Treatment of trigeminal neuralgia – A review

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Abstract
Trigeminal neuralgia (TN) causes severe, intermittent electric shock like pain on the face. The treatment of trigeminal neuralgia continues to be a major therapeutic challenge. Medication is often the first line of treatment. Traditionally, it is only when medications fail or severe side effects develop that the patient are offered surgical options. The present article provides an overview of the various treatment modalities available for the management of trigeminal neuralgia.

Key words: Trigeminal neuralgia; Medicinal management; Surgical management; LASER.

Introduction
Trigeminal neuralgia (TN) is a relatively rare condition that causes severe, intermittent, electric shock-like pains in the face. The treatment of trigeminal neuralgia continues to be a major therapeutic challenge. There is a lack of certainty regarding the aetiology and pathophysiology of TN and there are a wide range of treatments available. The condition is not itself life-threatening, and therefore a decision to have surgery is not a matter of life or death in the conventional sense. However, the pain and its effect on quality of life is distressing and treatments can be costly. As a result, patients and practitioners encounter considerable uncertainty when making treatment decisions. Medication is often a first line of treatment.

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Traditionally, it is only when medications fail or severe side effects develop that patients are offered surgical options (1).

Treatment modalities available in the management of trigeminal neuralgia are

1. Medicinal management
   - Carbamazepine
   - Phenytoin
   - Baclophen
   - Gabapentin
   - Oxycarbazepine
   - Lamatrige
   - Pimozide
   - Tizanidine hydrochloride
2. Surgical management
   - Peripheral nerve branch procedures
   - Peripheral alcohol injection
   - Peripheral neurectomies
   - Percutaneous procedures
   - Percutaneous radiofrequency lesions
   - Glycerol injections
   - Balloon compression
   - Open procedures
   - Trigeminal root section
   - Sectioning of the trigeminal tract in the lower medulla
   - Microvascular Decompression Surgery
   - Gamma knife Radiosurgery
   - Cryosurgery
   - LASER

Medicinal treatment

Medicinal therapy is initially effective for most patients with TN. Unfortunately about half of TN sufferers eventually become dissatisfied with medical therapy, because of incomplete control of pain or drug-related side effects that are almost always experienced.

Carbamzepine (Tegretol)

Carbamzepine (Tegretol) has been in use since 1960s in the treatment of epilepsy and its usage in treating TN was introduced no later than 1962 (2). The earliest reports on its effect in TN were by Blom in Sweden, Bonduelle et al (3) in france, and Spillane and Taylor (4) in England. Carbamazepine is an immunostilbine. Its main pharmacological action is that of an anticonvulsant without narcotic or analgesic effects. It affects the polysynaptic lingual mandibular reflex and depresses synaptic transmission. (2)

A double blind comparison of carbamzepine (600 mg daily) and placebo was conducted in 9 patients with typical trigeminal neuralgia by Rockliff BW et al (5) in 1966. Each patient received crossed over three days courses of both medications in random sequence. Relief of pain in each patient was compared and the results were analyzed. After nine paired trials the superiority of carbamzepine was demonstrated with less than a 5% probability of error.

Later in 1968 Killian and Fromm (2) evaluated the efficacy of carbamzepine in treating TN. They conducted a double blind clinical study among 42 patients, of whom 30 had trigeminal neuralgia, 6 post herpetic neuralgia, two tabetic neuralgia and 4 atypical pains. Identical tablets containing 200 mg of carbamzepine or placebo were randomized and administered for 5 days each. At the end of the ten day trial, the tablet producing the best response was continued for three months at which time the code was broken and tablet was identified. Relief of trigeminal neuralgia was classified as complete (no pain or occasional painful sensation), very good (occasional pains mainly of trigger origin and relief satisfactory to patient), fair (improved but unsatisfactory to patient) and no response. The entire patients showed initial response to carbamzepine with either disappearance or decrease in trigeminal pain. Placebo responses were minimal or absent in all patients. In contrary to the treatment benefits achieved it was observed that the drug was associated with side effects like vertigo, drowsiness, diastolic hypertension, bradycardia and rash while laboratory side
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effects included leucopenia, neutropenia and abnormal liver function. Hence it is suggested that a complete blood cell count and liver function tests should be done periodically on patients treated for longer periods.

Phenytoin (Dilantin)

Phenytoin relieves tic pain in over half of TN sufferers at doses of 300 to 500 mg, divided into three doses per day. Phenytoin may also be administered intravenously to treat severe exacerbations of TN. These dose-dependent side effects include nystagmus, ataxia, dysarthrias, ophthalmoplegia as well as drowsiness and mental confusion. Other effects of the medication may include gingival hyperplasia and hypertrichosis (6).

Baclophen (Lioresal)

Baclophen is an aminobutyric acid receptor agonist that has the least serious adverse effects (7).

Baclophen is not as effective as carbamazepine or phenytoin for TN, but may be used in combination with these medications. However a double blind crossover study by Fromm et al showed a significant decrease in the number of TN attacks when treated with baclofen, even in patients who had become unresponsive to carbamazepine (8).

The starting dose of baclophen is usually 5 mg two or three times a day, and may be gradually increased. The usual dosage taken for complete pain relief is between 50 and 60 mg per day. Baclophen has a short duration of function so sufferers with severe TN may need to take doses every 3 to 4 hours. The most common side effects associated with baclophen include drowsiness, dizziness, nausea and leg weakness.

Gabapentin (Neurontin)

Gabapentin is an anti-epileptic drug that is structurally related to the neurotransmitter GABA. This drug is almost as effective as carbamazepine but involves fewer side effects. The starting dose is usually 300mg three times a day and this is increased to a maximal dose. The most common adverse reactions include somnolence, ataxia, fatigue, and nystagmus. In addition to the above mentioned traditional drugs, various other formulations are also in use (9).

Trileptal (Oxycarbazepine)

Oxcarbazepine, a keto derivative of carbamazepine has been reported to have significant efficacy in patients with TN. Like Tegretol, it is an anti-seizure drug, but the side effects are less severe and less frequently experienced and its effects are also short lived. The dose usually begins at 300 mg twice a day and is gradually increased to achieve pain control. The maximum dose is 2400-3000 mg per day. Common side effects are nausea, vomiting, dizziness, fatigue and tremors (10).

Lamotrigine (LTG)

Lamotrigine (lamictal) acts by stabilizing the slow inactivated conformation of type II neuronal sodium channels resulting in inhibition of repetitive firing of action potentials under conditions of sustained neuronal depolarization (11).

A double blind placebo controlled cross over trial was conducted using lamotrigine in 14 patients with refractory trigeminal neuralgia. Patients continued to take steady dose of carbamzepine or phenytoin throughout the trial over 31 day period. Each arm of the trial lasted for 2 weeks with an intervening 3 day wash out period. The maintenance dose of lamotrigine was 400 mg. One patient withdrew from the study due to severe pain during the placebo arm of the trial. Eleven of the 13 patients eligible for inclusion showed better efficacy on lamotrigine compared with placebo. Statistical evaluations further suggested that
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patients did better on lamotrigine than placebo \( (P = 0.025) \). (12)

**Pimozide**

Pimozide (2 - 12 mg/day) is a neuroleptic that has shown significant relief of pain when compared with carbamazepine in a double-blind crossover trial by Lechin et al. Patients in this study had been diagnosed as having TN for at least 2 years and were treated with carbamazepine or pimozide. Adverse effects were common with pimozide, but mild, and no patients stopped the treatment because of side effects (13).

**Tizanidine hydrochloride**

Tizanidine hydrochloride (2-4 mg/day) has neurochemical activity similar to that of baclofen and carbamazepine. A double-blind crossover study by Fromm et al evaluated its efficacy in patients with TN who were not responding to carbamazepine and found short-term improvement, with recurrence of pain in 1 to 3 months (14).

Other drugs include valproate sodium, racemic ketamine, proparacaine hydrochloride, and topical capsaicin cream. Moreover, Valproate sodium (600-1200 mg/d) was beneficial in a small group of patients studied by Peiris et al (15).

Besides, Racemic ketamine (0.45 mg/kg - 1M) an anesthetic, showed some benefit when treating acute pain but was ineffective for pain lasting more than 5 years (13).

The use of topical ophthalmic anesthetics such as proparacaine hydrochloride has been reported to relieve TN pain in some patients, but a randomized trial by Kondziolka et al showed no change in the frequency or severity of attacks (16). Even, topical Capsaicin cream showed improvement in patients using it in an open trial.

Capsaicin enhances release of and inhibits the reuptake of substance P, which results in depletion of substance P in the central and peripheral nervous system. Substance P is mediator of nociceptive impulses and may be a principal neuropeptide in pain transmission. Desensitization of C-nociceptors has been demonstrated with topical and systemic application of capsaicin. Capsaicin has a short duration of action and repeated applications are needed. Pain relief may require 2 -4 weeks of application with maximum response after 4 weeks. The most common side effect of topical application of capsaicin was burning at the site of application (17).

**Surgical management**

Neurosurgical interventions are considered when medical therapy proves ineffective in controlling TN pain. Each type of surgery carries with it potential benefits as well as risks of complications or long-term side effects. Thus, one must select the type of surgery carefully, with a complete understanding of all possible outcomes. None of the surgical interventions are effective in every case, and there is no way to accurately predict who will benefit from which procedure. The results of any procedure are known to be dependent upon the experience, expertise, and specific techniques unique to the neurosurgery team. These important variables must be taken into account when selecting a treatment.

**History of surgical management of trigeminal neuralgia** (18)

<table>
<thead>
<tr>
<th>Year</th>
<th>Procedure</th>
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<tbody>
<tr>
<td>1862</td>
<td>Carotid ligature</td>
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<tr>
<td>1870</td>
<td>Local galvanic stimulation</td>
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<tr>
<td>1916</td>
<td>Diathermy and appendicectomy</td>
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<tr>
<td>1916</td>
<td>Partial colonic resection</td>
</tr>
<tr>
<td>1930</td>
<td>Contra later hand in painfully hot water</td>
</tr>
<tr>
<td>1933</td>
<td>Artificial pyrexia</td>
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<tr>
<td>1949</td>
<td>Electrically induced convulsions</td>
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Various surgical techniques used in the management of TN include radiofrequency, generated thermal energy...
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(peri-cutaneous rhizotomy), mechanical energy (balloon compression), and physical energy (surgical nerve section). Microvascular decompression aimed at removing the cause of trigeminal neuralgia or chemical manipulation of the nerve, such as that performed in glycerol rhizotomy.

Peripheral nerve branch procedures

Alcohol nerve injections or neurectomy of terminal nerves may be effective if these are the areas affected by pain. Anesthetic blocks of localized trigger points also may be attempted to prevent pain provocation. These procedures are simple and safe, and they do not require hospitalization.

Peripheral alcohol injection

The role of peripheral alcohol injections in the management of trigeminal neuralgia (TN) remains controversial. Injections of alcohol have been suggested in management of TN since the early 20th century. Although they are reasonably effective in producing short- to medium-term pain relief in sufferers, the procedure does carry risks and is only temporary.

A study assessed the effectiveness of peripheral alcohol injections in the management of trigeminal neuralgia for which a retrospective case audit of patients who received peripheral alcohol injections in 1994-1999 was conducted in Moriston hospital in 141 patients. Effects of peripheral alcohol injection lasted for a mean of 11 months. Their effectiveness and complication rates were not affected by age or repeated administration. Their use did not affect, nor was their effectiveness affected by, the use of other surgical treatments. The study concluded that Peripheral alcohol injections continue to have a role in the management of trigeminal neuralgia.

Glycerol has also been used for peripheral injections but the increased viscosity compared to absolute alcohol results in marked difficulty in administration.

Even streptomycin and anesthetic agents like lidocaine have been in use in the treatment of TN by peripheral injections. Stajc described the use of peripheral injection of streptomycin or lidocaine in the treatment of TN, there were only 17 patients in his study, 9 having streptomycin and lidocaine and 8 lidocaine only. No complications were recorded but the sample was too small to be significant.

Peripheral neurectomies

Neurectomy indicates the sectioning and avulsion of terminal branches of the trigeminal nerve. It is suggested that its canal is subsequently obliterated to the regrowth of terminal fibers. Complete anesthesia of the nerve distribution is the inevitable sequela. Recurrence of the pain is to be expected, and retreatment attempted or alternative techniques used. Because of the removal of the terminal nerve, there is no further role for peripheral techniques in these patients, and this is one reason its use has largely abandoned. Complications include local infections.

Percutaneous procedures

Several percutaneous operations on the gasserian ganglion have been found to be safe and effective. These procedures all involve mechanically or chemically damaging the trigeminal rootlets.

They do not require general anesthesia and usually are done on an outpatient basis. However, the patient must be able to assist in identifying the appropriate location for the procedure.

The three percutaneous procedures currently in use are radiofrequency lesions of the gasserian ganglion, glycerolization of the trigeminal cistern and balloon compression of the gasserian ganglion.
Percutaneous radiofrequency lesions

Radiofrequency lesions, or RFL, of the gasserian ganglion are known also as controlled differential thermocoagulation, radiofrequency percutaneous retrogasserian controlled rhizotomy and thermorhizotomy. The procedure was developed by Sweet and Wepsic (21).

The RFL procedure is highly effective (>97 percent initial response rate) in treating TN. RFL is considered safe, even in patients who are elderly and those who are ill. In 22,000 RFL procedures, only 17 deaths were reported (19). The complication rate is slightly higher among patients whose operations were performed by less experienced neurosurgeons. The most commonly reported risks include hypertension during the procedure, anesthesia dolorosa (a constant burning/aching that may replace lancinating pain after otherwise successful treatment of TN) in 2 to 4 percent of cases and meningitis in 0.3 percent of cases (22). The rate of sensory loss is higher with RFL than with the other percutaneous procedures, and the relapse rate is approximately 10 percent (23). During RFL, the patient is given short-acting sedative anesthetic while his or her blood pressure is monitored. An electrode needle is inserted through the cheek under fluoroscopy into the foramen ovale. The patient is awakened briefly while a small electrical stimulus is delivered. Adjustments to needle electrode location are made as necessary under anesthesia until stimulation reproduces the patient's facial pain. When the appropriate location has been identified, the patient is again anesthetized and a larger electrical impulse is delivered to damage the gasserian ganglion. After the procedure, the patient is awakened completely and examined to determine the degree to which he or she has lost facial sensation (hyperalgesia is desired), corneal reflexes and masseter and pterygoid strength. The patient is observed for a few hours, then discharged and asked to continue any preoperative TN medications for a few days before tapering them off.

Glycerol injections

Glycerol is injected into Meckel's cave, a cerebrospinal fluid filled cavity through which the trigeminal rootlets course. The procedure is performed under fluoroscopy. Injection of 0.2 to 0.4 milliliters of pure glycerin is performed in tiny aliquots until the lesion is complete. The glycerol is believed to damage the trigeminal nerve fibers through dehydration. Studies have found an initial cure rate of 80 percent' and a high incidence of relapse (50%). Production of facial sensory loss correlates with a higher success rate for pain relief (24).

Balloon compression

This procedure was introduced in the early 1980s by Mullan and Lichtor as a mechanical destructive technique. A tiny (no. 4 Fogarty) catheter is inserted using fluoroscopic guidance. A 0.7-millimeter balloon is inflated for one to two minutes. Although considered technically simple, balloon compression is not selective and therefore cannot be confined to a single division of the trigeminal nerve (25).

This procedure's risks include intraoperative bradycardia, which can be treated medically. Balloon compression may affect the motor root, causing ipsilateral pterygoid muscle paralysis. Relapse occurs in approximately 10 percent of patients.

Open procedures

Several open surgical procedures have been developed for the treatment of drug-resistant TN. Open procedures generally are performed after percutaneous options have failed; sometimes, however, these operations are used first, especially in younger patients, for whom the surgery holds less risk than for older patients. These procedures include sectioning of the
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trigeminal root or tract and microvascular nerve root decompression

**Trigeminal root section**

Trigeminal root section, or TRS, is an intradural procedure usually done via a posterior fossa craniectomy. TRS is considered last-resort procedure for patients in whom no vessel is found during microvascular decompression surgery or in whom TN has recurred after percutaneous procedures despite facial anesthesia. The procedure may be selective or complete. Selective TRS cuts the trigeminal sensory root while sparing most of the motor root. If a patient has persistent TN despite anesthesia from a prior procedure, then a complete section may be effective as it cuts the motor root, which may contain sensory fibers responsible for refractory pain (26).

**Sectioning of the trigeminal tract in the lower medulla**

Cutting the descending trigeminal tract in the lower medulla is very successful in terms of pain relief and produces nearly no postoperative dysesthesias. This operation is rarely performed today, however, because the percutaneous procedures can achieve similar selective destruction of pain fibers with much less risk (27).

**Microvascular Decompression Surgery**

Microvascular decompression, originated in the observations of Dandy WE, a surgeon who noted an abnormal relationship between the trigeminal nerve and an adjacent artery in several patients with facial pain (28). MVD was subsequently popularized by Jannetta and is currently the most common open TN operation (29).

For microvascular decompression, a posterior fossa craniectomy is performed, with exposure of the trigeminal nerve at the root entry zone. An abnormal blood vessel, usually the superior cerebellar artery impinging on the nerve, generally is identified and separated from the nerve with a nonabsorbable insulating sponge. Occasionally, a bony prominence is found instead and is removed. If no compressive pathological condition is identified, bipolar cauterization of the nerve may be performed. Because it involves general anesthesia and craniectomy, MVD is generally not recommended for patients older than 65 years. Although the overall mortality of the procedure has been reported as less than 2 percent, the morbidity is higher in older patients and in patients who have other surgical risk factors (30).

Complications include aseptic (noninfectious) meningitis, hearing loss, vertigo, double vision and facial weakness. MVD carries a success rate of 75 to 80 percent over three to five years and approximately 50 percent in eight years. The recurrence rate is lowest when a large artery (most commonly the superior cerebellar artery) is noted at surgery and is lifted off the nerve (31).

Fred G Barker et al in 1996 conducted a study on 1185 patients who underwent microvascular decompression of the trigeminal nerve for medically intractable trigeminal neuralgia. The outcome of the procedure was assessed prospectively with annual questionnaires. 10 years after surgery, 70 percent of the patients had excellent final results, that is, they were free of pain. An additional 4 percent had occasional pain that did not require long term medication. Ten years after the procedure, the annual rate of the recurrence of tic was less than 1 percent. Thus, it was concluded that Microvascular decompression is a safe and effective treatment for trigeminal neuralgia, with a high rate of long-term success (32).

**Gamma knife Radiosurgery**

Leskell first introduced this technique in 1953. This allows for focused radiation to be delivered to the trigeminal nerve root and produces injury. Gamma
Knife radiosurgery is performed by applying a frame to the patient’s head and then obtaining a MRI. The patient is then positioned in the Gamma Knife, where up to 201 focused beams of cobalt radiation are directed at the trigeminal nerve root. This affects a delayed injury upon the trigeminal nerve and reduces TN pain within a few weeks in most patients. Higher doses of radiation may produce better pain control, but increase risks of developing facial numbness and other side effects.

Douglas et al conducted a study on 106 patients with refractory trigeminal neuralgia in 1998. A single 4mm isocenter of radiation was focused on the proximal trigeminal nerve just anterior to the pons. For follow-up an independent physician who was unaware of treatment parameters contacted all patients. After radiosurgery, 60% became free of pain and required no medical therapy (excellent result), 17% had a 50% to 90% reduction (good result) in pain severity or frequency (some still used medications), and 9% had slight improvement.

Poorer results were found in patients with multiple sclerosis. Twelve patients developed new or increased facial paresthesias after radiosurgery (10%). No patient developed anesthesia (33).

Cryosurgical treatment

In 1976, Lloyd introduced surgical technique in which a peripheral branch of 3 major divisions of TG is exposed and frozen by direct application of cryoprobe with a tip temperature ranging from 50 to 70 centigrade. However, the patient requires intra venous sedation or general anaesthesia and is a painless procedure (34).

LASER

Laser treatment has also been used experimentally for trigeminal neuralgia. In a study, human subjects received irradiation of the skin overlying peripheral nerves with a helium-neon laser for 20 seconds to each selected site. The treatment was accompanied by irradiation of the skin overlying painful areas for 30 to 90 seconds. Control subjects received placebo treatment. Laser or placebo therapy was repeated 3 times weekly for 10 weeks. Subjects in the experimental group exhibited a statistically significant reduction in the intensity and frequency of painful episodes (35).

Eckerdal and Lehmann have observed from a double blind, placebo controlled study that low reactive-level laser therapy (LLLT) is effective in the treatment of trigeminal neuralgia. They have concluded that LLLT treatment is an effective method and an excellent supplement to conventional therapies used in the treatment of trigeminal neuralgia (36).

Conclusions

It is essential that clinicians recognize and diagnose trigeminal neuralgia correctly for patients to receive appropriate referral and therapy for this relatively treatable condition. Meanwhile, patients with trigeminal neuralgia deserve an accurate and dispassionate explanation of the merits and drawbacks of all methods of treatment from the outset. Collaborative research is destined to yield new targets for drug treatment and, more broadly, new knowledge of pain mechanisms

References
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