator implantation [41]. Many studies consider surgical treatment after injury, but they are insufficient to verify the efficacy of surgery [41]. In particular, it has been reported that in the case of PTTN that persists for more than 3 months, permanent central and peripheral changes occur, making surgical treatment very less effective in improving pain and sensation [10].

5. Conclusions

Considering these gaps in current research, more comprehensive and well-structured studies are urgently needed. Future research efforts should aim to increase sample size to improve the reliability and applicability of results. Additionally, standardization of research methodology is needed to ensure consistency and comparability across diverse research efforts. Long-term follow-up is essential to evaluate the immediate effectiveness of these treatments and the long-term effects, potential side effects, and overall patient outcomes.

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