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Review

TREATMENT OPTIONS FOR TRIGEMINAL NEURALGIA

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ABSTRACT – Trigeminal neuralgia causes severe to excruciating pain that often cannot be successfully reduced with current forms of treatment. The International Association for the Study of Pain (IASP) defines trigeminal neuralgia as a sudden, usually unilateral, powerful, short, stabbing, recurrent episode of pain in the distribution of one or more branches of the trigeminal nerve. Trigeminal neuralgia can be caused by vascular compression of the trigeminal nerve or a tumor process. Pressure on the nerve itself causes nerve demyelination, which is the cause of abnormal depolarization, resulting in the development of ectopic impulses. Pain can be provoked by brushing teeth, shaving, eating, cold, heat, etc. After diagnosing trigeminal neuralgia, magnetic resonance imaging should be performed to rule out multiple sclerosis, a tumor process that can secondarily cause trigeminal neuralgia. The drug of choice for treating trigeminal neuralgia is still carbamazepine. If pharmacological treatment fails, invasive surgical microvascular decompression, stereotactic radiation therapy (gamma knife), percutaneous balloon micro compression, percutaneous glycerol rhizolysis, and percutaneous radiofrequency (RF) may be used.

Keywords: *trigeminal neuralgia, unilateral facial pain, ganglion Gasseri*

INTRODUCTION

Trigeminal neuralgia is a painful condition of the face[1]. Often incredibly severe pain cannot be reduced. Patients sometimes resort to suicide for fear of a new attack because they can no longer tolerate such intense pain, which is why this disease is also called suicidal illness[1].Trigeminal neuralgia is defined by the International Association for the Study of Pain (IASP) as a sudden, usually unilateral, severe, brief, stabbing, recurrent episode of pain in the distribution of one or more branches of the trigeminal nerve.[2] Trigeminal neuralgia is the most common form of facial pain in people over 50. Various epidemiological studies have shown that the annual incidence is about 4-5 new patients per 100.000. The highest incidence occurs between the ages of 50 and 70; in 90% of cases, the symptoms begin after the age of 40. Trigeminal neuralgia is more common in women than men, with a ratio of 1.5:1.[3]

PATHOPHYSIOLOGY

Pathophysiology, despite previous knowledge, is still unclear. Based on clinical observations, compression of the trigeminal nerve by blood vessels or tumor tissue near the origin of the brainstem, the so-called root entry zone, can cause trigeminal neuralgia. Local pressure causes demyelination leading to abnormal depolarization and ectopic impulses.[4] Recent evidence suggests that patients with more atypical forms of trigeminal neuralgia may have changes that are more significant. They have been shown to have excessive

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activation of central facilitation of trigeminal nociceptive processing rather than just peripheral changes[5]. Trigeminal neuralgia is further divided into idiopathic and symptomatic types. Symptomatic trigeminal neuralgia is less common. The primary cause has been identified, such as benign or malignant tumor, demyelination such as that occurring in multiple sclerosis, or less frequently arterial or venous malformations[5].

DIAGNOSIS

Trigeminal neuralgia is characterized by very severe gunshot pain. Pain can be triggered by brushing teeth, feeding, shaving, cold, heat, draft, etc.[6]

The International Headache Society has described the following criteria for essential trigeminal neuralgia:

1 Paroxysmal pain lasting from a split second to two minutes occurs in one or more branches of the trigeminal nerve.
2 Pain has at least one of the following characteristics:
   - intense, sharp, superficial, or stabbing.
   - precipitated from the area of the trigger or trigger factors.
3 The patient stereotypically describes the patient's attacks.
4 No signs of neurological disorders.
5 Other disorders do not cause seizures.

The pain most often occurs in the area of the maxillary and mandibular branch of the trigeminal nerve. Pain rarely occurs only in the ophthalmic branch. If this happens, differentially diagnosed autonomic trigeminal cephalalgias should be ruled out.[8,9]

Powerful to unbearable pain is the cause of the development of depression in patients because patients are in constant fear of the next attack and the pain they will have to suffer.[10]

When the diagnosis of trigeminal neuralgia is made, the patient needs to undergo a magnetic resonance imaging (MRI) scan to exclude specific pathologies such as a tumor or multiple sclerosis, which could cause secondary trigeminal neuralgia. The MRI scan can also be used if a suspected compression of the nervus trigeminus is in the fossa cranial posterior. Sometimes the MRI scan is sensitive enough to detect blood vessels that have come in contact with the nervus trigeminus. The role of venous compression in the pathogenesis of trigeminal neuralgia is controversial. Notably, on MRI scanning, compressing blood vessels are seen in one-third of asymptomatic patients.[11,12]

Differential diagnosis

Dental pathologies, temporomandibular joint pain, eye pain (including glaucoma, orbital cellulitis, and trauma), facial trauma and bony fractures, tumor of the facial bones or the trigeminal nerve, giant cell arteritis. Tolosa-Hunt syndrome (idiopathic inflammation in or around the cavernous sinus), trigeminal autonomic cephalgias (such as cluster headache and paroxysmal hemicrania) and other primary headache syndromes (including migraine and tension-type headache) can cause facial pain.[13]

Any unilateral, episodic pain needs to be assessed as potential symptomatic neuralgia, as not all such pain will be neuropathic initially. The other primary class of conditions to consider is the trigeminal autonomic cephalalgia. The major differentiating factor is that these pains tend to occur in the first division rather than in the second and third divisions of the trigeminal nerve. In patients with one of these conditions, each pain attack might last longer.[13] Episodes may not exhibit a refractory period and can be more numerous. Patients with these conditions are often restless and agitated, whereas patients with trigeminal neuralgia want to keep very still. Patients will report autonomic features including tearing, redness of the eye, meiosis, oedema of the upper eyelids, stuffy nose or rhinorrhea, redness of the face, and a feeling of fullness in the ear. These patients should not undergo surgical treatments.[14] Less frequently, trigeminal neuralgia is seen in younger patients.Multiple sclerosis must always be considered in differential diagnoses, especially in bilateral cases[14].

TREATMENT OPTIONS

Conservative treatments

The mainstay of managing trigeminal neuralgia is the antiepileptic drugs, which have been used since 1860. However, the introduction of carbamazepine in 1962 revolutionized the management of this condition, and this drug has remained the gold standard.[15,16] Other medications that can be tried are gabapentin, pregabalin, and baclofen.[14]

Recommendations on pharmacological treatment are:

- In acute exacerbations, in-hospital treatment may be necessary for titration of antiepileptic drugs and rehydration.

- For long-term treatment, carbamazepine (200–1200 mg/day) or oxcarbazepine (300–1800mg/day) remain the most effective medications, especially in the early stages of TN.
- If these drugs become ineffective or result in poor tolerability, other medication need to be considered.
- Based on low to insufficient evidence, lamotrigine, gabapentin, botulinum toxin type A, pregabalin, baclofen, and phenytoin may be monotherapy or combined with carbamazepine or oxcarbazepine when first-line drugs fail due to either efficacy or tolerability.
- It is crucial that patients are instructed to increase and decrease dosages slowly over several days.
- It remains the responsibility of the managing doctor to ensure that the patient is aware of neurosurgical options and can make an informed decision about the choice of treatment.[15]

Up to 10% of patients will not respond to these drugs and will still qualify as candidates for interventional treatments if no other underlying aetiology is found.

Interventional treatments

An invasive treatment can be carried out if the medical treatment is unsuccessful or has too many side effects.

These are currently five clinically reasonable possibilities:

1. Surgical Microvascular Decompression (MVD).
2. Stereotactic radiation therapy, Gamma knife.
3. Percutaneous balloon micro compression.
4. Percutaneous glycerol rhizolysis.
5. Percutaneous radiofrequency (RF) treatment of the Gasserian ganglion[12-14].

Surgical Microvascular Decompression (MVD)

Microvascular Decompression aims to relieve pressure from a pulsating vessel pressing against the trigeminal nerve, causing painful impulses from the face. The procedure is done under general anesthesia. The hair behind the ear is shaved, and a small part of the skull is removed. The nerve is identified, and pieces of Teflon are placed between the nerve and the offending blood vessel(s). The small area of bone removal is then covered with a thin metal mesh. Microvascular Decompression is an invasive procedure and, while safe in expert hands, does have potential rare/infrequent risks, including:

- Infection
- Hearing loss, facial numbness, and facial weakness (usually temporary, rarely permanent)
- Spinal fluid leak
- Difficulty with speech or swallowing
- Stroke or hemorrhage (very rare)[16]

Sensorineural hearing loss is a rare MVD surgery complication for trigeminal neuralgia. This hearing loss should be distinguished from middle ear effusion, identified as a sense of fullness in the ear caused by fluid accumulation in the middle ear from opening the mastoid air cells during craniotomy. This feeling of ear fullness is temporary.[12,17]

Stereotactic radiation therapy, Gamma knife

The lack of mortality and the low risk of facial sensory disturbance, even after repeated surgery, argue for the use of primary or secondary radiosurgery in this setting. Repeated radiosurgery remains an acceptable treatment option for trigeminal neuralgia patients who have failed other therapeutic alternatives[18]. The Gamma knife, a stereotactic radiotherapy method, entails high dose irradiation to a small section of the nervus trigeminus. This results in nonselective damage to Gasserian ganglion. The advantage is that this is a non-invasive treatment that can be applied under local anesthesia and light sedation. Although an increasing number of studies are being conducted on the effectiveness of this treatment, the initial efficacy appears to be limited; between 60% and 70% indicate a reduction in pain.[19] Following radiosurgery of trigeminal neuralgia, the main complication was new sensory facial symptoms caused by partial trigeminal nerve injury.[19]

Percutaneous balloon micro compression

An alternative means to affect a percutaneous trigeminal rhizotomy is with a balloon compression procedure. This is performed under general anesthesia. The needle advanced to the Gasserion ganglion is larger in calibre and allows for the passage of a special catheter fitted with an inflatable balloon. The balloon

is inflated to compress and mechanically injure the trigeminal nerve root and Gasserion ganglion.[19] In micro compression of Gasserian ganglion, the nervus trigeminus is compressed by a small balloon and percutaneously introduced into Meckel›s cavity using a needle. The effect of this technique relies on ischemic damage of the ganglion cells. This form of percutaneous rhizotomy is particularly effective for pain involving the upper face, as it has a small chance of causing permanent loss of sensation to the cornea. However, many patients develop at least temporary weakness of the chewing muscles following this balloon compression procedure. The degree of facial numbness is often more severe than with a glycerol rhizotomy.[20] Although there are insufficient qualitative data, this technique about efficacy appears to be comparable with percutaneous RF treatment of Gasserian ganglion. The advantage of this technique is that it is also suitable for treating trigeminal neuralgia of the first branch, allowing the corneal reflex to remain intact.[17] Asplund et al. have compared two percutaneous methods, percutaneous glycerol rhizolysis (PRGR) and percutaneous balloon micro compression (PBC), for the treatment of TN. They propose PBC over PRGR as the percutaneous technique of choice for the primary treatment of TN because of its pain-relieving effect similar to that of PRGR but with fewer side effects and complications, especially dysesthesia and corneal hypesthesia.[21]

Percutaneous glycerol rhizolysis

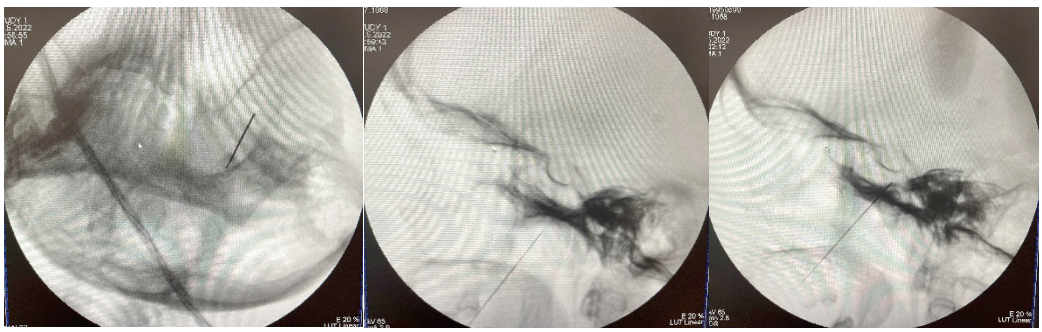
Glycerol is a colorless, odorless, viscous liquid.[22] In concentrations above 99%, glycerol is highly hypertonic and causes neurolysis by myelin fragmentation or directly penetrating the perineurium.[23] Percutaneous stereotactic radiofrequency rhizotomy (PSR) is a minimally invasive procedure that relieves pain caused by trigeminal neuralgia, glossopharyngeal neuralgia, and cluster headache. During percutaneous glycerol rhizolysis, a needle is introduced into the cisterna trigeminal, visualized using fluoroscopy. This is performed under a local anesthetic. A needle (typically a 3.5" x 20 G spinal needle) is inserted in the skin beside the mouth and directed through an opening at the base of the skull (through the *foramen ovale*). In a seated patient with the head flexed, a contrast dye can be injected to determine the size of the cisterna. Then, after the contrast dye is aspirated, an equal volume of glycerol is injected.[14] Xu et al. described their experience with 3370 patients and expressed pain relief in 73% of the patients after one injection.[24] The success rate increased with increasing injections, with an overall success rate of 99.58% after four injections. Of a total of 2.750 follow-up patients, 21% had pain recurrence within five years. The overall rate of pain recurrence over the length of the study was 33%, other extensive case series report an initial pain relief rate of 70 to greater than 90%.[21] However, 20 - 40% of the patients experience pain recurrence within 20 - 60 months after the procedure. Complications of glycerin rhizotomy are usually related to facial hyperesthesia, hypoalgesia, and dysesthesia. Other perioperative complications include nausea/vomiting, trigeminal motor weakness, hematoma, meningitis, and optic nerve injury. Hypoesthesia of the superior trigeminal division may result in keratitis ulcers and ocular complications.[25]

Percutaneous RF treatment of the Ganglion Gasseri

Percutaneous radiofrequency treatment of the trigeminal, or Gasserian, ganglion (RF-G) is regularly used in refractory patients with comorbidities. RF-G involves complex needle maneuvering to perform selective radiofrequency heat treatment of the affected selective trigeminal nerve divisions.[26] Needle placement is verified as previously described above with fluoroscopic assistance (Figure 1). The needle obturator is removed, and the electrode is introduced. Electric stimulation is typically achieved at 0.2–1 V (50 Hz for 0.2ms). The electrode is then replaced with the thermocouple, and lesions are made at a maximum of 0.5 V, 75 cycles per second at 55°C to 80°C for 30 - 120s. The electrode and cannula are then removed. In some cases, selective V2 or V3 targeting with ultrasound guidance via the pterygopalatine fossa may be used.[27] RF treatment of Gasserian ganglion should be considered in the elderly patient. The treatment outcome of Gasserian ganglion is reportedly less favorable than with open operation (MVD), but it is less invasive and has low morbidity and mortality rate.[28]

Several extensive studies have demonstrated the success of radiofrequency ablation. Wu et al. reported outcomes on 1860 patients, with 79% experiencing immediate pain relief and 18% experiencing improved pain.[11] Pain recurrence was encountered in 11.1% during the first year; 25% of the patients had recurrent pain by two years. Kanpolat et al. described their 25-year experience treating 1.600 patients with

2.138 radiofrequency ablation procedures.[30] Acute pain relief was achieved in 97.6% of the patients. Early pain recurrence within six months was observed in 7.7% of the patients, and late pain recurrence was observed in an additional 17.4%. Complete pain relief was achieved in 58% of the patients who underwent a single procedure at five years; this number decreased to 52% at ten years and 41% at 20 years. Complications of radiofrequency ablation include diminished corneal reflex, masseter weakness, dysesthesias, keratitis, and cranial nerve palsies. Rarely, CSF leak, carotid-cavernous fistula, meningitis, and anaesthesia dolorosa/trigeminal deafferentation pain may be encountered.[30-31]



A B C

Figure 1 A Passage of the needle through the lateral part of the foramen ovale, B advancement of the needle towards the Gasseri ganglia, C position of the needle for radiofrequency ablation of the ganglia gasseri

Recommendations on interventional treatment are:

- Based on low-quality evidence but extensive clinical experience, a strong recommendation is given that MVD is preferred over other ablative ganglion Gasseri procedures in patients with classical TN.
- Based on low-quality evidence, a weak recommendation is given that M VD may be considered preferential over other neuroablative treatments.
- No recommendation for choosing between neuroablative treatments and MVD when an MRI scan fails to show significant nerve compression (idiopathic TN).
- Neuroablative treatments should be preferred if MRI does not demonstrate any neurovascular compression (NVC).[15]

CONCLUSION

The treatment of a patient with essential trigeminal neuralgia should be multidisciplinary. The various treatment options (MVD, Gamma knife, and RF treatment of Gasserian ganglion) and their risks should be discussed with the patient. About the elderly patient with comorbidities, RF treatment of Gasserian ganglion can be recommended. MVD19 may be considered in younger patients.[19]

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Sažetak

MOGUĆNOSTI LIJEČENJA TRIGEMINALNE NEURALGIJE

I. Radoš

Trigeminalna neuralgia izaziva vrlo jaku do neizdrživu bol koja se često ne može uspješno smanjiti dosadašnjim oblicima liječenja. Međunarodna udruga za proučavanje boli (IASP) definira trigeminalnu neuralgiu kao iznenadnu, obično jednostranu, vrlo jaku, kratku, ubodnu, ponavljajuću epizodu boli u distribuciji jedne ili više grana trigeminalnog živca. Neuralgija trigeminusa može biti uzrokovana vaskularnom kompresijom trigeminalnog živca ili tumorskim procesom. Pritisak na sam živac uzrokuje demijelinizaciju žive, što je razlog abnormalne depolarizacije, što rezultira razvojem ektopičnih impulsa. Bol može biti provocirana pranjem zubi, brijanjem, jelom, hladnoćom, vrućinom, propuhom itd. Nakon diferencijalne dijagnostičke dijagnoze neuralgije trigeminusa potrebno je napraviti snimku magnetskom rezonancom, kako bi se isključilo postojanje multiple skleroze, tumorskog procesa koji mogu sekundarno uzrokovati neuralgiju trigeminusa. Lijek izbora za neuralgiju trigeminusa i dalje je karbamazepin. Ako je farmakološko liječenje neuspješno, može se primjeniti invazivno liječenje kirurškom mikrovaskularnom dekompresijom, stereotaktičnom terapijom zračenjem (gama nož), perkutanom balonskom mikro kompresijom, perkutanom glicerolnom rizolizom i perkutanom radiofrekvencijom (RF).

Ključne riječi: *trigeminalna neuralgia, jednostrana bol lica, ganglij Gasseri*