TRIGEMINAL NEURALGIA – A COMPREHENSIVE CLINICAL REVIEW

Dr Prabha Choudhary[1] , Dr Santokh Singh[2] , Dr Chandan Choudhary[3], Dr Rajni Bala[4] , Dr Meetika[5] , Dr Richa Sehgal[6]
Dentist, Snow White Dental Clinic, Ludhiana [1]
JR Department of Periodontology, Desh Bhagat University [2]
Dentist, Snow White Dental Clinic, Ludhiana [3]
Dentist, Snow White Dental Clinic, Ludhiana [4]
Former Student LBDC, Patiala [5]
Former Student IDEAS Gwalior M.P [6]

Abstract

Trigeminal Neuralgia, also known as Tic douloureux, is a chronic neuropathic pain associated with the fifth cranial nerve (Trigeminal nerve) which carries sensation from the face to brain and some of the motor functions like biting and chewing. The aim of this review paper was to determine the current aspects about trigeminal neuralgia including its classification, etiology, diagnosis, and treatment options. The review was conducted using previous research, review, and case studies. The average onset for trigeminal neuralgia is between 50-70 years, although can be found in younger age too. A complete and thorough history is the most important diagnostic tool as well as for prognosis of the disease. Though vascular compression induced morphologic changes in the nerve being the most common cause of trigeminal neuralgia, other variants of its clinical phenotype and etiological factors must also be considered. New MRI methods have helped in proper diagnosis, providing insight about the TN pathogenesis and prognosis. Various new drugs have promising results though more larger scale studies are required. Microvascular decompression is the major and widely accepted method for long lasting pain relief in trigeminal neuralgia.

Introduction

Trigeminal neuralgia (TN) is a chronic condition characterized by pain coming from the one or the more branches of the fifth cranial nerve. It is clinically characterized as unilateral, bouts of electric shock like pain in one or more divisions of the trigeminal nerve[1]. Based on etiology, the international classification of headache disorders (ICHD-3) divides TN into three distinct categories, classical, secondary, and idiopathic[2]. The typical or "classic" form of the disorder (Type 1, or TN1) involves severe burning facial pain, electric shock bouts and each episode lasts from few seconds to two min. At times, onset of pain may occur in clusters that lasts for several hours at a time[3]. Contrary to this, the "atypical" form TN(Type2,orTN2) is described as constant, characteristically burning, and stabbing pain though of lesser severity than TN[1]. This type is mostly found in old age, but can be seen in patients of any age, as some rare cases are diagnosed in children too. TN is usually sporadic, but sometimes familial inheritance can also be seen[4,5]. It mostly involves second and third division of the trigeminal nerve. In contrary, recent studies showed less than 5% cases of involvement of first division of trigeminal nerve and presence of autonomic symptoms on the same side in 31% of patients including tearing, miosis, ptosis, sweating, and clogged nose along with intermittent pain[6].

Etiology

Majority of patients (80–90%) are diagnosed with a vascular anomaly where the vasculature compresses the trigeminal nerve at its exit from the pons resulting in morphological changes in nerve[7].This neurovascular compression can either be primary or secondary depending upon the progression of the vasculature. Primary compression is visual compression of the nerve by a vessel with no secondary cause. In secondary compression there could be brain tumors such as meningiomas, vestibular schwannomas, aneurysms, arteriovenous malformations, and even cysts responsible for neurovascular compression[8]. The compressing vessel is usually found in superior cerebellar artery, but it has also been reported involvement of anterior superior vein as the etiology of trigeminal neuralgia[9].

In Secondary trigeminal neuralgia there is some neuropathic disease present like tumor at cerebellopontine angle or multiple sclerosis, etc. as etiological factor[10]. In 15% of patients, it has been reported that trigeminal neuralgia occurs due to tumor formation at cerebellopontine angle or multiple sclerosis [11].

Other predisposing factors which increase the risk of trigeminal neuralgia are chronic sinusitis, multiple sclerosis, and diabetes.

According to review (Andrew J.Arifin et al.),15% of the cases were identified with some structural changes on imaging, as an etiological factor for trigeminal neuralgia. A literature search by them on trigeminal neuropathy secondary to lymphoma found a report of primary trigeminal nerve lymphoma, also a single case of sino nasal lymphoma with perineural spread.There are various modes of metastasis of tumors including direct invasion, hematologic and lymphatic spread and Perineural invasion (PNI).The metastasis through multitude of molecules in the nerve microenvironment results in perineural invasion. Examples of tumors showing PNI are head and neck squamous cell carcinoma, and salivary gland malignancies such as adenoid cystic carcinoma. In contrast, PNI of lymphomas is not readily described in the literature. Andrew J. Arifin et al. presented a rare case of a primary lymphoma of the tongue which was presented as trigeminal neuralgia. So thorough examination is important to know the exact etiology of trigeminal neuralgia[7].

Diagnosis

According to American Academy of Neurology and European Federation of Neurology Society a complete history, physical examination, head imaging and electrophysiologic testing are the diagnostic tools of trigeminal neuralgia[12].

The clinical diagnosis of trigeminal neuralgia is confirmed by the presence of pain characteristics involving unilateral, transient, or paroxysmal episodes of pain in one, two or three divisions of the trigeminal nerve, lasting from few seconds to 2 minutes. Pain can be triggered by factors such as talking, chewing, touching, or shaving the face, brushing the teeth, or putting on makeup. These sensitive areas on patient's face when touched cause attack and are known as trigger points or zones. These trigger points are important for diagnosis. Frequency of the pain attacks may range from 1 to over 50 a day. This diagnosis should have pain-free breaks between the pain episodes and should not be continuous[13].

Imaging

Once the diagnosis of TN is suspected clinically, neuroimaging is recommended to help distinguish classic from symptomatic TN. This can be accomplished with magnetic resonance imaging (MRI) or computed tomography (CT). CT scan has limited use in evaluation of brainstem and cisterns. But is an important tool in visualizing the trigeminal nerve root entry zone and nearby vasculature when MRI is contraindicated in patients e.g., with artificial pacemaker. MRI with and without contrast is preferred for improved visualization of the trigeminal nerve and adjacent structures which can aid in diagnosing the neurovascular compression of the trigeminal nerve, which should not include a secondary cause for nerve compression[14]. MRI may reveal neurovascular contact in asymptomatic trigeminal nerve roots. As shown by a meta-analysis of 9 high-quality blinded and controlled studies, 36% of asymptomatic cases showed neurovascular contact[15]. So, MRI showed neurovascular contact is not only the diagnostic criteria. Imaging and special testing may be used to rule out alternative diagnoses such as herpes zoster, trigeminal nerve trauma, migraine, cluster headache, occipital or glossopharyngeal neuralgia, multiple sclerosis, temporomandibular joint pain, dental problems, cerebral aneurysms, tumors, and intracranial hemorrhage. The secondary TN diagnosis can be continuous or near continuous and is associated with a triggering pathology causing the pain. Most pain in these circumstances is caused by arteriovenous malformations,certain brain tumors,or multiple sclerosis. A third form, idiopathic trigeminal neuralgia, is diagnosed when symptoms occur but without a clear cause of neurovascular compression or secondary causes based on negative MRI and other neurophysiologic tests. In patients that cannot undergo MRI, trigeminal evoked potentials and neurophysiologic recordings of trigeminal reflexes are the alternatives for classifying the trigeminal neuralgia. By correctly identifying the trigeminal neuralgia as well as its classification type one can improve the treatment strategies as well as patient satisfaction to a larger extent[5]. Other conditions like malignancy, congenital malformations and multiple sclerosis may present with similar symptoms of trigeminal neuralgia but can be differentiated from it by the presence of neurologic symptoms in addition to the typical paroxysmal pain pattern[16].

Advanced MRI

Advanced MRI techniques further allow for visualization of structural changes within the root that are highly suggestive of physical alteration and provide high predictive value for pain relief after decompression [17]. The degree of morphologic root changes is therapeutically relevant. Long-

term outcome after surgical revision of mere neurovascular contact is uncertain compared to the decompression of dislocated, distorted, or flattened nerve roots [18].

The visualization of trigeminal nerve root and vessels can be improved using 3D reconstruction of special imaging techniques e.g.,3D T2-weighted MRI, for a detailed examination of cisternal and cavernous nerve segments, 3D time-of-flight magnetic resonance angiography for the visualization of arteries, and 3D T1-weighted MRI with gadolinium or phase-contrast MRI for the visualization of veins [19,20].

Neurophysiologic testing

This test is helpful in differentiating classic trigeminal neuralgia from secondary trigeminal neuralgia. In secondary trigeminal neuralgia, more abnormal neurophysiological finding has been found due to damage to the sensory pathway by the pathology than classic trigeminal neuralgia [21].

Diffusion tensor imaging (DTI) and fiber tractography

In classic TN, Vessels compressing the nerve, causes focal axonal degeneration and demyelination of the nerve thus interrupt the transmission of normal nociceptive stimuli. Demyelination of the trigeminal pathway is the main cause of pain in MS related TN. DTI can reveal these microstructural changes in the nerve, improve diagnosing the type of TN, deciding patients which are more suitable for surgical treatment, as well as treatment outcome [22]. DTI can assess tissue integrity and changes in the trigeminal nerve.Fibertractography (FT) is a 3D reconstruction technique to assess neural tracts using data collected by diffusion tensor imaging. According to a study DTI showed loss of anisotropy and increase in diffusivity in affected nerve. After surgery, Fraction of Anisotropy (FA) remains the same while Apparent Diffusion Coefficient (ADC) normalized suggesting improvement in diffusion of the nerve [23]. DTI has the potential in understanding the pathophysiology of trigeminal neuralgia and treatment effects and merits further research.

Treatment

Certain (63%) trigeminal neuralgic patients resolve their symptoms spontaneously, completely for many years, which is not found in other neuropathic diseases [5].

Treatment should be according to diagnosis. According to classic trigeminal neuralgia, treatment begins with medication then MVD surgery or other surgical procedures and if secondary TN find out the cause and treat accordingly e.g., if lymphoma of the nerve or any other structure is causing the trigeminal neuralgia, then treatment of lymphoma or respective treatment will relieve the patient from pain. In a case report, by Arifin et al. lymphoma of the tongue, presented primarily as trigeminal neuralgia, was treated with combination of medicines e.g., R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone). Patient completed 4 cycles of chemotherapy and positron emission tomography demonstrated complete disease response. At the time of this report, the patient found minimal return of sensation to the left tongue and mandibular area of her face; however, her pain was completely subsided[7].

First Line Medications

For treatment of Trigeminal neuralgia medical pharmacotherapy is considered as first step. Drugs such as anticonvulsants and tricyclic antidepressants comes under first line of treatment with medications. Carbamazepine is the most relevant and drug of choice for TN[5]. Mechanism of Carbamazepine is stabilizing the sodium channels in an inactive state. It has been reported by a high-quality meta-analysis to be the most efficacious drug for the trigeminal neuralgia [24]. 70% of the patients showed complete relief from the symptoms as shown by a study [25]. Common side effects are dizziness, nausea, diplopia, ataxia, increase of enzyme transaminases and reduction in sodium level. Dose of the drug starts from 100 mg showing effects in some patients to maintenance dose of usually 300-800 mg daily divided into two or three doses. Usually, high dose of this medication given for pain relief results in disabling side effects. Some of the potentially serious though uncommon side effects are allergic rash, myelosuppression, hepatotoxicity, lymphadenopathy, systemic lupus erythematosus, Stevens-Johnson syndrome [26].

The alternative first line of therapy is oxcarbazepine which has lesser side effects. Its dose ranges from starting with 150 mg twice daily to maintenance dose of 300-600 mg twice daily [27].

Second Line Medications

Patients' refractory to first line of treatment, or due to major side effects are treated by Second-line medications including baclofen, a GABAB

receptor agonist, lamotrigine, a sodium channel inhibitor.

Baclofen, used alone or in combination with carbamazepine, shows effect by depressing excitatory neurotransmission by acting as an agonist on GABA receptors[28]. Maintenance dose ranges from 60-80mg per day9. Side effects of this drug includes drowsiness, sedation, lassitude, nausea. Sudden withdrawal of this drug causes seizures and hallucinations. Baclofen is considered as the most scientifically proven drug next to CBZ, in the treatment of trigeminal neuralgia.

Lamotrigine, an anticonvulsant, which is mainly used for the treatment of bipolar disorder. In an open label study of 15 trigeminal neuralgic patients, this drug showed a beneficial response proportionate to a maximum dose of 400 mg/day[29]. There was a double-blind placebo-controlled crossover trial performed, which showed that combination of carbamazepine and 400 mg lamotrigine was more effective than placebo[30]. The dose is initiated at 25mg per day to a maintenance dose of 200-400 mg twice daily. Side effects associated with this drug are dizziness, blurred vision, headache, ataxia, nausea. Skin rashes are seen in 7-10 % of patients, that get resolved with continued therapy. While I in 10,000 patients develop Stevens- Johnson syndrome require prompt discontinuation of the treatment[31].

Third line treatment

The third line drug therapies include levetiracetam, topiramate,gabapentin, pregabalin, and botulinum toxin A[32]. In refractory cases, drugs such as baclofen, gabapentin, lidocaine, and misoprostol are found efficient [5].

Gabapentin, another drug, shows minimal interactions with other medications and lesser side effects[33]. It is a new generation antiepileptic drug, used in the treatment of epilepsy, postherpetic neuralgia & diabetic peripheral neuropathy. There are not many studies on its efficacy in the treatment of trigeminal neuralgic pain. A retrospective study was conducted on 92 patients, observed it as an alternative treatment option and as a safe profile34. There was another study reviewing Randomized controlled trials (RCTs) of Gabapentin in the treatment of Idiopathic Trigeminal Neuralgia. This study identified only 2 RCTs studying the efficacy of GBP in the management of idiopathic TN. One study was by Debta et al. which showed efficacy of GBP was 60-80% on newly diagnosed trigeminal neuralgic patients and it was 50-60% in refractory patients. Despite this, they found GBP to be inferior to Oxcarbazepine[35]. Second study was conducted by Lemos et al. which showed five months after 28 days research found combination of ropivacaine, and GBP showed least no. of daily pain episodes than GBP alone[36]. So, from these 2 studies it was concluded that GBP is an effective alternative to CBZ and OXC only when these first line drugs are intolerable to patients. As this study involved only 2 RCTs, so more evidence is required to show the efficacy of GBP. Gabapentin is efficient both alone and in combination with ropivacaine to block trigger points in patients of Trigeminal Neuralgia. Dose of this drug is usually 300-1800 mg per day.

Pregabalin is analog of GABA that is structurally related to gabapentin. In an open label study of 53 patients with 1-year observational period, pregabalin was found to be effective in reducing pain by more than 50% in 74% of patients. Treatment was more effective in patients without accompanying facial pain than patients with chronic facial pain[37].

Topiramate blocks voltage gated calcium channels by binding to non- benzodiazepine GABA receptors. Its usual dose is 100-400 mg per day. In a small (8 patients) sample of study, drug was effective in 75% of cases[38].

Levetiracetam shows less drug interactions and no routine blood tests while treating TN patients. Usual dose of the drug is 1000-4000mg per day. In an open label study of 10 trigeminal neuralgic patients, 40% patients showed improvement of 50-90%[39]. Though more studies are required to prove these findings.

The next studied drug is Botulinum toxin. BTX deactivate sodium channels and inhibit the release of mediators of inflammation and peripheral neurotransmitters from sensory nerves[40]. BTX-A changes the sodium flow of excitable membrane of a neuron, and it controls sodium current with a non-concentration dependent manner that differentiate it from other drugs like antiepileptics, tetrodotoxin and local anesthetics[41]. The meta-analysis of 10 Randomized Controlled Trials (RCTs) on the efficacy and safety of Botulinum Toxin A (BTX-A) in treating Trigeminal Neuralgia (TN) and Peripheral Neuropathic Pain (PNP) was conducted by Jiangshan Wei et al. In these 10 RCTs, method of conducting trial was quite variable including duration of follow up ranging from 8-24 weeks, administration route

(sub cutaneous, sub mucosal, intradermal), injection site, dosage of BTX-A from 25 U in study of Zhanget et al. (2014) to 300 U in study of Attal et al. (2016).The final analysis was that there was remarkable reduction in pain score for BTX-A group than placebo(at the 3rd month).Adverse reactions were also mild, transient and nonsystemic. It was concluded from this study that BTX-A is safe and efficacious in treating trigeminal neuralgia and peripheral neuropathic pain compared with placebo[42]. No doubt there is risk of bias in this meta-analysis because of moderate evidence due to limited studies and small sample size. More future trials are required to know the exact dose and duration of treatment and route of administration of botulinum toxin for pain relief.

Surgical treatment

Patients who failed medical treatment with at least 3 medications, or suffered from some intolerable/serious side effects, or symptoms coming back again are the candidates for surgical management of TN5. Though right time for surgical intervention over medical treatment is still to be determined. While some patients may consider surgery as an option beside getting relieved by the medication because of the fear of the severe pain and side effects of medication43. Surgical treatments are either destructive, where trigeminal nerve sensory functions are destroyed (percutaneous rhizotomy) or non-destructive to trigeminal nerve, where sensory functions are preserved (MVD)[5]. The decision to perform either treatment should be made based on both clinical and neuroimaging findings.

MVD (Micro Vascular Decompression)

This is the treatment of choice in young patients and individuals showing neurovascular conflict (NVC)[44]. Though it is the most invasive procedure but most successful treatment too in terms of permanently treating the pain. It is a major surgery involving retro sigmoid craniotomy to reach the trigeminal nerve. Offending artery is identified and dissected free from the nerve and Teflon pledget is placed between the nerve and the vessel9. If surgeons do not find neurovascular compression, they perform sectioning (retrogasserian rhizotomy) or briefly compress the nerve. It has been proved by many studies that MVD has long lasting pain relief in more than 70% of the treated patients[45,46]. This treatment results in immediate pain relief in 90% of patients, after 5 years in 68-88% of patients and after 10 years in 61-88% of patients[47]. Complications associated with this procedure includes aseptic meningitis (11%), sensory loss (7%), hearing loss (10%), cerebrospinal fluid leakage, infarcts/ hematoma (4%), death (0.2- 0.5%)[48]. MVD shows better treatment response in classic trigeminal neuralgia and arterial compression of nerve. Patients of atypical facial pain shows less response rates with MVD as compared to classic TN[49]. In case of venous compression, vein is divided to decompress the nerve. Endoscopic MVD is also suggested as an alternative option to microscopic MVD especially in cases of bony ridge obscuring the view of trigeminal nerve or with a very distal vascular compression or both[50]. It was reported that 8.5% of cases which were not solved by microscopic MVD showed better visualization with endoscopic MVD.

Percutaneous Rhizotomy

In this surgical technique, selective destruction of A-delta and C pain nerve fibers is performed while A-alpha and beta sensory nerve fibers are preserved. The rhizotomy can be performed by three methods including mechanical by balloon compression of the gasserian ganglion, chemical by glycerol injection of the trigeminal cistern, and radiofrequency thermal in which heat is applied to damage the trigeminal nerve ganglion5. In all these techniques foramen ovale, located through radiological guidance, is used to gain access to the trigeminal ganglion[51]. So, locating the foramen ovale under fluoroscopic guidance, correctly, can leads to success or failure of the treatment. Many studies described the methods to locate foramen ovale but has limitation of poor reproducibility. Kang Sup et al. did a retrospective analysis on 72 3D facial computed tomography scans of anatomically normal skull base to come out with a method to locate foramen ovale. According to them, the mandibular angle and the occipital cortical line were overlapped and then turned by 15° oblique rotation using the software package. They found a good grade of visibility of foramen ovale[52]. But this study is still lacking clinical applications and comparative data to the submental view.

In 80-90% of patients, surgical intervention by balloon compression provides a significant relief from the pain without any medication in a period of 2-3 years[53].

Glycerol rhizotomy results in high but short-term rate of success with more than 90% of patients showing initial pain relief and more than 50% of patients remained symptom free after three years[54].
Radio frequency thermocoagulation (RFT) is used in elderly, unilateral or bilateral pain, recurrence after MVD or other neurosurgeries, TN with atypical facial pain, vertebrobasilar dolichoectasia and multiple sclerosis[55]. Previous studies showed recurrence after RFT ranging from 17.2% to 46%56. After RFT adverse events like facial numbness, absence of corneal reflex, and masseter muscle weakness were observed[57]. To check long term outcome of recurrence free survival (RFS) after RFT and risk factors associated with recurrence, a multicenter retrospective analysis of data from 1481 patients with TN, underwent treatment with RFT from 2005-2017 in 2 large teaching hospitals in China, was performed by Shuyue Zheng, Xiuhua Li, et al. It showed initial efficiency rate of pain relief after RFT of 92.39%. The median RFS was 136 months, and rates of RFS was 85.5% at 1 year, 74.6% at 3 years, 68% at 5 years and 54.9% at 10 years and 35.18% in a 14 year of follow up period, respectively. There are independent risk factors associated with recurrence of TN after treatment with RFT which includes atypical facial pain at baseline, past RFT treatment, at least 2 past neurosurgeries and existing facial hypesthesia of BNI class II (mild facial numbness, not bothersome). The risk is 17fold with atypical facial pain, 1.642fold with MVD, 2.808fold with history of RFT, 3.832fold with previous neurosurgeries,2.473 fold/ 3.288 folds for patients with BNI class II/III facial hypesthesia before RFT, respectively. Adverse event like facial hypesthesia of scale II was observed in 54.56%, class III in 36.33% and class IV in 4.52% of cases, respectively. Rate of facial numbness was higher with increase in RFT temperature i.e., in 80° C group than in 70 and 75 degrees. While 18.20% showed resolution of their facial numbness gradually during follow up. Rate of masseter muscle weakness was also found to be higher in 80° C group than in other groups. It was found that temperature range of 68°-70°C showed good results with less complications and efficiency was better at 66-80° C[55]. Though future larger scale long term randomized studies are needed to approve these values, but these findings would be helpful in some way to perform RFT procedure.
These percutaneous procedures are considered less invasive as compared to microvascular decompression surgery but have its own disadvantages including risk of sensory loss in the trigeminal distribution (50%), dysthesias (6%), anesthesia dolorosa (4%—a feared complication consisting of numbness and pain in the targeted dermatome), corneal numbness leading to keratitis.
Gamma knife radiosurgery (GKRS) is an alternative procedure for patients reluctant to invasive procedures or poor candidates for surgical treatments[58]. In this stereotactic, outpatient procedure high doses (70– 100 Gy) of submillimeter radiation beams is focused on the trigeminal root entry zone causing necrosis over time, thus decreasing pain[59].

Neuromodulation

Motor Cortex Stimulation & Deep Brain Stimulation are the two types of neuromodulations suggested as possible treatment options for refractory cases of trigeminal neuralgia. According to some studies MCS has resulted in pain relief in 75-100% of patients of neuropathic pain[60,61]. Similarly, several experiments are conducted over the use of DBS using posterior hypothalamus as the target organ in the brain since 1997 [62-65]. As posterior hypothalamus has been hypothesized as controlling unit between neuropsychological circuits of pain behavior and neurovegetative system. According to a systematic review patient of refractory trigeminal neuralgia due to MS get benefitted from DBS within the first trigeminal branch66. Yet, limited studies are done on the use of MCS and DBS, merits further research.

Peripheral nerve/field stimulation

Though it is used to treat variety of conditions like chronic, neuropathic, and refractory pain but limited studies are done in the treatment of TN. A case report described a refractory trigeminal neuralgia case treated with peripheral nerve stimulation with a supraorbital, infraorbital, and frontoparietal leads, resulted in complete pain relief [67]. Peripheral nerve stimulation could be a promising result though more future studies are required.

Transcranial magnetic stimulation

An emerging technology that assesses the outcome of treatment by direct epidural cortical stimulation by estimating the response by this noninvasive method of cortical stimulation. In a study it showed 45% reduction in pain in patients undergoing treatment with repetitive transcranial magnetic

stimulation at motor cortex for 2 weeks at 20 Hz68. In another study on 12 patients, it was found to be effective in relieving more than 30% pain in 58% of patients[69].

Conclusion

Detailed history and examination are the prime requirements for diagnosing the type and etiology of trigeminal neuralgia. A case discussed in this review, of oral lymphoma presented as trigeminal neuralgia, highlights the importance of complete history and examination as there are multiple differentials for this condition. Advanced MRI has helped a lot in understanding the pathogenesis of the disease. Though neurovascular conflict is the most common etiological factor in pathogenesis of trigeminal neuralgia, but other factors should always be considered for successful and alternative treatment options. Recent studies have found Carbamazepine to be 100% effective in relieving pain in 70% of patients. Alternative oxcarbazepine, of similar efficacy and lesser side effects is used. Failure or intolerance to these drugs can be minimized by switching to or Combination therapy with lamotrigine, pregabalin, topiramate drugs. Drugs with better tolerability should be explored. For middle aged and elderly people, where drug side effects and complications of surgery are Intolerable, BTX-A provide efficient and safe treatment option, lasting several months.

The right time to start surgical intervention is yet to be decided. Microvascular decompression is safe, reliable, and effective treatment option in classic trigeminal neuralgia due to neurovascular compression and especially in young patients who want to preserve facial sensitivity. Modern high resolution T2 imaging is quite helpful in diagnosing such neurovascular contact. Patients who fail medical treatment, Classic trigeminal neuralgia secondary to multiple sclerosis, or patients not able to tolerate MVD surgery, where etiology is not neurovascular compression, percutaneous rhizotomy and radiosurgery are effective treatment options. Gamma knife radiosurgery has proved to be effective in relieving pain in 69% of patients up to 1 year and in 52% of patients up to 3 years. Neuromodulation, emerging technique needs more data to support its usefulness in the treatment of trigeminal neuralgia. Similarly peripheral nerve stimulation has proved effective in various neuropathic and chronic pain conditions, but more research is needed regarding its use in trigeminal neuralgia.

References

1. Wu S, Lian Y, Zhang H, Chen Y, Wu C, et al. Botulinum Toxin Type A for refractory trigeminal neuralgia in older patients: a better therapeutic effect, Original Research. Journal of Pain Research 2019: 12 2177-2186.
2. Headache Classification Committee of the International Headache Society (IHS) The InternationalClassification of Headache Disorders, 3rd edition. CEPHALALGIA. 2018; 38:1-211.
3. Krafft RM. Trigeminal neuralgia. Am Fam Physician. 2008;77: 1291–6.
4. McMillan R. Trigeminal Neuralgia - a debilitating facial pain. Rev pain SAGE Publications; 2011; 5:26–34.
5. Jones Mark R., Uritis Ivan, Ehrhardt Ken P., et al. A comprehensive review of trigeminal neuralgia; Current Pain and Headache (2019) 23:74
6. Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Trigeminal neuralgia–a prospective systematic study of clinical characteristics in 158 patients. Headache. 2014; 54:1574–82.
7. Arifin Andrew J., Lam Selay, MacNeil S. Danielle, A case report of primary lymphoma of the tongue presenting as trigeminal neuralgia: Case Report; Arifin et al Journal of Otolaryngology- Head and Neck Surgery 2019 48:37.
8. Montano N, Conforti G, Di Bonaventura R, Meglio M, Fernandez E, Papacci F. Advances in diagnosis and treatment of trigeminal neuralgia. Ther Clin Risk Manag. 2015; 11:289–99 A review of advances in management of TN.
9. Tai Alexander X., Nayar Vikram V., Update on trigeminal neuralgia, Curr Treat Options Neurol (2019) 21:42
10. Cruccu Giorgio, Finnerup Nanna B., et al., Trigeminal neuralgia -New classification and diagnostic grading for practice and research. Neurology.2016 Jul 12; 87(2): 220–228.
11. Gronseth G, Cruccu G, Alksne J, et al. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. Neurology 2008; 71:1183–1190. [PubMed] [Google Scholar]
12. Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, et al. AANEFNS guidelines on trigeminal neuralgia management. Eur J Neurol. 2008; 15(10):1013–28.
13. Bope ET, Kellerman RD, Conn HF (Howard F. Conn's current therapy 2016.
14. Gronseth G, Cruccu G, Alksne J, Argoff C, Brainin M, Burchiel K, et al. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies: 2008 Oct 7;71(15):1183-90.
15. Antonini G, Di Pasquale A, Cruccu G, et al. Magnetic resonance imaging contribution for diagnosing symptomatic neurovascular contact in classical trigeminal neuralgia: a blinded case-control study and meta-analysis. Pain 2014; 155:1464–1471. [PubMed] [Google Scholar]
16. Gonella MC, Fischbein NJ, So YT. Disorders of the trigeminal system. Semin Neurol. 2009;29(1):36–44.
17. Leal PR, Barbier C, Hermier M, Souza MA, Cristino-Filho G, Sindou M. Atrophic changes in the trigeminal nerves of patients with trigeminal neuralgia due to neurovascular compression and their association with the severity of

compression and clinical outcomes. J Neurosurg 2014; 120:1484–1495. [PubMed] [Google Scholar]
18. Sarsam Z, Garcia-Finana M, Nurmikko TJ, Varma TR, Eldridge P. The long-term outcome of microvascular decompression for trigeminal neuralgia. Br J Neurosurg 2010; 24:18–25. [PubMed] [Google Scholar]
19. Leal PR, Hermier M, Souza MA, Cristino-Filho G, Froment JC, Sindou M. Visualization of vascular compression of the trigeminal nerve with high-resolution 3T MRI: a prospective study comparing preoperative imaging analysis to surgical findings in 40 consecutive patients who underwent microvascular decompression for trigeminal neuralgia. Neurosurgery 2011; 69:15–25. [PubMed] [Google Scholar]
20. Shimizu M, Imai H, Kagoshima K, Umezawa E, Shimizu T, Yoshimoto Y. Detection of compression vessels in trigeminal neuralgia by surface-rendering three-dimensional reconstruction of 1.5- and 3.0-T magnetic resonance imaging. World Neurosurg 2013; 80:378–385. [PubMed] [Google Scholar]
21. Bendtsen L, Zakrzewska JM, Abbott J, Braschinsky M, Di Stefano G, Donnet A, et al. European academy of neurology guideline on trigeminal neuralgia. Eur J Neurol. 2019;26(6):831–4.
22. Willsey MS, Collins KL, Conrad EC, Chubb HA, Patil PG. Diffusion tensor imaging reveals microstructural differences between subtypes of trigeminal neuralgia. J Neurosurg. 2019 Jul 19:1-7. doi: 10.3171/2019.4. JNS19299. [Epub ahead of print] PubMed PMID: 31323635.
23. Leal PRL, Roch J, Hermier M, Berthezene Y, Sindou M. Diffusion tensor imaging abnormalities of the trigeminal nerve root in patients with classical trigeminal neuralgia: a pre- and postoperative comparative study 4 years after microvascular decompression. Acta Neurochir (Wien). 2019 May 2. doi: 10)1007/s00701-019-03913-5. [Epub ahead of print] PubMed PMID: 31049710.
24. McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. BMJ. BMJ Publishing Group; 1995; 311:1047–52.
25. Zakrzewska JM, Linskey ME. Trigeminal neuralgia. BMJ. 2014;348: g474–4.
26. Obermann Mark: Treatment Options in trigeminal neuralgia: Ther Adv Neural Disord (2010) 3(2) 107- 115
27. Al-Quliti KW. Update on neuropathic pain treatment for trigeminal neuralgia. The pharmacological and surgical options. Neurosciences (Riyadh). Medical Services Division, Ministry of Defense; 2015; 20:107–14.
28. Maarbjerg S, Di Stefano G, Bendtsen L, Cruccu G. Trigeminal neuralgia – diagnosis and treatment. Cephalalgia. 2017; 37:648–57.
29. Lunardi G, Leandri M,AlbanoC, Cultrera S, Fracassi M, RubinoV, et al. Clinical effectiveness of lamotrigine and plasma levels in essential and symptomatic trigeminal neuralgia. Neurology. 1997; 48:1714–7.
30. Zakrzewska JM, Chaudhry Z, Nurmikko TJ, Patton DW, Mullens EL. Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo-controlled crossover trial. Pain. 1997; 73:223–30.
31. Wiffen PJ, Rees J. Lamotrigine for acute and chronic pain. In: Wiffen PJ, editor. Cochrane Database Syst Rev. Chichester: John Wiley & Sons, Ltd; 2007. p. CD006044.
32. Al-Quliti KW. Update on neuropathic pain treatment for trigeminal neuralgia. The pharmacological and surgical options. Neurosciences (Riyadh). Medical Services Division, Ministry of Defence; 2015; 20:107–14.
33. Poa Ta Patrick Chieu, et al. Efficacy of Gabapentin in the treatment of trigeminal neuralgia: A systematic review of randomized controlled trials: J Investig Clin Dent. 2019 Nov;10(4): e12448
34. Cheshire WP Jr. Defining the role for gabapentin in the treatment of trigeminal neuralgia: a retrospective study. J Pain. 2002;3(2):137-142.
35. Debta FM, Ghom AG, Shah JS, Debta P. A comparative study between oxcarbazepine and gabapentin regarding therapeutic efficiency and tolerability in the treatment of trigeminal neuralgia. J Indian Acad Oral Med Radiol. 2010;22(1):10-17.
36. Lemos L, Flores S, Oliveira P, Almeida A. Gabapentin supplemented with ropivacain block of trigger points improves pain control and quality of life in trigeminal neuralgia patients when compared with gabapentin alone. Clin J Pain. 2008;24(1):64-75. https ://doi.org/10. 1097/AJP.0b013 e3181 58011a
37. Obermann, M., Yoon, M.S., Sensen, K., Maschke, M., Diener, H.C. and Katsarava, Z. (2008) Efficacy of pregabalin in the treatment of trigeminal neuralgia. Cephalalgia 28: 174_181.
38. Domingues, R.B., Kuster, G.W. and Aquino, C.C. Treatment of trigeminal neuralgia with low doses of topiramate. Arq Neuropsiquiatr 2007 ;65: 792_794.
39. Jorns, T.P., Johnston, A. and Zakrzewska, J.M. (2009) Pilot study to evaluate the efficacy and tolerability of levetiracetam (Keppra) in treatment of patients with trigeminal neuralgia. Eur J Neurol 16: 740_744.
40. Park, J., & Park, H. J. (2017). Botulinum toxin for the treatment of neuropathic pain. Toxins (Basel), 9(9), 260. https ://doi.org/10.3390/toxins 9090260
41. Cui, M., Khanijou, S., Rubino, J., & Aoki, K. R. (2004). Subcutaneous administration of botulinum toxin A reduces formalin-induced pain. Pain, 107(1–2), 125–133. https ://doi.org/10.1016/j.pain.2003.10.008
42. Jianngshan Wei,Xiangyu Zhu, Guan Yang, et al. The efficacy and safety of botulinum toxin type A in treatment of trigeminal neuralgia and peripheral neuropathic pain: A meta-analysis of randomized controlled trials.Brain and Behaviour.2019;00:e01409.https://doi.org/10.1002/brb3.1409.
43. Spatz, A.L., Zakrzewska, J.M. and Kay, E.J. (2007) Decision analysis of medical and surgical treatments for trigeminal neuralgia: how patient evaluations of benefits and risks affect the utility of treatment decisions. Pain 131: 302_310.
44. Zacest AC, Magill ST, Miller J, Burchiel KJ. Preoperative magnetic resonance imaging in Type 2 trigeminal neuralgia. J NEUROSURG. 2010; 113:511-515.
45. Ko AL, Ozpinar A, Lee A, Raslan AM, McCartney S, Burchiel KJ. Long-term efficacy and safety of internal neurolysis for trigeminal neuralgia without neurovascular compression. J Neurosurg. 2015; 122:1048–57.
46. Tronnier VM, Rasche D, Hamer J, Kienle AL, Kunze S. Treatment of idiopathic trigeminal neuralgia: comparison of long-term outcome after radiofrequency rhizotomy and microvascular decompression. Neurosurgery. 2001; 48:1261–8.
47. Barker FG 2nd, Jannetta PJ, Bissonette DJ, Larkins MV, Jho HD. The long-term outcome

of microvascular decompression for trigeminal neuralgia. N Engl J Med.1996;334(17):1077–83.
48. Gronseth, G., Cruccu, G., Alksne, J., Argoff, C., Brainin, M., Burchiel, K. et al. (2008)Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (anevidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. Neurology 71: 1183_1190.
49. Zacest AC, Magill ST, Miller J, Burchiel KJ. Preoperative magnetic resonance imaging in type 2 trigeminal neuralgia. J Neurosurg. 2010;113(3):511–5.
50. Sandell T, Ringstad GA, Eide PK. Usefulness of the endoscope in microvascular decompression for trigeminal neuralgia and MRI-based prediction of the need for endoscopy. Acta Neurochir (Wien) 2014;156(10):1901–1909. [PubMed] [Google Scholar]
51. Montano N, Conforti G, Di Bonaventura R, Meglio M, Fernandez E, Papacci F. Advances in diagnosis and treatment of trigeminal neuralgia. Ther Clin Risk Manag. 2015; 11:289–99 A review of advances in management of TN.
52. Kim Sup Kang, Lee Hyun Sung, et al. A novel method of locating foramen ovale for percutaneous approaches to the trigeminal ganglion: Pain Physician 2019; 22: E345-E350.
53. Baabor MG, Perez-Limonte L. Percutaneous balloon compression of the Gasserian ganglion for the treatment of trigeminal neuralgia: personal experience of 206 patients.
Acta Neurochir Suppl. 2011; 108:251–4.
54. Slettebø H, Hirschberg H, Lindegaard KF. Long-term results after percutaneous retrogasserian glycerol rhizotomy in patients with trigeminal neuralgia. Acta Neurochir. 1993; 122:231–5.
55. Zheng Shuyue, et al. Factors associated with long term risk of recurrence after percutaneous radiofrequency thermocoagulation of the gasserian ganglion for patients with trigeminal neuralgia: A multicenter retrospective analysis: The Clinical Journal of Pain Publish Ahead of Print: 2019 Dec; 35(12): 958-966
56. Ran B, Wei J, Zhong Q, Fu M, Yang J, Chen X, et al. Long-term Follow-up of Patients Treated with Percutaneous Radiofrequency Thermocoagulation via the Foramen Rotundum for Isolated Maxillary Nerve Idiopathic Trigeminal Neuralgia. PAIN MED. 2019.
57. Huang Q, Liu X, Chen J, Bao C, Liu D, Fang Z, et al. The Effectiveness and Safety of Thermocoagulation Radiofrequency Treatment of the Ophthalmic Division (V1) and/or Maxillary (V2) and Mandibular (V3) Division in Idiopathic Trigeminal Neuralgia: An Observational Study. PAIN PHYSICIAN. 2016;19: E1041-E1047.
58. Montano N, Conforti G, Di Bonaventura R, Meglio M, Fernandez E, Papacci F. Advances in diagnosis and treatment of trigeminal neuralgia. Ther Clin Risk Manag. 2015; 11:289–99 A review of advances in management of TN.
59. Young RF, Vermulen S, Posewitz A. Gamma knife radiosurgery for the treatment of trigeminal neuralgia. Stereotact Funct Neurosurg. 1998;70(suppl 1):192–199. [PubMed] [Google Scholar]
60. Levy R, Deer TR, Henderson J. Intracranial neurostimulation for pain control: a review. Pain Phisician. 2010;13(2):157–165. [PubMed] [Google Scholar]
61. Buchanan RJ, Darrow D, Monsivais D, Nadasdy Z, Gjini K. Motor cortex stimulation for neuropathic pain syndromes: a case series experience. Neuroreport. 2014;25(9):715–717. [PubMed] [Google Scholar]
62. Broggi G, Franzini A, Leone M, Bussone G. Update on neurosurgical treatment of chronic trigeminal autonomic cephalalgias and atypical facial pain with deep brain stimulation of posterior hypothalamus: results and comments. Neurol Sci. 2007;28(suppl 2): S138–S145. [PubMed] [Google Scholar)
63. Rasche D, Rinaldi PC, Young RF, Tronnier VM. Deep brain stimulation for the treatment of various chronic pain syndromes. Neurosurg Focus. 2006;21(6): E8. [PubMed] [Google Scholar]
64. Franzini A, Marras C, Tringali G, et al. Chronic high frequency stimulation of the posteromedial hypothalamus in facial pain syndromes and behaviour disorders. Acta Neurochir Suppl. 2007;97(pt 2):399–406. [PubMed] [Google Scholar]
65. Cordella R, Franzini A, La Mantia L, Marras C, Erbetta A, Broggi G. Hypothalamic stimulation for trigeminal neuralgia in multiple sclerosis patients: efficacy on the paroxysmal ophthalmic pain. Mult Scler. 2009;15(11):1322–1328. [PubMed] [Google Scholar]
66. Franzini A, Ferroli P, Leone M, Broggi G. Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. Neurosurgery. 2003;52(5):1095–1099. discussion 1101. [PubMed] [Google Scholar]
67. Abd-Elsayed AA, Grandhi R, Sachdeva H. Effective management of trigeminal neuralgia by neurostimulation. Ochsner J Ochsner Clinic, L.L.C. and Alton Ochsner Medical Foundation. 2015; 15:193–5.
68. Khedr, E.M., Kotb, H., Kamel, N.F., Ahmed, M.A., Sadek, R. and Rothwell, J.C. (2005) Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry 76: 833_838.
69. Lefaucheur, J.P., Drouot, X., Menard-Lefaucheur, I., Zerah, F., Bendib, B., Cesaro, P. et al. (2004) Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. J Neurol Neurosurg Psychiatry 75: 612_616.