Review Article

Submitted: Nov 12, 2020
Accepted: Mar 14, 2021
Published: Mar 24, 2021

Management of Trigeminal Neuralgia: A Narrative Review

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ABSTRACT

Trigeminal neuralgia is sudden, severe facial pain. It is often described as sharp shooting pain or like having electric shock in the jaw, teeth or gums. Clinical features are so specific that it usually suffices the diagnosis in maximum cases. The general trend for management is to start with medical therapy and consider surgical procedures in patients refractory to medical treatment. Altering the doses of various drugs in "hit and trial" method is commonly practiced. Adjuvants have supra-additive effect to medical therapy. Decision to continue or discontinue medical therapy is the interplay between patient's age, systemic condition, and response to drug therapy. Surgical options are reserved because of lack of identifiable cause(s) of disease and the associated complications. The cost of surgery is still a luxury for many of the patients. Various adjuvant measures are being tried specially with medical therapy and have shown various degree of success for pain relief. The aim of this narrative review was to compile together the latest updates in the management of trigeminal neuralgia in all possible fields such as medical and surgical management and adjuvant measures.

Keywords: Medical management; surgical therapy; trigeminal neuralgia.

INTRODUCTION

Trigeminal Neuralgia (TN) is also known as "suicide disease".[1] In 1756 Andre' described the convulsive-like condition called tic douloureux; Fothergill in 1773 described it as "a painful affection of the face".[1] The International Association for the Study of Pain (IASP) defined trigeminal neuralgia as "sudden usually unilateral severe brief stabbing recurrent pains in the distribution of one or more branches of the fifth cranial nerve".[2]

Trigeminal Neuralgia is the most commonly experienced facial pain among facial pain syndromes. Its prevalence in the general population is 0.015% and the overall incidence of TN has remained constant ranging from 12.6/100,000/year to 27/100,000/year. It has female preponderance between sixth to eighth decades of life with right side of the face being affected more than left.[3] The aim of this narrative review is to compile together the latest updates in the management of trigeminal neuralgia in all possible fields that is medical and surgical management and adjuvant measures. The best treatment option is yet to be identified and defined. This review will help summarise all possible available treatment options and their outcome, so that oral physicians can choose the

Citation
Luitel A, Rimal J, Maharjan IK, Regmee P, Adhikari S, Tamang R, et al. Management of trigeminal neuralgia: A narrative review.. J Nepal Dent Assoc. 2021 Jan-Jun;21(32):67-74.

best treatment option for patients in easy way when they are at the door.

SEARCH METHODOLOGY

The authors conducted a literature search using Medline, EMBASE and Cochrane collaboration database. The different terms and phrases used to conduct literature search was "trigeminal neuralgia", "medical management of trigeminal neuralgia", "surgical management of trigeminal neuralgia", "adjuvant measures for management of trigeminal neuralgia". The studies on TN from 1984 to 2018 were included based on purpose and convenience.

MANAGEMENT OF TRIGEMINAL NEURALGIA

In addition to guidelines from general medical/ dental practitioners and specialists, systematic reviews including Cochrane collaborations, describe the use of drugs in TN. Unfortunately, there are very few high-quality Randomised Controlled Trials (RCTs).[4] The common pattern is to start with medical therapy and consider surgical procedures for patients' refractory to medical treatment. However, studies comparing medical and surgical treatment directly are still missing.[5-8]

MEDICAL MANAGEMENT

The following drugs have been used for management of trigeminal neuralgia.

First-line Therapy

Carbamazepine is considered most effective drug for management of all cases of TN and oxcarbazepine, probably effective drug for controlling pain in patients hypersensitive or allergic to TN. The different guidelines recommend carbamazepine (200-1200 mg/d) or oxcarbazepine (600-1800 mg/d) as a first-line therapy for TN.

Carbamazepine (CBZ): It acts by inhibiting voltage-gated sodium channels, reducing the excitability of nerve membranes. It potentiates gamma aminobutyric acid (GABA) receptors made up of alpha1, beta2, and gamma2 subunits, relevant to its efficacy in neuropathic pain. The starting dose is 100 to 200 mg twice daily which is increased by 100 mg every alternate day until sufficient pain relief is achieved or side effects prevent upward titration. The maintenance dose is 300-800 mg/day in 2-3 divided doses and maximum suggested total dose is 1200 mg/day. The dose should be gradually tapered once pain is controlled, since remission may occur. In patients with attacks during sleep extended release CBZ is useful as night dose. This also reduces side effects as high serum peaks are not achieved.[4,9]

Common side effects are sedation, dizziness, nausea, vomiting, diplopia, memory problems, ataxia, and elevation of hepatic enzymes, and hyponatremia. Potentially serious but uncommon side effects are leucopenia, aplastic anaemia, allergic rash, systemic lupus erythematous, hepatotoxicity, and Stevens-Johnson syndrome (SJS). The risk of CBZ induced SJS is high in people with the allele HLA-B*1502. Those who test positive for HLA-B*1502 should not start CBZ treatment unless the benefits clearly outweigh the risk of SJS. Complete blood count, serum sodium, and liver function tests are investigated several weeks after starting therapy to detect any complications.[4,5]

Oxcarbazepine (OXC): It is keto-analogue of CBZ, converted into its pharmacologically active 10-monohydroxy metabolite. Bypassing the liver cytochrome system, it results in an improved side effect profile and fewer drug interactions than CBZ.[4]

OXC is started at 150 mg twice daily and increased as 300 mg every third day until pain subsides. Maintenance doses range between 300-600 mg twice daily and maximum suggested dose is 1800 mg/day. The risk of allergic cross reactivity between CBZ and OXC is around 25%, so OXC is best avoided when CBZ allergy is evident.[10,11] Complete blood count, serum sodium, and liver function test should be performed within several weeks after initiation of treatment to detect complications.[12,13]

Second-line Therapy

Second-line treatment is based on very little evidence. Lamotrigine, baclofen, and pimozide are commonly used drugs.[4,14]

Lamotrigine: It acts at voltage-sensitive sodium channels, stabilises neural membranes, and inhibits the release of excitatory neurotransmitters. The initial dose is 25 mg twice daily, increased to a maintenance dose of 200-400 mg/day in two divided doses. The dose required for adequate pain relief lies between 100-400 mg/day. Sleepiness, dizziness, headache, vertigo, and ataxia are common side effects. Severe rash, desquamation, fever or lymphadenopathy indicative of SJS requires immediate discontinuation.[4,5]

Baclofen: It is skeletal muscle relaxant and GABA analogue that activates GABA-B receptors depressing excitatory neurotransmission. It may be used alone or in combination with CBZ. The starting dose is 10 mg/day for three days increased to 10-20 mg/day every three days. The maximum tolerated dose is 60-80 mg/day in three to four divided doses. If used as add-on therapy, the dose of CBZ can be reduced to 250 mg twice daily to maintain a synergistic effect. Drowsiness, dizziness, weakness, fatigue, nausea, hypotension, and constipation are typical side effects. Sudden discontinuation can cause withdrawal symptoms (hallucinations and seizures). Baclofen till date has strongest evidence for efficacy in treatment of TN after carbamazepine.[4,14,15]

Pimozide: Pimozide, a dopamine receptor antagonist is used in the management of Tourette syndrome.[4] Displaying encouraging results at a dose of 2-12 mg/day in TN treatment, it is seldom used because of multiple potential serious side effects including arrhythmias, acute extrapyramidal symptoms, and Parkinsonism.[4,5,14]

Third-line Therapy

Gabapentin, pregabalin, topiramate, and levetiracetam are newer Anti-Epileptic Drugs (AEDs) tried for past few years.[4,16-18]

Gabapentin: A GABA receptor agonist, acts primarily on presynaptic calcium channels of neurons to inhibit the release of excitatory neurotransmitters. It is used in RCTs of neuropathic pain and proven to be effective. Its use and effectiveness were also reported in several TN studies.[16]

It is started at a dose of 300 mg/day gradually increased by 300 mg every two to three days. The dose can be increased to 1800 mg/d. Gabapentin has many advantages like faster titration, no known drug interactions and idiosyncratic skin reactions, and favourable side effect profile, with mild somnolence, dizziness, headache, confusion, nausea, and ankle edema. Hyperlipidaemia is an important side effect to watch for.[3,4,16]

Pregabalin: It is GABA analogue related to gabapentin that acts by interacting with the alpha-2-delta subunit of voltage-gated calcium channels. Although a potentially useful drug for neuropathic pain in some patients, evidence is scant in TN.[16] Pregabalin (150-600 mg/day) is proven to be effective in reducing TN pain by more than 50-74% of patients. Side effects are less; most common being dizziness and sleepiness.[3,4,16]

Topiramate: The exact mechanism of action is not known. Pain-modulating effect might be related to blockage of the voltage-gated sodium channel and an augmentation of GABA activity by binding to a non-benzodiazepine site on the GABA receptor. Topiramate (100-400 mg/day) is found effective in patients with classic TN. The most common side effects are dizziness, somnolence, cognitive impairment, and weight loss.[3,4,16,17]

Levetiracetam: Levetiracetam, a newer AED has been tried for TN. Though exact mechanism is unknown, it is thought to target high-voltage, N-type calcium channels as well as the synaptic vesicle protein 2A, impeding impulse conduction across synapses. The effective dose range in TN is 1000-4000 mg/day. The advantages are fewer drugs interactions, absence of auto-induction and no need for routine blood tests. Nasopharyngitis, sleepiness, headaches, and irritability are side effects at beginning. A wide-range of RCTs are warranted before any definitive claim.[3,4,16]

Other Drugs

Many other drugs have been tried for treating TN showing limited benefit. These include oral and intravenous phenytoin, fosphenytoin, clonazepam, valproic acid, misoprostol, tocainide, topical capsaicin cream, intranasal lidocaine, tizanidine,

sumatriptan, and amitriptyline.[4,18]

Acute Neuralgia Attack Treatment: Phenytoin is proven effective in managing neuralgia crisis in few case series. A loading dose of 14 mg/kg delivered intravenously relieved the pain for 1-2 days, enough for alternative oral drug therapy to kick in when initiated simultaneously.[19] Intranasal lidocaine 8% was effective in temporarily relieving maxillary division neuralgic pain.[20] Sumatriptan 3 mg subcuatneous is superior to placebo in providing prompt and marked analgesia in 80% of patients in a double-blind RCT of 24 patients with refractory TN. The median duration of pain relief reported was eight hours.[20]

Emerging Medical Therapy

Botulinum toxin A (BTX-A): Of the seven antigenically different neurotoxins derived from Clostridium botulinum, BTX-A appears to be the most potent subtype.[3,21,22]

The mechanism of analgesia is unclear, it is believed that it causes local release of anti-nociceptive neuropeptides like substance P, glutamate, and calcitonin-gene related peptide, inhibiting central and peripheral sensitisation and also inhibits the release of pro-inflammatory neuropeptides.[3,21] Micheli et al.[23] reported successful treatment of patient with hemifacial spasm with TN with BTX-A opening the future possibilities. The systemic review revealed subcutaneous or mucosal injection effective for adult TN patients. Though patients showed significant reduction in intensity of pain at 6-9U, most commonly used dose is 20-75U.[24]

Gabapentin and regular ropivacaine: According to recent overview, gabapentin combined with regular ropivacaine injections into trigger sites improved pain control and quality of life. Gabapentin upto 900 mg/day with 4 mg regular ropivacaine is injected into each trigger point weekly.[4,20]

MANAGEMENT OF PHARMACORESISTANT PATIENTS

Treatment fails for a number of reasons but needs to be addressed before moving to the next strategy. Reconsidering the diagnosis is worthwhile if drugs no longer provide adequate pain relief. The neurosurgeons should discuss early with the patients, the surgical options as it is difficult for them to consent for any surgical procedures once the pain becomes worse with high-dose medication.[4,25] A study on how patients decide about treatment suggests that, in a hypothetical situation, patients opt to have surgical treatment rather than medical.[4]

SURGICAL MANAGEMENT

Patients with debilitating pain, refractory to an adequate trial of at least three drugs including CBZ in sufficient dosage are ideal candidates for surgical therapy. Performing an invasive neurosurgical or minimally invasive stereotactic procedure is based on the clinical presentation and not only on neuroimaging findings.[19,26,27]

Customising outcome for individual patients is difficult. Evidence shows that patients with classic trigeminal neuralgia, evidence of vascular compression, shorter duration of disease, and no previous surgery respond better to all treatment options.[28,29]

Two types of surgical procedure are available:

1. Microvascular decompression (MVD), where the posterior fossa is explored and the compressing vessel and trigeminal nerve root are separated.
2. Ablative treatments that targets the trigeminal nerve in different ways.[30]

The interventions are performed at three target areas:

- Peripheral or distal to the Gasserian ganglion at specified trigger points.
- Gasserian ganglion level.
- Posterior fossa at the root entry zone.[4]

Different surgical approaches have been proposed for the treatment of drug-resistant TN.[4,5,11,14,30-40]

Microvascular Decompression (MVD):

- MVD is based on theory that compression of trigeminal nerve by vascular loop is the direct cause of TN. Thus, pre-operative radiological

studies are mandatory to identify the relation between abnormal vessel and nerve. It is one among most common treatment providing long term pain relief.[39]

- After five years, the percentage of pain free patient ranges from 58% to 78%. Unfortunately RCTs of reasonable quality are absent.[39]
- Complications include infections, facial palsy, facial numbness, cerebrospinal fluid leak, and hearing deficit with a mortality of 0.1%.[30,35,37-39]

Percutaneous Balloon Compression (PBC):

- Because of low cost, simplicity and the advantage of being the only percutaneous procedure performed with the patient under general anaesthesia, it is extensively used for treatment of TN. The immediate postoperative pain relief ranges from 80% to 90% and a pain free time without medication ranges between two to three years. Common complications include numbness, dysaesthesia and masseter weakness that resolve in few months, meningitis and cranial nerve deficits are rare.[38]

Glycerol Rhizotomy:

- Glycerol injection to the trigeminal cistern relieves pain due to demyelination and axonal fragmentation. This technique provides initial pain relief of more than 90% and a rate of pain free patients at three years of almost 50%.[31,32]
- A concentration of 10% phenol in amorphous glycerol is injected under fluoroscopy guidance under sedation. This preferentially damages the nerve interfering with pain signals to brain.[31,33]
- Dysesthesias, corneal numbness, masseter weakness, and herpes labialis are reported as common complications.[31-33]

Radiofrequency Thermocoagulation:

- It is based on an attempt to electrocoagulate the trigeminal nerve and Gasserian ganglion rootlets. Initial pain relief of more than 90% with a recurrence rate up to 25% is reported. The side effects, such as masticatory weakness, dysaesthesia, and corneal numbness are related to significant individual variation of somatotropic organisation of trigeminal nerve.[40]

Gamma Knife Radiosurgery (GKRS):

- It is a treatment modality for patients with existing medical illness, who are poor candidates for MVD or refuse more invasive procedures.[40]
- The root entry-zone of trigeminal nerve is used as target with the dose range of 70-100 Gy.[40]
- Permanent dysaesthesias and anaesthesia dolorosa affecting the quality of life have been reported.[40]

Cyber Knife in Trigeminal Neuralgia:

- Intrinsic limitations of current stereotactic radiosurgical devices have given birth to image-guided robotic radiosurgery with principles embodied in the CyberKnife® System. It allows conformal treatment along the nerve and permitting high collimator radiation beams near the dorsal root entry zone. In Cyber Knife radiosurgery study, no patient developed facial paresthesia following the treatment.[40]

ADJUVANT MEASURES

Transcutaneous Electrical Nerve Stimulation (TENS):

TENS is safe, cheap, and promising option for management of neuralgic patients as an adjunct there by reducing the dose of the drugs and minimising the side effects.[41,42]

Mechanism:

- **Gate control theory:** Substantia gelatinosa of spinal cord acts as a gate control system. As the frequency of stimulation increases, conduction decreases resulting in physiological block.[41]
- **Endogenous pain inhibitory system:** Peripheral electrical stimulation excites naloxone dependent anti nociceptive mechanisms (via endorphins, enkephalins, and dynorphins) operating at spinal and supraspinal levels.[41,43]
- **Physiological block:** Presynaptic inhibition in the dorsal horn, direct inhibition of an abnormally excited nerve and restoration of afferent input causes physiological block.[41,43]

Complication and contraindication:

The TENS is remarkably free of side effects. The common problem is allergic dermatitis which patient may experience due to the adhesive tape holding the electrodes. The only absolute contraindication is patients with pacemakers or other implanted electrical devices, which may be affected by the field of modulator.[41]

Acupuncture Therapy

The authors, to the best of literature search, could not find any literatures regarding the effect of acupuncture on TN. The acupuncture-induced analgesic effect has been used widely to alleviate various pain conditions.[44,45]

Mechanism: Insertion of an acupuncture needle into acupuncture point produces de-qi sensation exciting all afferent fibers of the muscle tissue. Mechanical stimulation passes signals via the sensory ganglia to the spinal cord and via interneurons modulating the activity of motor neurons in the brain stem network, resulting in activation of various opioid receptors, which induces analgesic effects through descending inhibition in the supraspinal region. The immediate analgesic effect is due to diffuse noxious inhibitory controls.[46]

Adverse effects: Reported adverse effects are very minimal and include bruising or haematoma at the needle site, metal allergy, and local infection.[47]

NEUROMODULATION: A CHANCE FOR TRIGEMINAL NEURALGIA

Two kinds of neuromodulation are reported as options for chronic pain, refractory to conventional medical and surgical treatment: motor cortex stimulation (MCS) and deep brain stimulation (DBS). According to hypothesis, the posterior hypothalamus, controls relationship between the neuropsychological circuits involved in pain behaviour and the neurovegetative system. The MCS for the treatment of trigeminal neuropathic pain achieves good to excellent pain relief. Deep brain stimulation has been applied for treatment of refractory chronic pain. However, neurostimulation might represent an opportunity in TN refractory to other surgical treatments.[3,48-50]

In a nutshell, TN is purely a clinical diagnosis. Investigations are done to rule out the differential diagnoses and explore whether there is an identifiable cause of the disease. This is best done using magnetic resonance imaging. The general recommendation is to start with medical therapy and consider surgical procedures in patients who are refractory to medical treatment. Haematological investigations at regular intervals are important in patient on drug therapy, especially carbamazepine. However, studies that compare medical and surgical treatment directly are still missing. Various adjuvant measures like TENS, acupuncture therapy, and neuromodulation are being tried and have shown various degree of success for pain relief.

JNDA

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