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Pilot study on neurophysiological recording for the identification of trigeminal roots during radiofrequency rhizotomy in trigeminal neuralgia

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Doctoral Thesis

This thesis has been carried out under the direction of Dr. Patricia Pozo Rosich and Dr Fuat Arikan Abelló and under the tutoring of Dr. Sergi Bellmunt Montoya

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To my wife Elena and my sons Alex and Víctor,

For their love and for being the most important part of my life

To my parents,

For teaching me the importace of hard work

ABBREVIATIONS

TN Trigeminal Neuralgia

BC Balloon compression

GR Glycerol Rhizotomy

MS Multiple sclerosis

MVD Microvascular decompression

RF Radiofrequency Thermocoagulation

RFC Radiofrequency Thermocoagulation Continuous

RFP Radiofrequency Thermocoagulation Pulsed

VAS Visual Analogic Scale

BNI Barrow Neurological Institute Scale

TABLE INDEX

FIGURE INDEX

INDEX

SUMMARY

Introduction

Trigeminal neuralgia is a painful disease with great impact on patients, causing disability and a low quality of life. Among the different surgical techniques for pain control are percutaneous techniques that include balloon compression (Mulla) and radiofrequency rhizotomy (RFC), which tend to be an effective technique in the short term but with high recurrence rates.

Scientific justification

The application of neurophysiological monitoring techniques during radiofrequency rhizotomy has not a good development to date, with some papers published with limited numbers of patients and the methodology and feasibility not being described in the scientific literature.

Hypotheses and objectives

The hypotheses proposed are that neurophysiological monitoring with the use of two electrodes, one for recording and one for lesion, is an applicable and reproducible technique. On the other hand, the identification of the trigeminal roots through antidromic stimulation is effective in making a more selective lesion and finally, the selectivity of the technique can improve effectiveness. The objectives are to determine the feasibility by measuring the association between

the monitored branches and the symptomatic branches, to analyze the results in a stratified manner between patients in whom a selective stimulus is obtained for the symptomatic branches and those who do not. Finally, it compares the results between the Radiofrequency group and another group performed with a balloon compression technique (Mullan) of comparable effectiveness.

Study design

This is a prospective observational study, with two cohorts of patients with similar characteristics, who underwent surgery between 2015 and 2022. These patients are monitored by obtaining data from the VAS pain scale and the BNI pain scale (Barrow Neurological Institute) in preoperative, immediate postoperative, at 3, 6 and 12 months, the affected branches and the selectivity of monitoring. Demographic data, type of neuralgia, comorbidities and complications are also obtained. A good result is determined as a decrease in the VAS scale >50% compared to the preoperative level. It includes a group of patients who underwent radiofrequency and monitoring and another group of patients who underwent balloon compression technique.

Results

The study includes 61 patients, 36 operated with RFC and 25 Mullan. 20/61 (32%) present symptoms of isolated V3 branches, 29/61 (32%) of V2 and V3 branches and 9/61 (14%) the three V1-V3 branches. Selectivity in monitoring could be achieved in 27/36 patients in the RFC group (75%). The initial result of the VAS scale in both groups was a good initial result in 57/61 patients (93%), however after one year the recurrence of pain occurred in 12/61 patients (20%). In the comparative analysis we obtained statistically significant differences when comparing the subgroup of RFC patients with selective monitoring and the non-selective group, with $p=0.0431$ ($p<0.05$). In the comparison of the RFC group with Mullan we did not obtain significant differences but when comparing the RFC subgroup with selective monitoring with the Mullan group we did obtain differences again with $p=0.025$ ($p<0.05$).

Conclusions

The study demonstrates the usefulness of neurophysiological monitoring for radiofrequency rhizotomy in trigeminal neuralgia. In those patients who achieve selective monitoring of the branches that are symptomatic, the result is good and last longer than those patients who do not achieve selective monitoring or who perform other similar techniques such as balloon compression. More studies are required to confirm the reproducibility of the technique, the longer-term effectiveness and to allow optimization of monitoring.

RFC (radiofrequency), Mullan (balloon compression).

RESUMEN

Introducción

La neuralgia de trigémino es un patología dolorosa con gran impacto en los pacientes, provocando discapacidad y deterioro de la calidad de vida. Entre las diferentes técnicas quirúrgicas para el control del dolor se encuentran las técnicas percutáneas que incluyen la compresión con balón (Mulla) y la rizotomía por radiofrecuencia (RFC), esta última siendo una ténica muy efectiva a corto plazo pero con tasas de recurrencia altas.

Justificación científica

La aplicación de técnicas de monitorización neurofisiológica durante la rizotomía por radiofrecuencia tiene escaso desarrollo hasta el momento, con algunos artículos publicados con número de pacientes limitados y no está descrita la metodología y ni la viabilidad en la literatura científica.

Hipotesis y objetivos

Las hipótesis que se plantean son que la monitorización neurofisiológica con la utilización de dos electrodos, uno de registro y otro de lesión, es una técnica aplicable y reproducible. Por otro lado que la identificación de las raíces trigeminales mediante estimulación antidrómica es efectiva para hacer una lesión más selectiva y por último que la selectividad de la técnica puede mejorar la

eficacia. Como objetivos se establece determinar la aplicabilidad midiendo la concordancia entre las ramas monitorizadas y las ramas sintomáticas, analizar los resultados de forma estratificada entre pacientes en los que se obtiene un estímulo selectivo por las ramas sintomáticas y aquellos que no. Por último compara los resultados entre el grupo de Radiofrecuencia y otro grupo realizado con técnica de compresión con balón (Mullan) de efectividad comparable.

Diseño del estudio

Se trata de un estudio observacional prospectivo, con dos cohortes de pacientes de características similiares, que se intervienen entre el año 2015 y 2022. Se realiza seguimiento de estos pacientes obteniendo datos de la escala EVA de dolor y la escala BNI de dolor (Barrow Neurological Institute) en preoperatorio, posteoperatorio inmediato, a los 3, 6 y 12 meses, las ramas afectadas y la selectividad de la monitorización. También se obtienen datos demográficos, tipo de neuralgia, comorbilidades y complicaciones. Se determina como buen resultado un descenso de escala EVA >50% respecto al preoperatorio. Se incluye un grupo de pacientes intervenido con Radiofrecuencia y monitorización y otro grupo de pacientes intervenidos con técnica de compresión con balón.

Resultados

El estudio incluye 61 pacientes, 36 operados con RFC y 25 Mullan. 20/61 (32%) presenta síntomas de ramas V3 aislada, 29/61(32%) de ramas V2 y V3 y

9/61(14%) las tres ramas V1-V3. Se pudo conseguir selectividad en la monitorización en 27/36 pacientes del grupo RFC (75%). El resultado inicial de la escala EVA en ambos grupo fue de buen resultado inicial en 57/61 pacientes (93%), no obstante al año la recurrencia del dolor se produce en 12/61 pacientes (20%). En el análisis comparativo obtenemos diferencias estadísticamente significativas al comparar el subgrupo de pacientes RFC con monitorización selectiva y el grupo no selectivo, con una p=0.0431 (p<0.05). En la comparación del grupo RFC con Mullan no obtenemos diferencias significativas pero al comparar el subgrupo RFC con monitorización selectiva con el grupo de Mullan si obtenemos e nuevo diferencias con una p=0.025(p<0.05).

Conclusiones

El estudo pone demuestra la utilidad de la monitorización neurofisiológica para la rizotomía por radiofrecuencia en la neuralgia de trigémino. En aquellos pacientes que se consigue una monitorización selectiva de las ramas que son sintomáticas, el resultado es bueno y más duradero que en aquellos pacientes en que no se consigue monitorización selectiva o que se realizan otras técnicas similares como la compresión con Balón. Se requieran más estudios que confirmen la reproducibilidad de la técnica, la eficacia a más largo plazo y que permitan la optimización de la monitorització

RFC (radiofrecuencia), Mullan (Compresión con balón).

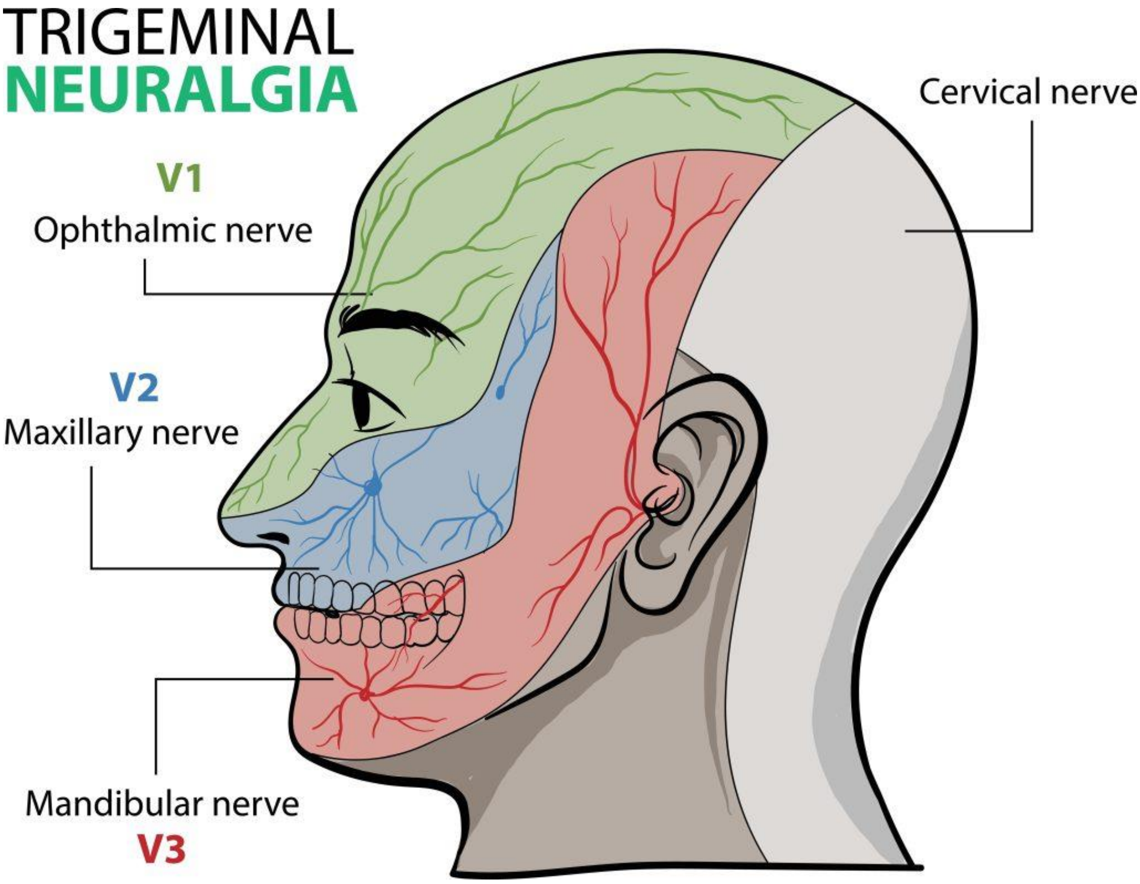
INTRODUCTION

1.1.Trigeminal Neuralgia

Trigeminal Neuralgia (NT) is the most frequently diagnosed type of facial pain, with a prevalence of 4-13 per 100,000 inhabitants according to different areas (1). It commonly affects patients over 50 years and the majority are women with a ratio of 1.5:1 compared to men. It is more frequent among patients diagnosed with multiple sclerosis (incidence of 1-2%). TN is associated with decreased quality of life, and has an impact on work capacity in 34% of patients (4), as well as the development of depressive symptoms.

It is a neuropathic disorder of the trigeminal nerve that causes episodes of severe pain in the sensitive innervation areas that depend on the three branches of the trigeminal nerve: V3 mandibular, V2 maxillary, V1 ophthalmic (Figure 1). The pain is shooting and is usually described by the patient as a sensation of electric shock that is limited to one branch or can affect several branches of the nerve. The duration of intense pain ranges from a few seconds to several minutes, mostly recurrent with pain-free intervals. Many patients point out trigger areas on the face that trigger pain when they are touched. Other activities that can trigger pain are chewing, talking, brushing teeth or applying facial cosmetics.

Figure 1. Trigeminal branches sensitive areas



1.1.1. Diagnosis, classification and etiology

There are two main types of TN, primary or idiopathic, and secondary. In the secondary forms it is evident that an extrinsic compression of the nervous structure is what triggers the pain, but regarding the pathophysiology of primary TN there are various hypotheses. The most recognised theory is compression of the dorsal trigeminal root when it comes out from the brainstem caused by vascular loops (1) Other theories propose that the demyelination of large fibers caused by various etiological processes (2) when produced in the Gasserian ganglion or in the dorsal root of the trigeminal nerve, would cause the formation of abnormal shunts that triggers the pain. These abnomal union of diferent fibres would be shaped by slow conduction nerve fibers, and can discharge through nearby unmyelinated axons by efapsis mechanism.

On the other hand, the pathophysiological theory described as the “epileptogenic theory”, argues that chronic irritation of the trigeminal nerve endings would produce an alteration in the segmental inhibitory systems of the sensitive trigeminal nuclei in the brainstem, and consequently the increase in the activity of these nuclei. The increased activity of the primary afferent fibres associated with deterioration of the inhibitory mechanisms of the sensory nuclei, is what would lead to the production of paroxysmal discharges of the interneurons of that nuclei in response to tactile stimulation (trigger), and as a result the painful crises (2). This mechanism can explain the effectiveness of antiepileptic drugs used in the pharmacological treatment of TN.

Nevertheless, evidence suggests that the most common chronic irritation that triggers the pathophysiological processes described for primary TN is vascular compression However, vascular compression of the nerve is not observed in all cases, which is why today it remains a controversial issue, and these cases are still considered primary or idiopathic TN (the International Headache Society includes these cases in the term Classic Trigeminal Neuralgia – see Table I).

Table I. Diagnostic criteria for classic trigeminal neuralgia according to the International Headache Society (IHS)

- Paroxysmal pain crisis lasting between one second to 2 minutes
- The pain must have at least one of the following characteristics: · Intense, superficial, electric and/or lancinating · Triggered in trigger zones or by external factors (chewing, speaking)
- No evidence of associated neurological déficits
- Not attributable to another concomitant condition

On the other hand, in secondary TN there is an initial disorder that is the origin of the structural or functional damage of the trigeminal nerve. The most common causes are multiple sclerosis that cause demyelination of the fibers of the nerve, or some brain tumors that compress the nerve and cause symptomatic TN. Classic TN usually presents with episodes that last several weeks or months followed by pain-free intervals, although some patients may have continuous residual pain, while in secondary TN there are no such pain-free periods, and there is usually chronic pain accompanied by paroxysms.

1.1.2. Treatment:

Medication is the first line of treatment, Carbamazepine and most recently Eslicarbazepine are the most widely used drugs.

In the treatment of patients with primary or (2) idiopathic TN, conservative management with drugs is considered the first line of action. The most used drug for decades has been carbamazepine. Several studies have demonstrated its effectiveness and it is also useful for diagnosis due to patients with idiopathic TN usually improve their symptoms (3). Patients with secondary TN or atypical facial neuralgia do not respond so well. The dose range between 200 and 1200 mg/day.

A systematic review by the AAN (American Academy of Neurology) published in 2008 determined that the response to treatment in the different studies carried out, with complete or almost complete resolution of pain, was around 58-100%, compared to placebo, which is 0-40% (4). Carbamazepine may sometimes be poorly tolerated, with a number needed to harm of 3 for mild adverse effects, and 24 for severe adverse effects. . However, it is still considered the first choice in cases of primary TN, with a moderate level of evidence (5).

Oxcarbazepine has also been shown to be effective in the treatment of primary TN. A randomized study included in the 2008 AAN review compared oxcarbazepine with carbamazepine in 178 patients with idiopathic TN. Both showed similar response with >50% reduction in pain attacks in 88% of cases. The dose range between 600 and 1800 mg/day. In some studies, oxcarbazepine shows better tolerability with a lower incidence of adverse effects compared to carbamazepine, however the level of evidence is lower (6) and it is considered a drug suitable for patients who do not respond or do not tolerate carbamazepine.

In addition, lamotrigine and baclofen have also shown efficacy, although to a more limited extent. Regarding lamotrigine, in a randomized double-blind study, 14 cases of TN refractory to carbamazepine were treated versus placebo, with 11/14 patients benefiting from the 400mg dose (7). The main limitation is that the initial dose is 25mg/day and must be increased by 50mg each week, so it takes several weeks to reach the effective dose of 400mg. With regard to baclofen, the evidence is limited to a double-blind study of 10 patients with TN in whom baclofen was administered (doses between 40 and 80 mg) versus placebo in another 10 patients with TN, in which it was obtained significant clinical benefit in seven of the patients treated with baclofen (6).

Recently, a relatively new antiepileptic drug such as lacosamide has been used, which has been shown to be effective intravenously in cases of acute pain attacks due to trigeminal neuralgia (4), and in observational studies in cases of patients with refractory neuropathic pain including series with trigeminal neuralgia.

However, the level of evidence for lacosamide treatment in trigeminal neuralgia remains to be determined.

Other drugs such as phenytoin, valproate, gabapentin or pregabalin have been used, suggesting their effectiveness, but there are no controlled studies to support it and the level of evidence is low. Some drugs such as gabapentin, pregabalin or levetiracetam have shown efficacy as adjuvants to first-line drugs. In most patients, 2 or more drugs, including carbamazepine, should be used before considering surgical options (5)

1.2. Surgery in trigeminal neuralgia

When medical treatment fails, open surgery or minimally invasive percutaneous techniques should be considered. Young, physically fit patients with vascular compression seen on imaging may be candidates for vascular microdecompression, while older patients or those with factors that imply a high surgical risk have been considered candidates for percutaneous rhizolysis (4). However, the optimization of percutaneous procedures, especially radiofrequency, has improved the results and may allow the indications to be expanded(8).

In relation to percutaneous techniques, which we will analyze below, three main procedures have been used: balloon compression of the Gasserian ganglion, rhizolysis with glycerol and rhizotomy or radiofrequency thermocoagulation. These procedures produce high symptomatic relief between 80-90% with pain recurrence rates higher than in vascular microdecompression, ranging between 20-30% after a period of 2 years (9) Complications include episodes of intraoperative bradycardia or asystole, facial hypoesthesia, paresis of the masseter muscle, and painful anesthesia. Currently, radiofrequency is one of the most used procedures given its good tolerance, especially in elderly patients, and the lower risk of complications compared to microvascular decompression or other percutaneous techniques (10). However, the main problem with percutaneous techniques, and especially radiofrequency thermocoagulation, is the tendency towards recurrence, which in some series reaches >60% after 2 years (11)

1.2.1. Percutaneous techniques

The percutaneous techniques used are balloon compression of the trigeminal ganglion, rhizolysis with glycerol, and rhizotomy by radiofrequency or thermocoagulation (12). These procedures produce a high symptomatic relief between 80-90% with higher pain recurrence rates than in vascular microdecompression, ranging between 20-30% after a period of 2 years (13) Complications include intraoperative episodes of bradycardia or asystole, facial hypoesthesia, masseter muscle weakness, and painful anesthesia. Radiofrequency is currently one of the most widely used procedures given its good tolerability, especially in elderly patients, and the lower risk of complications compared to microvascular decompression and other percutaneous techniques (9).

Initially described by Rethi in 1913 (14), it was not until 1975 that thermocoagulation of the trigeminal nerve and Gasserian ganglion was used as a treatment for TN pain (15). The first attempts confirmed its effectiveness regarding pain improvement, but the development of dysesthesias was also observed in a large number of treated patients (16). The subsequent development of thinner electrodes and with less diffusion of temperature made it possible to increase the selectivity of the lesion (17).

However, as less extensive lesions were achieved and paresthesias were reduced, less effectiveness was also observed in terms of pain reduction and greater recurrence (13)

-1.2.1.1. Balloon Compression (Mullan technique)

This technique originates in the work of Shelden and Pudenz in 1952 on posterior decompression of the Gasserian ganglion, whose subsequent evolution led them to formulate the hypothesis in which surgical trauma as well as decompression could produce symptomatic pain relief. However, it was not until 1983 when

Mullan and Lichtor developed the technique of percutaneous balloon compression of the Gasser ganglion (18).

In animal models, nerve compression appears to primarily damage medium and large myelinated pain fibers, leading to a disruption of the ephapsis-like mechanism of pain transmission (19)

The procedure consists of introducing a No. 4 Fogarty catheter through a cannulated Tuohy-type needle or a biopsy needle. Under general anesthesia, which does not require the patient's cooperation, the puncture is performed and the catheter is introduced into the foramen ovale (Figure 2). The tip of the catheter is left one centimeter behind Meckel's cavum and the balloon is inflated with 0-5-1 ml of 50% radiological contrast, so that it can be visualized with intraoperative fluoroscopy (Figure 3). The balloon should acquire a pear shape once inflated, and remain for between 2 and 3 minutes, although this time varies greatly between different authors (20).

It provides initial symptomatic relief rates of 91-94% (10), while at 3 years recurrence can be up to 56%. Regarding adverse effects, complications such as dysesthesias are reported in >20%, and hypoesthesia in up to 57%.

There are several reasons why balloon compression may not be effective. On the one hand, the shape of the Meckel's cavum is variable, and not in all cases the balloon will homogeneously compress the lymph node (example: in a very large

Meckel's cavum, it is likely that the balloon will not produce enough compression to obtain a therapeutic effect). Furthermore, the pressure of the balloon once inflated must be taken into account, since high pressure has been correlated with a greater number of dysesthesias, hypoesthesia and weakness of the masseter muscles, while low pressure in the balloon is associated with less symptomatic relief. and increased recurrence (21)

It has been postulated that balloon compression may offer advantages in patients with pain in the first branch V1, since the small fibers that conduct the corneal reflex would not be affected, so there would be a lower risk of being affected than in other techniques (19) . Also compared to other techniques, and mainly with respect to radiofrequency rhizotomy, it can offer advantages such as being performed under general anesthesia, which improves the patient's comfort and does not require their collaboration. It has not been possible to clearly establish the superiority of one percutaneous technique over another in trigeminal neuralgia(22). The few variations in the methodology since the appearance of balloon compression, and the optimization of other procedures, such as radiofrequency, that improve safety, have led to less use of this technique in recent years. Despite this, and taking into account its effectiveness, it can still be considered as a therapeutic option.

Figure 2. Fogharty number 4 for the Ballon Compression

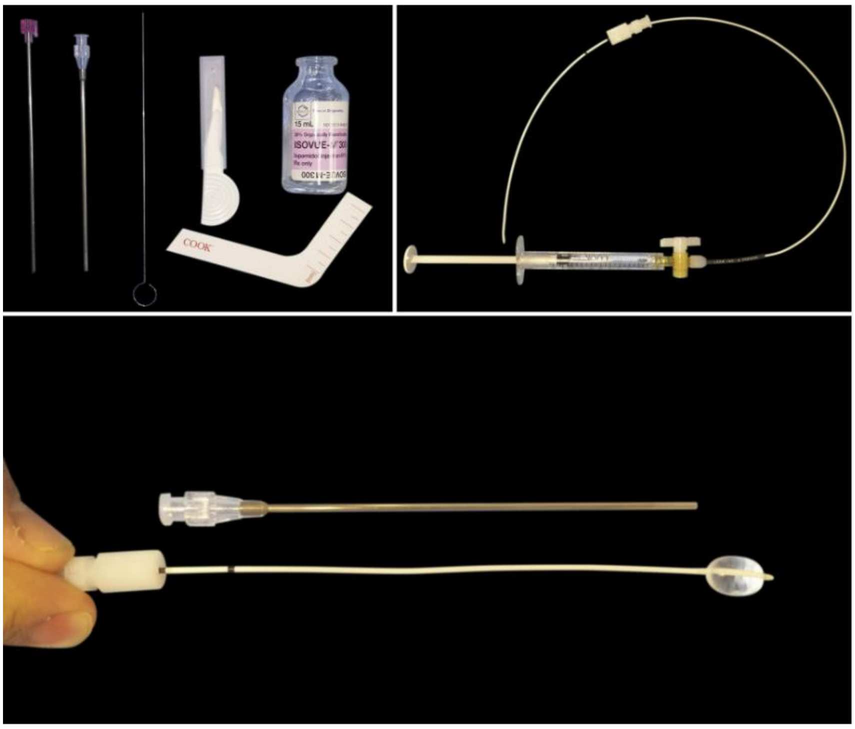


Figure 3. Ballon of the Fogharty catheter inflated through de foramen oval (into the Cavum of Meckel)

-1.2.1.2. Glycerol rhizolysis

Proposed by various authors since 1911, the injection of alcohol or other substances into the Gasser ganglion as a treatment for trigeminal neuralgia has been a widely used technique. The use of glycerol was initiated by Häkanson in 1981, coincidentally, due to the introduction of glycerol as a carrier of the tantalum isotope in a study of the treatment of TN by radiosurgery. They observed a symptomatic improvement after the introduction of glycerol, and in subsequent studies the technique was developed, which is based on the destruction of long fibers that cause pain through demyelination and axonal fragmentation (23)

The procedure can be performed under local or general anesthesia. A needle is introduced into the foramen ovale and through it first 1ml of contrast for fluoroscopy visualization of the Gasser ganglion cistern, and then 0.2-0.5ml of glycerol (23). Positive results range between 75-96%, but recurrence is high. Pain recurrence at 6 months is 20% on average, while at 3 years it is around 50% (21). The most frequent complication is facial hypoesthesia, between 20 and 40% of cases, which is usually associated with a decrease in pain, which is why it has been indicated as a positive predictive factor for clinical improvement (18). Other complications described are reactivation of cold sores (12%), dysesthesias or allodynia (4-11%) and aseptic meningitis (0-7%) (19)

With similar results and indications to balloon compression, both are non-selective techniques, since the procedure is not modified regardless of the symptomatic trigeminal roots. There are no comparative studies that establish differences between percutaneous techniques for TN, although some observational studies have suggested that glycerol injection may offer a lower rate of pain relief compared to radiofrequency thermocoagulation (19)

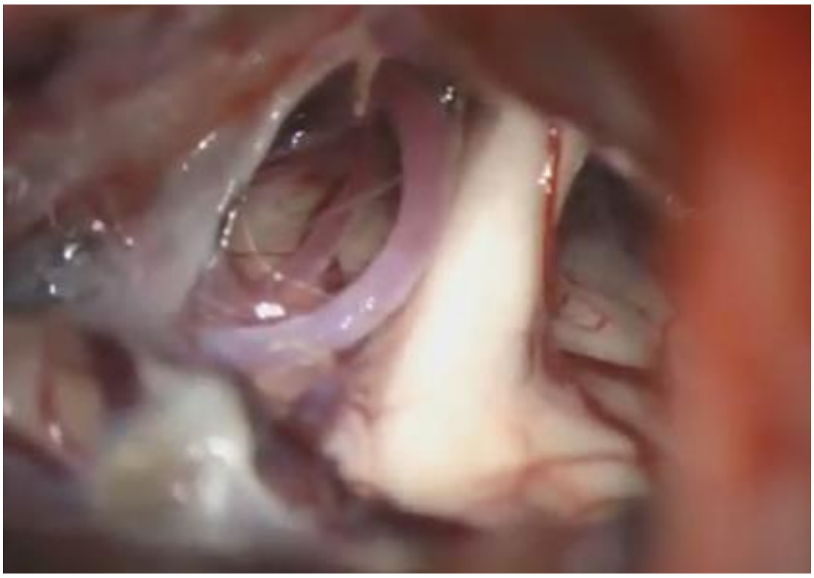
1.2.2. Microvascular decompression

The microvascular decompression (MVD) has been widely used as a non-ablative technique, based on the theory of compression of the trigeminal nerve as it exits the brain stem by a vascular structure, the most common being the superior cerebellar artery (24). The technique consists of performing a retrosigmoid craniotomy and separating the trigeminal nerve from the vessel that contacts it using a synthetic material, usually Teflon(25).

It is considered a technique that provides symptomatic relief to a high percentage of patients (>70%) and in a lasting manner, with less need to repeat the procedure compared to percutaneous ablative techniques (26) On the other hand, this technique has a higher postoperative morbidity, with a 5% incidence of complications such as ipsilateral hearing loss, CSF fistula or postsurgical hemorrhage (27). However, despite being considered the first-choice surgical technique in many centers, the majority of published studies are observational or retrospective, and there is no class I evidence that clearly determines the superiority of this technique over the others (28)

Figure 4. a: An artery (Superior Cerebelar Artery) attached to the trigeminal nervio y prepontine area. b: separation of the artery from the nerve. c: Introduction of Teflon matherial to maintain the separation. d: final position of the Teflon separating the nerve and de artery.

a:



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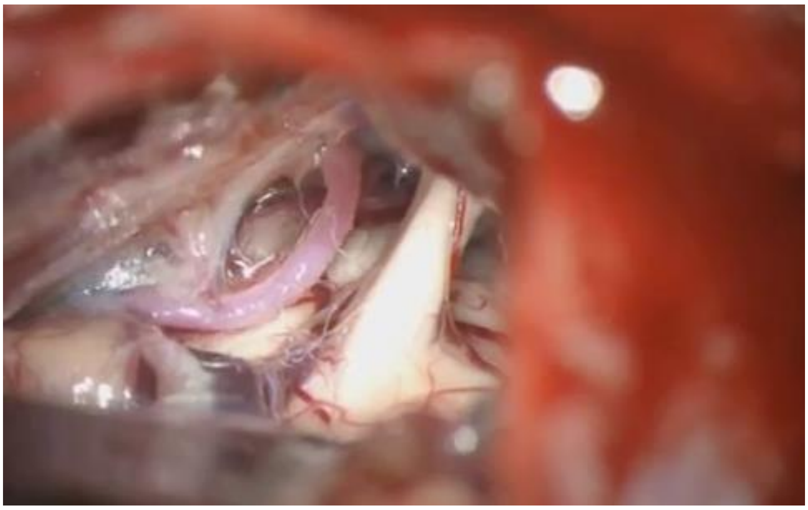

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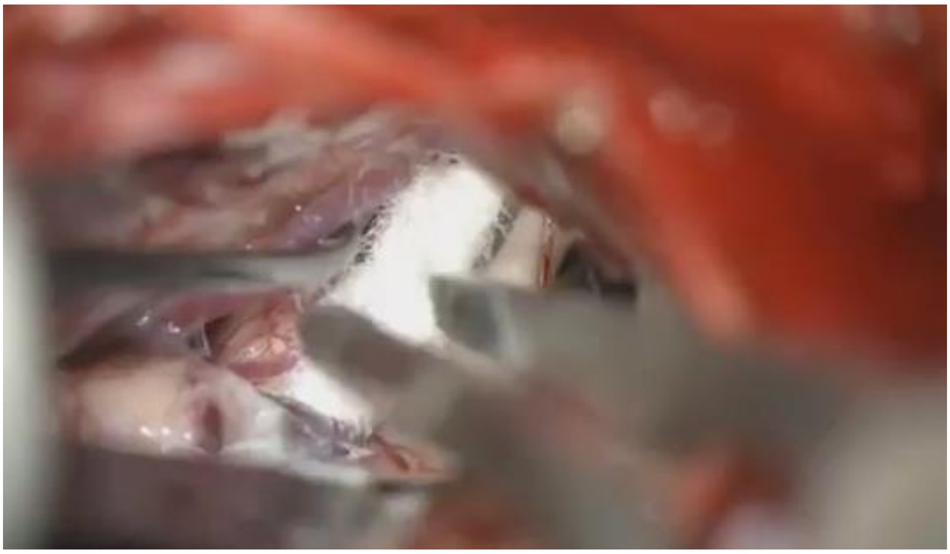

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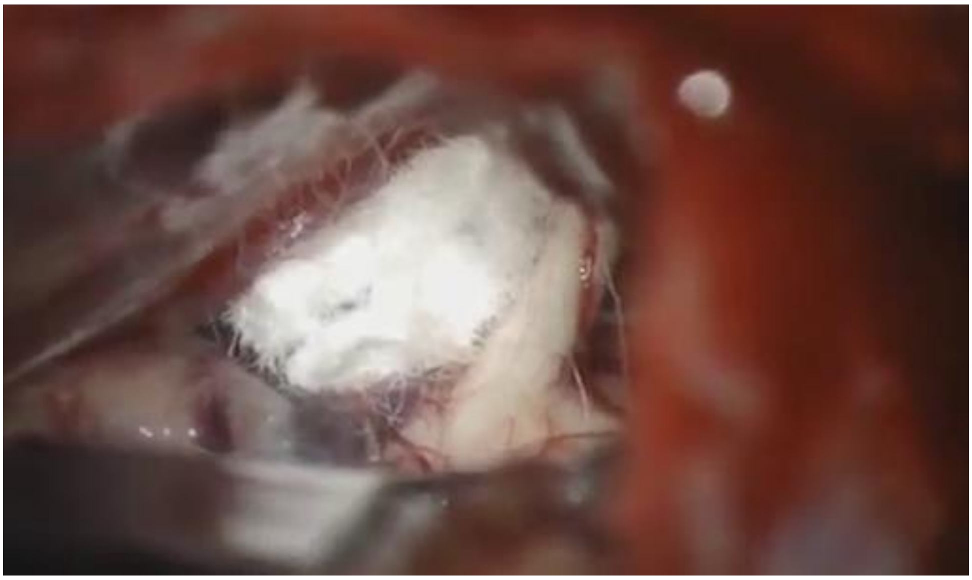


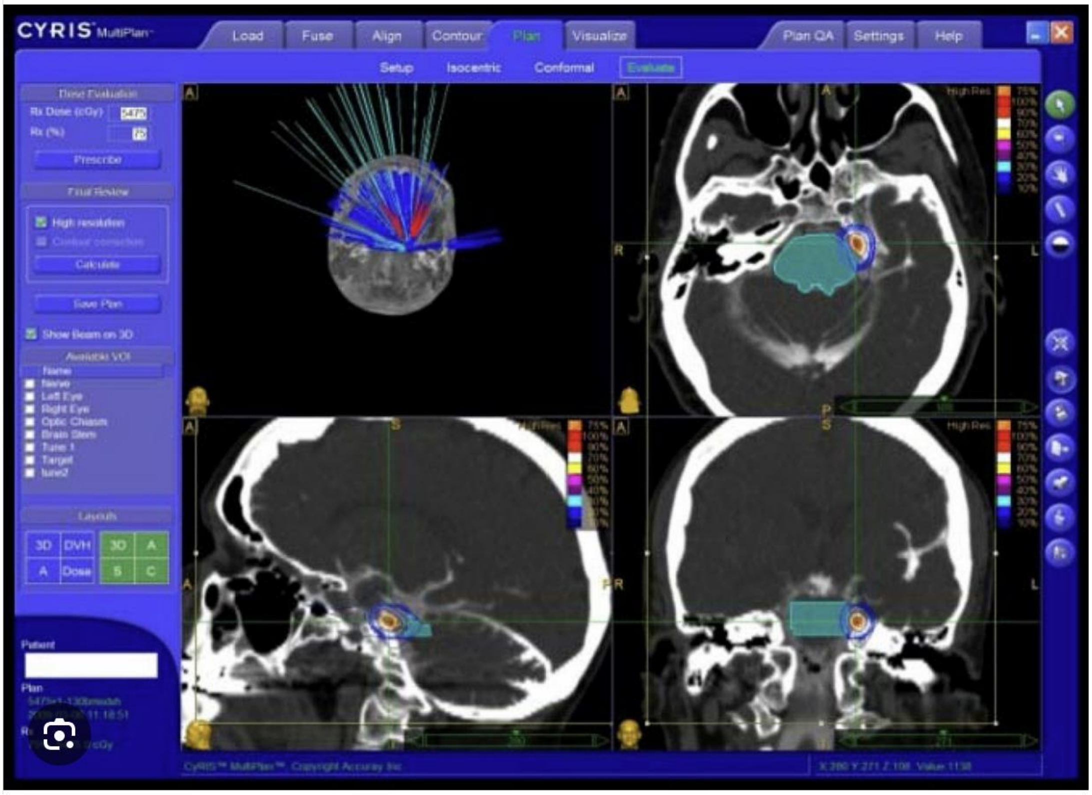
1.2.3. Radiosurgery

Ablative techniques include most percutaneous techniques and stereotactic radiosurgery (Gamma knife or Linac) (Figure 5), a technique that has been used more and more frequently in recent years. The difference between radiosurgery and other techniques is that the symptomatic relief is not immediate, but appears about two weeks after the start of treatment. On the other hand, it also achieves improvement in 80% of cases and is one of the most appropriate techniques in elderly patients or with pathologies that contraindicate surgical treatment, given the low risk of complications. It also requires anatomical feasibility in the prepontine area and a very accurate planification (Figure 6). In a recent study of 30 patients with idiopathic TN with contraindication for surgery, radiosurgery was performed using a linear accelerator (Linac) (29), obtaining a 90% significant clinical improvement at a mean time of 1.6 months after surgery (range 1 week-4 months). , with a mean recurrence-free time of 62.7 months (30)

The improvement after treatment could be different depending on the etiology, in some cases of secondary neuralgy, such as multiple sclerosis cases, the clinical benefit could be lower (31)

Figure 5. Stereotactic Radiosurgery for Trigeminal Neuralgia

Figure 6. Planification for Radiosurgery in Trigeminal Neuralgia

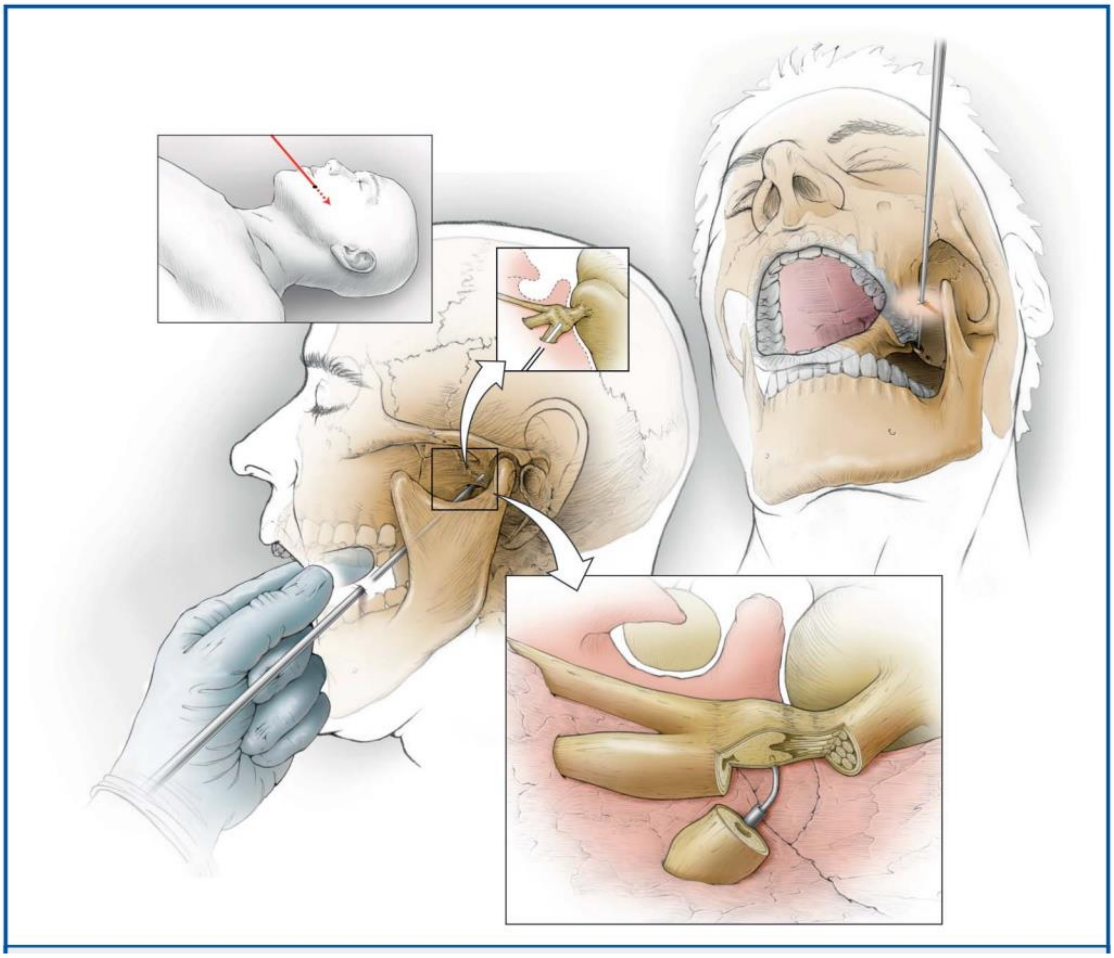


1.3.Radiofrequency rhizotomy

It was initially described by Rethi in 1913, but it was not until 1975 when thermocoagulation of the trigeminal nerve and Gasser's ganglion was used as a treatment for TN pain (32). The first attempts confirmed its effectiveness in terms of pain improvement, but development of dysesthesias was also observed in a large number of treated patients. The subsequent development of thinner electrodes with less temperature diffusion made it possible to increase the selectivity. However, the less extensive lesions were achieved and paresthesias were reduced, the less effectiveness was also observed in terms of lowering pain and greater recurrence (33)

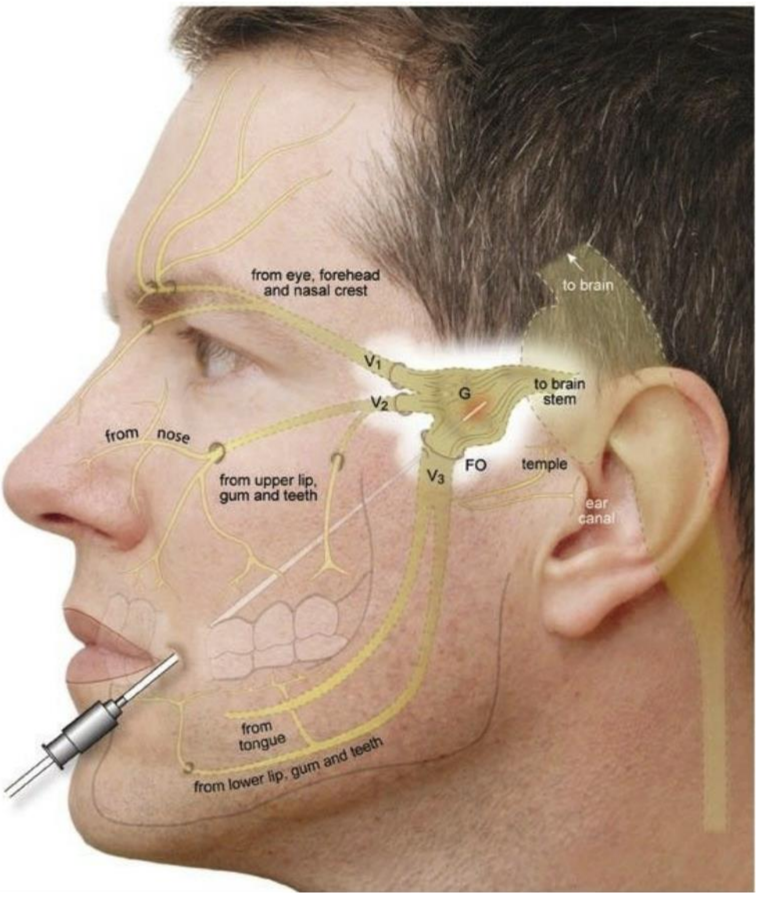
The procedure consists of radiofrequency thermocoagulation of the Gasserian ganglion through a percutaneous puncture guided by fluoroscopy. The patient is placed in a supine position with the head slightly extended and the fluoroscopy arc is placed in an oblique submental projection in order to visualize the foramen ovale. At the point located 2-3 cm from the labial commissure, a cannula (22g) is introduced after instillation of local anesthesia, which is directed towards a path located between the confluence of the midpupillary line and a point 3 cm anterior to the external auditory canal(34) (Figure 7). A finger must be placed in the oral cavity to prevent the cannula from penetrating the oral mucosa, with the consequent risk of contamination. When the cannula reaches the foramen ovale, its depth in Meckel's cavum is controlled using a lateral fluoroscopic projection, until reaching at most the point of union between the petrous bone of the temporalis and the clivus (35).

Figure 7. Introduction of the cànula and landmarks



At this time, the stylet is removed from the cannula, and the electrode is inserted (Figure 8). Before causing the injury, a stimulation test must be performed, which is usually carried out with the patient awake. If motor stimulation is performed at a frequency of 2 Hz, and contraction of the masseter muscle is obtained, it can be confirmed that the cannula has crossed the foramen ovale and is in contact with the mandibular nerve (V3 or third branch of the trigeminal)(36). Sensory stimulation is performed at a frequency of 50 Hz and a voltage between 0.1-0.5 V, with which paresthesias must be obtained in the territory of the nerve branch closest to the electrode (V1, V2 or V3). If paresthesias only occur with a voltage higher than 0.5 V, it is considered that the electrode is too far from the nerve roots to perform the lesion, and the cannula should be repositioned until a response is obtained at a lower voltage (37)

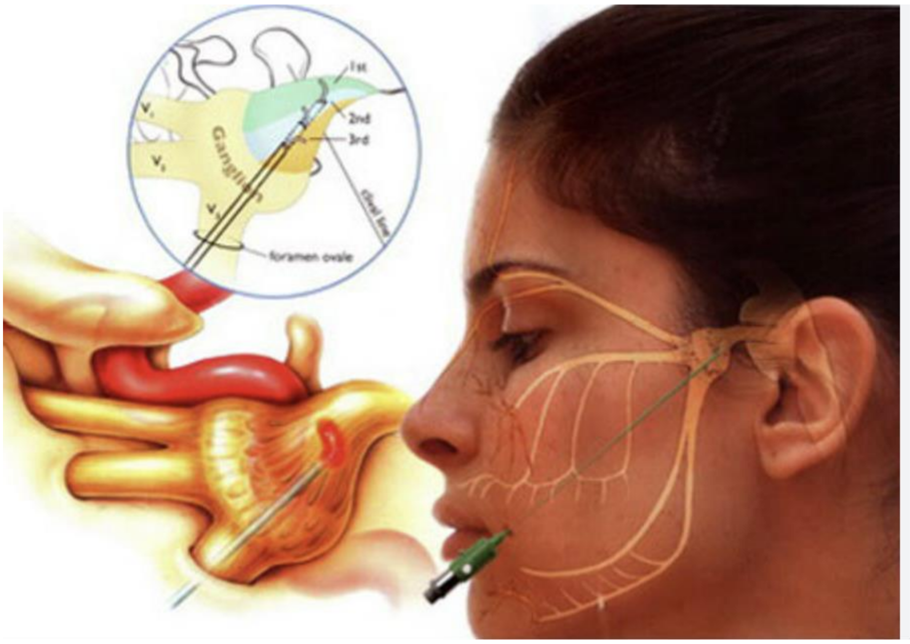
Figure 8. Radiofrequency Electrode introduced into the Gasserian Ganglion



The lesion can be performed using continuous conventional radiofrequency (RFC), usually with a temperature of 60ºC for 60 seconds, or using pulsed radiofrequency (RFP). The latter is a less destructive method of nerve injury with energy transmitted by radiofrequency, which, in contrast to conventional radiofrequency, transmits short pulses of energy at 42ºC or higher, interspersed by pauses that allow the heat to dissipate in the tissue. surrounding the electrode.

The objective of radiofrequency is the injury of type A-delta and C nerve fibers, which are responsible for pain transmission. RFC has been shown to be more effective than RFP in symptomatic pain relief (37). but it has been associated with a greater number of complications, producing thermal injuries in the A-beta fibers that transmit touch, rather than in the A-delta and C fibers that are the primary target of the injury (38) On the other hand, regarding the results of RFP, it has been observed that the greatest effectiveness is achieved in cases carried out with higher intensity or voltage parameters, thus obtaining better and longer results (39) Depending of the position of the electrode in de Gasserian Ganglion of the Trigeminal Nerve, deeper or superficial, it will be affecting fibers depending of each three branches of the nerves.

Figure 9. Gasserian Ganglion and disposition of fibers from each branch



Radiofrequency thermocoagulation is a very effective procedure in terms of initial pain relief, with clinical improvement having been described in up to 97% of cases (40) Pain recurrence percentages are difficult to establish due to the variability in follow-up in different studies. Early recurrence at 6 months has been described in up to 25%, and persistence of pain relief without recurrence in 52.3% at 10 years (41) The most frequent complications related to thermocoagulation are facial hypoesthesia (1-9%) and corneal anesthesia (0-17%) (42).

However, the degree of postoperative hypoesthesia has been correlated with the durability of the long-term therapeutic effect (43) On the other hand, the use of intraoperative sensory stimulation with the patient awake has reduced other unwanted complications such as severe dysesthesia from 5 to 2% and painful anesthesia from 1.6 to 0.2%. In a 2004 systematic review (44) nine observational studies comparing percutaneous techniques and stereotactic radiosurgery were identified. Among the conclusions, it was indicated that radiofrequency thermocoagulation may offer better rates of complete pain resolution compared to glycerol injection, and also compared to radiosurgery. On the other hand, it was also associated with a higher percentage of complications (45)

Thermocoagulation or radiofrequency rhizotomy is a very effective procedure in terms of initial pain relief, with clinical improvement having been described in up to 97% of cases (46). Pain recurrence percentages are difficult to establish due to the variability in follow-up in different studies (47). Early recurrence at 6 months has been described in up to 25%, and persistence of pain relief without recurrence in 52.3% at 10 years (26). The most frequent complications related to thermocoagulation are facial hypoesthesia (1-9%) and corneal anesthesia (0-17%). However, the degree of postoperative hypoesthesia has been correlated with the durability of the long-term therapeutic effect (28). On the other hand, the use of intraoperative sensory stimulation with the patient awake has reduced other unwanted complications such as severe dysesthesia from 5 to 2% and painful anesthesia from 1.6 to 0.2% (26).

The determining factor for a good clinical result will be the adequate location that allows selective injury in the fibers corresponding to the painful territory.

Classically, the procedure has been performed using local anesthesia and sedation, keeping the patient awake at the time of sensory stimulation with the same electrode that caused the lesion, so as to describe the territory where the paresthesias are perceived.

This methodology can sometimes be uncomfortable and painful, generating stress and decreasing the degree of patient satisfaction. In 2012, Berdensky and others (48) described the technique of monitoring somatosensory potentials of the three branches of the V pc and the selective localization of the branches to be treated using antidromic stimulation. Various variations have been carried out in recent years (48) with different monitoring techniques and different electrodes (49).

RATIONALE OF THE STUDY

The Trigeminal Neuralgia is a terrible disease for patients who suffer from it, and as a specialist I have always been interested in optimizing and improving the techniques that we can offer to these patients.

This is a study I have been doing for more than 7 years. Initially, it was an idea that came from reviewing a study that attempted to monitor radiofrequency rhizotomy of the trigeminal nerve, but neither the methodology nor the electrodes used were explained. We had an idea, with we came into with the Neurophysiologist at that time at the Joan XXIII University Hospital in Tarragona (Dr Vicenç Pascual), to manufacture an electrode, which we did with the help of the Hospital's Electromedicine team. The first attempts were promising but the methodology and the interpretation of the record obtained was still very preliminary.

Shortly after, I moved to another city and started a new position as a neurosurgeon at the Vall d'Hebron University Hospital in Barcelona. At that time, with the support of Dr J. Sahuquillo, my tutor and director at the moment, and after designing the study, speaking with the Neurophysiological Monitoring team (Dr Dulce Moncho) and obtaining approval from the ethics committee, I started this study and became PhD candidate. I operated all the patients recruited and collected all the data myself from them over the years from 2015 to 2022. In the first cases performed, the electrode utilized was not precise enough. I searched for a specific electrode by size and length that would be used to tunnel from a trocar punctured in the facial region to the foramen ovale. It was not easy at all, since none of these characteristics existed on the market. After speaking with several commercial companies, I found out that we could design one with the appropriate length and thickness.

HYPOTHESIS

The hypotheses to be confirmed or refuted in this study are the following:

H1. Intraoperative neurophysiological monitoring for the identification of trigeminal roots is applicable through the use of two electrodes, one specific for stimulation and the other for applying the radiofrequency lesion.

H2. Identification of trigeminal roots by antidromic stimulation is effective for selective rhizotomy in trigeminal neuralgia.

H3. The improvement in the selectivity of the radiofrequency procedure may improve its effectiveness compared to other percutaneous techniques such as balloon compression (Mullan) in the surgical treatment of trigeminal neuralgia.

OBJECTIVES

MAIN OBJECTIVE: To determine the applicability of neurophysiological monitoring with two electrodes for the identification of trigeminal roots and radiofrequency.

SECONDARY OBJECTIVES:

O1. Accurately describe the territory and the roots that trigger the pain, and determine the concordance between the roots monitored and whose stimulation is obtained selectively, and the level of symptomatic relief.

O2. Determine the effectiveness of assisted radiofrequency with selective monitoring compared to other techniques such as balloon compression (Mullan), whose effectiveness compared to conventional radiofrequency in the literature is comparable.continuous radiofrequency with parameters of time and intensity in low or middle range, and determine if good results of symptomatic relief are obtained.

METHODS

This is a prospective study of a cohort of 36 adult patients, aged between 18 and 85 years, with trigeminal neuralgia not controlled with pharmacological treatment and who do not present a contraindication or major indication for any of the other techniques. They will be studied consecutively in the Neurosurgery Service of the Vall d'Hebron University Hospital in Barcelona. Patients who meet all the inclusion criteria and none of the exclusion criteria detailed in the following section will be prospectively included.

Table 2. Inclusion and Exclusion criteria

Inclusion:

1. Diagnosis of trigeminal neuralgia, primary or secondary to other causes whose treatment has not resolved the neuralgia symptoms.

2. Persistent symptoms despite pharmacological treatment with two drugs at optimal doses, one of which should include carbamazepine or stilcarbazepine (except allergies). In case of severe side effects or non-tolerability to pharmacological treatment, surgery may also be indicated.

3. Patients must read and sign an informed consent for their participation in the study.

Exclusion:

1) Atypical facial neuralgia or in which the painful territory does not correspond to trigeminal roots

2) Record of psychiatric or neurological diseases that may interfere with the perception of pain or the result of the technique

3) Secondary TN due to causes whose specific treatment could solve the symptoms

4) who do not agree to participate in the study.

All patients included will have recorded the following variables, which will be collected in a database specifically designed for this study: demographic data and comorbidities, duration of neuralgia, painful territory, pain intensity (VAS scale – Figure 10, Barrow Neurological Institute scale – Figure 11), surgical treatment or previous interventional techniques.

The evaluation of the result of the surgery will be carried out based on the symptomatic relief produced. Pain intensity will be evaluated pre- and postoperatively using the Visual Analog Scale (VAS) and symptomatic relief will be considered in the absence of trigeminal pain or a >50% decrease in the VAS scale. The correspondence of the area of hypoesthesia with respect to the branches located through intraoperative stimulation is also analyzed. There is also recorded the selectivity of de intraoperative stimulation.

The minimum follow-up carried out is 1 year, with a preoperative visit in which the surgical procedure is decided and consent is obtained to include in the study, the preoperative assessment at 24 hours post-surgery, and follow-up visits at 3, 6, and 12 months.

Figure 10. VAS (visual analog scale for pain)

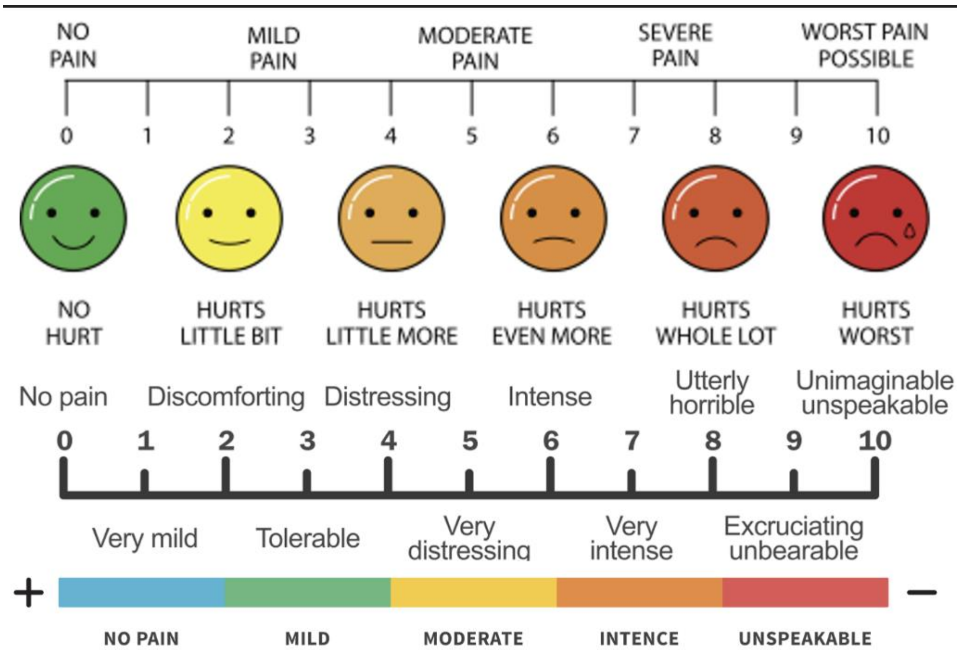


Figure 11. BNI (Barrow Neurological Institute) Scale of Pain

BNI pain intensity scale	
Score	Pain description
I	No pain, no medications
II	Occasional pain, no medications required
III	Some pain, adequately controlled with medications
IIIa	No pain, continued medication
IIIb	Persistent pain, controlled with medication
IV	Some pain, not adequately controlled with medications
V	Severe pain or no pain relief

In these 36 patients who meet inclusion criteria, radiofrequency surgery on the trigeminal gasser ganglion is performed under neurophysiological monitoring. In the following sections we describe the surgical procedure. These 36 patients underwent surgery between 2015 and 2022. The monitoring procedure, although it does not differ from usual clinical practice, was included in a study protocol and approved by the Vall d'Hebron University Hospital research ethics committee (CEIC 80 /2013).

On the other hand, another cohort of patients operated on using another balloon compression technique (Mullan) was obtained. These are 25 patients with similar characteristics. They were operated between 2016 and 2021, all using the same technique (described in the introduction). It should be noted that many of them were operated on in the year 2020-21 because the circumstances of the COVID pandemic prevented the introduction of external material, such as radiofrequency devices, into the operating rooms of our Vall d'Hebron University Hospital.

That’s why that the majority of these patients treated with the Mullan technique are demographically and clinically similar, and many of them were treated with this technique due to the technical difficulties in obtaining all the equipment necessary to perform the radiofrequency technique. In some cases, it is a technique that is preferred in case of selective involvement of V1, but we have avoided including patients with these characteristics to avoid bias when comparing the results between both techniques.

5.1 Surgical Technique

Under general anesthesia and with the patient intubated or with a laryngeal mask, somatosensory evoked potentials are initially performed to place needle electrodes in the three ophthalmic, maxial and mandibular branches (Figure 12). A multichannel electromyography/evoked potential machine was used for neurophysiological monitoring (Figure 2). We developed this technique with the important collaboration of the Neurophisiology department of Univervisity Hospital Vall d'Hebrón of Barcelona (Dra Kimia Rahnama, Dra Angie Sanchez, Dra Dulce Moncho) and Hospital Joan XXIII of Tarragona (Dr Vicenç Pascual).

Figure 12. Electrodes for recording in the three trigeminal branches

The patient is then placed in a supine position with the head slightly extended and the fluoroscopy arc is placed in an oblique submental projection in order to visualize the foramen ovale. At the point located 2-3 cm from the labial commissure, a cannula (22g) is introduced after instillation of local anesthesia, which is directed towards a path located between the confluence of the midpupillary line and a point 3 cm anterior to the external auditory canal. A finger must be placed in the oral cavity to prevent the cannula from penetrating the oral mucosa, with the consequent risk of contamination. When the cannula reaches the foramen ovale, its depth in Meckel's cavum is controlled using a lateral fluoroscopic projection, until reaching at the point of union between the petrous bone of the temporalis and the clivus. At this time, the stylet is removed from the cannula, and the stimulation electrode is introduced. Stimulation is performed in the Gasserian ganglion, mapping from its entrance in the foramen ovale to the confluence between the petrosal bone and the sella turcica. The potential response is observed to determine the correspondence of the fibers with the trigeminal branch (Figure 13). We can compare this process with that carried out in the study by Berdensky et al (Figures 14 and Figure 15), and we see its reproducibility, despite the use of different electrodes. In Berdensky's study (48), the same electrode is used for recording and lesion, being a very thin monopolar electrode that can conduct the lesion by radiofrequency. In our case we used two different electrodes, one for stimulation and the other for injury. We believe this can improve the selective mapping of the fibers and produce a more effective lesion.

Figure 13. Selective stimulation response in V3 – Neurophisiological stimulation in our screen

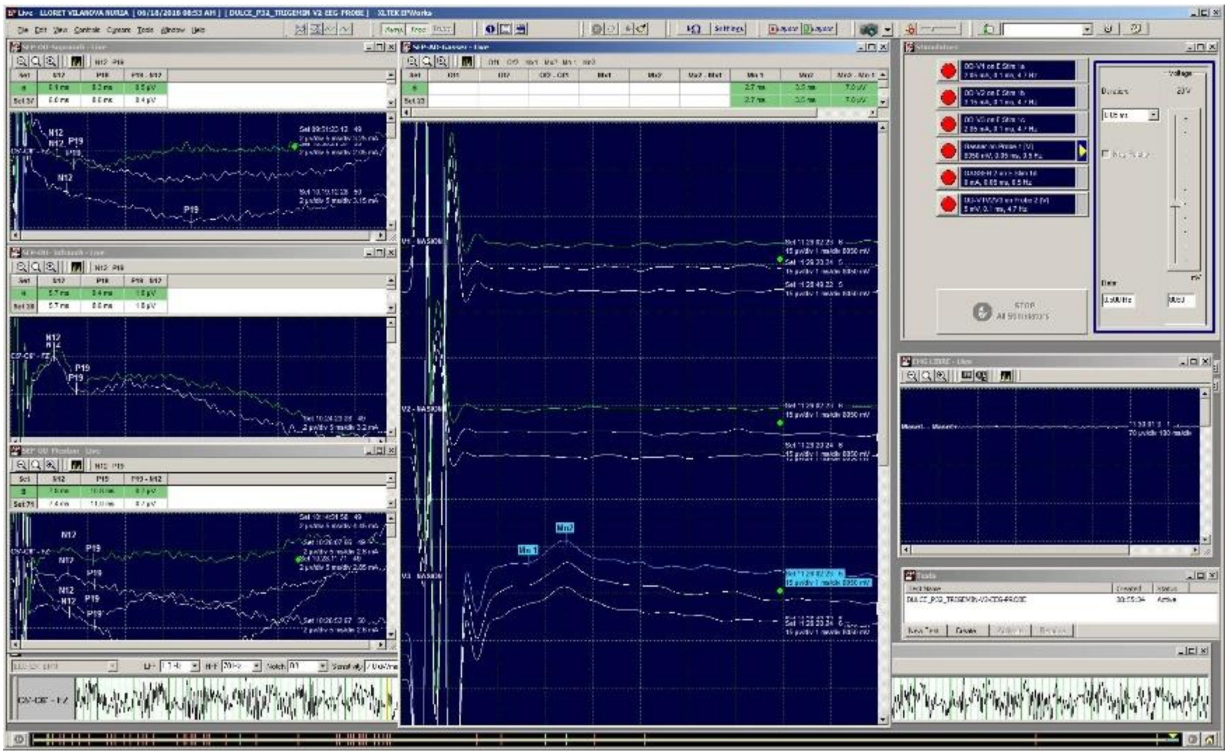


Figure 14. Picture from Berdensky et al., expected type of recording for each branch

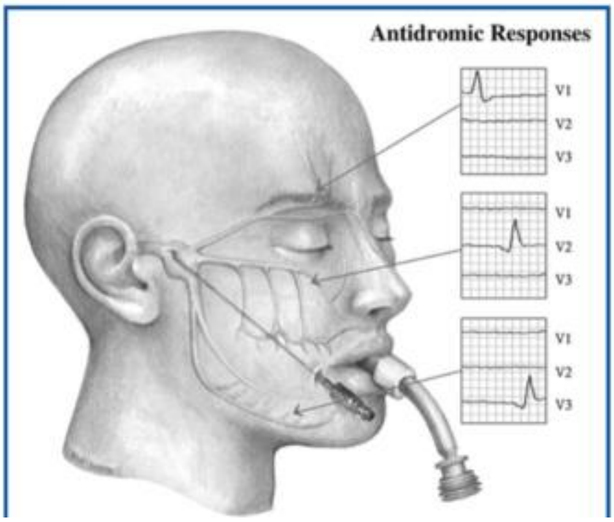
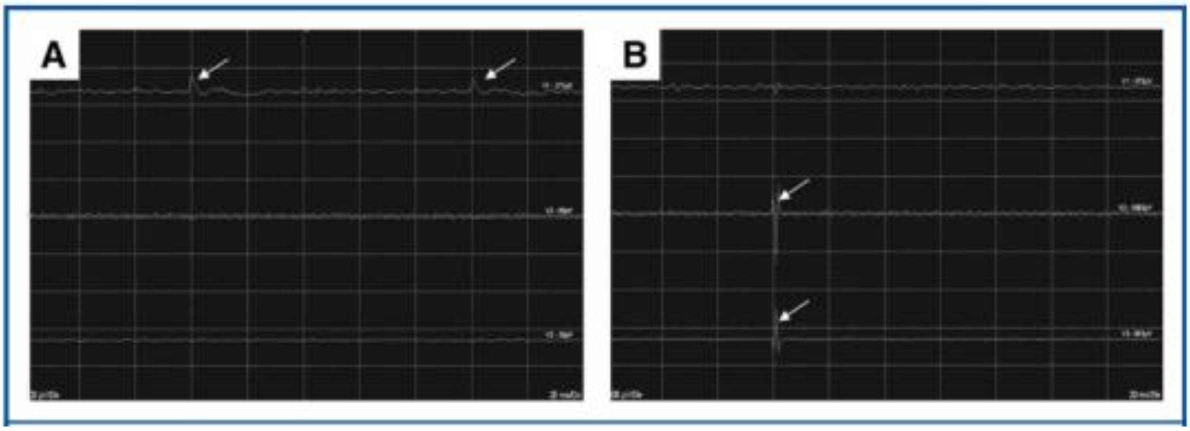


Figure 15. Picture from Berdensky et al., Neurophisiological stimulation in their study



Once the location has been decided, a lesion is performed using a radiofrequency electrode. It can be performed using continuous conventional radiofrequency (RFC), usually with a temperature of 60ºC for 90 seconds, or using pulsed radiofrequency (RFP). The RFP is a less destructive method of nerve injury with energy transmitted by radiofrequency, which, in contrast to conventional radiofrequency, transmits short pulses of energy at 42ºC or higher, interspersed by pauses that allow the heat to dissipate in the tissue. surrounding the electrode.

The objective of radiofrequency is the injury of type A-delta and C nerve fibers, which are responsible for pain transmission. RFC has been shown to be more effective than RFP in symptomatic pain relief. but it has been associated with a greater number of complications, producing thermal injuries in the A-beta fibers that transmit touch, rather than in the A-delta and C fibers that are the primary target of the injury. On the other hand, regarding the results of Radiofrequency, it has been observed that the greatest effectiveness is achieved in cases carried out with higher intensity or voltage parameters, thus obtaining better and longer results. The choice of parameters in our series is the RFC at 60º for 90 seconds.

In a first cohort of 15 patients, the same electrode was used for stimulation and lesion, through a modification of the cable with two terminals. The first patients obtained good potentials after antidromic stimulation, but variability was observed in the intensity of the response and conduction through several branches. For this reason, in the study cohort of 30 patients, a stimulator with a specific size and morphology design for antidromic stimulation was used on the one hand (Figure 16, 17), and radiofrequency electrodes with similar active tip (5mm, Figure 18, 19) on the other). They are guided by external marking and fluoroscopy localization to perform the lesion at the same stimulation point.

Figure 16. Specific Recording Electrode Design for Trigeminal Monitoring

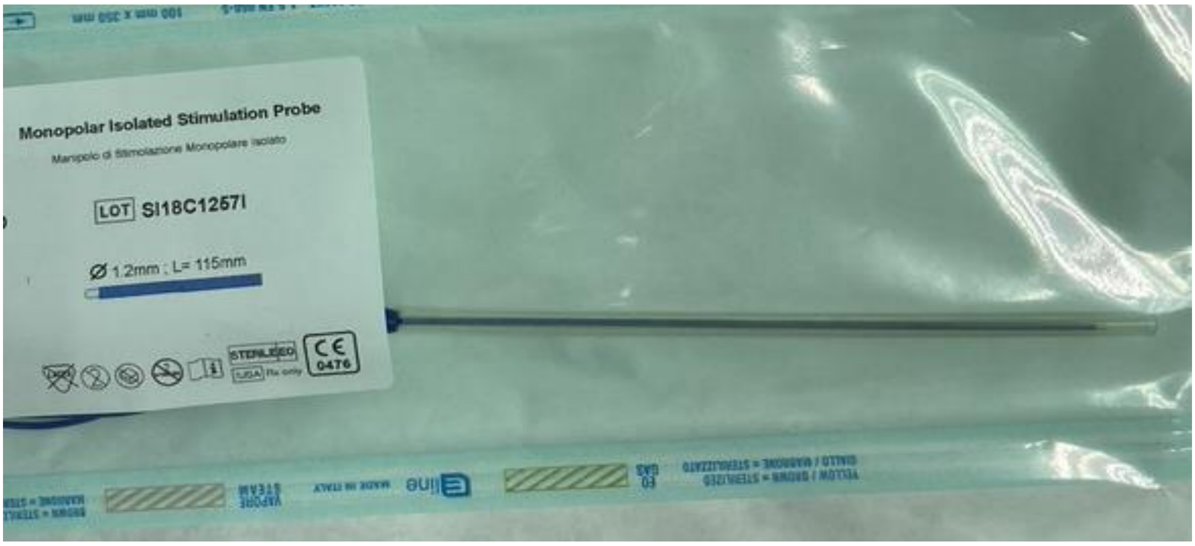


Figure 17. Intraoperative introduction of the Recording Electrode through cannula 22G

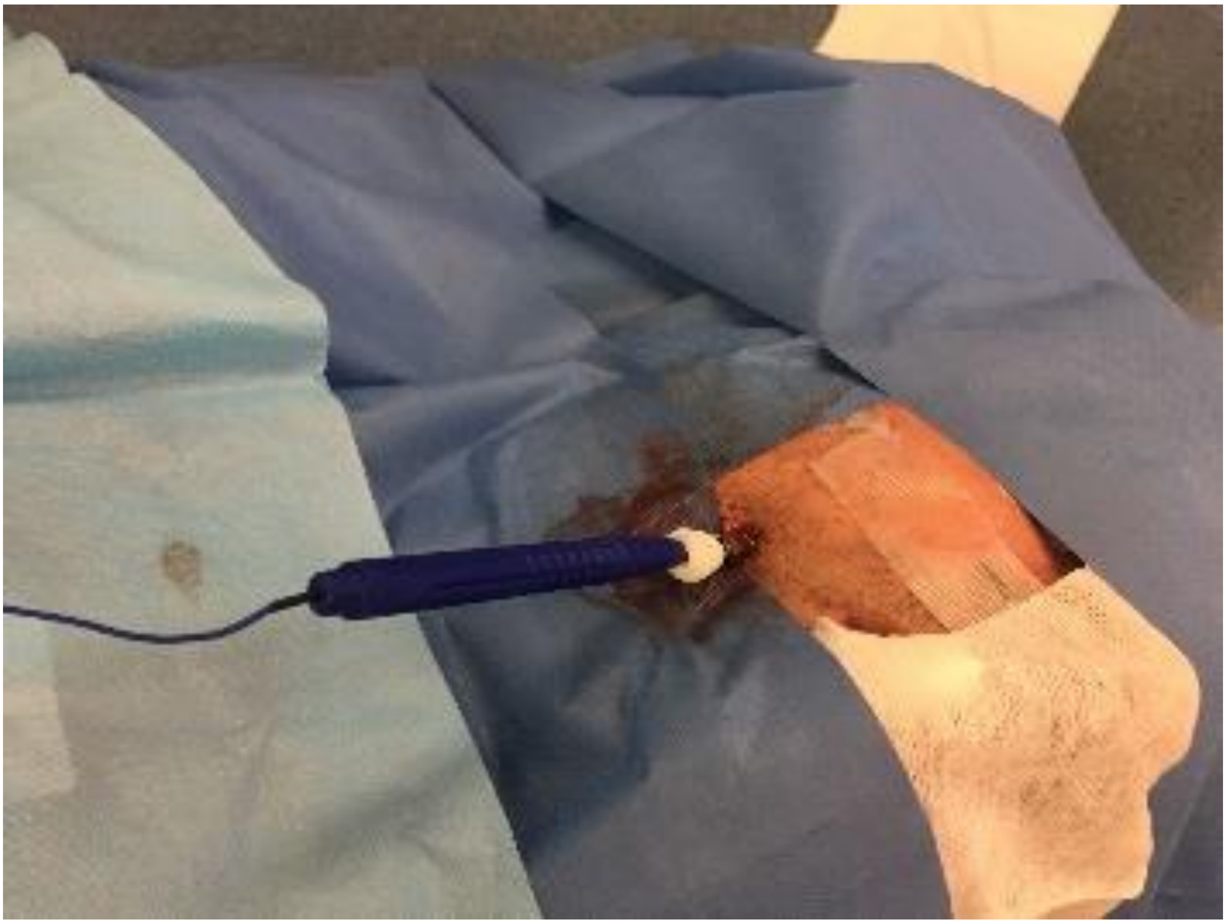


Figure 18. Radiofrequency Electrode

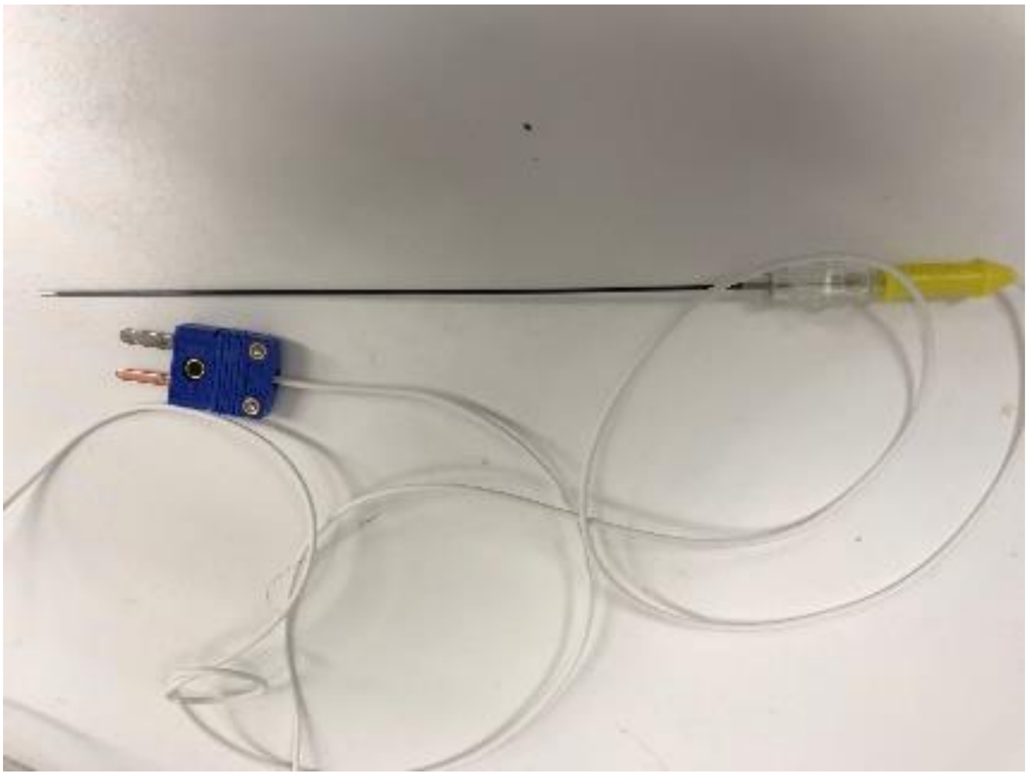
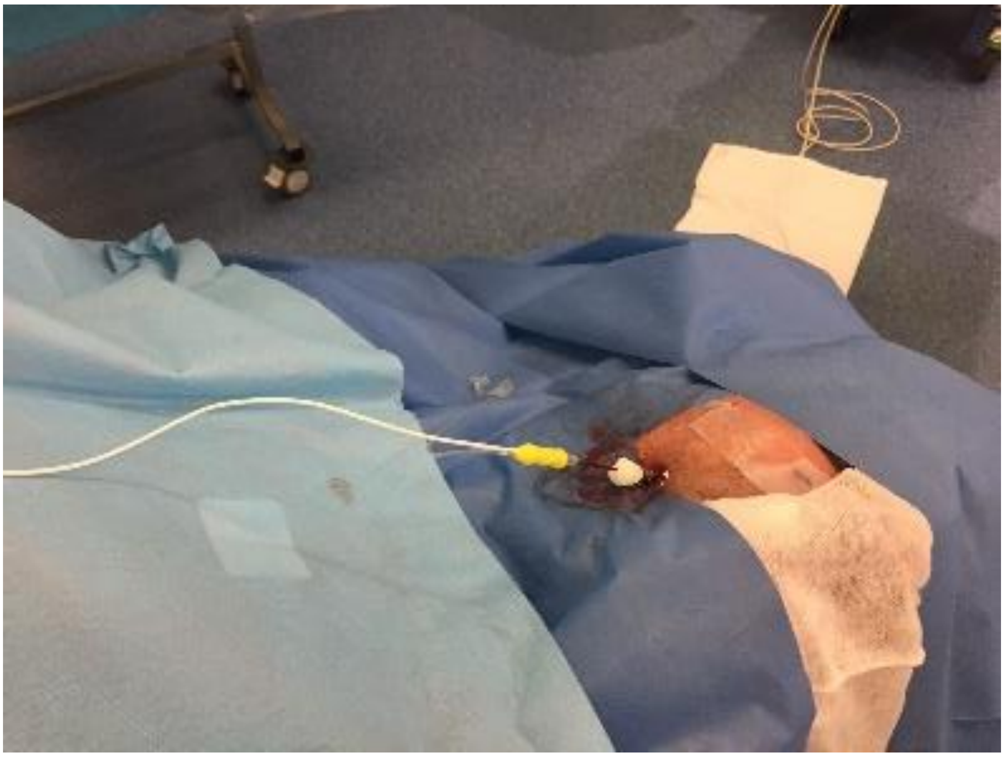


Figure 19. Intraoperative Introduction of the Radiofrequency Electrode



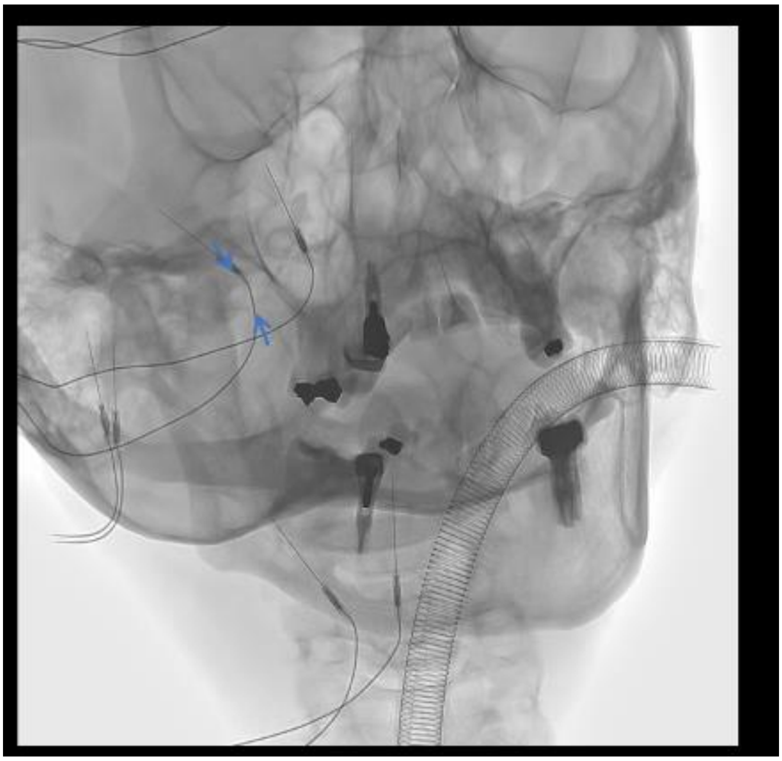
5.2. Step by step procedure

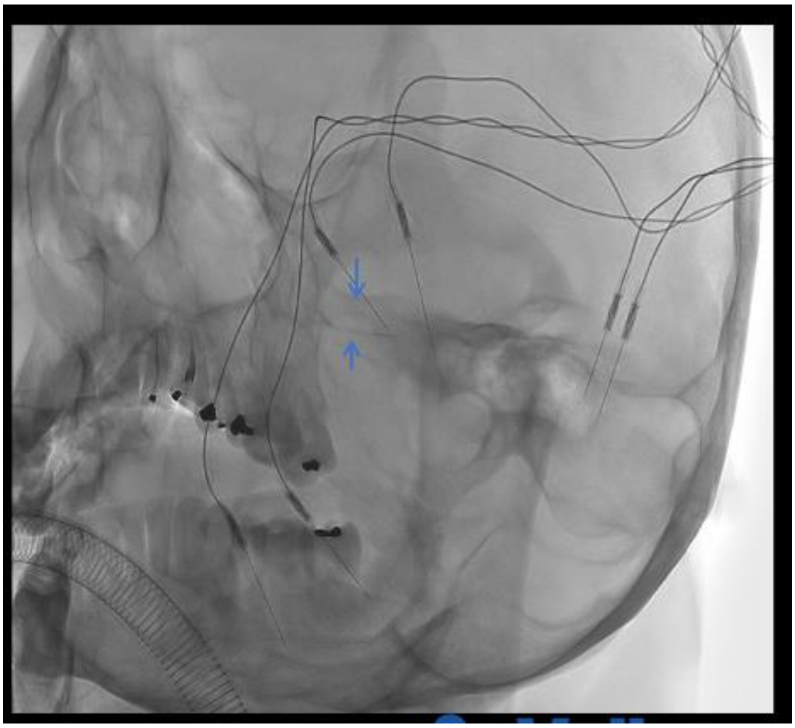
1 Placement of subcutaneous electrodes in the 3 subdivisions of the trigeminal nerve (Figure 20)

2. Sensory potentials / orthodromic stimulation (in the direction of the fibers)

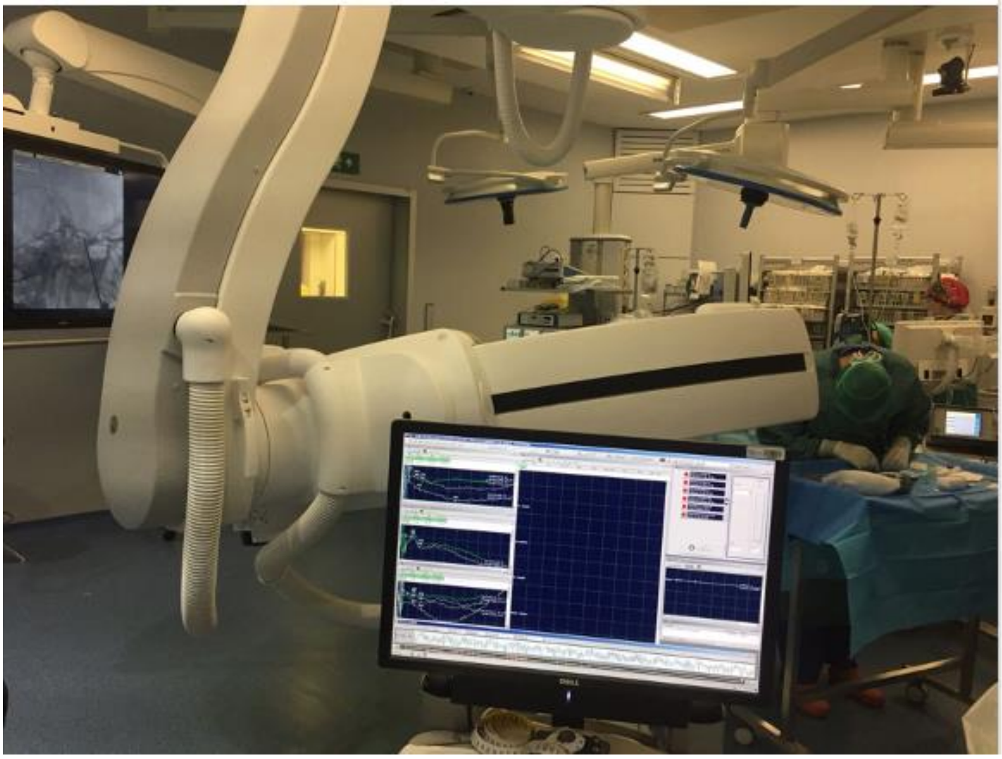
(Figure 21)

3. Location of foramen ovale, oblique AP projection (Figure 22)

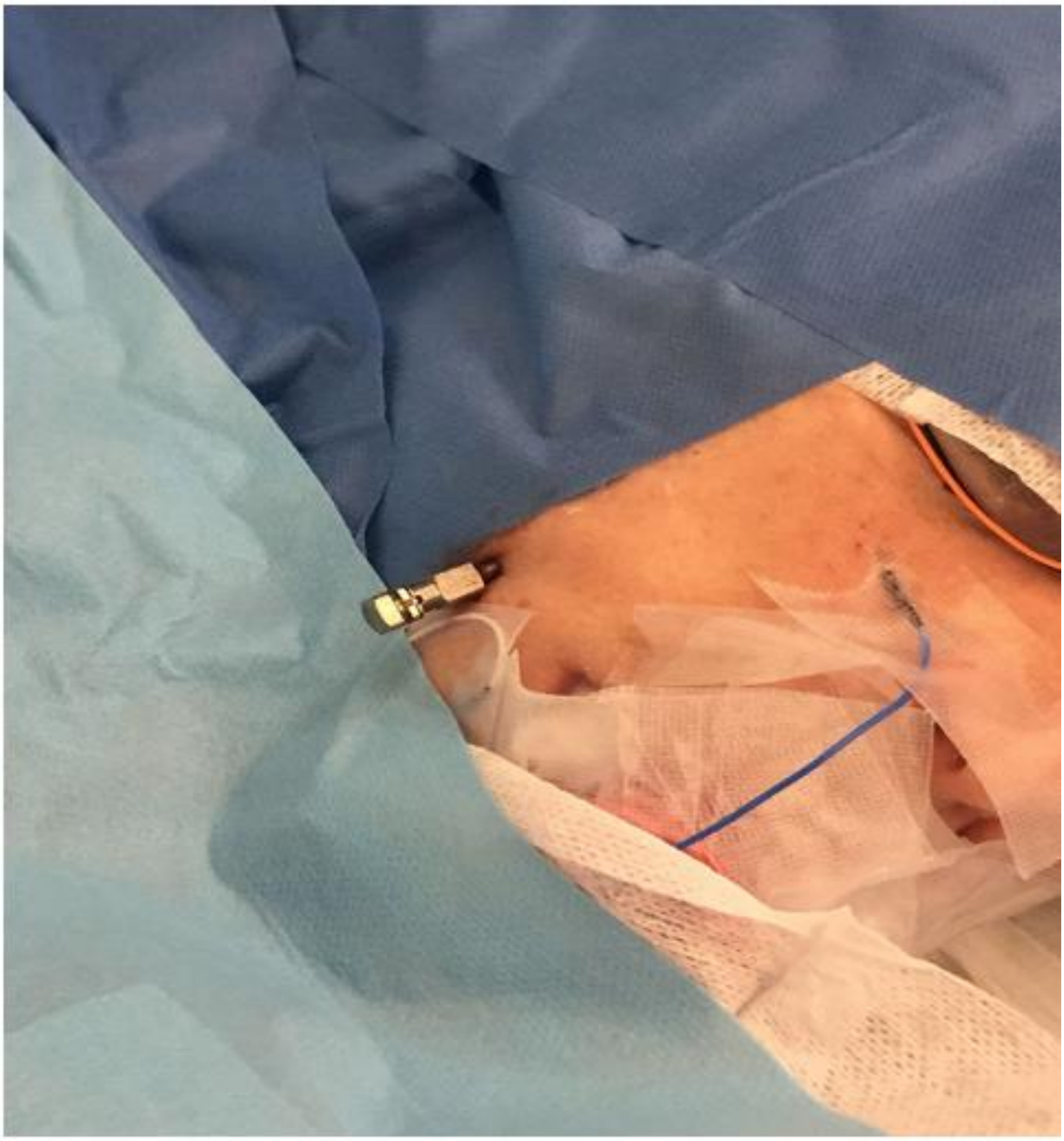




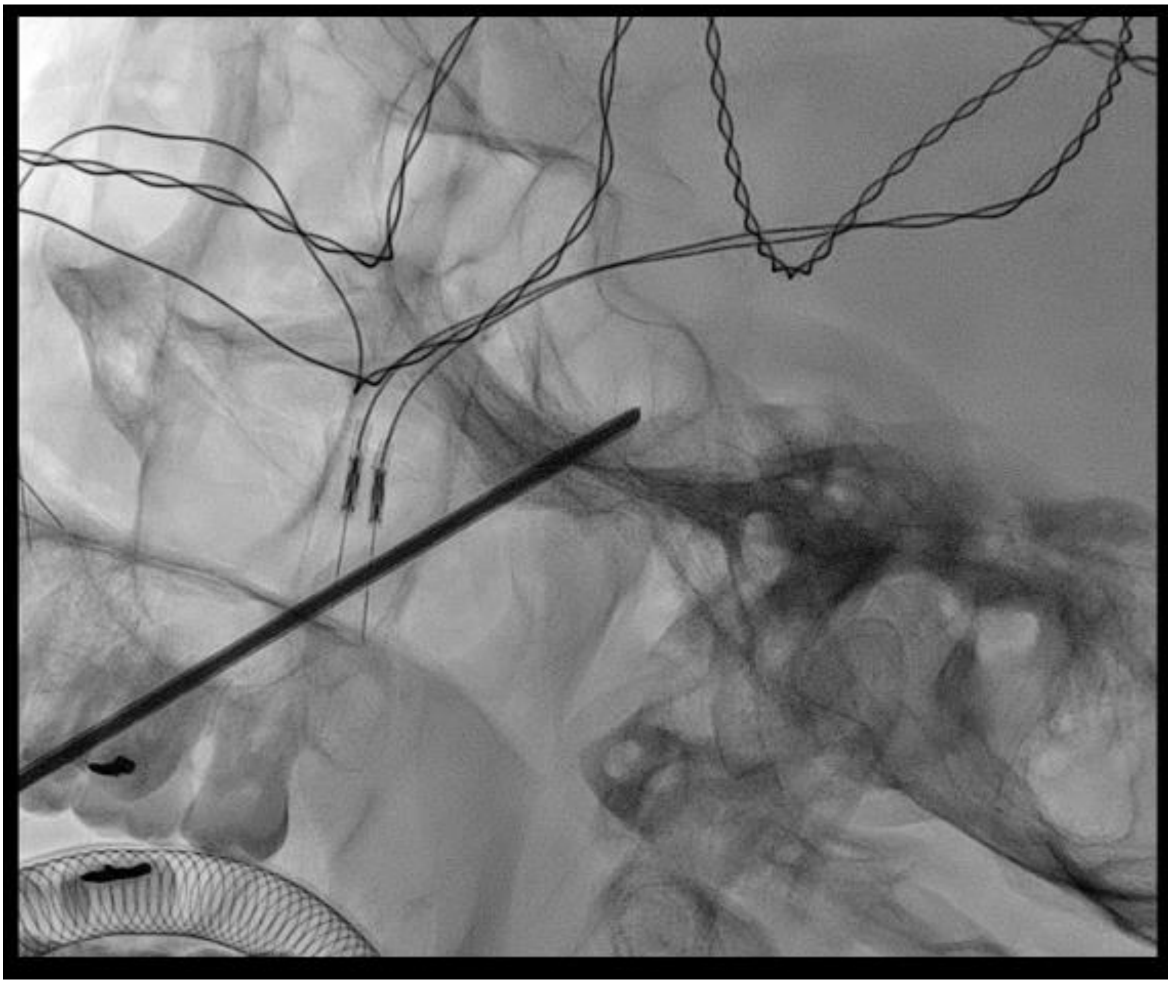
4.Operating room layout (Figure 23)



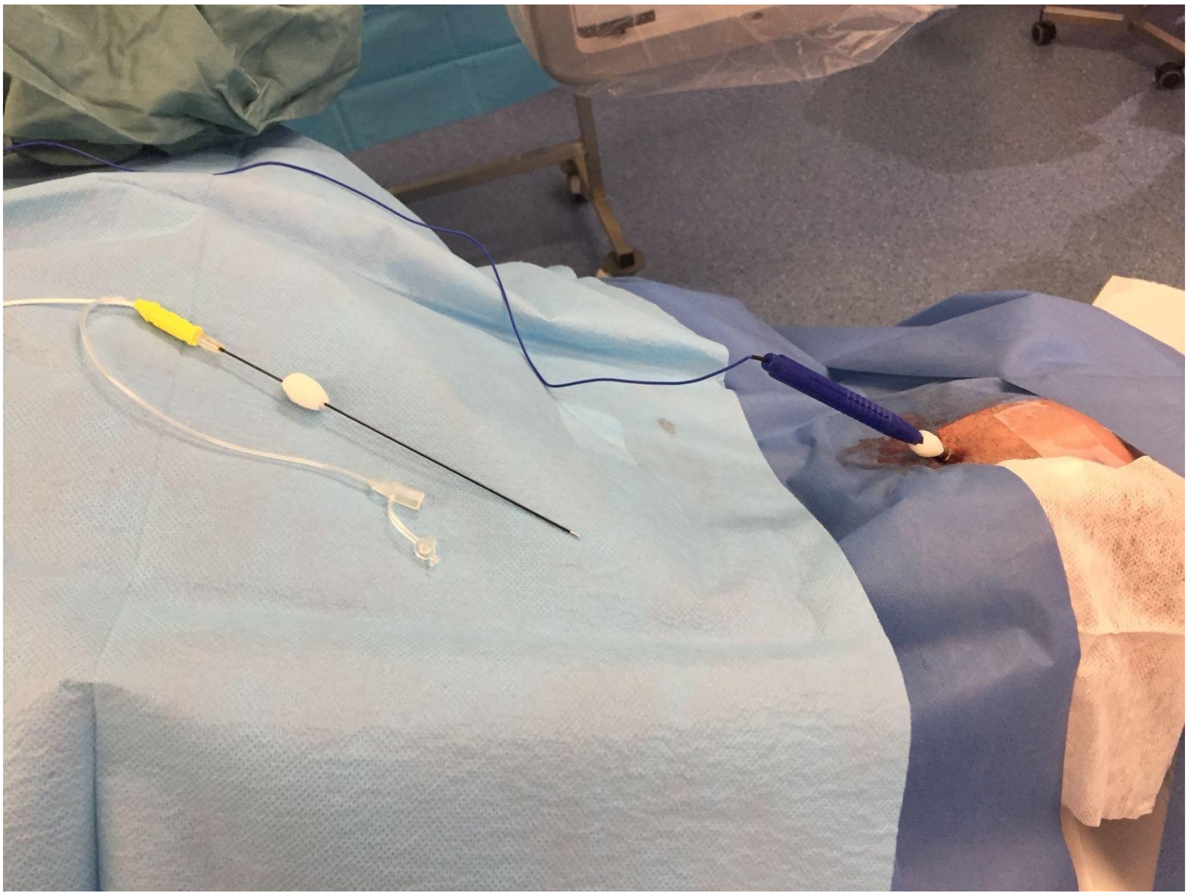
5. Puncture and introduction of trocar through which the two recording and lesion electrodes are introduced alternately (Figure 24)



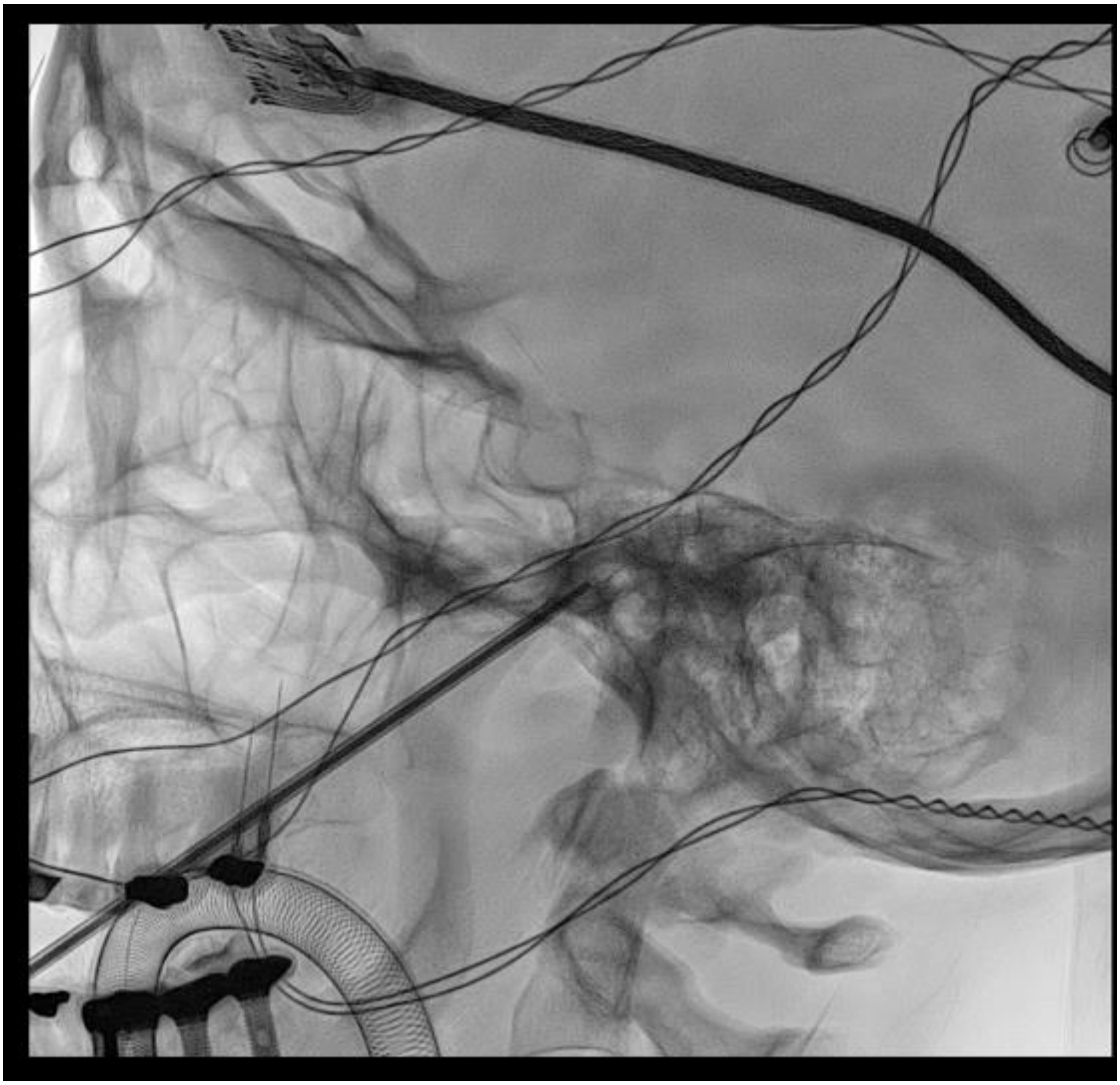
6.Lateral fluoroscopy image to control trocar Depth (Figure 25)



7.Introduction of recording/stimulation electrode (blue electrode). The stimulation electrode introduced and the lesion/radiofrequency electrode in the surgical field (Figure 26).

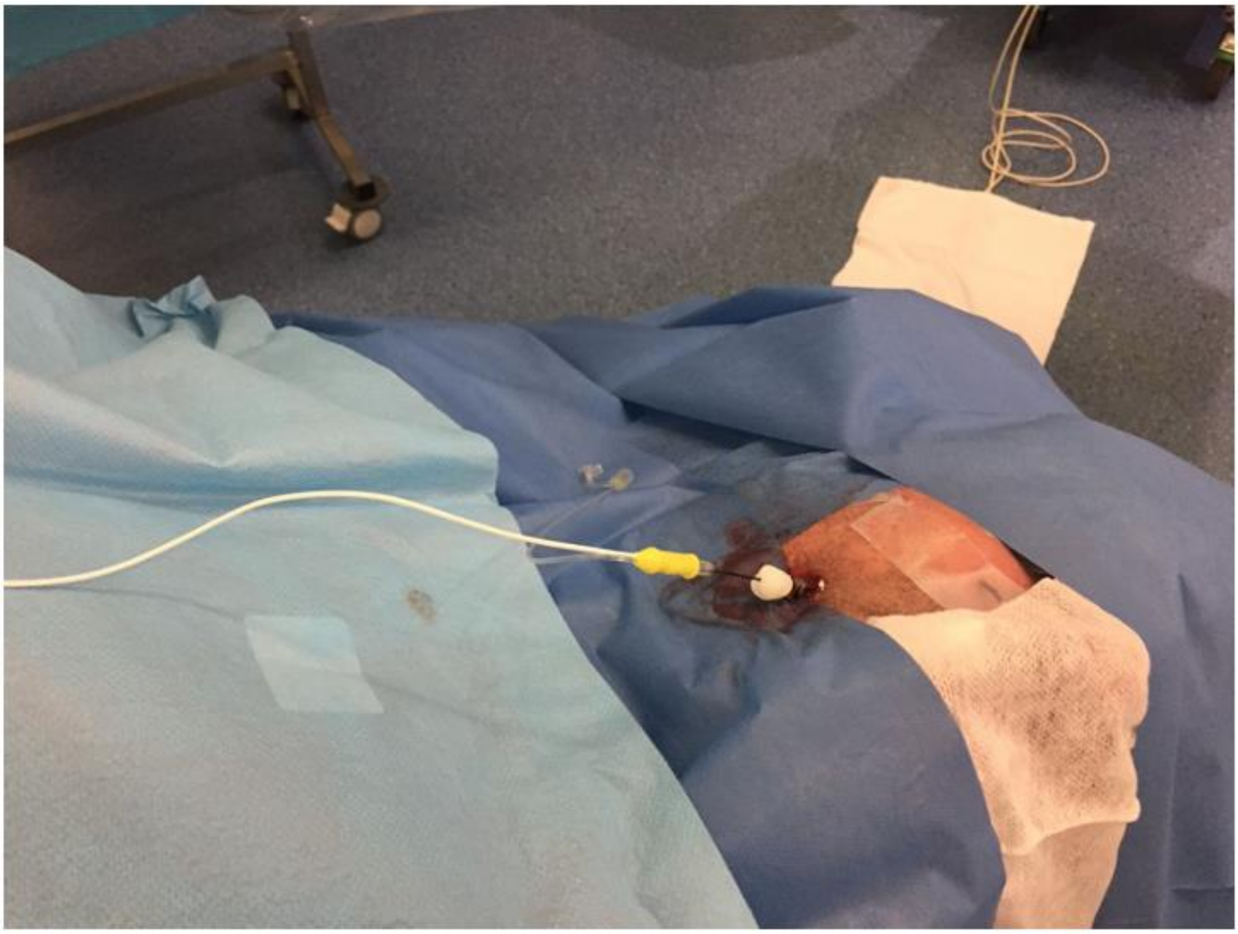


8.Lateral fluoroscopy image after introduction of recording electrode (Figure 27).



9.Stimulation of V2 nerve formation fibers. Fluroscopy (Figure 28).

10.Performing a 60º radiofrequency lesion for 90 seconds (Figure 29).



11.Radiofrequency electrode during treatment in the Fluoroscopy (Figure 30)

5.3. Analysis

Data collection was carried out through a data collection notebook, and were obtained from the preoperative visit, the day after surgery, the visit after 3 months, 6 months and 12 months.

All variables were included in a Table in the Excel program of the Office 2022 package. The data were exported to the statistical analysis program R and Rstudio version 4.2.2. The statistical packages base graphics and ggplot2 were used to create the tables and the nortest library for studies of normality and inferential statistics.

RESULTS

The study group includes 61 patients, 36 treated by radiofrequency, and 25 by Balloon Compression (Mullan). The average age is 58 years with a range of 35 to 78 years. Regarding the symptoms depending on the branches of the trigeminal nerve (V1, V2 or V3), we found 20 patients with symptoms in the V3 territory (20/61 32%), 29 patients with V2 and V3 symptoms (29/61 47%, those are the most freqüent affected branches), and 9 patients with symptoms of the three branches (V1, V2 and V3) (9/61 14%). As we previously mentioned in the methods section, we have avoided including patients with isolated V1 symptoms to avoid bias, given that they may have a better response to Balloon Compression (Mullan).

The type of neuralgia is primary in 47 cases (77%), and secondary in 13 (21%), including 10 cases of Neuralgia secondary to Multiple Sclerosis and 3 of Postherpetic Neuralgia (Herpes Zoster).

In the initial statistical analysis we found that the effectiveness of both techniques, considering as a good result a decrease in VAS>50% than in the preoperative period, is initially high. In the immediate postoperative period, a 93% (57/61) good results are obtained. At 3 months it remains high with a 91% (56/61).

By performing neurophysiological monitoring and intraoperative recording, it was possible to selectively isolate the affected branches in 27/36 (75%). Radiofrequency patients, while in 9 cases it was not possible to selectively isolate. In these 9 cases, action potentials are obtained during the recording in several branches, and despite the stimulus being greater in the symptomatic branch, it is not considered good selectivity.

This is the summary table of the results (Table 2), it shows the results of the VAS scale in preoperative, in the initial postoperative period, and in those in which the VAS scale decrease is >50.

A significant decrease in pain can be observed on the VAS scale in both procedures. In most cases, the decrease is greater than 5 points (50% compared to preop VAS) as seen in the table.

In two cases there is no record of the preoperative VAS because it was not collected in the preoperative visit.

Table 2. Results all patients VAS scale early postoperative

	Procedure (RFC/Mullan)	Preop VAS	Postop VAS	Postop VAS<50%
1	RFC	8	1	Si
2	RFC	9	3	Si
3	RFC	7	3	Si
4	RFC	9	6	No
5	RFC	8	3	Si
6	RFC	8	1	Si
7	RFC	7	2	Si
8	RFC	8	1	Si
9	RFC	8	3	Si
10	RFC	*NA*	3	Si
11	RFC	7	2	Si
12	RFC	9	4	Si
13	RFC	9	1	Si
14	RFC	8	6	No
15	RFC	7	3	Si
16	RFC	8	2	Si
17	RFC	8	1	Si
18	RFC	8	1	Si
19	RFC	7	3	Si
20	RFC	*NA*	3	Si
21	RFC	9	6	No
22	RFC	8	4	Si
23	RFC	8	2	Si

23	RFC	8	2	Si
24	RFC	7	1	Si
25	RFC	8	3	Si
26	RFC	7	2	Si
27	RFC	8	3	Si
28	RFC	7	3	Si
29	RFC	9	4	Si
30	RFC	8	1	Si
31	RFC	8	1	Si
32	RFC	8	2	Si
33	RFC	8	3	Si
34	RFC	9	3	Si
35	RFC	8	3	Si
36	RFC	8	1	Si
37	Mullan	8	3	Si
38	Mullan	7	3	Si
39	Mullan	7	2	Si
40	Mullan	8	4	Si
41	Mullan	8	2	Si
42	Mullan	9	2	Si
43	Mullan	8	2	Si
44	Mullan	8	3	Si
45	Mullan	9	3	Si

When we pay attention to the evolution on the VAS scale throughout the follow-up of 3, 6 and 12 months, we see that in most cases the improvement is maintained but in some (marked in red in the sections of the RFC follow-up tables and Mullan) some cases present an increase in pain at 12m which will constitute a recurrence. This is relevant given that the problem with percutaneous techniques results in pain recurrence after one year. In the literature it is estimated between 15-20% annual recurrence, in some series it is higher (50).

Table 3. Results VAS scale RFC follow-up

RFC TABLE FOLLOW-UP

	Procedure (RFC/Mullan)	VAS 3Months	VAS 6Months	VAS 12Months
1	RFC	2	2	2
2	RFC	4	4	4
3	RFC	3	3	3
4	RFC	7	7	7
5	RFC	3	3	3
6	RFC	1	0	1
7	RFC	2	3	5
8	RFC	2	2	2
9	RFC	3	4	6
10	RFC	3	3	5
11	RFC	2	2	3
12	RFC	4	4	4
13	RFC	2	2	3
14	RFC	6	6	7
15	RFC	3	3	3
16	RFC	2	2	2
17	RFC	2	2	7
18	RFC	1	1	1
19	RFC	3	3	3
20	RFC	3	3	3
21	RFC	6	6	6
22	RFC	4	4	4
23	RFC	2	2	2

Table 4. Results VAS scale Mullan follow-up

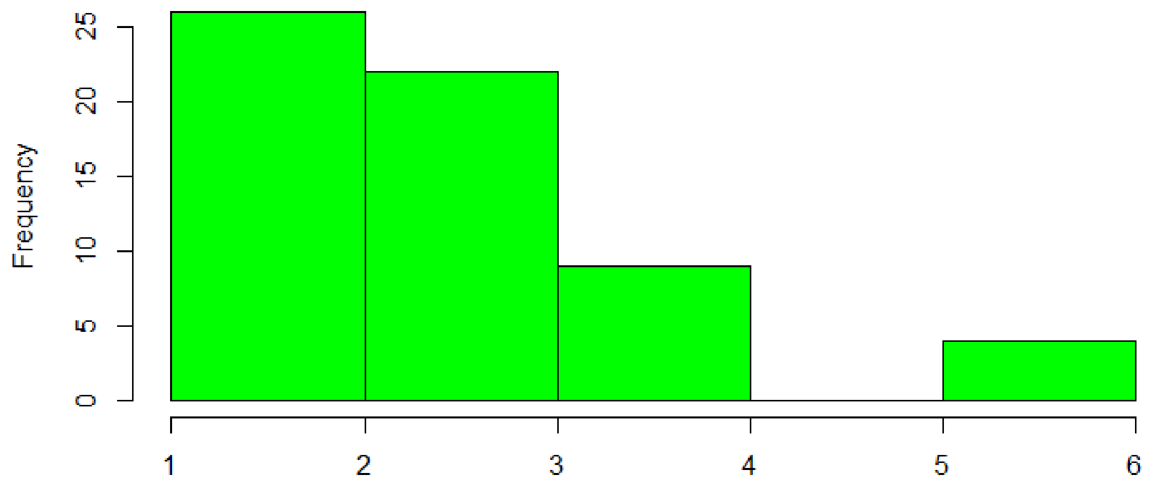
MULLAN TABLE FOLLOW-UP

47	Mullan	1	3	7
48	Mullan	2	2	2
49	Mullan	2	2	2
50	Mullan	3	3	3
51	Mullan	4	4	4
52	Mullan	2	4	6
53	Mullan	6	6	7
54	Mullan	4	4	4
55	Mullan	4	4	4
56	Mullan	1	1	1
57	Mullan	3	3	3
58	Mullan	3	3	3
59	Mullan	4	4	4
60	Mullan	2	6	5
61	Mullan	4	4	4

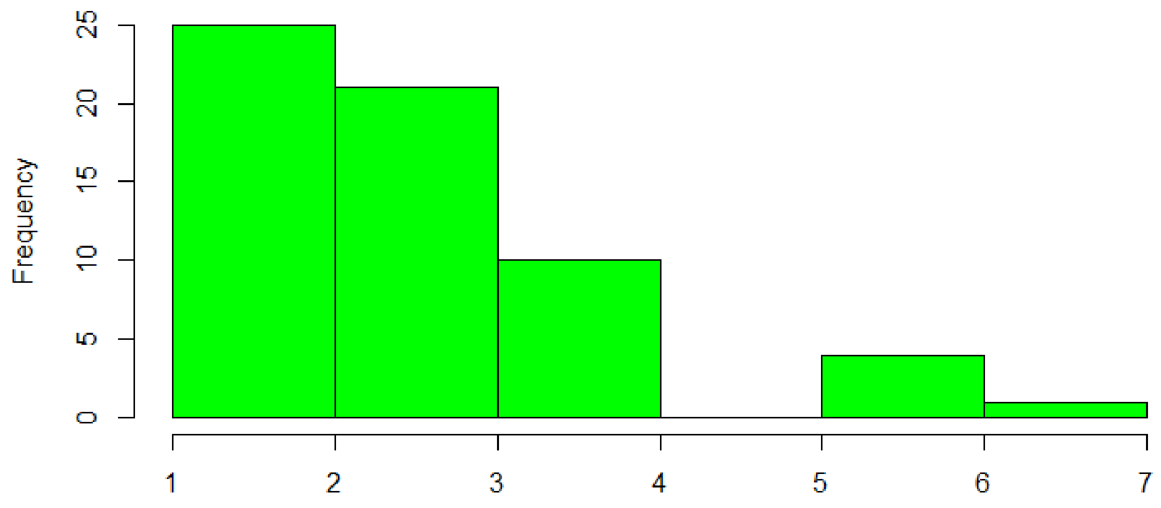
6.1.Results VAS scale all procedures

We can appreciate this evolution through the evolution of the frequencies through time of follow-up. As we observe initially, the majority of cases are located to the left among the lowest VAS scores, but as the follow-up becomes longer, more cases come to the right area, that represents higher VAS scores.

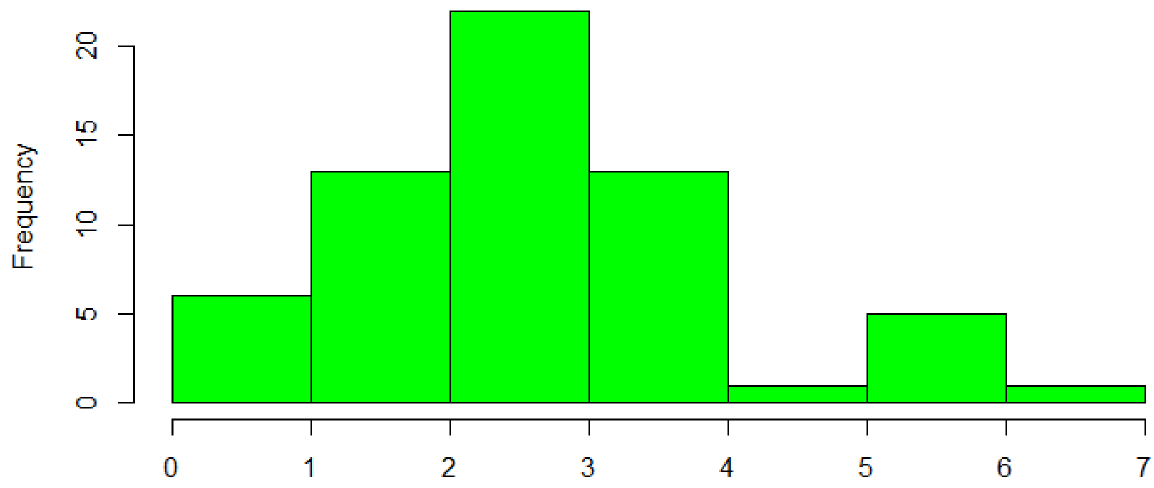
VAS SCALE AFTER SURGERY



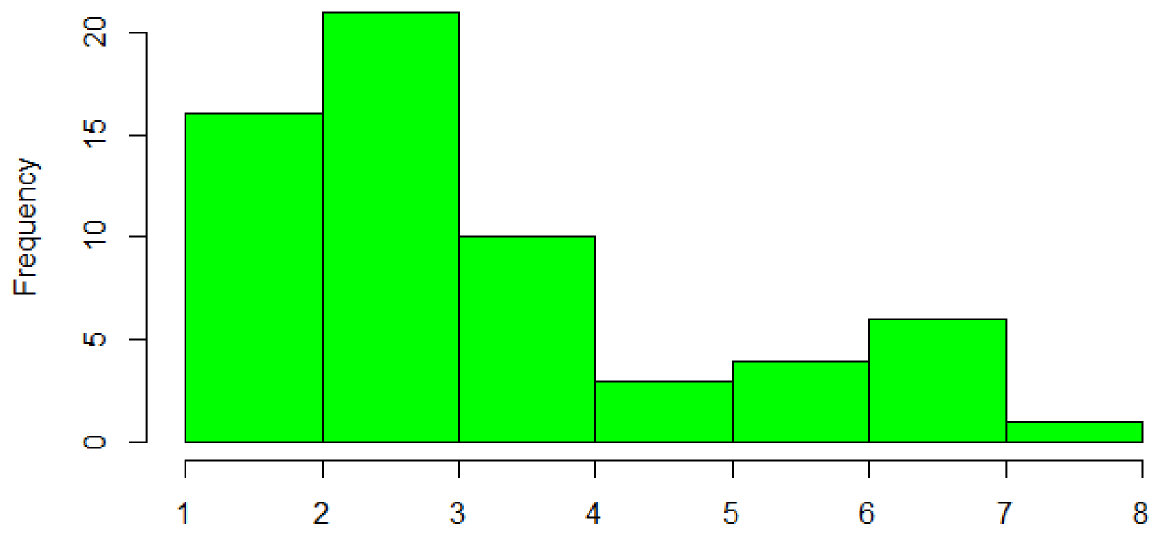
VAS SCALE AT 3 MONTHS



VAS SCALE AT 6 MONTHS



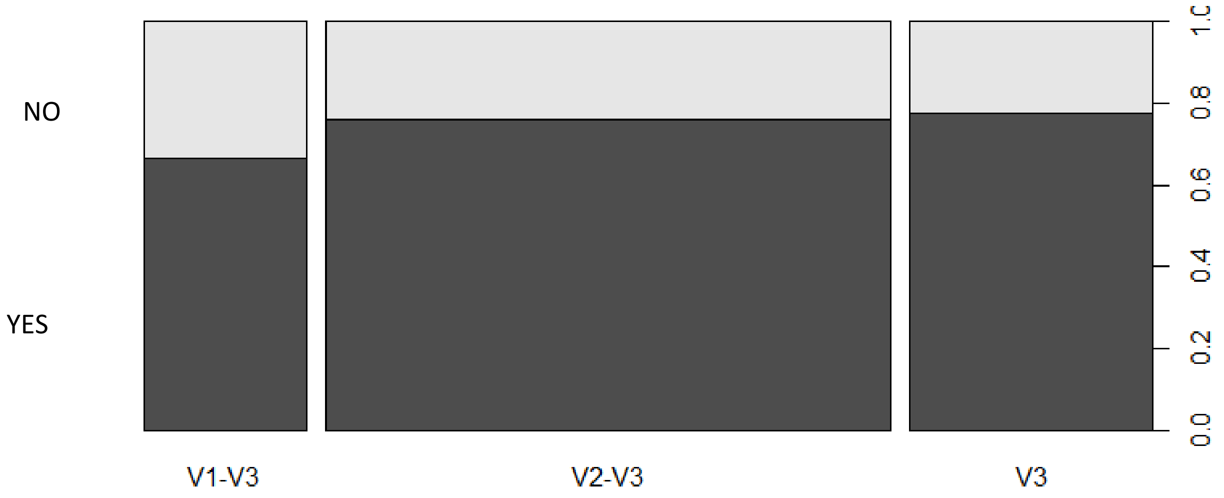
VAS SCALE AT 12 MONTHS



6.2. Feasibility of Neurophysiological Monitoring

The first hypothesis of the study was to determine the applicability of the monitoring technique in radiofrequency rhizotomy of the trigeminal nerve. At this point, we have carried out the analysis of the relationship between the branches selectively isolated during monitoring and the branches that were symptomatic in patients with trigeminal neuralgia.

RELATIONSHIP OF MONITORED BRANCHES CONCORDANT WITH SYMPTOMATIC BRANCHES



We conclude fromt the graphic that to obtain selective reproducible potentials for each affected branch is feasible in most cases, in total 75% (27/36 monitored patients). We can also observe that for branches V2 and V3 it is easier to obtain selective potentials, but more difficult in cases affected by the three branches which include V1.

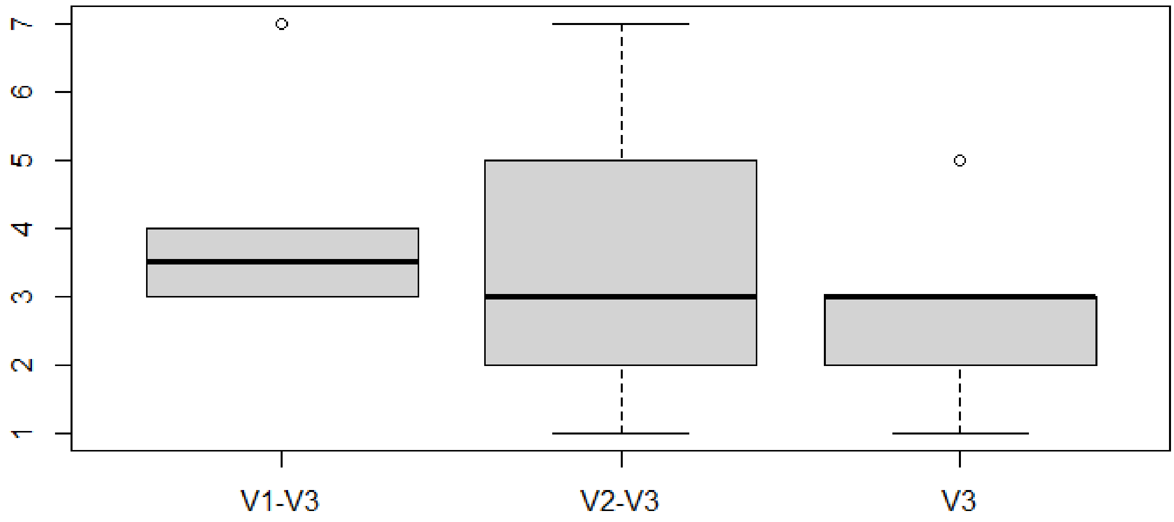
AFFECTED BRANCHES

The connection between monitoring and symptomatic branches will also have implications regarding the results depending on which of the branches are affected.

If we perform a stratified analysis of the affected branches and the final result at 12 months, we see that patients affected by isolated V3 neuralgia have a better prognosis than patients affected by more branches (V2-V3 or V1-V3).

This is consistent with what has been described in other papers and is important, given that obtaining selective monitoring of the V3 branch in patients selectively affected by it will result in a better final outcome.

VAS RESULTS AFTER 12 MONTHS DEPENDING ON BRANCHES

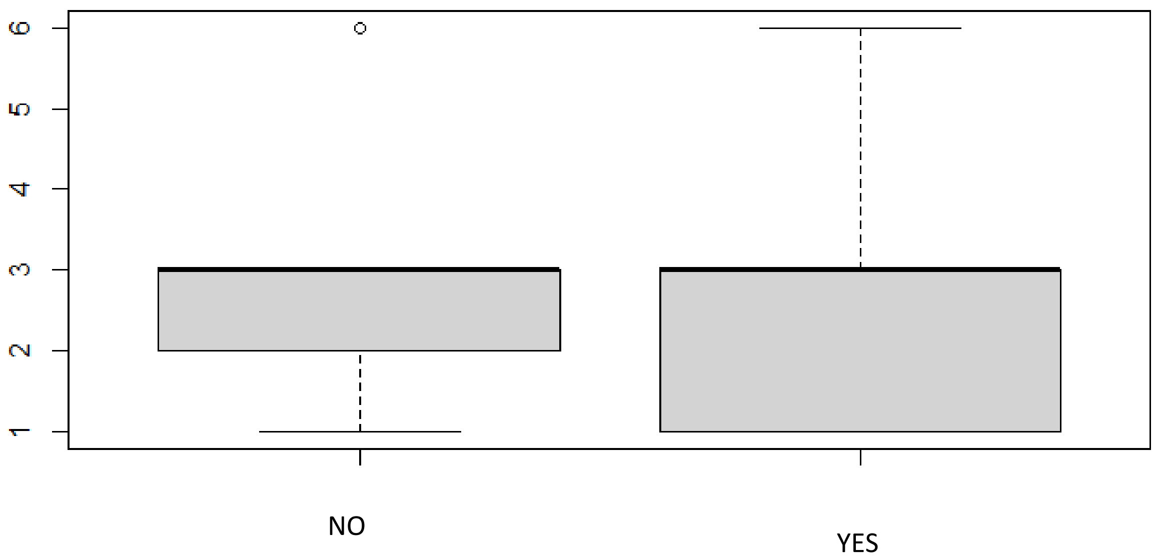


6.3. Impact of Neurophysiological monitoring

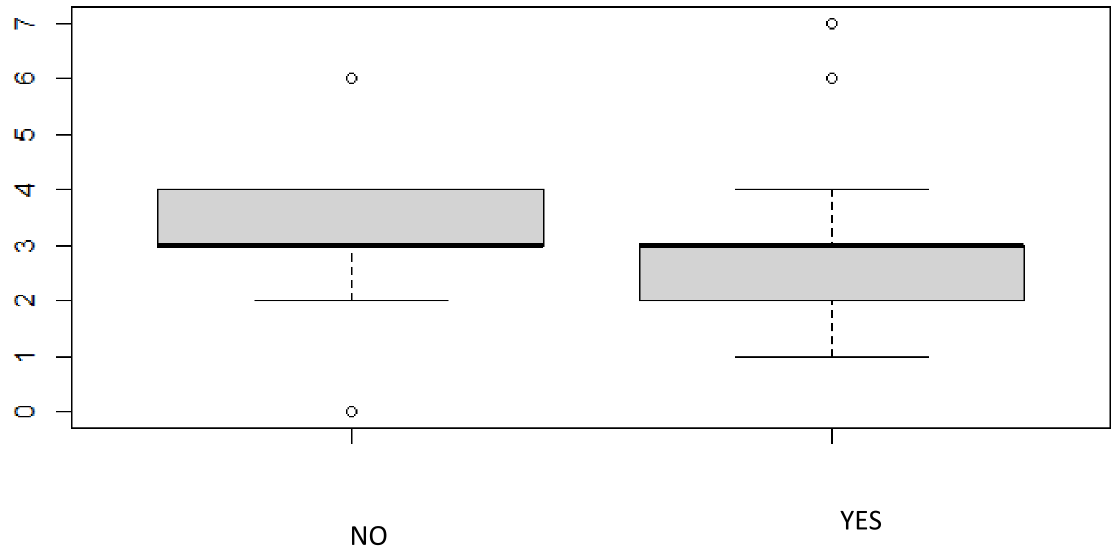
The second hypothesis of the study is to verify whether neurophysiological monitoring in this type of procedure provides usefulness in terms of greater effectiveness in terms of clinical improvement or greater durability, given that the main problem of radiofrequency procedures in neuralgia of the trigeminal is recurrence.

At this point it will be interesting to analyze in the RFC group, those in which selectivity in intraoperative monitoring has been achieved, how the pain scales tend to be in the follow-up in comparison with the rest of the patients.

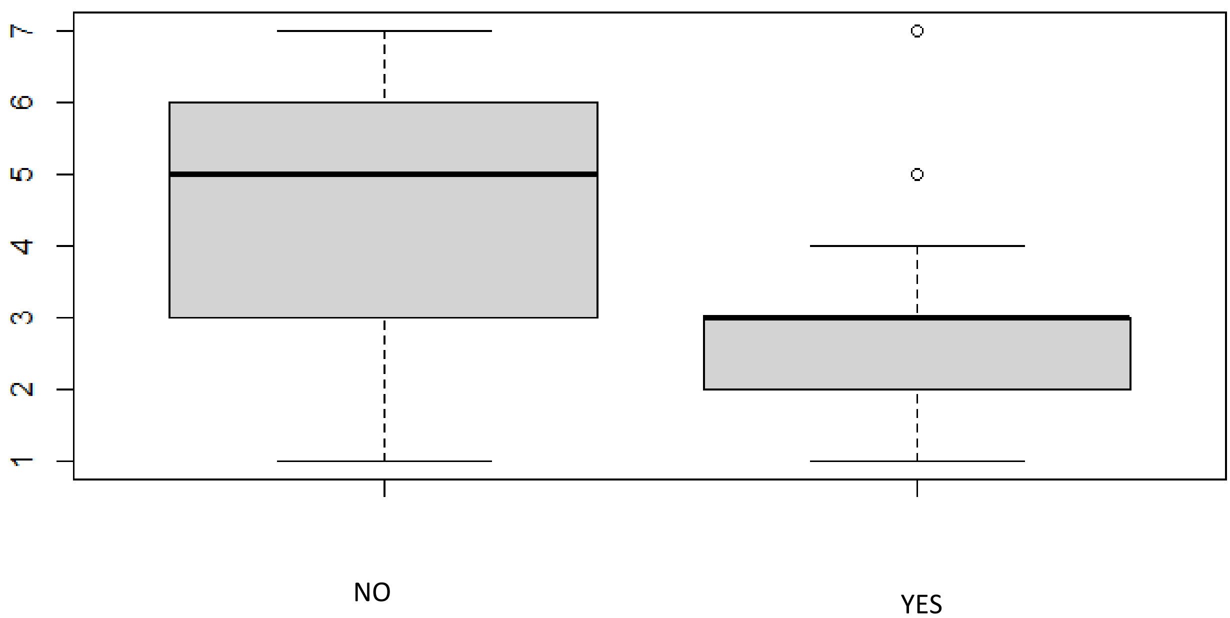
VAS RESULTS IN PACIENTS WITH SELECTIVE MONITORING VS NOT, INMEDIATE AFTER SURGERY



VAS RESULTS IN PACIENTS WITH SELECTIVE MONITORING VS NOT, 6 MONTHS AFTER SURGERY



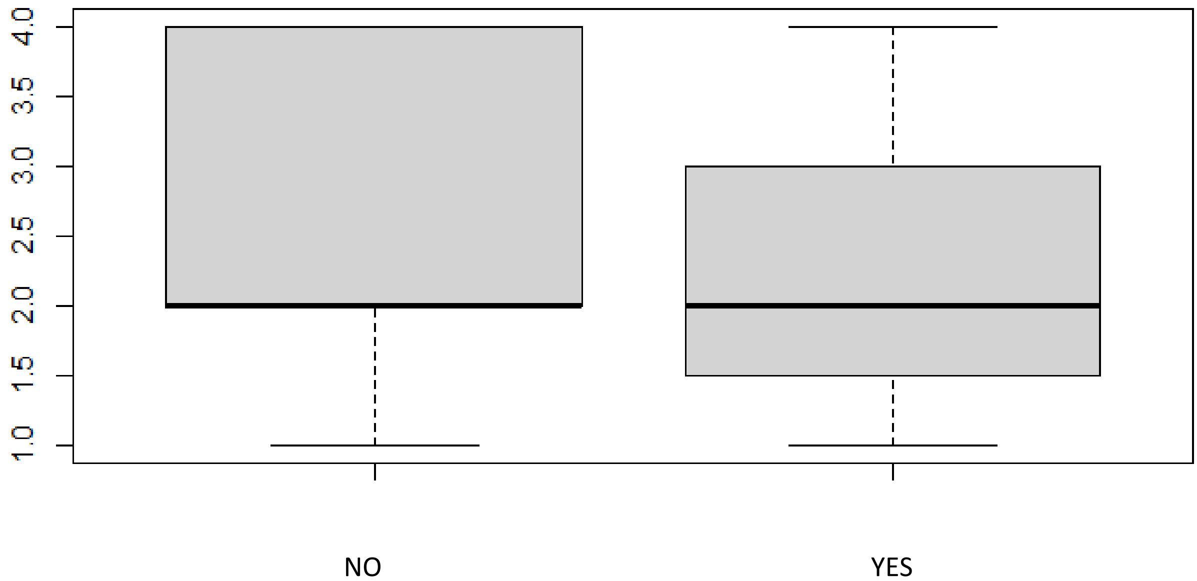
VAS RESULTS IN PACIENTS WITH SELECTIVE MONITORING VS NOT, 12 MONTHS AFTER SURGERY



As are shown in the graphs, although the initial postoperative results seems quite similar, the analysis at 6 months and 12 months clearly shows differences in the evolution of the result. Patients in whom selective monitoring of the painful branches was obtained presented greater consistency and durability in clinical improvement.

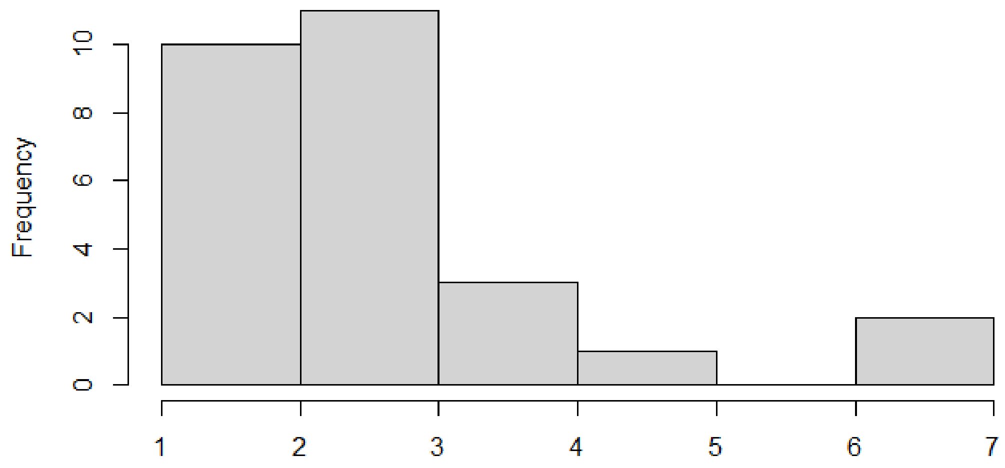
This pattern is repeated again when applying the result on the BNI scale.

BNI RESULTS IN PACIENTS WITH SELECTIVE MONITORING VS NOT, 12 MONTHS AFTER SURGERY

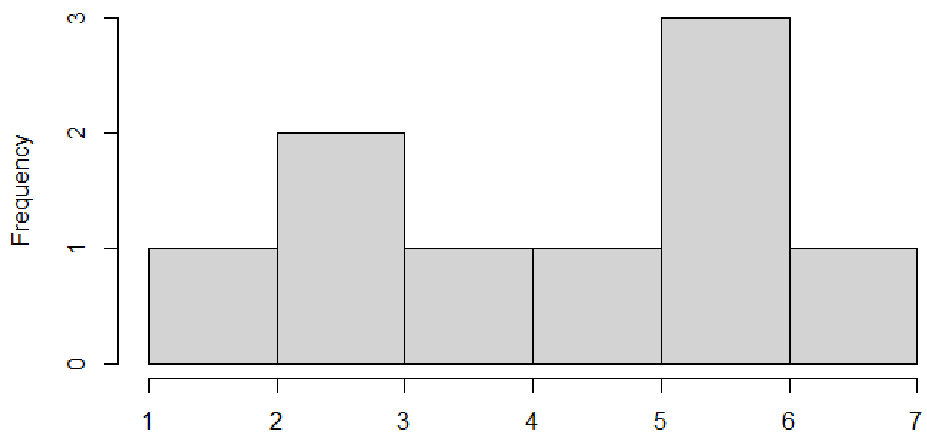


If we analyze the VAS variable at 12 months of follow-up, this is when we find the most divergence between the group with selective monitoring and the one without. Looking at the frequency histogram we can clearly point out the difference in the distribution of the variable.

SELECTIVE MONITORING, VAS SCALE AT 12 MONTHS FOLLOW-UP



NO SELECTIVE MONITORING, VAS SCALE AT 12 MONTHS FOLLOW-UP



In order to execute the comparative analysis, we observe that the variable does not follow a normal distribution. We apply Shapiro-Test for quantitative variable <50 cases and it is confirmed that it does not follow a normal distribution.

We then make a comparison between mean values using T-Test for 95% confidence interval, with the aim of confirming whether these differences have statistical significance.

Table 5. Data VAS scale follow-up and T-Test comparison

Mean VAS Scale	Selective Monitoring Trigeminal Symptomatic Branches	No Selective Monitoring	T-Test comparison
Early postoperative	2.3	2	0.1167
3 Months	2.2	2.2	0.4157
6 Months	2.3	2.8	0.378
12 Months	2.4	4	0.04311

The results show, on the one hand, that we did not find significant differences in the comparison between the selectivity group and the non-selectivity group in the early postoperative period, nor at 3 and 6 months. However, at 12 months of follow-up we found a statistically significant difference for $p<0.05$, being 0.043 at 12 months.

We apply the same comparison with the BNI (Barrow Neurological Institute) scale variable.

Table 6. Data BNI scale follow-up and T-Test comparison

Mean BNI Scale	Selective Monitoring Trigeminal Symptomatic Branches	No Selective Monitoring	T-Test comparison
Early postoperative	2.5	2.6	0.183
3 Months	2.6	3.2	0.306
6 Months	2.7	3.6	0.456
12 Months	3	4	0.05307

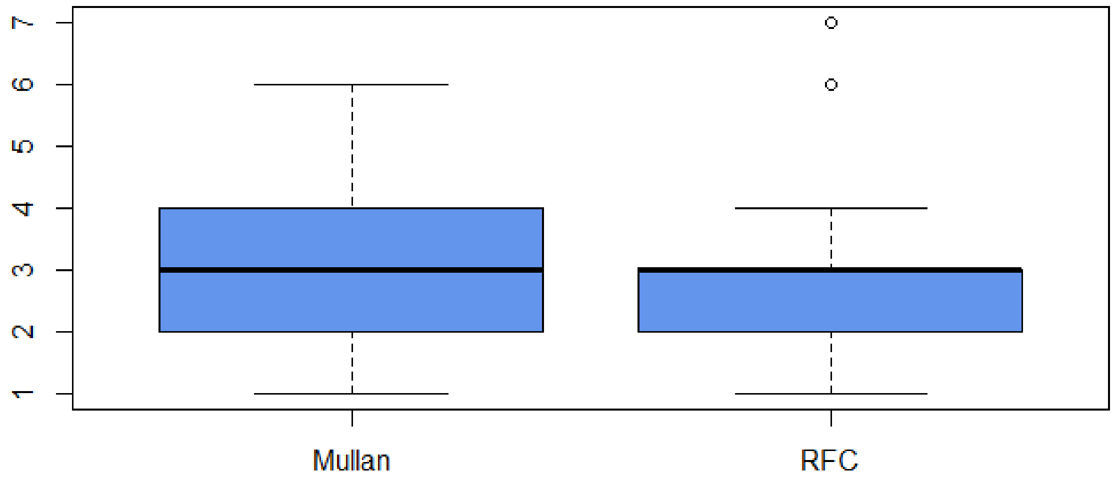
In this case, when executing the comparison we did not obtain statistically significant differences, although at 12 months for the BNI variable comparing the selective monitoring group and the non-selective group the p=0.053, for an objective p<0.05. This result is close but we are no table to consider it as signific ant. If we observe the differences between mean values in both groups at 12 months, it is 3 for the selective group and 4 for the non-selective group, a smalle r margin of difference than in the case of the VAS scale, which is 2.4 and 4 res pectively.

Furthermore, this shows that depending on the pain measurement scale and its sensitivity, these differences can be detected more accurately or not.

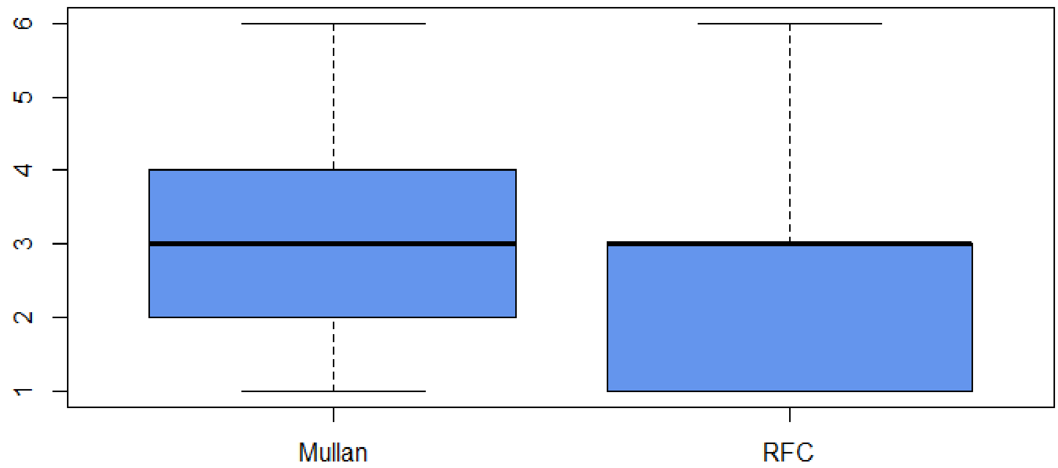
6.4. RFC vs Mullan Comparison

If we compare the initial result between both techniques we will obtain similar results, although in the RFC group the improvement is slightly greater.

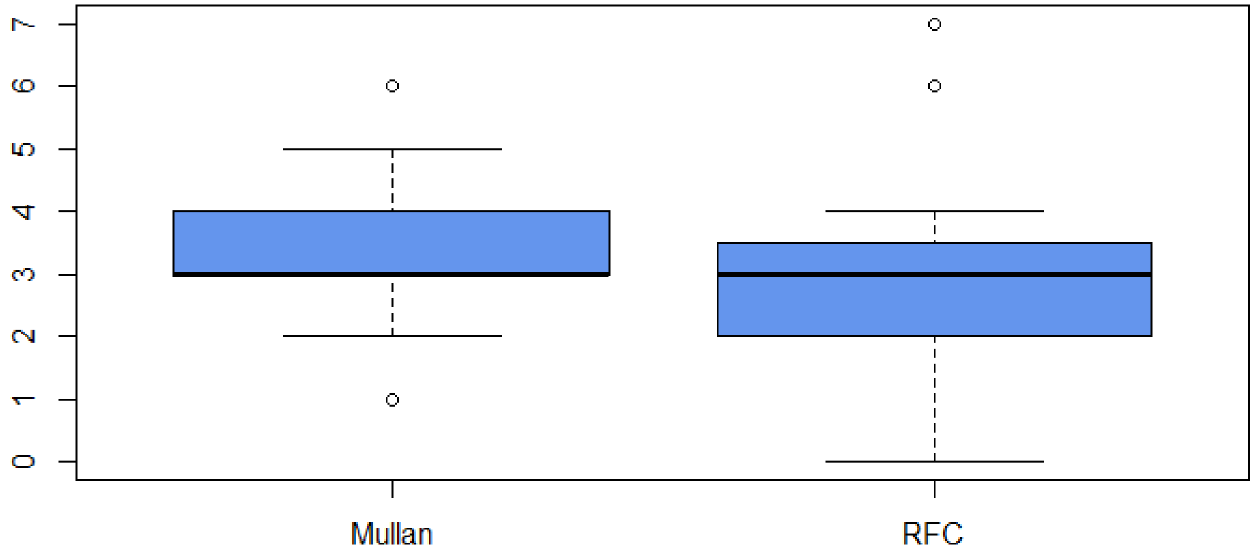
INMEDIATE RESULTS AFTER SURGERY MULLAN VS RFC (VAS SCALE)



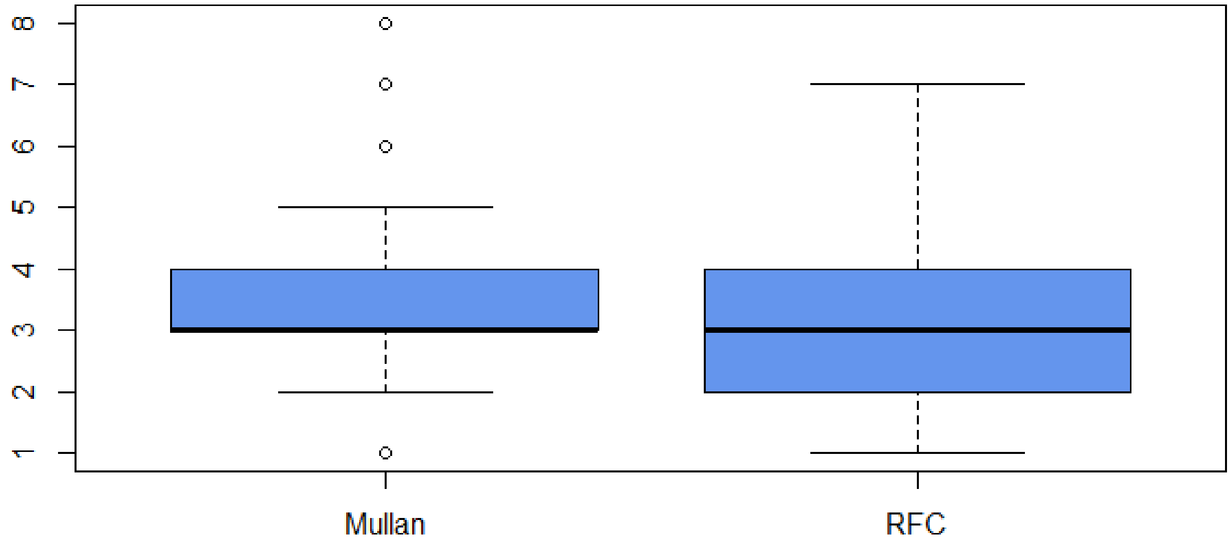
RESULTS AFTER 3 MONTHS MULLAN VS RFC (VAS SCALE)



RESULTS AFTER 6 MONTHS MULLAN VS RFC (VAS SCALE)



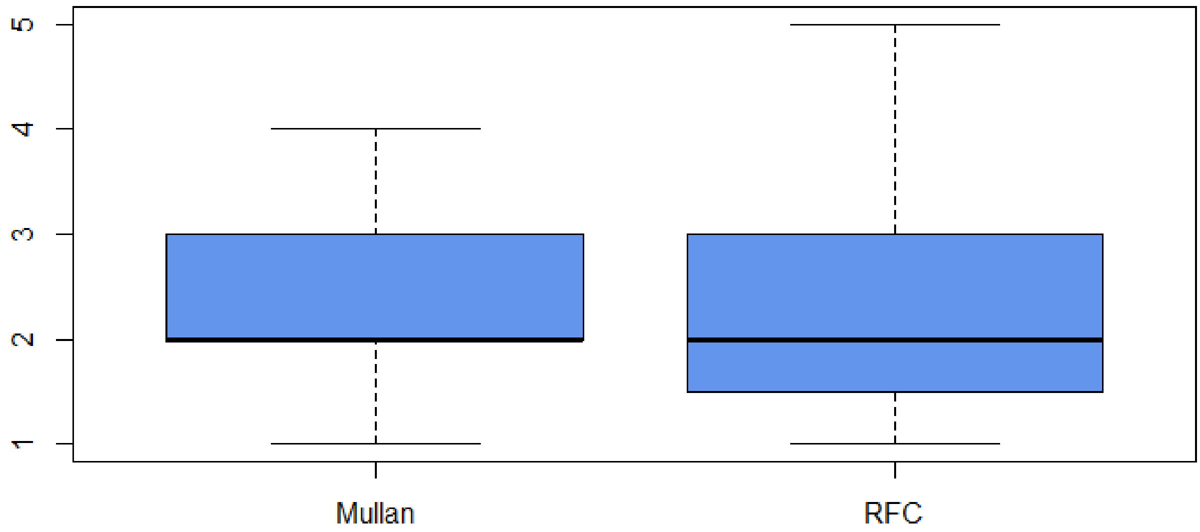
RESULTS AFTER 12 MONTHS MULLAN VS RFC (VAS SCALE)



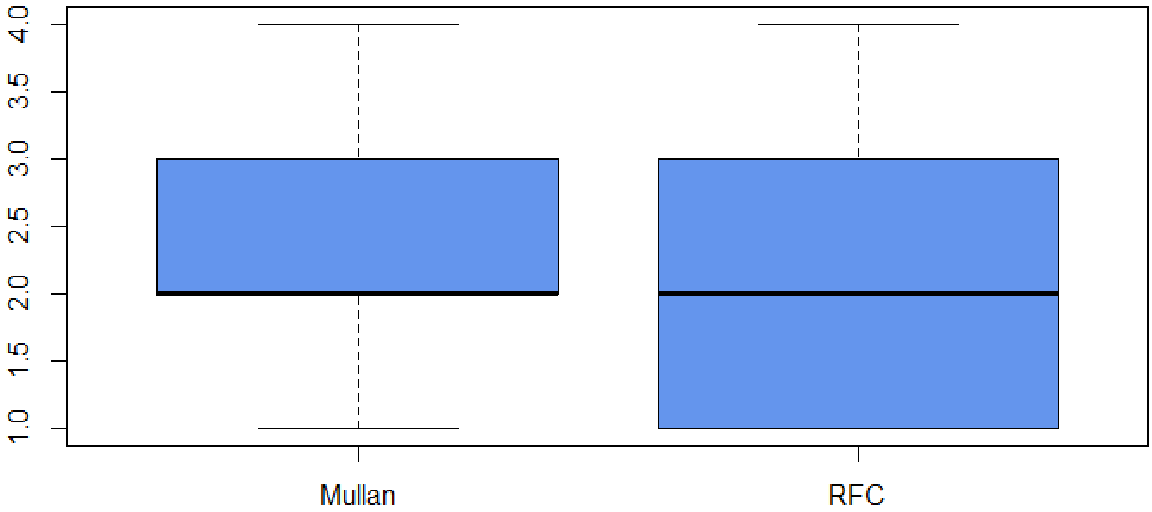
These slight differences are consistent over time, and somewhat lower values are observed on the VAS scale at 3, 6, 12m, although in general terms they remain at similar levels.

If we perform the same analysis with the data obtained from the BNI scale, we will see the same trend of lower values on the scale in RFC patients, although the difference is small.

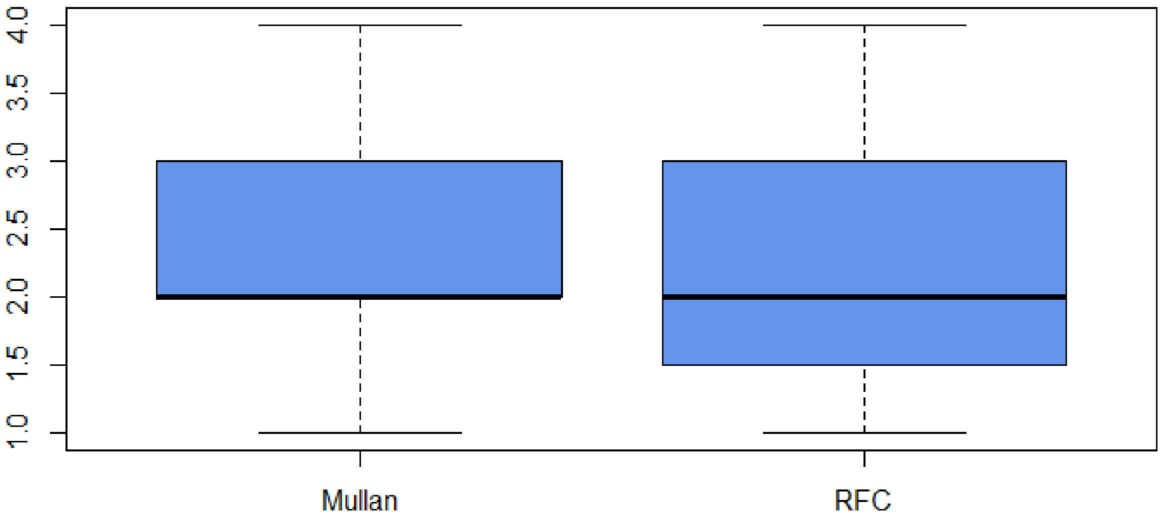
INMEDIATE RESULTS AFTER SURGERY MULLAN VS RFC (BNI SCALE)



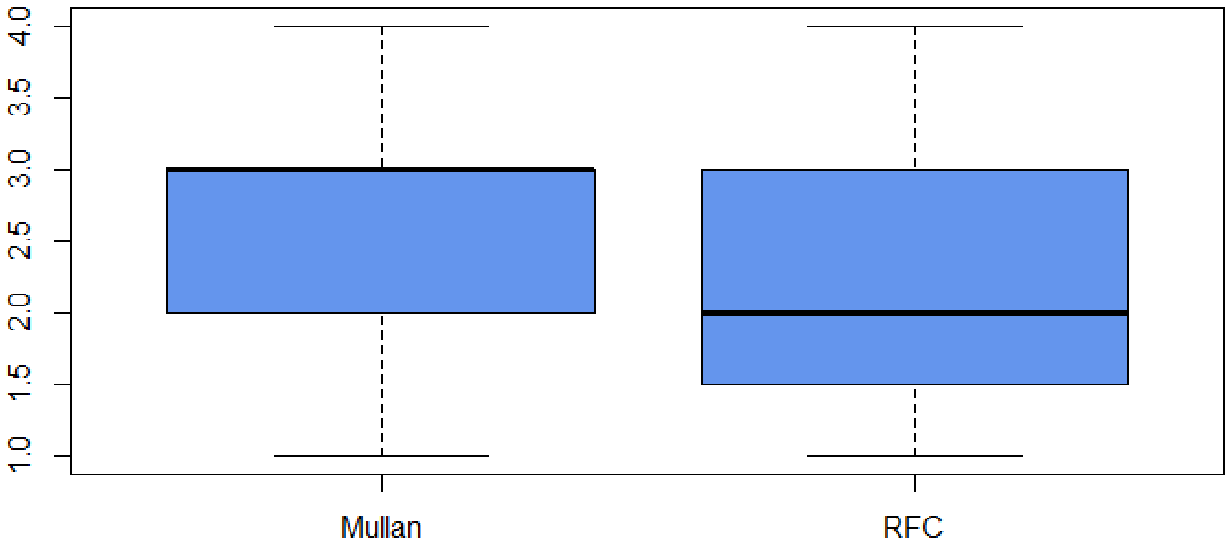
RESULTS AFTER 3 MONTHS MULLAN VS RFC (BNI SCALE)



RESULTS AFTER 6 MONTHS MULLAN VS RFC (BNI SCALE)

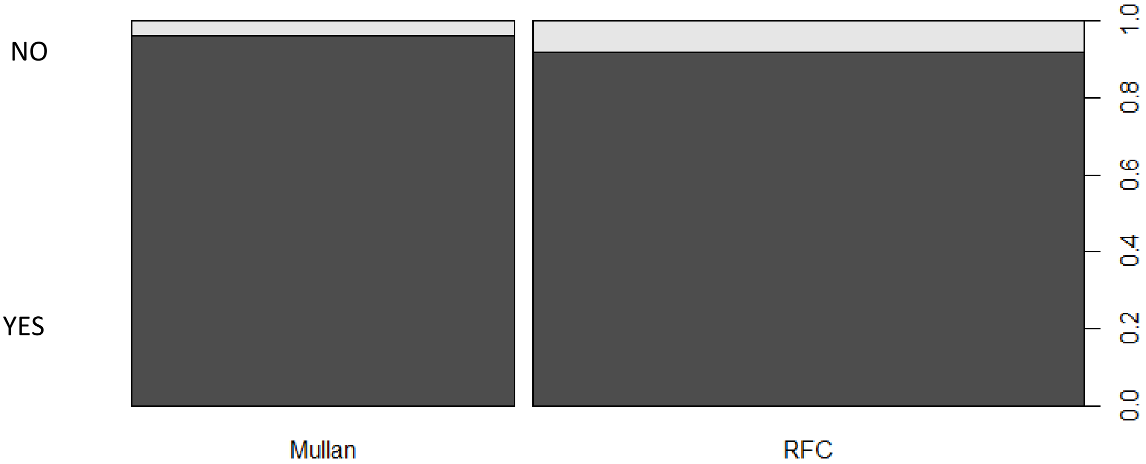


RESULTS AFTER 12 MONTHS MULLAN VS RFC (BNI SCALE)

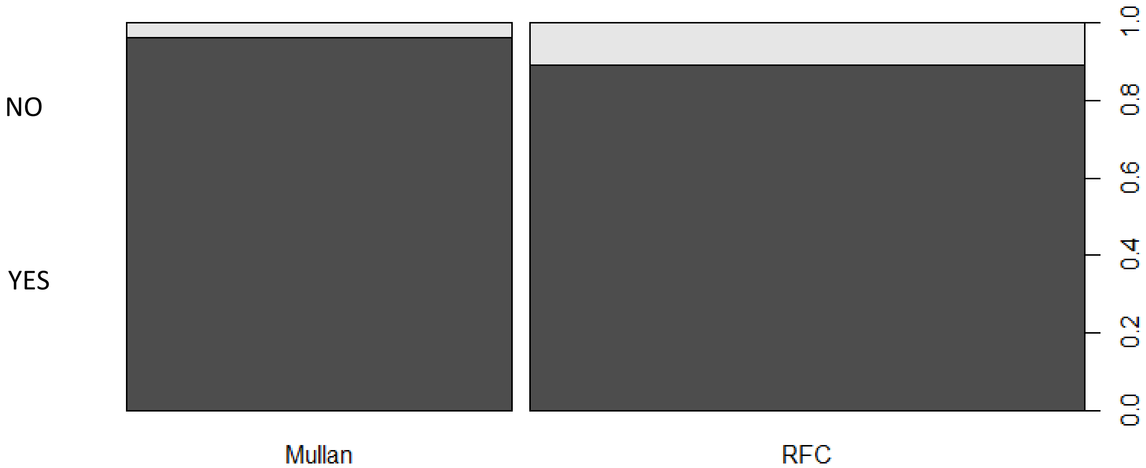


After performing the analysis with the assessment of good results (VAS decrease >50%), we can see that over time the number of patients whose VAS has not decreased sufficiently or who no longer present clinical improvement compared to preoperatively also increases slightly.

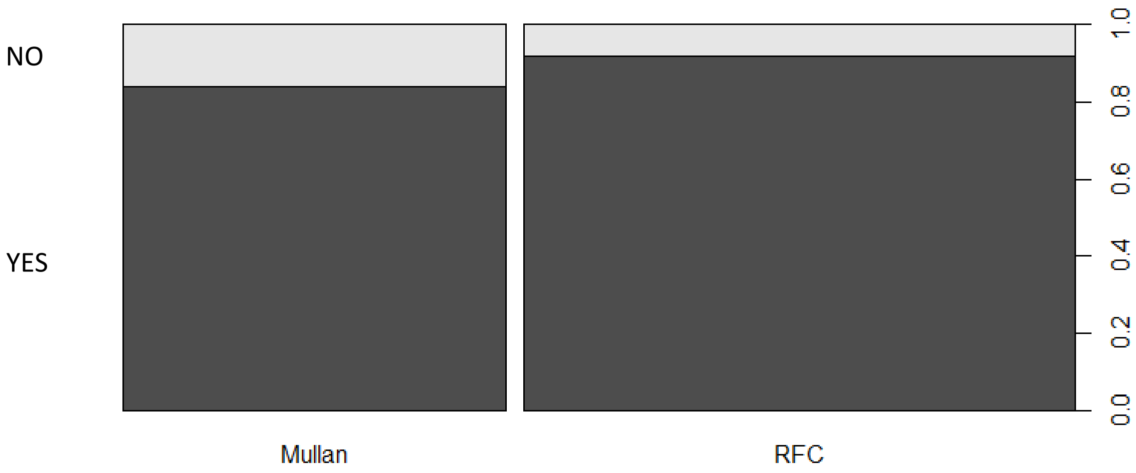
VAS DECREASE >50% INMEDIATE AFTER SURGERY



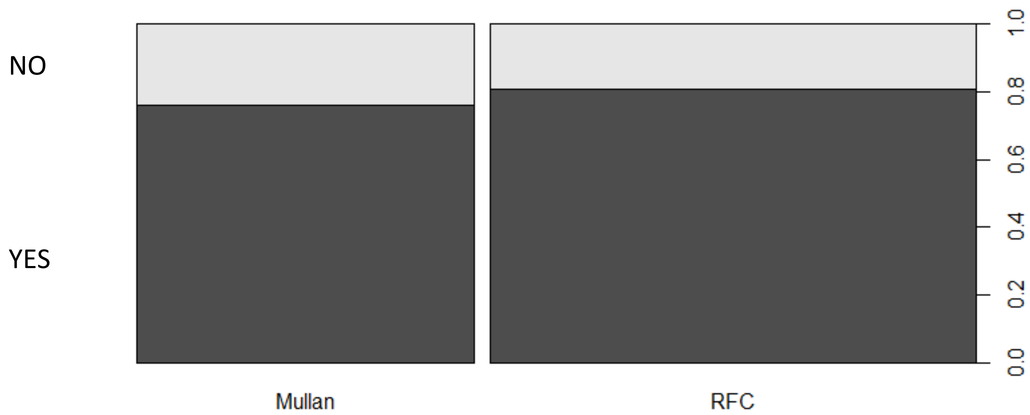
VAS DECREASE >50% AT 3 MONTHS



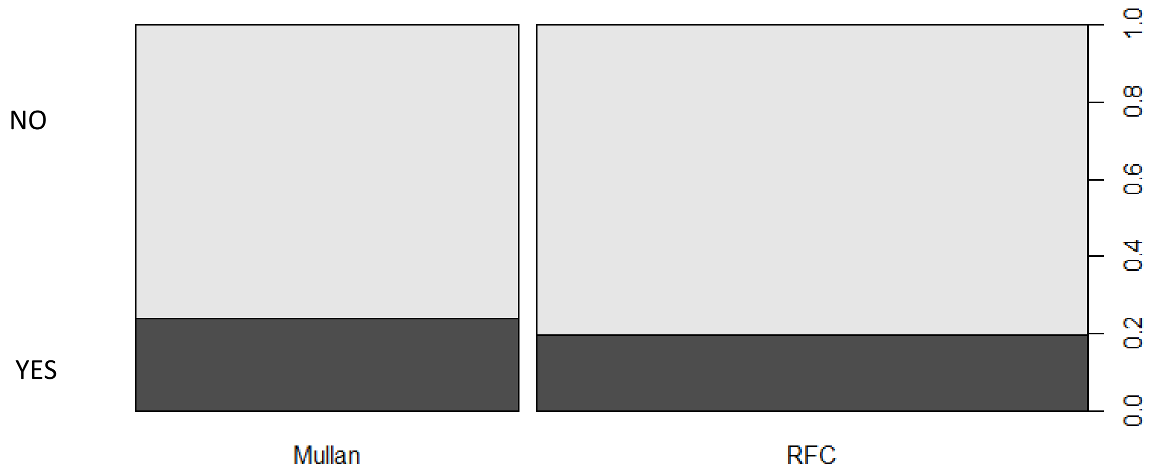
VAS DECREASE >50% AT 6 MONTHS



VAS DECREASE >50% AT 12 MONTHS



RECURRENCE AT 12MONTHS



The total recurrence in both is 12/61 patients, 20%. Of these 12 patients, 5 are from the RFC group and 7 from the Mullan group.

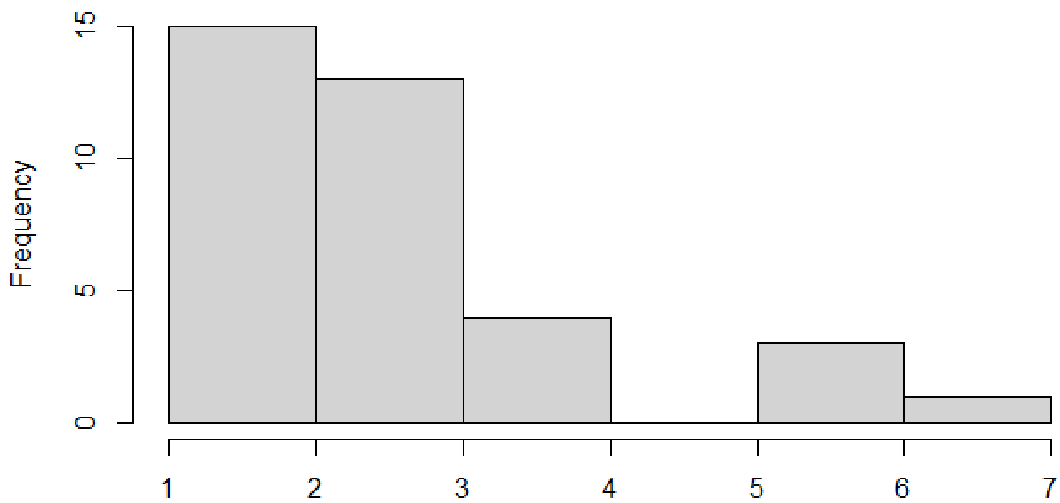
This recurrence rate matches with the recurrence that is described in the different published papers. Although there is great variability depending on the techniques performed and the number of patients included, the percentage usually described is between 15-20%, although in some series up to 30% is described (51), (52) In the last hypothesis of the study we propose that the application of monitoring can result in better results compared to other percutaneous techniques such as Mullan. In the previous analysis we have observed that selectivity can favor better results and we obtained statistical differences in RFC patients between selective monitoring group and no selective. .

On the other hand, our sample of 36 RFC patients can be compared with the group of 25 Mullan patients. For this we use the quantitative variable VAS scale.

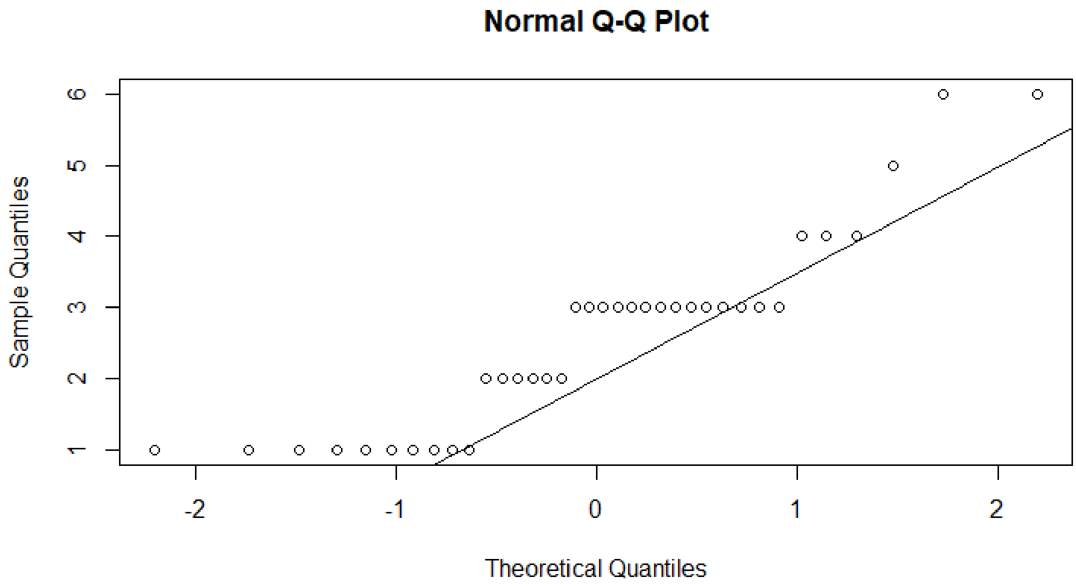
First of all we try to establish whether or not the VAS variable is normally distributed.

As we can see in the distribution of the variable, it does not seem to follow a normal distribution.

VAS SCALE EARLY POSTOPERATIVE RFC GROUP



If we apply distribution graphs (qqplot) we see that the points are dispersed with respect to the line so it does not fit the normal distribution.



However, we will apply statistical tests to finally establish its distribution. Using the Rstudio data analysis software, we applied the Shapiro Test obtaining p<0.05 for the immediate postoperative VAS variables, at 3, 6 and 12 Months in RFC patients.

The objective is to observe the divergence in both sides (left or right) in the distribution of the VAS variable in RFC to the mean in the VAS variable in Mullan.

Table 7. Data VAS scale follow-up and RFC-Mullan T-Test comparison

Mean VAS Scale	RFC	Mullan	T-Test comparison
Early postoperative	2.2	2.5	0.07456
3 Months	2.3	2.6	0.7376
6 Months	2.8	3.2	0.6485
12 Months	3	3.5	0.1857

As a result, for a $p<0.05$, no statistically significant differences were obtained in terms of the results of the VAS variable in the early postoperative period, at 3, 6 and 12 months of follow-up.

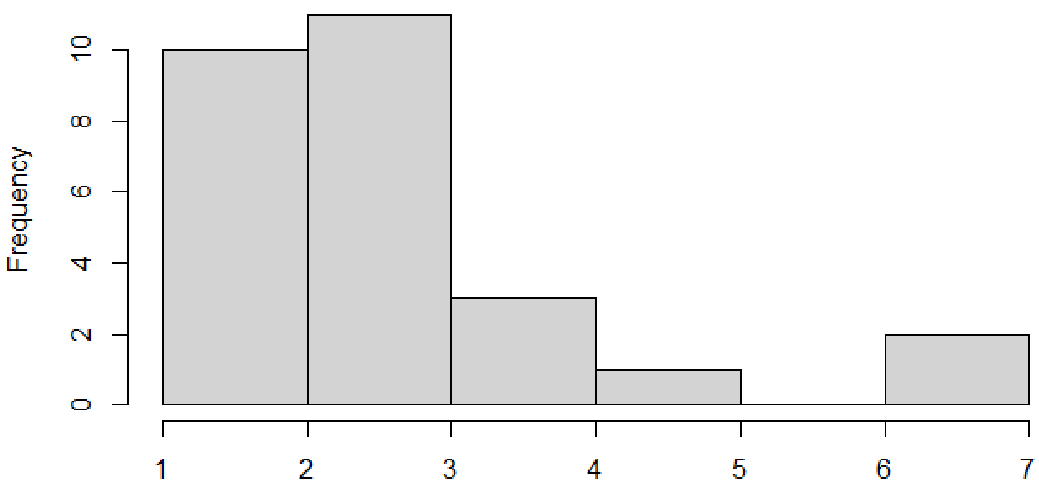
Studying the BNI variable, the results are similar and no significant differences are obtained. This also has to do with the lower range of the BNI variable.

These results are obtained from the comparison between the total RFC group and the Mullan group.

Due to the comparison in the RFC group between the selective and non-selective monitoring subgroup, statistically significant differences have been obtained, we make the comparison between the RFC selective monitoring group and the Mullan group.

In the distribution of the variables from these two groups, differences can be pointed out.

VAS SCALE SELECTIVE MONITORED RFC GROUP 12 MONTHS FOLLOW-UP



VAS SCALE MULLAN GROUP 12 MONTHS FOLLOW-UP

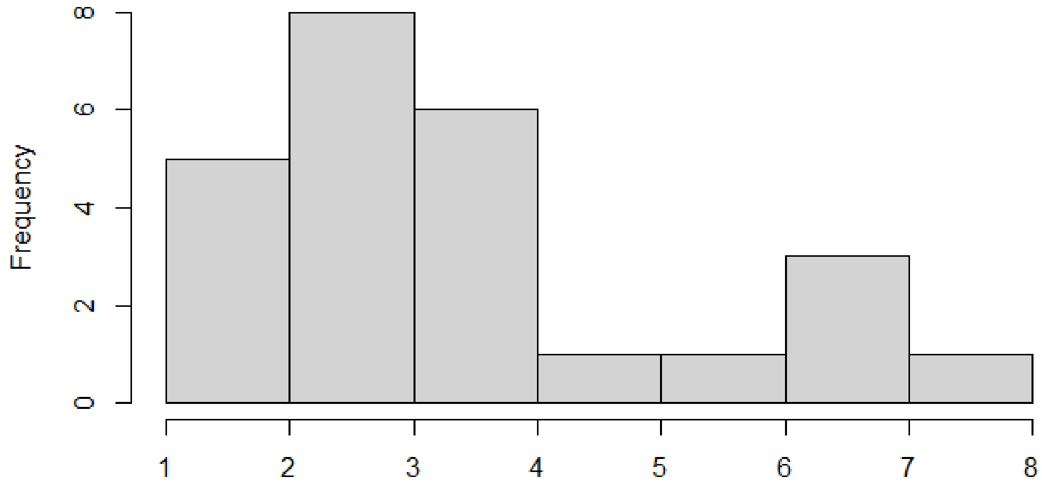


Table 8. Data VAS scale follow-up and RFC selective monitoring subgroup-Mullan T-Test comparison

Mean VAS Scale	Selective monitored branches RFC	Mullan	T-Test comparison
Early postoperative	2.3	2.5	
3 Months	2.2	2.6	

6 Months	2.3	3.2	
12 Months	2.4	3.5	0.02449

In this case we only established the comparison between both groups at 12 months since in the comparison between RFC subgroups differences were only obtained at that time of follow-up. Once again, in the subgroup of RFC patients with selective monitoring, we obtained statistically significant differences in terms of the result of the VAS scale compared to the subgroup with the Mullan balloon compression technique.

DISCUSSION

Currently, radiofrequency is one of the most used procedures given its good tolerance, especially in elderly patients, and the lower risk of complications compared to microvascular decompression or other percutaneous techniques (33) However, the main problem with percutaneous techniques, and especially radiofrequency thermocoagulation, is the tendency towards recurrence, which in some series reaches >60% after 2 years (37)

Percutaneous ablative techniques in the treatment of trigeminal neuralgia have been used extensively for years (53) and there is extensive knowledge of their effectiveness and complications (54). However, the evidence is based on observational studies and there are no randomized clinical studies that provide evidence of the superiority in terms of efficacy and safety of one technique over another, or that compare these with Vascular Microdecompression or Radiosurgery (55).

In a Cochrane review published in 2011 by Zakrzewska et al (1)a search was conducted for articles published in relation to neurosurgical procedures in the treatment of TN. 528 articles extracted from the main databases of biomedical literature (Medline, Embase, etc.) were analyzed, of which only 11 met the inclusion criteria of this review, which limited the search mainly to randomized clinical trials. Of these 11 articles, 8 were excluded due to poor description of clinical results and the presence of important biases, all contributing to a low level of evidence. Finally, only 3 studies had sufficient data and the description of the results was adequate to proceed with their análisis.

Regarding radiofrequency thermocoagulation, there is great variability in the way the technique is applied (56) (57). We can observe that repeated RFC, and with greater temperature and injury time, increases the risk of dysesthesias (58). On the other hand, the voltage and intensity parameters may also be different depending on the pulse generator used, which causes variations in the clinical result (5)(59) (60)These differences are confusing factors that make it difficult to determine the real effectiveness of the technique (61).

To ensure the adequate location of the electrode before applying radiofrequency, imaging methods such as intraoperative X-ray or neuronavigation are used that allow visualization of the foramen ovale and Meckel's cavum where the Gasserian ganglion is located. In the other study from the 2011 Cochrane review that refers to thermocoagulation, Xu et al (21), compares a series of patients in whom X-ray is used to guide electrode placement and another series in those used by neuronavigation. In the neuronavigation group, a higher rate of clinical remission was obtained one year after treatment (77% neuronavigation vs. 54% X-ray), which highlights the importance of precision in electrode placement (62)

However, in addition to adequate visualization of the anatomical structures, the determining factor to objectify the physiological situation of the electrode is the intraoperative stimulation through the nerve (63). To date, the most widely used method to locate the trigeminal branches that are the target of radiofrequency injury has been to analyze the patient's verbal response to sensory stimulation. This is only possible if the patient is kept awake during the procedure, which can be stressful and painful (64). Furthermore, discomfort and autonomic nervous system responses to pain, coupled with other factors, can lead to inadequate verbal response, lack of collaboration, or respiratory and cardiovascular complications that increase morbidity. With the intention of avoiding this stress, some studies have been carried out carrying out the technique with the patient asleep and without waking up intraoperatively, using only motor stimulation to locate the V3 mandibular branch (64) (65)Despite having also obtained good pain relief rates, this technique has the limitation of not being able to adequately localize the branches of the nerve that are symptomatic through sensory stimulation, so the parameters for carrying out the injury will tend to be of greater intensity. increasing the risk of complications and injury to unwanted trigeminal territories (66).

For this reason, attempts have been made to develop more effective methods of locating the trigeminal branches and more comfortable for the patient. When a nerve is electrically stimulated, a response is generated that can be monitored directly or indirectly with recording electrodes (67). The conduction that generates the response to the electrical stimulus is called orthodromic if the action potential goes in the same direction as the physiological conduction (in the case of the afferent sensory trigeminal branches, from the terminals on the skin surface of the face, to the body). neuronal in the Gasserian ganglion), or antidromic if it spreads in the opposite direction (from the Gasserian ganglion to the distal sensory terminals on the skin surface) (68). Some previous studies have been performed with neurophysiological monitoring using orthodromic stimulation and recording evoked potentials of the trigeminal nerve, but the procedure and its interpretation are complex and the results are variable(69) (70)

On the other hand, antidromic stimulation of sensory nerves generates a response of greater amplitude, better definition and long duration. In this regard, Berdensky et al (48) carried out a novel study in 2012 using antidromic stimulation as a method of neurophysiological monitoring in radiofrequency injury of the trigeminal nerve, for localization of the three branches of the nerve in patients under general anesthesia (71). The antidromic responses obtained for each trigeminal branch allowed selective lesions to be performed on the 3 branches, with good pain relief results. Similarly, Nie et al carried out a study comparing a series of 30 patients treated with guided radiofrequency with monitoring of the 3 branches of the nerve in their cutaneous subdivisions, with another 30 patients in the control group in which the response verbal of the patient of the patient awake conventionally. In the study group with monitoring, a higher rate of immediate remission of pain and duration of the analgesic effect was obtained, as well as a significantly lower rate of side effects (72).

However, there are also certain limitations of the monitoring technique, such as prolongation of surgical time. Furthermore, the interpretation of the potential generated after antidromic stimulation of the trigeminal nerve can be difficult, since variations in the adjustment of the deep electrode, and the arrangement of the surface electrodes with respect to the subdivisions of the trigeminal nerve can result in variations in the potential. Registered (73).

In our study carried out with the described methodology, we observed good applicability of the technique, obtaining potentials in the branches that correspond significantly to the area of hypoesthesia generated by the radiofrequency lesion. The improvement results correspond to what is described in the literature (74) (75). On the other hand, it is observed that the presence of comorbidities may be a worse prognostic factor in terms of the risk of recurrence. This could be due to the presence of polypharmacy that on the one hand can interact with the medication used in trigeminal neuralgia and on the other hand to the baseline situation of greater functional limitation and support requirements that make the perception of pain and patient's functionality is worse (76)

Regarding the relationship with the duration of the symptoms, the results suggest that the longer the duration (77), the greater the risk of recurrence after radiofrequency injury (78). This may be due to the greater degree of demyelination or ephapsis that worsens the response to radiofrequency. (79)

Within the 36 patients operated, 10 (27%) had secondary TN (most common multiple sclerosis) and in this subgroup the percentage of improvement is 60%. They are also figures corresponding to the literature.

8 patients (28%) presented (the majority had high blood pressure and diabetes). In the stratified analysis in this subgroup, the initial response is good, 90% initial improvement, but the percentage of recurrence is higher (26%). On the other hand, in the differential analysis based on the time of evolution, differences are found, although not statistically significant, in the response to the intervention based on the time of evolution. While in cases of neuralgia with a shorter duration the recurrence rate is 9%, in cases with a longer duration the recurrence increases to 18%.

7.1. Objectives and Results

The objectives of the study were in first place to determine the applicability of neurophysiological monitoring with two electrodes for the identification of trigeminal roots and radiofrequency.
The results obtained demonstrate that the applicability of the technique is viable. We have obtained 75% selective responses, which translates into better specificity when performing the radiofrequency lesion.

However, the monitoring technique has its issues. On the one hand we have found some differences in terms of the placement of the stimulus return signal. When it is placed in different anatomical parts it can result in obtaining different potentials. For example, placed on the mastoid or shoulder, we can see some differences. In mastoid, being closer to the V3 facial branch, it has a tendency to obtain a higher potential in V3, which is damped when the return signal is placed on the shoulder.

On the other hand, the recording electrode that we use is a monopolar type electrode of 115mm in length and 1.2mm in diameter. This electrode was designed through a commercial company (Neomedic) specifically for this procedure. It had to comply with a length >100mm (10cm, which is the length of the trocars that we use for puncture of the trigeminal Gasser's Ganglion) and also a diameter <1.3, which is the diameter of the trocar.

The 3mm monopolar active tip can produce greater stimulus dispersion than a bipolar tip, however we have not been able to develop a bipolar electrode with the necessary diameter and length characteristics, since there is no similar one on the market that we are aware of (80).

The recording electrode has a 3mm active tip and the radiofrequency lesion electrode usually has a 5mm active tip. We do not know if this difference may be relevant when it comes to the greater extent of the radiofrequency lesion than the fibers we were monitoring. There is also no radiofrequency electrode with an active tip <5mm on the market, as far as we are aware. For this reason we have used this combination.

In the preliminary phases of this study, we attempted to use a manufactured electrode that can do both recording and radiofrequency lesioning functions. My initial experience in another Hospital (University Hospital Joan XXIII of

Tarragona) was positive although the potential obtained was not very accurate. After starting the study with the equipment at the Vall d'Hebron University Hospital, the applicability of this electrode was not good, so I had to develop the concept of two electrodes, one for recording, the other for radiofrequency lesion.

On the second hand, we wanted to determine the concordance between the roots monitored and whose stimulation is obtained selectively, and the level of symptomatic relief.

As we have been able to extract from the data analysis, when we stratify the results on the VAS scale, in patients treated with RFC, those in whom it has been possible to selectively monitor those branches that were previously symptomatic obtain better results, especially in duration of the benefit.

Nevertheless, this has been observed in 27/36 patients, while the remaining 9 show worse results in the graphics. When we apply statistical comparison between both groups, we demonstrate at 12 months of follow-up significant differences. This demonstrates, on the one hand, that the application of the selective monitoring technique can provide a clinical benefit, which does not come into better results initially, nor in the first months of follow-up. However, after one year of follow-up we found differences with better results in the selective monitoring group, which indicates that it can help to maintain the durability of the clinical improvent, which is a very important factor in these patients.

Finally, we were aiming to determine the effectiveness of assisted radiofrequency with selective monitoring compared to other techniques such as balloon compression (Mullan), whose effectiveness compared to conventional radiofrequency in the literature is comparable continuous radiofrequency, and determine if good results of symptomatic relief are obtained.

After analyzing the results, we cannot establish statistically significant differences. This may be due to the sample size. If we look at the results of patients with RFC and selectivity of monitoring, especially during the final follow-up at 12 months, they have a clear tendency to maintain the initial clinical benefit, so it seems that recurrence is lower in this subgroup. We managed to compare the subgroup of RFC patients which obtained selective monitoring of the branches which caused the pain, and the group of Mullan patients. This time at 12 months of follow-up we obtained statistical significant differences which confirm that our monitoring technique may provide a benefit in terms of the duration of the effect of the radiofrequency lesion. We can conclude that it could be a technique more effective compared to other percutaneous techniques such as Mullan or rhizolysis with glycerol.

The principle of applying monitoring in these patients has two parts. On the one hand, the possibility of doing this technique with deep sedation or general anesthesia to avoid the stress of waking up the patient to ask them which area of their face the symptoms reproduce before performing the radiofrequency lesion.

On the other hand, and no less important, is the possibility that by applying a mapping of the fibers of the Gasser ganglion, we can produce a more effective lesion, not only to respect the other branches that are not affected, but also to capture the maximum number of fibers involved in the pain of each branch. Our pilot study allows us to validate, at least in this sample, the usefulness of monitoring. In cases where we have been able to detect selective stimuli in the affected branches, the lesion has been more effective and has lasted longer. However, this remains to be demonstrated if this duration extends much further in time, or if recurrence occurs not long after. For this reason, we must continue with longer-term follow-up studies and with a larger number of patients may help determine the reliability of these results.

Furthermore, the indication of the radiofrequency technique in trigeminal neuralgia is always limited by the risk of recurrence. When we present surgical options to patients diagnosed with trigeminal neuralgia, in those with vascular compression evidenced by MRI, the indication for vascular microdecompression is evident. Despite being a more complex procedure with higher risk for the patient, compared to radiofrequency it has a clearer clinical benefit profile given its much higher durability, and is often curative.

Another important idea would be to be able to optimize this radiofrequency technique with the help of monitoring, so that it would present a longer duration profile, and could be offered to a greater number of patients. Even in those with an indication for vascular microdecompression, it could be a sensible alternative because its lower risk, but this would make sense if we could offer greater durability than that currently obtained.

CONCLUSIONS

1.This study shows that neurophysiological recording for the identification of trigeminal roots during radiofrequency rhizotomy in trigeminal neuralgia is an applicable technique if specific stimulators and lesion electrodes are available. The technique is not complex, although monitoring requires a learning curve and experience, but the results are reproducible.

2.The clinical results are good and comparable to the literature, although so are the recurrence rates. The comparison between the RFC and Mullan groups does not obtain significant differences, probably due to the sample size. The subgroup of RFC patients with selectivity in monitoring is probably the group with the greatest clinical improvement, as demonstrated when comparing the results between this subgroup and the other subgroup of patients without selective monitoring. The result is statistically significant when we compare it at 12 months of follow-up, although the initial result and in the first months between both groups is similar. Likewise, when comparing the same subgroup of RFC patients with selectivity in monitoring, with the Mullan group at 12-month follow-up, we also obtained statistically significant differences. This validates the usefulness of our monitoring technique in terms of being able to perform a more effective and longer lasting radiofrequency lesion.

3.The use of the radiofrequency technique as part of the therapeutic management in trigeminal neuralgia could change its indication if we manage to obtain a longer duration of effectiveness. Although it will be difficult to displace the vascular microdecompression technique, it can complement it more effectively.

4.Given the novelty of these techniques, it is advisable to carry out more studies to confirm their applicability, effectiveness, and analyze the appearance of complications related to the technique.

FUTURE RESEARCH

The optimization of surgical techniques as well as the innovation and emergence of new techniques are necessary to improve the management of patients with pathologies as devastating as trigeminal neuralgia.

Although there are currently a number of applicable techniques, as well as the emergence of many forms of neuromodulation (cortical stimulation, deep brain stimulation), management has not really changed in a relevant way in the last 10-15 years.

Following the line of this study, research should go along the lines of optimizing the monitoring material, such as developing more selective bipolar electrodes and optimizing the monitoring parameters and antidromic response signals to establish a definitive protocol. Likewise, a large cohort will be required for this, in addition to allowing the real benefit of the technique applied to patients to be established.

Neuromodulation has been an expanding field in Neurosurgery in recent years. In the same way that the lesion of some deep brain nuclei such as the subthalamus or pallidum for movement disorder pathologies has been replaced by a deep stimulation system, a possible line of research may be the stimulation of the Gasserian Ganglion, not with the objective of mapping , if not with clinical objective.

Finally, another possible line of research may be related to the stimulation and/or concomitant radiofrequency of the Gasser ganglion and the sphenopalatine ganglion, whose activity is at the center of craniofacial sensitivity and represents a modulator in craniofacial painful pathology.

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