



Treatment Options in Trigeminal Neuralgia an Update

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ABSTRACT

Trigeminal neuralgia(TN) is a severe unilateral paroxysmal facial pain that causes intense distress and often compromises the quality of life of the patient. The aetiology and pathophysiology of TN is still not clear. Numerous treatment options for TN are available. Medical therapy is the first choice and surgical modalities are used only when medical therapy fails. The challenge lies in assessing and selecting the treatment which best fits each patient. This article reviews the various treatment options available for trigeminal neuralgia.

Key words: Trigeminal Neuralgia, botulinum toxin, microvascular decompression, radiofrequency ablation.

Trigeminal Nöraljide Tedavi Seçenekleri

ÖZET

Trigeminal nevralsi (TN) hastanın yaşam kalitesini düşüren şiddetli, unilateral, paroksizmal baş ağrısıdır. Etiyolojisi ve patofizyolojisi henüz tam olarak bilinmemektedir. Tedavisinde çok sayıda seçenek mevcuttur. Medikal tedaviler ilk tercihtir, cerrahi yöntemler ancak medikal tedavilere cevap alınmadığı durumlarda düşünülmelidir. Her hasta için tedavi yöntemi durumuna göre belirlenmelidir. Bu makalede trigeminal nevralsi ve güncel tedavi seçenekleri gözden geçirildi.

Anahtar kelimeler: Trigeminal nöralji, botilium toksin, mikrovasküler dekompresyon, radyofrekans ablasyon

INTRODUCTION

Trigeminal neuralgia (TN) is a unilateral disorder characterized by brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve(1). The pain is severe, lancinating and is triggered by cutaneous stimuli. Simple stimuli like breeze on the face to daily activities such as talking, brushing, chewing food, washing the face can trigger the pain. Pain is episodic with spontaneous remissions. The clinical presentation and the factors triggering the pain are well known ,but the pathophysiology is still not clear. Trigeminal Neuralgia(TN) is classified into two types based on the etiology (1).

Primary or idiopathic TN. This type is not associated with a clear cause and there is no underlying neurologic disease. Symptomatic-This type is associated with an underlying cause such as Multiple sclerosis, tumor or cyst. TN associated with vascular compression is generally classified as primary. From a clinical viewpoint TN is classified into typical and atypical TN. TN is considered typical when only paroxysmal pain is present and atypical when both paroxysmal and constant pain is present (6,7). Various etiological factors have been proposed which include

Neurovascular compression

Evidence suggests that about 80-90% of cases that are technically classified as idiopathic are caused by com-

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pression of trigeminal nerve close to its exit from the brain stem by an aberrant loop of artery or vein (2,3). Compression is at the root entry zone, where axons are coated with central nervous system myelin, rather than peripheral nerve myelin. Symptomatic TN is associated with an identifiable lesion such as a benign intracranial tumor or cyst or multiple sclerosis (2,3) and constitute about 10 -15% of the patients of TN.

Multiple sclerosis

Demyelination of the trigeminal root by the MS plaques and ephaptic transmission in the nerve lead to TN (3).

Tumor and Cyst

Tumoral compression of the nerve root or vascular compression of the root by a displaced vessel have been proposed as the causative mechanisms(4). Other factors cited are Diabetes mellitus, HSV infection, and allergy, but the mechanism is not clear (5).

Diagnosis

Trigeminal neuralgia is essentially a clinical diagnosis. The International headache society diagnostic criteria for classic trigeminal neuralgia are as follows (1).

ClassicTN

- Paroxysmal attacks of pain lasting from a fraction of a second to two minutes that affect one or more divisions of the trigeminal nerve
- Pain has at least one of the following characteristics intense, sharp, superficial, or stabbing precipitated from trigger areas or by trigger factors
- Attacks are similar in individual patients
- No neurological deficit is clinically evident
- Not attributed to another disorder.

Symptomatic TN

All the diagnostic criteria are the same as Classic TN except that a causative lesion, other than vascular compression, should be demonstrated by special investigations and/or posterior fossa exploration (6,1).

Investigations

There are no specific investigations for the diagnosis of TN however, radiographs of the teeth, temporomandibular joint can help in ruling out other causes of facial pain (8,9). Magnetic resonance imaging is useful in evaluating

patients with TN by facilitating identification of multiple sclerosis or masses compressing the trigeminal nerve (10,11).

Management

Trigeminal neuralgia is not a life threatening condition, but pain associated is severe. During the episodes patient may be unable to talk, eat and interact normally. Even between the episodes, the patient remains fearful of initiating the pain (8,12). This severely affects the physical and emotional quality of life (13) and leads to.

- Impairment in daily function.
- Fear
- Anxiety
- Depression

It was once called the “suicide disease” because of the depression and associated suicidal tendencies. Thus all the patients diagnosed with TN should be treated promptly. The goals of management should include

1. Sustained pain relief
- 2.Improvement of quality of life.

Management of this condition is both challenging and frustrating to the physician. Assessment of pain is the first step in the management. Use of a good assessment tool to evaluate outcome measures is important initially and further to determine the efficacy of interventions. Quality of life should also be assessed before and during the treatment. The choice of pain scale depends on patient ability, the time available and experimental design.

VAS has been demonstrated to be an easy to use, sensitive and reproducible pain scale for assessment of pain and to assess the effectiveness of medical and surgical therapies, but the limitation is that it measures pain only in a single dimension (6). The McGill Pain Questionnaire (MPQ) is the most widely used multidimensional pain assessment instrument, providing adjectives describing various sensory qualities. The MPQ emphasizes the difference between pain syndromes and can be used as an aid to diagnosis. Short form of McGill pain questionnaire is easy to use, less time consuming and equally effective as the MPQ (6).Barrow neurological institute pain intensity score is a composite scale and has been recommended as a simple and reliable scale in Trigeminal neuralgia (14). Chen et al. created a new pain assessment tool- BPI-Facial and recommended it is a useful instrument to measure pain and

in the assessment of treatment outcomes in patients with trigeminal neuralgia (15). There are numerous treatment modalities available but medical management remains the first choice. Surgical options are given only when pharmacotherapy fails or if severe side effects develop.

Pharmacotherapy

Trigeminal neuralgia continues to be best managed using anticonvulsant drugs, the primary ones being carbamazepine and oxcarbazepine (8,16-23). Carbamazepine is the first line drug in the management of TN. Several studies and systematic reviews have shown that this is the most effective drug in trigeminal neuralgia. It is considered the gold standard drug in treatment of symptoms of Trigeminal neuralgia (8,16,18,20-25,26-30). The advised dosage is 200-1200 mg/day according to the current evidence based guidelines (18,21). Side effects such as drowsiness, dizziness and ataxia have been reported with the use of carbamazepine (31). There is a high rate of occurrence of severe hypersensitivity reactions (what is the rate?) including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (TEN) with the use of carbamazepine. The rates are high among people of Asian origin (32) and is reported in association with the expression of HLA B*1502 allele (33-35). The FDA has recommended for screening of the HLA B*1502 allele for all people of Asian origin before initiating treatment with carbamazepine. It recommended that those Asians who tested positive for the allele should avoid exposure to carbamazepine (36). CBZ can induce the syndrome of inappropriate antidiuretic hormone (SIADH) and lead to hyponatremia (37,38). Carbamazepine should be started or stopped by changing the dose in increments over several days to reduce side effects. (23) A complete blood count, blood electrolytes, liver and renal function tests, are important before starting CBZ therapy and should be monitored periodically during the treatment (24).

Oxcarbazepine a prodrug of carbamazepine has been shown to have equal efficacy but with less side effects and better tolerance (18,23,30,39). In a review of 3 RCTs it was found that reduction in attacks were similar with CBZ and oxcarbazepine (40). Studies on Oxcarbazepine monotherapy in patients not responding to CBZ found that it is a good and safe alternative (39,41). At present it is the first line of treatment for trigeminal neuralgia in Scandinavian countries and second line after carbamazepine in North America (39). The advised dosage range is 600-1800mg/day (18,21,39). A notable side effect is hyponatremia, up to 30% was reported in a study by

Zakrzewska et al. (39), but similar studies reported lesser incidence. Nausea, vomiting, dizziness and somnolence are the other side effects reported.

First line therapy fails → second line therapy
(Adverse effects, Tolerance)

The second line therapy is based on very low quality evidence (23). Lamotrigine is an anticonvulsant drug which is used for add on therapy when the first line treatment fails. Lamotrigine was used as add on medication in a double blind placebo controlled trial and evaluations suggested that patients did better on Lamotrigine than placebo (42). Shaikh et al., in 2010 compared the efficacy and safety of Lamotrigine to carbamazepine in an open crossover clinical trial and concluded that LTG is more effective and safer than CBZ (43). The maximum dosage is up to 400mg/day. Skin rashes are the most severe side effect reported. Other side effects reported are nausea, dizziness constipation, drowsiness (42-44). The main disadvantage is that the dosage of Lamotrigine must be escalated slowly to avoid rashes and so cannot be used for acute management. It is considered most effective for long term control of moderate pain (42-44).

Baclofen is a GABA_B receptor agonist and it acts by depressing excitatory neurotransmission. Steardo L et al., conducted a clinical trial in pain conditions including trigeminal neuralgia and the results substantiate that Baclofen is useful in the treatment of trigeminal neuralgia and other painful conditions (45). Parmar et al., studied the effect of Baclofen on twenty patients with trigeminal neuralgia and concluded that the action of this drug is similar to that of carbamazepine and has less undesirable side-effects (46). Fromm et al. reviewed 3 studies on the use of Baclofen in trigeminal neuralgia. The results indicated that Baclofen is a useful drug in the treatment of trigeminal neuralgia (47). The initial dose required is 10mg, 3 times daily and the maintenance dose required is 50-60mg/day (24,45).

Gabapentin 900-3600 mg/day (48) and Pregabalin 150-600mg/day (49) are effective in neuropathic pains but evidence available for use in trigeminal neuralgia is minimal (23,24,50). Amytriptylline is an antidepressant drug effective in neuropathic pain. It is the second most commonly prescribed drug for trigeminal neuralgia in Britain (51). Other drugs that have been used include, Topiramate-100-400mg/day (52), Tizanidine-10mg/day (53), and topical capsaicin (54). Peripheral trigeminal

nerve block may be used as an adjunct to pharmacotherapy to achieve immediate and intermediate-term pain relief. A number of agents have been used including 60% alcohol, 10% phenol and glycerol 2%. Elderly patients who are refractory to pharmacotherapy but unwilling to undergo trigeminal nerve intervention may be offered this procedure. The treatment is safe and provides immediate symptom relief. The effect is only temporary and the duration of relief depends on the agent used (55).

Botulinum toxin type A (BoNT/A) is a new drug used effectively in pain management. It inhibits the release of acetylcholine from the neuromuscular junction and blocks the release of neurotransmitters like substance P and CGRP (56). Piovesan et al., in 2005 in an open trial used BoNT/A for TN in 13 patients and concluded that it is an effective treatment with minimal side effects (57). Other open studies carried out also concluded that it could be a useful adjunctive tool in the management of trigeminal neuralgia (58-60). The toxin is injected in the trigger zones. The dosage used is 20 to 100 units. The side effects noted were facial wrinkles and transient weakness in the muscles of the region (57-60). The consensus on the effectiveness of Botulinum toxin type A in TN is not clear. More randomized controlled studies are required.

Surgical treatment options.

Surgical treatment is generally reserved for patients with debilitating pain refractory to a trial of at least three drugs which should include carbamazepine (17). The medical status and the biological age of the patient also should be considered before surgery is advised (30). Side effects and contraindications of the medication may also be the reason for considering surgery (17,30). Studies measuring quality of life have shown that outcomes were best in patients who underwent surgical management and suggested that surgery should be considered earlier in all patients of TN (61,62). Presently there is no standardized protocol available to determine the optimal timing for a surgical intervention. Various surgical options available are

1. Peripheral neurectomy.

2. Ablative procedures

Radiofrequency ablation.

- Balloon Compression.
- Glycerol Injection.

- Radio surgery-Gamma knife surgery

3. Open procedures

- Microvascular Decompression.
- Trigeminal root section. .

The decision to use a specific surgical approach should be based on the clinical presentation, age and medical status of the patient. The class of evidence available for the efficacy of most neurosurgical procedures for trigeminal neuralgia is low because of the poor quality of the trials. All procedures produce variable pain relief, but most result in sensory side effects. There is very little evidence to help in comparative decision making about the best surgical procedure (23,63) MR imaging is not helpful in selecting patients for a particular surgery (11). Ablative procedures on the gasserian ganglion intentionally destroy the trigeminal nerve function. They are done under short acting anaesthesia, and are minimally invasive.

Radiofrequency ablation is a procedure by which a controlled dose of electric stimulation is delivered to the gasserian ganglion. It is done at 60°C for 60 seconds under local anesthesia and a short intravenous analgesia (64). This destroys nerve fibers in the ganglion. In a follow up study of 1600 patients, who underwent radiofrequency ablation acute pain relief was achieved in 97.6% of patients and complete pain relief in 57.7% at 5 years (65). The mean time of recurrence of pain is reported as 36-40 months. A significant drop in depression and anxiety were also noted post-operatively (66). Most of the trials report a recurrence rate of 15- 25% (13,65,67) but the procedure can be easily repeated. Complications reported are diminished corneal reflex, masseter weakness and paralysis, dysesthesia, anesthesia dolorosa, and transient paralysis of Cranial Nerves III and VI. (65) There are no vital hazards for the patients reported (64).

Percutaneous glycerol rhizotomy (PGR) is a procedure by which nerve fibers in the gasserian ganglion are damaged by injecting glycerol into the trigeminal cistern. In a long term follow up study the immediate success rate of the procedure was found to be 97.1% and the long-term success rate was 81.18% (68). No serious side effects other than mild sensory loss and dysesthesia were observed (67,69,70). Percutaneous balloon compression is a mechanical destructive technique by which the nerve is damaged by compression with an inflatable balloon. Best results for balloon compression has been reported for TN in older patients, in TN associated with multiple scler-

rosis and neuralgia involving the V1 territory of trigeminal nerve (71). It is also a useful treatment for patients with recurrent TN who have already been treated surgically (72). The risks reported are ipsilateral pterygoid muscle paralysis, corneal anaesthesia and anaesthesia dolorosa (72). Percutaneous procedures are the preferred choice in elderly and in patients who are not suitable candidates or are not willing to undergo microvascular decompression (10). Adequate controlled trials and comparative studies are not available, however observational evidence suggests that radiofrequency thermocoagulation may offer higher rates of pain relief than other percutaneous procedures (23)

Gamma knife radio surgery (GKS) has been in use for treatment of pain for many years (73). Gamma knife surgery involves irradiation of small volume targets inside of the cranium with high dose radiation in a single session. The optimal dose used for TN is 70-80gy (14,74). Rogers et al., in a follow up study found that radio surgery is an effective treatment in TN and is the least invasive non pharmacologic procedure(14). Lopez et al., in a review of studies on radiosurgery in TN concluded that the outcomes are comparable to other ablative techniques and is best used as a primary procedure (75,14). Dhople et al., in one of the longest follow up study of TN patients treated with GKS found high rates of initial pain relief, when performed as a primary procedure (76). Park et al., found no significant differences in radiation dose, time to initial response, recurrence or pain relief when GKS was used as a primary or a secondary procedure for idiopathic TN (77). Some studies report higher failure rate when GKS is performed as a secondary procedure (76,78). It was also found to be an effective treatment option for trigeminal neuralgia patients with multiple sclerosis (79), but the study was based on a small group of patients. Mild facial sensory changes are the commonly reported side effects (18,76,21,14). Low rates of complications, high success rates and patient satisfaction allows GKS to be increasingly used as primary intervention for trigeminal neuralgia(6,1,80). The main disadvantages are delayed onset of pain relief and high treatment expense (81)

Microvascular decompression (MVD) of the nerve root is considered a well established and superior method of choice among the neurosurgical procedures TN (82,83) MVD is based on the observation of an abnormal relationship between the trigeminal nerve and an adjacent vessel in several patients with TN (24,84). There are no

clinically important results from RCTs about microvascular decompression (23),but consensus suggests MVD is a safe and effective procedure to relieve TN (83,61) It is effective in immediate and long term, sustained relief of pain in TN (17,23,82,84). It has been suggested that MVD should be proposed as the first choice among surgeries to the patients with. In this surgery an abnormal impinging vessel is identified and separated from the trigeminal nerve root. The main advantages are that it treats primary etiology of the disease and the trigeminal nerve is not damaged, but MVD has all the disadvantage of an open surgical procedure. MVD carries a success rate of 75 to 80% over three to five years and approximately 50% in three years (84). A mean pain free period of 28 months has been reported (61). The experience of the surgeon reduces the number of negative results considerably (85) and can be the least costly approach in the long term (82).

Trigeminal root section is also an open surgical procedure done via a posterior fossa craniectomy. This is rarely done nowadays. It is a last-resort procedure for patients in whom no impinging vessel is found during microvascular decompression surgery or in whom TN has recurred after repeated percutaneous procedures (24).

Trigeminal neuralgia is a chronic pain disorder which has a serious impact on the quality of life of patients. Treatment of the disease is imperative once diagnosed. Medical management remains the treatment of choice. Carbamazepine is the most effective drug till date. Surgical options are at present considered only when pharmacotherapy fails or when there is a surgically remediable cause. Presently there is no standardized protocol available to determine the optimal timing for a surgical intervention in a patient. Inability to conduct adequate controlled trials to test new drugs or compare the available treatment options is the problem which plagues research in TN. As a consequence the point at which the patient should be offered different treatment options is not clear. Since it is difficult to carry out strict controlled trials, other forms of evidence should also be taken into consideration in TN. Other than pain control, the quality of life of the patient should also play an important role in selecting various treatment options available.

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