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REVIEW ARTICLE

Trigeminal Neuralgia: The New Medicinal Treatment Modalities

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ABSTRACT

Trigeminal neuralgia has been considered as a painful condition since long time. Pain is perceived in one or more divisions of the trigeminal nerve, mostly unilaterally. Pain is shooting, lancinating, sharp, agonizing and described as an electric shock. Usually lasts seconds to minutes with repetitive bursts every few seconds. The patient is symptom-free between the attacks. Common evidence can be the trigger effect of some routinely actions involving territories innervated by the affected root, such as speaking, swallowing, chewing, brushing the teeth, or sensitive stimuli applied in these regions like simple light touch, cold, or an air blow. Medicinal therapy is the main stay of treatment in trigeminal neuralgia. This review focuses on the drug therapy in neuralgic patients.

KEY WORDS: Pain, Neuralgia, Trigeminal nerve, Medicinal therapy.

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INTRODUCTION

Trigeminal neuralgia, "tic douloureux", or Fothergill disease is a well-known condition that neurologists and neurosurgeons are familiar with. It can be defined as sudden, usually unilateral, severe, brief, stabbing and recurring pain in the distribution of one or more branches of fifth cranial nerve (The International Association for the Study of Pain) (1,2). The prevalence of Trigeminal Neuralgia is 0.1-0.2 per thousand and over all incidence is about 4-5/100,000/year and after the age of 60 up-to 20/100,000/year. The female to male ratio is 3:2. The right side of the face is 5 times more commonly involved than the left. It is typically idiopathic but may be due to structural lesions. No racial risk factors have been reported (3).

First descriptions of this clinical entity date back to the second century AD (4), but also Arabs had some knowledge of trigeminal neuralgia during the 11th century. The first report of medical treatment is attributed to John Locke, a British physician and philosopher, who prescribed "laxatives" to an affected patient in Paris, in 1677 (5).

Trigeminal Neuralgia can be diagnosed by history and clinical examination. Radiographic assessment is necessary to identify any intracranial pathology. Pain is evoked by certain stimuli like washing, shaving, talking, yawning, smoking and brushing the teeth, and/or may also occur spontaneously (6,7). The pain usually appears as sudden shooting or stabbing. The onset and termination of pain is abrupt and may remit for varying periods. Attacks may occur during the day or night but rarely during sleep. Frequency of attack also varies, sometimes it may be once a day, once a month and in some cases it may be several attacks in a day or a week. There may be no pain for a prolonged period of time. The pain is very cruciating and causes disturbance in daily routine (2,7). The condition can lead to irritability, severe anticipatory anxiety and depression, and life-threatening malnutrition. Suicidal depression is not uncommon. Pain is almost unilateral in 97% cases, affecting maxillary and mandibular branches, in few cases (< 5%), ophthalmic division is affected. Local Anesthetic block at different location of nerve distribution is usually used to identify specific nerve involvement (7).

In a more recent past, treatment has become surgical, ranging from dental extraction (often result of misdiagnosis), to chemoneurolisis (by means of direct injection of chloroform and alcohol in the Gasserian ganglion, or glycerol in the trigeminal cistern), from radiofrequency technique, to trigeminal nerve compression (3). All treatments carried significant side effects (loss of sensitivity, muscle weakness, herpes virus infection, etc.) and early recurrence (5). Microvascular decompression (MVD) is the treatment of choice. Radiation Therapy (4) and Stereotactic Radiosurgery (8) are a recent adjunct to the therapeutic options for trigeminal neuralgia. The latter, by means of Gamma Knife (9), assumes a peculiar interest in the light of the spreading availability of robotic frameless stereotaxy (10). Long-term results still have to be carefully evaluated with the time of long follow-up.

Today, dentistry has entered an exciting era of high technology offering the dentist not only a window, but a door into high-technology. Recently, considerable breakthroughs have been made in the diagnosis and treatment of this disease and the day when the final mysteries that surround this disease will be unraveled. The purpose of this paper is to provide an overview of various clinical parameters of trigeminal neuralgia which have been developed for patient relief in dental practice. It also provides in more detail several key clinical applications which are attracting a high level of interest. Further, it focuses on the rationale for treatment in neuralgic patients.

Types of trigeminal neuralgia

Seven forms of trigeminal neuralgia can be defined (11):

- Typical trigeminal neuralgia
- Atypical trigeminal neuralgia
- Pre- trigeminal neuralgia
- Multiple-sclerosis-related trigeminal neuralgia
- Secondary trigeminal neuralgia
- Post-traumatic trigeminal neuralgia (trigeminal neuropathy)
- Failed trigeminal neuralgia

These forms of trigeminal neuralgia should be distinguished from idiopathic (atypical) facial pain, as well as other disorders causing cranio-facial pain.

MANAGEMENT

Medications are the first line of treatment for trigeminal neuralgia. As the disease progresses and pain becomes more frequent and severe, increased doses of medications are required which may lead to intolerable side effects and/or inadequate pain control. Each sufferer has differing tolerance to these medications and pain, but at least half will eventually find that medications do not adequately control their progressively worsening condition. The surgical procedures then considered are either microvascular decompression surgery or some form of nerve injury procedure (rhizotomies).

Today, trigeminal neuralgia is usually treated with drugs called anti-convulsants, which include mainly carbamazepine, phenytoin, oxy-carbamazepine and gabapentin. Treatment is usually initiated with one drug, such as carbamazepine or gabapentin. The dose is increased as needed and tolerated. If any single drug proves ineffective, alternative drugs may be tried alone or in combination with other drugs. Medical therapy is initially effective for most patients with trigeminal neuralgia. Unfortunately; about half of trigeminal neuralgia sufferers eventually become dissatisfied with medical therapy, because of incomplete control of pain or drug related side effects that are almost always experienced. Surgical treatments are then considered (12,13).

DRUG THERAPY/MEDICINAL TREATMENT

Carbamazepine

Carbamazepine was first marketed as a drug to treat trigeminal neuralgia in 1962. It has been used as an anticonvulsant in the United Kingdom since 1965, but only approved in the United States since 1974. It is the drug of choice for trigeminal neuralgia and has remained the mainstay of treatment ever since it was introduced 35 years ago. It is found to be more effective than any other drug and causes fewer side effects. Almost all typical trigeminal neuralgia sufferers experience significant pain relief with carbamazepine. The starting daily dose is 100 mg to 200 mg twice or thrice a day, which is gradually increased according to patient's response, need, and tolerance. Good relief of pain may be achieved at low doses, but the usual effective dose ranges from 600 to 1600 mg divided in three or four doses per day.

Carbamazepine is chemically related to the tricyclic antidepressants. It exerts both anticonvulsant and antineuralgic effects. It decreases the response of trigeminal mechanoceptive neuron to peripheral stimulation and prevents paroxysms of trigeminal neuralgia without impairing sensation. Side-effects includes Gastric upset, dry mouth, drowsiness, mental confusion, dizziness, nystagmus (rapid movements of the eye), ataxia (decreased coordination), diplopia (double vision), nausea, and anorexia (loss of appetite).

Trileptal (Oxycarbazepine)

Trileptal, or oxycarbazepine, is a form of carbamazepine that is becoming more widely prescribed for a variety of conditions. It has recently been found to be effective for some patients with trigeminal neuralgia. Like carbamazepine, it is an anti-seizure drug; the side effects are less severe and less frequently experienced, but must be taken in higher doses to provide adequate pain control.

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. Side-effects includes Nausea, vomiting, dizziness, fatigue and tremors. Less frequent symptoms are rash, respira-

tory infections, fatigue, asthenia, CNS/GI disturbance, acne, Stevens-Johnson syndrome, toxic epidermal necrolysis, thrombocytopenia, hepatitis, loss of hair, double vision, and changes in electrolytes in blood.

Phenytoin

Phenytoin relieves 'tic' pain in over half of trigeminal neuralgia 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 trigeminal neuralgia. Adults: Initially 3-4mg/kg daily or 150-300mg Dose dependent side effects include nystagmus, ataxia, dysarthria, ophthalmoplegia as well as drowsiness and mental confusion. Other effects of the medication may include gingival hyperplasia and hypertrichosis. daily (in 2-3 divided doses), increased gradually as required. Maximum dose is 600mg. Children: initially 5mg/kg daily in 1-2 divided doses. Usual dose is 4-8mg/kg. Maximum dose is 300mg.

Baclofen

Baclofen is not as effective as carbamazepine or phenytoin for trigeminal neuralgia, but may be used in combination with these medications. Usually 5 mg two or three times a day, and may be gradually increased. Maximum: 100mg daily. Children: maximum 2.5mg/kg daily in divided doses. Haemodialysis patients: 5mg/day. The usual dosage taken for complete pain relief is between 50 and 60 mg per day. Baclofen has a short duration of function so sufferers with severe TN may need to take doses every 3 to 4 hours. Side-effects includes drowsiness, dizziness, nausea, leg weakness, muscle fatigue, hypotension, respiratory/cardiovascular depression, dysuria and enuresis. The incidence of these side effects is reduced by starting with a low dose that is gradually increased.

Gabapentin

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. Dose-Starting dose is increased gradually to 300mg three times a day and this is increased to a maximal dose. Maximum: 800mg thrice daily. Children: not recommended. Special precautions - Elderly, renal impairment, haemodialysis, absence seizures, pregnancy, lactation, history of psychotic illness. Discontinuation of Gabapentin and/or addition or substitution of alternative therapy should be gradual, over a minimum of 1 week.

Clonazepam

Clonazepam is a benzodiazepine derivative with highly potent anticonvulsant, muscle relaxant and anxiolytic properties. Clonazepam is a chlorinated derivative of nitrazepam and a nitrobenzodiazepine like nitrazepam. Clonazepam is the second most abused benzodiazepine in the United States. Clonazepam may be prescribed for: epilepsy, anxiety disorders, panic disorder, initial treatment of mania (together with firstline drugs such as lithium, haloperidol or risperidone), hyperexplexia, restless legs syndrome, treatment of acute and chronic akathisia, muscle relaxant (off label use), sedative for sleep (off label use). Its long half-life sometimes makes it useful for treating middle of the night insomnia (waking up too early), but may also lead to next-day effects. Side effects - Drowsiness, impairment of cognition and judgment, irritability and aggression, psychomotor agitation, lack of motivation, loss of libido, impaired motor function, impaired coordination, impaired balance, dizziness, cognitive impairments, increased sleepwalking (if used in treatment of sleepwalking), hallucinations, short-term memory loss, anterograde amnesia (common with higher doses).

Lamotrigine

Lamotrigine is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. For epilepsy it is used to treat partial seizures, primary and secondary tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome. Lamotrigine also acts as a mood stabilizer. Lamotrigine has relatively few side-effects and does not require blood monitoring in monotherapy. Mechanism of action - In vitro pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating pre-synaptic transmitter release of excitatory amino acids. Side effects includes life threatening skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis can occur. It is estimated that 5 to 10 % of patients will develop a rash. Nearly all cases appear in the first 2 to 8 weeks of therapy and if medication is suddenly stopped then resumed at the normal dosage.

Sumatriptan

Sumatriptan is a triptan drug including a sulfonamide group for the treatment of migraine headaches. Several dosage forms for sumatriptan have been approved, including tablets, solution for injection, and nasal inhalers. Sumatriptan was the first triptan available (in 1991), and, in the United States and most developed countries, is available only by medical prescription. Mode of action - Sumatriptan is structurally similar to serotonin (5HT), and is a 5-HT (type's 5-HT1D and 5-HT1B) agonist. Sumatriptan was also shown to decrease the activity of the trigeminal nerve, which may partially explain sumatriptan's efficacy in treating cluster headaches. The injectable form of the drug has been shown to abort a cluster headache within fifteen minutes in 96% of cases. Side Effects - Sulfhemoglobinemia (at large dosage), serious cardiac events, coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation, atypical sensations like burning and numbness, palpitations, syncope.

Pregabalin

Pregabalin is an anticonvulsant drug used for neuropathic pain and as an adjunct therapy for partial seizures with or without secondary generalization in adults. It has also been found effective for generalized anxiety disorder. It was designed as a more potent successor to gabapentin. Recent studies have shown that pregabalin is effective at treating chronic pain in disorders such as fibromyalgia and spinal cord injury. It is considered to have a low potential for abuse, and a limited dependence liability if misused. Treatment of neuropathic pain from diabetic neuropathy or post herpetic neuralgia, adjunctive therapy in adults with partial seizures with or without secondary generalization, fibromyalgia pain, generalized anxiety disorder.

Topiramate

Topiramate is an anticonvulsant drug. It was discovered in 1979 by Drs. Bruce E. Maryanoff and Joseph F. Gardocki. Indications - Epilepsy (in children and adults), antidepressant, treatment of Lennox-Gastaut syndrome (a disorder that causes seizures and developmental delay in children), prevention of migraines. Other off-label and investigational uses of topiramate include: treatment of bulimia nervosa, obsessive-compulsive disorder, treatment of alcoholism, smoking cessation, pseudotumor cerebri, and treatment of neuropathic pain. Side effects - Tiredness, pins and needles in the fingers and toes, dizziness, lowered sense of feeling in the skin, difficulty with language, nausea, diarrhea, indigestion, dry mouth, weight loss, decrease in appetite, drowsiness, difficulty with concentration or attention, insomnia, anxiety, mood swings, depression, changes in taste and vision disorders.

Conclusion

Trigeminal neuralgia is a painful condition. Other types of facial pain may mimic trigeminal neuralgia and can thus lead to the incorrect diagnosis, which will then result in inappropriate treatment, and, ultimately, failure of treatment. Once the diagnosis has been established, all patients should undergo a trial of medical therapy. Failure to respond to medical therapy should encourage the clinician to carefully reassess the diagnosis. All patients also should undergo appropriate imaging studies (brain computer tomograph with enhancement or brain magnetic resonance imaging scan), preferably by a magnetic resonance imaging scan, to rule out possible mass lesions. Medicinal therapy is the main stay or treatment and should be given as suited to the patients. However, in refractory patients surgical treatment should be taken into consideration.

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