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AN OLD TALE OF TRIGEMINAL NEURALGIA IN A NOVEL & COMPREHENSIVE MANNER

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ABSTRACT

Trigeminal neuralgia (TN) is a rare disorder presenting with lancinating pain in the face in the area distributed by the trigeminal nerve. Both medical and surgical modalities exist in the treatment of patients with TN. Carbamazepine still remains as the gold standard drug in terms of efficacy in TN. Several other drugs can be used as alternatives for TN such as oxacarbazepine, baclofen, lamotrigine, levetiracetam, gabapentin, valproate, botulinum toxin injection. This paper reviews the clinical evidence and the safety profile of these drugs for the treatment of TN.

INTRODUCTION

Trigeminal Neuralgia (TN) is a chronic pain condition of intense pain in the face. Also known as prosopalgia, suicide disease, and fothergill's disease, the pain stems from the trigeminal nerve that sends information from the face to the brain. It is characterized by a recurrent, unilateral sharp pain in the distribution of one or more branches of the trigeminal nerve. The pain is usually in the distribution of the mandibular or maxillary branches and has a prevalence of 4 per 100,000 people [1]. Given that the diagnosis is made on a clinical basis, controversy still exists in regard to the best method of diagnosing the disorder [2, 3]. In general, facial pain may be due to vascular, neurologic, or dental origins. Many patients with TN originally mistake the pain as dental pain and are hence seen and treated by several dentists, who fail to improve their condition. This is understandable since dental pain is much more common than TN and most dentists will only encounter 3-4 cases of TN in a practicing lifetime. There is increasing agreement that the pain in TN is caused by the demyelination of the trigeminal nerve, due to either vascular compression, multiple sclerosis, amyloid infiltration, or other sources of trauma [4].

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Epidemiology It usually affects patients during middle and old age. There seems to be a predominance of women with TN. No known racial or ethnic risk factors exist. Patients with multiple sclerosis may develop trigeminal neuralgia as a secondary symptom. However, this occurrence is relatively rare, involving only approximately 1% of patients with multiple sclerosis [5].

Diagnostic Criteria It is defined by the International Association for the study of Pain (IASP) as “a sudden, usually unilateral, severe, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial nerve”[6]. International Headache Society (IHS) defined TN as “painful unilateral affliction of the face, characterized by brief electric shock like pain limited to the distribution of one or more divisions of the trigeminal

nerve. Pain is commonly evoked by trivial stimuli including washing, shaving, smoking, talking, and brushing the teeth, but may also occur spontaneously. The pain is abrupt in onset and termination and may remit for varying periods" [7]. IHS described criteria for the diagnosis of classical and symptomatic TN [8].

White and Sweet proposed diagnostic criteria for TN. The criteria includes 5 major features-

1. Paroxysmal pain-Paroxysmal attacks of pain are the key feature, and invariably the presenting complaint. It has an electric shock like pain, sudden in onset and often severe in intensity, resulting in facial grimace.TN patients are typically symptom free between attacks. A patient who experiences significant dull pain between attacks does not fit TN diagnostic criteria [9].
2. Pain provoked by light touch to the face. (Trigger zones)- A TN "trigger zone" is an area of facial skin or oral mucosa where low intensity mechanical stimulation (light touch, an air puff, or even hair bending) can elicit typical facial pain. TN trigger zones are few millimeters in size and seen exclusively in the peri-oral regions [10].
3. Pain confined to the trigeminal nerve distribution-Pain paroxysms in TN are confined to the sensory distribution of the trigeminal nerve one side. The lancinating pain attacks occur most frequently in the third trigeminal division and radiate along the mandible. Less often, pain occurs in the second division or in both divisions. Rarely, first division pain occurs. Characteristically, pain attacks are stereotyped i.e. each attack has a similar quality, location and intensity [11, 12].
4. Pain is unilateral. Right side of the face is more commonly involved than the left side. This could be attributed to the narrower foramens (Rotundum and Ovale) on the right side.
5. Normal clinical sensory examination.

The underlying neurophysiologic mechanisms of TN are not understood [13]. The preferred theory of causation is vascular compression of the trigeminal root adjacent to the pons [14, 15, 16]. The nerve impingement in the trigeminal root entry zone is often accompanied by a demyelination. It is believed that these alterations promote ectopic firing from the injured nerve fibers as well as allow transmission of painful impulses [17]. There are various evidences which support the theory of nerve compression. (a) Imaging modalities (MRI) during posterior fossa surgery for TN have revealed close approximation of a blood vessel with the nerve root [18].
(b) Most patients got long term pain relief after elimination of compression [19]. (c) Intra-operative recordings showed immediate improvement in nerve conduction following decompression and the patients wake up from the operation pain free [20]. (d) Sensory functions recover following decompression (although recovery is slower than in nerve conduction) [21]. Current theory also includes the possibility that TN is a symptom of a central nerve disease characterized by a failure of central inhibitory mechanisms [22, 23]. Other authors regard TN as a symptom of a primarily vascular disease of the trigeminovascular system. This system is characterized by a functional interplay between a sensory trigeminal plexus and blood vessels localized in the pia and dura mater [24]. Also, damage to the myelin sheath can cause trigeminal pain. This type of damage typically occurs in connection with multiple sclerosis [25].

Diagnosis A detailed history is very important for the diagnosis. Physical examination includes neurologic examination and the finding of typical trigger zones verifies the diagnosis of trigeminal neuralgia. Imaging is carried out to rule out other causes of compression of trigeminal nerve such as mass lesions, or vascular malformations. Imaging modalities includes MRI: 3 dimensional constructive interfaces in steady state (3-D-CISS) showed the proximity between trigeminal nerve and the region of neuralgic manifestation [26].

Differential Diagnosis The list of disease which should be considered in the differential diagnosis is long. However, some of the lesions which should not be ignored are specific and non specific facial pains, TMJ disorders, dental disorders, vascular migraine, cluster headache, chronic paroxysmal hemicranias, cracked tooth syndrome, post herpetic neuralgia and giant cell arteritis [27].

Treatment There is indeed a gamut of medical and surgical treatment modalities available for trigeminal neuralgia. As per AANEFNS (American Academy of Neurology- European Federation of Neurological Societies) guidelines, medical therapy is started and surgical options are considered only if there is failure to respond to medical therapy. Other treatment modalities include TENS, Acupunture and psychological methods [28].

PHARMACOLOGICAL TREATMENT

Carbamazepine Since its introduction in TN therapy more than 30 years ago, the anticonvulsant carbamazepine (Tegretol) is considered to be the drug of choice for the initial and long term management of TN. Among all pharmacologic agents used for this purpose, it shows the greatest effectiveness. It is a tricyclic imipramine first synthesized in 1961 and introduced for treatment of trigeminal neuralgia by Blom [29]. The mechanism of action may be related to its ability to block voltage sensitive sodium channels which result in stabilization of the hyper excitable trigeminal neural membranes. Dosage used may range from 100 mg to 1200 mg per day, and most patients respond to 200 to 800 mg per day in two-three divided doses. However, adverse reactions are common. Typical complaints during the initial phase of carbamazepine therapy are transient and dose-dependent. They include drowsiness, dizziness, confusion, vertigo,

nausea and vomiting. Hepatotoxic and hematologic side effects, including agranulocytosis, aplastic anemia, leukopenia, or pancytopenia may develop [30].

Complete hematologic and liver function evaluation is recommended before and during the therapy and should include a complete blood cell count (CBC), serum ionized calcium concentration, liver function tests, and plasma carbamazepine concentration. The patient should have regular monitoring blood tests. The laboratory tests should be monthly during the first year and quarterly thereafter [31]. Additional adverse drug reactions to carbamazepine can occur. Possible gastrointestinal manifestations are abdominal pain, diarrhea, constipation, anorexia, stomatitis, glossitis, and dryness of the mouth and pharynx. Potential skin manifestations include pruritus and erythematous rashes, urticaria, and photosensitivity. Other adverse reactions may affect the nervous system (blurred or double vision or nystagmus), the cardiovascular system (aggravation of hypertension), the respiratory system (pulmonary hypersensitivity), the genitourinary system (oliguria), and the musculoskeletal system (arthralgia and myalgia). Drug interactions with erythromycin may occur, the antibiotic erythromycin increases the plasma levels resulting in toxicity of carbamazepine [32].

Oxycarbazepine is a keto analogue of carbamazepine which has a better toxicity profile. It may be a useful alternative in patients who do not tolerate carbamazepine. It was associated with substantially fewer adverse events than carbamazepine; in particular, there were fewer incidences of vertigo, dizziness, ataxia and fatigue. Tolerability was reported as ‘good’ to ‘excellent’ by 62% of patients receiving oxcarbazepine, compared with 48% of patients receiving carbamazepine [33].

Baclofen (Lioresal), a muscle relaxant and antispastic used for the treatment of signs and symptoms associated with multiple sclerosis was introduced for the therapy of TN in 1984 [34]. It is prescribed if monotherapy with carbamazepine has failed. It can be used alone or in combination with carbamazepine or phenytoin, respectively [35]. Initial dose is 5 mg tid for three days and the dose may be increased to 10 to 20 mg / day every 3 days, and the maximum tolerated dose is 50 to 60 mg / day. Typical adverse effects of baclofen include drowsiness, dizziness, weakness, fatigue, and nausea. Abrupt discontinuation of baclofen can cause severe withdrawal symptoms such as hallucinations and seizures. Neverthless, baclofen has the strongest evidence for efficacy of trigeminal neuralgia after carbamazepine. Patients with multiple sclerosis and trigeminal neuralgia derive special benefit with baclofen as the drug can target the symptoms of both the diseased conditions [36].

Phenytoin (Dilantin) is an antiepileptic agent that has been used for TN management for a long time. It was first reported in the literature 30 years ago. Long-term success can be achieved in only 25% of the cases when phenytoin is used alone. Therefore phenytoin is often prescribed in combination with baclofen. The more common possible adverse effects of phenytoin include ataxia, slurred speech, decreased coordination and nausea. Initially given at a dose of 100 mg twice or thrice daily, and gradually increasing the dose as required to a maximum daily dose of 800 mg. Many patients gained benefit within one to two days [37].

Lamotrigine is a phenyltriazine derivative developed for the treatment of partial and generalized tonic clonic seizures. It acts as a voltage sensitive sodium channel and stabilizes neural membranes. Initial dose is 25 mg twice daily and it can be increased gradually to a maintenance dose of 200- 400 mg/day in two divided doses. Fewer side effects are encountered, the most common being sleepiness, dizziness, headache, vertigo and rash. Steven-Johnson syndrome can occur in 1 in 10,000 patients taking the drug. This reaction, which is more common at the advent of therapy, can be prevented to a certain extent by taking care not to escalate the dose too rapidly [38].

Gabapentin It is an anti epileptic drug has shown adequate efficacy alone and in combination with local injections of ropivacaine used to block trigger points in TN**.** Treatment should be started at a dose of 900 mg/day (300 mg/d on day 1, 600 mg/d on day 2, and 900 mg/d on day 3). The dose can also be increased to a maximum of 1800 mg/d for greater efficacy. Some patients may be requiring up to 3600 mg/d. However the effective dose should be individualized based on response and tolerability. Hyperlipidemia is one of the important side effects known to occur while other side effects such as dizziness, coordination problems, infections, nausea, vomiting are usually self-limiting within ten days of initiation of therapy [39].

Pregabalin is a GABA analogue structurally related to gabapentin which modifies the synaptic or non-synaptic release of GABA. It interacts with the α2d subunit of voltage-gated calcium channels by increasing the brain concentration and rate of synthesis of gamma aminobutyric acid. Pregabalin (150-600 mg/day) proved to be effective in reducing TN pain by over 50% in 74% of patients [40].

Topiramate is a newer antiepileptic drug acts by sodium channel blockade, enhancing GABA activity by binding to a non-benzodiazepine site on GABA A receptors, and selectively blocking AMPA/kainite glutamate receptors. Topiramate (100-400 mg/day) was effective in 75% of patients in a very small sample of only eight patients. Dizziness, sedation, cognitive impairment, fatigue, nausea, blurred vision and weight loss are the common side effects [41].

Miscellaneous Drugs Other drugs that have been suggested for the treatment of TN are the anticonvulsants clonazepam and sodium valproate, and the antipsychotic drug pimozide. The efficacy of these drugs remains unclear. Clonazepam, given in the dose of 4-8 mg / day, is the drug of choice in patients in whom carbamazepine is contraindicated [42]. Botulinum toxin has been found to effective in the treatment of several pain syndromes such as migraine and occipital neuralgia. Injection of botulinum toxin causes inhibition of acetylcholine release in nerve endings causing relaxation of muscles and pain relief. Another hypothesis is that botulinum stops secretion of some nociceptive neuropeptides which prevent pain sensation [43]. Other drugs which can be used in TN include topical capsaicin, lidocaine, amitriptyline, sumatriptan, and intranasal lidocaine [44].

Surgical treatment Surgical treatment is considered in cases refractory to pharmacological therapy. Various surgical procedures that are currently practiced are:

1. Microvascular decompression.
2. Ablative procedures:

· Percutaneous radiofrequency thermal rhizotomy
· Glycerol rhizolysis
· Balloon compression of trigeminal ganglion.

3. Gamma knife radiosurgery
4. Other procedures-neurectomy, cryotherapy, and alcohol injections

The surgical procedure is recommended for patients who continue to experience severe pain or side effects from medications. While considering a surgical technique one must consider many factors. There are some important neurosurgical procedures. Each one is effective, but not always and occasionally has to be repeated. These are divided into extra-cranial and intra-cranial procedures:

EXTRACRANIAL

• Peripheral nerve injections- Local anesthetic agents, alcohol.
• Peripheral Neurectomy.
• Cryosurgery.
•Stereotactic radiofrequency thermocoagulation at gasserion ganglion.

INTRACRANIAL

• Radiofrequency thermocoagulation.
• Percutaneous retrogasserian rhizotomy with a. Glycerol injection, b. Alcohol injection.
• Nerve decompression- a. Microvascular decompression (MVD), b. Balloon microcompression (BMC).
• Medullary and Midbrain tractotomy

Retrograssean balloon compression of the trigeminal nerve is a common treatment modality used for the treatment of TN in patients without multiple sclerosis (MS), but is not commonly used in patients diagnosed with MS, where the facial pain is a result of scar tissue or demyelinating plaques. Approximately 10 percent of patients with MS have a diagnosis of TN. Most patients develop other symptoms of multiple sclerosis and optic neuritis before the facial pain and the diagnosis of MS is usually established before they develop chronic facial pain. These patients are more likely to develop the symptoms on both sides of the face than those without MS, but rarely anyone has both sides of the face are affected at the same time. The treatment of TN in patients with MS presents a dilemma. The difficulty of demyelinating disease is identifying the source of pain and finding the best treatment for the symptoms. This is the primary challenge for neurosurgeons in treating MS patients with atypical facial pain. Micro vascular decompression should not be considered as primary treatment of trigeminal neuralgia in this patient population, where the target plate and not the neurovascular conflict related trigeminal neuralgia. Stereotactic Radio surgery can be a good treatment option, but there is a lack of published data to support the treatment in acute setting after failure of treatment by Radiosurgery. Retrograssean balloon compression by neuro-navigation could be a successfully rescue technique in acute complex trigeminal neuralgia in MS patients [45].

ALTERNATIVE TREATMENT MODALITIES

Acupuncture is a treatment with the use of fine needles inserted into the skin along specific meridians in the body. These energy meridians are supposed to be the channels along which the energy or Chi in the body flows. Whenever there is a disturbance or obstruction in these meridians the free flow of the Chi gets affected causing various ailments. With the help of acupuncture these disturbances and obstructions are removed and the patient gets relief from the ailment. The holistic nature of acupuncture makes it one of the effective natural cures for trigeminal neuralgia [47].

Homeopathy is another holistic method or treatment which works on the principle of 'like cures like'. Hence the substances which cause a certain problem in a large dose cure the same problem in the homeopathic preparations. However, homeopathy is a highly specialized science and one should not attempt self-treatment. Always take the help of a professional homeopathic practitioner in order to gain benefit from this system.

Homeopathy is strongly recommended for:

- Patients who are only partially better with the traditional medicines/surgery
- Patients who are resistant to the traditional medicines
- Fresh cases that may not be willing to go for conventional medicines.

Homeopathic Remedies for Trigeminal Neuralgia have a great role to play in the reducing the recurrence of attacks ; not only do they relieve the pain associated with

this nerve disorder but a well prescribed homeopathic medicine also makes sure that the recurrence of the attacks also wither away slowly .

Homeopathic Medicines for TN when Right Side of the Face is affected.

Magnesium phosphoricum is a very useful homeopathic medicine for TN of right side of the face. The main indicating symptom for its use is that the right side is affected, pain is better by applying warm applications and pressure. Kalium phoshphoricum is also for right sided facial pains of TN. For this medicine to be used pains get better by cold applications.

Homeopathic Remedies Spigelia and Lachesis for left sided Facial pain.

Spigelia is a one of the most effective homeopathic remedies for TN when facial pain is on left side. The pain is very severe and is worse from touch. Another medicine for left sided condition is Lachesis when much heat in face and head are present along with the pain. Homeopathic Remedies for TN in which facial pain is accompanied by numbness. Chamomilla is a wonderful medicine for facial pain with numbness. The person feels that one side of face is red and hot other side being pale and cold. Another medicine for this condition is Verbascum Thapsus when left side is involved. The condition gets worse by slightest change in temperature. And if this complaint affects right side of face then medicine Mezereum gives very good result. The main indication towards this medicine being worse from eating.

Homeopathic Treatment for TN in which facial pain is accompanied by twitchings: Belladona is very well indicated medicine for this condition when the face is very red hot and swollen. Another medicine Agaricus Muscarius is a medicine when there is sensation of icy cold needles piercing through the face.

Homeopathic Medicines When TN is caused by Injury

When TN starts after an injury two medicines need special mention. First one is Allium cepa when left side is affected; second one is Hypericum perforatum when on the right side.

Homeopathic Remedies When TN is triggered by Emotions

If Trigeminal Neuralgia is triggered by emotional excitement, Coffea cruda is the best choice.

Homeopathic Medicines When TN is triggered by exposure to cold air

If the complaint begins from cold exposure two medicines Aconitum napellus and *Dulcamara* can be used. The differentiating point between the above medicines is that the former is used after dry cold wind exposure and the latter after wet cold wind exposure.

Homeopathic Medicines When TN is caused by Tooth Extraction

For TN arising after tooth extraction, homeopathic medicine Hekla lava is nearly specific in treating it .For neuralgias arising due to caries of teeth, medicine Plantago major works wonders. This medicine also works well if the condition occurs due to middle ear infection [48].

Reiki is a well-known system of treatment with its roots in Tibet and is one of the popular natural cures. Rediscovered by a Japanese doctor called Dr. Mikao Usui, this system makes use of the cosmic energy to heal various problems of the body and mind. The Reiki practitioners undergo a procedure called attunement which makes them able to access the cosmic energy and channelize it. The practitioners of this healing system claim that Reiki not only works on humans, but also animals, plants and non-living objects.

Cranial Sacral Healing This is an alternative system of treatment that is becoming increasingly popular because it does not cause any harm even if it may not treat the problem effectively. The practitioners of this system follow the theory that the cranial and sacral bones vibrate at a certain frequency in harmony with each other. When this harmony is disturbed it causes various ailments. The treatment focuses on bringing harmony back to the vibrations of these two bones [48].

Chiropractic Manipulation This method of treatment should always be undertaken by a certified chiropractor. This is because it involves the manipulation of the **spinal column and an unskilled person could do more harm than good** in applying this system of treatment which is one of the natural cures of trigeminal neuralgia.

AYURVEDIC TREATMENT Aconitum ferox (vatsanabha) is one of the deadly poison in Ayurveda. It is categorized in mahavisha varg in all Ayurvedic texts. But as mentioned by Acharya Craak that even poison in small amount acts like nectar. So, this poison also acts as a beneficial medicine in various ailments of the body. It is also known as smanchen, "great medicine"; the crushed roots, mixed with bezoar stones, are used as a universal antidote. The root is also used to treat malignant tumors. The root is used in vataroga (diseases of nervous system) [49].

CONCLUSION

Trigeminal neuralgia is a common neuropathic pain characterized by paroxysmal pain, along the distribution of trigeminal nerve. Diagnosis is made clinically by characteristic signs and symptoms. Anticonvulsants form the mainstay of treatment and surgery is considered when medicinal therapy fails. Dentists should be aware of this common facial pain entity and should make accurate and early diagnosis of this debilitating entity.

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