Trigeminal Neuralgia

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33.1 Introduction

Trigeminal neuralgia (TN) is a unique and most common facial neuropathic pain disorder characterized by agonizing unilateral paroxysmal pain occurring in one or more divisions of the trigeminal nerve territory [1]. It is generally considered a complex and dynamic disease, leading to a chronic course in more than half of patients. Spontaneous recovery in TN is rare, and the condition is cyclical with periods of partial or complete remission and recurrence.

Apart from experiencing sensory pain, patients with chronic TN are also at high risk for cognitive deficits, with subsequent negative impact on normal socioprofessional life [2]. Hence, along with a neuropathic pain condition, TN must also be considered a social, emotional, and psychologic disorder that requires a personalized and multidisciplinary strategy. In this chapter, we shall review the historical aspects, clinical features and diagnostic criteria, pathophysiology, and various treatment modalities of this rare and unique clinical entity.

33.2 Historical Aspects

The first account of TN in history has been accredited to the earliest descriptions of migraine headache in the second century by Aretaeus of Cappadocia [3]. Approximately 900 years later (AD 1037), Avicenna provided detailed description of facial pain consistent with TN. In 1756, Nicolas André conceptualized the disease in terms of convulsions and termed it "tic douloureux," referring to the characteristic wince associated with pain paroxysm. In 1773, John Fothergill published the first case series of 14 cases describing TN as a clinical entity, thereafter referred to as "Fothergill's disease." In the early nineteenth century, several notable clinicians and anatomists including Charles Bell, Herbert Mayo, and Francois Magendie provided the detailed account of the clinical anatomy and separate functions of the facial and trigeminal nerve. It was then that "tic douloureux" was finally known to be related to some pathophysiological derangement in the trigeminal nerve and hence named "trigeminal neuralgia."

The earliest treatment modalities of TN focused on maintaining an adequate sleep, diet, and exercise, limiting the use of addictions like tobacco and alcohol, and inhalation of trichloroethylene. Surgical treatment of TN by removing the trigeminal (Gasserian) ganglion was first reported by Carnochan in 1858 [4]. In the ensuing years, varied surgical approaches were developed for Gasserian ganglionectomy including the middle fossa approach, the subtemporal approach, and the cerebellar or lateral suboccipital approach by Dandy. Compared to middle fossa approaches, Dandy's posterior fossa approach was relatively bloodless and had lower

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risk of facial paralysis and sensory loss. Furthermore, Walter Dandy was also the first clinician to observe the mass effect and pressure on the trigeminal nerve by neighboring vessels and tumors. Dandy's surgical findings (through naked eyes) were later confirmed by Peter Jannetta in 1967, who became the first neurosurgeon to surgically decompress the trigeminal nerve through posterior fossa approach using an operating microscope. Jannetta recommended decompressing the nerve by moving the offending vascular loop and securing them with a small, nonabsorbent, synthetic Teflon. This leads to the development and worldwide acceptance of the microvascular decompression (MVD) surgery, also referred to as Jannetta's procedure, as the open surgical procedure of choice for treatment of TN.

33.3 Epidemiology

The reported prevalence of actual TN in the literature is that of 0.07% in the general population [5]. The incidence of TN ranges between 4.5 and 28.9 per 100,000 per year, increasing with age and having a slight prevalence in women over men (age adjusted ratio, 1.74:1) [6–8]. Patients usually become symptomatic after 40 years of age, with peak observed between 50 and 80 years. In case patients <40 years of age are symptomatic for TN, a secondary cause for the disease should be suspected, present in approximately 14–20% of TN patients [6].

33.4 Pathophysiology

To date, there is uncertainty about the exact pathophysiology of TN, in view of lack of satisfactory animal models, and the difficulty in obtaining essential data from the physiologic pathways of patients. However, several theories and mechanisms have been proposed to explain the pathophysiology of TN, which resolves around a complex interaction of peripheral and central mechanisms [9–13].

As per the most popular neurovascular compression hypothesis, the pulsatile compression of demyelinated axons by an overlying blood vessel may be responsible for initiating the aberrant impulses in some patients [14]. The term neurovascular conflict (NVC), in general, accounts for a gamut of clinical or radiological findings, ranging in severity from simple contact (without nerve displacement or distortion) to severe compression and/or displacement of the nerve. Historically, it has been believed that vascular compression causes focal demyelination only when the NVC occurs at the transition zone between the central oligodendroglia and peripheral myelin, which is found 2–3 mm from the root entry zone (REZ), also called the Obersteiner-Redlich line. Examination of trigeminal nerve roots from patients with nerve root compression by an overlying blood vessel has revealed focal demyelination in the region of compression, with close apposition of demyelinated axons and an absence of intervening glial processes [11].

The other recognized cause of TN is a mass lesion compressing the nerve. It has been suggested that both structural and morphologic changes that occur in the affected trigeminal nerve may be involved in the pathophysiology of TN [15]. Structural abnormalities, such as axonal loss and demyelination may lead to morphologic changes in the nerve including nerve distortion, deviation, groove formation, and ultimately nerve atrophy as a late consequence of the chronic physical stress by vascular compression. Cheng et al. have found that in patients with idiopathic TN, volume of the affected trigeminal nerve was significantly reduced in comparison to that of the nonaffected side and controls [16]. A small posterior fossa volume may also be a risk factor of NVC [17]. Apparently, posterior fossa overcrowding can lead to a closer nerve vessel relationship, thus leading to a higher incidence of NVC.

Neurovascular compression hypothesis alone may not explain the pathogenetic mechanism of TN, as shown by the very high incidence (up to 39%) of vascular compression at the REZ even in asymptomatic population [18]. Similarly, as many as 11–24% of patients with TN do not show

REZ NVC in magnetic resonance imaging (MRI) scans [19]. Apparently, trigeminal REZ NVC, as detected by MRI, is highly likely to be symptomatic when it is associated with anatomical nerve changes [19].

The ignition hypothesis proposed by Devor and colleagues highlights the role of focal demyelination in the pathogenesis of TN [10]. Focal demyelination of primary sensory afferents primarily contributes to their hyperexcitability. In addition, these groups of afferents are also linked functionally, thus leading to generation of spontaneous ectopic impulses and synchronized high-frequency afterdischarges, responsible for the short-lasting spontaneous TN attacks [10, 11]. The substantial loss of myelin as well as abnormal close apposition of trigeminal axons in the area of injury promotes ephaptic transmission between low-threshold, large-caliber sensory afferents (A-b) and smaller-caliber nociceptive sensory axons (A-d and C fibers) which may account for the paroxysms of intense pain triggered by innocuous stimulation [15]. Again, focal demyelination does not occur in all individuals with the vascular contact, and there must be some individual susceptibility which predisposes to the development of focal demyelination at the REZ by vascular contact, thereby causing TN.

The refractory period between pain paroxysms may be explained by the hyperpolarization of the sensory neurons [10]. Their incomplete remyelination and reduced excitability may further explain the unpredictable periods of complete remission that occur in patients with TN.

Sabalys et al. have suggested that the peripheral pathophysiology of TN may involve progressive dystrophy of the trigeminal nerve branches, caused either by compression of nerve by surrounding vessels or by allergic-immune reaction (mast cell degranulation and histamine release) [12]. This progressive dystrophy then stimulates the central pathogenesis mechanism of neuralgia, involving the reticulate, mesencephalon structures, limbo nuclei, limbic system, and brain cortex. Hyperactivity of primary sensory afferents has been proposed to secondarily induce central sensitization of wide-dynamic-range neurons in the spinal trigeminal nucleus [20].

Central mechanisms may also account for the occurrence of TN in patients with no structural damage on the trigeminal nerve. Current literature also shows that TN induces gray and white matter abnormalities in central nervous system (CNS) areas involved in pain perception, pain modulation, and motor function, which are important for sensory and cognitive-affective dimensions of pain [21, 22]. It is also possible that TN-induced structural alterations can have functional consequences, resulting in central manifestations of TN pain [23].

Demyelination plaques present in the pontine area have long been ascribed as the causative factor in patients with MS presenting with TN (MS-related TN) [24]. However, recent literature suggests a dual, concurrent mechanism, in which both inflammatory demyelination and mechanical demyelination may coexist and damage the primary trigeminal afferents [24, 25]. The other sensory disturbances, including continuous ongoing pain and dysesthesia, may arise from damage to the second-order neurons in the spinal trigeminal complex.

33.5 Etiology

The vascular compression of the trigeminal nerve by the surrounding vessels in the cerebellopontine cistern is the most common etiological cause of TN, seen in up to 80–90% of TN cases. The blood vessels mostly implicated include the superior cerebellar artery (SCA) followed by the anterior inferior cerebellar artery (AICA), posterior inferior cerebellar artery (PICA), vertebral artery, or rarely a tortuous basilar artery [26, 27]. The implication of venous compression alone as a cause of TN remains a matter of debate. As per literature, the rates of venous compression alone TN range from 3.3% to 29% [28]. Superior petrosal vein and its tributaries are the main veins that commonly compress the trigeminal nerve [29].

Posterior fossa tumors (including acoustic schwannomas, meningiomas, epidermoids, and arachnoid cysts) may lead to compression of the trigeminal nerve root either by the tumor itself or by an interposed blood vessel or by distortion of

the contents of the posterior fossa with displacement of the nerve root against a blood vessel or the skull base [12].

Neurovascular compression at the REZ can also be caused by an aneurysm, vessel aggregation, occlusion due to arachnoiditis, and arteriovenous malformation (AVM) [30]. TN caused by cerebral aneurysms has been reported on different aneurysmal locations, namely, SCA, AICA, vertebrobasilar artery, PCA, persistent trigeminal artery, cavernous ICA, and supraclinoid ICA. Posterior communicating artery aneurysms (PComAAs) cause atypical TN most commonly involving the first and second trigeminal distributions [31]. PComAAs also have a higher tendency to cause oculomotor nerve palsy due to their large size.

It has been suggested that morphological and volumetric changes in posterior fossa may play a role in the genesis of NVC [17]. Several cases of TN have been associated with diseases that include crowded posterior fossa either due to lesions or malformations, such as Paget's disease, distorted petrous bone, Chiari's malformation, achondroplasia, and Dandy-Walker malformation.

The risk of TN in patients with MS is 20 times higher than in the general population, with an approximate prevalence of 2–6% [32]. Diabetes mellitus, rheumatism, otolaryngological pathology, and allergy are some other proposed etiologies of TN that have an indirect supporting evidence [12]. A recent study has demonstrated that gain-of-function Na_V 1.6 mutation potentiates transient and resurgent sodium currents, thus leading to increased excitability in trigeminal neurons in TN patient [33].

33.6 Clinical Features and Classification

To date, numerous terminologies and classifications of TN have been proposed from time to time, often leading to confusion among the clinicians and dishomogeneity in the research being carried out. Nonetheless, the recently published classification system and diagnostic criteria for TN make an earnest attempt to solve this dilemma, by providing detailed description of different types and subtypes of TN, based on a consensus statement of the International Association for the Study of Pain (IASP) and the International Headache Society (IHS) [1].

Trigeminal neuralgia (previously described as primary trigeminal neuralgia) is characterized by "recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the TN and triggered by innocuous stimuli, like chewing, brushing teeth, washing the face, shaving, speech touching the affected dermatome or exposure to a cool breeze." The most frequent maneuvers are gentle touching of the face and talking. Recent literature suggests the presence of trigger zones in more than 90% of patients diagnosed with TN [1, 34]. In a study by Di Stefano et al. using three dimensional (3-D) face model, a trigger capable of provoking a paroxysm could be identified in nearly all patients with the diagnosis of TN based on ICHD-3 beta [34]. Trigger zones were most frequently located in the nasal and perioral region and were variable in size. Other than the triggering phenomenon, most patients with TN fail to show sensory abnormalities within the trigeminal distribution unless advanced methods such as quantitative sensory testing are employed [35]. Nonetheless, in a prospective systematic study of clinical characteristics of TN patients, sensory abnormality (particularly hypesthesia) has been reported in up to 29% of patients with TN [6].

Patients may variably experience multiple painful episodes in a day (ranging from 0 to more than 50), each lasting from few seconds to a maximum of 2 min. Following a painful paroxysm, there is usually a refractory period during which pain cannot be triggered. When very severe, the pain often evokes contraction of the muscles of the face on the affected side (tic douloureux). Mild autonomic symptoms such as lacrimation and/or redness of the ipsilateral eye may be present. Nightly attacks are less common in TN than in cluster headache,

where they are a prominent feature. Spontaneous remission from pain can occur for weeks, months, or years [36].

Classical TN (CTN) is defined as TN developing without apparent cause other than neurovascular compression and not simply contact. The morphological changes in the trigeminal nerve root typically involve nerve root atrophy and/or displacement due to neurovascular compression, demonstrated either on MRI or during surgery [16]. CTN usually affects the right side of the face, in the first and second nerve divisions, probably because of the somatotopic distribution of sensory fibers in the trigeminal root [37]. It rarely occurs solely in the first division, unlike postherpetic neuralgia. Bilateral TN is very rare, except for STN in MS (reported frequency of slightly <10%) [5]. Primary bilateral CTN accounts for 0.3–6% of TN cases [38].

Classical TN with concomitant continuous pain (previously described as atypical TN or TN type 2) have features of CTN along with continuous or near-continuous dull background facial pain in the affected trigeminal nerve territory. Continuous pain may arise either as a result of progressive nerve root damage or because of central facilitation of pain processing pathways [20]. Nonetheless, these patients are significantly resistant to both medical and neurosurgical treatment modalities that are generally effective for CTN.

Secondary TN (STN) is caused by an underlying pathology such as tumors in the cerebellopontine angle (CPA), AVM, skull base bone deformity, dural arteriovenous fistula, MS, connective tissue disease, genetic causes of neuropathy or nerve hyperexcitability, and, rarely, fungal infection or bacterial infections [1, 7, 8, 12]. Compared to patients with CTN, sensory abnormalities are present in significant majority of these patients. In addition to neuroimaging, routine electrophysiological studies such as blink reflex (BR) or trigeminal evoked potentials are also helpful in evaluating STN [7, 39]. Electrophysiological testing of trigeminal reflexes has been able to differentiate CTN from STN with a high degree of sensitivity (96%) and specificity (93%) [39].

The term idiopathic TN (ITN) denotes cases with no abnormality detected either during neuroimaging or during electrophysiological testing. Though NVC may be observed in MRI (a common finding in healthy subjects as well), there is no evidence of any concomitant nerve root atrophy and/or displacement.

Patients with severe, long-standing, and medically intractable pain are at a high risk for cognitive impairments and social withdrawal, which may negatively impact their quality of life. A conscious effort to avoid touching of trigger zones on face ultimately leads to poor personal hygiene along with significant dehydration and weight loss. Furthermore, patients may experience depression, anxiety, mood disorders along with dysfunction in memory, psychomotor speed, reaction time, complex attention, cognitive flexibility, and general cognitive functioning [2]. Cheng et al. have demonstrated the prevalence of depression in patients with TN to be 64.8%, higher than in general population (5–8%) [40]. Female, high pain intensity, ineffective medical treatment, single patients (compared to the married), and patients who were unemployed were at a significant risk for depression and anxiety. Considering these psychological ill effects of the disease, TN has also been called the "suicide disease."

33.7 Diagnosis

Though the symptomatology seems fairly straightforward, clinical diagnosis is often very complex, as the symptoms are frequently mistaken for dental or jaw pain, leading to unnecessary radiological investigations and surgical interventions. In the absence of definitive laboratory or diagnostic tests, the diagnosis of TN is primarily clinical and is determined by a careful history. Investigations including radiological imaging are needed to establish the likely etiology. The latest diagnostic criteria of TN are as per ICHD-3 [1]. The common differential diagnosis for TN includes other cranial neuralgias, trigeminal autonomic cephalalgias, and painful ophthalmoplegias (Table 33.1) [5, 7, 8, 41].

Table 33.1 Differential diagnosis of trigeminal neuralgia [5, 7, 8]

Cranial neuralgias • Glossopharyngeal neuralgia • Hemifacial spasm • Nervus intermedius neuralgia • Tic convulsif • Vagal neuralgia
Trigeminal autonomic cephalalgias • Cluster headaches • Chronic paroxysmal hemicrania • Hemicrania continua • Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) • Short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (SUNA)
Painful posttraumatic trigeminal neuropathy
Persistent idiopathic facial pain
Painful trigeminal neuropathy attributed to acute herpes zoster
Painful trigeminal neuropathy caused by a connective tissue disease or genetic disorder
Painful ophthalmoplegia • Tolosa-Hunt syndrome • Ocular diabetic neuropathy • Ophthalmic herpes zoster • Ophthalmoplegic migraine
Odontogenic facial pain • Cracked tooth • Caries or pulpitis

33.8 Role of Neuroimaging

The broad spectrum of arterial and venous vessels involved in the pathophysiology of TN necessitates use of a highly sensitive and reliable diagnostic imaging modality to clarify the diagnosis as well as to prepare for the specific anatomical details for surgery. Special high-resolution isotropic 3-D MRI reconstruction sequences which have been shown useful in identifying vascular compression include constructive interference in steady-state (CISS) MRI imaging (for a detailed anatomical examination of the cisternal and cavernous segments of the trigeminal nerve) and time-of-flight magnetic resonance angiography (TOF-MRA) (for visualization of arteries) [42]. In addition to confirming the diagnosis, preoperative imaging may help in surgical decision-making by determining the need of an endoscopically assisted MVD in patients with unclear surgical anatomy [43].

Recently introduced diffusion tensor imaging (DTI) provides better understanding of microstructural tissue changes of the trigeminal nerve root, while fiber tractography helps to measure focal demyelination and edema [44]. Thus, the addition of comprehensive presurgical DTI assessment of trigeminal nerve in patients with TN may play a prognostic role in predicting treatment success by MVD [23].

In the setting of persistent or recurrent pain after MVD, postoperative imaging may allow assessment of the relationship of the nerve, vessel, and interposed pad, pledget, or sling (depending on method of decompression) and for additional sources of NVC or masses compressing on the nerve (e.g., Teflon granulomas and dense arachnoid adhesions).

33.9 Measurement of Trigeminal Neuralgia Pain

To date, multiple scales have been developed to rate and quantify TN. However, their limited use and lack of uniformity have made it difficult to compare the outcomes of varied interventions across multitude of studies. Five commonly used scales to measure TN pain includes the visual analog scale, numeric rating scale, McGill Pain Questionnaire, Barrow Neurological Institute Pain Intensity Score (BNI-PS), and Penn Facial Pain Scale (PFPS).

The BNI-PS is an easy-to-use scale with excellent face validity [45]. However, it is useful only for clinicians to classify patient pain control and medication intake and is not focused on patient's pain perceptions. Recently, the PFPS has been proposed to assess patient's pain and treatment outcomes [46]. PFPS includes a Brief Pain Inventory and seven additional items specific for facial pain disorders, validated by a group of TN experts, and thus seems a solid option for pain measurement in TN.

33.10 Multimodal Management of Trigeminal Neuralgia

Although the exact origin of TN remains elusive, the unique nature of the symptoms and inciting events of this disease have led to the development

Table 33.2 Treatment modalities of trigeminal neuralgia [1, 5, 8, 36, 47–56]

Pharmacological	First line: carbamazepine, oxcarbazepine Second line: baclofen, lamotrigine, pimozide Add-on medications: gabapentin, pregabalin, topiramate, levetiracetam, botulinum neurotoxin type A, topical formulations (phenytoin, ketamine, baclofen, lidocaine)
Interventional	
Peripheral nerve procedures	Infraorbital nerve block Greater occipital nerve block
Percutaneous ablation techniques	Percutaneous balloon compression Percutaneous radio-frequency thermocoagulation Percutaneous glycerol rhizotomy
Radiosurgery	External beam stereotactic radiosurgery Gamma Knife radiosurgery (Gamma Knife®) Linear accelerator radiosurgery CyberKnife
Surgical intervention	Microvascular decompression
Neuromodulation techniques	Peripheral nerve stimulation (supraorbital nerve, infraorbital nerve, and the greater occipital nerve pulsed stimulation) Transcutaneous electrical nerve stimulation Subcutaneous peripheral nerve field stimulation Gasserian ganglion pulsed stimulation Cervicomedullary junction stimulation Noninvasive brain stimulation (repetitive transcranial magnetic stimulation or transcranial direct current stimulation) Motor cortex stimulation Deep brain stimulation

of numerous treatment modalities over the years (Table 33.2). These modalities broadly include medications that affect nerve conduction, peripheral denervation techniques, and surgical decompression of the site of NVC. Though these therapies can provide pain control in most of the cases, their clinical efficacy may vary over time, and many patients need more than one treatment to achieve effective pain control [1, 5, 8, 36, 47–56]. Furthermore, before starting any treatment, the neuropsychological evaluation of patients suffering from chronic pain should also be taken into account. A dynamic and personalized multimodal approach of treatment is then formulated, taking into account all the available TN therapies and the neuropsychologic support to patient. The goal of treatment is to have a patient completely pain-free at an acceptable level of side effects and without fear of its sudden recurrence.

33.11 Pharmacological Management

Pharmacological therapy is the mainstay treatment for TN since it generally carries a lower risk compared with major surgical procedures and is suitable for medically compromised patients who are unfit for such procedures [36, 47, 48]. However, there remain few subtypes such as postherpetic neuralgia of the trigeminal nerve, posttraumatic or surgery-related supraorbital or infraorbital nerve neuralgia, MS or space-occupying lesion-related TN, which resemble neuropathic pain conditions with a high risk of failure of medical therapy [57].

Before starting therapy, an accurate medical history (in order to exclude cardiac disease, pregnancy, and other possible relevant medical conditions) and laboratory analysis of kidney and liver function tests are essential [8]. Laboratory testing should be also repeated if higher doses are used and significant side effects are reported. ECG is needed when a cardiac conduction abnormality is suspected on the basis of medical history, because both first-line medications (carbamazepine and oxcarbazepine) are contraindicated in patients with atrioventricular block.

To date, numerous drugs including anticonvulsants such as carbamazepine, oxcarbazepine, phenytoin, gabapentin, valproic acid, pregabalin, topiramate, clonazepam, levetiracetam, lamotrigine, and lacosamide, muscle relaxants such as baclofen and tizanidine, antipsychotics (pimozide), local anesthetics (lidocaine and proparacaine),

misoprostol (prostaglandin E1 analog), and antiarrhythmics such as tocainide have been investigated as the treatment options in TN [47–50, 58].

Patients with TN frequently have an excellent response to some selected drugs. However, this efficacy is often limited by their disabling side effects, causing either treatment withdrawal or a dosage reduction to an insufficient level in many patients. Hence, it's imperative for the physician to be acquainted with the side effects and dose management of these drugs and the alternative options available (Table 33.3).

Table 33.3 Commonly used medications for trigeminal neuralgia [5, 7, 8, 36, 47–50]

Drug	Main mechanism of action	Starting dose	Titration	Max dose	Main adverse events
Carbamazepine	Voltage-gated sodium channel blocker	200 mg	Increase 200 mg every 3 days	1200 mg (400 mg) (t.i.d.)	Neuropsychologic side effects: drowsiness, ataxia, and a significant reduction of postural stability and alertness Other commonly reported side effects: skin reactions, nausea, vomiting, elevation of transaminases, hyponatremia Serious but uncommon side effects: myelosuppression, leukopenia, irreversible aplastic anemia, hepatotoxicity, lymphadenopathy, systemic lupus erythematosus, Stevens-Johnson syndrome Potent enzyme inducer-accelerated metabolism of concurrently prescribed anticonvulsants, tricyclic antidepressants, antipsychotics, steroid oral contraceptives, glucocorticoids, oral anticoagulants, cyclosporin, theophylline, chemotherapeutic agents, and cardiovascular drugs Short half-life—needs to be administered 3–4 times a day
Oxcarbazepine	Voltage-gated sodium channel blocker	300 mg	Increase 300 mg every 3 days	1800 mg (600 mg) (t.i.d.)	Allergic cross-reactions with carbamazepine Drowsiness Ataxia Dizziness Hyponatremia (6–8% of patients) Transaminase induction

Table 33.3 (continued)

Drug	Main mechanism of action	Starting dose	Titration	Max dose	Main adverse events
Lamotrigine	Acts at voltage-sensitive sodium channels, stabilizes neural membranes, and inhibits the release of excitatory neurotransmitters	25 mg	Increase 25 mg every 7 days	400 mg (200 mg) (b.i.d.)	Dizziness Nausea Headache Blurred vision Vertigo Ataxia Skin rash (7–10% of patients) Stevens-Johnson syndrome (one in 10,000 patients)
Baclofen	Depresses the excitatory synaptic transmission in the spinal trigeminal nucleus	15 mg (5 mg) (t.i.d)	Increase 5 mg t.i.d. every 3 days	60–80 mg/day, administered 3–4 times per day	Lassitude Drowsiness Dizziness Nausea Gastrointestinal discomfort Nausea Constipation Hypotension Withdrawal symptoms on abrupt discontinuation with seizures and hallucinations
Gabapentin	GABA receptor agonist, binds to alpha$_2$-delta subunits of voltage-gated calcium channel inhibiting the release of excitatory neurotransmitters	300 mg/day	Increase 300 mg every 2–3 days	3000 mg (1000 mg t.i.d.)	Drowsiness Unsteadiness Nausea Headache Confusion Weight gain Peripheral edema Hyperlipidemia
Pregabalin	Analog of GABA, structurally related to gabapentin Binds to alpha$_2$-delta subunits of voltage-gated calcium channel	75 mg	Increase 75 mg every 3 days	600 mg (300 mg b.i.d. or 200 mg t.i.d.)	Drowsiness Unsteadiness Weight gain Peripheral edema

(continued)

Table 33.3 (continued)

Drug	Main mechanism of action	Starting dose	Titration	Max dose	Main adverse events
Botulinum neurotoxin type A	Blocks acetylcholine release from presynaptic nerve endings by interfering with the activity of SNARE (soluble *N*-ethylamide-sensitive factor attachment protein receptors) proteins Causes local release of antinociceptive neuropeptides such as substance P, glutamate, and CGRP	–	Mean dose: 3.22 units/cm^2 subcutaneously can be administered intradermally and/or submucosally	20–75 units	Transient facial weakness Focal edema Dysphagia Myasthenia Allergic reactions

Current evidence supports the use of both carbamazepine and its keto-analog oxcarbazepine as first-line pharmacological treatment in TN, initially effective in approximately 90% of patients [47, 48, 59, 60]. However, oxcarbazepine is generally preferred for better tolerability and decreased potential for drugs interactions [59, 60]. The effectiveness of carbamazepine and oxcarbazepine reflects the primary mechanism of paroxysmal pain in TN, i.e., the focal demyelination of primary afferents near the REZ. Both drugs block voltage-gated sodium channels in a frequency-dependent manner, stabilizing hyperexcitable neural membranes and inhibiting repetitive firing, thus reducing both the intensity and frequency of attacks.

Although generally considered effective, these treatments are limited by poor tolerability, the need for well-managed titration, and potential for significant drug interactions [60]. Hence, the doses of the chosen drug should be gradually increased to the maximum allowed daily dose until adequate relief is acquired. Apparently, after a period of stability at a given dose, these medications may lose their efficacy owing to their metabolism consequent to hepatic enzyme induction, thus necessitating even higher doses. Nevertheless, in case patient is having the maximum prescribed dosage of first-line medications without attaining adequate pain relief, it is unlikely that any other medication would be effective. Hence, in these patients surgical MVD should be proposed as second line of management [5, 8].

However, there still remain some patients who are either unable to take carbamazepine or oxcarbamazepine as a result of contraindications or may require their discontinuation because of certain side effects (allergic dermatitis, aplastic anemia with carbamazepine, and CNS depression [more frequent with carbamazepine than oxcarbazepine]). In such subset of patients, second-line medications, including baclofen, lamotrigine, and pimozide, may be beneficial [59].

While patients with TN manifesting with purely paroxysmal pain find adequate relief from carbazepine or oxcarbamazepine, patients suffering from continuous pain between the paroxysms are more resistant to these drugs. Though never tested clinically in a trial, both gabapentinoids and antidepressants are expected to be more efficacious in continuous than paroxysmal pain and are often used as an add-on treatment in this patient population [5].

Baclofen and misoprostol have been most frequently used in patients with MS-related TN. However, recent literature review suggests that the same pharmacological management approach should be used for MS-related TN as recommended for non-MS TN (carbamazepine or oxcarbazepine as the first-line medications and lamotrigine, baclofen, gabapentin, and pregabalin as second-line drugs), as it would help to reduce side effects and potential exacerbations of existing MS symptoms [58].

Topical formulations of analgesics (lidocaine, ketamine, baclofen) have certain advantages, such as lack of side effects, no drug-drug interactions, and higher concentrations of active compound at the pain area, over other systemic medications. Intraoral application of 8% lidocaine is found to drastically reduce paroxysmal pain without serious side effects, thus simplifying the treatment of TN [61]. Phenytoin in topical formulation has been found to act synergistically with other active analgesics in topical formulations (e.g., compounded ketamine 10% cream and baclofen 5% cream), causing faster onset of action, longer duration of analgesia, and intensified pain-relieving effect [62]. Furthermore, phenytoin might be able to reinstate reduced analgesic effect seemingly related to tolerance.

Chemo-denervation with botulinum toxin type A (BoTN-A) has also been found to be useful for treatment of drug-resistant ITN, in terms of efficacy and safety [63, 64]. BoTN-A is a potent neurotoxin that blocks acetylcholine release from presynaptic nerve endings by interfering with the activity of SNARE (soluble N-ethylamide-sensitive factor attachment protein receptors) proteins [63]. This appears to be mediated by the local release of antinociceptive peptides and inhibition of central as well as peripheral sensitization. Current literature supports a moderate evidence regarding the efficacy of BoTN-A in treating trigeminal and postherpetic neuralgia [63]. However, caution should be taken while injecting the drug, as it can lead to unwarranted paralysis, if injected in or spread to the wrong muscle group. Even conventional injection has the possibility to cause dysphagia, myasthenia, or allergic reactions.

Nav1.7 is a sodium ion channel present in the nociceptive neurons at dorsal root ganglion and the trigeminal ganglion. BIIB074, a voltage- and frequency-dependent selective Nav 1.7 sodium channel blocker, has recently been investigated for its safety and clinical efficacy in patients with TN [65]. Overall, BIIB074 seem to have better tolerability profile compared with other drugs used in TN, with lower reported frequency of cognitive impairment and drowsiness.

To date, there have been several meta-analyses which conducted pair-wise comparisons between the abovementioned drugs. However, the lack of a systematical comparison makes the results of each study incomplete, inconclusive, and sometimes contradictory. Moreover, there is a paucity of randomized controlled trials (RCTs) with adequate sample size which hampers the generalizability of trial results. In terms of therapeutic efficacy, a recent systematic review using comprehensive system of comparison and network meta-analysis has suggested using lidocaine, BoTN-A, and carbamazepine as the first possible choice for clinical application [48].

33.11.1 Treatment of Acute Exacerbation

In patients who develop severe exacerbations of unremitting pain, in-hospital treatment may be necessary for intravenous drug therapy, rehydration, and management of hyponatremia (seen with carbemezepine and oxcarbemezepine). Intravenous fosphenytoin is preferred over phenytoin because of better parenteral tolerance [66]. Moreover, the combined use of intranasal local anesthetic (LA) application and intravenous fosphenytoin also seems to be an effective acute pain control therapy [67].

33.12 Neurosurgical Management

Though pharmacologic treatment remains the first-line therapy for TN, surgical intervention may become imperative for patients who are either refractory to pharmacotherapy or are

unable to tolerate medications owing to their adverse effects. Furthermore, patients with psychiatric conditions, vascular disease (cardiovascular, cerebrovascular, or peripheral vascular disease), hepatic disease, or renal disease are often on polypharmacy that may negatively interact with TN medications, thereby limiting the pharmacological treatment option.

At present many surgical techniques, ranging from minimally invasive stereotactic-based Gamma Knife radiosurgery (GKRS) to more invasive percutaneous ablative procedures and surgical MVD, and the latest neuromodulation techniques are available within the armamentarium of a neurosurgeon. Surgical treatment modalities either aim to decompress the nerve (as is done in MVD) or disrupt the afferent pain fibers in trigeminal nerve complex (denervating procedures). Percutaneous ablative procedures [percutaneous radio-frequency thermocoagulation (RFT), percutaneous glycerol rhizotomy (PGR), or percutaneous balloon compression (PBC)] and stereotactic radiosurgery (SRS) are primarily denervating procedures. Purposeful denervation is sometimes carried out during surgical MVD, either when the offending vessel is deforming the nerve and is hard to mobilize, or not present at all [36].

Surgical aneurysmal clipping provides complete trigeminal pain relief in all patients with intracranial aneurysms as the etiological cause. For patients with MS-related TN, there is insufficient evidence at present to either support or refute the effectiveness of surgical interventions [58]. However, considering the plausible dual-concurrent mechanism of pathophysiology of MS-related TN, surgical options (including ablative procedures) should be considered if pain control is poor with medications alone [25, 58, 68].

33.12.1 Intraoperative Monitoring

Neurophysiological monitoring during neurosurgical interventions for TN plays an important role not only in the protection of cranial nerve function but also in the prediction of clinical outcomes [69]. Commonly used intraoperative neuromonitoring techniques used includes brain stem auditory evoked potentials (BAEPs), brain stem trigeminal evoked potentials (BTEPs), electromyography free run, BR, and direct trigeminal and facial nerve stimulation.

Vestibulocochlear nerve is at greatest risk of injury, and implementing intraoperative neuromonitoring, specifically with BAEPs, may reduce the risk of hearing loss postoperatively [69, 70]. BTEPs are a neurophysiological monitoring technique which reflects the function of trigeminal nerve, trigeminal nerve nuclei, and trigeminal nerve conduction pathway. These are not affected by general anesthetics, muscle relaxants, or the consciousness of the patient and hence can monitor trigeminal nerve function in clinical application. With the assistance of BTEP, affected nerve fibers and offending vessels can be accurately localized, which may improve surgical efficacy and reduce the occurrence of complications after MVDs [71]. As evaluated by Zhu et al., the improvement and restoration of BTEP waveforms are closely related to the postoperative curative effect, thus providing guidance for MVD surgery and prognosis evaluation [72].

Intraoperative BR recording, obtained by the electrical stimulation of the supraorbital nerve, might be useful in monitoring the sensory part of the trigeminal nerve, the brain stem connections, and the facial nerve during MVD for TN [73].

33.12.2 Percutaneous Ablative Procedures

33.12.2.1 Peripheral Nerve Procedures

Peripheral nerve procedures, such as nerve blocks, have been used as diagnostic tests and can be effective for many of the patients who are refractory to medical therapy or are awaiting MVD surgery. Commonly performed nerve blocks for TN includes either infraorbital nerve blockade or blocking one or more of the occipital nerves (including greater occipital nerve) [54]. Peripheral nerve blockade for pain suppression is based on the ability of low concentrations of LA to selectively block sensory fibers in

mixed nerves. Ethyl alcohol injected peripherally in the vicinity of the three divisions of the trigeminal nerve at their respective foramina under LA offers transient symptom relief. The procedure is, however, painful with discomfort lasting several days, and fibrosis makes repeat injections technically difficult.

Cryoablation of the peripheral branches of the trigeminal nerve at the infraorbital or the mandibular foramen produces a reliable nerve block with reversible loss of sensation and no aggravation of symptoms [52, 74]. In cryosurgery, a cryoprobe with either nitrous oxide or liquid nitrogen (as a refrigerant) is applied at −50 to −140 °C, in the same way as a needle for a nerve block at the infraorbital or mental foramen, by an intraoral approach. Complete analgesia is achieved within 10–14 days of procedure [74]. However, recurrences have been observed as early as 6–8 months after treatment.

Transient sensory loss and motor weakness appear to be the main disadvantages of peripheral ablative techniques, and pain is expected to recur in most patients.

33.12.2.2 Sphenopalatine Ganglion Blockade

The sphenopalatine ganglion (SPG) is an autonomic ganglion located in close proximity to the maxillary division of trigeminal nerve in the pterygopalatine fossa. SPG blockade through intranasal lidocaine application in the nostril ipsilateral to the pain has been shown to provide temporary relief in TN [75]. Recently, an SPG blockade device called the Tx360 has been designed to minimize discomfort and side effects from the traditional noninvasive cotton swab applicators and the inaccuracy of a nasal spray [76].

33.12.2.3 Percutaneous Procedures for the Treatment of Trigeminal Neuralgia

Percutaneous procedures are minimally invasive and an effective treatment alternative for patients with medically refractory TN, who are either unfit or not willing for more invasive surgical MVD. These approaches center on three types of lesioning methods to disrupt aberrant neuronal activity in the trigeminal nerve complex: mechanical compression by balloon inflation during PBC, chemical lesion by injection of high-concentration glycerol during PGR, and thermocoagulation by radio frequency during RFT [52–54].

The procedures are generally performed either under general anesthesia (GA) or under conscious sedation with short-acting agents such as propofol (for RFT and PGR). The patient is positioned supine with head in 15° of extension. All procedures rely on Hartel's anatomical landmarks to gain entry into the foramen ovale, an oval-shaped opening in the middle cranial fossa located at the posterior base of the greater wing of the sphenoid bone (Fig. 33.1). Percutaneous cannulation of the foramen ovale provides direct access to Meckel's cave, which is a space between two layers of the dura mater at the petrous apex. It contains the Gasserian ganglion, trigeminal cistern, and postganglionic trigeminal rootlets. Dynacomputed tomography and neuronavigation systems may be used to improve visualization and navigation of the cannula to the foramen ovale, especially for patients with anatomic variants. Entry into the trigeminal cistern may at times result in flow of cerebrospinal fluid (CSF) through the needle, which was earlier thought to be associated with better treatment outcomes

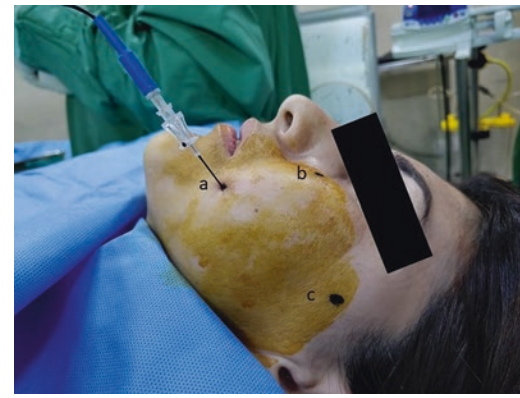

Fig. 33.1 Figure showing percutaneous radio-frequency thermocoagulation needle entering at the skin insertion point, 2.5 cm lateral to the corner of the mouth (a) and following a trajectory toward a point in line with the medial ipsilateral pupil (b) and 3 cm anterior to the external auditory meatus (c)

after PGR [77]. However, recent studies refute any correlation between the presence of CSF flow during needle placement with either the success rate or duration of pain relief [68, 78].

During percutaneous ablative procedures, mechanical stimulation or compression of the trigeminal ganglion (upon needle entry into the foramen ovale or advancement and inflation of balloon) may result in a transient trigeminal depressor response with significant bradycardia and hypotension. Hence, atropine is usually administered prophylactically, except during PBC, where the response is monitored to assess for adequacy of trigeminal compression. Nonetheless, intravenous atropine should be ready for emergent use, and an external transcutaneous or transesophageal pacemaker may be placed preoperatively or after anesthetic induction.

Percutaneous Balloon Compression PBC is performed under GA. A 14-gauge needle is advanced under fluoroscopic guidance until the foramen ovale is entered. A straight guiding stylet is now introduced through the cannulae, till its tip reaches 10–15 mm beyond the needle tip at foramen ovale. Once correctly positioned, the stylet is removed, and a no. 4 balloon catheter is introduced in the same place as the guiding stylet. The balloon is now inflated for 60–90 s with 0.75–1.0 mL of radiocontrast dye to attain a target pressure of 750–1250 mm Hg. According to Chen et al., 90 s of compression provides better long-term results, without apparent added complications [79]. The balloon assumes a classic pear-like shape when correctly positioned and inflated, thus ensuring the safety and maximum success of the procedure. The balloon is now deflated and taken out together with the cannula. The skin entrance site is then compressed for some time followed by sterile dressing. An ice pack may be applied to reduce postoperative swelling of the cheek.

Radio-Frequency Thermocoagulation This procedure involves controlled, selective thermocoagulation lesioning of the trigeminal nerve root complex. A radio-frequency electrode is passed through the 20-G cannula, with its tip into Meckel's cave at the level of foramen ovale (Fig. 33.2). The third, second, and first divisions of trigeminal nerve are then stimulated at 0.2–1 V at 50 Hz (0.2 ms) in sequence by slowly advancing the needle tip by 2–4 mm. A combination of electrophysiological motor and sensory nerve root testing and neuronavigation technology may be used to identify the exact trigeminal nerve division. Lesioning is then done using a thermocouple at 55–75 °C for 30 s to 2 min. In comparison with the conventional RFT, use of pulsed radio-frequency current involves short stimulation bursts at similar temperature but with less thermal damage to the tissues. However, the best treatment results have been obtained with a combination of pulsed radio-frequency and RFT treatments in succession than by either modality alone [80].

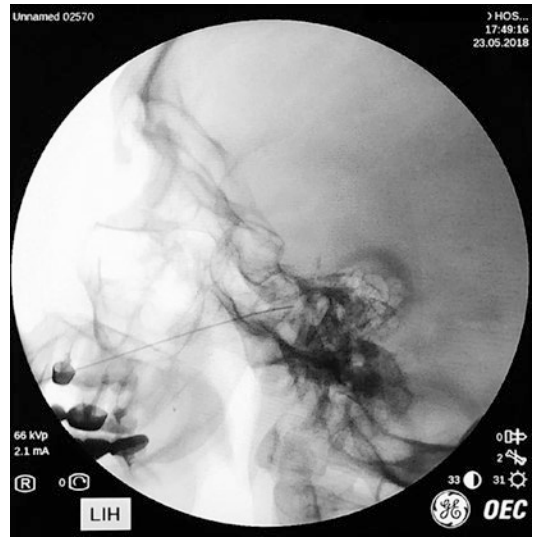

Fig. 33.2 Figure showing the correct position of the tip of radio-frequency thermocoagulation electrode into Meckel's cave, at the level of foramen ovale

Percutaneous Glycerol Rhizotomy PGR is performed by injecting 0.25–0.40 mL of anhydrous glycerol into the cistern of Meckel's cave. After the injection, the patient is made to sit in the upright position to avoid spillage of glycerol out of the cistern. The trigeminal depressor response may be observed again upon injection of glycerol and needs to be managed.

Table 33.4 Complications of percutaneous ablative procedures [36, 52–54, 79, 81]

Percutaneous balloon compression	Percutaneous radio-frequency thermocoagulation	Percutaneous glycerol rhizotomy
• Postoperative facial numbness (4.6% of cases) • Herpes simplex labialis (33.1%) • Masseter weakness (3.4–6.2%) • Dysesthesias (2.8–11.4%) • Hearing and olfactory disturbances • Diplopia (1.6%) • Diminished corneal reflex (0–2.3%) • Conjunctivitis (3.1%) • Anesthesia dolorosa (rarely) • Corneal keratitis (rarely) • Arteriovenous fistula development (rarely) • Meningitis (rarely) • Intracranial hemorrhage (rarely)	• Mild to moderate postoperative facial numbness (>90%) • Anesthesia dolorosa (0.5–25%) • Deficit of the corneal reflex (1–35%) • Corneal keratitis (0–20%) • Dysesthesia (1–24%) • Masseter weakness (8–65%), mostly transient • Diplopia (0.2–4%) • Meningitis • Carotid-cavernous fistula formation • Intracranial hemorrhage (rarely)	• Postoperative facial numbness (60%) • Mild to moderate hypalgesia (seen in up to 70% cases) • Trigeminal hyperesthesia (in 20% of cases) • Corneal anesthesia (0–16%, average 8.1%) • Herpes reactivation (up to 77% cases) • Anesthesia dolorosa (0–5.0%) • Masticatory weakness (0–4.1%) • Hearing loss (1.9%) • Meningitis (1.5%) • Corneal keratitis (rarely) • Intracranial hemorrhage (rarely)

33.12.2.4 Procedural Complications

The close anatomical location of the brain stem and internal carotid artery to the foramen ovale and the trigeminal depressor response observed upon its engagement lead to a plethora of complications during the percutaneous ablative procedures. Though the reported periprocedural mortality is very low (0–0.2%), other commonly encountered complications include hearing loss, postoperative facial numbness or hypesthesia, dysesthesias, masseter weakness, anesthesia dolorosa, corneal hypesthesia, keratitis, cranial nerve palsy, arteriovenous fistula development, carotid-cavernous fistula formation, CSF leak, meningitis, herpes simplex labialis, and, rarely, intracranial hemorrhage [36, 52–54, 81, 82] (Table 33.4). Compared to other treatment modalities, these procedures are associated with a high recurrence rate [81].

33.12.2.5 Selection of Procedure

The existing literature on percutaneous ablative procedures consist of single-center prospective observational or retrospective studies, without a single RCT comparing the three techniques. Furthermore, each procedure has operator-dependent technical variations (such as the level of pressure achieved and duration of compression by balloon during PBC, the amount of glycerol injected into Meckel's cistern during PGR, and the type of electrode and radio-frequency current used for RFT) that limit comparisons via a formal meta-analysis. Hence, the best treatment modality out of three is still dubious, with each technique having its own merits and limitations.

Tatli et al. reviewed 28 studies with at least 5 years of follow-up data on varied surgical techniques for treatment of TN, including MVD, RFT, PBC, PGR, SRS, and partial sensory rhizotomy [83]. As per the review findings, PBC and MVD had similar efficacy and much superior effects compared to those of the other modalities ($P < 0.001$). RFT provided a high rate of initial pain relief but was also associated with the greatest number of various complications and high treatment failures. In comparison, PGR was associated with both low initial pain relief as well as high pain recurrence rates. Among all the surgical techniques, MVD provided the highest success rate and long-term pain relief. According to another review of the three procedures by Cheng et al., PBC provided pain control rates of up to 91% at 6 months and 66% at 3 years, while RFT provided initial pain relief in up to 97% of patients, with only 58% of patients being pain-free at 5 years. PGR offered similar pain-free outcomes of 90% at 6 months and 54% at 3 years but with higher complication rates (25% vs. 16%) compared with PBC [81].

Of the three percutaneous procedures, RFT allows somatotropic nerve mapping and is most division-selective. In general, RFT preferentially damages the small unmyelinated pain fibers which mediate nociceptive pain transmission. Compared to PBC and PGR, RFT carries a higher risk of corneal deafferentation and keratitis, especially with higher lesioning temperatures and in uncooperative patients. On the other hand, PBC and PGR preferentially damage medium and large myelinated pain fibers, sparing the smaller ones. PBC is a safe and effective treatment, especially suitable for patients with persistent or recurrent TN after MVD and first division (ophthalmic) TN pain [84]. In the long-term follow-up of patients treated with PBC, 62% of patients had successful relief from one procedure that persisted for at least 7 years [79]. However, it is associated with significant bradycardia and hypotension and requires GA, thus making it less appropriate for patients with medical (esp. cardiac) comorbidities. On the other hand, RFT or PGR may be preferred for a modest denervation, with acceptable pain relief and minimal side effects (less motor denervation, cheek hematoma, diplopia, avoidance of GA) than with PBC [85]. Nonetheless, controlled lesioning by RFT may be difficult to perform in elderly and uncooperative patients.

To conclude, the procedure of choice is individualized for each patient, considering the expertise of the operator and the advantages and disadvantages of each procedure.

33.12.3 Microvascular Decompression

MVD surgery targets the NVC at the nerve REZ of the trigeminal nerve via a retrosigmoid approach to the CPA in the lateral decubitus position [14]. The primary aim of the surgery is to relieve the conflict between the offending vessel and nerve and to maintain this separation in order to avoid surgical failure. The separation techniques are broadly classified as either "interposing techniques" or "transposing techniques." The interposing techniques involve placing a material between the vessel and the nerve, such as autologous tissue (muscle, fascia, or arachnoid membrane), Teflon, Surgicel, Gelfoam, cotton pads, surgical glue, radiopaque sponge, Silastic ring, and Sundt clips. The transposing techniques (also known as sling techniques) consist of repositioning of the offending vessel with the purpose of avoiding the contact between the two, using either Prolene stitch, aneurysm clips, or titanium bone fixation plates.

Original procedure, as described by Jannetta, involved placing of Teflon pledgets, in view of its good nervous tissue compatibility and soft and elastic fiber structure, thus acting as an effective "shock absorber" [14]. However, the review of cases with surgical failures have revealed the presence of severe adhesions and Teflon granulomas (reported incidence of 1.2–5%), suggesting that it is not absolutely inert and may induce an inflammatory foreign body reaction [69, 86]. Henceforth, in recent years, there is a trend toward an increase in the use of transposition techniques to prevent recurrence.

The ideal surgical management of patients with NVC involving SPV is still dubious [26, 29, 87–89]. Pathmanaban et al. have reported that the incidence of venous infarction associated with SPV obliteration during MVD surgery is <0.5%, with an overall rate of venous complications of 2.7% [87]. SPV sacrifice, thus, may be used where necessary to optimize visualization of the REZ and maximize the chance of effective decompression of the trigeminal nerve. On the other hand, there are many reports in the literature relating both minor and life-threatening complications to SPV sacrifice during MVD [88, 89]. These include brightly colored visual hallucinations and contralateral hearing loss due to venous congestion in the inferior colliculus, facial nerve palsy secondary to ischemia in the middle cerebellar peduncle, sigmoid sinus thrombosis with cerebellar hemorrhage, and vasogenic edema or infarcts in the midbrain and pons causing hemiparesis. During MVD, Liebelt et al. have reported complications secondary to venous congestion in 4.8% of patients when SPV was coag-

ulated and divided to gain better exposure to the nerve REZ, while no such complications were observed in patients in whom the SPV was preserved intraoperatively [89]. Authors, thus, advocate preserving the SPV unless it is deemed absolutely necessary for successful cranial nerve decompression. Alternatively, one may intraoperatively assess the safety of venous sacrifice using either temporary clipping of the SPV while monitoring for BAEPs or assessing the collateral venous drainage with indocyanine green. The use of fully endoscopic or endoscope-assisted microsurgery with and without angled optics may further minimize the extent of venous sacrifice required to obtain optimum visualization during MVD [43].

MVD offers an excellent initial pain control at the rate of 76.4–98.2% along with long-term durability, with 70% of the patients having an excellent result 10 years after surgery and a 73.4% of patients being pain-free at 15 years [30, 69, 83, 90, 91]. Pain relief after MVD is generally instantaneous, although a delay of up to 1 month has been reported. A greater degree of neurovascular compression, greater nerve atrophy, and presence of preoperative trigger points have been associated with better long-term outcomes in some studies [16, 30, 90].

Though MVD is considered safe and an effective treatment option for patients with PBTN, bilateral pain is, nonetheless, correlated with worse outcomes [90]. With regard to the side that should be treated first in patients with PBTN, selection should be based on the severity of pain and 3-D TOF-MRA findings [28]. The role of MVD in patients without NVC is not yet clearly defined [58, 91].

33.12.3.1 Complications

Despite being most invasive procedure, MVD is safe in experienced hands, with a reported mortality rate of 0.15–0.8% [51]. Other perioperative complications reported in the literature include postoperative transient or permanent cranial nerve palsies (i.e., trochlear, oculomotor, or facial nerve palsies, 0.66%), facial dysesthesia (2.30%), hearing loss (1.51%), vertigo (3.53%), aseptic meningitis (11%), CSF leak (2.73%), pseudomeningocele formation, hydrocephalus, cerebellar infarct or hematoma, and the combined percentage of cerebrovascular, cardiac, pulmonary, or thromboembolic events with an incidence of 3.92% [26, 51, 69, 83, 91–93].

The reported annual recurrence rate after MVD varies from 3% to approximately 30% [83]. The varied causes responsible for recurrence include inadequate separation of vessel and nerve, Teflon granuloma formation, adhesion of the interposed Teflon material, excessive Teflon insertion, improper and inadequate operative techniques, Teflon dislocation, and venous compression after the MVD procedure. Predictive factors of eventual recurrence described in the literature include female sex, symptomatology of more than 8 years, venous vascular etiology, inadequate pain relief immediately after surgery, redo surgery, and atypical pain patterns [69, 90].

The existing literature on the safety and efficacy of MVD in elderly has conflicting results [92, 94]. A meta-analysis assessing the difference in outcomes of elderly versus younger patients undergoing MVD for TN found that elderly patients were associated with higher risk of stroke, thromboembolic events, and mortality, while the recurrence rate was low [94]. There was, however, no significant difference in partial or complete success rates and complications such as cranial nerve deficits, cerebellar hematoma, CSF leak, and meningitis. Another recent study found no significant difference in surgical outcome and rate of complications between <60 and more than 60 age group patients [92]. Overall, MVD may be considered a safe and viable alternative for treating intractable TN in older patients.

Intraoperative use of an endoscope may lead to enhanced visualization of the operative site anatomy with better identification of offending vessels, minimal cerebellar retraction, and smaller craniotomy openings when compared with microscopic MVDs [43]. However, in terms of reducing surgical complications, endoscopic MVD may be more suitable for younger patients and those with a narrow CPA [95].

33.12.4 Stereotactic Radiosurgery

SRS for TN involves application of a single large dose of radiation, using x-ray beams, to a stereotactically localized target with minimal radiation delivered to surrounding tissue. SRS causes nonselective, dose-dependent axonal degeneration and necrosis and, thus, may block the nociceptive signals [96]. Some believe that pain relief may be caused by the indirect destruction of ionic sodium channels through slow chemical reactions [97].

With advancement in neuroimaging and external beam technology, newer technologies such as the GKRS, linear accelerator radiosurgery (LINAC RS), and CyberKnife RS have evolved. GKRS can precisely irradiate the cisternal segment of the trigeminal nerve by gamma-ray photons [98]. GKRS was primarily indicated for elderly patients with medically refractory TN and with comorbidities, for whom more invasive procedures are contraindicated. Nonetheless, in recent years more and more young patients are opting for GKRS to avoid GA, prolonged hospital stay, and a higher risk of complications.

The procedure is performed after application of a Leksell G frame to the skull either under monitored anesthesia care or conscious sedation with short-acting anesthetic agents. After frame placement, MRI of the brain is performed, including CISS images. In almost all instances, the cisternal segment of the symptomatic trigeminal nerve is treated using a single 4 mm isocenter to a maximum dose of 70–90 Gy [98]. For recurrent TN, the dose range is 60–90 Gy [99, 100]. The individual dose, however, depends on the radiation dose received by the brain stem as a cumulative brain stem dose of more than 12 Gy tends to be associated with trigeminal nerve deficit.

Recently, Tuleasca et al. performed a systematic review of 65 studies (45 GKRS, 11 LINAC RS, and 9 CyberKnife RS), evaluating the role of SRS in the treatment of TN and developed consensus guideline recommendations [101]. According to these guidelines, SRS yields a better initial response if it is performed in the first 3 years after pain onset (level III evidence).

33.12.4.1 Complications

Most common side effects reported after SRS include permanent trigeminal dysesthesia (mainly hypesthesia, although paresthesias have also been described). Hypesthesia ranges from 0 to 68.8% for GKRS, from 11.4 to 49.7% for LINAC, and from 11.8 to 51.2% for CyberKnife. Other complications include dysesthesias, paresthesias, dry eye, deafferentation pain, and keratitis.

A considerable linear annual risk of recurrence has also been reported, possibly as a result of the persistence of the underlying cause. Recurrence rates range from 0 to 52.2% for GKRS, 19–63% for LINAC, and from 15.8 to 33% for CyberKnife [99]. Another meta-analysis, comparing the safety and efficacy of microsurgical and radiosurgical treatment of TN, showed that at 36 months after the intervention, median percentage of recurrence was 11% for MVD and 25% for SRS management of TN [93]. Facial dysesthesias were more frequent after SRS (28.8% vs. 2.3%), while anesthesia dolorosa (0.04%), tinnitus (0.15%), brain stem edema (0.06%), chronic fatigue (0.79%), and keratitis (2.50%) were reported only after SRS compared to MVD.

Overall, GKRS remains a safe and effective treatment even after a second procedure, with comparable or better initial pain cessation rates, despite a higher toxicity, which appears to be the trade-off for maintaining pain relief [99].

33.12.5 Neuromodulation

Neuromodulation is the latest introduction into the treatment paraphernalia of medically resistant TN. It involves electrical stimulation of the central and peripheral nervous system to alter neuronal function. The techniques range from noninvasive brain stimulation techniques such as repetitive transcranial magnetic stimulation

or transcranial direct current stimulation and the transcutaneous electrical nerve stimulation to less invasive peripheral nerve stimulation (supraorbital nerve, infraorbital nerve, and the greater occipital nerve pulsed stimulation), subcutaneous peripheral nerve field stimulation, Gasserian ganglion pulsed stimulation, and cervicomedullary junction stimulation and finally to more invasive measures including the motor cortex stimulation and deep brain stimulation [36, 56].

To date, these modalities have been evaluated in small case series and few prospective or controlled trials with limited number of patients and short-term follow-up periods. Henceforth, at present there is no consensus about their role in the treatment paradigm of resistant TN. Nonetheless, the advent of newer miniature wireless devices and less invasive implantation techniques should allow for more widespread use of neurostimulation as a therapeutic modality in resistant TN. Larger studies need to be conducted comparing the traditional pharmacological therapies and emerging interventional pain techniques.

33.13 Summary

Trigeminal neuralgia is a unique and complex neuropathic pain disorder that continues to intrigue neurologists, neurosurgeons, and neuropain physicians alike. Though its recognition as a separate clinical entity dates back to the nineteenth century, its pathophysiological mechanism is still not entirely understood. Consequently, the optimal management modality, either pharmacological or surgical, remains elusive.

With an ongoing research into the pathophysiology of TN, using modern 3-D imaging techniques and electrophysiological studies, clinicians will have a better understanding of this disease, and newer and more effective treatment modalities may become available in the future. Nevertheless, a multimodal treatment approach, targeting the clinical symptoms as well as the neuropsychologic aspects of chronic pain, shall remain at the center stage of the management repertoire of this distinct clinical condition.

Key Points

- Trigeminal neuralgia is a unique neuropathic pain disorder characterized by agonizing unilateral paroxysmal pain occurring within one or more divisions of the trigeminal nerve territory, mostly triggered by non-noxious light mechanical stimuli.
- Neurovascular compression of the trigeminal nerve by an artery (most commonly superior cerebellar artery) at its root entry zone in pons, with focal demyelination of underlying nerve and ephaptic transmission of excitation, accounts for most of the pain paroxysms.
- Pharmacotherapy, with either carbamezepine or oxcarbamezepine, as the first line of treatment is the mainstay of clinical management.
- Surgical microvascular decompression offers effective long-term pain relief and is the procedure of choice if the patient reaches the maximum dosages of either carbamezepine or oxcarbamezepine, without achieving the desired pain relief, or has undesirable side effects.
- Percutaneous ablative procedures, botulinum toxin injections, stereotactic radiosurgery, and neuromodulation are other therapeutic options, useful for patients who have medically refractory pain and wish to avoid surgery or are at high surgical risk.
- Patients with chronic trigeminal neuralgia are also at high risk for cognitive deficits, with subsequent negative impact on normal socioprofessional life, thus necessitating a thorough neuropsychological evaluation and support.

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