University of Latvia
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Diploma Work

Trigeminal Neuralgia: Analysis of Treatment after Microvascular Decompression Surgery

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LIST OF ABREVIATIONS

AB	Alcohol Blockade
ACAI	Arteria Cerebellaris Anterior Inferior
ACI	Arteria Cerebellaris Inferior
ACS	Arteria Cerebellaris Superior
AH	Arterial Hypertension
AMT	Amitriptyline
BC	Balloon Compression
BCL	Baclofen
BNI Scale	Barrow Neurological Institute
Botox	Botulinum Toxin
CBZ	Carbamazepine
CFS	Cerebrospinal Fluid
COD	Codeine
CPA	Cerebellar Pontine Angle
GBT	Gabapentin
IHS	International Headache Society
LI	Lidocain Injection
LTG	Lamotrignine
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Image
MVD	Microvascular Decompression
NR	Neurectomy
OXC	Oxcarbamazepine
PGB	Pregabalin
PHT	Phenytoin

PMZ	Pimozide
PTGG	Percutaneous Technics of the Gasser Ganglion
REZ	Root Entry Zone
RS	Radiosurgery
RSGN	Radiosurgery with Gamma Knife
TC	Thermocoagulation
TN	Trigeminal Neuralgia
TRA	Tramadol
V CN	V Cranial Nerve
VAS	Visual Analogue Scale
VB	Vena Basilaris
VPI	Vena Petrosa Inferior
VPS	Vena Petrosa Superior

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ABSTRACT:

Introduction: The TN is a syndrome that causes severe facial pain, characterized by electric-shock-like, stabbing, paroxystic pain, felt in one or more divisions of the trigeminal nerve. It is believed that the etiology is a chronic neurovascular contact of a vessel over a nerve, causing lesion on the nerve, provoking demyelization, consequently hyperexcitability of the nociceptive fibers, leading to the pain. There is no cure and the diagnosis is normally established late. The initial medical treatment is done with Carbamazepine (CBZ), and after its ineffectiveness, surgery should be considered. Considering that vascular compression is the cause of most cases of primary TN, a cure can be achieved in the majority of patients with the microvascular decompression (MVD) technique, which has shown very good succefful rate and prognosis.

Objective: to present the result of MVD surgery performed in 52 patients diagnosed with primary TN, analyzing clinical variables such as postoperative complications, vessel conflict, location and degree of the conflict and 24h postoperative result.

Material and Methods: this retrospective study included 52 patients (33 females and19 males) with mean age of 63.6 years-old, who undergone to microvascular decompression surgery in PSKUS between January, 2005 to January, 2016. Patients' case history were assessed and clinical data were taken: patients' gender and age, onset of pain, degree of pain, period of hospitalization, postsurgical complications, radiological findings, anatomical vessel conflict, affected side of the face, trigeminal branch involvement, degree of conflict and surgery results in 24h.

Results: the majority of the patients were older than 65 years-old and described the pain as horrible or agonizing prior to the surgery. Full recovery was achieved by 47 patients (90.38%) in the first 24h after surgery. The most affected side was the left one (53.85%), the majority of the conflicts occurred in the branch V2+V3 (40.38%) and the highest incidence of venous compression was found over the ACS (30.77%). Minimal postoperative complications was observed: two subarachnoidal hematoma (3.85%) and 3 cranial nerve deficit (5.77%)

Conclusion: MVD surgery is still a reliable treatment, presenting a high satisfactory outcome for patients who suffered from TN. Possible complications are very mild and their occurrence are very rare. The involvement of the trigeminal branches can be alone or associated, and rarely the first branch (V1) is involved. Conflict between vessels and nerve is always present and it is normally associated with the ACS, and less associated with veins.

KOPSAVILKUMS:

Ievads: Trigemināla neiralģija (TN) ir sindroms, kas izsauc ļoti stipras lēkmjveida sāpes, kas izstaro sejā un ko var raksturot kā durošus, līdzīgus elektriskai strāvai paraksizmus. Ir uzskatīts, ka TN etioloģijas pamatā ir hroniskais neirovaskulārais kontakts (t.s. neirovaskulārais konflikts) starp asinsvadu un nervu. Rezultātā asinsvads spiež uz nervu, veidojas nervu mielīna apvalka bojājums, pastāvīgs nervu šķiedru nociceptīvo receptoru kairinājums, kas izpaužas ar sāpēm. Visbiežāk patoloģiju diagnosticē diezgan vēli. Terapija sākumposmā ir *Carbamazepine (CBZ)*, Un ja tas nav efektīvs, tad jādomā par operatīvo ārstēšanu. Ņemot vērā, ka vaskulārā kompresija ir visbiežākais iemesls primārai TN, lielākai pacientu daļai var veiksmīgi pielietot t.s. mikrovaskulāru dekompresiju (MVD), kura rada ļoti labus rezultātus, runājot par ārstēšanas efektu un prognozi.

Mērķis: prezentēt MVD operācijas rezultātus, kas bija savākti no 52 pacientiem, kam bija diagnosticēts primārā TN, analizējot tādus klīniskus parametrus kā pēcoperatīvas komplikācijas, neirovaskulāro konfliktu, konflikta vietu un pakāpi un 24 stundu pēcoperatīvo rezultātu.

Materiāli un metodes: šī retrospektīvā pētījumā bija iekļauti dati par 52 pacientiem (33 sievietes un 19 vīrieši), ar vidējo vecumu 63.6 gadi, kam bija veikta MVD operācija PSKUS starp 2005. gada janvāri un 2016. gada janvāri. Pacientu slimības vēstures bija apskatītas un sekojoši dati bija paņemti: pacientu dzimums un vecums, sāpju sākums, sāpju raksturojums, hospitalizācijas periods, pēcoperatīvas komplikācijas, radioloģiskas atradnes, anatomisko neirovaskulāro konfliktu, skārtu sējas pusi, trigemināla nerva zaru iesaisti, konflikta pakāpi un operācijas rezultātus 24 stundu laikā.

Rezultāti: lielāka pacientu daļa bija vecāki par 65 gadiem un pirms operācijas raksturoja sāpes kā "briesmīgas" vai "agonizējošas". Pilna izveseļošana bija sasniegta 47 pacientiem (90.38%) pirmo 24 stundu laikā pēc operācijas. Biežāk bija skarta kreisā puse (53.85%), lielākā konfliktu daļa bija V2+V3 zaros, un vislielākais venozas kompresijas biežums bija atrasts pāri *ACS* (30.77%). Bija novērotas minimālas pēcoperatīvas komplikācijas: 2 subarahnoidālas hematomas (3.85%) un 3 kraniālo nervu deficīti (5.77%).

Secinājumi: MVD operācijas joprojām ir efektīva ārstēšana ar labu iznākumu un lielu acientu apmierinājumu. Iespējamas komplikācijas ir ļoti vieglas un rētas. Trigemināla nerva zaru iesaiste var būt ar vienu zaru vai ar vairākiem, un reti kad ir iesaistīts pirmais zars (V1). Konflikts starp asinsvadiem un nerviem ir visos gadījumos un normāli asociējas ar *ACS* un mazāk ar vēnām.

1. INTRODUCTION

The Trigeminal Neuralgia (TN) is known to cause one of the most severe neuropathic pain. According to the International Headache Society (IHS), it is a rare facial syndrome characterized by electric-shock-like, stabbing, paroxystic pain, felt in one or more divisions of the trigeminal nerve, responsible for the sensibility on the face (*Al-Quliti, 2015*). The TN is not a life-threatening condition, however, it is considered one of the most painful and debilitating syndrome, decreasing the quality of life as well as generating a socioeconomically overload for the patients (*Ibrahim, 2014*). It has sudden onset and resolution, affecting the area of one or more branches of the nerve and is triggered by harmless stimulus (*Bes et al, 2013*). The trigeminal nerve, or the V cranial nerve (V CN), has mixed function (sensitive and motor), in which the sensitive function predominates. It controls the facial feeling and the masticatory muscles (*Iro et al, 2005, 2005; Leocádio et al, 2014*). Every pain offense lasts some seconds, but it can be so repetitive, that, in a short interval, can be mistaken as the previous one. Frequently the pain is accompanied by facial spasms called "tics" and is triggered by stimuli originated on the skin, mucosa or teeth, leading daily activities like eating, speaking, brushing the teeth or sleeping somehow difficult, resulting in a decreased life quality of the patient. Clinically the TN is divided in essential or secondary. The etiology of the essential TN is not clear, and it is believed that the most probable cause is a neurovascular contact. The chronic contact of a vessel over a nerve can cause lesion on the nerve, provoking demyelization on the site, and consequently, hyperexcitability of the nociceptive fibers, leading to pain (*McMillan, 2011*). The cause of the secondary type is evident, because it is accompanied by a neurological deficit and is caused usually by tumors localized in the cerebellopontine angle (*Iro et al, 2005 et al, 2005; McMillan, 2011*). The diagnosis of TN is basically clinic, however, if there is neurological deficit associated to this condition, imaging studies should be required (*Gronseth et al, 2008*). There is no cure for the TN, the treatment is complex and the diagnosis is commonly late due to misdiagnosis caused by the lack of knowledge on this disease by the health care professionals, which can result in unnecessary dental procedures and ineffective opioid prescription (*Chen et al, 2014*). The initial treatment approach is done with medicines. CBZ is the first choice and can be later associated with other drugs. Surgical treatment is indicated, when the patient is refractory to pharmacotherapy. The kind of surgery to be perform depends of the patient's condition and of the evaluation of risk-benefits of each modality. Nowadays the tendency is to perform surgery of less possible morbidity and less risk, such as the microvascular decompression of the trigeminal nerve. It is a safe, relatively easy and quick procedure with very few collateral effects (*Al-Quliti, 2015*).

Based on the hypothesis that vascular compression is the cause of most cases of primary TN, a cure can be achieved in the majority of patients with the MVD technique. Although alternative surgical techniques such as alcohol blockage (AB), neurectomy (NR), radiofrequency thermocoagulation (RT), balloon compression (BC) and radiosurgery (RS) are less invasive, it has been shown that these techniques have slightly higher recurrence rates. (*Chen et al, 2014*)

1.1. Objectives

The aim of this retrospective study is to present the result of microvascular decompression surgery performed in 52 patients diagnosed with primary TN, which have been undergone MVD, analyzing variables such patient sex and age, pain onset, period of hospitalization, postoperative complications, vessel conflict, location and degree of the conflict and 24h postoperative result.

2. BIBLIOGRAPHIC REVIEW

2.1. History of Trigeminal Neuralgia and its Treatment

The pain syndrome caused by the TN have been rarely registered in the old history. The first mention about this syndrome is attributed to Aretaeus of Cappadocia, who reported it for the first time as *a headache accompanied with spasms and semblance distortion*. Later, in the XI Century, Avicena described in his bood “Quanun” a severe facial pain, which treatment was based on wine and sleep in a dark room. In 1973, Nicolas Anché, from France, reported many cases of TN, giving the name of “tic douloureux”. The complete definition of this condition was proposed by the English doctor John Fothergill in his work “On a Painful Affliction of the Face", and the therapy suggested by him was *Conium maculatum* (water hemlock). In 1900, total ablation of the Gasser ganglion was performed by Cushing; and in 1902, Osler describe the neuralgia in such words: “*in patients with TN in advanced stage, the paroxysm arises one after the other, without any evident cause, and during the intervals, the patients could never be free of the pain. The crisis begun due to any external stimuli, such as an air flow, facial muscular movement or touch on the affected area*” (Singh et al, 2011). Surgical intervention is necessary, once the majority of the cases of TN derives from compression of the sensorial root of trigeminal nerve, and advanced cases are refractory to pharmacotherapy. Microvascular decompression was performed at first by Gardner and Milkos, in 1959, and then popularized by Jannetta, in 1967 (*Wuilker, 2005*).

2.2. Anatomy

The trigeminal nerve is a mixed nerve, with the sensitive component more prominent. The sensitive root is formed by the prolongation of the sensitive neurons, located in the trigeminal ganglion, also called Gasser ganglion, situated over the petrous part of the temporal bone, in the fossa media (*Haller et al, 2016*). It is situated in a fold of the dura mater that form a invagination around the posterior 2/3 of the ganglion, called Cavum of Meckel. The peripheral prolongation of the sensitive neurons of the Gasser ganglion originates distally to the ganglion of the three trigeminal branches: Ophthalmic (V1), Maxilar (V2) and Mandibular (V3) (*Leocádio et al, 2014*).

The sensitive aspect is formed by afferent somatic fibers that conduct impulses such as touch, proprioception and pain from the anterior 2/3 of the tongue, teeth, cornea, dura mater, mouth mucosa, nose and paranasal sinuses. The motor portion is formed by fibers connected to the mandibular branch and innervates the masseter, masticatory and pterigoideus muscle and also the tensor tympani muscle, milohyoideum and digastric (*Leocádio et al, 2014*; *Haller et al, 2016*).

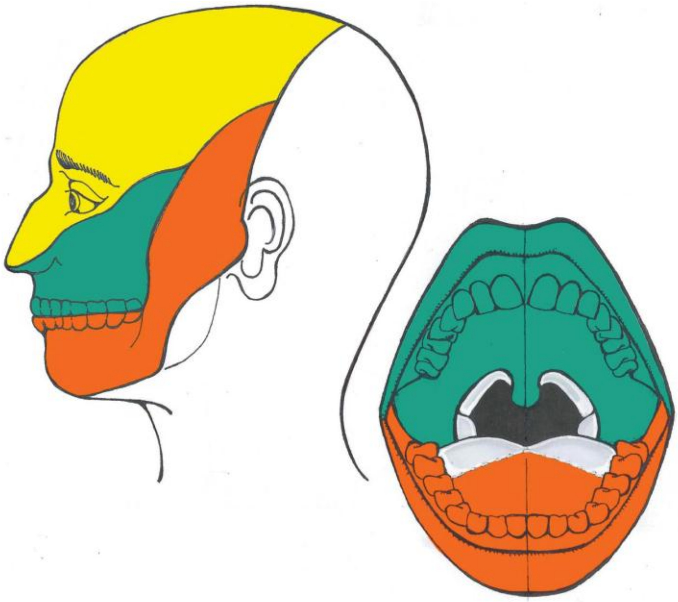


Figure 1: Innervation Territories of the Trigeminal Nerve, showing its areas. In yellow: ramus Ophtalmicus; in green: ramus Maxillaris; In orange: ramus Mandibularis. SOURCE: *Cruccu*, 2016.

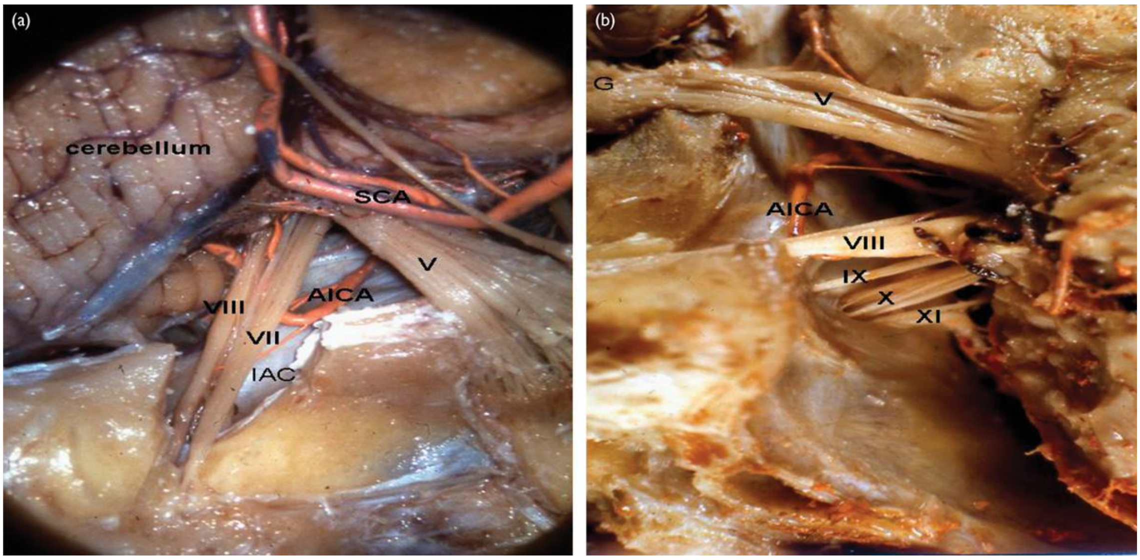


Figure 2: (a) Right superior view and (b) right posterior view of the posterior cranial fossa shows the anatomy of cranial nerves. Superior cerebellar artery (SCA), anterior inferior cerebellar artery (AICA), facial nerve (VII), cochleovestibular nerve (VIII), internal auditory canal (IAC), trigeminal nerve (V), gasserian ganglion (G), glossopharyngeal nerve (IX), vagus nerve (X), and accessory nerve (XI). SOURCE: *Elaini S*., 2013.

2.3. Epidemiology

The TN is one of the most frequent types of facial pain. (*Haller et al, 2016; Leocádio et al, 2014; Yuan et al, 2016),* presenting an incidence of four to 28.9 cases for 100.00 inhabitants (*Al-Quliti 2015 ; Zhang et al*, *2014*). In the UK, it corresponds to 26.8 for 100.000

inhabitants. In countries like USA and the Netherlands, with more strict definitions, the incidence is much lower and vary from 5.9 to 12.6 for 100.000 inhabitants (*Leocádio et al, 2014*; *Zakrzewska and Linskey, 2014*). Women are more affected than men in a proportion of 1:1.7. Familial cases are rare, and the majority of the patients have a sporadic disease (*Kumar et al, 2013*). The onset of this disease occurs between the age of 40 to 60 years old and it is not common before 40 years old (*Al-Quliti, 2015*). The incidence increases with the patient's age, occurring in 25.9 for each 100.000 people per year in individuals older than 80 years old (*Leocádio et al, 2014*).

2.4. Classification

The TN is classified in classical (or idiopathic) and secondary (somatic), based on its etiology (*McMillan, 2011*).

Classical TN, or idiopathic, is the most common kind and includes all the cases without known etiology, or cases with a neurovascular compression of the trigeminal nerve, without clinical evidence of neurological deficit (*Al-Quliti, 2015*; *McMillan, 2011; Zakrzewska, 2013*). Secondary TN, or Somatic, also known as painful trigeminal neuropathy (*Burmeister et al, 2015*), is caused by a cerebral lesion and not by a neurovascular compression of the trigeminal nerve and are diagnosed in case of cerebral tumors (benign or malign), cranial base deformities, trigeminal nerve trauma, arteriovenous malformation (AVM) or plaques of multiple sclerosis (MS). The clinical picture can be the same in both cases, but it results from a structural lesion (*McMillan, 2011; Zakrzewska, 2011*). If a patient does not fit in the IHS diagnostic criteria, the disease is classified as atypical (*Zakrzewska, 2011*).

2.5. Pathophysiology

It is recognized that TN is a neuropathic type of pain, which can be explained by the "ignition hypothesis": The pain occurs due to injury of the trigeminal axons in the nerve root or ganglion after compression of the nerve in the root entry zone (REZ) by vascular structures (*McMillan, 2011*). The majority of the TN is originated in neurovascular compression associated to degenerative process that occurs over the sensitive root, in the entrance segment of the trigeminal root in the pons (*Zakrzewska, 2011*). Jannetta, 2005, stated that the vascular compression would be the cause of the majority of the TN. He also observed a high incidence of vascular loops in contact with the trigeminal nerve, and then he established the concept of neurovascular conflict and proposed its decompression as a way of treatment. The compression of a root of the trigeminal nerve by a blood vessel, more frequently, by the superior cerebellar artery (SCA), or, sometimes, by a tortuous vein, correspond to 80 to 90% of the classical TN (*Holanda et al, 2015).*

The mechanism of pain seems to be related with the demyelination in an area around the compressed nerve. The physiopathological mechanism of the demyelination is however not very clear (*Eugene, 2015).* The symptoms are a result of an ectopic generation of an action potential in the afferent fibers sensible to pain of the trigeminal nerve. Compression or other pathology can lead to demyelination of the fibers that does not conduct the impulse for pain, but became hyper-excited and electrically associated to the small fibers related with pain, not myelinated or less myelinated with near proximity, by the transmission mechanism: lateral contact point between the fibers in which the impulses can be directed transmitted by the cellular membrane and not by synapsis. It can explain why tactile stimuli conducted by the large myelinated fibers leads to pain paroxysm (*Zakrzewska, 2011)*. Some authors state that, in the case of vascular compression, the degenerative processes related with the aging, which occur due to atherosclerotic changes in the arteries that increase the thickness and vascular tortuosity, can explain the prevalence of TN in the old population. When the TN occurs in a young patient, or when it is bilaterally, the presence of demyelinating conditions like MS should be investigated. (*Leocádio et al, 2014*).

Another hypothesis stablishes that the origin can be viral, specifically neurotropic virus such as Herpes simplex virus and Herpes zoster virus, which infect the trigeminal nerve ganglion. According to this hypothesis, the pathological base of the TN would be an ionic channel resulting of the genome activation of the virus, which is latent since the childhood in the infected nucleus of the infected neurons, in nociceptive fibers of the trigeminal nerve (*Tacon, 2014*).

Patients diagnosed with secondary TN, in which an extrinsic compression of the nerve is the cause of the pain, caused by another pathology that is the origin of the structural or functional lesion of the trigeminal nerve, show detectable causes in the clinical presentation. The causes can vary from cerebral tumor like gliomas, or metastasis, vascular alterations, like arteriovenous malformation, cranial deformity and MS (Tacon, 2014). In the MS, a demyelization plaque occurs normally in the entrance zone of the trigeminal root, although vascular compression is also observed in this patients (*Leoádio, 2014).* Diabetis Mellitus, odontological inflammatory diseases and otorrhinolaringology illnesses like sinusitis are also possible causes of TN (*Iro et al, 2005; Montano et al, 2015*). There is also an association between TN and arterial hypertension (AH), because it can cause alteration in the blood vessel, causing neurovascular contact (*Maarbjerg et al, 2014*).

Table 1 - Classification of Trigeminal Neuralgia according to its causative agent.

Classical	- Vascular compression over V CN
Secondary	- Extrinsic compression caused by tumor, arteriovenous malformation, cranial malformation, multiple sclerosis
Other causes	- DM, odonatological inflammatory process, sinusitis, hypertension

2.6. Patient Interview and Clinical Signs

The anamnesis provides an important clue and is the main diagnostic tool. In the classical TN, the presentation of the disease is one of the most consistent among all the neurological diagnosis. The pain is usually reported with the same nuances, as an electric shock, punch, stab or pullout. Around 60% of the patients complain of stabbing pain from the *rima buccale* towards the mandibular angle, and 30% report painful discharges from the superior lip or canine teeth towards the eye or eyebrow (*Tacon, 2014*).

The classical TN has a very characteristic presentation. It appears as an agonizing excruciating pain, like electric shock, unilaterally, affecting more frequently the V2 and V3 branches of the trigeminal nerve, and rarely the V1 branch (*Leocádio et al, 2014; Maarbjerg et al, 2014*). The pain occurs suddenly and is very short, not lasting for more than one minute. It is so strong, that can cause contraction of the muscles of the affected side (*McMillan, 2011*). The paroxysm related to the classical TN can be felt as single hits that occurs frequently, in irregular intervals, during the day or at night, sometimes along many weeks, with periods of pain remission, without pain, which can last for weeks or months (*Tacon, 2014*).

The region of the pain is a key characteristic in which the patient can signalize its location. The side where the pain occurs is fundamental for the diagnosis of facial pain: unilateral or bilateral presentation can have different causal implications and should be elucidated in the history. A key point is the diagnosis of the trigger points, since they are present in more than 50% of TN cases and are usually localized around the mouth or nose. The triggers can be a single touch, some head movement, speaking, brush the teeth, swallow, bite, a cold air flow, etc. It can occur spontaneously, even during speaking or smiling. There is also triggering zones that leads to pain episodes, which are located in the areas of the trigeminal branches. Patients avoid to massage the affected area or apply ice, in opposite to what happen in other facial syndromes. Moreover, the neurological examination of these patients are usually normal. (*Leclercq et al, 2013*).

Table 2 - Clinical characteristics of the classical TN, adapted from Zakrzewska, 2010

Intensity or nature	- Electrical shock, gunshot or knife stab - Moderate/Intense
Duration	- Paroxysmal - Rapid onset - Short - 1s to 2min - Remission period
Localization	- Unilaterally - In one or more branches of the trigeminal nerve - Rare in the V1 - Not radiating beyond the nerve distribution
Aggravating factors	- Spontaneous attack - Trigger zones - Precipitated by harmless stimuli

The clinical picture of the secondary TN is, however, different from the classical type. The pain is generally continuous, with paroxysm normally lasting from three to four hours. The pain can be bilaterally, can affect the three dermatomes and there is no trigger zones. Else, the neurological examination of the patient is abnormal (*McMillan, 2011; Leclercq et al, 2013; Andrade et al, 2013*).

The pain starts to revert after some seconds generating a burning sensation, which can least some minutes. The pain can start or finish spontaneously, and as far as the disease progresses, the intervals between each pain episode can become shorter. The patients become stunted after each episode, further more when the frequency increases and the pain is severe. Reliving factors are not common in pain caused by TN, but patients can report that after some medication the pain can disappear or decrease. Patients with secondary TN caused by MS normally are younger than 40 years old, and the pain attacks occur only in advanced state of the disease. Any kind of systemic disease such as fever, loss of weight, malignancy should be well explored, because they are always an indicative of neurological alterations (Camargo, 2001).

2.7. Physical Examination

A full body examination is mandatory in case of craniofacial painful syndrome. Trigger points should be assessed together with the sensibility of the paranasal sinuses, non-common skin lesions and lymphadenopathy. Patient can also have problems to eat or talk, being afraid to start the pain. Full neurological examination carefully attending the cranial nerves are essential. Classical TN is not associated with neurological deficit, so any abnormal finding should be followed by radiological evaluation, in order to rule out a secondary cause (*Tacon, 2014*).

2.8. Diagnosis

The diagnosis of TN is basically clinic and takes into account the clinical characteristics of the disease. There is no specific test for its confirmation, making it a big problem faced by the professionals. (*Leocádio et al, 2014; Zakrzewska, 2014; Flor et al, 2016*). In this way, the clinical history of the patient and the physical examination are the most useful signs for the diagnosis of this disease (*Zakrzewska, 2011*). Diagnosis mistake or unnecessary interventions are very common, and procedures like tooth extraction often happens in the majority of the patients presenting the characteristic symptoms, before being diagnosed. It creates a significant obstacle for appropriated therapeutic methods (*Allsop et al, 2015*). The delay in the diagnosis of the TN still takes a long time and it has not being improved (*Zakrzewska, 2014*).

The symptom of pain should be characterized carefully, describing its nature, intensity, period, localization, irradiation, facial sensitive points, pain-free periods, provoking factors and relief factors. Moreover, the experience of the physician is necessary for a correct diagnosis and adequate treatment (*Leocádio et al, 2014*).

During the neurological examination, it is mandatory to access the anatomical distribution of the three branches of the V CN, emphasizing the sensorial function in all its branches, corneal reflex and masticatory muscles examination (*Tacon, 2014; Maarbjerg et al, 2014*). Not infrequently, the neurological examination of the classical TN is normal and it does not present neurological deficit. Patients with long history of classical TN can, on the other hand, present subtle trigeminal sensorial deficit (*Leocádio et al, 2014*).

The presence of trigeminal sensorial deficit or bilateral involvement of the trigeminal nerve, in the initial diagnosis for secondary TN and is reinforced in case of refractory treatment. In this way, they should be taken into consideration in the identification of the secondary TN. In the case of doubt, more tests should be provided. Trigeminal reflexes and radiological examination are the next investigation for such illness (*Gronseth et al, 2008*).

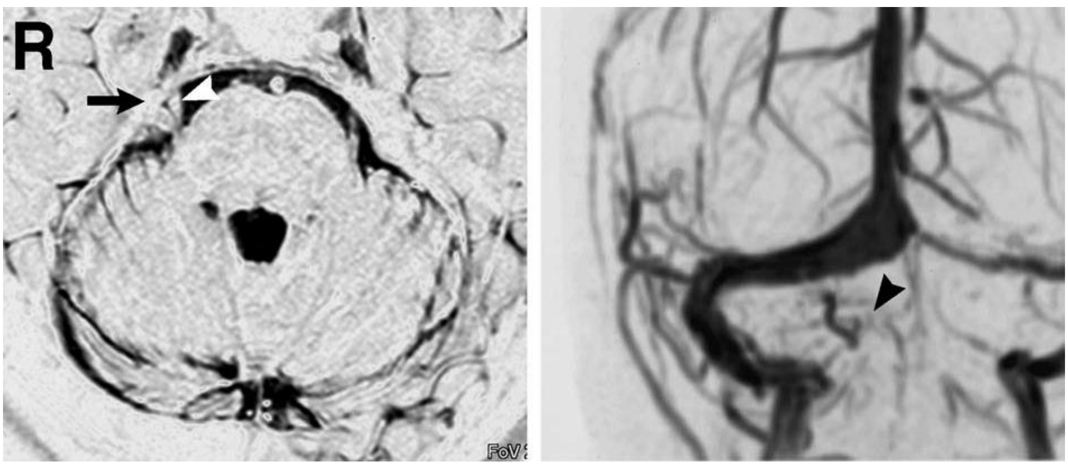


Figure 3: Magnetic Resonance showing anatomical abnormality over the V CN. **Left**: Anatomical magnetic resonance image through the level of Meckel's cave (arrow) demonstrating the dilated draining vein compressing the right trigeminal nerve and the root entry zone (arrowhead), and extending through the brain stem to the petrosal sinus. **Right**: Magnetic resonance venogram showing abnormally dilated vessels (arrowhead) in the right posterior fossa. SOURCE: *Yamamoto* et al, 2013.

If the patient is a young adult or the TN is bilateral, MS should be considered. Frequently, on physical examination, it can be detected sensorial loss on the face. Cases that the cause is secondary to expansive lesions generally are indicated with objective signs of sensorial loss in the distribution of the trigeminal nerve. The American Academy of Neurology (AAN) together with the former European Federation of Neurological Societies (EFNS) - today European Academy of Neurology (EAN) - released recommendations with the aim to help in the diagnosis and treatment of the TN, taking in consideration medicine based in evidence (*Gronseth et al, 2008*).

2.8.1. Diagnosis Criteria

The diagnosis criteria for idiopathic TN, according to the IHS, are the following (*Flor et al, 2016*):

a) At least three attacks of unilateral facial pain fulfilling criteria B and C
b) Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution
c) Pain has at least three of the following four characteristics:
    1. Recurring in paroxysmal attacks lasting from a fraction of a second to 2 min
    2. Severe intensity
    3. Electrical shock-like, shooting, stabbing or sharp in quality
    4. Precipitated by innocuous stimuli to the affected side of the face
d) No clinical evidence of associated neurologic deficit
e) Not better accounted for by other ICHD-3 diagnosis

Presence of hypoesthesia and hypoalgesia in the affected region, according to the ICHD, indicates axonal lesions, therefore it indicates trigeminal neuropathy or secondary trigeminal neuropathy. In such cases, it must be considered a broad diagnosis study to detect the cause. Additionally, from the clinical point of view, according to this new classification, it is suggested to differentiate the classical TN from the atypical TN, which is characterized by unpleasant and constant facial pain, but with less intensity (*Andrade et al, 2013*). The atypical

TN has been associated to unsuccessful pharmacotherapy and neurosurgical interventions (*Di Stefano et al, 2014*).

2.8.2. Differential Diagnosis

It is important to distinguish the classical TN from other causes of head/facial pain, or diseases from the jawbone, teeth or perinasal sinuses (*Kasper et al, 2015*). The symptoms of classical TN are very clear, nevertheless, they can be result of other autonomic headaches from the trigeminal nerve, as well as odontogenic pathologies and temporomandibular illnesses. (*Zakrzewska, 2014*). It is mandatory to assess the patient's clinical history carefully, thereby; many differential diagnosis can be excluded (*Oesman and Mooij, 2011*).

According to Camargo (2001), any painful syndromes on the face can simulate a classical TN, such as:

1. Facial neuralgia
2. Atypical trigeminal neuralgia
3. Post-herpetic neuralgia
4. Facial neuralgia associated with sclerosis
5. Facial pain secondary to intracranial expansive processes
6. Facial pain due to neoplastic facial processes
7. Facial pain associated with temporomandibular arthropathy
8. Neuralgia of the nerve intermediate
9. Neuralgia of the glossopharyngeal and vagus nerves
10. Reflex sympathetic dystrophy of the face
11. Pain due to dental conditions
12. Inflammatory processes of the meninges of the base of the skull
13. Acromegaly

2.8.3. Imaging Examination

In order to differentiate the classical TN from the secondary TN, it is recommended brain imaging (*Kumar, 2013*). The goldstandard examination is the nuclear magnetic resonance (NMR), which is very important for diagnosis, and especially for pre-surgery evaluation of patient with TN. It is also used to evaluate possible structural lesions, which could be cause of a secondary TN (*Leocádio et al, 2014*). Furthermore, high-resolution resonance and resonance associated with angiography are useful to identify etiological neurovascular compression in the classical TN. This method can help to select patients who would be candidates for MVD surgery (*Kumar et al, 2013*).

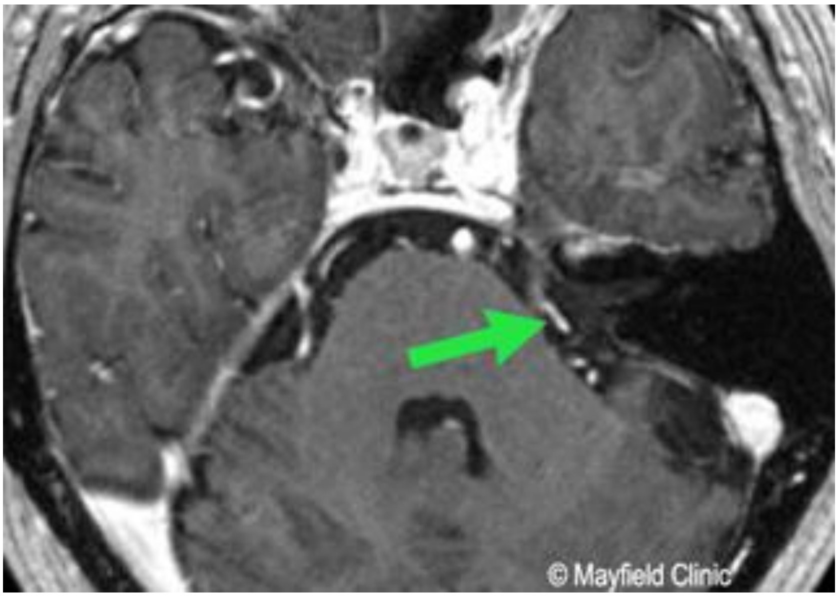


Figure 4: FIESTA MRI can detect blood vessels (arrow) that may be compressing the trigeminal nerve. SOURCE: *Elaini, 2013.*

Tomography can identify spatial infiltration lesions and nerve bone compression. In cannot, nevertheless, indicate small tumors, preganglionar segments and MS plaques, even using a contract media. For such findings, NMR has higher sensibility for intracranial lesion findings, better resolution, as well as it does not use ionizing radiation. In addition to NMR, it can be used with angiography for the identification of vessels in the entrance area of the trigeminal root. In this way, the use of tomography is not so reasonable, if resonance is more effective. Selective indications for the investigation with NMR in TN include patients younger than 60 years old, those with atypical clinical presentation or specific clinical picture, such as involvement of more than one trigeminal nerve division, bilateral involvement or presence of other abnormalities in the nerve (*Tacon, 2014; Ibrahim, 2014*).

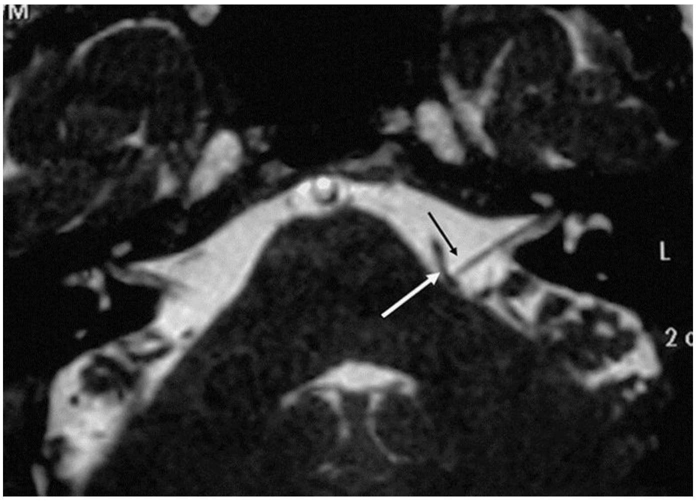


Figure 5: MRI T2 axial cut showing PICA (white arrow) in contact with the REZ of the left facial nerve (black arrow). PICA, posterior inferior cerebellar artery; REZ, root exit zone. SOURCE: *Elaini, 2013*.

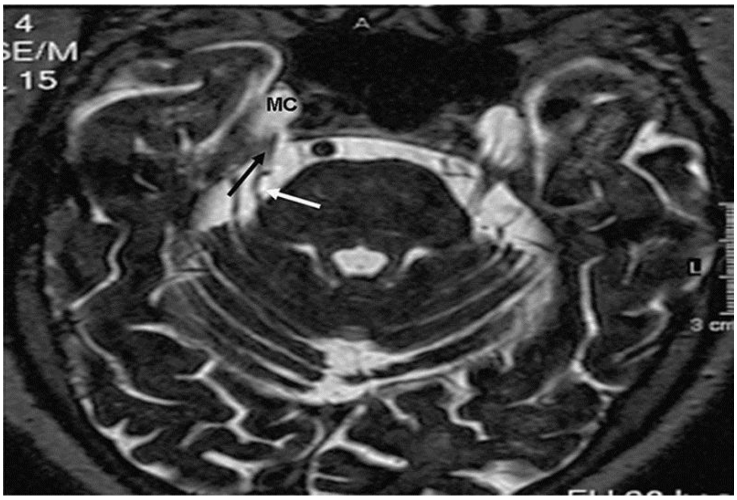


Figure 6: MRI T2 axial cut showing SCA (white arrow) in contact with the right trigeminal nerve (black arrow) along its course from REZ to Meckel's cave (MC). REZ, root exit zone; SCA, superior cerebellar artery. SOURCE: *Elaini, 2013*.

There are many studies about the utility of fast three-dimensional imaging using steady-state and MRI-angiography during surgical planning and anticipation of surgical findings during temporomandibular dysfunction and it was demonstrated a correlation of more than 95% between this method and the surgical findings (*Montano et al, 2015*).

Electrophysiological tests do not distinguish classical TN from secondary TN, therefore are not important for the diagnosis evaluation of this disease. However, the evaluation of the trigeminal reflexes are useful for the distinction between these two types of neuralgia (*Kumar et al, 2013*). In case of secondary TN, neurophysiological tests of trigeminal reflexes seem to have the same sensibility (95%) and specificity (93%) similarly to magnetic resonance (*Montano et al, 2015; Kumar et al, 2013*). This technic is easy, not harmful, and any finding of any abnormality suggests a subjacent structural lesion (*Kumar et al, 2013*).

2.9. Treatment

The TN is related as one of the most painful experience that a patient can report. There is no medicinal treatment that can resolve completely and definitely the crises of pain (*Eugene, 2015; Lemos and Linskey, 2011; Faryabi and Joolhar, 2014*). The patients, who suffer from TN, must be immediately treated. The aim of the treatment should include pain relief and improve in life quality (*Sreenivasan et al, 2014*). Nowadays, the initial approach of the classical TN include conservative treatment with medicines, and, in case of a negative result, it should be considered surgical procedure. (*Faryabi and Joolhar, 2014*).

Table 3: Clinical approach for the treatment of trigeminal neuralgia, adapted from *Zakrzewska, 2014; Eugene, 2015; Puniyani and Jasuya, 2012.*

Pharmacological Approach**:**	Surgical Approach**:**
- **First line:** carbamazepine, oxcarbamazepine or phenytoin - **Second line**: lamotrigine, baclofen - **Third line**: levitiracetam, gabapentin, pregabalin - **Acute treatment**: lidocaine - **New approach**: botox-A	- Criteria: after employment of three different medicines, or severe side effects - **Microvascular decompression**: invasive, for young patients, better results and big risk of complications - **Radiosurgery with gamma knife**: least invasive, for all kinds of patient, very expensive - **Percutaneous technics**: minimally invasive, suitable for elderly patients, high recurrence risk

In TN, the success of pharmacotherapeutical treatment is defined as at least 50% of pain relief. In the other hand, a surgical treatment is accomplished, only if complete relief of the pain is achieved (*Zakrzewska, 2015; Faryabi and Joolhar, 2014*). Each treatment support should be adequate to the patient's necessity and conditions, age, area of the trigeminal nerve, medical comorbidity, surgeon experience and risks that the patient is willing to have (*Lemos, 2011*). Up to now, there are only few studies comparing the pharmacotherapy treatment with the surgical treatment. It is also not clear when the patient with TN should be sent to surgery or how many different drugs the patient should undertake before going to surgery (*Emril and Ho, 2010*). When the patient is unable to proceed with surgical intervention, due to patient's refusal or due to patient's incapacity to suffer an intervention, there is no guideline, which can show the next therapeutic step (*Ong and Keng, 2003*). It is very important to have a protocol to evaluate the initial results, and to evaluate the success of the interventions using a pain scale to assess the degree of pain and efficacy of the treatment. Choosing an adequate pain scale depends of the physical and mental capacity of the patient. Life quality should also be evaluated before and after the treatment (*Kumar et al, 2013; Sreenivasan et al, 2014; Oh et al, 2008*).

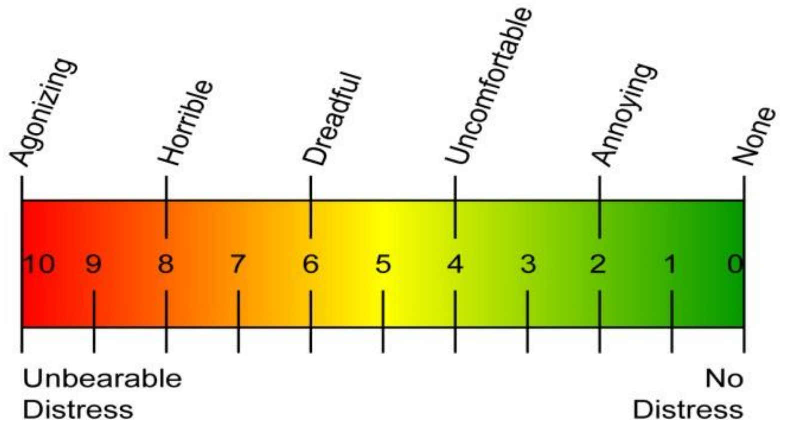


Figure 7 - Visual Analogue Scale: sensitive reproductable pain scale, used in TN. It reproduces the pain intensity and is also used to evaluate MVD intervention. SOURCE: *Kumar, 2013*

BNI pain intensity score	Definition
I	No trigeminal pain, no medication required
II	Occasional pain not requiring medication
III	Some pain adequately controlled with medication
IV	Some pain not adequately controlled with medication
V	Severe pain, no pain relief

Figure 8 - Barrow Neurological Institute Pain Scale: assess the level of pain in patients with trigeminal neuralgia, before and after the surgery. Adapted from: *Lai, 2015; Kang, 2016*

2.9.1. Pharmacotherapy

The first approach for the patient with TN is pharmacological therapy. Its objective is to decrease the pain and allow symptomatic relief (*Puniyani and Jasuya, 2012*). Classical TN and secondary TN pain are recommended to be treated in the same way. In addition, it is observed that the patients with secondary TN have a satisfactory response to these drugs. (*Khalid, 2015*). The treatment begins usually with only one drug, increasing its posology until the pain is relieved or satisfactorily decreased. In the case that the patient feels relieve only using high doses of a drug, which can lead to collateral effects, the addition of a secondary drug should be considered, and in this case, an antiepileptic medicament is the drug of choice because it will provide a synergic effect for the treatment. However, considering that the antiepileptic drugs have different mechanism, as well as different pharmacodynamics effects, the selection of a drug from this group should be done cautiously. In contrast, there is no established combination, which should increase the efficacy. Moreover, treatment using many drugs can cause cumulative effect, leading to an increased risk in surgery complication, especially in elderly. (*Ibrahim, 2014; Lemos, 2011; Emril and Ho, 2010*).

2.9.1.1. First Line Treatment

The first line treatment for pain control in TN consists of anticonvulsants: phenytoin (PHT), carbamazepine (CBZ) and oxcarbamazepine (OXC) (*Eugene, 2015; Montano et al, 2015; Zhou et al, 2016*). The mechanism of CBZ and OXC are the same, they block the sodium channel blockers voltage dependents (*Di Stefano et al, 2014*). The combination of drugs in the TN treatment is still not detailed as it is in the treatment of epilepsy (*Lemos et al, 2011*). Long-term therapy using these drugs shows decreased efficacy, due to drug resistance development when used for a long time. In addition, the secondary effects also increase due to long time treatment. The patients can then be treated with surgery, or with second line drugs, although there is no evidence of treatment efficacy in this case (*Maarbjerg et al, 2014*).

Dosage of CBZ for the treatment of TN is 600 mg, and OXC, 1200 mg. After an average of about nine months, around 25% of the patients who were using CBZ developed considerable side effects, leading to the interruption of the treatment and reduction of the posology to a subtherapeutical dose. With OXC, the same findings were observed after 13 months. The most common side effects observed (dizziness, drowsiness and postural imbalance) occur in the nervous system (*Di Stefano et al, 2014*). Failure in the treatment with these two medicines is not caused by any pharmacodynamics discrepancy. Instead, by the adverse effects, when the dosage reaches a level that causes the treatment interruption or adjust of posology for a subclinical level. Ideal would be new drugs with better tolerability (*Maarbjerg et al, 2014; Di Stefano et al, 2014*).

Carmabazepine: it is considered the goldstandart drug in the treatment of TN. Its efficacy is well known and it has being used as the main drug for many years (*Cruccu et al, 2016*). The fully pain control starts to develop within some days (*Zakrzewska, 2011*). It is also a diagnosis tool, once the patients with classical TN have a positive result with CBZ, while patients with secondary TN or atypical TN do not have an adequate therapeutic result. The dose vary from 200 to 1200 mg/day. The adverse effects have an impact in the nervous system and are dose-dependent. Therefore, to avoid this adverse effects, it is recommended to initiate the treatment with the lower therapeutic dose, and increase it during the treatment, according to the necessity. In patients diagnosed with TN, therefore, the initial dose should be from 100 to 200 mg two times/day. The daily dose can be increased every second day in 100 mg until the pain is successfully controlled, to minimize the side effects. The maintenance dose is 300 to 800 mg/day and the maximum dose is 1200 mg/day. It is possible to reach the pain control in 75% of the patients after adequate dose balance (*Khalid, 2015*). It is suggested that the efficacy of the treatment with CBZ reaches complete or almost complete pain control in 28-100% of the patients (*Gronset, 2008*). The adverse effects of the CBZ include nausea, vomiting, dizziness, somnolence, ataxia, diplopia, memory problems, hyponatremia and increase of hepatic enzymes. Less common it is possible to find leucopenia, aplastic anemia, skin allergy, systemic lupus erythematosus and hepatotoxity. (*Khalid, 2015*).

Oxcarbamazepine: this drug is a derivative of the CBZ and is the first choice of medicine for treatment of TN in the Scandinavian countries (*Zakrzewska and Linskey, 2014; Puniyani and Jasuja, 2011*). There is an agreement between the specialists, which state that the efficacy of the OXC is the same of the CBZ, concerning reduction of trigeminal pain. In addition, the OXC presents less adverse effect frequency, less tolerability and lower drug interaction potential (*Di Stefano et al, 2014*). OXC is an alternative for those patients who do not tolerate the CBZ. The initial dose of the CBZ is 150 mg two times/day. The dose can be increased in 300 mg every three days, until the therapeutic response can be reached. The maintenance dose is 300-600 mg, two times/day, and the maximum dose should not exceed 1800 mg/day (*Gronseth et al, 2008*).

2.9.1.2. Second Line Treatment

Second line treatment for TN, which shows some efficacy in the pain control of classical TN, are performed with drugs such as baclofen (BAC), lamotrigine (LTG) and pimozide (*Leocádio et al, 2014; Puniyani and Jasuya, 2011*).

Baclofen: it is a $GABA_B$ receptor agonist derivative which works as skeletal muscle relaxant, because it depresses the excitatory neurotransmission (*Khalid, 2015; Sreenivasan et al, 2014*). The initial dose is 15 mg/day, with gradually increase until the maintenance dosage of 50-80 mg/day (*Kumar et al, 2013*). For an optimal synergic effect of BCL with CBZ, the dose of this should be reduced for 500 mg/day (*Khalid, 2015*). This association can also be employed in patients with MS, once the BAC is a muscle relaxant (*Puniyani and Jasuya, 2011*). Considerable side effects of BAC were reported such as somnolence, dizziness, fatigue, constipation and hypotension. Sudden discontinuation of this drug can cause abstinence symptoms such as hallucination and convulsion (*Khalid, 2015; Zakrzewska, 2014*).

Lamotrigine: it is an antiepileptic drug used in patients who cannot tolerate CBZ, or in synergy with CBZ, when its effects decrease (*Sreenivasan et al, 2014*). The initial dose of LTG is 25 mg/day, with increments of 50 mg/week, until the effective dose of 400 mg is reached. This drug is normally used for the long time treatment, in the case of moderated pain, and is not recommended for acute pain treatment (Zakrzewska, 2014). Some patients report skin rashes during the first two months of treatment, as an adverse effect. Other side effects are dizziness, ataxia and sleepiness. These side effects can be prevented with gradual increase of the dose of LTG (*Khalid, 2015*).

Pimozide: it is used one or two mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less (*Puniyani and Jasuya, 2011*). It is discouraged in the treatment of trigeminal syndrome due to its severe adverse effects like arrhythmia, parkinsonism, acute extrapyramidal effects and anticholinergic effects (*Khalid, 2015; Bajwa et al, 2016*).

2.9.1.3. Third Line Treatment

In the last years, the most used medicines used for the treatment of TN were gabapentin (GBP), pregabalin (PGB), topiramate (TPM) e levetiracetam (LEV) (*Khalid, 2015*).

Gabapentin: it is a GABA receptor antagonist and is used to treat neuropathic pain, due to its interaction over the pre-synaptic calcium channels of the neurons, inhibiting the release of excitatory neurotransmitters. This medicine has shown efficacy in the treatment of TN, especially in patients with MS. The initial posology is 300 mg/day, increasing the dose 300 mg every three days, if tolerated by the patient, until it is reached 1800 mg/day, which is the ideal dose. One of the advantages of the GBP is the rapid increased of its dosage without severe side effects such as skin rashes, although the patient can present dizziness, somnolence, headache, confusion, and ankle edema. Hyperlipidemia is an important side effect that must be monitored (*Khalid, 2015*).

Pregabalin: it is an analog of the GABA, which acts in the alpha-2 subunit of the calcium channels voltage dependents. Dose of 150 to 600 mg/day was seen effective in reducing TN pain by over 50% to 74% of patients with minor efficacy reduction over the 1-year observational period. It is considerable useful in cases of neuroleptic pain, nevertheless, there is not so much evidence of its use in TN. The most accentuated side effects are dizziness and sleepiness, although less severe than the other antiepileptics (*Khalid, 2015; Emril and Ho, 2010*).

Topiramate: it blocks the calcium channel voltage dependent and increase the $GABA_A$ activity, binding in a non-benzodiazepinic $GABA_A$ receptor. The most common side effects are dizziness, somnolence, loss of weight and mental deficit (*Khalid, 2015*).

Levetiracetam: it is the newest antiepileptic used to treat TN, targeting the calcium channel type N of high voltage, putting out of action the neuronal impulse through the synapsis (*Khalid, 2015*). Nevertheless, it has not been used so oft in the treatment of TN (*Khalid, 2015; Emril and Ho, 2010*). The dose of LEV varies from 1000 to 4000 mg/day for the treatment of TN (*Khalid, 2015*).

Table 4: Mechanism of Action and dose of the most used drugs for the treatment of TN, adapted from *Khalid, 2013; Zakrzewska, 2010; Punyani, Jasuja, 2012*

Medicine	**Mechanism**	**Dose**	**Note**
CBZ	Acts in the sodium channels and block the type 2 calcium channels	200-1200 mg/day	Need monitoring
OCX	Same as CBZ	300-1800 mg/day	Better tolerability than CBZ
BAC	$Gaba_B$ receptor agonist causing muscle relaxation	50-80 mg/day	Useful for patients with MS or CBZ intolerance
LTG	Acts in sodium and calcium channels, modulating the liberation of aspartate and glutamate	200-400 mg/day	Not to be used in acute trigeminal pain, needs to be titrated
PMZ	Dopamine receptor antagonist	2-12 mg/day	Severe adverse effects
GBP	GABA receptor agonists	300-3600 mg/day	Safe and good synergism with ropivacain
PGB	Analogue of GABA	150-600 mg/day	Peripheral edema in high dosage
TPM	Block sodium channel voltage dependent	100-400 mg/day	
LEV	Partial inhibition of type calcium channel voltage regulated	1000-4000 mg/day	Less drug interaction

2.9.1.4. Acute Treatment of Trigeminal Neuralgia

Acute and severe attacks should be treated with lidocaine injection (LI) and not with opioids, which are inefficient. Topic LI in the trigger points provides prompt relieve, but it lasts very short time (*Zakrzewska, 2011*).

2.9.1.5. Botulinum Toxin A

It is a new alternative for the treatment of the TN, because very frequently the classical pharmacotherapy is inefficient in a long term; the drugs are often not enough to stop the pain and the side effects are as well as unbearable (*Burmeister et al, 2015*). The botulinum toxin A (Botox) presents, besides muscle relaxation effect, also analgesic effect. It acts on neurogenic inflammatory mediators, controlling the release of neurotransmitters from the autonomic and sensorial neurons, which are involved in chronic and unbearable pain caused by TN (*Gutiérrez et al, 2016*). The botulinum toxin is injected in the subcutaneous or mucosal tissue, and, in an efficient way, relief the pain in the cases when the patient was refractory to the drugs. It is a safe and efficient new method that can treat the pain for long term in patients that cannot proceed to surgery (*Obermann, 2010*).

There is still no standard dose, but the subcutaneous injection is performed with 25-75 U. It shows rapid onset, 1-2 weeks, and the maximum effect is obtained after 4-6 weeks. It is a simple procedure and can be performed without anesthesia (*Zhang et al*, 2014). After the injection, there is no systemic reaction or severe side effect, nevertheless it was reported hematoma, pruritus, facial asymmetry and pain in the injection site, which were felt for a short period and didn't interfere in the patients' normal activities (*Shehata et al, 2013*).

2.9.2. Surgical Treatment

Surgery is indicated for those patients who are refractory to pharmacotherapy of at least three different drugs including CBZ, or for those who are affected by the collateral effects. In this case, surgery treatment is an option. The kind of surgery will depends on the experience of the physician, risk benefit for the patient, as well as patient's age and general condition (*Eugene, 2015; Lemos, 2011*).

Due to a lack of scientific evidence about the efficacy of the drug treatment, there is no consent about how many different therapeutic regimes should be applied before the physician consider a surgery (*Heinskou, 2015*). Surgical interventions are normally aimed for patients with disabling conditions after failure of therapy with three different drugs, or when the drug starts to cause intolerable adverse effects (*Al-Quliti, 2015*).

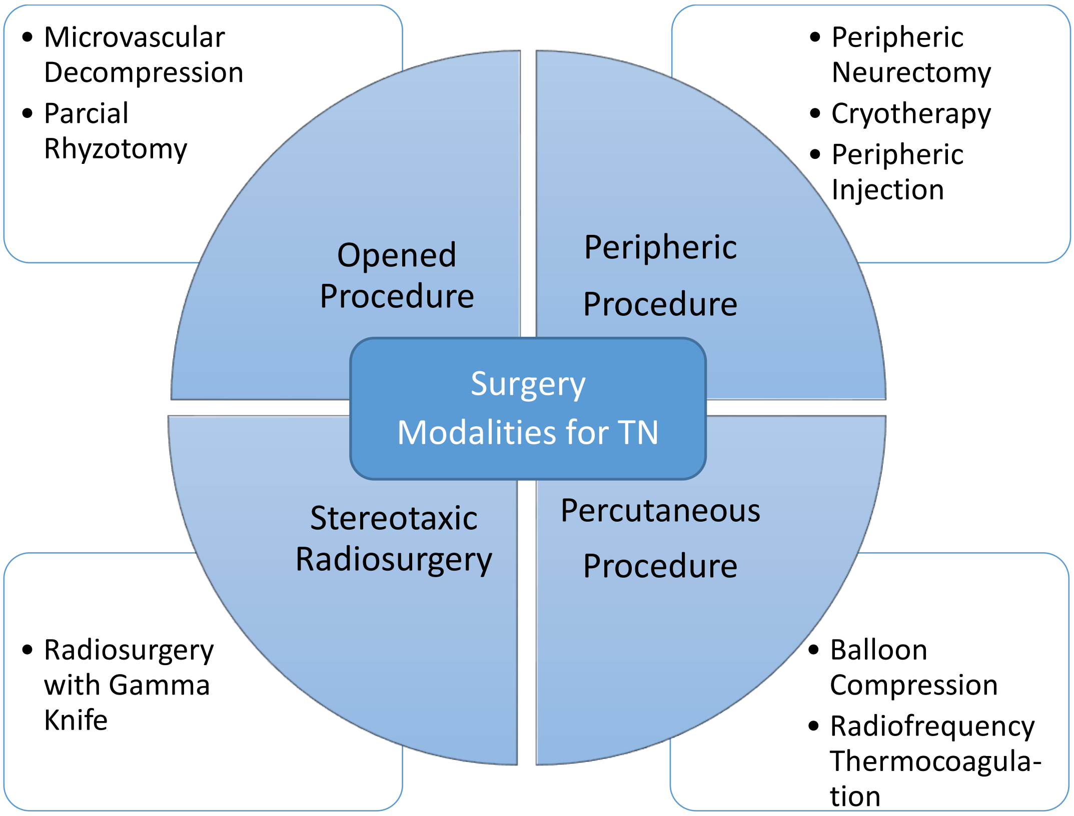
The AAN and the EFNS suggest that the treatment of the TN can be effective with MVD, percutaneous technics of the Gasser ganglion (PTGG) and the radiosurgery with gamma knife (RSGN) (*Lemos, 2011*).

The procedures are performed in three different regions: peripheral, at the level of the GG, and in the posterior cranial fossa. Surgical intervention are divided into two main categories: ablation and non-ablation. The MVD is an example of non-ablative procedure; therefore, it maintains untouched the trigeminal nerve function. In all the other procedures, the sensorial function of the trigeminal nerve is lost intentionally. The MVD is an invasive procedure and has very low surgical complications. The ablative interventions are less invasive, but has an increased recurrence rate. An example is the incidence of facial numbness, which is possible to be caused by rhizotomy, more than with MVD and RSGN (*Bajwa, 2016*). The peripheral neurectomy (PN), in the other hand, for the same treatment of TN, is not effective (*Gronseth et al, 2008*).

Young patients with positive vascular compression proved by neuroimaging are good candidates for MVD. In opposition, elderly patients or those with surgical high risk are preferred to be treated with percutaneous technic of GG (Yang, 2014). Although the surgical treatment of the TN is well tolerated, it can present post-surgical complication: post-traumatic painful trigeminal neuropathy. It is characterized by painful anesthesia in the denervated region, which can be persistent and can hurt more than the classical TN. By this reason, surgical treatment should be carefully decided. Painful anesthesia are more common to occur in rhizotomy procedures or thermocoagulation, nevertheless it is a rare condition (*Bajwa, 2016*).

All the procedures lead to relief of the pain, but they all have variable adverse effect. There is few evidence, that can say which procedure is better to be chosen (Ong and Keng, 2003). The AAN and the EFNS concluded that there is no comparative study to determine which surgical technic is better or more efficient. Indirect comparisons of different studies results suggest that the MVD can control the pain for a longer time than the other surgical interventions in the TN syndrome (*Gronseth et al, 2008*). More than that, two kinds of neuromodulation was suggested for optional treatment for the chronic pain, refractory to the conventional drug or surgical therapy. This is stimulation of the motor cortex and deep brain stimulation. Because there are few studies on this field, it is difficult to evaluate the efficacy of these two new procedures (*Montano et al, 2015*).

Table 5: Modalities of Surgical Treatment of Trigeminal Neuralgia



2.9.2.1. Microvascular Decompression

It is an effective, well-accepted and non-destructive surgery, which is based in a retrosigmoid craniotomy and microsurgical exploration of the posterior fossa, realized under general anesthesia (*Al-Quliti, 2015; Chen et al, 2014; Kher et al, 2016*). This technique was developed by Jannetta between the 60's and 70's and is nowadays one of the most eminent approaches for the treatment of TN (*Oesman and Mooij, 2011; Rzaeva et al, 2016*).

The MVD is considered the first line for the treatment of classic TN, which is not treated effective with pharmacotherapy, mostly in young patients (*Lemos et al, 2011*), and can be considered the treatment of choice for emergency patients with acute TN (*Zakrzewska, 2014*). The aim is to clear neurovascular contact, releasing the trigeminal nerve from any compression, by inserting a Teflon plaque between the vase and the nerve. (*Oesman and Mooij, 2011; Yang et al., 2014; Punyan and Jasuja, 2012*). It is based in the theory of trigeminal nerve compression at the exit from the cerebellar trunk by a vascular structure, for exemple, the ACS (*Kher, 2016*). According to Anichini (2016), the most common and identified vessels are the SCA, AICA, the dolichoectatic basilar artery and the transverse pontine vein.

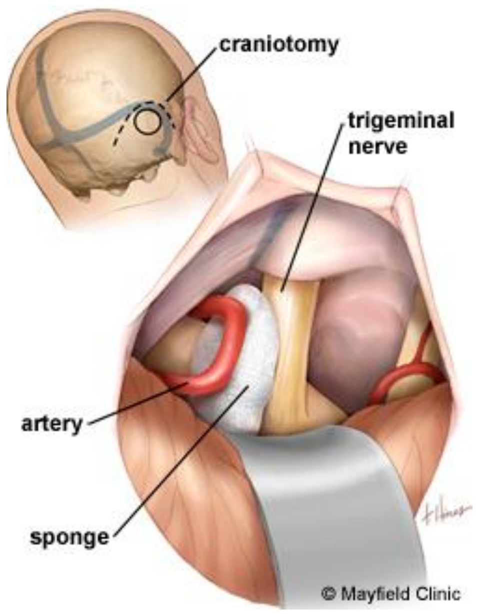


Figure 8 - Illustration showing MVD: During MVD, a sponge is inserted between the trigeminal nerve and the blood vessel to relieve the compression that causes the painful neuralgia attacks. SOURCE: *Mayfeld Brain and Spine*. Retrieve 05.12.2016 from http://www.mayfieldclinic.com/PE-TRIN.htm

The initial relief for the pain reaches 90% of the patients, more than 80% are free of pain in the first year, and 73% in five years. Complication are aseptic meningitis, auditory loss, bleeding and infection (*Oesman and Mooij, 2011*). Severe adverse effects, such as leak of cerebrospinal fluid, infarct or hematoma are very rare, and the mortality rate does not overcome 0.5% (*Oesman and Mooij, 2011; Gronseth et al, 2008*). Teflon granulomas occur in 1.1 - 7.3% of all MVD cases performed in accordance with the Jannetta procedure. They can cause pain in 13 - 50% of all recurrent neuralgias. The time from MVD to granuloma-associated pain recurrence ranges from one month to 8.5 years; facial pain often recurs within the first two years (*Rzaev, 2016*).

The MVD is a safe and efficient surgical treatment for typical and atypical TN, although in the last one it has increased recurrence rate. Besides of that, the MVD has lower efficacy in the treatment of TN in patients with MS related with TN, because the pain can be related with a different mechanism from the classic TN, in this way, MVD is not the first choice for patients with MS associated with TN (Zakrzewska, 2014).

2.9.2.1.1. Surgical Technique of MVD

The procedure is performed under general anesthesia, in the lateral position. The patient is placed in half-sitting position with the head flexed and rotated towards the side of the surgical field. The incision length is approximately 10 cm, vertically, one cm medial to the posterior border of the digastric groove. After the subperiosteal dissection, a craniectomy of approximately three cm in diameter is performed, exposing the margins of the transverse and sigmoid sinuses. The dural opening is performed in curved form, following the internal margin of the lateral sinus. After positioning the microscope, the region of the trigeminal nerve is accessed by tilting the cerebellum at the border between its tentorial and petrous surface. Once visualized, the nerve is exposed throughout its cisternal path, with special interest in the entrance area (at the level of the protuberance). Once the vascular conflict is found, the Teflon is placed separating the vessel from the nerve. Finally, the dura is closed tightly (*Oh et al*, 2008).

2.9.2.1.2. Indications of MVD

MVD can be performed in all patients refractory to pharmacotherapy whose health condition allows to undergo to general anesthesia (*Zhong et al, 2014*). Ruiz-Juretcheke et al, 2015, reported that "the age associated with illnesses that increase the anesthesia risk is considered one of the main contraindications for the treatment of TN using MVD".

3. Material and Method

3.1. Study Design

From January, 2005 to January, 2016, 97 patients were submitted to MVD surgery in Paula Stradiņa Klīniskā Universitātes Slimnīca. Of these sample, 52 patients with diagnosis of classical TN were selected (33 females and 19 males, with a mean age of 63.6 years), which had no lesion or section of the trigeminal nerve and had not performed any other surgical treatment before the surgery. Patients with neuralgia secondary to aneurysm, tumors, other vascular malformation and MS were not included in this research. The decision to proceed with MVD surgery was made due to decreased effectiveness of the medicaments or due to increased side effects.

All the patients were taking CBZ alone or in combination with other drugs before the surgery. The second drug of the combination was not found in the patient's case history. After the surgery, the drug therapy was taken away. All demographic and clinical data were taken from the patients' case history.

Imaging investigation (MRI) were conducted before the operation to analyze and indicate the etiology and the position of the anatomical compression of the V CN by the offending vessel. The imaging findings were classified in "compression" or "no findings". The pain distribution was categorized by the respective trigeminal branch involved (V1, V2, V3 and combinations: V1+V2, V2+V3 and V1+V2+V3) and was registered, as well as the side of the face where the syndrome happened: left or right.

The degree of the conflict was categorized, by intraoperative findings, as contact, adhesion and adhesion with indentation. The degree of pain before the surgery was evaluated by the physician qualitatively and in this work it was categorized in two groups: annoying/uncomfortable and horrifying/agonizing.

The surgery result was assessed by the surgeon qualitatively and subjectively within the first 24 hours after the operation, during the hospitalization period. Results were categorized in this work as excellent (no trigeminal pain and no medication required) and satisfactory (occasional pain and no medication required), unsatisfactory (some pain adequately controlled by medication), according to findings in the patient's clinical history.

3.2. Ethical Consideration:

This research was approved by the Ethics Committee of the University of Latvia, in Riga, and the data collection was accepted by the direction of the Neurosurgery Department of the Paula Stradiņa Klīniskā Universitātes Slimnīca, as well as by the direction of Science Department of the same institution. Confidential and anonymous data were used solely and exclusively for the context of the research.

3.3. Statistical Analysis:

Data were analyzed using the software STATISTICA® (version 8.0) for the treatment and analysis of the statistical data, and a $p \leq 0.05$ was considered statistically significant. The results were then submitted to a descriptive qualitative analysis for the categorical variables (degree of pain before surgery, surgery result, anatomical vessel conflict e trigeminal branch) and quantitative for the numeric variables (age and pain onset).

4. RESULTS

The sample consisted of 52 patients, 33 females and 19 males, with a mean age of 63.6 years. The sample had a mean age of 64 ± 12.3 years (mean ± standard deviation) among women and 62.89 ± 10.8 years among men (TABLE 06). All the patients underwent to surgery after inefficient pharmaceutical treatment, describing the pain, before the surgery, as horrible or agonizing. The radiological findings, before the surgery, were positive for nerve compression in all the patients.

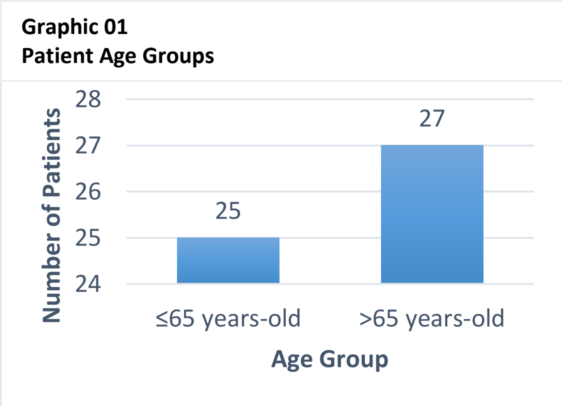
Applying the resampling technique - bootstrap - it was possible to observe that, by estimating the proportion of women in the population, the percentage found was 63.72% of women, when performed 10.000 simulations. The resampling data are very close to the initial proportion of the sample, which is 63.46% of women. To test the normality of the samples, separating it by gender, it was used the Shapiro-Wilk normality test. This test is used to analyze representative samples of a population. After applying this test for the female sample, it does not present statistical significance ($p = 0.5229$), therefore it is not possible to reject the null hypothesis, but it is possible to confirm the normality of this sample. After applying the same test in the male sample, the result was similar ($p = 0.823$), accepting the normality hypothesis, at a significance level of 5%.

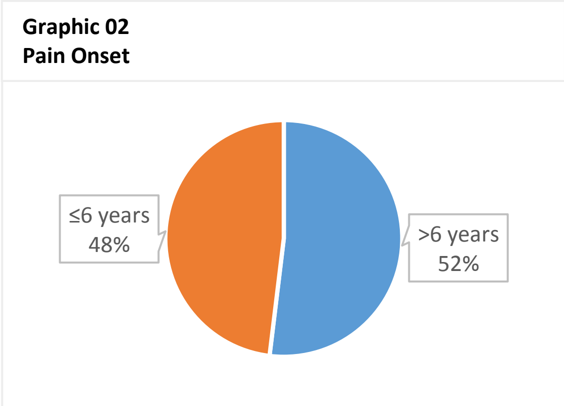
The patient gender, patient age, onset of pain and pain severity before surgery are summarized in the TABLE 06. The period of hospitalization, complications and surgery results are summarized in the TABLE 07. And the vessel conflict, side of conflict, degree of conflict, trigeminal branch involvement and radiological findings are presented in the TABLE 08.

Table 06
Clinical and demographic characteristics of the patients

	Number of patients	(%)
Patient gender		
Male	19	36.54
Female	33	63.46
Patient age		
≤ 65 years-old	25	48.08
> 65 years-old	27	51.92
Onset of the pain		
1-6 years	28	53.85
> 6 years	24	46.15
Pain severity before surgery		
Annoying/Uncomfortable	-	-
Horrible/Agonizing	52	100

The majority of the patients were older than 65 years-old (27 patients - 51.92% - Graphic 01), and the time when most of the patients started to suffer from the pain was within the last 6 years, before the surgery (28 patients - 53.85% - Graphic 02).





The hypothesis that the pain intensity before the surgery is not related with the onset of pain (6 years or less or more than 6 years) was performed with the Kolmogorov-Smirnov test. It was found that for women and men the intensity of pain is not related with the time that the patient started to feel the pain (pain onset). It was not possible to reject the null hypothesis ($p = 0.092$), therefore, for these samples, the intensity of the pain is independent with the period of pain onset.

For the hypothesis that the pain intensity before the surgery is not related with the patient age, for the two distinct groups (less than or equal to 65 years-old and above 65 years-old), it was found that for women and men the pain intensity does not have relation with the age ($p=0.085$).

TABLE 07: table showing period of hospitalization, complications and surgery results after 24h

	Number of patients	**(%)**
Period of hospitalization		
1-5 days	17	32.69
6-10 days	23	44.23
> 10 days	12	23.08
Complications		
None	47	90.38
Subaracnoidal hematoma	2	3.85
Cranial nerve deficit	3	5.77
Surgery results in 24 hours		
Excellent	47	90.38
Satisfactory	5	9.62

There were occasional occurrences of postoperative complications in only five patients, all in women. There were two incidences of subarachnoid hematoma (mean age 80 years) and three incidences of cranial nerve deficit (mean age 73 years). It was not possible to identify statistical relevance in the analysis of these samples.

Testing the hypothesis that the evaluation of the patient, concerning the degree of satisfaction 24h after surgery, improved in relation to the degree of pain, evaluated before the surgery, it was found that for women and men the level of satisfaction was significantly higher compared to the level of pain before the surgery.

Table 08: table showing vessel conflict, side of conflict, degree of conflict, trigeminal branch involvement and radiological findings

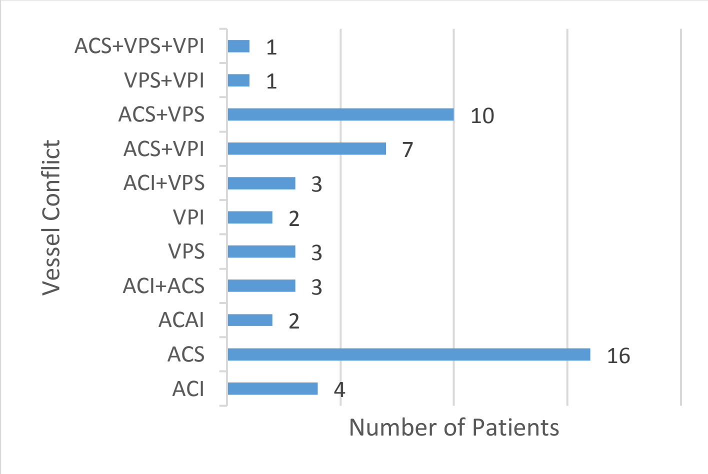
	Number of patients	(%)
Vessel conflict		
ACI	4	7.69
ACS	16	30.77
ACAI	2	3.85
VPS	3	5.77
VPI	2	3.85
ACI+ACS	3	5.77
ACI+VPS	3	5.77
ACS+VPI	7	13.46
ACS+VPS	10	19.23
VPS+VPI	1	1.92
ACS+VPS+VPI	1	1.92
Side of the conflict		
Left	28	53.85
Right	24	46.15
Degree of conflict		
Touching	40	76.92
Adhesion	4	7.69
Adhesion + indentation	8	15.38
Trigeminal branch involvement		
V1	-	-
V2	9	17.31
V3	7	13.46
V1+V2	12	23.08
V2+V3	21	40.38
V1+V2+V3	3	5.77
Radiological findings		
Contact	52	100
No finding	-	-

In the postoperative period of 24h, it was verified that 47 were evaluated as *excellent* (fully recovered), while only five surgeries were evaluated as *satisfactory*. Of the five *satisfactory* surgeries, one patient was male and the other four were female. The anatomical vessel affected in these patients were: in one case the ACAI, in two cases the ACI, in one case the VPI, and in another case, the ACS together with the VPI.

It was not possible to analyze the statistical relevance of these five cases due to the low incidence of the result *satisfactory*, when compared with the result *excellent*. It can be affirmed that the intervention was strongly accepted by the patients and that the surgery interventions categorized as *satisfactory* has no direct relation with any specific anatomical vessel affected.

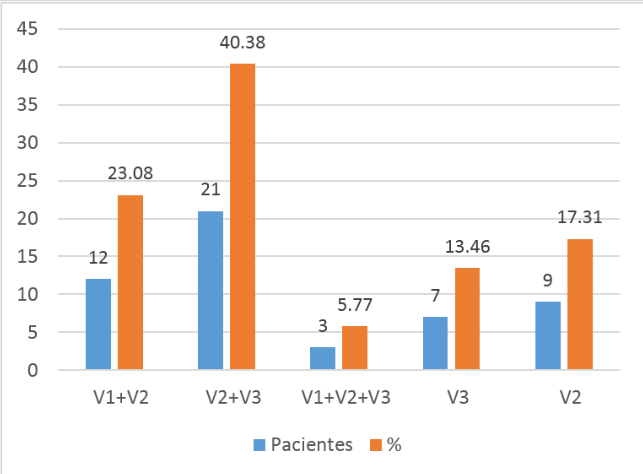
The highest incidence of vessel compression was observed with the ACS in 16 patients, being 11 occurrences in women and five in men. And the branches that were most affected were V2 and V3 concomitantly, in a total of 21 patients, being eleven occurrences in women and ten in men.

Graphic 03
Anatomical conflict vessel



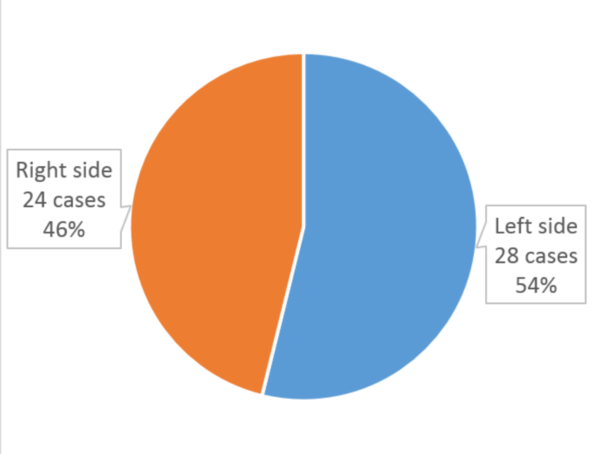
The predominance of occurrence of the ACS is superior in relation to the occurrence in other vessels, as well as the predominance of occurrence in the V2 and V3 branches at the same time is superior to the occurrence in other branches. The predominant side of the face is the left one, but it does not represent any statistical significance, in relation to the right side ($p=0.075$). In addition, all the patients presented the classical type of trigeminal neuralgia (primary type) - unilateral occurrence.

Graphic 04
Trigeminal Branch Involvement



There is no association between the anatomical branches where the pathology occurs and the patient gender. This was verified with the use of correlations by means of the Coefficient of Contingency C. The coefficient, for these two categories, presented a value of 0.4051 and p = 0.4224. This correlation evaluates the association between variables at an ordinal level.

Graphic 05
Side of the face where trigeminal neuralgia occurred



Using the same kind of analysis, it is possible to verify a strong association between the gender and the degree of conflict, in which the coefficient presented a value of 0.4008 and p = 0.0069; and the occurrence of degree of conflict *touching* is significant lower in males. By the same kind of analysis, there was no association between the gender and the terminal branch of the nerve involved in the conflict. The coefficient presented a value of 0.4126 and p = 0.0583.

Graphic 06
Surgery satisfaction

5. DISCUSSION

The main objective of this retrospective study is to evaluate the efficacy of MVD surgery in patients with primary TN, analyzing the clinical and demographic variables that could influence on its results.

The idea that a vessel is responsible to cause TN due to nervous compression appears in the first time with Dandy and later it was better understood and evaluated by Jannetta (*Oesman and Mooij, 2011; Wuilker, 2005*). The first medical therapy used to treat this syndrome is Carbamazepine (*Montano, 2015*), but the severe adverse effects and ineffectiveness of treatment in the long term directs the patient to choose surgical intervention (*Al-Quliti, 2015*). MVD surgery is an effective treatment for primary TN and it has been extensively used for the treatment of TN, as concluded by many authors (*Punyani, 2012; Wei et al, 2016*).

5.1. Patient Gender and Age:

In this study, more than the half of the patients, who have been submitted to MVD, were older than 65 years-old (51.92%), and most of the patients were female (63.43%). These findings follows the same tendency found by Tucer (2012), who had in his research the participation of 67.6% of female patients; and of Maarbjerg (2014), who reported 60% of female patients. In addition. Concerning the patients age, Al-Qulity (2015) stated that it is not common the occurrence of this disease in patients younger than 40 years-old and suggests that the tendency to develop the disease increases with the age.

5.2. Pain Intensity and Age:

Considering the finding that pain intensity before the surgery is not related with the patient age, as observed in this research, it can be inferred that the degree of contact and/or pressure of the vessel the nerve, which is the causative agent of the pain, is not related with the age, but with physiological and anatomical individual factors.

5.3. Pain Intensity and Onset of the Pain:

In this study, all the patients have reported an extreme sensation of pain, describing it as “agonizing” or “horrible”, meaning that the pharmacotherapy has a limited time of effect, since the onset of the pain until the necessity of doing the operation. It was also found, that the pain intensity is not related with the onset of the pain. This explains, in part, why the majority of the patients have been submitted to the surgery (53.85%) within 6 years after its onset.

5.4. Anatomical Vessel Conflict:

The most common anatomical vessel conflict found was the ACS (30.77%), followed by the ACS+VPS (19.23%). In this study, that ACS appears in 71% of the cases, alone or together with other vessel. This finding is supported by Du: in Toda (2012), who founded the ACS as responsible for nerve compression in 75% of the cases; and Campero, who reported 61.11% of cases having the ACS involvement. Tucer (2012) presents in his study 80% of compression being made by the ACS, and only four cases of vein compression. Many studies, such as Zhong (2014), reported the VB pressing the trigeminal nerve. In this study, however, the VPS (5.77%) and VPI (3.85%) were found and there was no occurrence of the VB.

5.5. Side of the Conflict:

The side of the conflict was balanced within the sample, occurring slightly more in the left side (53.85%). This percentage is similar which the findings of Lai (2015), in which the left side had 56.1% of involvement.

5.6. Complications:

One of the advantages of this surgery is the low incidence of complications. In the whole sample, there were only 5 complications (two subarachnoidal hematoma and three cranial nerve deficit). According to Toda (2015), MVD has a “low risk of morbidity and very low risk of mortality”. He also adds that patients older than 65 years-old can safely be submitted to MVD with excellent results. In his study, he observes that subarachnoidal hematomas has a frequency of 0.7 to 4.0%, value that is conform the two cases of this present study. In the study of Tucer (2012), there was no case of subarachnoidal hematoma, but only one case of cranial nerve deficit, which improved within the following six months. Psychosis, hearing loss and wound infection were the other complications reported by him.

5.7. Degree of the Conflict:

The most frequent degree the conflict was touching (76.92%) followed by adhesion + indentation (15.38%). This result is in disagreement with the findings of Tucer (2012), who reported a 62.2% of cases being adhesion + indentation. In his study, touching was found only in one case (2.7%). It was also found, that the degree of conflict touching was significantly lower in men than on women.

5.8. Trigeminal branch Involvement:

In this study, the branch of the trigeminal nerve with more involvement were V2+V3. These two branches together totalized 40.38% of the cases and were followed by V1+V2 with 23.08% of the cases. There was no involvement of the ophthalmic branch (V1) alone. This findings are in agreement with Leocádio (2014) and Maarbjerg (2014), who also reported increased tendency of V2+V3 involvement and rarely implication of the V1 branch. This is also sustained by the study of Lai (2015), who described 39% of the trigeminal neuralgia cases with association of V2+V3, and the minor case was with V1 alone (4.9%); and also by Kang (2016), who registered 35.2% of V2+V3 involvement in his study.

5.9. Imaging Findings:

All the patients (100%) presented venous compression according to MRI findings, performed previous to surgery. According to the hospital's directives, the realization of MVD surgery is authorized only when there is a positive imaging finding. This follows the idea of Toda (2015), that admits that advanced high resolution analysis and investigations should be done in order to improve the outcomes of the procedure. However, in the study of Elaini (2012), it is observed that MRI has a 97% of sensitivity, pointing out that use of endoscope can detect the "offending vessel in 100% of the cases". In the study of Tucer (2012), "a significant relationship was found between the radiological finding and the presence of compression". Ni in: Punyani (2012) recommends "an enhanced three-dimensional fast spoiled gradient recalled MRI and three-dimensional magnetic resonance angiography with a 3.0-Tesla MRI system to detect the anatomic relationship of neural and vascular structures at the trigeminal root entry zone preoperatively".

5.10. Period of Hospitalization:

It was not possible to analyze statistically the relevance of the period of hospitalization with the surgery results or other variables. The prolonged hospitalization period by many patients in this study occurred, because of socioeconomic conditions. Many patients avoided travelling back to their cities and decided to remain the hospital, waiting the time when they needed to remove the sutures.

5.11. Surgery Results in 24 Hours:

As is it presented in the literature, the degree of satisfaction of the MVD procedure is high. In this study, the surgery was a success for 90.38% of the patients. And it has decreased the degree of pain of pain of 100%, considering that the rest 9.62% didn't have a poor surgical result nor have to make use of medicines, as they did before the surgery, after the realization of the MVD. It was found that for women and men the level of satisfaction was significantly higher compared to the level of pain before the surgery. These findings are supported by Toda (2012), who describe that after MVD "80% will remain pain-free at 1 year"; and also by Campero (2014), who describes the remission of MVD, in the first months "higher than 80%". In the study of Lai (2015), "90.5% of the patients have achieved pain relief immediately after the MVD". In Tucer (2012),

However, Montano (2015), emphasizes that "a lack of a full comprehension of the complex pathogenesis… remains a key factor explaining the result that are not always satisfying with the medical therapy".

6. CONCLUSIONS

MVD surgery is still a reliable treatment, presenting a high satisfactory outcome for patients who suffered from TN. Possible complications are very mild and their occurrence are very rare. Radiological findings must be always requested by the surgeon, prior to the operation. The involvement of the trigeminal branches can be alone or associated, and rarely the first branch is involved. Conflict between vessels and nerve was always present and it is normally associated with the ACS, and less associated with veins. The degree of conflict doesn't always follows a frequency and can vary between studies. The side of the conflict is not associated with the surgery results.

6.1. Recommendations:

1. Surgical results should be measured using the Barrow Neurological Institute grading score (Annex 01). They allow some degree of standardization across treatment modalities and more accurate measurement of success of the MVD surgery.
2. Pre-surgical degree of pain should be measured with the VAS scale (Annex 02).
3. Follow-up of patients should be provided after 3, 6 and 12 months after the surgery. It is important to monitoring the degree of satisfaction of the patient, as well as pain recurrence.
4. Use of 3D MRI-angiography should be performed during the operation to more effectively locate and access the vessel.
5. Registration of other clinical parameters of the patients to more effectively understand the disease and its course and equally promote a better data base for future studies. An example of which parameters should be accessed is found in the annex 3.

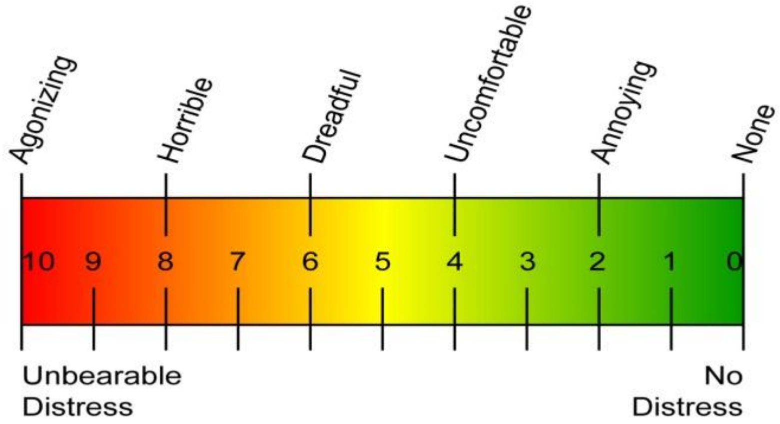
7. ANNEX

7.1. Barrow Neurological Institute Grading Scale

Barrow Neurological Institute Pain Intensity Score	
Score	**Pain description**
I	No pain, no medications
II	Occasional pain, no medications required
III	Some pain, adequately controlled with medications
IV	Some pain, not adequately controlled with medications
V	Severe pain or no pain relief

Annex 01 - Adapted from Ruiz-Juretschke, 2016

7.2. VAS SCALE



Annex 02 - SOURCE: Kumar, 2013

7.3. Parameters for Pre-surgery Patient Clinical Evaluation

1) **Gender**
    a. Male
    b. Female
2) **Age of patients?**

3) **Onset of pain** (when the pain started)

4) **Duration of the pain** (in seconds pro episode)

5) **VAS Scale (before operation)**
    a. Annoying (2/3)
    b. Uncomfortable (4/5)
    c. Horrible (6/8)
    d. Agonizing (9/10)

6) **Treatment before surgery + period**

7) **Period of Hospitalization**

8) **Postoperative complications**

9) **Radiological findings**
    a. Compression
    b. „no findings“

10) **Anatomical vessel conflict**

11) **Side fo the face**
    a. Left
    b. Right

12) **Trigeminal branch involved**
    a. V1
    b. V2
    c. V3
    d. V1 +V2
    e. V2+V3
    f. Other: _______________

13) **Location of the conflict in relation with Root Entry Zone**
    a. Superior
    b. Inferior
    c. Anterior
    d. Posterior

14) **Degree of conflict**
    a. Contact
    b. Contact + Indentation
    c. Adhesion
    d. Adhesion + Indentation

15) **Surgery results after 24h**
    a. Excellent (BNI I)
    b. Good (BNI II)
    c. Moderate (BNI III)
    d. Poor (BNI IV)

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