

## The Progress in Diagnosis and Treatment of Trigeminal Neuralgia

Lingaowa Ta<sup>1</sup>, Xd Wang<sup>1</sup>, Xin Wu<sup>2\*</sup>

<sup>1</sup>Inner Mongolia Autonomous Region People's Hospital, Hohhot, China, 010010.

<sup>2</sup>Department of Ultrasound Medicine, Hospital of Traditional Chinese Medicine, Inner Mongolia Autonomous Region, Hohhot, China, 010000.

**\*Corresponding Author:** Xin Wu, Department of Ultrasound Medicine, Hospital of Traditional Chinese Medicine, Inner Mongolia Autonomous Region, Hohhot, China, 010000.

### Abstract

Trigeminal neuralgia (TN) is characterized by recurrent facial acupuncture like, electric shock like, burning like pain and other common clinical cranial nerve diseases in the trigeminal nerve distribution area. Around the world, people who are 40 or more are at risk. The incidence rate of TN of female is slightly higher than that of male and most of the affecting areas are on the right side unilaterally, which affects maxillary nerve and mandibular nerve, yet seldom ophthalmic nerve. Although controversy exists in the pathogenesis of TN, the most accepted theory is microvascular compression, which forces on the demyelination of the sensory axon of the trigeminal nerve root. Additionally, slight touch, conversation and chewing may cause intolerable pain. The diagnosis of TN mainly depends on clinical manifestation. The treatment mainly includes medicine, operation, and some supplementary methods. Among them, antiepileptics and tricyclic antidepressants are the first-line treatment. Surgical treatment is mainly used for patients with TN who have failed in drug treatment, have intolerable side effects or no effect at all. The methods of operation include destructive or non-destructive operation. Deep brain stimulation and motor cortical neuron regulation stimulation are new therapeutic techniques recently. This method is expected to alleviate the refractory TN with poor drug control or ineffective conventional surgical treatment. At present, this method has not been approved for clinical treatment. Of course, more clinical data collection processes are in progress.

**Keywords:** trigeminal neuralgia, chronic pain, neuropathic pain, anticonvulsant drugs, microvascular decompression, nerve regulation

### 1. INTRODUCTION

Trigeminal neuralgia (TN) is one of the most common cranial nerve diseases with recurrent short-term electric shock like pain in the trigeminal nerve distribution area, which has a high prevalence in elderly patients [1]. Annual morbidity rate of TN is 4.3-28.9/10 million in the world, and most of them are over 40 years old with slightly higher incidence in women than that in man. The characteristics of pain is unilateral, and the right side is more than the left side. Most of TN syndromes involve the maxillary and mandibular nerves, yet the ophthalmic nerve is rarely seen [2-3], and the most common inducing factors are direct facial stimulation (speech, face washing, tooth brushing, etc.). A majority of patients can alleviate the symptoms by oral anticonvulsant drugs, but patients always have difficulties in the long-term medication compliance due to efficacy decline and side effects during long-term medication, which seriously affects the

quality of life, work, and social interaction abilities of patients. In recent years, with the ever-illuminating process of etiology of TN, and the progress of clinical practice, more and more effective methods of TN treatments emerges. The surgical treatments of TN mainly include microvascular decompression (MVD), retrogasserian glycerol rhizotomy, stereotactic gamma knife radiotherapy, percutaneous radiofrequency thermocoagulation of trigeminal semilunar ganglion, balloon compression, endoscopic assisted vascular decompression, which are mainly applicable to the cases of patients with ineffective drug treatments or intolerable side effects.

### 2. DIAGNOSIS AND SUB CLASSIFICATIONS OF TN

#### 2.1. Diagnosis of TN

TN is a clinical diagnosis that mainly depends on symptoms. The diagnosis of TN must meet the following two conditions: first, pain must occur in a branch of trigeminal nerve, and there

is no correlation between pain and nerve loss or radiation injury outside the distribution of trigeminal nerve; second, the characteristics of pain must meet two of the following three conditions: (a) severe pain; (b) electric shock or tingling nature of pain; (c) paroxysmal attack lasts from 1s to 2min (maximum time is 2min). Another diagnostic factor is that the pathological side of TN can be induced by a harmless stimulus to produce severe pain symptoms [4-5].

The classic TN pain is characterized by short-term, paroxysmal pain caused by neurovascular compression. The pain is intermittent, but not persistent. In addition, imaging and special examinations are used to exclude other diseases, such as herpes zoster, trigeminal injury, migraine, cluster headache, glossopharyngeal neuralgia, multiple sclerosis, temporomandibular joint pain, dental disease, cerebral aneurysm, tumor, and intracranial hemorrhage [6]. Once clinical TN is suspected, neuroimaging is recommended to help distinguishing between typical TN and symptomatic TN, and it can be assisted by magnetic resonance imaging (MRI) or computed tomography (CT). Enhanced MRI or non-enhanced MRI can distinguish the trigeminal nerve and its adjacent structures more clearly, which is helpful to diagnose the neurovascular compression of TN [7]. Secondary TN is mostly caused by arteriovenous malformations, brain tumors, multiple sclerosis, etc. [4-5] and the etiology of idiopathic TN remains elusive. Some of the possible explanations including neurovascular compression or other secondary causes, in which neuroimaging and neurophysiological testing cannot provide a positive basis [7].

Cruccu has tried to optimize the diagnostic criteria of TN. Briefly speaking, there are three simple conditions for the diagnosis of TN: (1) unilateral onset; (2) paroxysmal attack; (3) trigeminal nerve distribution. Cruccu recommends early appointment for MRI or other imaging methods at the beginning of disease diagnosis to ensure the accuracy of diagnosis and its classification. If MRI exhibits pathological changes like vascular compression in the root of trigeminal nerve, it can be classified as classical TN; If MRI shows trigeminal nerve invasion such as tumor and AVM, it should be classified as secondary TN; presuming that no positive results are demonstrated by MRI, and the symptoms meet

the above criteria, it should be identified as idiopathic TN. Cruccu's main idea is to establish a simple method to avoid the inaccuracy of the TN classification, as well as to take a rapid and appropriate treatment for the confirmed patients. For patients who can't be diagnosed by MRI, trigeminal nerve evoked potential and trigeminal reflex electrophysiology are recommended in classification of TN. Correct diagnosis and classification help to optimize treatment strategies and improve patient satisfaction [8].

### 2.2. International Classification of TN

The International Headache Society (IHS) divides TN into two different categories: "classic TN" and "symptomatic TN". The typical symptom of classic TN (TN1) is paroxysmal severe burning facial pain, which lasts for no more than 2 min at a time; there are also occasional clustering pain that lasts for several hours at a time [9]. In contrast, non classical TN (TN2) is described as a burning, stabbing sensation that is much less intense than TN1 [10].

### 3. EPIDEMIOLOGICAL HISTORY OF TN

TN was first recorded in the works of the famous Greek physician Galen in the 1<sup>st</sup> century A.D., but it was not found in the official exact description until the 17<sup>th</sup> century. In 1756, Nicholas Andre coined the term "painful twitch" because he saw a unique facial spasm accompanied by electric shock. In 1773, a British physician named John Forstergill, for the first time, gave a complete and exact description in a presentation entitled "suffering from facial pain" to the London Medical Committee. Since then, the disease has also been known as "Forstergill's disease".

The incidence of TN is rare (about 4-13 per 100000 people per year), accounting for 0.015% of the total population. Despite of the low incidence rate, TN is the most common cause of diseases with facial pain syndromes. In addition, age is an independent risk factor for TN. The disease mainly affects people over the age of 50, and the incidence rate of people over 80 years is 25.9 people per 100,000 people. However, TN can occur at any age, including children. In adults, the incidence rate of women is more than that of men, about 1.5 (1.7): 1. Most of the cases are sporadic, and there is no report of familial genetic aggregation. Interestingly, TN occurs mainly on the right side, and is extremely rare on both sides.

## 4. ETIOLOGY HYPOTHESIS OF TN

### 4.1. Ignition theory

According to the theory, axon demyelination and myelination disorder will cause axon damage, increase autonomic excitability of neurons, and the spontaneous or triggered ectopic pulses will generate impulses in abnormal positions, and cause biological resonance between nerves. The synapses of adjacent damaged nerve fibers can enhance the excitability of heterotopic pacemaker by positive feedback mechanism to activate adjacent nerve fibers. The chain reaction will form the quick paroxysmal impulse transmission which leads to burst pain, and pulse discharge will eventually stop with neurons returning to its resting state. During the burst,  $\text{Ca}^{2+}$  enters the neuron and activates  $\text{Ca}^{2+}$  activated  $\text{K}^+$  channel.  $\text{K}^+$  then flows out of neurons through these channels, which leads to hyperpolarization of neurons. The outward  $\text{K}^+$  current also stops the transmission of nerve impulses to enter the refractory period, and then generate the post pain relief. The theory of TN kindling combines the demyelination of trigeminal nerve, which can well explain the generation of pain and its clinical syndromes of sudden arrest and remission.

### 4.2. Biological resonance theory

This theory holds that the trigeminal nerve immersed in CSF vibrates at its own natural frequency. When the vibration frequency of the peripheral structure is close to its natural frequency (e.g. change of blood pressure, heart rate, intracranial pressure, or the position of tortuous blood vessels near the nerve), the resonance of trigeminal nerve occurs. This kind of biological resonance will increase the amplitude and then damage the nerve, which causes a series of electrophysiological changes and eventually leads to the transmission of abnormal trigeminal nerve impulse, and may eventually generate pain sensation. At the same time, resonance mechanical energy can also convert other forms of energy, such as bioelectricity, which will affect the permeability of cell membrane, and even cause a series of changes in organelles that ultimately affect the activity of enzyme [13-14]. Therefore, the resonance mechanical energy will eventually affect the biological oxidation process, energy metabolism process and reduce the antioxidant function. This view has been proved by ultrastructural changes and immunochemical tests. According to the theory of biological

resonance, the mechanism of surgical treatment of TN is to change the natural frequency of trigeminal nerve or the vibration frequency of surrounding structure to avoid the occurrence of trigeminal resonance. For instance, the vibration frequency of blood vessel can be changed by moving blood vessel or by placing gasket between blood vessels and nerves. The natural frequency of trigeminal nerve fiber can be changed by destroying part of trigeminal nerve fiber, or the occurrence of biological resonance can be avoided by partial sensory rhizotomy or selective percutaneous radiofrequency thermocoagulation. This theory can explain almost all the TN syndromes, but it has not been confirmed by experimental data. At present, it is only at the stage of theory. In the future, it is possible to design an "anti-biological resonance therapeutic apparatus" as treatment for TN to verify the effectiveness of this theory.

### 4.3. Allergic reaction theory and bone compression theory

The subjective feeling of pain is most related to the stimulation of inflammatory factors around the nerve. Some researchers found the release of histamine on the trigeminal nerve branch of TN patients[15], which aggravates edema of the nerves, and causes the trigeminal nerve to be jammed at the place where it exits the skull (foramen rotundum and foramen ovale) that results in nerve injury. In terms of anatomic structure, the right foramen ovale and foramen rotundus of human body are relatively narrow than that on the left side, which might explain why the incidence of TN on the right side is more than that on the left side.

### 4.4. Microvascular compression theory

The vascular contact of the nerve root entry zone (REZ) can cause TN, that is, the compression of microvasculature demyelinates the sensory axon in the trigeminal nerve root. Jannetta et al. has recorded a high proportion of vascular compression in patients with TN [16], which also showed that MVD can relieve pain. Therefore, it is speculated that relieving the compression of trigeminal nerve can promote the regeneration of myelin sheath to relieve pain [17-18]. Normal arterial pulsation is not enough to cause trauma and produce TN, whereas stroke caused by long arterial rings leads to radiculopathy, which might cause TN by severe root impression or near root distortion. In addition to arterial compression, compression of some veins or combined arterial are also the causes of TN. However, there are still some unexplained problems in the theory of

microvascular compression. For example, demyelination alone does not directly indicate the characteristic symptoms of the disease. Nerve impulses in myelinated sensory axons are usually associated with tactile and vibrational sensation rather than pain. In addition, demyelination itself may block the transmission of nerve impulses, thus producing numbness rather than pain. However, there is still a problem in clinical observation. There is still a part of TN patients who do not suffer from microvascular compression, and microvascular compression could be found in the normal population without TN attack [19].

### 5. TREATMENT OF TN

The treatment of TN includes medicine, surgery, and comprehensive treatment, with drug therapy being the preferred choice for TN. Anticonvulsants and tricyclic antidepressants are the main choices. Besides, surgical treatments should be considered as early as possible in patients with drug failure. The main surgical methods are MVD, Meckel balloon compression (PBC), percutaneous radiofrequency thermocoagulation (RFT) of trigeminal semilunar ganglion, stereotactic gamma knife radiotherapy (SRT). Recently, it has been reported that motor cortical stimulation (MCS) and deep brain stimulation (DBS) may be new and promising methods for patients with intractable TN.

#### 5.1. Drug treatment

The most effective standard drug for TN is carbamazepine, and its mechanism of action is to stabilize sodium channel and make it inactive. Four randomized controlled trials involving 147 patients has confirmed the efficacy of carbamazepine in the treatment of TN[20], which was proved effective in patients in these trials. About 58% to 100%of patients in the carbamazepine group achieved complete or nearly complete pain control, whereas the percentage is only 0 to 40% in the placebo group. However, the most common side effects of carbamazepine are fatigue, dizziness, inattention, and serious complications including agranulocytosis, aplastic anemia, drug interaction, etc. Oxcarbazepine is an alternative first-line drug with the same therapeutic effect as carbamazepine and less side effects [22].

Second line drugs include baclofen, a GABA receptor agonist, and lamotrigine, a sodium channel inhibitor. Baclofen can be used alone or in combination with carbamazepine, through

inhibiting excitatory neural transmission. Like carbamazepine, common side effects of Baclofen include syncope, fainting, fatigue, and nausea. Withdrawal syndrome will occur when the drug is stopped suddenly, which will lead to epilepsy and hallucination. Lamotrigine is an anticonvulsant, and can also be used to treat bipolar disorder. Like other antiepileptic drugs, lamotrigine has side effects such as sleep disorder, dizziness, headache, and vertigo. Among them, 7% - 10% will have rashes, which will gradually disappear as the treatment progresses. Only 1 / 10000 of the patients will have Stevens Johnson syndrome, whose require drug withdrawal immediately.

With the increasing number of antiepileptic drugs, many patients will not take surgery as an option for many years. Other three-line drugs, such as levetiracetam, topiramate, gabapentin, pregabalin and botulinum toxin A can also be considered.

#### 5.2. Surgical treatment

Surgical treatment is suitable for patients who fail to take at least three kinds of drugs, have serious side effects or repeated symptoms. According to the literature, about half of the patients will eventually choose surgery at a certain period of their illnesses [25-26]. The main surgical methods are MVD, Meckel balloon compression (PBC), percutaneous radiofrequency thermocoagulation (RFT) of trigeminal semilunar ganglion, stereotactic gamma knife radiotherapy (SRT), and trigeminal cistern glycerin injection.

##### 5.2.1. Microvascular decompression (MVD)

MVD is one of the most satisfactory neurosurgical operations for both surgeons and patients. In contrast, although MVD is an invasive operation, it has the highest first postoperative remission rate with the lowest incidence of sensory loss complications. Long term studies have shown that MVD can achieve long-term pain relief in more than 70% of patients. Therefore, it is a better choice for the patients with healthy condition and non-invasive treatment failure [28-29]. Microvascular decompression is a major operation in neurosurgery, and the procedure includes proper posture, craniotomy, exposure and determination of the responsible vessels, effective decompression of the trigeminal nerve into and out of the brainstem area, and the most common one is the dilated superior cerebellar artery. Due to the major trauma through surgery,



the average operation time was 4-5h. Because most patients with TN are over 50 years old, the operation requires the patients to have enough constitution to tolerate general anesthesia and surgical trauma. However, a recent study has shown that the long-term pain relief of patients aged 60 and over after MVD is significantly better than that of young patients [30-31]. According to five TN MVD studies using independent outcome assessment identified by the American Academy of Neurology and the European Federation of neurosciences, 90% of patients achieved initial pain relief; but at 1, 3, and 5 years, the pain relief rate decreased to 80%, 75%, and 73%, respectively, with a mean mortality rate of about 0.2% [32-33]. Compared with radiofrequency thermocoagulation and gamma knife radiotherapy, the postoperative pain relief rate of MVD was significantly higher, yet the postoperative complications and recurrence rate were not significantly different.

In recent years, with the improvement of technology and the progress of researches, the curative effect of MVD (E-MVD) under neuroendoscope has been affirmed. There was no significant difference in the rate of pain relief and complications between E-MVD group and MVD group. A systematic evaluation and meta-analysis of the efficacy comparison between E-MVD and MVD showed that the relief rate of postoperative pain in the two groups was similar; but in terms of postoperative complications and recurrence rate, the E-MVD group was superior to that of the traditional MVD group. At the same time, the operation time of E-MVD is shorter and the trauma is smaller than MVD, which makes it possible to replace the traditional MVD as the first-line treatment of TN in the future. Intraoperative wake-up MVD is a new technology, which is mainly used to determine whether the degree of decompression is appropriate through intraoperative wake-up test. Through the anesthesia program of intraoperative arousal, and the corresponding scale evaluation and test, people can evaluate the intraoperative pain to identify and reduce the trigeminal nerve decompression insufficiency. The results show that intraoperative awake test can improve the postoperative pain relief rate of MVD, but it still needs to be confirmed by large sample study.

### 5.2.2. Balloon compression (PBC)

This operation is aimed to protect the  $\alpha$ -alpha and beta sensory nerve fibers by selectively damaging the nerve fibers of A-delta and c-

conduction pain. Mullan et al. reported the operation and effect of PBC for the first time. The patient was in supine position, general anesthetized, and electrocardiographic monitored. The puncture point was 2.5 cm above the angle of the patient's mouth. During the puncture, attention should be paid to the changes of heart rate and blood pressure. Under X-ray fluoroscopy, the puncture needle enters the oval hole, exits the core of the puncture needle, leads into the balloon sleeve, injects iodine containing contrast agent to fill the balloon (the volume of the balloon usually ranges from  $568.2\text{mm}^3$ - $891.4\text{mm}^3$ , with an average of  $769.5\text{mm}^3$ ) [38]. Afterwards, the depth and position of the balloon catheter will be adjusted until the "pear shaped" or "dumbbell shaped" balloon appears (compression time is 3-5min) after removing the contrast agent. The puncture point was compressed for 5 minutes. During the operation, increased blood pressure, decreased heart rate and even a cardiac arrest might occur. Thus, it is critical to monitor the heart rate and blood pressure during the operation. Atropine or sodium nitroprusside can be used to treat the decrease of heart rate and the increase of blood pressure. Severe heart disease should be controlled before PBC. If necessary, temporary pacemaker should be used as a preventive measure. In addition, it is necessary to avoid puncturing the round hole and the oral mucosa. If it is difficult to puncture, multiple fluoroscopy can be used to adjust the direction of puncture. If necessary, three-dimensional CT reconstruction should be performed to determine the position of the puncture needle and the shape of the oval hole. The puncture needle should be replaced in time in oral mucosa damage to avoid intracranial infection. Asplund et al. believed that the main body of the saccule across the slope might compress the abductor nerve and cause ophthalmoplegia [39]. The compression time of saccule should not be too long. Generally, it should be controlled in 3-5 minutes. The compression time is not enough to affect the curative effect, but long time of compression will cause the increase of complications, such as the decrease of masseter strength, the increases incidence of keratitis or corneal ulcer. It has been reported that PBS can relieve the pain in 80-90% of patients immediately, which does not need drug control within 2-3 years [40-41]. Skirving et al. reported that the recurrence rate within 5 years was 19.2% [42]. This technique has good clinical effect, simple and safe operation procedures, quick recovery period, and operation under the

condition of general anesthesia without pain. It has gradually become an important treatment method, especially for the elderly patients, patients with recurrence after MVD decompression and those who are unwilling to accept craniotomy.

### 5.2.3. Radiofrequency thermocoagulation (RFT)

Radiofrequency thermocoagulation is also a kind of minimally invasive percutaneous treatment, which is a classic operation for TN treatment. Its principle is to destroy the A-delta and C-type unmyelinated nerve fibers that conduct pain sensation. At a temperature of 60-70°C, these fibers will be coagulated, degenerated and necrotic, whereas the myelinated nerve fibers that conduct tactile sensation and control movement are less likely to be damaged at this temperature. It has been found that in patients with TN, RFT was performed at 62 °C, 65 °C and 68 °C, respectively, without changing other RF parameters. The results suggest that 68 °C is the most appropriate temperature for the treatment of pain in the maxillary and mandibular branches of the trigeminal nerve [43]. According to a large sample survey of 1600 patients over 25 years, 97.6% of the patients had complete pain relief in the early stage, 57% of the patients had complete pain relief after 5 years and 52.3% after 10 years [44]. The operation of RFT is to reach the foramen rotundus and foramen ovale through percutaneous puncture, and to treat the pain of maxillary branch and mandibular branch respectively. For the pain in the distribution area of ophthalmic branches, the probability of serious complications such as keratitis and corneal ulcer is comparatively higher. According to the latest report, continuous radiofrequency thermocoagulation combined with pulsed radiofrequency can significantly reduce the postoperative complications, especially in the treatment of ophthalmic branches. These procedures can reduce the complications of corneal hyporeflexia, prevent keratitis and corneal ulcer, and shorten the postoperative recovery time [45].

At present, in order to achieve the accurate location of the trigeminal nerve branches, the application of stereotactic CT guidance and neuronavigation is becoming more and more common with decreasing occurrence of complications [46-47]. Zakrzewska et al. have demonstrated that compared with RFT without neuronavigation guidance, patients treated by

neuronavigation system could obtain a more lasting pain relief and fewer adverse reactions, especially for those who have difficulty in foramen rotundus and foramen ovale puncture [48].

### 5.2.4. Stereotactic radiotherapy

Stereotactic radiosurgery, a gamma knife radiosurgery for TN, is suitable for patients with poor surgical effect, serious basic diseases or unwilling to receive further invasive surgeries. Since this technology came out in 1951, more than 60000 cases have been completed all over the world. This method uses stereotactic technique and high dose (70-80gy) submillimeter radiation beam to focus on the trigeminal nerve root into brainstem area, and leads to nerve root necrosis to reduce the transmission of pain signals without affecting the transmission of normal synapses. At present, the application of thin-layer MRI based on stereotactic technology can clearly delineate the trigeminal nerve root. Trigeminal nerve root is the densest nerve fiber, which is the central myelin cells transformed into the area of peripheral myelin cells more sensitive to radiation. With a smaller dose, the maximum radiobiological effect can be achieved. Therefore, the treatment of TN by radiation focuses on trigeminal nerve root. At present, there is no unified result on the relationship between the radiation dosage and the treatment effect and complications, and the best radiation dosage of trigeminal nerve has not been determined. At present, the dosage of 70-90 Gy has been proved to be a more reasonable option. Boling et al. reviewed and compared the treatment effect of 80 Gy and 85 Gy dosages on typical TN [50], which revealed that the pain relief effect of 85 Gy group was more lasting than that of 80 Gy group, and the incidence of facial sensory disturbance was not significantly increased. The disadvantage of this method lies in the low rate of relieving pain symptoms and the high rate of recurrence.

### 5.2.5. Trigeminal nerve retrogasserian glycerol rhizotomy (GR)

This method is suitable for the cases of ineffective drug treatment, serious basic diseases, MS, unilateral or bilateral pain and MVD failure. This surgical technique was discovered by Hankanson, a Swedish neurosurgeon, and gradually popularized. This method is safe, effective, repeatable and cost-effective. The disadvantage is that postoperative facial numbness or sensory disturbance will

occur on the affected side, with a high recurrence rate [27].

### 5.2.6. Other Treatments

Although the curative effect of motor cortical stimulation (MCS) and deep brain stimulation (DBS) for nutrireulation remain uncertain, they have been described as possible treatments for refractory TN in previous literatures. It has also been reported that 75-100% of patients with neuropathic pain syndrome can use MCS to relieve pain effectively. Most of the patients in this literature are patients with complex local pain syndrome, and only a few of them are classic TN. Since 1997, DBS has been used to treat pain cases that are difficult to treat with drugs and surgical treatments. The hypothalamus is assumed to be the central mechanism of pain behavior and nerve psychological loop of autonomic nervous system, so it has been the target nucleus of DBS in the treatment of pain. Up to now, there is no evidence suggesting that DBS is the only way to treat refractory TN.

Peripheral nerve or regional electrical stimulation is used to treat refractory chronic pathological pain in a wider range of cases, but there are few literatures supporting its effect on the treatment of TN. However, some small sample size studies have already been reported. In a case report published in 2015, Abd-Elsayed described a TN patient who was intolerable to both conservative drug treatment and trigeminal block. Therefore, after the patients were implanted with peripheral nerve stimulator, the pain was relieved completely and the quality of life was significantly improved. This case study shows that peripheral nerve stimulation is a promising alternative therapy for refractory TN, which is worthy for further studies.

## 6. OUTLOOK

TN is a common cranial nerve disease. At present, the basic researches and clinical treatment of TN have made great progress. Although the pathogenesis of TN is still not fully understood, neurovascular conflict is now a well-known theory. For drug treatment, carbamazepine or oxcarbazepine is recommended as the first choice. Lamotrigine, gabapentin, botulinum toxin A, pregabalin, baclofen and phenytoin can also be used alone or as additional therapy. If the pain cannot be adequately controlled by drugs or the tolerance of drug treatment is poor, surgical treatment is recommended [30]. It is necessary to choose

appropriate surgical treatment according to the specific situation of patients, and provide psychological and nursing support for patients.

## 7. AUTHOR CONTRIBUTIONS

Lingaowa Ta, Xd Wang, Xin Wu contributed equally to this work.

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