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THERAPEUTICAL PROCEDURES IN PATIENTS WITH TRIGEMINAL NEURALGIA - LITERATURE REVIEW

ТЕРАПЕВТСКИ ПРОЦЕДУРИ КАЈ ПАЦИЕНТИ СО ТРИГЕМИНАЛНА НЕУРАЛГИЈА - РЕВИЈАЛЕН ТРУД

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Abstract

Trigeminal neuralgia (TN) is the most common pathological condition of the cranial nerves and the most common cause of pain in the orofacial region. More and more literary data indicate that a in significant number of patients, TN is caused by compression on the root of the trigeminal nerve, close to its entry into the pons in the aberrant arterial or venous loop leading to pathohistological changes in the nerve while in most of the same, the etiological factor for the pathology of TN remains a mystery. Numerous medical and surgical procedures are available, usually without a number of randomized clinical trials and studies of placebo-controlled groups. As a result, most patients experience refractory pain, which has a significant effect on reducing their quality of life. It is still unclear how available treatment methods can be best used. Medical treatment consists of anticonvulsant drugs, muscle relaxants and neuroleptic agents, alternative treatments with botulinum toxin. In patients resistant to drug therapy, promising i.e. recommended surgical procedures include microvascular decompression, gamma-knife surgery, and percutaneous techniques of the Gasser ganglion. In this paper we will present a systematic review of the literature and investigate the outcome of different types of therapeutic procedures in patients with trigeminal neuralgia. **Keywords:** Trigeminal neuralgia, anticonvulsant drugs, pain.

Апстракт

Тригеминалната неуралгија (ТН) е најчестата патолошка состојба на кранијалните нерви и најчест причинител на болка во орофацијалната регија. Се повеќе литературни податоци укажуваат дека кај значителен број на пациенти, ТН е предизвикана од компресија врз коренот на тригеминалниот нерв, близу до неговиот влез во понсот во аберантната артериска или венска јамка која доведува до патохистолошки промени во нервот додека кај поголемиот број од истите, етиолошкиот фактор за патологијата на ТН останува мистерија. Достапни се бројни медикаментозни и хируршки процедури, обично без поголем број рандомизирани клинички испитувања и студии контролирани со плацебо групи. Како резултат на тоа, повеќето пациенти доживуваат рефракторна болка, која има значително влијание врз намалување на квалитетот на живот. Сè уште останува неизвесно како е најдобро да се употребат достапните методи на терапија. Медикаментозниот третман се состои од антиконвулзивни лекови, мускулни релаксанти и невролептични агенси, алтернативни третмани со ботулински токсин. Кај пациентите отпорни на медикаментозна терапија, перспективни т.е. препорачливи се хируршки процедури, микроваскуларна декомпресија, гама-нож хирургија и перкутани техники на гасеровиот ганглион. Во овој труд ќе направиме систематски преглед на литературата и ќе го истражиме исходот од различните видови терапевтски процедури кај пациенти со тригеминална неуралгија. **Клучни зборови:** Тригеминална неуралгија, антиконвулзивни лекови, болка.

Introduction

Trigeminal neuralgia (TH) is defined by the International Classification of Headache Disorders as „*Disorder characterized by recurrent, unilateral short electrical pain in the form of shock, with sudden onset and termination, limited to the distribution of one or more trigeminal nerve divisions, and caused by insignificant stimuli*."[1] The new classification sets 3 etiological categories of: idiopathic TN (without neurovascular contact or neurovascular contact without morphological changes of the trigeminal root), classic TN (due to neurovascular compression with morphological changes of the trigeminal root) and secondary TN (due to a neurological disease such as tumor of the cerebellopontine angle or multiple sclerosis). Also, 2 phenotypes are classified: clear paroxysmal TN (only with paroxysmal pain) and TN with continuous constant pain[2]. In early descriptions, the disorder was called tic douloureux[3]. The incidence is estimated at 4 to 13 people per 100,000 per year.

The pain is limited to an area innervated by one or more branches of the trigeminal nerve. In 60% of cases it is only one branch, maxillary (V2) or mandibular (V3), while in 35% of cases both branches are involved. On the other hand, the ophthalmic branch (V1) is rarely included (in less than 4% of patients)[4].

TN symptomatology is very characteristic, patients report intense stabbing, severe pain localized on the face, nose, teeth, or jaws caused by provocation at the trigger points or by spontaneous (sudden) onset. Depending on whether it is primary or secondary, TN may vary based on the characteristics of the disease. In patients with neurological deficits, extratrigeminal symptoms, bilateral occurrence, and appearance in young individuals are very characteristic[5].

Accurate diagnosis of the orofacial pain is the first step in successful disease management. This is primarily based on the patient's history, because there are still no definite (specific) paraclinical-diagnostic or therapeutic-clinical tests. In 1936, Riley's classic pain analysis highlighted 11 essential issues, which should be included in the history of pain. These aspects apply today, too[6]. As part of diagnostic procedures, it is recommended to use magnetic resonance imaging (MR), because a lack of clinical features may preclude secondary TN. If MR is unavailable or contraindicated, trigeminal reflexes shall be used to distinguish between primary and secondary TN[7]. Differential diagnostics should be distinguished: maxillary sinusitis, temporomandibular disorders, postherpetic neuralgia, posttraumatic trigeminal neuralgia, glossopyrosis, glosopharyngeal neuralgia, idiopathic facial pain, SUNA and SUNCT[8]. There is also a serious lack of evidence for diagnostic criteria[9].

The purpose of this review paper is to systematize the evidence obtained from previously published articles on the outcome of various therapeutic procedures in patients diagnosed with trigeminal neuralgia.

There are a number of conservative and surgical therapeutic procedures for TN. The general recommendation is to start drug therapy and consider surgical treatment in patients who are refractory to it[10]. There is still a lack of sufficient number of studies that directly compare medical and surgical treatment. Medical therapy begins as monotherapy, followed by a combination therapy with various drugs that can be used when the effectiveness of monotherapy is low[11,12]. Antiepileptic drugs **Carbazepine** and **Oxcarbazepine** are the first line of treatment in TN[13]. **Lamotrigine** and **Baclofen** are considered a second line of treatment, while **Topiramate, Levetiracetam, Gabapentin, Pregabalin** and **botulinum toxin type A** are alternative treatments[14]. There are several surgical treatment options available to **TN** patients and it is important to choose the most appropriate surgery for the patient[15]. **Microvascular decompression** is a non-destructive procedure and is considered the golden standard of surgical therapy[16]. The other widely used technique is the **gamma knife**[17]. Of the destructive techniques, the most widely used are **the percutaneous techniques of the Gasser ganglion**, which have the advantage of selectively targeting the affected trigeminal divisions[18].

Materials and methods

In the paper, we did research and meta-analysis of all available literary data using a wide range of data up to date (from 1966 to 2020) for all studies related to **TN** treatment. Research was conducted electronically using studies published in English. The databases used in the selection of studies are: **PubMed/MEDLINE, Embase and Cohrane Library.**

Results and discussion

This review paper provides an overview of the results, measures, and prognosis of the end result by using the TN medication and surgical treatments until today. Treatments are performed by experienced therapists from different countries around the world and highlight the variability of the choice of measures used to achieve a positive result.

Conservative procedures

Regardless of the classification system, TN treatment always begins with drug therapy. Of the drugs currently used for treatment, all were originally developed for other indications (antiepileptics, myorelaxants, opioids, etc.). In addition, only a small proportion have been examined in large controlled studies, and many of the studies so far have methodological inconsistencies[19].

Anticonvulsant drugs

Carbamazepine acts inhibitory on sodium channels and reduces the excitability of nerve membranes. It also highlights gamma aminobuteric acid gamma receptors GABA composed of alpha 1, beta 2, and gamma 2 under units relevant to its role in the reduced transmission of neuropathic pain. **Oxcarbazepine** is a keto analogue of carbamazepine. With long-term treatment, carbamazepine (200–1200 mg/daily) or oxcarbazepine (300–1800mg/daily) remain the most effective drugs in the early stages of TN[20]. Literature also contains described situations that require even higher doses. If

these medications become ineffective or result in poor tolerance, then other medications should be considered. From systematic examinations[21] and randomized controlled trials[22-24], carbamazepine proves more effective than placebo groups, but more patients withdraw from use due to side effects. The most common side effects include somnolence, dizziness, and orthostatic hypotension. Oxcarbazepine has comparable efficiency in regard to cocarbazepine, but greater tolerance[25], except for the risk of hyponatraemia and low drug interaction potential[26, 27]. In the study of Zakrzewska, there is evidence that **Lamotrigine was** used as additional effective therapy[28], while there is little evidence that other anticonvulsant drugs like **clonazepam, gabapentin, pregabalin and valproate** have a beneficial effect[29]. Several review papers have investigated the comparative efficacy and safety of anticonvulsant drugs[30-32]. A paper based on 16 randomized controlled trials compared the effects of carbamazepine and gabapentin. Gabapentin is associated with fewer side effects than carbamazepine and oxcarbazepine[33]. We still have difficulty determining the best treatment for pain relief with minimal side effects. The failure of treatment is usually not due to the ineffectiveness of the medication, but rather to the side effects that cause discontinuation of treatment or reduction of the dose to an ineffective level. Combined treatment (carbamazepine or oxcarbazepine with lamotrigine, baclofen, pregabalin or gabapentin) should be taken into account when carbamazepine or oxcarbazepine may not reach the required dose due to side effects. Each of the drugs has clinical application as monotherapy, although the available evidence are weak[34].

Muscle relaxants

Baclofen (60-80 mg/daily), skeletal muscle relaxant is a GABA analogue that activates GABAb receptors and reduces excitatory neurotransmission. Clinical trials have shown that baclofen is effective as monotherapy or in combination with carbamazepine in the treatment of TN[35]. According to the research of Hassan and associates[36], after carbamazepine, baclofen shows the greatest effectiveness in the treatment of TN. Typical side effects include drowsiness, dizziness, fatigue, hypotension.

Opioids

Opioids are drugs used to treat acute and chronic pain. According to numerous studies, it is not recommended as the first line of therapy due to the danger of side effects that would occur during abuse and overdose[38, 39]. In recent years, Fentanyl has been used in the treatment of many chronic types of pain40. Coven, in his research, uses fentanyl in the treatment of TN type 2 as a blockage in the sphenopalatinal ganglion and gets successful results[41]. However, according to Cochrane, in the review papers there is insufficient evidence for the use of opioids in the treatment of neuropathic pain[42].

Botulinum toxin A

Botulinum toxin is a neurotoxin produced by the bacterium Clostridium botulinum. It blocks the release of acetylcholine on the neuromuscular synapse. It binds to C-fibers, has an analgesic effect and reduces muscle spasms[43]. In 2002, Micheli and associates[44] published a successful treatment of a patient with hemifacial spasm associated with TN with onabotulinumtoxin, which opens up new possibilities for its use. In the Bohluli study[45], 47% of patients did not require further treatment, nonsteroidal anti-inflammatory drugs were sufficient to relieve pain in 33% of patients, while 20% of patients again required anticonvulsant therapy after toxin administration. Recently, three examinations demonstrated that botulinum toxin could provide a clinically significant benefit in the treatment of TN[46-48]. A recent review by Jiangshan suggests that botulinum toxin is effective and safe in the treatment of TN and peripheral neuropathic pain[49]. The duration of the therapeutic effect and the doses that would be applied for the given pathology are issues that shall be researched in the future in well-thought-out examinations.

Surgical procedures

Patients who have persistent pain or cannot tolerate drug therapy due to side effects are referred for surgical treatment. These procedures have different success rates and risk profiles. Three descriptive studies have been identified that address the issue when TN patients should be offered surgical treatment[20,50,51]. Studies have shown that patients who are refractory to drug therapy may prefer early surgical treatment. A prospective study reported that 65% of patients referred to specialist centers could be managed with drug therapy for 2 years after referral with satisfactory results. 35% of them underwent surgery[52].

Microvascular decompression

Microvascular decompression (MVD) is a type of neurosurgery used in the treatment of TN caused by vertebrobasilar compression. Surgery is not without risk, it can cause recurrent facial pain and other side effects (insult, paralysis, paresis, lethal outcome). It was first

introduced by Jannetta[53] and after many years of improvement, MVD has become the most effective of TN surgical treatments .MVD in TN is a surgical treatment that has the least chance of failure, according to a study of 195 patients by Hitchon[54]. However, there are still patients who cannot achieve long-term outcomes. For patients who are not suitable for pure MVD, MVD combined with partial sensory rhizotomy can be considered as an effective alternative[55]. Leakage of vascular structure results in incomplete relief of symptoms after intervention[56]. Endoscopically assisted microsurgery helps to optimize surgical procedures, especially in identifying the overall course of the cranial nerve and avoiding the leakage of vascular structures[57]. The initial success rate of the therapy is usually high, but in 5% of the patients there is little or no pain relief after MVD. 10-30% of patients have recurrent neuralgia on follow-up, with an annual risk of recurrence of 1 to 4%[58,59]. In a recent review and meta-analysis[60], it has been concluded that about three-quarters of patients with TN resistant to drug therapy have been relieved of pain after MVD. Shorter duration of pain, arterial compression, and type 1 Burchiel classification predict a more favorable outcome.

Gamma knife

Gamma knife radiosurgery is an increasingly used, minimally invasive treatment option for TN patients who are refractory to drug treatment[61]. The use of radiosurgery in the treatment of TN dates back to Leksell (Sweden, 1950) who performed radio ganglionotomies on the gasserian ganglion[62]. Later, he began using the Gamma knife used in the form of multiple focal rays from cobalt-60 sources. Several retrospective and several prospective studies have reported good short-term and medium-term safety and effectiveness of the gamma knife[63,64,65]. The long-term outcome has not yet been well documented, as evidenced by a historical cohort study[66]. According to one review paper, the gamma knife is an effective single and multiple treatment option. Their cumulative research suggests that patients treated once show the same control of facial pain compared to patients who have been treated multiple times. The second group of patients is more likely to experience numbness and other sensory changes in the face compared to the first group[67].

Percutaneous techniques of the gasserian ganglion

Professional procedures performed at the level of the ganglion, trigeminal radiofrequency thermocoagulation (RFT), percutaneous balloon compression (PBC), percutaneous glycerol rhizolysis of the gastric ganglion (PRGR) are more effective than peripheral procedures, but no approach can guarantee long-term pain relief. The first two procedures are non-destructive and can cause sensory loss and distension[68].

RFT of the Gasser ganglion is a widely accepted, minimally invasive technique for the treatment of TN. Efforts are still being made to improve the details of each procedure, reduce perioperative pain, reduce surgical complications, and enhance analgesic efficacy[69]. Understanding and mastering surgical details varies between different hospitals[70]. Two RFT approaches are most commonly used: conventional radio frequency CRF and pulsed radio frequency PRF. According to previous examinations, CRF is the preferred treatment option (higher pain reduction rate, less frequent recurrent pain)[71]. New technologies, such as 3D printed lead board that allow for more precise interventions, have been proven in recent studies[72].

In 1983, Mullan and Lichtor introduced PBC by modifying the technique of nerve compression while performing a craniotomy. Initial studies have shown that PBC is successful, safe, with a small number of relapses, making it particularly popular with elderly patients[73,74]. In one review[75], the authors presented data from the largest cohort of patients with the longest follow-up for this procedure. The PBC procedure has the advantage of being a quick and simple procedure that can be performed in a short period of general anesthesia without discomfort to the patient. This makes it an attractive choice in TN treatment. In their study, Bergenheim and associates[76] presented the complications of the procedure (cardiovascular stress, local haemorrhage, postoperative sensory disturbance, masseur muscle weakness, affections, and transient diplopia). Measures to minimize side effects have been proposed.

In 1981, Hakanson introduced the PRGR technique in which he uses anhydrated glycerol and has since found use as a routine procedure[77]. Several studies have shown that PRGR is a simple, safe, relatively inexpensive method of treating TN[78,79]. The number of side effects and complications during the intervention is relatively small. A second application may be effective in recurrent pain and in patients who do not respond to the first application[80]. Predictive success factors include patients without persistent facial pain, patients with nomadic facial pain during glycerol injection, and patients with new trigeminal defects after PRGR[81]. One of the alternatives to the new PRGR technique is neuronavigation to place the needle in the oval opening and inject glycerol under sedation. This technique is the simplest and safest if the surgeon has previous experience in it[82].

Conclusion

Conservative (drugs) therapy with antiepileptic drugs, an individualized dose of CARBAMAZEPIN is still the gold standard in the treatment of TN worldwide. A combined therapy, guided by the literature base, did not make a significant difference in the fight against pain compared to monotherapy, and the use of alternative therapies in the form of botulinum toxin treatment requires further studies to determine the exact dose and the time period of drug action. Surgical procedures and studies that have been developed are a good basis for progress in their development using new 3D technology and the introduction of new recommendations and work protocols that would drastically reduce the percentage of risks and complications and make them more accessible to patients.

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