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Review Article

Recent advances in management of trigeminal neuralgia and prosthodontic implications – A narrative review

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INTRODUCTION

The nervous system is a complex network of human body that empowers an organism to interact with its surroundings. Sensory components recognize environmental stimuli, and motor components provides skeletal, cardiac, and smooth muscle control, as well as control of glandular secretions, are coordinated in a system to compel appropriate motor responses to the stimuli or sensory inputs that have been collected, stored, and processed.[1]

The oral cavity, or more commonly known as the mouth or buccal cavity, serves as the first portion of the digestive system. Although a small compartment, the oral cavity is a unique and complex structure with several different nerves and blood vessels inside it. This intricate network is necessary for its unique and diverse role in human life. The oral cavity is surrounded by the lips and is composed of two separate regions, the vestibule, the area between the cheeks, teeth, and lips, and the oral cavity proper. The oral cavity proper is mostly filled with the tongue and bounded anteriorly and on the sides by the alveolar processes containing the teeth and posteriorly by the isthmus of the fauces. Anteriorly, the roof forms by the hard palate and posteriorly by the soft palate. The uvula hangs downwards from the soft palate. The mylohyoid muscles constitute the floor of the oral cavity proper. A mucous membrane known as the oral mucosa is composed of stratified squamous epithelium and forms the inner lining of the mouth. Several submandibular and sublingual salivary glands secrete viscous and mucoid fluid to lubricate and keep the oral cavity moist.[2]

TRIGEMINAL NERVE

It is the fifth and largest cranial nerve that provide sensory innervation to scalp, face, oral and nasal cavities and motor innervation to muscles of mastication. The central component of the trigeminal nerve is within the brain stem. It is comprised of 4 nuclei: • The Spinal trigeminal nucleus, • The Major sensory nucleus, • The Mesencephalic nucleus • The Motor nucleus.3The various branches of trigeminal nerve along with innervations have been summarized in Table-1

Table 1: Branches of trigeminal nerve and its major supply

TRIGEMINAL NERVE BRANCHES	INNERVATIONS
Ophthalmic nerve	Sensory innervation to dura, forehead, iris, ciliary body, sphenoidal, ethmoidal air sinuses and lacrimal gland.
Maxillary nerve	Sensory supply to dura of middle cranial fossa nasal cavity, hard and soft palate, posterior cheek and maxillary teeth and its periodontium, and skin of nose & upper lip.

Mandibular nerve	Motor supply to muscle of mastication mylohyoid and anterior belly of digastric muscles. Sensory innervation to lower 3rd of face, mandibular teeth and its periodontium, anterior two third of tongue, TMJ, external auditory meatus and tympanic membrane.

TRIGEMINAL NEURALGIA

Among the disorders involving trigeminal nerve and its branches, trigeminal neuralgia is of prime importance. Trigeminal neuralgia (TN) is one of the most common diseases of cranial nerves. Furthermore, it is the most frequently diagnosed form of facial pain with a prevalence of 4 per 100000 in the general population. French physician Nicolaus Andre in 1756 gave the name "tic douloureux" because of the facial spasms that would accompany the attacks. English physician John Fothergill in 1773 first defined the major clinical features of TN, hence the name Fothergill's disease.[4]

TN is a chronic facial pain condition that affects one or more divisions of the trigeminal nerve (5th cranial nerve), which carries sensation from face to brain. This nerve has three major branches: the ophthalmic nerve (V1), the maxillary nerve (V2), and the mandibular nerve (V3). Any single or multiple branches can contribute to the cause of the pain. The mandibular branch is the most frequently affected division.[5]

Pain is precipitated or triggered by a variety of stimuli including eating, talking, togue or lip movements, yawning, touching the skin of the face, draughts, sudden movements of the head, and, occasionally walking, loud noises or bright light. It affects women more than men; the onset is usually after the 45th year.[6]

DEFINITION

The International Association for Study of Pain (IASP) has defined TN as "sudden, usually unilateral, severe, brief, stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve."[7]

REFRACTORY PERIOD AND TRIGGER FACTORS

Many patients experience a refractory period after a paroxysmal attack where new attacks cannot be elicited. The pathophysiological mechanism of this phenomenon is unknown. It has been proposed that it is caused by hyper-polarization of the sensory neuron. In early studies by Kugelberg and Lindblom, the presence and duration of the refractory period in TN was a function of the intensity and duration of the preceding attack.

LOCALISATION

TN most frequently affects the 2nd and/or 3rd trigeminal division and the right side is slightly, but significantly, more often affected than the left side. Bilateral TN is very rare in classical TN, and should raise suspicion of secondary TN.[8]

EPIDEMIOLOGY

The epidemiology of TN ranges from 4-13 new cases/100000/year. Almost twice as many women are affected as men. The incidence gradually increases with age and is rare below 40.[9]

The epidemiology of TN is variably reported between studies, with a range from 4.3-27 new cases/100000/year. The incidence is higher among women and increases with age. The lifetime prevalence was estimated to be 0.16-0.3% in population-based studies. The average age of onset is 53years in classical TN and 43years in secondary TN, but the age of onset can range from early to old.[8]

TYPES OF TRIGEMINAL NEURALGIA

There are two varieties of TN: type 1 (classical TN) and type 2 (atypical TN). Occurrence of pain in type 1 is intermittent as described earlier. In type 2, the pain is constant with less severity and is described as burning or pricking, rather than a shock. A subset of patients can progress from type 1 to type 2 TN over time; thus, both types may coexist in the same person. A more recent and simple classification of TN has categorized TN into three types for simplicity of treatment options: possible TN, classical TN, and idiopathic TN.[10]

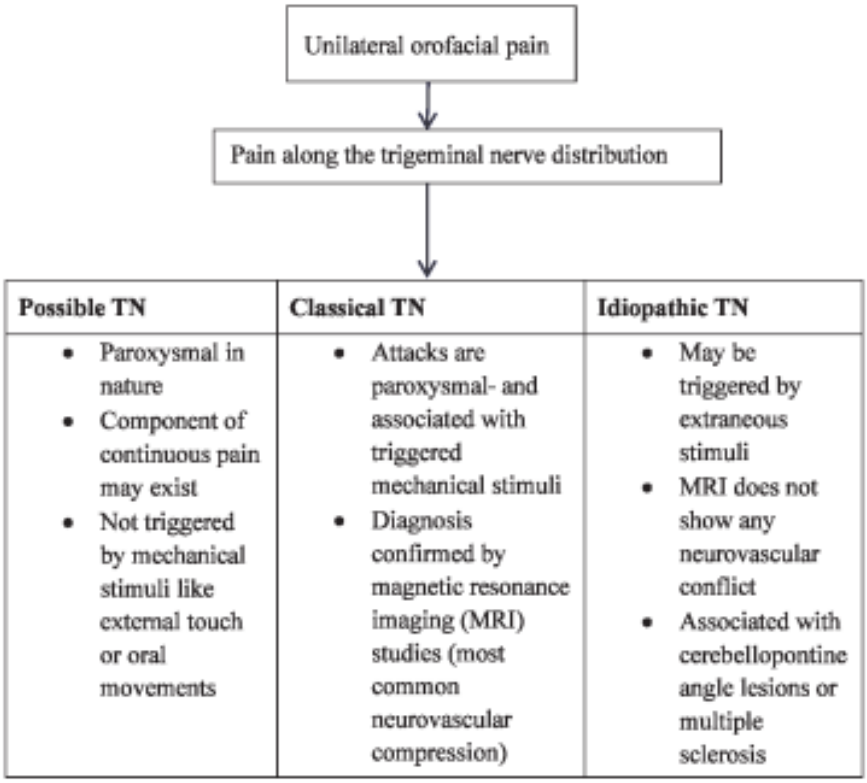


Fig. 1 New classification and diagnostic flowchart of trigeminal neuralgia (TN).

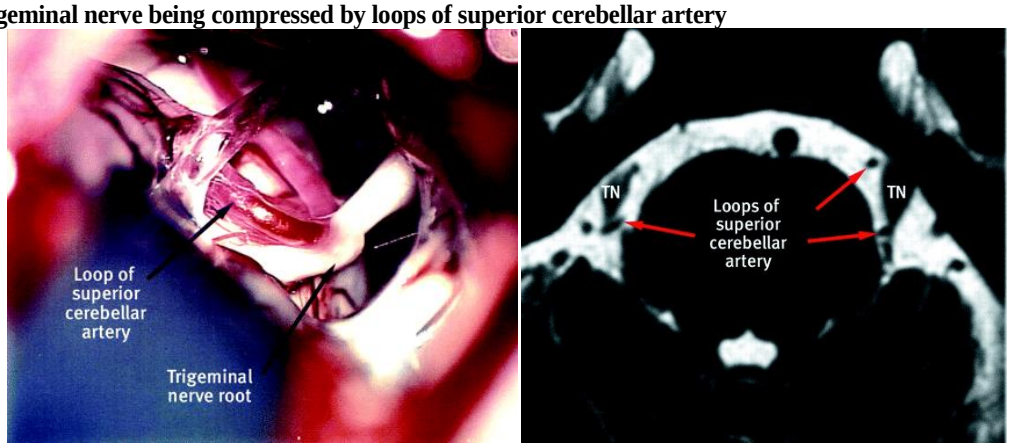
ETIOLOGY

Etiologically established TN, that is based on identification of a cause for the trigeminal neuralgia, corresponds to 2 categories: classical and secondary TN are defined by an underlying cause. Both diagnostic entities qualify as definite neuropathic pain. However, in a relatively small proportion of patients with clinically established TN, even the most advanced diagnostic investigations fail to show a cause. This condition is categorized as idiopathic trigeminal neuralgia.11 80-90% of cases that are technically still classified as idiopathic are caused by compression of trigeminal nerve close to its exit from brain stem by an aberrant loopof artery or vein. Importantly, compression is of the root entry zone, where axons are coated with central nervous system myelin rather than peripheral nerve myelin. Similarly, vascular compression of the facial and glossopharyngeal nerve is thought to be responsible for most cases of hemifacial spasm and glossopharyngeal neuralgia, respectively.[9]

Classical TN is defined as a specific category of TN in which MRI demonstrates vascular compression with morphologic changes of trigeminal nerve root.11As early as 1934, Dandy proposed that in at least 30% of TN patients the pain was caused by a blood vessel compressing the trigeminal nerve. Today, it is generally agreed that the most common cause of classical TN is compression or other morphological changes of the trigeminal nerve by a blood vessel, usually an artery, in the cerebellopontine cistern. This is termed a neurovascular conflict with compression. Anatomical studies documented that the transition from Schwann cell myelination to oligodendroglia myelination in many specimens tapers gradually along the proximal 25% of the nerve. Possibly, this ‘‘transition zone’’ represents a particularly vulnerable area to, for example, pressure from a blood vessel.[8]

In secondary TN, pathophysiological mechanism is most likely the same as in classical TN but the etiology is dependent on the specific structural lesion, most frequently an multiple sclerosis(MS) plaque affecting the trigeminal root or a space-occupying lesion in the cerebellopontine cistern such as epidermoid tumors, meningiomas, arteriovenous malformations or aneurysms.[11]

Fig.2 Trigeminal nerve being compressed by loops of superior cerebellar artery



THEORIES OF TRIGEMINAL NEURALGIA

Trigeminal convergence projection theory

•The continuous nociceptive inputs that are received from the head and neck converge in the spinal trigeminal nucleus. The neurotransmitters released from the nucleus excite the second-order neurons which gives rise to a type of chronic neuropathic pain.

Bioresonance hypothesis

•This is a new hypothesis which proposes that if the vibration frequency of a structure near the trigeminal nerve becomes close to its natural frequency, the resonance of the trigeminal nerve occurs. This can cause abnormal transmission and results in pain.

Ignition hypothesis

•Injury to the trigeminal afferent neurons in the root entry zone(REZ) makes the axons hyperexcitable and leads to synchronized discharge activity. Described by Devor et al and is most widely accepted theory.

DIAGNOSTIC CONSIDERATIONS

The diagnosis of TN is primarily based on patient history, as there are no definitive laboratory or diagnostic tests. There are a variety of differential diagnoses to be considered when dealing with a suspected case of TN.12When obtaining patient history, special attention should be paid to the potential pitfalls leading to misdiagnosis such as a symptomatic cause of pain, odontogenic pain and associated autonomic symptoms (Table 2). When obtaining patient history, one should pay special attention to the onset of pain; if the pain was preceded by or coincided with a herpes zoster rash in the ipsilateral trigeminal distribution, painful trigeminal neuropathy attributed to acute herpes zoster should be considered. In pain preceded by a relevant trauma to the ipsilateral side of the face, such as invasive dental procedures or fractures, painful post-traumatic trigeminal neuropathy (PPTN) is more likely the correct diagnosis. Studies have shown that pain in PPTN may be comparable to TN pain with short, intense triggered pain, but in PPTN there are usually clear-cut sensory abnormalities, including both loss and gain of function, corresponding to the damaged peripheral nerve. Also, important when obtaining the patient history is the

location of pain; pain originating distinctly or diffusively from the teeth should be evaluated by a dentist because, for example, a cracked tooth may present with TN-like pain evoked by chewing hard foods. In bilateral constant pain located in the temporomandibular area, tension-type headache, temporomandibular joint disorder and persistent idiopathic facial pain should be considered. If the short-lasting, intense stabbing pain is isolated to the scalp or occipital area, diagnoses such as occipital neuralgia, primary stabbing headache and paroxysmal hemicrania should be considered. Glossopharyngeal neuralgia is located to the back of the tongue, the soft palate and the pharynx, and nervusintermedius neuralgia is located deep in the ear. Finally, associated symptoms are important; if each pain attack is accompanied by autonomic symptoms such as conjunctival injection, miosis or lacrimation, SUNA, SUNCT or paroxysmal hemicrania are important differential diagnoses.[8]

Table 2: Differential diagnosis of Trigeminal neuralgia

The symptomatology of trigeminal neuralgia is typically very characteristic, with patients reporting intense stabbing touch-evoked unilateral facial pain in the cheek, the area of the nostrils, teeth or jaw. Primary and secondary, i.e. pain secondary to multiple sclerosis or space-occupying lesion, TN may be indistinguishable based on pain characteristics. Meanwhile, in patients with secondary TN, neurological deficits, extra-trigeminal symptoms, bilateral pain and young onset are more frequent.

Primary and secondary headache and facial pain differential diagnosis includes:

- **Glossopharyngeal neuralgia** causes evoked stabbing pain located to the back of the tongue, the pharynx or deep in the ear. Trigger factors are somewhat different from TN and include swallowing, coughing, sneezing
- **Painful posttraumatic trigeminal neuropathy** can cause stabbing and touch-evoked pain similar to TN, but pain is by definition preceded by trauma and there are usually clear-cut neurological abnormalities of both gain and loss of function corresponding to the affected peripheral nerve
- **Persistent idiopathic facial pain** causes touch-evoked or spontaneous dull or aching constant pain
- **Painful trigeminal neuropathy attributed to acute herpes zoster** causes burning and stabbing pain preceded by a herpetic rash in the trigeminal distribution. Tingling sensations and neurological abnormalities with both gain and loss of function are frequent
- **Short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (SUNA), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)** or **paroxysmal hemicrania** cause touch-evoked and spontaneous stabbing orbital, supraorbital or temporal pain accompanied by ipsilateral autonomic symptoms. Unlike TN, pain may change side
- **Cluster headache** causes orbital, supraorbital or temporal pain accompanied by ipsilateral autonomic symptoms and restlessness. Duration is from 15–180 minutes. Unlike TN, pain may change side
- **Primary stabbing headache** causes stabbing spontaneous pain in the scalp and is not accompanied by autonomic symptoms

Odontogenic differential diagnosis:

- **Cracked tooth** can cause evoked shooting pain when chewing hard foods
- **Caries** or **pulpitis** can cause evoked pain at intake of sweet, cold or hot foods. The pain can last from ten minutes up to hours

*Autonomic symptoms are conjunctival injection, lacrimation, rhinorrhea, nasal congestion, sweating, miosis, ptosis and eyelid edema.

INVESTIGATIONS

Investigations are done to:

- Clarify differential diagnosis for e.g. By taking dental x-ray
- Investigate whether there is an identifiable cause of the disease, particularly with a view to surgical cure. This is best done using MRI.[9]

PROGNOSIS

A correct diagnosis is the paramount factorfor adequate treatment and thus a good outcome. Differentiating trigeminal autonomic cephalalgias (for example, cluster headache, SUNCT, and paroxysmal hemicrania) and other craniofacial pain syndromes or persistent idiopathic facial pain is very important, as treatment is fundamentally different. Patients with firstdivision trigeminal pain only may have symptomatic TN (STN) (that is, due to multiple sclerosis or tumour), which is more difficult to treat. Routine head imaging with magnetic resonance imaging (MRI) can detect structural causes in as many as 15% (95% confidence interval [CI] 11–20%) of patients excluding those with microvascular conflict. The blink reflex and other trigeminal reflex tests have a high accuracy to identify patients with STN.

MRI plays a major rolein the pre-surgical assessment in order to determine the presence of microvascular conflict. Specificities and sensitivities are variable (specificity 29 to 93%, sensitivity 52 to 100%) between studies and this is probably related to different MRI sequences used in different investigations. The most common causes for severe neurovascular contact were arteries in 98% of cases. Excellent outcome and concomitant persistent pain, current age, or disease duration were not correlated. Outcome after microvascular decompression surgery was only slightly worse; recurrence rates were 9.23% in the age group younger than 65 years and 13.33% in the group older than 65 years. However, long-term outcome was determined by concomitant pain as these patients developed TN recurrence in 60.3% following microvascular decompression surgery whereas patients without concomitant pain did not show signs of recurrence in 91.8% within a mean follow-up period of 20.6 months. Depression and anxiety, along with a deterioration in quality of life, are common in patients with TN21. About 2% of

patients with multiple sclerosis were reported to have symptoms similar to those of patients with TN. TN commonly runs in families, but there have been reports of an increased risk in people living in the same household, which suggests that environmental factors may influence the disease. Genetic variants of TN were also suggested in two investigated families: autosomal dominant in one family and autosomal recessive in the other.[13]

TREATMENT

CONVENTIONAL MODALITIES

The classical treatment of trigeminal neuralgia was alcohol injection of the Gasserian ganglion.[6] Treatment recommendations are generally the same in classical and secondary TN.[8]Pharmacological and surgical treatment options are numerous, widely used, and not seldom efficacious. Medical therapy should be the first choice, and only after two failed treatment attempts may surgical interventions be considered in patients. Between 33 and 50% of patients may require surgical intervention at some point. No direct comparison studies between medical and surgical treatment exist. Active support group participation may help patients to better cope with their condition and stay compliant with medication.Carbamazepine (CBZ) (200–1200 mg/day) and oxcarbazepine (OXC) (600–1800 mg/day) should be considered first-line therapy, according to commonly accepted treatment guidelines.[13]In a comparison between these two drugs, efficacy is very similar but tolerability is better with oxcarbazepine.[10] Second-line therapy includes add-on therapy with lamotrigine (400 mg/day), change to lamotrigine monotherapy, or the use of baclofen (40–80 mg/day). Pimozide (4–12 mg/day) is seldom in clinical use. Different antiepileptic drugs were investigated in open-label studies with small patient numbers. Efficacy was described for clonazepam, pregabalin, gabapentin, phenytoin, topiramate, valproate and tocainamide(12mg/day).[13]Polytherapy is useful when patients are unable to tolerate higher doses of carbamazepine. Opioids are considered ineffective against TN and, thus, should not be prescribed. A multidisciplinary approach using antidepressants and antianxiety drugs such as amitriptyline and duloxetine is needed for the management of emotional status. Acupuncture can be an option in the treatment of idiopathic TN due to its analgesic effect in both idiopathic TN and secondary myofascial pain associated with it.[10]

Peripheral nerve blocks using local anaesthetic along with absolute alcohol or glycerol is also very effective in reducing pain. If nerve blocks are administered appropriately, patient may feel asymptomatic for few months to even years. It also reduces the number and doses of drugs. Small studies have shown that botulinum toxin type A (BTX-A) injections may reduce pain from TN in people who are no longer helped by medications. A recent meta-analysis showed a pooled reduction of pain by –3.009 points on a 0 to 10 verbal rating scale (95% confidence interval [CI], $p < 0.001$) after treatment with BTX-A and confirmed moderate efficacy. However, more research needs to be done before this treatment is widely used for this condition.[10]

NEUROMODULATION TECHNIQUES

Neuromodulation offers an alternative worth considering for patients whose neuropathy pain is refractory to pharmacotherapy. Central and peripheral neuromodulation are available, but the clinical evidence base is very limited. Options include electrical Gasserian (trigeminal) ganglion stimulation, peripheral nerve stimulation, and invasive motor cortex stimulation and non-invasive cortex stimulation. Patient self-conducted motor cortex transcranial direct-current stimulation (t-DCS) showed excellent efficacy on pain reduction in patients with classic TN. Anodal t-DCS over the course of two weeks may become a valuable treatment option for patients otherwise unresponsive to standard medical treatment.[13]

SURGICAL TECHNIQUES

Surgery is normally recommended only after medication has proved ineffective, or if side effects of medication are intolerable.[10]According to the international guidelines it is advised that ‘‘if any of these sodium-channel blockers is ineffective, referral for a surgical consultation would be a reasonable next step’’. Surgery should also be considered when drugs, although effective, cannot reach the therapeutic dosage due to adverse events.[8]

Microvascular decompression is surgical treatment of choice in TN resistant to medical management, particularly, in young individuals. Patients with significant medical comorbidities are generally advised to undergo gamma knife radiosurgery, percutaneous balloon compression, glycerol rhizotomy, and radiofrequency thermocoagulation procedures. Partial sensory root sectioning is indicated in negative vessel explorations during surgery and large intraneural vein. Endoscopic technique can be used alone for vascular decompression or as an adjuvant to microscope.[10]

Percutaneous techniques to the Gasserian ganglion are all destructive and consist mainly of percutaneous glycerol rhizolysis, radiofrequency thermocoagulation, and balloon compression. Relief of pain was reported by 90% of patients undergoing these procedures. Approximately 68 to 85% of patients remain pain-free after 1 year but this deteriorates to 54 to 64% after 3 years and only 50% are still pain-free after 5 years. Sensory loss (50%) is the most common side effect with high impact on quality of life for these patients, followed by dysesthesias (6%), corneal numbness with risk of keratitis (4%), and anaesthesia dolorosa (4%).

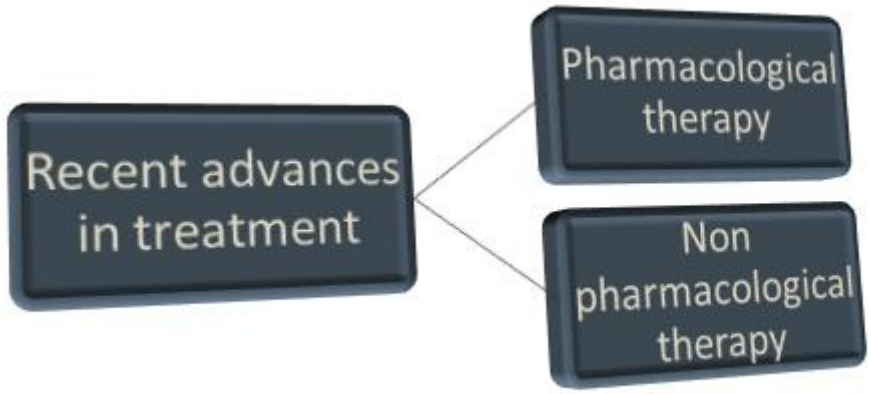
Gasserian ganglion treatments are generally minor, overnight procedures with very low mortality.[13]

Gamma knife surgery uses a focused radiation beam to sever the trigeminal root in the posterior fossa. Sixty-nine percent of patients were reported to remain pain-free 1 year after gamma knife surgery without additional medication. After 3 years, this was down to 52%. Pain relief may require up to several weeks (mean of 1 month) in order to develop. Sensory complications were reported in 6% of patients with a delay of up to 6 months, including paraesthesia in 6 to 13%, and facial numbness in 9 to 37% that may improve with time. Quality of life improves by 88%. However, gamma knife surgery is quite expensive, limiting its more widespread usage. This makes it a treatment reserved for patients unfit to bear conventional surgery or with blood coagulation disease or medication (for example, warfarin).[13]

The most sustained pain relief was reported following microvascular decompression surgery. Ninety percent of patients had initial pain relief. More than 80% were still pain-free 1 year after surgery and this fell to 75% after 3 years and 73% after 5 years. However, it is a major surgical intervention including craniotomy in the posterior fossa to reach the trigeminal nerve. Mortality rates range from 0.2 to 0.5% on average, and about 4% of patients have serious adverse events such as infarcts, hematomas, or cerebrospinal fluid leakage. The most frequent complications are aseptic meningitis (11%), hearing loss (10%), and sensory loss (7%).[13]

RECENT ADVANCES IN TREATMENT MODALITIES

The recent advances in treatment modalities may be classified into pharmacological or non-pharmacological therapy.



RECENT ADVANCES IN PHARMACOLOGICAL THERAPY

The constant search for new drugs led to the development of few recent medications that act via novel pathways for reducing the electrical activity of the already excited nerve.

1. **Vixotrigine**: A novel substance finished its phase II trial last year with promising results. BIB074 (formerly known as CNV1014802, proposed name vixotrigine, formerly raxatrigine) is a new sodium channel blocker with potency and selectivity of the Na_v 1.7 sodium channel over the different tested subtypes (Na_v 1.1, Na_v 1.2, Na_v 1.3, Na_v 1.5, Na_v 1.6, and TTX-R) for the depolarized and resting states. Sodium channel blocking quantity increases in parallel to increased stimulation frequency of Na_v 1.7 and of Na_v 1.2 and Na_v 1.6. BIB074 preferentially targets and inhibits higher frequencies (10 Hz and more) induced during seizures or by noxious stimuli.[13]In an open-labelled study, vixotrigine 150 mg administered thrice daily in patients with TN was compared with placebo and showed successful pain relief in the final week of therapy.[14] The drug was administered for 21 days. There was a reduction in the number of paroxysms by 60% compared with only 12% in placebo, and pain severity decreased by 55% compared with placebo. The treatment failure rate was 33% with this new drug and no serious adverse event was noted. A multicentric prospective phase III randomized controlled trial is already underway and its results will throw further light on this drug.[15]
2. **Eslicarbazepine**: It is a third-generation antiepileptic drug belonging to the dibenzepine group. The drug targets the voltage-gated sodium channels and is currently approved as adjunct therapy for focal seizures. In a recent open-labelled trial, eslicarbazepine was administered in a dose of 200 to 1200 mg/day in patients suffering from TN. Around 88.9% patients had good pain relief but there was high incidence of side effects to the tune of 71%.[16]
3. **Sumatriptan**: It is a 5-hydroxytyptamine receptor (1A/B/C) receptor blocker agonist. It

has been used extensively in migraine and cluster headaches with good pain relief efficacy. The drug inhibits vasodilation and demyelination near the inflamed trigeminal nerve root. The drug comes in a formulation of tablets, nasal spray, or injections. Two randomized controlled trials tested the effect of subcutaneous injection of sumatriptan 3 mg and the oral administration of 50 mg twice daily. Fifteen minutes after injection of sumatriptan, the baseline pain scores decreased.[17,18]After oral treatment, the visual analog score for pain also decreased significantly, and this effect persisted after treatment discontinuation for a week. The main side effect like dizziness and rebound headaches are common for which there is lack of adherence to therapy.

4. **Intranasal carbon dioxide (CO2):** CO_2 has always been considered a pain modulator in hyperactive neurons. Recent studies have shown that CO_2 is a nociceptive modulator of afferent active trigeminal neurons based on the hypothesis that CO_2 causes a decreased mucosal pH and that in turn activates the nociceptive effect of primary trigeminal afferent neurons.[19] A controlled, randomized, parallel-group study investigated the effects of intranasal CO_2 on the transient receptor potential cation channel subfamily V member 1 (TRPV1)–mediated experimental trigeminal pain in healthy volunteers. Only mild modulatory effect of intranasal insufflation of CO_2 at flow rates of 1 L/min was found, but the clinical utility seemed limited since changes in pain ratings were therapeutically irrelevant.[20]Hence, another phase 2 placebo-controlled trial was undertaken in which CO_2 and placebo were administered in TN patients for 1 minute. All patients received three doses of CO_2 and placebo each, and it was found that CO_2 had improved effect on VAS scores. The trial is underway and its results are yet to be published (ClinicalTrials.gov identifier: NCT02473016).[21]
5. **Calcium channel blockers (CCBs):** Usually, in patients with continuous pain mediated by other pathophysiological mechanisms, a monotherapy with sodium channel blocker is not sufficient to control pain and other drugs are usually needed. CCBs and antidepressants have been advocated in the treatment of trigeminal neuralgia in patients not relieved by monotherapy with sodium channel blockers.[22] Thus, apart from few case reports or cohort studies there is very little evidence on management of continuous pain and more studies with CCBs are warranted.
6. **Miscellaneous drugs:** Various other medications like topical capsaicin, lignocaine, misoprostol, and intranasal lignocaine are available but their widespread use is not advocated at present. Misoprostol, a prostaglandin E1 analogue, showed efficacy in TN. Few studies reported the efficacy of misoprostol in a total of 27 patients with TN secondary to multiple sclerosis.[23] However, there is insufficient evidence to support or refute the use of this drug in TN.

RECENT ADVANCES IN NONPHARMACOLOGICAL THERAPY

Nowadays apart from conventional RFA, new modalities utilizing reinforced RF doses for short periods called pulsed RF and other attenuated laser therapy are gaining importance. The list below enumerates the novel new therapeutic modalities.

1. **Pulsed radiofrequency (PRF):** PRF uses brief pulses of higher frequency alternate current to produce the same voltage or even higher fluctuations than during conventional radiofrequency (RF) treatment. PRF does not produce thermal lesions but there are micro-damages within axonal microfilament and microtubules, especially in the pain-carrying C fibers.[24] Recent studies have shown that combination of both PRF and RF lesioning (RFL) has similar results in achieving a pain relief with lesser side effects than RFL alone.[25]There are less number of complications like anaesthesia dolorosa and hyperesthesia with PRF. To achieve better results, PRF and RFL should be used in tandem rather than using these modalities separately.
2. **Ozone injection around gasserian ganglion (OIAGG)**: Some newer studies have explored the role of OIAGG. In a multicentric retrospective study, the authors injected an ozone–oxygen mixture gas at a concentration of 30 μg/mL into the area around the gasserian ganglion performed under C-arm X-ray guidance. The results showed that pain relief rates at posttreatment, 6 months, 1 year, and 2 years after the procedure were 88.35%, 86.87%, 84.46%, and 83.30%, respectively ($p < 0.05$).[26] A regression analysis found out that preoperative structural nerve damage was associated with less clinical effect or poor outcome. The study confirmed that OIAGG is a safe and effective modality for pain management in refractory TN.
3. **Cryotherapy:** To overcome the drawbacks of conventional cryotherapy such as incomplete pain relief and recurrence, few modifications have been suggested. These include (a) the use of a curved cryoprobe, (b) maintaining optimal temperature and pressure throughout the surgical procedure, (c) scoring of the epineurium, (d) application of petroleum jelly around the nerve before the introduction of the cryoprobe, and (e) delivery of three cycles of 3-minute freezing and 5-minute thawing to each nerve.[27]

   In a study, Bansal et al showed that a closed curved cryoprobe tip when used with nitrous

oxide at a temperature of–98°C and a pressure of 70 kg/cm or 100 psi provided excellent analgesia. Almost 48.97% patients had pain-free interval of 36 to 40 months. The side effect was loss of fine and crude sensation over face for 6 to 24 months.[28]

4. **Neuromodulation:** It is a new prospect in the management of TN patients, targeting either neural stimulation or inhibition to restore normal neurological function. Various neuromodulation techniques have been recently explored for the management of TN. These include transcranial magnetic stimulation, motor cortex stimulation, deep brain stimulation, spinal cord stimulation, transcutaneous electrical nerve stimulation, and peripheral nerve stimulation. A recent study is underway to establish the feasibility of using transcranial magnetic stimulation (TMS) for chronic orofacial pain in the interim period before surgery. Participants were randomized to either receive TMS or sham-TMS (a nontherapeutic TMS coil which sounds and feels similar to normal TMS), or standard treatment during the weeks of wait time before surgery. The sham TMS is a subtherapeutic level of magnetic stimulation which makes the same sound as normal TMS and causes a similar tingling of the skin. All study patients were asked to fill out an online survey about pain during different time points of the study. The complete results are not yet available, but preliminary results indicate that TMS, when applied to the head for a few minutes, has been shown to reduce pain in people with chronic orofacial pain of TN (ClinicalTrials.gov identifier: NCT04120129).[29] Few studies have been conducted based on these techniques with variable success rate.[10] Repetitive transcranial magnetic stimulation (r-TMS) is also a relatively novel technology introducing the possibility of testing the responsiveness of patients with trigeminal neuropathic pain to invasive epidural cortical stimulation. The results of treatment conducted on 24 patients by Khedr EM, Kotb H, Kamel NF, et al., TN was treated with daily 20-Hz motor cortex stimulation over the course of five days. Ratings of pain decreased by 45% for at least 2 weeks.[30]. A different investigation included 12 patients who failed surgery with intractable TN, out of which 58% reported more than 30% reduction of pain intensity following rTMS.[13]
5. **Low level laser therapy (LLLT):** LLLT uses a single wavelength light source and works on the principle that irradiation with monochromatic light may affect cell function.[31]This technique involves irradiation of the region of interest followed by laser puncture at predetermined points along the course of the nerve. In a recent systematic review (8 randomized controlled trials, 2 prospective studies, and 3 case series) which evaluated the efficacy of LLLT for the therapeutic management of neuropathic orofacial pain, Pedro et al found a reduction in pain intensity in all studies (most of them significant).[32] However, more quality studies assessing all outcome measures of chronic pain are warranted.
6. **Carbon dioxide laser:** A CO_2 laser is used to ablate the peripheral nerve in patients with drug refractory TN. Recently, it has been shown to reduce the pain scores in TN and persistence of pain relief till 12 months.[33]] The authors ablated peripheral nerves using low-power defocused mode; however, there was prolonged paraesthesia of the affected nerves with this technique.
7. **Neural prolotherapy**: Neural prolotherapy has been described in relation to the management of TN. It is also known as perineural injection therapy (PIT) and is one of the latest advancements in regenerative medicine. First described by Dr. Paul Pybus and Dr. Roger Wyburn-Mason, PIT targets neurogenic inflammation in subcutaneous nerves that potentially generates pain.[34]The technique involves injection of hypertonic dextrose saline with local anaesthetics at the trigger points and usually requires multiple sittings.[35]
8. **Nerve combing**: Nerve combing, also called internal neurolysis, is a kind of surgical strategy that splits the branches of trigeminal nerve longitudinally using a special fibre knife based on preoperative pain locations and intraoperative finding. Jie et al studied 60 patients who achieved good pain relief following nerve combing.[36] Nerve combing has a much higher pain relief rate in patients without vascular compression than those with vascular compression.
9. **Complimentary medicine**: Apart from standard conventional therapy there are several complimentary therapies that aid in pain relief of TN. These include standard acupuncture, electroacupuncture, and spinal regulation therapies.[37] Other modalities include sound therapy; low-intensity and low-frequency acoustic ultrasound patch; and vitamin B, C, and biofeedback.[10]

ADDITIONAL PROSTHODONTIC CONSIDERATIONS

Prosthodontics difficulty in patients with trigeminal neuralgia[3]

Problems

1. Trigger zones are triggered during impression making, jaw relation and establishing occlusion during fabrication of dentures.
2. Trigger zones are also stimulated in old patients having overclosure denture and inlongtime

denture wearers without compensating ridge resorption.
3. During implant placement, there is chance for damage to the inferior alveolar nerve, mental nerve and incisive nerve in mandibular region and nasopalatine canals, and posterior alveolar nerve in maxillary region.
4. The zygomatico-facial nerve and infraorbital nerve are frequently injured during zygomatic implant placement and during reflection of the soft tissue over it. There will be loss of the sensation in the check region.
5. The nerve injuries by implant fixtures occur during drilling and compression of bone producing, hematoma, edema, abnormal mandibular nerve canal, and reactive bone augmentation. In some patients, there is thinning of missing of upper layer of bone surrounding the mandibular canal, leading to fracture if peri-implantitis occur.
6. Greater palatine nerve injury is detected during implant placement in pterygomaxillary areas.

Management

1. Carbamazepine (100mg) is the first drug of choice in trigeminal neuralgic attack during any procedure. Local anesthetic agents in acrylic stent/tray is given for immediate pain relief to the patient.
2. Some studies have shown modification in complete denture fabrication methods such as

a. Temporary complete dentures with sliding plates are fabricated to reestablish the vertical dimension at occlusion and also provide deprogramming of neuromuscular process and jaw closures in physiologic postures.
b. By increasing jaw separation with an acrylic biteplane in lower denture provides flat surfaces against upper denture so that muscles are in normal physiological position. After pain is relieved, new dentures with same jaw relation can be fabricated.
c. Laser therapy increases blood flow, oxygenation and has analgesic effects. It is followed by interocclusal splint to reestablish occlusion and then removable dentures are fabricated with properly mechanical and functional support.[3]

CONCLUSION

Trigeminal nerve is one of the main nerves that provide sensory and motor innervation to most parts of face and rimaoris. The knowledge of the anatomy, physiology and distribution of trigeminal nerves is essential to know the location for the fabrication of dentures since many surgical and non-surgical procedures performed by a prosthodontist may have the possibility of causing injury to peripheral branches of the cranial nerve.

There is a huge clinical burden of TN in our society. The age of presentation varies and hence there is a wide array of treatment options available. The treatment options need to be catered according to the age of the patient and the mode and type of presentation. The treatment modalities range from standard medical therapy and peripheral blocks to surgical procedures. Newer and novel techniques have arrived that show promising results. However, large randomized controlled trials are required for the validation of such techniques. The best technique should be simple, noninvasive, and achieved in a single setting with few recurrences, and provide long-term pain relief.

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