HUGO STERMAN NETO

Avaliação comparativa dos efeitos da termocoagulação por radiofrequência e neurotomia percutânea com balão no controle da dor a longo prazo em pacientes com neuralgia trigeminal idiopática

Comparative evaluation of the effects of radiofrequency thermocoagulation and balloon compression neurotomy for long-term pain control in patients with idiopathic trigeminal neuralgia

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Programa de Neurologia

Orientador: Prof. Dr. Daniel Ciampi Araujo de Andrade

São Paulo
2022

HUGO STERMAN NETO

Avaliação comparativa dos efeitos da termocoagulação por radiofrequência e neurotomia percutânea com balão no controle da dor a longo prazo em pacientes com neuralgia trigeminal idiopática

Comparative evaluation of the effects of radiofrequency thermocoagulation and balloon compression neurotomy for long-term pain control in patients with idiopathic trigeminal neuralgia

Thesis presented to the Faculdade de Medicina, Universidade de São Paulo to obtain the degree of Doctor in Science Graduate

Program of Neurology

Advisor: Prof. Dr. Daniel Ciampi Araujo de Andrade

Sao Paulo
2022

Dados Internacionais de Catalogação na Publicação (CIP)

Preparada pela Biblioteca da
Faculdade de Medicina da Universidade de São Paulo

Sterman Neto, Hugo
Avaliação comparativa dos efeitos da termocoagulação por radiofrequência e neurotomia percutânea com balão no controle da dor a longo prazo em pacientes com neuralgia trigeminal idiopática / Hugo Sterman Neto. -- São Paulo, 2022.
Tese(doutorado)--Faculdade de Medicina da Universidade de São Paulo.
Programa de Neurologia.
Orientador: Daniel Ciampi Araujo de Andrade.

Descritores: 1.Neuralgia do trigêmeo 2.Rizotomia 3.Denervação 4.Procedimentos neurocirúrgicos 5.Ensaio clínico 6.Ablação percutânea por cateter

USP/FM/DBD-037/22

Responsável: Erinalva da Conceição Batista, CRB-8 6755

À Maria Ignez e nossos filhos, Rafael, David e Maria Olivia. Minhas maiores inspirações e propósitos para seguir sempre em frente.

AGRADECIMENTOS

Ao Prof. Dr. Daniel Ciampi de Andrade, pela amizade ao longo dos anos, ensino e parceria durante esse projeto.

Ao Prof. Manoel Jacobsen Teixeira, pela formação, ensino e estímulo a sempre buscar mais do que lugar comum.

Ao Prof. Dr. Robson Amorin, pela amizade e criação desse projeto.

Ao Prof. Dr. Erich Fonoff, pela parceria e ensino na área de dor.

À Profa. Dra. Silvia Siqueira, pelo auxílio em aprender sobre um tema tão rico e complexo.

Ao Dr. Ricardo Galhardoni, pela parceria e ajuda no desenvolvimento do projeto.

À Dra. Cristiane Fukuda, pela parceria em desenvolver e executar esse trabalho longo e complexo.

Ao Dr. Mario Gilberto Siqueira, pela amizade paternal, paciência, oportunidade de me tornar um neurocirugião melhor.

Ao Dr. Roberto Sérgio Martins, pela amizade e oportunidade de aprender mais todo dia.

Ao Dr. Iuri Neville, pela amizade e parceria nos momentos de dúvida.

A minha esposa, Maria Ignez, pelo companherismo e paciência.

Aos meus pais, por me fornecerem a oportunidade de ser quem sou hoje.

Aos médicos residentes, pela ajuda na realização do projeto.

E principalmente aos pacientes, motivo e razão da existência do nosso trabalho, empenho e dedicação ao realizar esse ofício.

Without music to decorate it, time is just a bunch of boring production deadlines or dates by which bills must be paid.

Frank Zappa

Esta tese está de acordo com as seguintes normas, em vigor no momento desta publicação:

Referências: adaptado de *International Committee of Medical Journals Editors* (Vancouver).

Universidade de São Paulo. Faculdade de Medicina. Serviço de Biblioteca e Documentação. *Guia de apresentação de dissertações, teses e monografias.*
Elaborado por Anneliese Carneiro da Cunha, Maria Julia de A. L. Freddi, Maria F. Crestana, Marinalva de Souza Aragão, Suely Campos Cardoso, Valéria Vilhena. 3ª ed. São Paulo: Divisão de Biblioteca e Documentações; 2011.

Abreviatura dos títulos dos periódicos de acordo com *List of Journals Indexed in Index Medicus*.

SUMMARY

LIST OF ABREVIATIONS, SYMBOLS AND INITIALS

BC	-	Balloon compression
BPI	-	Brief Pain Inventory
CONSORT	-	Consolidated Standards of Reporting Trials
CTN	-	Classic trigeminal neuralgia
CT-scan	-	Computed Tomography Scan
d	-	Days
DN-4	-	Douleur Neuropathique
HAD	-	Hospital Anxiety and Depression Scale
HCFMUSP	-	Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo
IASP	-	International Association for the Studies of Pain
ICHD-3	-	The International Classification of Headache Disorders, 3rd Edition
IHS	-	International Headache Society
IRB	-	Internal Review Board
m	-	Months
MQSv3	-	Medication Quantification Scale, third version
MRI	-	Magnetic Resonance Imaging
MVD	-	Microvascular decompression
NPSI	-	Neuropathic Pain Symptom Questionnaire
NR	-	Not reported
NRS	-	Numeric Rating Scale
PCS	-	Pain Catastrophyzing Scale
RF	-	Radiofrequency
SF-MPQ	-	McGill Pain Questionnaire-Short Form
TG	-	Trigeminal ganglion
TN	-	Trigeminal neuralgia
V0	-	Baseline evaluation

V1	-	7-days post-operatory evaluation
V2	-	30-days post-operatory evaluation
V3	-	60-days post-operatory evaluation
V4	-	90-days post-operatory evaluation
V5	-	180-days post-operatory evaluation
WHOQoL	-	World Health Organization-Quality of Life
y	-	years

LIST OF FIGURES

LIST OF CHARTS

LIST OF TABLES

RESUMO

Sterman Neto H. *Avaliação comparativa dos efeitos da termocoagulação por radiofrequência e neurotomia percutânea com balão no controle da dor a longo prazo em pacientes com neuralgia trigeminal idiopática* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2022.

Introdução: a neuralgia trigeminal, a despeito de reconhecida há séculos, continua sendo a síndrome dolorosa neuropática facial mais fascinante e desafiadora no que se refere ao seu tratamento. Apesar de sua primeira descrição formal ter ocorrido no século 18, os tratamentos mais eficazes surgiram somente após meados do século 20. Contudo, há uma escassez de dados em estudos comparativos com alto nível de evidência entre os métodos. Dessa forma, o presente estudo comparou a eficácia dos procedimentos percutâneos mais frequentemente utilizados no controle álgico dos pacientes com neuralgia trigeminal. Métodos: trata-se de um ensaio clínico prospectivo aleatorizado, duplamente encoberto, que incluiu 33 pacientes com diagnóstico de neuralgia trigeminal, em dois grupos: BC (neurotomia por balão) e RF (termocoagulação por radiofrequência). Os pacientes foram avaliados em seis momentos distintos: antes do procedimento (V0), sete (V1), 30 (V2), 60 (V3), 90 (V4) e 180 (V5) dias após. Foram utilizadas escalas para avaliação de dor (BPI, NPSI, DN4, SF-MPQ), quantidade de medicação utilizada (MQS), qualidade de vida (WHOQoL – BREV) e funções psicológicas e humor (PCS e HADS). Dados sociodemográficos foram analisados entre os grupos. Foi utilizado, como desfecho primário, o terceiro item do BPI (escala numérica de dor nas últimas 24 horas). Após randomização, os pacientes foram submetidos ao procedimento sorteado. O desfecho primário foi analisado utilizando modelo de regressão linear. Teste t de Student foi usado para variáveis de distribuição normal e o teste de Mann-Whitney e qui-quadrado para variáveis de distribuição não-normal. Fora realizada análise interina pré-planejada com pelo menos metade dos pacientes planejados. Resultados: para a análise interina, dados de 33 pacientes estavam disponíveis. A idade média foi de 62,18 ± 9,4 anos. O objetivo primário não apresentou diferença estatisticamente significativa entre os grupos ao final do estudo. A taxa de complicação foi semelhante. A influência da dor nas atividades de vida diárias, as dimensões da dor, sintomas de dor neuropática, humor, quantidade de medicação em uso e qualidade de vida, avaliados com questionários específicos, também não apresentaram diferença estatisticamente significativa. O grupo de RF apresentou mais sintomas parestéticos do que o grupo BC (2,08±1,99; 3,97±1,96; p = 0,017) nos 30 dias subsequentes à intervenção, a despeito de não ter crises de dor (4,55±0,78, 5±0; p = 0,015). A presença do componente de dor contínua foi semelhante nos grupos. O estudo foi interrompido por insignificância clínica. Conclusão: os dois métodos possuem capacidade de controle de dor semelhante. Registro do ensaio no ClinicalTrials.gov – NCT02427074.

Descritores: Neuralgia do trigêmeo; Rizotomia; Denervação; Procedimentos neurocirúrgicos; Ensaio clínico; Ablação percutânea por cateter.

ABSTRACT

Sterman Neto H. *Comparative evaluation between radiofrequency thermocoagulation and balloon compression neurotomy on long-term pain control in patients with idiopathic trigeminal neuralgia* [thesis]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2022.

Introduction: trigeminal neuralgia, despite being recognized for centuries, remains the most fascinating and challenging facial neuropathic painful syndromes in terms of its treatment. The most effective treatments appeared after the middle of the 20th century. However, well-designed studies comparing the main therapeutic methods are lacking. The aim of this study was to compared the effectiveness of the most frequently used percutaneous procedures for pain control in patients with trigeminal neuralgia. Methods: a prospective randomized, double-blind, intention-to-treat, clinical trial, was performed: 33 patients diagnosed with trigeminal neuralgia were available for the pre-planned interim analysis. Patients were randomized using an online program. After randomization, patients were divided in two groups: balloon compression (BC) and radiofrequency (RF). Patients were evaluated at six different times: before the procedure (V0), and 7 (V1), 30 (V2), 60 (V3), 90 (V4) and 180 (V5) days after the procedure. Scales were used to assess pain (BPI, NPSI, DN4, SF-MPQ), quantity of medication used (MQS), quality of life (WHOQoL - BREV) and psychological functions and mood (PCS and HADS). Sociodemographic data were compared between the groups. The primary outcome was the third item of the BPI (numerical scale of the worst pain in the last 24 hours). The main outcome was assessed using generalized estimation equations. Student t-test was used for the normally distributed variables and Mann-Whitney and Pearson's chi-square test for the non-normally variables. A pre-planned interim analysis was performed when at least half of the estimated sample size was allocated. Results: thirty-three patients were available for the interim analysis (18 in BC and 15 in RF group). The average age was 62.18 ± 9.4 years. The primary objective showed no difference statistically significant between groups at the end of the study. Both groups presented similar complication rates. The influence of pain on daily activities of life, dimensions of pain, symptoms of neuropathic pain, mood, quantity of medication in use and quality of life, assessed with specific questionnaires, also showed no statistically significant difference. The RF group had more paresthetic symptoms than the BC group (2.08±1.99, 3.97±1.96; p=0.017) in the 30 days after the intervention, despite having no pain attacks (4.55±0.78, 5±0; p=0.015). The presence of continuous pain was similar in both groups. The study was interrupted due to futility. Conclusion: both methods show similar capacity in pain control. ClinicalTrials.gov Registry – NCT02427074.

Descriptors: Trigeminal neuralgia; Rhizotomy; Denervation; Neurosurgical procedures; Clinical trial; Percutaneous catheter ablation.

1 INTRODUCTION

Trigeminal neuralgia (TN) is characterized by shock-like paroxystic attacks distributed in one or more trigeminal branches. These attacks may occur spontaneously, or may be evoked by mechanical triggers such as lightly touching the skin, brushing teeth, chewing or even talking (Casey, 2005). It has been hypothesized that TN is triggered by contact between vessels and the root entry zone of the fifth cranial nerve (Nurmikko and Eldridge, 2001). However, recent data suggest that not only nerve deformation caused by a vessel, but also other factors relating to the trigeminal ganglion, the trigeminal nucleus or abnormalities in sodium channels may play a role in the initiation of symptoms (Siqueira *et al*., 2009; Montano *et al*., 2015). It has been estimated that TN affects from 4 to 13 per 100,000 individuals-year, and that it tends to affect predominantly women (1:1.5 to 1:1.7). The right side of the face is affected more commonly than the left side (Katusic *et al*., 1990; MacDonald *et al*., 2000; Casey, 2005; Gronseth *et al*., 2008; Obermann and Katsarava, 2009; van Kleef *et al*., 2009; Maarbjerg *et al*., 2017).

TN is initially managed with medication. Based on systematic reviews and randomized controlled trials, carbamazepine (CBZ) has been strongly recommended as the initial drug of choice (Campbell *et al*., 1966; Rockliff and Davis, 1966; Killian and Fromm, 1968; Rasmussen and Riishede, 1970; Wiffen *et al*., 2014). Oxcarbazepine (OXC) is a good option with better tolerability than CBZ and reasonable pain control, although no comparison with placebo has been made (Liebel *et al*., 2001; Beydoun, 2002; Besi *et al*., 2015).

Despite the fact that up to 90% of individuals will initially achieve pain control through pharmacological treatment, some will eventually need surgical intervention in order to alleviate pain, either because of intolerable side effects or refractory pain. There are no large studies addressing long-term pharmacological failure, but some small studies have suggested that approximately half of TN patients will eventually fail to respond to medical treatment over a ten-year period (Taylor *et al*., 1981; McQuay *et al*., 1995; Fields, 1996; Casey, 2005; Cruccu *et al*., 2008; Holland *et al*., 2015). The surgical interventions that have been applied include posterior fossa procedures (commonly microvascular decompression, MVD) (Jannetta, 1967) and trigeminal ganglion (GG) interventions such as radiofrequency thermocoagulation (RF) and balloon compression (BC) (Sweet and Wepsic, 1974; Mullan and Lichtor, 1983). The RF and BC approaches are destructive procedures that led to various degrees of sensory changes. MVD can achieve long-term pain relief in up to 70% of patients (Brisman, 2007; Linskey *et al*., 2008; Pollock and Schoeberl, 2010; Wang *et al*., 2018) with no sensory disturbance in the postoperative period, albeit its highest risk of postoperative complications (stroke, meningitis, cerebral spinal fluid leak, hemorrhage in 2% and death in 0.4% of the patients) (Huibin *et al*., 2009; Zakrzewska and Linskey, 2009). Despite the increasing number of series reporting good outcomes after MVD, percutaneous procedures are still commonly used worldwide (Noorani *et al*., 2016; Yao *et al*., 2016).

Since trigeminal ganglion procedures are less invasive and available, they became the intervention of choice in most pain centers (Sweet, 1975; Apfelbaum, 1977; Lichtor and Mullan, 1990; Tronnier *et al*., 2001; Teixeira *et al*., 2006; Baabor and Perez-Limonte, 2011; Koopman *et al*., 2011; Kundu and Rolston, 2018). Up to

80% of the subjects treated with BC and RF may be free of pain depending on the follow-up period (Kanpolat *et al*., 2001; Bendtsen *et al*., 2019; Jones *et al.*, 2019), although the end-points are not clear in the literature. The degree of pain control achieved through ablative approaches varies among the published reports (Sengupta and Stunden, 1977; Skirving and Dan, 2001; Teixeira *et al*., 2006; Tatli *et al*., 2008; Texakalidis *et al.*, 2019). Facial hypoesthesia can occur in 19% of individuals in RF and 14% in BC; masticatory weakness 6% in RF and 4.5% in BC; corneal numbness in 6.6% in RF and 0.7% in BC and painful anesthesia in 0.1 to 4% in both, although the latter more frequent in RF (Bendtsen *et al*., 2019; Jones *et al.*, 2019).

Trigeminal neuralgia classification is another issue that evolved through time and still is a matter of debate. Predate to formal classification, facial pain was divided into three major types: typical TN (*tic* douloureux), atypical TN and atypical facial pain, depending on the predominant symptom (paroxysms in typical, constant in atypical TN and no paroxysms in atypical facial pain) (Burchiel and McCartney, 2015).

Another form of classification published in early 2000's (Burchiel, 2003; Eller *et al*., 2005), classified the pain originated in the trigeminal nerve in specific groups, based on patient history and symptom onset (spontaneous or post-injury): TN1, TN2, trigeminal neuropathic pain, trigeminal deafferentation pain, symptomatic TN, postherpetic TN and atypical facial pain.

The 2004 IASP/HIS Classification separated TN individuals in two groups: classic TN (essential and idiopathic) and symptomatic TN (similar pain to classic TN but with demonstrated structural anomaly other than vascular compression) (Obermann and Katsarava, 2009).

Over time, classification has evolved until Cruccu *et al*. (2016) and IASP/IHS later, stablished the current definition and subtypes (Chart 1). It accounts for two major groups: TN and painful trigeminal neuropathy. The latter is subsequently divided in classical, secondary and idiopathic. In order to classify TN, individuals must perform a MRI, since vascular compression must be investigated. The classification also incorporated some terms referring to prevailing symptoms: "purely paroxysmal" and "with concomitant continuous pain", which does not carry any relation to etiology. Chart 2 summarizes the evolution of terms overtime.

Chart 1 - Diagnostic criteria of TN according to IASP/HIS (Headache Classification Committee, 2018)

A)	Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond, and fulfilling criteria B and C
B)	Pain has all of the following characteristics: 1. Lasting from a fraction of a second to two minutes 2. Severe intensity 3. Electric shock-like, shooting, stabbing or sharp in quality
C)	Precipitated by innocuous stimuli within the affected trigeminal distribution
D)	Not better accounted for by another ICHD-3 diagnosis

Chart 2 - Evolution of TN classification over time

	Until 2000's	2003-2005	IASP/IHS 2004	Since 2016	
TN	Tic doulourex	TN1	Classic TN	TN (Classical and idiopathic)	Every type can present: - Purely paroxysmal - With concomitant continuous pain
TN	Atypical TN	TN2	Classic TN	TN (Classical and idiopathic)	Every type can present: - Purely paroxysmal - With concomitant continuous pain
Others	Atypical facial pain	trigeminal neuropathic pain	Symptomatic TN	Secondary TN	Every type can present: - Purely paroxysmal - With concomitant continuous pain
Others	Atypical facial pain	trigeminal deafferentation pain	Symptomatic TN	Painful trigeminal neuropathy	Every type can present: - Purely paroxysmal - With concomitant continuous pain
Others	Atypical facial pain	symptomatic TN	Symptomatic TN	Painful trigeminal neuropathy	Every type can present: - Purely paroxysmal - With concomitant continuous pain
Others	Atypical facial pain	postherpetic TN	Symptomatic TN	Painful trigeminal neuropathy	Every type can present: - Purely paroxysmal - With concomitant continuous pain
Others	Atypical facial pain	atypical facial pain	Symptomatic TN	Painful trigeminal neuropathy	Every type can present: - Purely paroxysmal - With concomitant continuous pain

Table presenting the changes throughout the years in TN classification and grouping

Despite not being addressed in the classification, classical and idiopathic TN may be referred to as primary (as in non-secondary) TN, since the use of the aforementioned terms impact more the therapeutic than diagnostic aspects (Bendtsen 2019).

The evolution of TN classification proved useful overtime since differences in pain presentation were not looked upon previously. Despite this improvement, the inclusion of MRI to the current criteria possesses a barrier to countries that present with limited resources. Even more, the presence of vascular compression may be only useful to individuals that may be prone to receive MVD. Nonetheless, percutaneous procedures are still largely used and, to these subjects, the presence of the deformation of the fifth nerve is not essential to select treatment. For this reason, the use of contrast-enhanced CT-scans, in order to discard space occupying lesions, still has its role and should not be overlooked.

Despite the results from percutaneous procedures having been extensively reported, no formal comparison between BC and RF has been studied. The available data comes from large case series and retrospective cohorts and, therefore, very low level of evidence exists (Attachment A). Until the present moment, it remains largely unknown which of the two techniques is the more effective and, moreover, what their real profiles of pain relief and prevalence of adverse events related to them are. In addition, TN may present with non-paroxysmal pain associated with its classical paroxysms (Zakrzewska and Akram, 2011). The effects of treatment on these different types of pain has never been formally addressed to date.

Here, we conducted an original prospective head-to-head randomized trial to assess superiority of RF over BC in controlling trigeminal pain.

2 OBJECTIVES

2.1 Primary Objective

The main objective of the present study was to evaluate the superiority of RF over BC in trigeminal pain control at six months from surgery.

2.2 Secondary Objectives

- To assess pain characteristics (presence of continuous pain and temporal features).
- To assess mood and quality of life.
- To assess and evaluate onset of new forms of pain and recurrence as well as their characteristics.

The questionnaires applied to evaluate the secondary objectives will be used in further thesis with the intention to analyze a prediction model of outcome.

3 REVIEW OF LITERATURE

3.1 Overview of the Historical Aspects

Trigeminal neuralgia is a unique neuropathic pain syndrome. Supposedly known for hundreds of years since first reports from Greek physicians, Arataeus of Cappadocia and Galen, in the 2nd century AD (Rose, 1999; Eboli *et al*., 2009), later studies suggested that these reports related more closely to atypical TN or migraine than to typical TN (Stookey and Ransohoff, 1959). Avicenna in the 11th century AD also described craniofacial disorders (Ameli, 1965), but he only portrayed two patients, one of which most likely had facial palsy (Lewy, 1938).

Although the first full description is credited to John Locke in 1677 (Lewy, 1938; Pearce, 1993; Rose, 1999) (whom, upon examining the wife of the English ambassador suffering from intense pain on the face and jaw, prescribed laxatives as treatment), the first documented report of TN was published in 1688, narrating the progressive deterioration of Johannes Laurentis Bausch of Germany until his death in 1665, due to starvation caused by excruciating facial pain that forbid him to dwell (Cole *et al*., 2005; Eboli *et al*., 2009).

Nicholas Andre in 1756, describing two individuals with TN, that presented with facial contraction (resembling that of epileptic seizures) during pain attacks, coined the term *tic douloureux* (Brown *et al*., 1999; Cole *et al*., 2005). He was also a pioneer in treating patients, following the works of Marechal (Stookey and Ransohoff, 1959; Pearce, 1993), who believing that “vicious nervous liquids”

distressed the nerve causing pain, frequently instilled caustic substances in the infra-orbital nerve until its destruction.

A complete and detailed documented description occurred in 1773 by Fothergill therefore later being also known as Fothergill's Disease (Eboli *et al*., 2009). Although not frequently cited, John Hunter had also contributed during that century because of his interest in nerve anatomy (Eboli *et al*., 2009). He is most likely to be the first to describe nerve pain.

Its pathophysiology, deemed complex in nature since many factors may play a role, could be better understood after the discovery of the trigeminal nerve, its difference from the facial nerve, and its relation to the disease, by Charles Bell in 1829 (almost simultaneously as Mangedie). Therefore, the trigeminal nerve was held responsible for the illness (Cole *et al*., 2005), and named trigeminal neuralgia.

In the 1930s, the observations of Dandy stablished that demyelinization at the root entry zone was probably caused by pulsation of micro vessels to the nerve (Dandy, 1934), confirmed later by the observations of Jannetta, in 1967. A common denominator was frequently present: demyelization of the root entry zone of the fifth cranial nerve, either by a compressing vessel, tumor, multiple sclerosis or infection. This event is thought to generate ectopic action potential through ephatic transmission by Aβ-fibers and, associated with neuronal reorganization, led to misrouting of non-painful stimuli (talking, chewing, wind, light touch) to painful paths (allodynia), which prompts the painful shock-like attacks and may explain the trigger zones of the face (Casey, 2005; Eller *et al*., 2005; Obermann and Katsarava, 2009). Albeit the discovery that neurovascular compression can play a more important role in initiation (Antonini *et al*., 2014), it may be seen in asymptomatic

individuals and, therefore, a predisposed condition may also account for this variability (Siqueira *et al*., 2009).

Another hypothesis has been proposed. Devor *et al*, in 2002, published an excellent work explaining the "Ignition Theory" in which morpho- and physiological changes created by demyelination could explain the disease as a whole.

3.2 Treatment Evolution

3.2.1 Medical treatment

Early medical treatment dates from the works of Fothergill, where he suggested the use of Peruvian bark, which contained quinine (an alkaloid agent) o treat TN. For the following 150 years, a number of medical treatments were proposed to mitigate the suffering of the individuals harboring this condition: all of them showing various degrees of toxicity and side-effects (Cole *et al*., 2005; Patel and Kiu, 2016). Even anecdotal use of sulphuric acid, applied directly to the face of an individual in the 17th century, has been reported (van Kleef *et al*., 2009).

In the early and mid-20th century, trichloroethylene (with Plessner in 1915) and stilbamidine (with Napier and Sen Gupta in the 1940s and Woodhall and Odom in the 1950s) became popular; however, their side-effects prevented them being used for long periods (Patel and Kiu, 2016).

Also in the 1940s, with the introduction of diphenylhydantoin, by Bergouignan (based on the hypothesis of Trousseau that TN was a type of sensory epilepsy) and in the 1960s, with carbamazepine by Blom (1962), non-surgical treatment became more feasible, tolerated and efficient, making way for a new era of medical treatment.

Since then, a wide range of similar medications have been tested (e.g. oxcarbazepine, pregabalin, gabapentin, baclofen), despite no formal comparison to placebo have been made (Gronseth *et al*., 2008; van Kleef *et al*., 2009; Bendtsen *et al*., 2019).

Further observation that common medication (i.ex. morphine) were ineffective, added to the fact that TN pain was essentially a form of allodynia (corroborated to imply large Aβ-fibers to the generation of pain) (Bowsher, 1997), would be critical to the development of percutaneous procedures.

3.2.2 Surgical treatment

3.2.2.1 Open Surgery

In 1750, a royal French surgeon, Maréchal, encouraged by the ideas of Nicholas Andres, as well as Veillard and Dussans, proposed severing the infra-orbital nerve as a form of treatment. After a series of unsuccessful procedures, this technique was abandoned (Stookey and Ransohoff, 1959).

In the 18th century, after the discoveries of Charles Bell brought enlightenment to the medical community, a first attempt to surgically treat the malady by accessing the gasserian ganglion was performed by John Murray Carnochan in 1858: a transmalar neurectomy of the second trigeminal division at the *foramen rotundum* was performed with success (Tubbs *et al*., 2010).

William Rose, in 1890, and Andrews in 1891, working separately, described the first ganglionectomy by an infratemporal approach (Stookey and Ransohoff, 1959), severing the maxillary and mandibular divisions at its respective *foramina* and following posteriorly to the GG. However, the approach revealed to be toilsome.

In 1891, an approach to the GG through a transcranial route was described (Stookey and Ransohoff, 1959). This middle fossa, intradural procedure allowed better access to the more proximal structures to perform the rizothomy, but possessed the inconvenient of possible cavernous sinus laceration in the attempt to do the ganglionectomy, which rendered the interruption of the surgery.

Two years later, Frank Hartley and Fedor Krause independently described a subtemporal extradural ganglionectomy which became known as the Hartley-Krause approach. A modification of the technique by Cushing in 1900 reduced mortality to 5% (Cole *et al*., 2005) since he advocated a more basal temporal transcranial route, which led to less intraoperative bleeding and temporal lobe retraction.

Despite their initial success, the approach to the ganglion was not very specific and total rizothomy was the rule: full-face anesthesia frequently complicated with corneal ulceration due to first division lesioning, and masticatory weakness due to third division sectioning. This led to modification and refinement of the technique by Spiller and Frazier in 1901, who, disregarding the GG, selectively severed the pre-ganglionic rootlets and described the preservation of the ophthalmic division and masticatory motor branches (Dandy, 1929) developing the partial sensory rizothomy (PSR). In 1959, Stookey and Ransohoff published the result of 700 PSR done over thirty years: 92% of the patients were pain free, 8% had facial palsy and 30% presented paresthetic symptoms. Gardner also published impressive results: up to 99% of patients remained pain-free (Gardner, 1962) and with acceptable risks, with the Spiller-Frazier procedure

In 1925, Walter Dandy, in an attempt to develop a less time-consuming and motor-preserving procedure, modified the middle fossa approach to a posterior fossa

one through a suboccipital craniotomy, associated with complete sensory rizothomy. He then, experimenting with partial rizothomy, achieved good results and preservation of skin sensation (of note, it is hypothesized that the rootles related to the ophthalmic division were spared because of technical difficulty, since through this approach they are located more medially and cannot be easily severed). Moreover, the risk of facial paralysis and blood loss were significantly lowered with this approach. In a series published in 1929, Dandy also suggested what would become the hallmark of the physiopathology: neurovascular compression by the superior cerebellar artery at the root entry zone. Even with this discovery, he continued to perform the selective rizothomy. Despite his enormous contribution (Dandy, 1932, 1934) with interesting results and intraoperative findings, the Spiller-Frazier procedure remained the gold-standard for treating TN for almost 50 years, since Dandy stated that his procedure was not proven to be better than the aforementioned one (although he himself abandoned it and continued using his own). As of interest, some blame the Dandy-Cushing feud for the lack of widespread publicity of Dandy's Work.

In 1967, Jannetta, an enthusiast of the routine use of the surgical microscope, started exploring the nerves of the posterior fossa, using the approach described by Dandy, reliving interest in open surgery. His observations in 100 patients submitted to surgery were published in 1976 (Jannetta, 1976) where he could confirm vascular compression on the Obersteiner-Redlich zone of the fifth nerve causing demyelinizition. He also stated that mitigation of pain in the post-operative period had relation to occurrence of intra-operative nerve trauma. He recommended that the vessel deforming the trigeminal nerve should be moved and secured with a synthetic

sponge. Since non-destructive technics were less successful than destructive ones, the surgical community failed to accept the technique until multiple reports of encouraging results started to be published (Apfelbaum, 1977; Bederson and Wilson, 1989; Barker *et al*., 1996).

Following a series of excellent outcomes, microvascular decompression (MVD) became the gold-standard in treating TN patients, especially in cases with proven pre-operative nerve deformity caused by vascular anomaly (Barker *et al*., 1996). It is expected that MVD led to 95% of relief and a rate of recurrence of 1% per-year (Tatli *et al*., 2008; Kundu and Rolston, 2018).

3.2.2.2 Chemoneurolysis

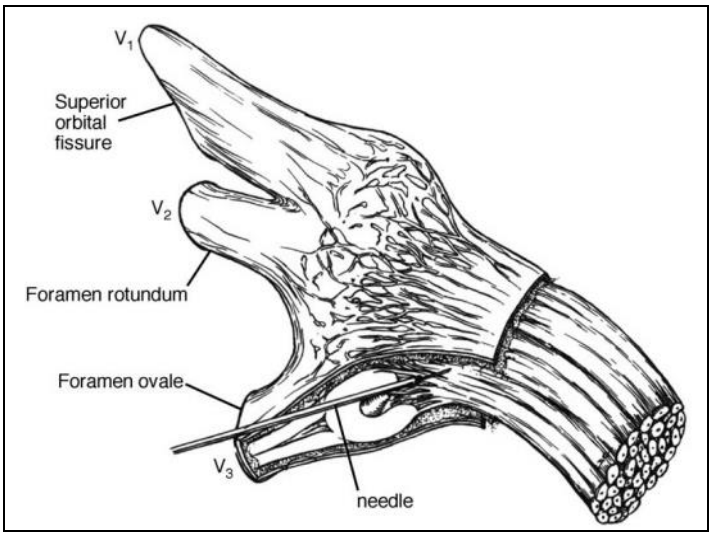
As mentioned before, the imputation of the disease to the trigeminal nerve incited the development of a number of techniques aiming at several degrees of nerve destruction in order to reduce skin sensation and, therefore, defuse the triggers of pain attacks. The excitement emerged by the results of destructive procedures to the GG and pre-ganglionic rootlets through an open approach stirred up the possibility of less invasive ablative ones: peripheral and percutaneous.

The first destructive procedure through a less invasive approach was done with chemoneurolysis in the late 19th century, when Bartholow in 1876 and Neuber in 1883 applied chloroform and osmic acid, respectively, to the nerve trunks in the face. Later, in 1888, Pitres and Vaillard conducted animal experiments with alcohol administration to nerve trunks and evaluating its effects on sensitive and motor functions, leading to the broad use of this chemical agent in treating patients (Stookey and Ransohoff, 1959).

In 1904, Schloesser introduced peripheral chemoneurolysis using alcohol injection into peripheral nerves. Due to short-lasting effects, more toxic agents were progressively researched. In 1907, Wright applied osmic acid into the GG through an open procedure (Stookey and Ransohoff, 1959).

In 1940, Harris published results from 30 years of percutaneously injecting alcohol into the GG, although a high number of them required repeated procedures until anesthesia was achieved. Despite the low mortality rate, the procedure often complicated with dysesthesia, *Herpes simplex* infection, hyperesthesia, keratitis, masticatory weakness (which took 3 months to resolve) and loss of taste. It is stated that the main limitation of the use of alcohol was its broad spread through the cisterns causing multiple cranial nerves deficiency (Cole *et al*., 2005).

The description of the *foramen ovale* puncuture by Härtel (1914), recommendation of the use of X-ray to precisely locate the tip of the needle in the GG (Pollock and Potter, 1916; Putnam and Hampton, 1936; Stookey and Ransohoff, 1959) and the development of an insulated needle that used electric stimulation for localization by Selverstone (Pollock and Potter, 1916; Putnam and Hampton, 1936; Stookey and Ransohoff, 1959) gave way to the safe delivery of substances in a more precise fashion (Figures 1, 2 and 3).



Fonte: Liu *et al*. (2007)

Figure 1 - Figure depicting the location of the needle in the trigeminal ganglion through the *foramen ovale* approach

Figure 2 - Anatomical model showing the trajectory of the percutaneous approach to the trigeminal ganglion through the *foramen ovale*

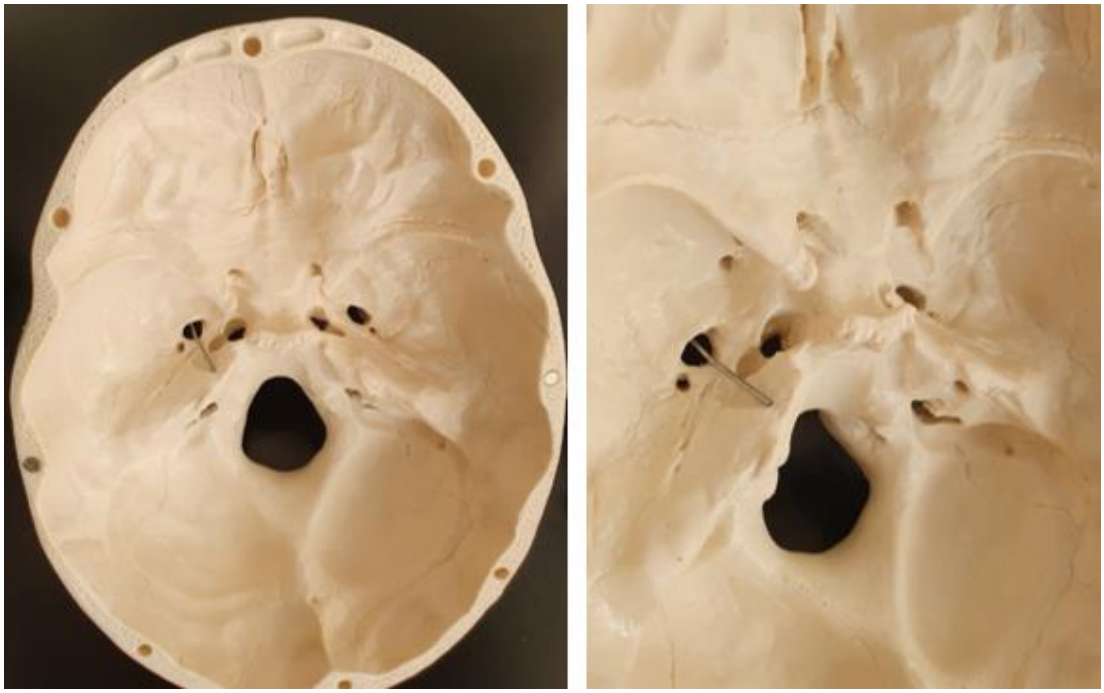


Figure 3 - Position of the needle through *foramen ovale,* from an intracranial view

Therefore, chemoneurolysis with alcohol was used for most of the 20th century, until glycerol was discovered at random (Hakanson, 1981). The latter agent was delivered in the retrogasserian region and, albeit the high recurrence rate, sensitivity sequelae was low. Due to its reasonable performance, percutaneous retrogasserian chemoneurolysis is still largely used.

The possibility of reaching the trigeminal ganglion and the pre-ganglionic rootlets gave rise to the pursuit of more advanced methods of ablation: more profound effects (reduced rates of recurrence) with less side-effects (avoidance of masticatory muscles weakness, intolerable paresthesia, painful anesthesia, keratitis and corneal ulceration). The principle of fiber destruction using chemical agents stimulated the development of other technics with the same purpose.

3.2.2.3 Percutaneous procedures

- Radiofrequency

The first physical method attempt was described by Rethi in 1913 (Wilkins, 2002). He applied electrocoagulation of the Gasserian ganglion. Followed by Kirschner in 1931 (Kirschner, 1963), both treated patients using Bovie, a monopolar cautery, with an insulated needle.

Overtime, more selective methods of fiber destruction were developed in association with modern anesthetic procedures that allowed the surgeon to awake patients and examine the areas of hypoalgesia (Schurmann *et al*., 1972).

In 1974, Sweet and Wepsic applied radiofrequency thermocoagulation of the preganglionic rootlets instead of electrocoagulation to the trigeminal ganglion, in order to overcome the frequent complications, for instance, blindness, ocular palsy and corneal ulceration (White and Sweet, 1969). Since radiofrequency thermocoagulation was deemed capable of preserving large fibers, skin sensation could be preserved (Letcher and Goldring, 1968; Frigyesi *et al*., 1975). The technique involved controlled coagulation by a radiofrequency generator and temperature control by a thermistor, associated with a potent short-acting sedative and electrical stimulation to help place the electrode in the right targeted division. Modification throughout the years were implemented and the use of neuroleptic anesthesia allowed aweakening the individuals and testing skin sensation. In 1996, Tew and Taha encouraged the use of curved thermistor in order to achieve even more selective lesions.

- Compression neurotomy

In 1952, Palle Taarnhøj, modifying the Spiller-Frazier technique, gave rise to the basis of the Mullan technique: he used the middle fossa intradural subtemporal approach in order to decompress the *dura mater* over the trigeminal ganglion (Taarnhøj, 1954, 1956), a procedure often called gangliolysis. Of the 70 treated patients, it was stated that more than half presented with remission and only 9 cases recurred, with no complications. Pudenz in 1952 (Stookey and Ransohoff, 1959) and Shelden *et al*. in 1955 also published decompression approaches, but to the second and third trigeminal divisions around the *foramina*.

Gardner and Miklos published a report of 112 individuals in 1959, known as the Cleveland series (the latter, known as the Copenhagen series), with 62% of excellent results. His technique was slightly different: after the dura being cut, the rootlets were gently brushed with cottonoid, causing a mild intra-operative nerve trauma. He stated that the compression, due to any abnormality present in the region, could be the cause of myelin loss. The relief of symptoms related to surgical trauma were also noted by Shelden *et al.* (1955, 1960) and Graf (1963). Although the rate of sensibility disturbance was low, the rate of recurrence was about 25%.

Based on these findings, Mullan and Lichtor (1983) introduced a percutaneous technique in 1978 that used a Fogarty catheter in order to mildly traumatize the trigeminal ganglion and pre-ganglionic rootlets. The catheter was placed in the TG and insufflated with a contrast agent until a pear-shape of the balloon, confirmed with fluoroscopy, was obtained. The compression was maintained for 3 to 10 minutes.

Some modifications to the original technique have been described but mainly regarding volume of the balloon, duration of compression, type of anesthesia and type of stylet (preferably blunt in order to avoid major vascular injury to the internal carotid artery in the *foramen lacerum*) (Brown *et al*., 1996). Although the technique possesses a 60% rate of facial numbness and 15% of masticatory weakness (that usually resolved in 3 to 12 months), its major complication is intraoperative cardiovascular event, namely bradycardia. In 2010, Tibano *et al.* (2010) stated that the ganglionic block with local anesthetic, preceding the balloon compression, reduced those effects.

- Contributions from University of Sao Paulo

Some unpublished data, minutely described in Dr. Manoel Jacobsen Teixeira's thesis, in 1984, who is an important researcher in TN, provides important aspects of University of Sao Paulo contribution, with Dr. Portugal's experience with partial ganglionectomy and Dr. Tenuto's works with retrogasserian fascicular sectioning (Teixeira, 1984).

4 METHODS

4.1 Patients

The individuals included in this study had the following characteristics: aged 18 years or older; primary (not-secondary) TN (despite the term primary is not present in the current classification criteria, it is used here to group classical and idiopathic cases) (Cruccu *et al*., 2016; Headache Classification Committee, 2018); no major signs of trigeminal neuropathy on examination; refractory to medical treatment (no pain control or uncontrolled side effects with the maximum tolerated dosage of conventional medication – carbamazepine, phenytoin, oxcarbazepine or baclofen – over the previous year, at least) (Wiffen *et al*., 2014) with involvement of second or third trigeminal division and no previous surgical procedure. Enrollment occurred between May 2015 and December 2018. The exclusion criteria were: involvement of the first trigeminal division or trigeminal neuropathy, previous surgery and/or procedure, patients who refused to participate or had difficulty in understanding the study protocol (Chart 3).

Chart 3 - Inclusion and exclusion criteria used in the present study

Inclusion Criteria 1. Diagnosis of Primary Trigeminal Neuralgia 2. Refractory/Intolerable medical treatment 3. Pain restricted to second or third trigeminal division 4. No previous surgical treatment
Exclusion Criteria 1. Secondary Trigeminal Neuralgia/Trigeminal Neuropathy 2. Pain restricted to the first trigeminal division 3. Refuse to participate 4. Unable to comprehend the questionnaires 5. Previous surgery and/or procedure

4.1.1 Patients

During study period, 87 patients were assessed for eligibility. After applying the inclusion and exclusion criteria, 33 were available for the interim analysis (25 females; 62.18 ± 9.4 years old) (see CONSORT flow-chart – Figure 4): 57.6% with the mandibular division affected and twenty-one with right-sided TN. Table 1 shows the subjects' characteristics and demographics, along comparisons between the groups. If patients failed to attend more than 20% of the visits, they were excluded from study protocol.

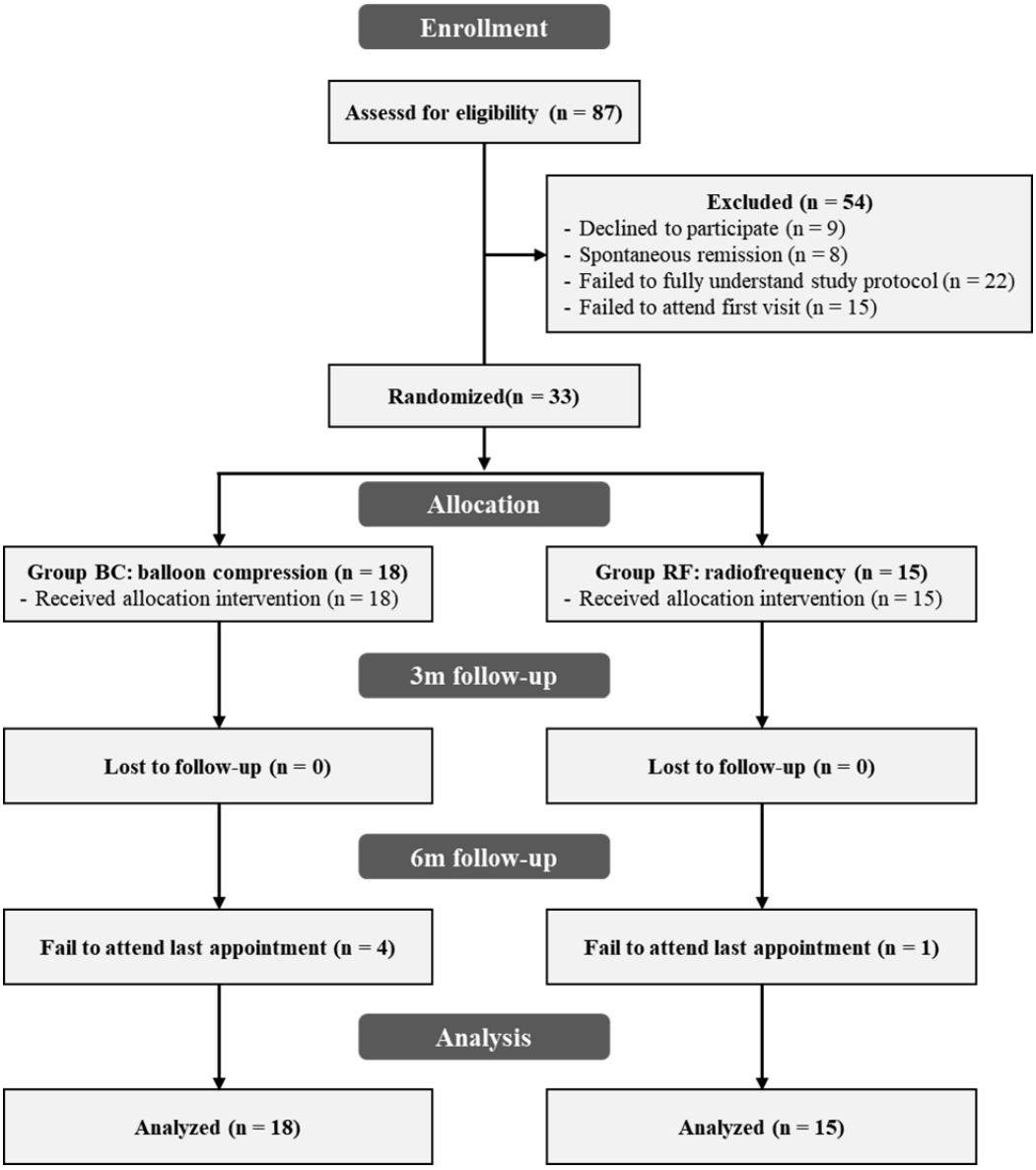


Figure 4 - CONSORT flowchart of the present study

Table 1 - Demographics and pain characteristics of all patients and subgroups

Characteristics		Total (33)	Group 1 (BC) (n=18)	Group 2 (RF) (n=15)	*p*
Age (in years)		62.18 ± 9.4 (40-78)	65 ± 9.42 (45-78)	58.8 ± 8.47 (40-71)	0.058
Sex	Male	8 (24.2%)	5 (16.7%)	5 (33.3%)	0.266
	Female	25 (75.8%)	15 (83.3%)	10 (66.7%)	
Skin colour	White	26 (78.8%)	14 (77.8%)	12 (80%)	0.458
	Brown	6 (18.2%)	4 (22.2%)	2 (13.3%)	
	Black	1 (3%)	0	1 (6.7%)	
Marital status	Maried	17 (51.5%)	9 (50%)	8 (53.3%)	0.772
	Divorced	6 (18.2%)	3 (16.7%)	3 (20%)	
	Widow	6 (18.2%)	4 (22.2%)	2 (13.3%)	
	Single	3 (9.1%)	2 (11.1%)	1 (6.7%)	
	Stable union	1 (3%)	0	1 (6.7%)	
Trigeminal Division	Second	14 (42.4%)	7 (38.9%)	7 (46.7%)	0.653
	Third	19 (57.6%)	11 (61.1%)	8 (53.3%)	
Laterality	R	21 (63.6%)	14 (77.8%)	7 (46.7%)	0.064
	L	12 (36.4%)	4 (22.2%)	8 (53.3%)	
Other previous non-trigeminal pain syndrome		18 (54.5%)	12 (66.7%)	6 (40%)	0.126

The values are presented as mean ± SD (range).
BC: balloon compression; RF: radiofrequency. R: right; L: left. Significance set at $p < 0.05$.

4.2 Location and Recruitment

This study was conducted at the pain center outpatient clinic of Hospital das Clínicas, University of São Paulo. Patients with the diagnosis of TN were referred from regional neurology and pain clinics in the State of Sao Paulo (approx. 44 million inhabitants) and were screened for participation by one of the researchers, either by phone or at in-person screening visits. The specific sites of each stage of the study is detailed below (Chart 4).

Chart 4 - Physical sites used in the study

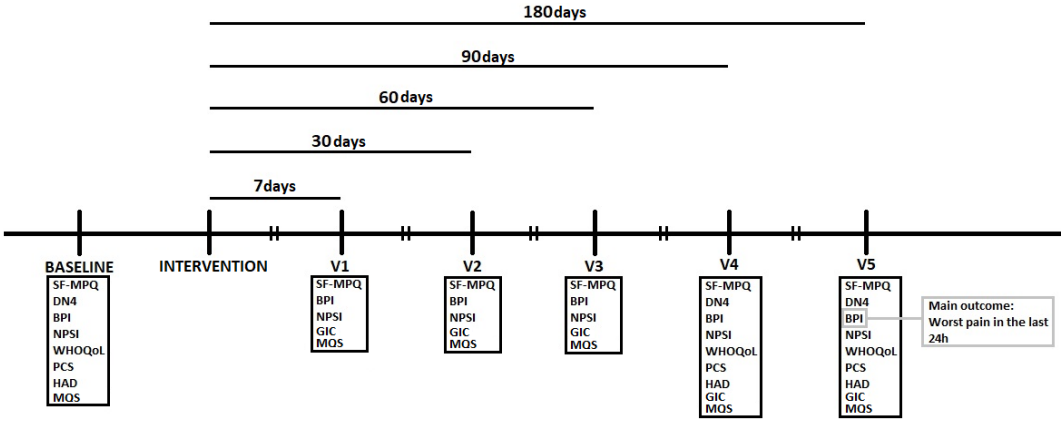
Stage	Location
Screening and recruitment	Outpatient pain clinic
Pre- and post-operative evaluations	Neurophysiology and Pain Center
Procedure	Surgical center of Instituto de Psiquiatria

4.3 Study design

A prospective double-blinded (subjects and rater) head-to-head randomized clinical trial was designed to compare the effects of BC and RF on the trigeminal ganglion for treating TN. Analysis were made on intention-to-treat basis. Since there was a paucity of formal clinical trials on ablative surgery for NT (Zakrzewska and Akram, 2011), no formal sample size calculation could be performed beforehand. Therefore, we designed a pragmatic clinical trial: we used a convenience sample of TN patients based on the sample size of previous studies (n = 30 per arm), in order to assess equivalence between arms (Erdine *et al.*, 2017; Zakrzewska and Akram, 2011).

A pre-planned interim analysis, previously approved by the institutional review board (IRB), was envisaged when half of the total sample was reached in both groups, in order to access safety and pain control data, and to assess whether there was any need to revise the number of subjects needed. The interim results were analyzed by an external research panel and one of the following decisions would be made: 1 – to stop the trial because significant differences between the arms had already been discerned; 2 – to stop the trial because it was futile to continue; or 3 – to pursue the trial with a new sample size calculated based on the information obtained from the first part of the study, with a new sample size target. This interim analysis was preplanned and was set forth in the registration document for this trial, which is available in the online open trial repository (clinicaltrials.org; NCT 02427074) (Attachment B).

After inclusion, patients were conducted as depicted in the Figure 5.



SF-MPQ: Short-Form McGill Pain Questionnaire; DN4: Douleur Neuropatique 4; BPI: Brief Pain Inventory; NPSI: Neuropathic Pain Symptom Inventory; WHOQoL: World Health Organization quality-of-life questionnaire; PCS: Pain Catastrophizing Scale; HADS: Hospital Anxiety and Depression scale; MQS: Medication Quantification Scale; GIC: Global Impression of Change.

Figure 5 - Scheme depicting follow-up and scheduled appointments

4.4 Primary outcome measurement

The primary outcome of the present study was assessed using the third item of the Brief Pain Inventory (BPI): numeric ranking scale (from zero to 10) of the worst pain in the last 24-hours.

4.5 Secondary outcome measurement

Secondary outcomes were measured using the specific questionnaires related below. Despite not being objective of analysis in the present thesis, data was collected for future studies and thesis aiming side-effects and prediction of response based on individual pain features, socioeconomics and psychological profile.

4.6 Randomization

Individuals were randomly allocated to either balloon compression or radiofrequency thermocoagulation at a 1:1 proportion. An electronic software (available at www.randomizer.org) was used to perform the randomization in blocks of 4.

4.7 Blinding

Blinding of the subjects was ensured by informing patients they would undergo one of two traditional percutaneous techniques for treating the symptoms of TN. The responsible for randomization and data plotting did not participate in the surgical procedure nor the postoperative appointments; moreover, had no access to the patients' intraoperative or outpatient visit records.

A standardized questionnaire was used to assess the blinding of the study, which was filled out at the end of the trial. It was composed of four questions: 1 – How much pain did you experience during the surgical procedure, on a numerical rating scale from 0 (no pain) to 10 (worst pain)?; 2 – Would you be able to tell which treatment you were receiving (yes/no)?; 3 – If so, which group do you think you were in (group 1/group 2)?; 4 – Would you be willing to undergo the procedure again if it was offered to you (yes/no)? (Rocha *et al*., 2014).

4.8 Ethics

The Institutional Ethics Committee approved this protocol (CaPPesq 1180/09, Attachments C, D and E). A consent form was obtained for all patients (Attachment F).

4.9 Safety

All percutaneous procedures were performed in a Surgical Suite by the same surgeon and under monitorization, followed-up closely by an independent anesthesiology staff member.

4.10 Instrumentalized evaluation

The subjects were evaluated using specific questionnaires.

4.10.1 Brief Pain Inventory

This consists of a 9-item questionnaire that includes a pain severity index (mean of questions 3-6, with a numerical rating scale that ranged from 0 to 10, such that the lower the score was, the lower the pain level was) and measurement of the interference of pain with daily activities (mean of questions 9A-9G, with a numerical rating scale that ranged from 0 to 10, such that the lower the score was, the less the interference was. In addition, this questionnaire can assist in gathering information about medications and dosage currently used by the subjects. The primary outcome used in the present study was the third question of this questionnaire, asked at the last evaluation (180 days after the procedure): “What was your worst pain level over the last 24 hours?” (Daut *et al*., 1983; Ferreira *et al*., 2011) (Appendix A).

4.10.2 McGill Pain Questionnaire - short form (SF-MPQ)

This questionnaire contains 15 descriptors of pain within three aspects and qualities of pain: sensory-discriminative, affective-emotional and cognitive-evaluative. The total score possible is 15, and each item is binary: present or absent (Melzack, 1987; Ferreira *et al*., 2013) (Appendix B).

4.10.3 Douleur Neuropatique 4 questionnaire (DN4)

This is a 10-item scale that evaluates the possible presence of a neuropathic component of pain. The screening is positive for scores ≥ 4 (Bouhassira *et al*., 2005; Santos *et al*., 2010) (Appendix C).

4.10.4 Neuropathic Pain Symptom Inventory (NPSI)

This is a validated instrument that encompasses various aspects of neuropathic pain. It is composed of 10 items that are presented as numerical rating scales with a range from 0 to 10, each referring to a specific feature: superficial spontaneous pain (question 1), deep spontaneous pain (mean of questions 2 and 3), paroxysmal pain (mean of question 5 and 6), evoked pain (mean of questions 8, 9 and 10) and paresthesia/dysesthesia (mean of questions 11 and 12). The possible total score is 100. The temporal aspects of continuous and paroxysmal pain are assessed in question 4 (duration of spontaneous pain over the last 24 h) and question 7 (number of pain attacks over the last 24 h). NPSI was also used here to evaluate non-paroxysmal pain: scores of 4 or higher than the mean in the first domain (superficial spontaneous pain) and second domain (deep spontaneous pain) were considered to

represent continuous pain (Bouhassira *et al*., 2004; de Andrade *et al*., 2011) (Appendix D).

4.10.5 World Health Organization quality-of-life questionnaire – brief from (WHOQoL-BF)

A short 26-item version of a full 100-item questionnaire which evaluates physical, psychological, social relationships and environmental relationships domains of quality of life. The higher the scores are, the better the quality of life is (Development, 1998; Fleck *et al*., 2000) (Appendix E).

4.10.6 Pain Catastrophizing Scale (PCS)

This is an instrument that evaluates the emotional distress and disability that pain causes in subjects. It consists of a 13-item scale, on which each item can be scored from 0 to 4 each, thus giving a total score of 0 to 52. The higher the score is, the more elevated the distress is (Sullivan *et al*., 1995; Sehn *et al*., 2012) (Appendix F).

4.10.7 Hospital Anxiety and Depression Scale (HADS)

This is a 14-item questionnaire (7 items for anxiety and 7 for depression symptoms, with scores ranging from 0 to 3 each) that aids in screening for mood disorders, with total scores from 0 to 21 for anxiety and for depression. Higher scores suggest depression/anxiety (Zigmond and Snaith, 1983; Pais-Ribeiro *et al*., 2007) (Appendix G).

4.10.8 Global Impression of Change (GIC)

This is a scale used by the patient (p-GIC) and evaluator (c-GIC) to rate the global evolution of their pain since the first visit. In both cases, the GIC included seven ranks ranging from 1 to 7 (1 = very much improved, 2 = moderately improved, 3 = slightly improved, 4 = no change; 5 = slightly worsened; 6 = moderately worsened; 7 = very much worsened) (Dworkin *et al*., 2005; de Andrade *et al*., 2011) (Appendix H).

4.10.9 Medication Quantification Scale version 3 (MQSv3)

This is a standardized scale for quantifying the medications used by the patient and their dosages. It provides a weighted final score for the "medication burden" (Harden *et al*., 2005).

4.11 Procedures

4.11.1 Anesthetic procedure and *foramen ovale* puncture

All patients fasted for six hours before the intervention. An intravenous access was placed and prophylactic antibiotic was given 1 hour before surgery. The anesthetic routine for the BC comprised administration of intravenous (IV) propofol (2.5 mg/kg), IV fentanyl (50 to 150 mcg), muscle relaxant (rocuronium, 1 mg/kg) and placement of endotracheal catheter.

The subjects received atropine (0.25 mg), and sedation was maintained with sevoflurane 1-1.2 MAC until the end of the procedure. For RF, the patients received mild sedation with propofol and fentanyl and an O_2 catheter was placed. They were

then awakened for skin sensory evaluation. Under complete aseptic conditions, the skin over the needle entry-point was infiltrated with 1% lidocaine. The patient was placed in the supine position with the head perpendicular to the horizontal plane. The entry point was set as 2.5 to 3 cm laterally to the labial commissure, depending on whether the target was the third (mandibullary) or second (maxillary) trigeminal division, respectively. The planes used to access the *foramen ovale* had previously been described (Härtel, 1914; Tew Jr. and Keller, 1977; Mullan and Lichtor, 1983): one that passes through the ipsilateral pupil and another one 3 cm anteriorly to the tragus, also ipsilaterally. Using radioscopic imaging (Siemens®, Siremobile, Erlenzen, Germany), the puncturing of the *foramen ovale* was confirmed (using the clival line as the reference for the second trigeminal division; and 5 mm anteriorly to the clival line for the third trigeminal division) (Figures 6 and 7).

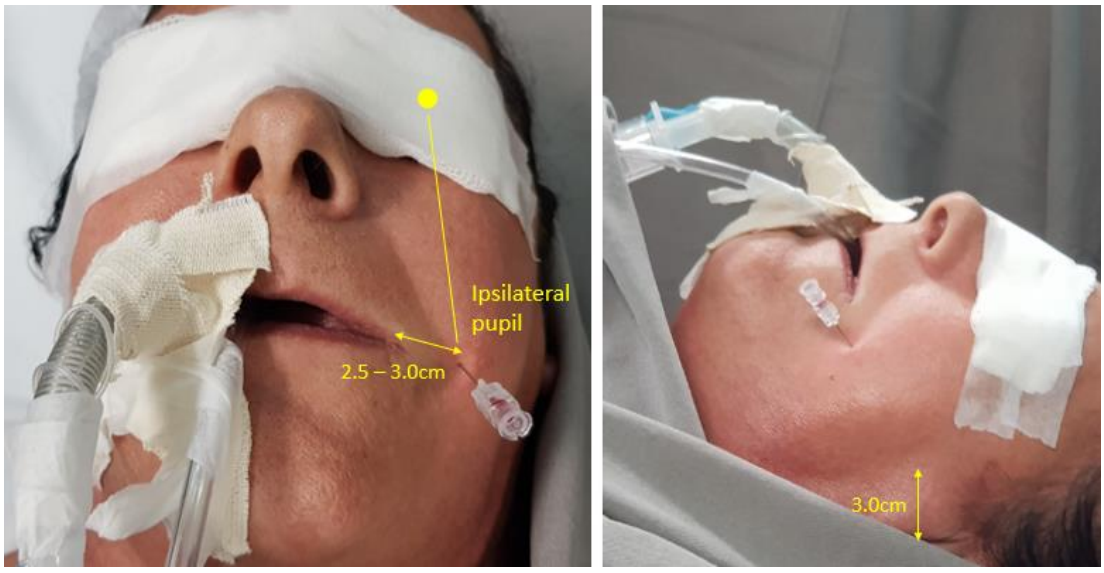


Figure 6 - Topographic references for *foramen ovale* puncture

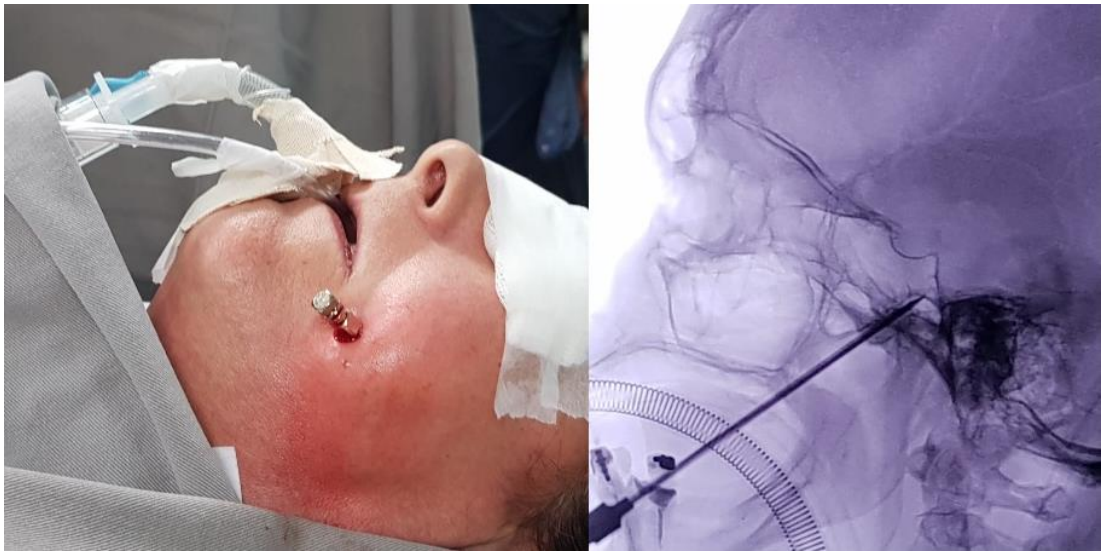


Figure 7 - LEFT: Photograph of the percutaneous approach to the trigeminal ganglion; RIGHT: respective fluoroscopy confirming the position

4.11.2 Balloon compression

For the BC technique, after puncturing the *foramen ovale* with a 14G needle (BR R Becton Dickinson, Juiz de Fora, MG, Brazil, Figure 8), 1% lidocaine was administered to the trigeminal ganglion until facial anesthesia was attained. Then, a 4F Fogarty catheter (American Edwars Laboratory, USA, Figure 8) was placed in the trigeminal cistern and insufflated with 0.7 mL of the contrast agent Iopamiron® (125R, Schering, São Paulo, Brazil) until the balloon assumed a "pear shape" (Figure 9) on the C-arm. Compression of the trigeminal division by the inflated balloon was maintained for 120 seconds. At the end, the balloon was deflated and the catheter and needle were removed. Mechanical compression was applied to the point of entry.

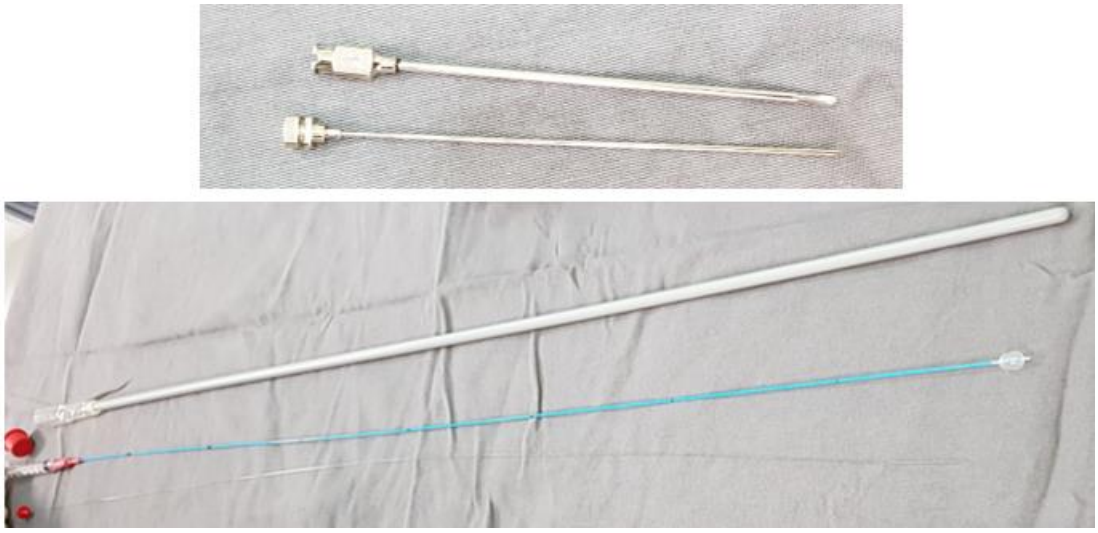


Figure 8 - Needle and Fogarty catheter used in balloon compression

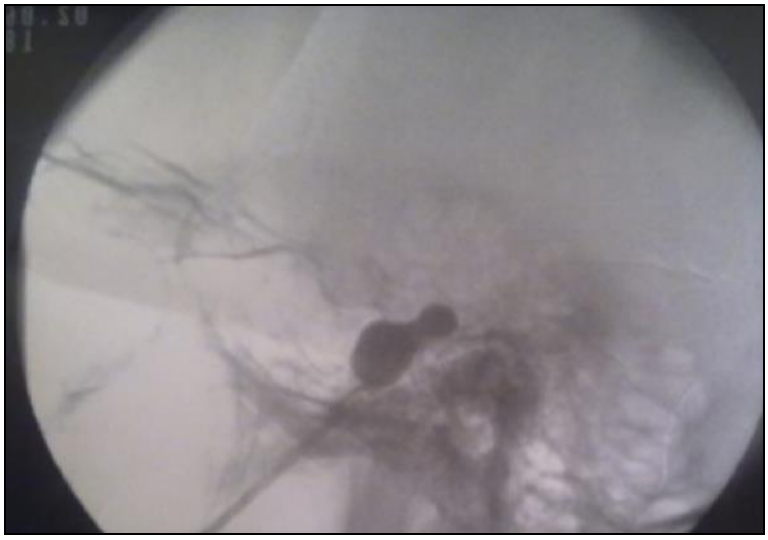


Figure 9 - Fluoroscopic image of the "pear-shape" of the balloon during compression

4.11.3 Radiofrequency thermocoagulation

For the RF technique, after puncturing the *foramen ovale* with the needle, an electrode (Radionics®, 15 cm, insulated, Figure 10) was inserted and connected to a Radionics® generator (RFG-3C Plus, Figure 10). After evaluating the impedance (250 - 300 ohms), the trigeminal division of interest was confirmed through

stimulation (sensory stimulation at 50 Hz and 0.1 to 0.5 V, with the patient awake to describe the area of paresthesia, and motor stimulation at a frequency of 2 Hz and 0.1 to 0.5 V, with the patient asleep, until masticatory movements were observed). After confirming which trigeminal division was to be targeted, we began inducing the thermocoagulation injuries, which was done at 70 °C for 60 seconds. The pinprick sensation was tested and compared to the contralateral side using a safety pin between cycles and this process was repeated until skin anesthesia over the targeted area had been achieved (an average of 2 to 3 cycles were necessary).

Figure 10 - RF electrode and radiofrequency generator utilized

4.12 Missing Data

For patients to be included in the analyses, a minimum of 80% attendance was required and provision of at least 80% of the information at each clinical visit. Data imputation was done by using the last-observation-carried-forward methodology.

4.13 Statistical Analysis

The variables were expressed using absolute values and frequencies (for categorical variables), and means and standard deviations along with minimum and maximum values for continuous variables. The effect of the interventions on the main outcome, i.e. 'worst pain level over the last 24 hours' was assessed using a series of generalized estimation equations (GEE). The measurements at the baseline and at seven, 30, 60, and 180 days after the intervention were evaluated longitudinally, and the fact that all measurements were estimated for the same patient was accounted for.

Since the outcome presented non-normal distribution, its raw numerical values were re-categorized as indicator variables with cutoff points greater than or equal to two, three, five or seven points (in doing this, differences between the procedures that were small and under or above five, could be tracked). These dichotomous values were analyzed through GEE with binomial distribution. The models evaluated the association between the outcome and the two interventions, and differences at the baseline were accounted for.

We reported the results as the predicted means for numerical outcomes and as odds ratios for categorical outcomes, along with 95% confidence intervals (Rutten-van Molken *et al*., 1994). The Kolmogorov-Smirnov test was used to test the normal distribution of variables. For non-normally distributed variables, comparisons between groups were made using the Mann-Whitney test and Pearson's chi-square test. The Student t test was used for normally distributed variables.

For the interim analysis, the sample size for the difference in slopes between the balloon compression and the conventional radiofrequency groups was calculated, to yield a power of 0.8 and detect a difference in slopes of 1.5, with a residual variance of 1 and a significance level of 0.05 (Diggle *et al*., 2002).

Statistical analyses were performed using IBM SPSS (Statistical Package for Social Sciences) v17.0 and R-Project (r-core team REF).

5 RESULTS

5.1 Social-demographic data

Eighty-seven patients were assessed for eligibility. Thirty-three were included for the interim analysis: 57.6% with the mandibular division affected and twenty-one with right-sided TN. Of the total, 25 were females with a mean age of 62.18 ± 9.4 years old. Table 1 shows the subjects' characteristics and demographics included in preplanned interim analyses, along with comparisons between the groups.

5.2 Baseline charactheristics

The two groups showed similar medication usage at the baseline, as depicted by the MQS score (10.63 ± 6.21 for BC; 12.47 ± 4.44 for RF; $p = 0.292$). The pain characteristics at the baseline were evaluated using several questionnaires (Table 2). There was no difference in the total SF-MPQ score between the BC and RF groups (12.89 ± 1.71 and 12.2 ± 2.51, respectively; $p = 0.617$). There was also no significant difference between the groups regarding positive DN4 scores (total score ≥ 4: 88.9% in BC group versus 80% in RF group; $p = 0.639$). In the BPI questionnaire, there was no difference between the groups regarding the worst pain level over the last 24 h (Figure 3), i.e. main outcome of the study (6.94 ± 3.55 and 8.2 ± 3.19, for BC and RF groups respectively; p =

0.292); or in relation to the pain intensity index (4.46 ± 2.68 in BC and 5.08 ± 2.66 in RF; p = 0.526). There was also no difference between the groups regarding pain interference (6.72 ± 2.95 in BC and 6.26 ± 2.61 in RF; p = 0.527).

Regarding the specific pain characteristics analyzed using the NPSI, the two groups presented similar subgroup features (spontaneous superficial pain: 6.28 ± 3.8 and 4.8 ± 4.75, p = 0.362; deep spontaneous pain: 3.39 ± 4.09 and 3.93 ± 4.6, p = 0.876; paroxysmal pain: 5.39 ± 3.87 and 6.53 ± 4.34, p = 0.262; evoked pain: 5.63 ± 3.76 and 5.38 ± 3.37, p = 0.828; and paresthesia/dysesthesia: 4.28 ± 3.41 and 4.6 ± 3.62, p = 0.729; BC and RF group, respectively). Regarding the duration of spontaneous pain, it was less than 1 h for 33.3% of the patients in the BC group and 53.3% in RF group. For 27.8% of the individuals in the BC group and 26.7% in the RF group, there were no pain attacks within the last 24 h, nor was the total score significant (49.28 ± 29.16 in BC group and 51.07 ± 32.89 in RF group; p = 0.857). Furthermore, none of the other features reported (PCS, WHOQoL and HAD) showed any differences.

Table 2 - Baseline characteristics of both groups and comparison between variables

	Group 1 (BC) n=18	Group 2 (RF) n=15	*P*
SF-MPQ			
Domain			
Sensitive (0-8)	6.28 ± 1.56 (2-8)	5.87 ± 1.77 (2-8)	0.540
Affective (0-5)	4.61 ± 0.61 (3-5)	4.33 ± 0.9 (2-5)	0.381
Evaluative (0-2)	2 ± 0 (2)	2 ± 0 (2)	1.000
Total (0-15)	12.89 ± 1.71 (9-15)	12.2 ± 2.51 (6-15)	0.617
DN4			
Total (0-10)	5.33 ± 2 (0-8)	5.87 ± 2.47 (1-9)	0.382
Neuropathic pain (≥ 4)	16 (88.9%)	12 (80%)	0.639
BPI			
Intensity of pain variables			
Worst pain last 24h (0-10) – Study main outcome	6.94 ± 3.55 (0-10)	8.2 ± 3.19 (0-10)	0.292
Least pain last 24h (0-10)	1.72 ± 2.78 (0-8)	1.8 ± 2.86 (0-9)	0.863
Average pain last 24h (0-10)	5.05 ± 3.08 (0-9)	6.27 ± 2.76 (0-10)	0.266
Pain right now (0-10)	4.11 ± 3.46 (0-10)	4.07 ± 3.95 (0-10)	0.882
Relief last 24h w/ medication (%)	48.89 ± 28.67 (0-100)	68.67 ± 28.9 (10-100)	0.238
Pain intensity index (0-10)	4.46 ± 2.68 (0-8.75)	5.08 ± 2.66 (0-9.75)	0.526
Interference			
General activity (0-10)	6.55 ± 3.99 (0-10)	5.4 ± 4.5 (0-10)	0.536
Mood (0-10)	6.67 ± 3.66 (0-10)	7.73 ± 3.71 (0-10)	0.255
Walking (0-10)	5.61 ± 4.39 (0-10)	5.53 ± 4.45 (0-10)	0.985
Normal work (0-10)	6.67 ± 4.39 (0-10)	5.8 ± 3.73 (0-10)	0.437
Relationship (0-10)	6.89 ± 3.83 (0-10)	6.87 ± 3.85 (0-10)	0.880
Sleep (0-10)	6.28 ± 4.31 (0-10)	5.27 ± 4.16 (0-10)	0.432
Enjoyment of life (0-10)	8.39 ± 2.61 (0-10)	7.2 ± 3.97 (0-10)	0.506
Pain interference in daily life (0-10)	6.72 ± 2.95 (0-10)	6.26 ± 2.61 (2.57-10)	0.527
MQS			
Score	10.63 ± 6.21 (0-22.8)	12.47 ± 4.44 (5.6-19.4)	0.292
NPSI			
Superficial spontaneous pain (0-10)	6.28 ± 3.8 (0-10)	4.8 ± 4.75 (0-10)	0.362
Deep spontaneous pain (0-10)	3.39 ± 4.09 (0-10)	3.93 ± 4.6 (0-10)	0.876
Paroxysmal pain (0-10)	5.39 ± 3.87 (0-10)	6.53 ± 4.34 (0-10	0.262
Evoked pain (0-10)	5.63 ±3.76 (0-10)	5.38 ± 3.37 (0-10)	0.828
Paresthesia/dysesthesia (0-10)	4.28 ± 3.41 (0-10)	4.6 ± 3.62 (0-10	0.729
Duration of spontaneous pain last 24h (1-5)	3 ± 1.81 (1-5)	3.33 ± 1.99 (1-5)	0.520
Number of pain attacks last 24h (1-5)	3.17 ± 1.65 (1-5)	2.8 ± 1.7 (1-5)	0.602
Continuous pain less than 1h last 24h	6 (33.3%)	8 (53.3%)	0.247
No pain attacks last 24h	5 (27.8%)	4 (26.7%)	1.000
Total (0-100)	49,28 ± 29.16 (0-99)	51.07 ± 32.89 (1-98)	0.857

to be continued

conclusion

	Group 1 (BC) n=18	Group 2 (RF) n=15	*P*
WHOQOL			
Domain			
Physical (7-35)	19.78 ± 5.45 (9-28)	19.07 ± 5.38 (8-31)	0.404
Psychological (6-30)	19.28 ± 4.7 (10-26)	17.6 ± 5.38 (7-29)	0.301
Social (3-15)	10.44 ± 1.76 (6-12)	10.4 ± 2.75 (5-15)	0.970
Environmental (8-40)	25.39 ± 4.53 (16-32)	26.6 ± 5.29 (12-36)	0.536
PCS			
Score (0-52)	35.89 ± 11.13 (13-52)	32.47 ± 11.35 (14-51)	0.395
HAD			
HAD-A (0-21)	10.11 ± 5.72 (3-21)	10.33 ± 4.7 (1-17)	0.744
HAD-D (0-21)	6.72 ± 6.04 (0-18)	6.8 ± 5.03 (0-17)	0.703
Total score (0-42)	16.83 ± 9.6 (3-36)	17.13 ± 8.79 (5-31)	0.899

The values are presented as mean ± SD (range) or n (%).
BC: balloon compression; RF: radiofrequency. SF-MPQ: Short-Form McGill Pain Questionnaire; DN4: Douleur Neuropatique 4 Questionnaire (neuropathic pain present ≥ 4); BPI: Brief Pain Inventory; MQS: Medication Quantification Scale version III; NPSI: Neuropathic Pain Symptom Inventory; WHOQOL: World Health Organization Quality of Life Questionnaire brief form; PCS: Pain Catastrophizing Scale; HAD: Hospital Anxiety and Depression Scale (HAD-A: anxiety symptoms; HAD-D: depression symptoms). Significance is set as $p < 0.05$.

5.3 Primary Objective

Numeric ranking scale over the last 24 hours between each group at six months revealed no significant difference (CI95% 0.6 – 3.84 and -0.64 – 2.24, for BC and RF, respectively). Table 3(a) displays information on the study's main outcome, which was categorized as higher or lower than five. We present data on this outcome and its association with the intervention groups, taking into account all the follow-up measurements up to the 180-day assessment, by using Generalized Estimated Equations (GEE) models. The results were corrected for age and race, and indicated that there were no statistically significant differences between the two groups. A similar pattern was observed when re-categorizing the worst pain level over the last 24 hours into higher or lower than two, three or seven, as depicted in

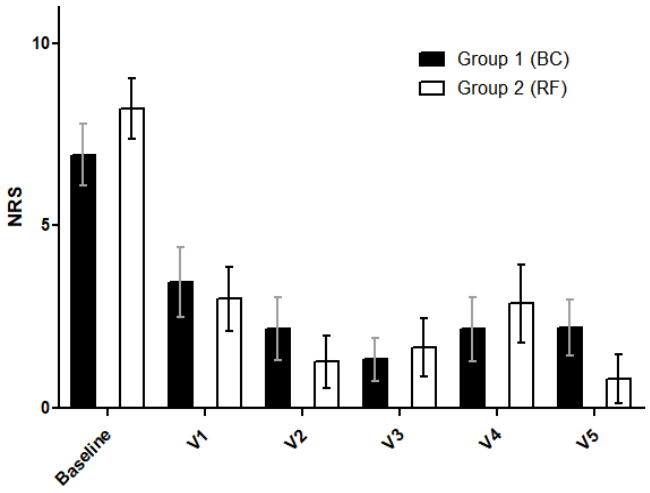
Table 3(b). Despite some change overtime could be observed in each group, this difference did not reach statistical significance. Graphic 1 illustrates the comparison of the worst pain level over the last 24 hours, over time, between the two intervention arms. Patients subjected to BC therapy or RF reported similar pain intensities over the study period. At 180 days after the intervention, the patients in the balloon compression group reported slightly higher levels of pain, compared with those in the radiofrequency group, although no significant difference was observed.

Table 3 - Predicted odds ratio and confidence intervals for the worst pain level over the last 24 hours

	Group 1 (BC) n=18	Group 2 (RF) n=15	*P*
a)			
Worst pain in the last 24 hours above 5[a]	1.12 (0.51, 2.49)	1 [Referent]	0.78
b)			
Worst pain in the last 24 hours above 2[b]	1.07 (0.48, 2.39)	1 [Referent]	0.86
Worst pain in the last 24 hours above 3[b]	1.06 (0.48, 2.33)	1 [Referent]	0.88
Worst pain in the last 24 hours above 7[b]	1.22 (0.51, 2.93)	1 [Referent]	0.66

Comparison of the "worst pain level over the last 24 hours" transformed to a dichotomous variable (a: above 5; b: above 2, above 3 and above 7).
The values are presented as odds ratio (95% confidence intervals). BC: balloon compression; RF: radiofrequency. Significance is set as $p < 0.05$.

Graphic 1 - Numerical rating scale (NRS) of main outcome (worst pain level over the last 24 hours)



Results expressed as mean and standard error between groups, in each appointment.

5.4 Secondary Objectives

Concerning the pain phenotype, patients in the RF group reported more paresthetic symptoms than those in the BC group (2.08 ± 1.99 versus 3.97 ± 1.96, respectively; p = 0.017). Moreover, there was a higher number of RF patients who were completely pain-free (100% of these individuals), compared with the BC group (4.55 ± 0.78 versus 5 ± 0; p = 0.015) at the first assessment (visit 1 at 7 days postoperatively). The paresthesia symptom scores were significantly higher in the RF group at 30 days (V2; p = 0.01), but these symptoms were resolved during the follow-up (V5; p = 0.294). At 90 days (V4), the individuals in the BC group presented lower NPSI total scores (9.61 ± 15.2 versus 15.07 ± 20.75 in the RF group; p = 0.038), but at the last evaluation, this difference was no longer present (p = 0.598).

Patients presenting with continuous pain at the baseline comprised 66.7% of the BC group and 53.3% of the RF group. At the last evaluation, these proportions were 5.6% and 20%, respectively. No difference was noted at either time: p = 0.435 and p = 0.308. Regarding purely paroxysmal pain, at the baseline this affected 16.7% in the BC group and 40% in the RF group. After the follow-up, these proportions were 72.2% and 66.7%, respectively. Again, no difference was observed (p = 0.239 and p = 0.730).

5.5 Pain and Associated Variables

In terms of presence of neuropathic pain using the DN4 questionnaire, 33.3% and 60% of the individuals, respectively in the BC and RF groups, scored 4 or more at 6 months (V5). Although these proportions were lower than at baseline (88.9% and 80% for BC and RF), no difference was observed between groups ($p = 0.126$).

Regarding the pain descriptors using the SF-MPQ, although some reduction over time was observed, no significant difference was found (12.89 ± 1.71 and 12.20 ± 2.51; 3.39 ± 4.23 and 2.20 ± 3.86; for BC and RF at the baseline and last appointment, respectively).

Evaluation of emotional distress and disability using PCS showed total scores at the last appointment of 13.50 ± 15.72 and 11.67 ± 14.40, for BC and RF respectively. These scores were not statistically different.

The medication usage, quantified using the MQS vIII, ranged from 10.63 ± 6.21 to 5.84 ± 6.60 for the BC group, and from 12.47 ± 4.44 to 5.82 ± 6.75 for the RF group, also with no difference between them.

Quality of life and its domains, assessed using WHOQoL did not show any significant differences, despite showing increased scores over time.

The mood symptoms of anxiety and depression, evaluated through the HADS questionnaire, showed improvement over the study period (total scores of 16.83 ± 9.6 and 17.13 ± 8.79 at the baseline and 8.17 ± 6.77 and 10.27 ± 8.67 at the last appointment, respectively for BC and RF). However, no significant difference between the groups could be seen.

5.6 Blinding Assessment

Pain during the procedure was evaluated because this is a possible source of blinding bias. The mean values (ranging from 0 to 10) and standard deviations for BC and RF were, respectively, 1.33 ± 2.06 and 4 ± 2.27 ($p = 0.02$). This revealed that the subjects in the RF group experienced more pain during the intervention than did those in the BC group.

After completion of the protocol, 44.4% of the individuals in group BC reported that they were able to tell which group they had been allocated to, and 66.7% of these individuals guessed it right. In group RF, the proportion was 37.5% for both ($p = 0.35$). When asked if they would be willing to undergo the procedure again if it was offered, the proportions were 55.5% and 50%, for groups BC and RF, respectively. None of these proportions were statistically significant.

5.7 Procedures and Safety

All the patients were discharged from hospital within 24 hours after the intervention. There was no difference in postoperative pain between the groups: patients in both groups experienced new pain after the procedure. However, this pain was self-limited and was relieved with common painkillers (the intensity and duration were similar).

5.8 Effect and Sample Size

The preplanned interim analysis was performed at the time when each arm reached half of the scheduled number of subjects, in order to evaluate the safety and effect size of the protocol. The power of the present study was 4.7%. Therefore, to show a real difference between the groups (with a power of 80% and a significance level of 0.05), if there truly was any difference whatsoever, 1500 individuals per arm would be needed, thereby rendering the value of the interventions doubtful. A calculation to update the sample size, so that it would be capable of showing any difference that might exist between the groups, using generalized estimated equations in future studies, indicated that 1457 individuals per arm would be needed. Therefore, the study was halted because it would have been futile to continue.

6 DISCUSSION

Here, we report the results from the first attempt to prospectively compare the two most commonly used percutaneous interventions for TN using a randomized double-blind trial. After a preplanned interim analysis, the study was halted because it would have been futile to continue. No significant effects were found in relation to the primary outcome, i.e. pain intensity after six months using the BPI questionnaire.

The sample size used in the present study was based on previous reports of the effect size in surgical TN trials (Zakrzewska and Akram, 2011). However, a post-hoc power analysis calculated using the effect sizes obtained in the present study suggested that, if a real difference in pain relief should exist between the two interventions, a clinical trial would require a large number of participants in each arm. This sample size is higher than the sum of all the patients enrolled in all TN trials performed to date, including pharmacological trials (Broggi *et al*., 1990; Taha and Tew, 1996; Skirving and Dan, 2001; Teixeira *et al*., 2006; Koopman *et al*., 2011). For example, the largest series published enrolled 1,600 patients over 25 years, which is approximately the number needed for just one arm (Kanpolat *et al*., 2001).

Although TN is a neuropathic pain syndrome, its paroxysmal and episodic nature imposes some obstacles in quantifying pain, as depicted by the low positivity of the DN4 at baseline. Therefore, the use of alternative instruments (eg., NPSI) may be helpful to characterize the other pain features such as its temporal pattern

(paroxysmal or continuous) and number of paroxysms per day. This is in accordance with an issue repeatedly stated in TN research: which is the best method to better evaluate a neuropathic pain that is episodic in nature. To our knowledge, this is the first study to use specific questionnaires to overcome this hindrance. Interestingly, some differences in secondary outcomes were observed between the groups: individuals receiving RF experienced more paresthetic symptoms after the procedure despite presenting no pain attacks at V1. This suggests that this symptom after percutaneous thermocoagulation may be expected as a side-effect but it will most likely subside after 4 weeks. On the other hand, the patients who underwent BC presented lower total NPSI scores at V4. At the last evaluation, the previously observed differences disappeared. We also used specific NPSI scores to evaluate occurrences of non-paroxysmal facial pain: no difference was observed between the baseline and the last appointment, despite a reduction over time.

The decision regarding which treatment to offer patients with trigeminal neuralgia has been an issue of great debate for a long time. Although adequate pain control has been achieved through use of carbamazepine (Campbell *et al*., 1966), some patients may suffer from unsustainable side-effects or may not reach satisfactory pain-attack control (Fields, 1996; Casey, 2005; Cruccu *et al*., 2008). Therefore, thorough evaluation of individuals and images are paramount in deciding which intervention should be proposed.

Percutaneous procedures have been used for over four decades without clear evidence regarding which of these is most effective for controlling TN pain. A number of large series of patients who underwent ablative interventions is available in the literature, but the outcomes have often been measured using different

instruments that exhibit poor clinical relevance. Moreover, the pain characteristics are often not considered in a comprehensive manner: for instance, number of pain attacks, intensity of pain attacks, reduction of medication burden, non-paroxysmal pain, etc (Attachment A - summarizes the largest and most important case-series and outcome measurements).

Taking into account procedure-related risks and technical difficulties, it appears that ablative procedures are preferred over MVD for a number of reasons (Cruccu *et al*., 2008; Gronseth *et al*., 2008): simplicity, outpatient management and a low profile of severe side effects. In addition, the outcomes of the latter appear to be better only in high-volume centers (Kalkanis *et al*., 2003). Historically, individuals often underwent percutaneous ablative procedures for the above mentioned reasons and because of the need for a learning curve for MVD (Broggi *et al*., 1990; Teixeira *et al*., 2006; Spatz *et al*., 2007; Zakrzewska and Linskey, 2009; Koopman *et al*., 2011; Jones *et al.*, 2019). Since the time when ablative procedures became part of the armamentarium of treatment options for NT (Sweet and Wepsic, 1974; Mullan and Lichtor, 1983), the procedures most used have been BC and RF. Despite their safeness, evaluation of the pain profile has not been formally addressed; the most commonly used outcome is recurrence rate; however, there is no well-established instrument for its measurement (Kanpolat *et al*., 2001; Bendtsen *et al*., 2019; Jones *et al.*, 2019).

Despite the lack of differences between the two interventions regarding the primary outcome, some technical difficulties ought to be pointed out: while BC demands use of a Fogarty catheter and general anesthesia, RF requires a disposable electrode, a radiofrequency generator and specialized anesthesia for a sleep-wake-

sleep procedure (because of the need to evaluate skin sensation after lesioning). Therefore, due to the need for a larger number of items and special conditions, RF is a method that may not be available in every pain center. On the other hand, BC is a very simple method and requires only a Fogarty catheter.

Recently, Gamma-knife surgery has been offered as an alternative treatment for TN. Despite the lack of invasiveness, the equipment is not widely available and the procedure lacks good results in pain-control when compared to other procedures (Lopez neurosurgery 2004; Regis j neurosurgery 2016; Wang j neurosurgery 2018). Moreover, after treatment, it may take up some time to mitigate pain (Nurmikko and Eldridge).

After thoroughly obtaining our patients' histories and physical examinations, they underwent head CT scans to assess secondary causes of TN, since our setting is one of limited resources and MVD was not the gold-standard method for treating TN at that time. As stated in the literature (Antonini *et al*., 2014), neurovascular compression (NVC) can be detected in 76% of symptomatic cases. The current classification of TN clearly states the need for MRI (in order to evaluated neurovascular conflict) (Cruccu *et al*., 2016; Headache Classification Committee, 2018), this only impacts the decision to which procedure to recommend (for instance, two patients may have the same clinical features and different MRI results: presence and absence of the vascular loop with morphological and signal changes). However, both of them could benefit from percutaneous procedures.

In our series, not all individuals were submitted to MRI scans, the high prevalence of NVC meant that we most likely included cases of classic and idiopathic TN, while excluding secondary TN, since all individuals had a normal

head CT scan. Therefore, inclusion of possible cases of CTN should not be considered to be a limitation. However, this raises the question of whether there is a role for CT scans in classifying TN: an issue that may be better evaluated in future studies, especially in resource-limited settings. And, therefore, it seems more logical to place Classical TN under primary TN in the classification.

6.1 Limitations

The sample was relatively small, given that we estimated a sample size based on the size of previous trials on TN. In a Cochrane metanalysis in 2011 (Zakrzewska and Akram, 2011), it was stated that the greatest issue with all studies was the lack of standardized clinical outcome. Therefore, direct calculation of the study power like in the present study was challenging. Based on the analysis of the papers described in this metanalysis, we estimated that 25 patients per group would be adequate. Nonetheless, we decided to add another 5 patients in each group. Some difficulties during recruitment were experienced, which led us to halt the recruitment once we had at least 15 patients in both groups and to perform the preplanned interim analysis.

The results from the present study could be used to calculate a more precise power for future studies. The sample size obtained was more appropriate and this revealed that a proper randomized clinical trial (RCT) may be unfeasible due to the large number of individuals harboring this rare condition that would be needed.

With regard to possible blinding bias, despite our attempts to blind subjects for the randomized intervention, the assessment using a pain questionnaire during the procedure revealed that the individuals who underwent RF are likely to be able to

identify their allocation group, which may have been detrimental to the study. Even though the blinding assessment revealed that the pain level during the procedure was higher in the RF group, the blinding was probably preserved since the remaining assessments did not show any differences between the groups.

Regarding the short follow-up period of 6 months, this was used in order to avoid losing patient follow-up for any reason and also to evaluate the effects of interventions over short and medium terms. Nonetheless, a 6-month period is a long time to sustain a clinical trial without any losses. On the other hand, given our lack of concrete information on the time that might be required for relapse to occur, setting the follow-up as a six-month period was arbitrary.

Despite the exploratory nature of the data reported here as secondary objectives of this study, their use may provide guidance on how to better evaluate this complex painful disorder, for future researches.

7 CONCLUSION

a) Regarding the primary objective, radiofrequency was not superior to balloon compression in controlling trigeminal pain in six months from surgery.

b) Regarding secondary objectives:

- continuous pain was equally present in both groups after follow-up.

- mood and quality of life improved significantly in both groups however no difference between them was present at follow-up.

- recurrence and frequency of pain after RF and BC was low and did not differ between groups at follow-up, despite patients receiving RF presenting more paresthetic symptoms the following month after the intervention,

8 ATTACHMENTS

Attachment A - Published data with outcomes in TN patients treated with percutaneous methods

Author	Year	Study design	N	Technique	Outcome	Instrument	FU (mean)	Results	Immediate relief
Nanjappa	2013	descriptive	15	RF	efficiency	NR	12m	100%	80%
de Siqueira	2006	prospective	105	BC	relapse at FU	Questionnaire	210d	16.20%	99%
Campos and Linhares	2011	prospective	39	BC	relapse at FU	NRS, QoL	50m	20%	93.50%
Singh	2014	prospective	18	RF	pain relief	NR	18m	33%	77.80%
Zakrzewska	1999	prospective longitudinal	48	RF	time to relapse	MPQ, HAD	30m	40m	NR
Burchiel	1981	retrospective	92	RF	relapse at FU	NR	5y	65%	NR
Nugent	1982	retrospective	800	RF	NR	NR	4.7y	NR	NR
Latchaw	1983	retrospective	96	RF	pain relief	NR	5y	52%	NR
Spincemaille	1985	retrospective	53	RF	success rate	NR	2y	96%	85%
Mittal	1986	retrospective	280	RF	success rate	NR	3.8y	94%	NR
Meglio	1989	retrospective	33	RF	time to relapse	NR	2y	18.5m	81.80%
Meglio	1989	retrospective	74	BC	time to relapse	NR	2y	6.5m	93.20%
Broggi	1990	retrospective	1000	RF	relapse at FU	NR	9.3y	18%	95%
Lichtor and Mullan	1990	retrospective	100	BC	relapse at FU	NR	5y	20%	97%
Choudhury	1991	retrospective	40	RF	relapse at FU	NR	2y	15%	NR
Sanders	1992	retrospective	240	RF	relapse at FU	NR	50m	8.30%	NR
Taha and Tew	1996	retrospective	500	RF	relapse at FU	Pain recurrence	9y	20%	98%
Oturai	1996	retrospective	185	RF	relapse at FU	NR	8y	49%	83%
Correa	1998	retrospective	187	BC	relapse at FU	NR	3y	8%	100%
Yoon	1999	retrospective	81	RF	relapse at FU	NR	8.5y	74%	87%
Kanpolat	2001	retrospective	1600	RF	relapse at FU	NR	68m	42.30%	97.60%
Skirving and Dan	2001	retrospective	531	BC	relapse at FU	NR	10.7y	31.90%	98%

to be continued

conclusion

Author	Year	Study design	N	Technique	Outcome	Instrument	FU (mean)	Results	Immediate relief
Omeis	2008	retrospective	29	BC	relapse at FU	NR	49m	54.50%	83.00%
Park	2008	retrospective	50	BC	relapse at FU	NR	42m	70%	92%
Fraioli	2009	retrospective	158	RF	relapse at FU	NR	8.8y	7.50%	100%
Keravel	2009	retrospective	121	BC	relapse at FU	NR	3.4y	35.50%	87.70%
Kouzounias	2010	retrospective	66	BC	pain relief	pain-free	60m	36% (20m)	85%
Huang	2010	retrospective	30	RF	pain relief	NRS, QoL, meds	3y	73.30%	86.70%
Son	2011	retrospective	38	RF	time to relapse	BNI	38.2m	26.1m	100%
Baabor	2011	retrospective	206	BC	relapse at FU	NR	3y	15%	93%
Chen	2011	retrospective	130	BC	recurrence at FU	NR	8.9y	37.70%	93.80%
Trojnik	2012	retrospective	33	BC	time to relapse	NR	74m	2-74m (15m)	93%
Abdennebi	2014	retrospective	901	BC	relapse at FU	qualitative	16.5y	38%	92.70%
Tang	2015	retrospective	1137	RF	pain relief	NR	46m	54-91%	98%
Kosugi	2015	retrospective	148	RF	time to relapse	NR	8y	9-36m	86.6-100%
Asplund	2016	retrospective	82	BC	pain-free time	NR	NR	20m	85%
Yadav	2016	retrospective	400	BC	pain relief	NR	4y	NR	88.25%
Ying	2017	retrospective	138	BC	relapse at FU	BNI	5y	27.10%	98.60%
Zheng	2019	retrospective	1481	RF	time to relapse	BNI	12y	136m	NR
Li	2019	retrospective	1624	RF	pain relief > 12m	BNI	12m	78.10%	NR
Jain	2019	retrospective comparative	20	BC x RF	pain relief	NRS	24m	no diference	100%

Table depicting published data regarding outcomes measured in TN patients receiving percutaneous treatment.

N, sample size; FU, follow-up; NR, not-reported; RF, radiofrequency thermocoagulation; BC, balloon compression; d, days; m, months; y, years; QoL, quality of life; NRS, numeric ranking scale; BNI, Barrow Neurological Institute scale for TN.

Attachment B - ClinicalTrials.gov receipt

ClinicalTrials.gov PRS
Protocol Registration and Results System

Contact ClinicalTrials.gov PRS
Org: USaoPaulo User: HSNeto Logout

Home > Record Summary > Release Confirmation

Release Confirmation

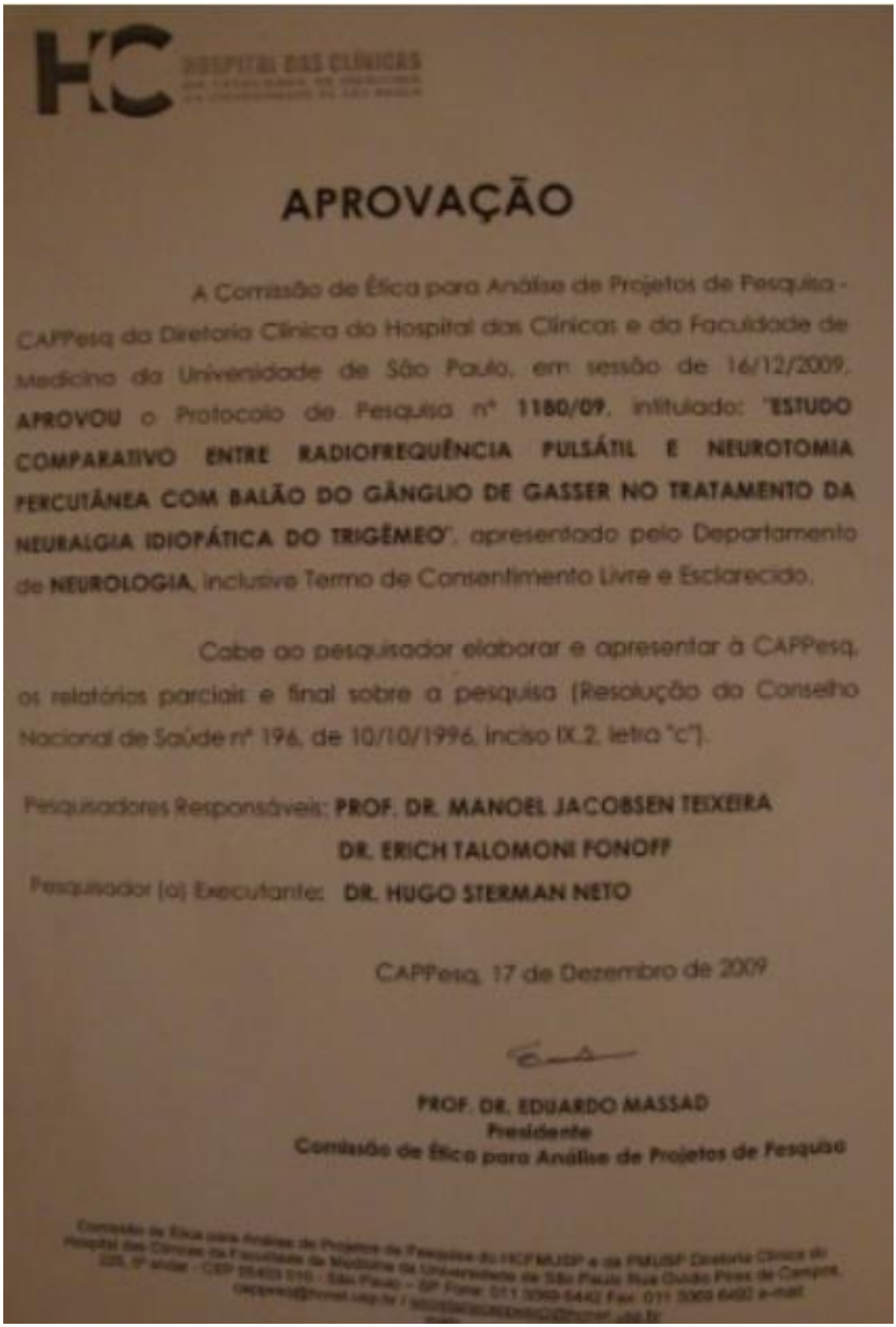
Home Record Summary Receipt (PDF) Preview

ClinicalTrials.gov ID:	NCT02427074
Unique Protocol ID:	1180/09
Brief Title:	Comparison Between Radiofrequency and Balloon Compression in the Treatment of Idiopathic Trigeminal Neuralgia
Overall Status:	Terminated
Primary Completion Date:	March 31, 2019 [Actual]
Verification Date:	February 2020

The record has been Released to ClinicalTrials.gov PRS for review.

Protocol registration Records are made available to the public through the ClinicalTrials.gov web site within 2 to 5 days of release, following system validation and PRS Review. **Records that contain Results may take up to 30 days**, if the study appears to be an applicable clinical trial under 42 CFR Part 11 or an NIH-funded study. Other types of study records with results will take longer for review.

Attachment C - Main project approval letter



HC HOSPITAL DAS CLÍNICAS

APROVAÇÃO

A Comissão de Ética para Análise de Projetos de Pesquisa - CAPPesq da Diretoria Clínica do Hospital das Clínicas e da Faculdade de Medicina da Universidade de São Paulo, em sessão de 16/12/2009, **APROVOU** o Protocolo de Pesquisa nº **1180/09**, intitulado: "**ESTUDO COMPARATIVO ENTRE RADIOFREQUÊNCIA PULSÁTIL E NEUROTOMIA PERCUTÂNEA COM BALÃO DO GÂNGLIO DE GASSER NO TRATAMENTO DA NEURALGIA IDIOPÁTICA DO TRIGÊMEO**", apresentado pelo Departamento de **NEUROLOGIA**, inclusive Termo de Consentimento Livre e Esclarecido.

Cabe ao pesquisador elaborar e apresentar à CAPPesq, os relatórios parciais e final sobre a pesquisa (Resolução do Conselho Nacional de Saúde nº 196, de 10/10/1996, inciso IX.2, letra "c").

Pesquisadores Responsáveis: **PROF. DR. MANOEL JACOBSEN TEIXEIRA**
DR. ERICH TALOMONI FONOFF

Pesquisador (a) Executante: **DR. HUGO STERMAN NETO**

CAPPesq, 17 de Dezembro de 2009

PROF. DR. EDUARDO MASSAD
Presidente
Comissão de Ética para Análise de Projetos de Pesquisa

Comissão de Ética para Análise de Projetos de Pesquisa do HC/FMUSP e da FMUSP/ Diretoria Clínica do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo Rua Ovídio Pires de Campos, 225, 5º andar - CEP 05403-010 - São Paulo - SP Fone: 011 3069-6442 Fax: 011 3069 6602 e-mail:

Attachment D - Additional groups inclusion approval letter

Hospital das Clínicas da FMUSP
Comissão de Ética para Análise de Projetos de Pesquisa
CAPPesq

Nº Protocolo: 1180/09

Título: ESTUDO COMPARATIVO ENTRE RADIOFREQÜÊNCIA PULSÁTIL E NEUROTOMIA PERCUTÂNEA COM BALÃO DO GÂNGLIO DE GASSER NO TRATAMENTO DA NEURALGIA IDIOPÁTICA DO TRIGÊMEO.

Pesquisador Responsável: Prof.Dr. Manoel Jacobsen Teixeira / Dr. Erich Talamoni Fonoff

Pesquisador Executante: Hugo Sterman Neto

Departamento: NEUROLOGIA

O Coordenador da Comissão de Ética para Análise de Projetos de Pesquisa – CAPPesq da Diretoria Clínica do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, **APROVOU / TOMOU CIÊNCIA *ad-referendum*** em 28/06/2012, do(s) documento(s) abaixo mencionado(s):

•Carta datada de 15/05/12:

- Mudança de título para: "Estudo comparativo entre radiofrequência tradicional, neurotomia percutânea com balão, radiofrequência pulsátil e bloqueio anestésico do gânglio de Gasser no tratamento de neuralgia idiopática do trigêmeo".

- Novo orientador: Dr. Daniel Ciampi A. de Andrade.

- Inclusão de dois grupos de comparação.

- Extensão do prazo por mais 36 meses.

- Novo Termo de Consentimento Livre e Esclarecido.

A CAPPesq em obediência à Resolução CNS 196/96, solicita ao pesquisador (a) a elaboração de relatório parcial e final.

No caso de relatório parcial é necessário informar o tempo previsto para a conclusão do protocolo e breve resumo dos resultados obtidos.

CAPPesq, 28 de Junho de 2012

PROF. DR. LUIZ EUGÊNIO GARCEZ LEME
Coordenador
Comissão Ética para Análise de Projetos de Pesquisa

Rua Dr. Ovídio Pires de Campos, 225 - Prédio da Administração - 5º andar - CEP 05403-010 - São Paulo - SP
Fone: 55 11 2661-6442 ramais 16, 17, 18 e 20 - e-mail: cappesq@hcnet.usp.br

Attachment E - Subproject analysis approval letter

Hospital das Clínicas da FMUSP
Comissão de Ética para Análise de Projetos de Pesquisa **CAPPesq**

Diretoria Clínica

Comissão de Ética para Análise de Projetos de Pesquisa - CAPPesq

PARECER

PROTOCOLO DE PESQUISA Nº: 1180/09	**Data da sessão: 21/02/2018**

TÍTULO DA PESQUISA: Estudo comparativo entre radiofreqüência tradicional, neurotomia percutânea com balão, radiofreqüência pulsátil e bloqueio anestésico do gânglio de Gasser no tratamento da neuralgia idiopática do trigêmeo em pacientes virgens de tratamento cirúrgico

PESQUISADOR(A) RESPONSÁVEL: Manoel Jacobsen Teixeira

DEPARTAMENTO: NEUROLOGIA

CONSIDERAÇÕES DO RELATOR:

Conforme solicitado no parecer anterior, os pesquisadores enviaram os subprojetos para avaliação. De fato, não houve alteração no risco, pois serão aplicados questionários aos participantes da pesquisa para avaliação do controle da dor (um braço do projeto inicial) e sensibilidade especial e geral da face (outro braço do projeto inicial). Em princípio, não fere a ética. Entretanto, seria adequado que a introdução dos projetos fosse direcionada para o objetivo de cada um, posto que os dois projetos somente diferem no título e objetivos primários, além de uma referência que foi acrescentada no segundo braço. O restante, inclusive os métodos, é idêntico. Provavelmente os questionários contenham informações que permitam as duas análises, mas a introdução deveria ser direcionada para o objetivo primário, o que recomendaria corrigir.

CONCLUSÃO: Aprovado com recomendação

ENVIAR À CONEP:	**SIM ( )** **INFORME A ÁREA TEMÁTICA:**	**NÃO (x)**

Prof. Dr. Alfredo José Mansur
Coordenador
Comissão de Ética para Análise de Projetos de Pesquisa - CAPPesq

Rua Dr. Ovídio Pires de Campos, 225 - Prédio da Administração - 5º andar - CEP 05403-010 - São Paulo - SP.
Fone: 55 11 2661-7585 - e-mail: cappesq.adm@hc.fm.usp.br

Attachment F - Consent term

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO-HCFMUSP

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

DADOS DE IDENTIFICAÇÃO DO SUJEITO DA PESQUISA OU RESPONSÁVEL LEGAL

1. NOME: .:.....

DOCUMENTO DE IDENTIDADE Nº : ..... SEXO : .M ☐ F ☐
DATA NASCIMENTO: ...../...../.....
ENDEREÇO ..... Nº ..... APTO: .....
BAIRRO: ..... CIDADE .....
CEP:..... TELEFONE: DDD (.....) .....

2.RESPONSÁVEL LEGAL .....
NATUREZA (grau de parentesco, tutor, curador etc.) .....

DOCUMENTO DE IDENTIDADE :.....SEXO: M ☐ F ☐
DATA NASCIMENTO.: ...../...../.....
ENDEREÇO: ..... Nº ..... APTO: .....
BAIRRO: ..... CIDADE: .....
CEP: ..... TELEFONE: DDD (.....).....

DADOS SOBRE A PESQUISA

1. TÍTULO DO PROTOCOLO DE PESQUISA: **ESTUDO COMPARATIVO ENTRE RADIOFREQÜÊNCIA TRADICIONAL, NEUROTOMIA PERCUTANEA COM BALAO, RADIOFREQUENCIA PULSATIL E BLOQUEIO ANESTÉSICO DO GÂNGLIO DE GASSER NO TRATAMENTO DA NEURALGIA IDIOPÁTICA DO TRIGÊMEO**

PESQUISADOR RESPONSÁVEL: Daniel Ciampi de Andrade

CARGO/FUNÇÃO: Coordenador do Grupo de Dor da Neurologia

INSCRIÇÃO CONSELHO REGIONAL Nº 108232

PESQUISADOR EXECUTANTE: Hugo Sterman Neto/Cristiane Yoko Fukuda

INSCRIÇÃO CONSELHO REGIONAL N 129.744/108230

CARGO/FUNÇÃO: Médico Residente/Assistente da Neurocirurgia Funcional

UNIDADE DO HCFMUSP: Divisão de Clínica Neurológica

2. AVALIAÇÃO DO RISCO DA PESQUISA:

RISCO MÍNIMO ☐	RISCO MÉDIO ☐
RISCO BAIXO X	RISCO MAIOR ☐

3.DURAÇÃO DA PESQUISA : 36 (trinta) meses

1 – Desenho do estudo e objetivo(s)

Essas informações estão sendo fornecidas para sua participação voluntária neste estudo, que visa comparar o uso de quatro métodos (radiofreqüência tradicional e pulsátil, compressão por balão e bloqueio anestésico) para tratar a dor causada pela neuralgia do trigêmeo. A comparação será feita em relação a efeito no alívio da dor (utilizando questionários e testes de sensibilidade na face), alterações na mastigação (questionários específicos) e na função de formação de saliva e sensibilidade ao cheiro e gosto (testes específicos)

2 – Descrição dos procedimentos que serão realizados, com seus propósitos e identificação dos que forem experimentais e não rotineiros;

O senhor(a) será submetido(a) à sedação ou anestesia local com ou sem bloqueio do gânglio, seguida de anestesia da pele no local da punção da face. Será colocada uma agulha que chegará até o nervo trigêmio do lado da dor na face. Será realizado, mediante sorteio, um dos seguintes tratamentos: radiofrequência tradicional, radiofreqüência pulsátil, compressão do nervo com a insuflação do balão ou bloqueio anestésico. A aplicação da radiofrequencia é um método onde o objetivo é causar alívio da dor, sem causar lesão extensa do nervo.

Serão feitas 6 (seis) avaliações no total: uma antes da cirurgia e cinco após a cirurgia a fim de avaliar se há melhora da dor e se há complicação do procedimento (diminuição da sensibilidade e alteração da mastigação).

3 – Relação dos procedimentos rotineiros e como são realizados – coleta de sangue por punção periférica da veia do antebraço; exames radiológicos;

Será realizada coleta de sangue para avaliação (hemograma completo, plaquetas, coagulograma e para pesquisa) e também durante procedimento será feita radioscopia para localizar balão/eletródio.

4 – Descrição dos desconfortos e riscos esperados nos procedimentos dos itens 2 e 3;

Apesar de ser um procedimento rápido algumas complicações podem ocorrer: sangramento no local e dentro do crânio, dor no local da punção, anestesia de parte da face, diminuição da força da mastigação e insucesso do procedimento (persistência da dor). No caso do bloqueio anestésico do gânglio exclusivo, se houver retorno da dor, o senhor(a) será recolocado em outro grupo, no caso de radiofreqüência pulsátil.

5 – Benefícios para o participante

Melhora da dor;

Comparar dois métodos consagrados no que tange o alívio da dor e alterações de sensibilidade e mastigação após

6 – Relação de procedimentos alternativos que possam ser vantajosos, pelos quais o paciente pode optar;

Outro tratamento cirúrgico consiste da abertura do crânio e do isolamento do nervo dos vasos que o comprimem.

7 – Garantia de acesso: em qualquer etapa do estudo, você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. Os principais investigadores são os Dr. Daniel Ciampi e o pesquisador executante Dr. Hugo Sterman Neto e Dra. Cristiane Yoko Fukuda. que podem ser encontrado no endereço av. Dr. Enéas de Carvalho Aguiar, 255.Telefone(s) 3069-6329/6275. Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – Rua Ovídio Pires de Campos, 225 – 5º andar – tel: 3069-6442 ramais 16, 17, 18 ou 20, FAX: 3069-6442 ramal 26 – E-mail: cappesq@hcnet.usp.br

8 – É garantida a liberdade da retirada de consentimento a qualquer momento e deixar de participar do estudo, sem qualquer prejuízo à continuidade de seu tratamento na Instituição;

09 – Direito de confidencialidade – As informações obtidas serão analisadas em conjunto com outros pacientes, não sendo divulgado a identificação de nenhum paciente;

10 – Direito de ser mantido atualizado sobre os resultados parciais das pesquisas, quando em estudos abertos, ou de resultados que sejam do conhecimento dos pesquisadores;

11 – Despesas e compensações: não há despesas pessoais para o participante em qualquer fase do estudo, incluindo exames e consultas. Também não há compensação financeira relacionada à sua participação.

12 - Compromisso do pesquisador de utilizar os dados e o material coletado somente para esta pesquisa.
Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo " **ESTUDO COMPARATIVO ENTRE RADIOFREQÜÊNCIA TRADICIONAL, NEUROTOMIA PERCUTANEA COM BALAO, RADIOFREQUENCIA PULSATIL E BLOQUEIO ANESTESICO DO GÂNGLIO DE GASSER NO TRATAMENTO DA NEURALGIA IDIOPÁTICA DO TRIGÊMEO**"

Eu discuti com o Dr. Hugo Sterman Neto sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Assinatura do paciente/representante legal	Data ___/___/___

Assinatura da testemunha	Data ___/___/___

para casos de pacientes menores de 18 anos, analfabetos, semi-analfabetos ou portadores de deficiência auditiva ou visual.
(Somente para o responsável do projeto)
Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

Assinatura do responsável pelo estudo	Data ___/___/___

Attachment G - Publication 1

Research Paper

PAIN

Balloon compression vs radiofrequency for primary trigeminal neuralgia: a randomized, controlled trial

Hugo Sterman Neto[a,b], Cristiane Yoko Fukuda[c], Kleber Paiva Duarte[d], Valquíria Aparecida da Silva[e], Antonia Lilian de Lima Rodrigues[a], Ricardo Galhardoni Geront[f,g], Silvia R.D.T. de Siqueira[h], José Tadeu Tesseroli de Siqueira[h], Manoel Jacobsen Teixeira[ij], Daniel Ciampi de Andrade[k,*]

Abstract

Surgical procedures are necessary in up to 50% of trigeminal neuralgia patients. Although radiofrequency (RF) is more widely used, it is associated with high intraprocedural costs and long technical learning time. Other simpler procedures such as balloon compression (BC) require a lower training period and have significant lower costs. We evaluated the effects of BC and RF in pain control in primary trigeminal neuralgia in a randomized, double-blinded, head-to-head trial. Individuals were randomly allocated in 1 of 2 groups: BC and RF. Throughout pain, psychological and quality of life measurements were performed at baseline and after surgery. The main outcome was the worst pain in the last 24 hours (0-10) at 6 months postoperatively. After the inclusion of half of the estimated sample, a preplanned interim analysis was performed when 33 patients (62.1 ± 9.4 y.) completed the study. Pain intensity (confidence interval [CI] 95% 0.6 to 3.8, and −0.6 to 2.2, for BC and RF) did not significantly differ. Complications, interference of pain in daily life (CI 95% −0.1 to 2.3 and −0.4 to 2.3, for BC and RF), neuropathic pain symptoms (CI 95% 1.7 to 3.6 and 3.0 to 5.7, for BC and RF), mood (CI 95% 4.8 to 11.5 and 5.5 to 15.1, BC and RF, respectively), medication use, and quality of life (CI 95% 80.4 to 93.1 and 83.9 to 94.2, for BC and RF) were also not different. Radiofrequency presented more paresthetic symptoms than BC at 30 days after intervention. Based on these results, the study was halted due to futility because BC was not superior to RF.

1. Introduction

Trigeminal neuralgia (TN) is characterized by shock-like paroxysmal attacks distributed in one or more trigeminal branches; it may occur spontaneously, or may be evoked by mechanical triggers.[14] Trigeminal neuralgia classification is based on the presence (secondary TN) or absence (primary TN) of a disease such as multiple sclerosis or a space occupying lesion affecting the trigeminal sensory system. Primary TN is further divided into classic (presence of neurovascular compression [NVC] with morphological changes of trigeminal nerve) or idiopathic TN (inexistence NVC exists). Classic and idiopathic TN can further be divided into purely paroxysmal or associated with concomitant nonparoxysmal pain.[35] Primary TN is initially managed with medication[4,78] because the majority of individuals will initially achieve pain control through pharmacological treatment. However, approximately half of TN patients will eventually need intervention in 10 years.[4,14,28] Surgical procedures offered to these patients include: microvascular decompression (MVD)[37] for individuals with classic TN or gamma-knife surgery (GKS)[46] as an alternative for those who cannot tolerate open cranial surgery. Radiofrequency thermocoagulation (RF),[69] balloon compression (BC),[51] and glycerol rhizolysis[32] are ablative procedures that may be repeated over time and are reserved for aged patients or for those who cannot tolerate or do not desire MVD/GKS.[51] Microvascular decompression has the highest risk of major postoperative complications (stroke, meningitis, cerebral spinal fluid leak, hemorrhage in 2%, and death in 0.4%),[80] despite providing long-term pain relief in up to 70% of patients and causing no major sensory deficits postoperatively.[58,77] Gamma-knife surgery has been offered as an alternative with fair results compared to MVD in low-quality studies: GKS may take up to 30 days to be effective,[53] it provides 75% pain relief after 3 months and then 50% in 3 years.[46,58,77] Importantly, the long-term pain beneficial effects of MVD have only been determined recently,[3,4,28] and GKS is still not widely available worldwide. For these reasons, percutaneous procedures (RF and BC) are still more commonly used worldwide,[42,52,73] due to their fair rates of good results, low cost, outpatient management, and low morbidity.[42,71,75]

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] *Instituto do Cancer do Estado de São Paulo Pain Center, School of Medicine, University of São Paulo, São Paulo, SP, Brazil,* [b] *Instituto de Ensino e Pesquisa da Rede D'Or—IDOR, São Paulo, SP, Brazil,* [c] *Department of Anesthesiologie and Pain Center, School of Medicine, University of São Paulo, São Paulo, SP, Brazil,* [d] *Department and Institute of Psychiatry, School of Medicine, University of São Paulo, Service of Interdisciplinary Neuromodulation, São Paulo, SP, Brazil,* [e] *Pain Center, School of Medicine, University of São Paulo, São Paulo, SP, Brazil,* [f] *Instituto do Cancer do Estado de São Paulo Pain Center, University of São Paulo, São Paulo, SP, Brazil,* [g] *School of Medicine, Federal University of ABC, São Bernardo do Campo, SP, Brazil,* [h] *School of Medicine, University of São Paulo, São Paulo, SP, Brazil,* [i] *Instituto do Cancer do Estado de São Paulo Pain Center, School of Medicine, University of São Paulo, São Paulo, SP, Brazil,* [j] *Service of Interdisciplinary Neuromodulation, São Paulo, SP, Brazil,* [k] *Pain Center Department of Neurology, University of São Paulo, SP, Brazil*

**Corresponding author. Address: Pain Center, Neurology Department, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Instituto do Câncer do Estado de São Paulo, Av. Dr. Enéas de Carvalho Aguiar, 255, 5 Andar, Sala 5084, 05403-900 São Paulo, Brazil. Tel.: 55 11 26 61 71 52. E-mail address: ciampi@usp.br (D. Ciampi Araujo de Andrade).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painjournalonline.com).

PAIN 00 (2020) 1–12

http://dx.doi.org/10.1097/j.pain.0000000000002070

Since its development, RF has been widely used because of its high selectivity and capacity in controlling pain.[4,38,40] However, it demands the use of expensive material,[36] highly trained anesthesiologist,[6] and experienced surgical team,[30] and carries elevated risks of sensorial disturbance, which may lead to painful anesthesia.[11,45,70] However, BC cheaper,[16,36] demands simple general anesthesia,[5,8] and is technically simpler,[2,66] providing lower rates of significant sensorial disturbances.[15,41,74]

Despite the fact that pain control may be achieved in up to 80% of the subjects treated with BC and RF, outcome measurements were heterogeneous and not well defined in the literature, and current data are mainly derived from results from large patient series.[4,38,73] No formal clinical trials directly comparing BC to RF have been conducted to date, and recent guidelines have acknowledged the lack of data allowing to recommend one technique over the other.[4] It still remains unknown whether BC can achieve good pain relief, if it can control nonparoxysmal continuous pain, and which is its side-effect profile in TN compared to more traditional RF.[4]

In this study, we conducted an original head-to-head randomized trial to assess the superiority and long-term effects of BC over RF on the different pain types of primary TN and their respective profiles of side effects.

2. Methods

This study was conducted at the pain center outpatient clinic of Hospital das Clinicas, University of São Paulo, Brazil. Patients with the diagnosis of primary TN were referred from regional neurology and pain clinics in the State of Sao Paulo. Written consent was obtained from all participants. The study was approved by our internal review board (CAPPesq 1180/09) and was registered in ClinicalTrials.gov (NCT 02427074). Enrollment occurred between May 2015 and December 2018.

2.1. Patients

Participants in the study had the following characteristics: aged 18 years or older; primary TN (according to the current criteria)[35]; no major signs of trigeminal neuropathy on examination; being refractory to medical treatment (no pain control or uncontrolled side effects with the maximum tolerated dosage of conventional medication—carbamazepine, phenytoin, oxcarbazepine, or baclofen—during the preceding year)[78]; involvement of the second or third trigeminal division; and no history of previous surgical procedure for TN. Subjects with involvement of the first trigeminal division or trigeminal neuropathy, or who refused to participate, or had difficulty in understanding the study were excluded. Brain imaging was performed on all patients to rule out secondary causes of neuralgia and make differential diagnoses. All subjects underwent a computed tomography scan of the head to rule out structural (or secondary) causes of TN. Magnetic resonance imaging (MRI) was performed in patients with suspected demyelinating diseases.

2.2. Study design

This was a prospective double-blind (subjects and raters) head-to-head randomized (superiority), clinical trial comparing the analgesic effects of BC over RF on the trigeminal ganglion for treating primary TN. The CONSORT (Consolidated Standards of Reporting Trials) recommendations were followed.[63] The patients were randomly allocated to either BC or RF in 1:1 ratio. Electronic software program (available at www.randomizer.org) was used to perform the randomization (blocks of 4). Allocation concealment was ensured by having the neurosurgeon responsible for the procedure informed of the randomization through sealed envelopes, which were handed over by a second investigator and opened as the patient entered the operating room. The surgeon responsible for all the procedures had no other role in the study. Evaluations were performed at the baseline (V0) and at 5 different postsurgical visits: 7 days, 30 days, 60 days, 90 days, and 180 days (referred to as V1, V2, V3, V4, and V5, respectively). The primary outcome of the study was the subjects' assessment of their worst pain level over the last 24 hours, at the 180-day evaluation, measured on an 11-point numerical rating scale anchored at 0 (no pain) and 10 (maximum pain imaginable) (**Fig. 1**). All the data were collected using dedicated Microsoft Excel files, stored in a cloud service, password-protected, accessible only for one investigator who was not involved in accessing or treating patients. AQ:3 [F1]

2.2.1. Blinding

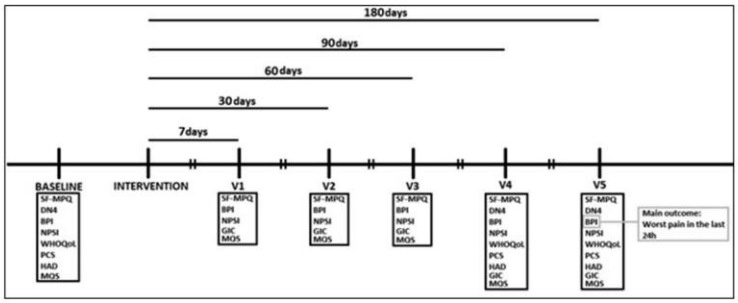
To ensure the blinding of the subjects, patients were informed that they would undergo 1 of 2 traditional percutaneous techniques for treating the symptoms of TN. The investigator responsible for the randomization and data collection never participated in the surgical procedure or in the postoperative appointments. Also, this researcher had no access to the patients' intraoperative or outpatient visit records.

A standardized questionnaire was used to assess the blinding of the study, which was filled out at the end of the trial. It was composed of 4 questions: (1) How much pain have you experienced during the surgical procedure, on a numerical rating scale from 0 (no pain) to 10 (worst pain)?; (2) Would you be able to tell which treatment you were receiving (yes/no)?; (3) If so, which group do you think you were in (group 1/group 2)?; (4) Would you be willing to undergo the procedure again if it was offered to you in the future (yes/no)?.[59]

2.3. Procedures

All the patients fasted for 6 hours before the intervention. An intravenous access was placed, and prophylactic antibiotic was given 1 hour before surgery. The anesthetic routine for the BC comprised administration of intravenous (IV) propofol (2.5 mg/kg), IV fentanyl (50-150 μg), muscle relaxant (rocuronium, 1 mg/kg), and placement of endotracheal catheter.

The subjects received atropine (0.25 mg), and sedation was maintained with sevoflurane 1 to 1.2 MAC until the end of the procedure. For RF thermocoagulation, the patients received mild sedation with propofol and fentanyl, and an O2 catheter was placed. They were then awakened for skin sensory evaluation. Under complete aseptic conditions, the skin over the needle entry-point was infiltrated with 1% lidocaine. The patient was placed in the supine position with the head perpendicular to the horizontal plane. The entry point was set as 2.5 to 3 cm laterally to the labial commissure, depending on whether the target was the third (V3) or second (V2) trigeminal division, respectively. The planes used to access the *foramen ovale* had previously been described[34,51,72]: one that passes through the ipsilateral pupil and another one 3 cm anteriorly to the tragus, also ipsilaterally. Using radioscopic imaging (Siemens, Siremobile, Erlangen, Germany), the puncturing of the foramen ovale was confirmed (using the clival line as the reference for V2; and 5 mm anteriorly to the clival line for V3).



AQ:6 **Figure 1.** Scheme depicting the follow-up and scheduled evaluations. Description: BPI, Brief Pain Inventory; DN4, Douleur Neuropathique 4; GIC, Global Impression of Change; HADS, Hospital Anxiety and Depression scale; MQS, Medication Quantification Scale; NPSI, Neuropathic Pain Symptom Inventory; PCS, Pain Catastrophizing Scale; SF-MPQ, Short-Form McGill Pain Questionnaire; WHOQoL, World Health Organization quality-of-life questionnaire.

For the BC technique, after puncturing the *foramen ovale* with a 14 G needle (BR R Becton Dickinson, Juiz de Fora, MG, Brazil), 1% lidocaine was administered to the trigeminal ganglion until facial anesthesia was attained. Then, a 4F Fogarty catheter (American Edwards Laboratory) was placed in the trigeminal cistern and insufflated with 0.7 mL of the contrast agent Iopamiron (125R, Schering, São Paulo, Brazil) until the balloon assumed a "pear shape" (**Fig. 2**) on the C-arm (approximate plateau pressure 1100 mm Hg ± 120 mm Hg).[44] Compression of the trigeminal ganglion was maintained for 120 seconds. At the end, the balloon was deflated, and the catheter and needle were removed. Mechanical compression was applied to the point of entry. For the RF technique, after puncturing the *foramen ovale* with the needle, an electrode (Radionics, 15 cm, insulated) was inserted and connected to a Radionics R generator (RFG-3C Plus). After evaluating the impedance (250-300 Ω), the trigeminal division of interest was confirmed through stimulation (sensory stimulation at 50 Hz and 0.1-0.5 V, with the patient awake to describe the area of paresthesia, and motor stimulation at a frequency of 2 Hz and 0.1-0.5 V, with the patient asleep, until masticatory movements were observed). After confirming which trigeminal division was to be targeted, we proceeded with making the lesion. This was done at 70°C lesion for 60 seconds, until static mechanical analgesia of the skin had been achieved (the pinprick sensation was tested using a safety pin and the 2 sides were compared). This process was repeated until skin anesthesia over the targeted area had been achieved.

[F2]

2.4. Pain and assessment of related factors

Subjects were evaluated using specific questionnaires, as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).[23,24,76]

2.4.1. Brief pain inventory

It is a questionnaire that includes a pain severity index (mean of questions 3-6, with a numerical rating scale that ranged from 0 to 10, such that the lower the score was, the lower the pain level was) and measurement of the interference of pain with daily activities (mean of the 7 items, with an intensity numerical rating scale ranging from 0 to 10, where zero meant no interference and 10 for maximal interference imaginable).[27] In addition, this questionnaire provided information on pain medications and dosing. The study's primary outcome was the worst pain level over the last 24 hours, ranging from 0 to 10 on numerical rating scale.

2.4.2. McGill pain questionnaire—short form

It has descriptors[14] of pain within 3 aspects and qualities of pain: sensory–discriminative, affective–emotional, and cognitive–evaluative.[26]

2.4.3. Douleur neuropathique 4 questionnaire

This is a 10-item questionnaire used to screen for neuropathic pain. It is positive when scores 4.[62]

2.4.4. Neuropathic pain symptom inventory

It is composed of 10 items that are presented as numerical rating scales with a range from 0 to 10, each referring to a specific feature: superficial spontaneous pain (question 1), deep spontaneous pain (mean of questions 2 and 3), paroxysmal pain (mean of question 5 and 6), evoked pain (mean of questions 8, 9, and 10) and paresthesia/dysesthesia (mean of questions 11 and 12).[19] The total score possible is 100. The temporal aspects of continuous and paroxysmal pain are assessed in question 4 (duration of spontaneous pain over the last 24 hours) and question 7 (number of pain attacks over the last 24 hours). Neuropathic pain symptom inventory was also used here to evaluate nonparoxysmal pain: scores of 4 or higher than the mean in the first domain (superficial spontaneous pain) and second domain (deep spontaneous pain) were considered to represent continuous pain.

2.4.5. Pain catastrophizing scale

It consists of a 13-item scale, on which each item can be scored from 0 to 4 each, thus giving a total score of 0 to 52.[64] The higher the score is, the more elevated the distress is.

2.4.6. Hospital anxiety and depression scale

It is a 14-item questionnaire (7 items for anxiety and 7 for depression symptoms, with scores ranging from 0 to 3 each) that

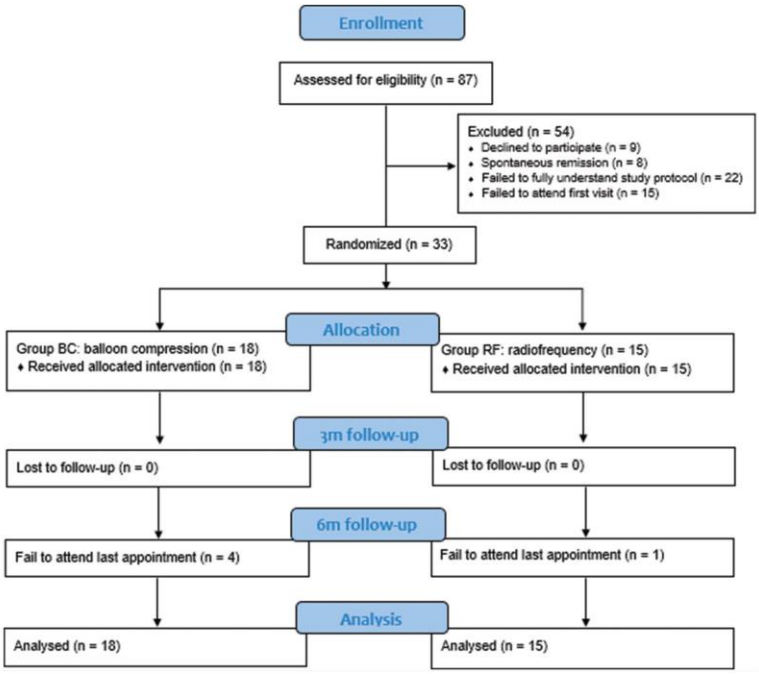


Figure 2. CONSORT flowchart of the study.

aids in screening for mood disorders, with total scores from 0 to 21 for anxiety and for depression.[54] Higher scores suggest depression/anxiety.

2.4.7. World Health Organization quality-of-life questionnaire—brief form

This is a short 26-item version of a standardized 100-item questionnaire that evaluates 4 domains of quality of life: physical, psychological, social relationships, and environmental relationships.[29] The higher the scores are, the better the quality of life is.

2.4.8. Global impression of change

This is a scale used by the patient global impression of change (p-GIC) and evaluator (c-GIC) to rate the global evolution of their pain since the first visit.[19,24] In both cases, the GIC included 7 ranks ranging from 1 to 7 (1 = very much improved, 2 = moderately improved, 3 = slightly improved, 4 = no change; 5 = slightly worsened; 6 = moderately worsened; 7 = very much worsened).

2.4.9. Medication quantification scale version 3

It is for quantifying the medications used by the patient and their dosages. It provides a weighted final score for the "medication burden."[33]

2.5. Statistical analysis

The variables were expressed using absolute values and frequencies (for categorical variables), and mean values and SDs along with minimum and maximum values for continuous variables. Data were analyzed as intention to treat. The effect of the interventions on the main outcome was assessed using a series of generalized estimation equations (GEE). The measurements at the baseline and at 7, 30, 60, and 180 days after the intervention were evaluated longitudinally, and the fact that all measurements were estimated for the same patient was accounted for. Because the outcome presented nonnormal distribution, its raw numerical values were recategorized as indicator variables with cutoff points greater than or equal to 2, 3, 5, or 7 points. These dichotomous values were analyzed through GEE with binomial distribution. The models evaluated the association between the outcome and the 2 interventions, and differences at the baseline were accounted for. We reported the results as the predicted means for numerical outcomes and as odds ratios for categorical outcomes, along with 95% confidence intervals.[60] The Kolmogorov–Smirnov test was used to test the normal distribution of variables. For nonnormally distributed variables, comparisons between groups were made using the Mann–Whitney test and Pearson chi-square test. The Student t test was used for normally distributed variables. For patients to be included in the analyses, they needed to have attended at least

80% of the visits and to have provided at least 80% of the information at each clinical visit. Data imputation was done by using the last-observation-carried-forward methodology. Because there was a paucity of formal clinical trials on ablative surgery for NT,[79] no formal sample size calculation could be performed beforehand. Therefore, we designed a pragmatic clinical trial: we used a convenience sample of NT patients based on the sample size of previous studies (n = 30 per arm),[25,79] to assess equivalence between arms. Variables at baseline were tested for differences because the trial presents a restricted number of participants. A preplanned interim analysis, approved by the institutional review board (IRB), was envisaged when half of the total sample was reached in both groups, to access safety and pain control data and to assess whether there was any need to revise the number of subjects needed. The interim results were analyzed by an external research panel and one of the following decisions would be made: (1) to stop the trial because significant differences between the arms had already been discerned; (2) to stop the trial due to futility; or (3) to pursue the trial with a larger sample size calculated based on the information obtained from the first part of the study. The statistical analyses were performed using IBM SPSS (Statistical Package for the Social Sciences) v17.0 and R-Project.[56] The sample size for the difference in slopes between the BC and the conventional RF groups was calculated based on previous published data,[25,79] to yield a power of 0.8 and detect a difference in slopes of 1.5, with a residual variance of 1 and a significance level of 0.05.[22] Individual patient's data will be available upon request. Reports regarding statistical analysis and study protocol can be obtained upon request to the corresponding author.

3. Results

3.1. Descriptive data and baseline assessment

Eighty-seven patients were assessed for eligibility. Thirty-three (25 females; 62.18 ± 9.4 years old) were included (see [F3] CONSORT flow-chart—**Fig. 3**) for the interim analysis: 57.6% had the mandibular division affected and 21 had right-sided TN. [T1] **Table 1** shows the subjects' characteristics and demographics, along with comparisons between the groups. The following results represent the outcomes from the preplanned interim analyses. Both groups showed similar medication usage at the baseline, as depicted by the MQS score (10.63 ± 6.21 for BC; 12.47 ± 4.44 for RF; $P = 0.292$). Main baseline variables were [T2] similar between groups (**Table 2**).

3.2. Results regarding pain and related factors

3.2.1. Main outcome

The main outcome of the study was not significantly different [T3] between groups ($P = 0.78$). **Table 3A** displays information on the study's main outcome, analyzed by GEE, which was categorized as higher or lower than 5. A similar pattern was observed when recategorizing the worst pain level over the last 24 hours into higher or lower than 2, 3, or 7, as depicted in **Table 3B**, although an expected reduction in pain intensity overtime in each group [F4] could be noted (**Fig. 4**).

3.2.2. Secondary outcomes

At 180 days after the intervention, the patients in the BC group reported higher levels of pain (Brief pain inventory—pain intensity index), compared with those in the RF group, although not clinically or statistically significant difference was observed (confidence interval 95% 0.17 to 2.58 and −0.63 to 1.93, BC and RF, respectively). The DN4 questionnaire was positive in 33.3% and 60% of the individuals, respectively, in the BC and RF groups at 6 months. These proportions were lower than at baseline (88.9% and 80% for BC and RF, respectively), but no difference was observed between the groups ($P = 0.126$). No significant difference was found on MPQ scores (12.89 ± 1.71 and 12.20 ± 2.51; 3.39 ± 4.23 and 2.20 ± 3.86; for BC and RF at the baseline and last appointment, respectively; $P = 0.292$ and $P = 0.94$). Concerning the pain phenotype, patients in the RF group reported more paresthetic symptoms than did those in the BC group (2.08 ± 1.99 vs 3.97 ± 1.96, respectively; $P = 0.017$). Moreover, there was a higher number of RF patients who were completely pain-free (100% of these individuals), compared with the BC group (4.55 ± 0.78 vs 5.00 ± 0.00; $P = 0.015$) at the first postoperative assessment (visit 1 at 7 days postoperatively), assessed by the specific item on number of pain attacks from the NPSI questionnaire. The paresthesia symptom scores were significantly higher in the RF group at 30 days (V2; $P = 0.01$), but these symptoms were resolved during the follow-up (V5; $P = 0.294$). At 90 days (V4), the individuals in the BC group presented lower NPSI total scores (9.61 ± 15.2 vs 15.07 ± 20.75 in the RF group; $P = 0.038$), but at the last evaluation, this difference was no longer present ($P = 0.598$). Global impression of change, despite presenting with no difference at the last appointment ($P = 1.0$), demonstrated elevated proportions of highly satisfied individuals in both groups (88.9% for BC and 86.7% for RF).

Patients with main paroxysmal pain but presenting concomitant continuous pain at baseline comprised 66.7% of the BC group and 53.3% of the RF group. At the last assessment, these proportions were 5.6% and 20%, respectively ($P = 0.308$). Patients with purely paroxysmal pain at the baseline were 16.7% in the BC group and 40% in the RF group ($P = 0.239$). After the follow-up, these proportions were 72.2% and 66.7% ($P = 0.730$). Other mood, quality of life, and medication used variables were not significantly different between groups and are presented in supplementary file (available at http://links.lww.com/PAIN/B174). Concomitant nonparoxysmal pain was present in 28% and 26%, harboring TN in maxillary and mandibular division, respectively. At 6 months, this proportion was 57% and 79%, respectively.

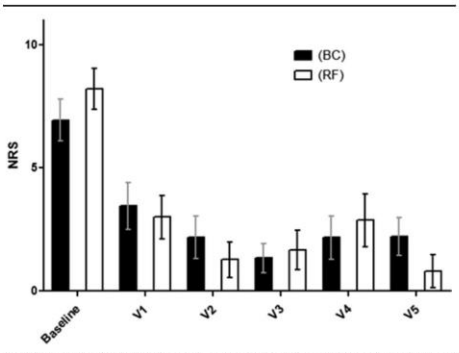


Figure 3. Numerical rating scale of main outcome (worst pain level over the last 24 hours). Description: Results expressed as mean and standard error between groups, over time. BC, balloon compression; RF, radiofrequency.

Table 1

Demographics and baseline pain characteristics of all patients and subgroups, and comparisons between the variables.

Characteristics	Total (33)	Group 1 (BC) (n = 18)	Group 2 (RF) (n = 15)	P
Age (in y)	62.18 ± 9.4 (40-78)	65 ± 9.42 (45-78)	58.8 ± 8.47 (40-71)	0.058
Sex				
Male	8 (24.2%)	5 (16.7%)	5 (33.3%)	0.266
Female	25 (75.8%)	15 (83.3%)	10 (66.7%)	
Skin color				
White	26 (78.8%)	14 (77.8%)	12 (80%)	0.458
Brown	6 (18.2%)	4 (22.2%)	2 (13.3%)	
Black	1 (3%)	0	1 (6.7%)	
Duration of symptoms (mo)	44.27 ± 13.1 (23-63)	40.44 ± 13.9 (23-63)	48.9 ± 10.7 (29-63)	0.065
Marital status				
Married	17 (51.5%)	9 (50%)	8 (53.3%)	0.772
Divorced	6 (18.2%)	3 (16.7%)	3 (20%)	
Widow	6 (18.2%)	4 (22.2%)	2 (13.3%)	
Single	3 (9.1%)	2 (11.1%)	1 (6.7%)	
Cohabiting	1 (3%)	0	1 (6.7%)	
Trigeminal division mainly affected				
V2	14 (42.4%)	7 (38.9%)	7 (46.7%)	0.653
V3	19 (57.6%)	11 (61.1%)	8 (53.3%)	
Laterality				
R	21 (63.6%)	14 (77.8%)	7 (46.7%)	0.064
L	12 (36.4%)	4 (22.2%)	8 (53.3%)	
Presence of other previous nontrigeminal chronic pain	18 (54.5%)	12 (66.7%)	6 (40%)	0.126

The values are presented as mean + SD (range). Significance set at $P < 0.05$.
BC, balloon compression; RF, radiofrequency; V2, maxillary division; V3, mandibular division; R, right; L, left.

3.3. Procedures

All the patients were discharged from hospital within 24 hours after the intervention. There was no difference in postoperative pain between the groups: patients in both groups experienced new pain after the procedure, easily controlled with common painkillers (the intensity and duration were similar). Radiofrequency patients required an average of 2 to 3 lesion cycles to achieve hypoalgesia in the trigeminal territory of interest.

3.4. Blinding assessment

Pain during the procedure was evaluated because this is a possible source of blinding bias. The mean values (ranging from 0 to 10) and SDs for BC and RF were, respectively, 1.33 ± 2.06 and 4 ± 2.27 ($P = 0.02$). After completion of the protocol, 44.4% of the individuals in group BC reported that they were able to tell which group they had been allocated to, and 66.7% of these individuals guessed it right. In group RF, the proportion was 37.5% for both questions ($P = 0.35$). When asked if they would be willing to undergo the procedure again if it was offered, the proportions were 55.5% and 50%, for groups BC and RF, respectively. None of these proportions were statistically significant ($P = 1.0$).

3.5. Effect and sample size

The preplanned interim analysis was performed at the time when each arm reached half of the scheduled number of subjects, to evaluate the safety and effect size of the protocol. The power of the study was 4.7%. An update of the sample size was made based on the results from this trial, to estimate the sample size necessary to detect a difference between groups in a subsequent trial using generalized estimated equations (power of 80% and a significance level of 0.05). The number necessary per arm was 1457, thus rendering uncertain the clinical value of the difference between BC and RF for TN. Therefore, the study was halted due to futility after a meeting between researchers and an external scientific board.

4. Discussion

We report the results from the first attempt to prospectively prove superiority of BC over RF for primary TN. No significant differences were found between BC and RF for the primary outcome. The decision regarding which treatment to offer patients with TN has been an issue of great debate for a long time. Although adequate pain control has been achieved through use of carbamazepine,[13] a significant proportion of patients will suffer from untenable side effects or may not reach satisfactory pain-attack control.[4,14,28] Percutaneous procedures have been used for over 4 decades without clear evidence regarding which of these is most effective for controlling TN pain or differences in safety. The literature has an abundancy of large series of patients who underwent ablative interventions, but the outcomes have often been measured using different and heterogeneous pain outcome measures, which hampers generalization. Moreover, the characteristics of the pain in TN are often not considered in depth: for instance, number of pain attacks, intensity of pain attacks, reduction of medication burden, and the presence of nonparoxysmal pain were rarely assessed systematically.[31]

Considering procedure-related risks and technical difficulties, it seems that ablative procedures are preferred over MVD for a number of reasons[4,31]: simplicity, outpatient management, and low profile of severe side effects. In addition, the outcomes of the latter have been suggested to be superior in high-volume

Table 2

Baseline characteristics of both groups and comparison between variables.

	Group 1 (BC) (n = 18)	Group 2 (RF) (n = 15)	*P*
SF-MPQ			
Domain			
Sensory (0-8)	6.28 ± 1.56 (2-8)	5.87 ± 1.77 (2-8)	0.540
Affective (0-5)	4.61 ± 0.61 (3-5)	4.33 ± 0.9 (2-5)	0.381
Evaluative (0-2)	2.00 ± 0.00 (2)	2.00 ± 0.00 (2)	1.000
Total (0-15)	12.89 ± 1.71 (9-15)	12.2 ± 2.51 (6-15)	0.617
DN4			
Total (0-10)	5.33 ± 2 (0-8)	5.87 ± 2.47 (1-9)	0.382
Neuropathic pain (≥4)	16 (88.9%)	12 (80%)	0.639
BPI			
Intensity of pain variables			
Worst pain last 24 h (0-10)—study main outcome	6.94 ± 3.55 (0-10)	8.2 ± 3.19 (0-10)	0.292
Least pain last 24 hours (0-10)	1.72 ± 2.78 (0-8)	1.8 ± 2.86 (0-9)	0.863
Average pain last 24 hours (0-10)	5.05 ± 3.08 (0-9)	6.27 ± 2.76 (0-10)	0.266
Pain right now (0-10)	4.11 ± 3.46 (0-10)	4.07 ± 3.95 (0-10)	0.882
Relief last 24 hours with medication (%)	48.89 ± 28.67 (0-100)	68.67 ± 28.9 (10-100)	0.238
Pain intensity index (0-10)	4.46 ± 2.68 (0-8.75)	5.08 ± 2.66 (0-9.75)	0.526
Interference			
General activity (0-10)	6.55 ± 3.99 (0-10)	5.40 ± 4.50 (0-10)	0.536
Mood (0-10)	6.67 ± 3.66 (0-10)	7.73 ± 3.71 (0-10)	0.255
Walking (0-10)	5.61 ± 4.39 (0-10)	5.53 ± 4.45 (0-10)	0.985
Normal work (0-10)	6.67 ± 4.39 (0-10)	5.8 ± 3.73 (0-10)	0.437
Relationship (0-10)	6.89 ± 3.83 (0-10)	6.87 ± 3.85 (0-10)	0.880
Sleep (0-10)	6.28 ± 4.31 (0-10)	5.27 ± 4.16 (0-10)	0.432
Enjoyment of life (0-10)	8.39 ± 2.61 (0-10)	7.20 ± 3.97 (0-10)	0.506
Pain interference in daily life (0-10)	6.72 ± 2.95 (0-10)	6.26 ± 2.61 (2.57-10)	0.527
MQS			
Score	10.63 ± 6.21 (0-22.8)	12.47 ± 4.44 (5.6-19.4)	0.292
NPSI			
Superficial spontaneous pain (0-10)	6.28 ± 3.80 (0-10)	4.80 ± 4.75 (0-10)	0.362
Deep spontaneous pain (0-10)	3.39 ± 4.09 (0-10)	3.93 ± 4.60 (0-10)	0.876
Paroxysmal pain (0-10)	5.39 ± 3.87 (0-10)	6.53 ± 4.34 (0-10	0.262
Evoked pain (0-10)	5.63 ±3.76 (0-10)	5.38 ± 3.37 (0-10)	0.828
Paresthesia/dysesthesia (0-10)	4.28 ± 3.41 (0-10)	4.60 ± 3.62 (0-10	0.729
Duration of spontaneous pain last 24 hours (1-5)	3.00 ± 1.81 (1-5)	3.33 ± 1.99 (1-5)	0.520
Number of pain attacks last 24 hours (1-5)	3.17 ± 1.65 (1-5)	2.80 ± 1.70 (1-5)	0.602
Continuous pain less than 1 hour last 24 hours	6 (33.3%)	8 (53.3%)	0.247
No pain attacks last 24 hours	5 (27.8%)	4 (26.7%)	1.000
Total (0-100)	49.28 ± 29.16 (0-99)	51.07 ± 32.89 (1-98)	0.857
WHOQOL			
Domain			
Physical (7-35)	19.78 ± 5.45 (9-28)	19.07 ± 5.38 (8-31)	0.404
Psychological (6-30)	19.28 ± 4.70 (10-26)	17.60 ± 5.38 (7-29)	0.301
Social (3-15)	10.44 ± 1.76 (6-12)	10.40 ± 2.75 (5-15)	0.970
Environmental (8-40)	25.39 ± 4.53 (16-32)	26.60 ± 5.29 (12-36)	0.536
PCS			
Score (0-52)	35.89 ± 11.13 (13-52)	32.47 ± 11.35 (14-51)	0.395
HADS			
HADS-A (0-21)	10.11 ± 5.72 (3-21)	10.33 ± 4.70 (1-17)	0.744
HADS-D (0-21)	6.72 ± 6.04 (0-18)	6.80 ± 5.03 (0-17)	0.703
Total score (0-42)	16.83 ± 9.60 (3-36)	17.13 ± 8.79 (5-31)	0.899

The values are presented as mean ± SD (range) or n (%). Significance is set as $P < 0.05$.

BC, balloon compression; BPI, brief pain inventory; DN4, Douleur Neuropathique 4 questionnaire (neuropathic pain present ≥ 4); HADS, Hospital Anxiety and Depression Scale (HADS-A, anxiety symptoms; HADS-D, depression symptoms); MQS, Medication Quantification Scale version III; NPSI, neuropathic pain symptom inventory; PCS, pain catastrophizing scale; RF, radiofrequency; SF-MPQ, Short-Form McGill Pain Questionnaire; WHOQOL, World Health Organization quality-of-life questionnaire, brief form.

centers.[39] Historically, individuals often underwent percutaneous ablative procedures for the abovementioned reasons and because of the need for a learning curve for MVD.[9,38,42,67,71,80] Since the time when ablative procedures became part of the armamentarium of treatment options for TN,[51,69] the procedures most used have been BC and RF. Despite their apparent safety, a

Table 3

Predicted odds ratio for the worst pain level over the last 24 hours.

	Group 1 (BC) (n = 18)	Group 2 (RF) (n = 15)	*P*
a)			
Worst pain in the last 24 h above 5a	1.12 (0.51, 2.49)	1 [referent]	0.78
b)			
Worst pain in the last 24 h above 2b	1.07 (0.48, 2.39)	1 [referent]	0.86
Worst pain in the last 24 h above 3b	1.06 (0.48, 2.33)	1 [referent]	0.88
Worst pain in the last 24 h above 7b	1.22 (0.51, 2.93)	1 [referent]	0.66

Comparison of the "worst pain level over the last 24 h" transformed to a dichotomous variable (a: above 5; b: above 2, above 3, and above 7). The values are presented as odds ratio (95% confidence intervals). Significance is set as $P < 0.05$.
BC, balloon compression; RF, radiofrequency.

deeper and standardized evaluation of their pain-relief effect is still lacking in the literature. The outcome most frequently used in most reports was the rate of recurrence, although patients under remission of paroxysmal pain often experience other types of pain (ie, nonparoxysmal)[41,73] and side effects of surgery (skin numbness and masticatory abnormalities).[11,15,20,21,43,49,50,55,68] Despite the lack of differences between the 2 interventions regarding the primary outcome in this study, some technical issues ought to be pointed out: although BC demands use of a Fogarty catheter and general anesthesia, RF requires a disposable electrode, an RF generator, and specialized anesthesia for a sleep–wake–sleep procedure (because of the need to evaluate skin sensation after lesioning). Although a larger number of items are needed, the fact that skin sensation was tested after each cycle of RF likely protected excessive deafferentation and possible subsequent long-term painful anesthesia. Therefore, because of the need for a larger number of items and special conditions, RF is a method that may not be readily available in every pain center. However, since BC is a simple method that demands fewer items, associated to the fact that it offers clinically similar pain-control capacity, restricted-resource centers with lower expertise in RF should consider BC for treating TN.

The sample size used in this study was based on previous reports of the effect size in surgical TN trials.[79] A *post hoc* power analysis calculated based on this study's results suggested that if a real difference in pain relief should exist between the 2 interventions, a clinical trial would require a significant number of participants in each arm, larger than the sum of all the patients enrolled in all TN trials performed to date.[9,42,66,70,71] For example, the largest series published enrolled 1600 patients over 25 years,[40] which strongly suggests that the clinical difference between both techniques are likely to be irrelevant.

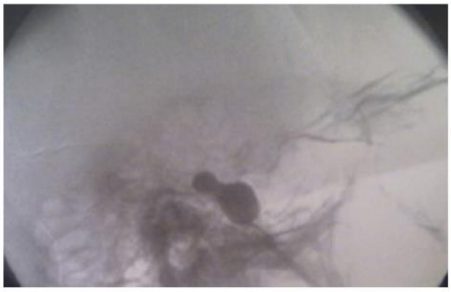


Figure 4. Balloon compression imaging. Description: Fluoroscopic image of the "pear-shape" of the Fogarty catheter during balloon compression of the trigeminal nerve.

The current IASP/IHS subclassification of TN is based on MRI assessment of the posterior fossa and detection of NVC.[35] Here, only 18% of the individuals had MRI. The remaining had secondary causes excluded with computerized tomography. It is known that 25% of individuals with typical TN may not have detectable NCV on MRI on the side of their pain.[1] This means that our sample probably included a largest proportion of patients with NVC, and would probably be classified with classic TN, should MRI assessment be performed systematically. Importantly, although MRI studies are mandatory when NVC is envisaged, its importance for patients undergoing ablative procedures remains to be determined. In latest recommendations, this point is further highlighted, and it is further acknowledged that although MRI is fundamental for the determination of microvascular compression of the trigeminal nerve (to classify primary TN as classic, subsequently enabling MVD as a surgical treatment possibility), it is not required for the diagnosis of TN per se.[4]

The peculiar main paroxysmal nature of TN imposes some challenges in quantifying pain because paroxysmal pain may not be well suitable for assessment by regular "general" pain intensity-based visual analogue scale or numeric ranking scale approaches. Nonparoxysmal concomitant pain in TN has been a recognized feature of the TN syndrome.[18] Indeed, TN was classified into 2 groups, according to the frequency of continuous nonparoxysmal pain: TN1 or typical TN when paroxysms are predominant, and TN2 or atypical TN when concomitant continuous pain occurs at least in 50% of the time.[7,10,12] In fact, TN patients frequently have secondary nonparoxysmal pain, which is less frequently assessed in both pharmacological and surgical trials, but may be disabling and negatively impact quality of life.[17,47] Here, we tried to overcome this limitation by assessing both the paroxysmal and nonparoxysmal pains using NPSI, which enables specific scoring of these different pain symptoms. Indeed, we found that both BC and RF decreased levels of paroxysmal and nonparoxysmal pain, with no difference between arms. Here, we used specific NPSI scores to evaluate occurrences of continuous pain. When compared to the baseline, despite the proportion of nonparoxysmal pain decrease after surgical treatments compared to baseline, no difference was observed between groups at the last appointment. These original findings suggest that the both approaches provide similar changes in continuous pain after percutaneous procedures. Continuous pain in TN may be due to a wide range of causes and their presence may have influenced previous publications where their presence was not specifically assessed.[48,57,61,65] Here, we also found that the proportion of this nonparoxysmal pain was higher in patients treated for TN mainly located in the mandibular division of the trigeminal nerve, which may be caused by postoperative masticatory weakness.[20,21]

We also found that patients receiving RF experienced more paresthetic symptoms after the procedure (one week and 4 weeks after surgery), despite presenting fewer pain attacks at 4 weeks compared to the BC group. This confirms that this symptom may be expected as a side effect after percutaneous RF, but may most likely subside after one month. Also, patients who underwent BC presented lower total NPSI scores at 90 days which, despite not being a main outcome of this study, corroborates the common knowledge that BC leads to less skin sensory disturbances. Importantly, these group differences disappeared in the last evaluation.

Some limitations of this study should be pointed out. With regard to possible blinding bias, despite our attempts to blind subjects for the randomized intervention, the assessment using a pain questionnaire during the procedure revealed that the individuals who underwent RF are likely to be able to identify their allocation group. Although the blinding assessment revealed that the pain level during the procedure was higher in the RF group, the blinding was probably preserved because the remaining assessments did not show any differences between the groups. The six-month follow-up period is relatively short and may not comprise the whole time to relapse. However, we chose this time-frame because it allows for the classification of pain as chronic (>3 months), while maintaining the double-blind nature of the trial. Also, the sample was relatively small, given that its estimation was based on the size of previous trials on TN, and no studies addressing direct comparisons between ablative procedures for TN were available. In a Cochrane meta-analysis,[79] it was stated that the greatest issue with all interventional TN studies was the lack of standardized clinical outcomes. Therefore, direct calculation of the study power like in this study was challenging and mainly based on previously published articles.[25,79] In fact, results from this study could be used to calculate a more precise power for future studies.

In summary, our study showed that pain relief after RF and BC was globally similar, with no superiority of BC over RF for primary TN. However, as we have shown, BC leads to less dysesthesia than RF (and potentially less postprocedural neuropathic pain). And, because BC requires less use of anesthetics, has a shorter technical learning curve, and has lower costs than RF, BC could be preferentially recommended to patients undergoing ablative procedures. We also found similar effects for other components of neuropathic pain such as nonparoxysmal pain, and a relatively small number of adverse events in both groups.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B174.

Article history:
Received 6 July 2020
Received in revised form 29 August 2020
Accepted 3 September 2020
Available online XXXX

AQ:4 ### References

[1] Antonini G, Di Pasquale A, Cruccu G, Truini A, Morino S, Saltelli G, Romano A, Trasimeni G, Vanacore N, Bozzao A. Magnetic resonance imaging contribution for diagnosing symptomatic neurovascular contact in classical trigeminal neuralgia: a blinded case-control study and meta-analysis. PAIN 2014;155:1464–71.
[2] Asplund P, Blomstedt P, Bergenheim AT. Percutaneous balloon compression vs percutaneous retrogasserian glycerol rhizotomy for the primary treatment of trigeminal neuralgia. Neurosurgery 2016;78:421–8; discussion 428.
[3] Barker FG, II, Jannetta PJ, Bissonette DJ, Larkins MV, Jho HD. The long-term outcome of microvascular decompression for trigeminal neuralgia. N Engl J Med 1996;334:1077–83.
[4] Benditsen L, Zakrzewska JM, Abbott J, Braschinsky M, Di Stefano G, Donnet A, Eide PK, Leal PRL, Maarbjerg S, May A, Nurmikko T, Obermann M, Jensen TS, Cruccu G. European Academy of Neurology guideline on trigeminal neuralgia. Eur J Neurol 2019;26:831–49.
[5] Bick SKB, Eskandar EN. Surgical treatment of trigeminal neuralgia. Neurosurg Clin N Am 2017;28:429–38.
[6] Brisman R Analgesia and sedation during percutaneous radiofrequency electrocoagulation for trigeminal neuralgia. Neurosurgery 1993;32: 400–5; discussion 405-406.
[7] Brisman R. Typical versus atypical trigeminal neuralgia and other factors that may affect results of neurosurgical treatment. World Neurosurg 2013; 79:649–50.
[8] Broggi G. Percutaneous retrogasserian balloon compression for trigeminal neuralgia. World Neurosurg 2013;79:269–70.
[9] Broggi G, Franzini A, Lasio G, Giorgi C, Servello D. Long-term results of percutaneous retrogasserian thermorhizotomy for "essential" trigeminal neuralgia: considerations in 1000 consecutive patients. Neurosurgery 1990;26:783–6; discussion 786-787.
[10] Burchiel KJ. A new classification for facial pain. Neurosurgery 2003;53: 1164–6; discussion 1166-1167.
[11] Burchiel KJ, McCartney S. Trigeminal neuralgia. In: Burchiel K, editor. Surgical Management of Pain. New York: Thieme, 2015. p. 175–9.
[12] Burchiel KJ, Slavin KV. On the natural history of trigeminal neuralgia. Neurosurgery 2000;46:152–4; discussion 154-155.
[13] Campbell FG, Graham JG, Zilkha KJ. Clinical trial of carbazepine (tegretol) in trigeminal neuralgia. J Neurol Neurosurg Psychiatry 1966;29:265–7.
[14] Casey KF. Role of patient history and physical examination in the diagnosis of trigeminal neuralgia. Neurosurg Focus 2005;18:E1.
[15] Chen JF, Tu PH, Lee ST. Long-term follow-up of patients treated with percutaneous balloon compression for trigeminal neuralgia in Taiwan. World Neurosurg 2011;76:586–91.
[16] Correa CF, Teixeira MJ. Balloon compression of the Gasserian ganglion for the treatment of trigeminal neuralgia. Stereotact Funct Neurosurg 1993;71:83–9.
[17] Cruccu G. Trigeminal neuralgia. Continuum (Minneap Minn) 2017;23: 396–420.
[18] Cruccu G, Finnerup NB, Jensen TS, Scholz J, Sindou M, Svensson P, Treede RD, Zakrzewska JM, Nurmikko T. Trigeminal neuralgia: new classification and diagnostic grading for practice and research. Neurology 2016;87:220–8.
[19] de Andrade DC, Ferreira KA, Nishimura CM, Yeng LT, Batista AF, de Sa K, Araujo J, Stump PR, Kaziyama HH, Galhardoni R, Fonoff ET, Ballester G, Zakka T, Bouhassira D, Teixeira MJ. Psychometric validation of the Portuguese version of the neuropathic pain symptoms inventory. Health Qual Life Outcomes 2011;9:107.
[20] de Siqueira SR, da Nobrega JC, de Siqueira JT, Teixeira MJ. Frequency of postoperative complications after balloon compression for idiopathic trigeminal neuralgia: prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102:e39–45.
[21] de Siqueira SR, da Nobrega JC, Teixeira MJ, de Siqueira JT. Masticatory problems after balloon compression for trigeminal neuralgia: a longitudinal study. J Oral Rehabil 2007;34:88–96.
[22] Diggle P, Diggle PJ, Heagerty P, Heagerty PJ, Liang K-Y, Zeger S, al e. Analysis of longitudinal data. Oxford: Oxford University Press, 2002.
[23] Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. PAIN 2005;113:9–19.
[24] Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR,

Stauffer JW, von Stein T, White RE, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105–21.
[25] Erdine S, Ozyalcin NS, Cimen A, Celik M, Talu GK, Disci R. Comparison of pulsed radiofrequency with conventional radiofrequency in the treatment of idiopathic trigeminal neuralgia. Eur J Pain 2007;11:309–13.
[26] Ferreira K, de Andrade DC, Teixeira MJ. Development and validation of a Brazilian version of the short-form McGill pain questionnaire (SF-MPQ). Pain Manag Nurs 2013;14:210–19.
[27] Ferreira KA, Teixeira MJ, Mendonza TR, Cleeland CS. Validation of brief pain inventory to Brazilian patients with pain. Support Care Cancer 2011; 19:505–11.
[28] Fields HL. Treatment of trigeminal neuralgia. N Engl J Med 1996;334: 1125–6.
[29] Fleck MP, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, Pinzon V. Application of the Portuguese version of the abbreviated instrument of quality life WHOQOL-bref [in Portuguese]. Rev Saude Publica 2000;34:178–83.
[30] Fraioli MF, Cristino B, Moschettoni L, Cacciotti G, Fraioli C. Validity of percutaneous controlled radiofrequency thermocoagulation in the treatment of isolated third division trigeminal neuralgia. Surg Neurol 2009;71:180–3.
[31] Gronseth G, Cruccu G, Alksne J, Argoff C, Brainin M, Burchiel K, Nurmikko T, Zakrzewska JM. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. Neurology 2008;71:1183–90.
[32] Hakanson S. Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. Neurosurgery 1981;9:638–46.
[33] Harden RN, Weinland SR, Remble TA, Houle TT, Collo S, Steedman S, Kee WG. Medication Quantification Scale Version III: update in medication classes and revised detriment weights by survey of American Pain Society Physicians. J Pain 2005;6:364–71.
[34] Härtel F. Die Behandlung der Trigeminusneuralgie mit intrakraniellen Alkoholeinspritzungen. Deutsche Z Für Chirurgie 1914;126:429–552.
[35] Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia 2018;38:1–211.
[36] Holland M, Noeller J, Buatti J, He W, Shivapour ET, Hitchon PW. The cost-effectiveness of surgery for trigeminal neuralgia in surgically naive patients: a retrospective study. Clin Neurol Neurosurg 2015;137:34–7.
[37] Jannetta PJ. Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. J Neurosurg 1967;26:159–62.
[38] Jones MR, Urits I, Ehrhardt KP, Cefalu JN, Kendrick JB, Park DJ, Cornett EM, Kaye AD, Viswanath O. A comprehensive review of trigeminal neuralgia. Curr Pain Headache Rep 2019;23:74.
[39] Kalkanis SN, Eskandar EN, Carter BS, Barker FG, II. Microvascular decompression surgery in the United States, 1996 to 2000: mortality rates, morbidity rates, and the effects of hospital and surgeon volumes. Neurosurgery 2003;52:1251–61; discussion 1261-1252.
[40] Kanpolat Y, Savas A, Bekar A, Berk C. Percutaneous controlled radiofrequency trigeminal rhizotomy for the treatment of idiopathic trigeminal neuralgia: 25-year experience with 1,600 patients. Neurosurgery 2001;48:524–32; discussion 532-524.
[41] Keravel Y, Gaston A, De Andrade DCA, Mencattini G, Le Guérinel C. Traitement de la névralgie trigéminale par la comprasion par ballon. Neurochirurgie 2009;55:197–202.
[42] Koopman JS, de Vries LM, Dieleman JP, Huygen FJ, Stricker BH, Sturkenboom MC. A nationwide study of three invasive treatments for trigeminal neuralgia. PAIN 2011;152:507–13.
[43] Latchaw JP, Jr., Hardy RW, Jr., Forsythe SB, Cook AF. Trigeminal neuralgia treated by radiofrequency coagulation. J Neurosurg 1983;59: 479–84.
[44] Lee ST, Chen JF. Percutaneous trigeminal ganglion balloon compression for treatment of trigeminal neuralgia–part I: pressure recordings. Surg Neurol 2003;59:63–6; discussion 66-67.
[45] Li Y, Yang L, Ni J, Dou Z. Microvascular decompression and radiofrequency for the treatment of trigeminal neuralgia: a meta-analysis. J Pain Res 2019;12:1937–45.
[46] Lopez BC, Hamlyn PJ, Zakrzewska JM. Systematic review of ablative neurosurgical techniques for the treatment of trigeminal neuralgia. Neurosurgery 2004;54:973–82; discussion 982-973.
[47] Maarbjerg S, Di Stefano G, Bendtsen L, Cruccu G. Trigeminal neuralgia - diagnosis and treatment. Cephalalgia 2017;37:648–57.
[48] Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Concomitant persistent pain in classical trigeminal neuralgia–evidence for different subtypes. Headache 2014;54:1173–83.
[49] Meglio M, Cioni B. Percutaneous procedures for trigeminal neuralgia: microcompression versus radiofrequency thermocoagulation. Personal experience. PAIN 1989;38:9–16.
[50] Mittal B, Thomas DG. Controlled thermocoagulation in trigeminal neuralgia. J Neurol Neurosurg Psychiatry 1986;49:932–6.
[51] Mullan S, Lichtor T. Percutaneous microcompression of the trigeminal ganglion for trigeminal neuralgia. J Neurosurg 1983;59:1007–12.
[52] Noorani I, Lodge A, Vajramani G, Sparrow O. Comparing percutaneous treatments of trigeminal neuralgia: 19 Years of experience in a single centre. Stereotact Funct Neurosurg 2016;94:75–85.
[53] Nurmikko TJ, Eldridge PR. Trigeminal neuralgia—pathophysiology, diagnosis and current treatment. Br J Anaesth 2001;87:117–32.
[54] Pais-Ribeiro J, Silva I, Ferreira T, Martins A, Meneses R, Baltar M. Validation study of a Portuguese version of the hospital anxiety and depression scale. Psychol Health Med 2007;12:225–35; quiz 235-227.
[55] Park SS, Lee MK, Kim JW, Jung JY, Kim IS, Ghang CG. Percutaneous balloon compression of trigeminal ganglion for the treatment of idiopathic trigeminal neuralgia : experience in 50 patients. J Korean Neurosurg Soc 2008;43:186–9.
[56] R-CoreTeam. R: a language and environment for statistical computing. In: RFfS Computing editor. Vienna, 2018. AQ:5
[57] Rasmussen P. Facial pain. II. A prospective survey of 1052 patients with a view of: character of the attacks, onset, course, and character of pain. Acta Neurochir (Wien) 1990;107:121–8.
[58] Regis J, Tuleasca C, Resseguier N, Carron R, Donnet A, Gaudart J, Levivier M. Long-term safety and efficacy of Gamma Knife surgery in classical trigeminal neuralgia: a 497-patient historical cohort study. J Neurosurg 2016;124:1079–87.
[59] Rocha Rde O, Teixeira MJ, Yeng LT, Cantara MG, Faria VG, Liggieri V, Loduca A, Muller BM, Souza AC, de Andrade DC. Thoracic sympathetic block for the treatment of complex regional pain syndrome type I: a double-blind randomized controlled study. PAIN 2014;155:2274–81.
[60] Rutten-van Molken MP, van Doorslaer EK, van Vliet RC. Statistical analysis of cost outcomes in a randomized controlled clinical trial. Health Econ 1994;3:333–45.
[61] Sandell T, Eide PK. Effect of microvascular decompression in trigeminal neuralgia patients with or without constant pain. Neurosurgery 2008;63: 93–9; discussion 99-100.
[62] Santos JG, Brito JO, de Andrade DC, Kaziyama VM, Ferreira KA, Souza I, Teixeira MJ, Bouhassira D, Baptista AF. Translation to Portuguese and validation of the Douleur neuropathique 4 questionnaire. J Pain 2010;11: 484–90.
[63] Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol 2010;63:834–40.
[64] Sehn F, Chachamovich E, Vidor LP, Dall-Agnol L, de Souza IC, Torres IL, Fregni F, Caumo W. Cross-cultural adaptation and validation of the Brazilian Portuguese version of the pain catastrophizing scale. Pain Med 2012;13:1425–35.
[65] Sindou M, Leston J, Howeidy T, Decullier E, Chapuis F. Micro-vascular decompression for primary Trigeminal Neuralgia (typical or atypical). Long-term effectiveness on pain; prospective study with survival analysis in a consecutive series of 362 patients. Acta Neurochir (Wien) 2006;148: 1235–45; discussion 1245.
[66] Skirving DJ, Dan NG. A 20-year review of percutaneous balloon compression of the trigeminal ganglion. J Neurosurg 2001;94:913–17.
[67] Spatz AL, Zakrzewska JM, Kay EJ. Decision analysis of medical and surgical treatments for trigeminal neuralgia: how patient evaluations of benefits and risks affect the utility of treatment decisions. PAIN 2007;131: 302–10.
[68] Spincemaille GH, Dingemans W, Lodder J. Percutaneous radiofrequency Gasserian ganglion coagulation in the treatment of trigeminal neuralgia. Clin Neurol Neurosurg 1985;87:91–4.
[69] Sweet WH, Wepsic JG. Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers. 1. Trigeminal neuralgia. J Neurosurg 1974;40:143–56.
[70] Taha JM, Tew JM, Jr. Comparison of surgical treatments for trigeminal neuralgia: reevaluation of radiofrequency rhizotomy. Neurosurgery 1996; 38:865–71.
[71] Teixeira MJ, Siqueira SR, Almeida GM. Percutaneous radiofrequency rhizotomy and neurovascular decompression of the trigeminal nerve for the treatment of facial pain. Arq Neuropsiquiatr 2006;64:933–9.
[72] Tew JM, Jr, Keller JT. The treatment of trigeminal neuralgia by percutaneous radiofrequency technique. Clin Neurosurg 1977;24: 557–78.
[73] Texakalidis P, Xenos D, Tora MS, Wetzel JS, Boulis NM. Comparative safety and efficacy of percutaneous approaches for the treatment of

trigeminal neuralgia: a systematic review and meta-analysis. Clin Neurol Neurosurg 2019;182:112–22.
[74] Trojnik T, Smigoc T. Percutaneous trigeminal ganglion balloon compression rhizotomy: experience in 27 patients. ScientificWorldJournal 2012;2012:328936.
[75] Tronnier VM, Rasche D, Hamer J, Kienle AL, Kunze S. Treatment of idiopathic trigeminal neuralgia: comparison of long-term outcome after radiofrequency rhizotomy and microvascular decompression. Neurosurgery 2001;48:1261–7; discussion 1267-1268.
[76] Turk DC, Dworkin RH, Revicki D, Harding G, Burke LB, Cella D, Cleeland CS, Cowan P, Farrar JT, Hertz S, Max MB, Rappaport BA. Identifying important outcome domains for chronic pain clinical trials: an IMMPACT survey of people with pain. PAIN 2008;137:276–85.
[77] Wang DD, Raygor KP, Cage TA, Ward MM, Westcott S, Barbaro NM, Chang EF. Prospective comparison of long-term pain relief rates after first-time microvascular decompression and stereotactic radiosurgery for trigeminal neuralgia. J Neurosurg 2018;128:68–77.
[78] Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2014;4:CD005451.
[79] Zakrzewska JM, Akram H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. Cochrane Database Syst Rev 2011;9: CD007312.
[80] Zakrzewska JM, Linskey ME. Trigeminal neuralgia. In: Zakrzewska JM, editor. Orofacial Pain. Oxford: Oxford University Press, 2009. p. 119.
[81] Zheng S, Li X, Li R, Yang L, He L, Cao G, Yang Z, Ni J. Factors associated with long-term risk of recurrence after percutaneous radiofrequency thermocoagulation of the gasserian ganglion for patients with trigeminal neuralgia: a multicenter retrospective analysis. Clin J Pain 2019;35: 958–66.

Attachament H - Publication 2

Correspondence

PAIN

AQ:1 AQ:2 **Reply to Nova et al.**

Letter to Editor:

We thank Venda Nova et al.[7] for their interest in our work. We fully agree that trigeminal neuralgia (TN), despite being a rare disorder, is a syndrome that would benefit from a joint effort from healthcare providers and patients to develop and validate outcome measurements that are comprehensive, relevant, and comprehensible for end users.

However, it must also be acknowledged that sources of pain and suffering are not only diverse in patients with TN[4] but may as well stem from undue effects of surgical treatments. That means that finding a common denominator relevant to all patients under a patient-reported outcome framework would only partially solve these challenges because it would provide a validated tool to assess TN but not necessarily help detangling all the variables influencing good outcomes after each of the treatment interventions. For instance, as we have highlighted,[9] pain in TN is paroxysmal by definition, but nonparoxysmal continuous ongoing pain may be present in a significant proportion of patients and may respond differently to treatments aimed at paroxysmal pain. To that, we have potential unwanted effects of surgical interventions such as chronic postcraniotomy pain[1] and hearing loss in the case of neurovascular decompression or posttraumatic neuropathic pain (with all its possible combinations of signs and symptoms) in a deafferented skin (or mucosa) secondary to ablative procedures. One may also add musculoskeletal pain in masticatory muscles originating after ablative procedures,[3,5] which are more frequent when the mandibular subdivision of the trigeminal nerve is affected. Not to mention one frequently forgotten issue: in clinical trials, individuals with non-TN pain syndromes co-occurring with TN are frequently excluded from studies. Because chronic pain affects at least 18%[8] of the general population, real-life patients with TN may potentially harbor concomitant causes of face or head pain, such as migraine and cervicogenic headache[6] or may be under central-acting medications for extracranial chronic pain conditions that may influence TN pain outcomes or increase adverse events to TN interventions. All these above-mentioned instances may influence the perception of improvement after interventional treatments and may add noise to the assessment of specific treatment efficacy.

Given these challenges, one could argue that a complementary and pragmatic approach would be to continue using general measurements of pain intensity as end points (that do need to be validated according to patient-reported outcome guidelines), and to them, add a comprehensive set of tools to characterize secondary outcomes and potential side effects of treatment individually. For instance, we used the Neuropathic Pain Symptom Inventory (NPSI)[2] as a measure of the temporal profile of TN paroxysmal and nonparoxysmal symptoms. Indeed, the NPSI allowed us to show that radiofrequency thermocoagulation leads to more paresthetic symptoms after the procedure (up to one-month postsurgery), decreasing afterwards to levels similar to the balloon compression group. In addition, the total scores of the NPSI were lower at 90 days postprocedure in the balloon compression group compared with the radiofrequency group. Again, these differences waned in time during long-term follow-up. Thus, the field of TN, one of the most challenging pain syndromes known, urgently needs the development and validation of (primary) outcome measurements that matter to those in pain, as well as a more comprehensive and detailed assessment of the different "pains" that may occur in TN and after its treatments.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

[1] Chowdhury T, Garg R, Sheshadri V, Venkatraghavan L, Bergese SD, Cappellani RB, Schaller B. Perioperative factors contributing the post-craniotomy pain: a synthesis of concepts. Front Med (Lausanne) 2017;4:23.

[2] de Andrade DC, Ferreira KA, Nishimura CM, Yeng LT, Batista AF, de Sa K, Araujo J, Stump PR, Kaziyama HH, Galhardoni R, Fonoff ET, Ballester G, Zakka T, Bouhassira D, Teixeira MJ. Psychometric validation of the Portuguese version of the neuropathic pain symptoms inventory. Health Qual Life Outcomes 2011;9:107.

[3] de Siqueira SR, da Nobrega JC, de Siqueira JT, Teixeira MJ. Frequency of postoperative complications after balloon compression for idiopathic trigeminal neuralgia: prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102:e39–45.

[4] de Siqueira SR, Teixeira MJ, de Siqueira JT. Orofacial pain and sensory characteristicsof chronic patients compared with controls. Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:e37–41.

[5] Ichida MC, de Almeida AN, da Nobrega JC, Teixeira MJ, de Siqueira JT, de Siqueira SR. Sensory abnormalities and masticatory function after microvascular decompression or balloon compression for trigeminal neuralgia compared with carbamazepine and healthy controls. J Neurosurg 2015;122:1315–23.

[6] Lin KH, Chen YT, Fuh JL, Wang SJ. Increased risk of trigeminal neuralgia in patients with migraine: a nationwide population-based study. Cephalalgia 2016;36:1218–27.

[7] Nova CV, Riordain RN, Baker SR, Zakrzewska JM. Looking beyond the obvious: the importance of outcomes and outcomes measures in trigeminal neuralgia. PAIN 2021. AQ:5

[8] Sá KN, Moreira L, Baptista AF, Yeng LT, Teixeira MJ, Galhardoni R, de Andrade DC. Prevalence of chronic pain in developing countries: systematic review and meta-analysis. Pain Rep 2019;4:e779.

[9] Sterman-Neto H, Fukuda CY, Duarte KP, Aparecida da Silva V, Rodrigues ALL, Galhardoni R, de Siqueira S, de Siqueira JTT, Teixeira MJ, Ciampi de Andrade D. Balloon compression vs radiofrequency for primary trigeminal neuralgia: a randomized, controlled trial. PAIN 2021;162:919–29.

Daniel Ciampi de Andrade[a]
Hugo Sterman-Neto[b,c]
Cristiane Yoko Fukuda[d]
Kleber Paiva Duarte[e]
Valquíria Aparecida da Silva[f]
Antonia Lilian de Lima Rodrigues[g]
Ricardo Galhardoni[h,i]
Silvia R.D.T. de Siqueira[j]
José Tadeu Tesseroli de Siqueira[j]
Manoel Jacobsen Teixeira[k]
[a]*LIM-62, Pain Center, Department of Neurology, University of São Paulo, São Paulo, Brazil*

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

PAIN 00 (2021) 1–2

[b]School of Medicine, Pain Center, Instituto do Cancer do Estado de São Paulo, University of São Paulo, São Paulo, Brazil
[c]Instituto de Ensino e Pesquisa da Rede D'Or – IDOR, São Paulo, Brazil
AQ:3
[d]Department of Anesthesiologie and Pain Center, School of Medicine, University of São Paulo, São Paulo, Brazil
[e]Department and Institute of Psychiatry, School of Medicine, University of São Paulo, Service of Interdisciplinary Neuromodulation, São Paulo, Brazil
[f]Pain Center, School of Medicine, University of São Paulo, São Paulo, Brazil
[g]Pain Center, School of Medicine, Instituto do Cancer do Estado de São Paulo, University of São Paulo, São Paulo, Brazil
[h]Pain Center, Instituto do Cancer do Estado de São Paulo, University of São Paulo, São Paulo, Brazil
[i]School of Medicine, Federal University of ABC, São Bernardo do Campo, Brazil
[j]School of Medicine, University of São Paulo, São Paulo, Brazil
[k]Pain Center, School of Medicine, Instituto do Cancer do Estado de São Paulo, University of São Paulo, Service of Interdisciplinary Neuromodulation, São Paulo, Brazil AQ:4
E-mail address: ciampi@usp.br (D. Ciampi de Andrade)
http://dx.doi.org/10.1097/j.pain.0000000000002350

9 REFERENCES

Ameli NO. Avicenna and trigeminal neuralgia. *J Neurol Sci*. 1965;2(2):105-7.

Antonini G, Di Pasquale A, Cruccu G, Truini A, Morino S, Saltelli G, Romano A, Trasimeni G, Vanacore N, Bozzao A. Magnetic resonance imaging contribution for diagnosing symptomatic neurovascular contact in classical trigeminal neuralgia: a blinded case-control study and meta-analysis. *Pain.* 2014;155(8):1464-71.

Apfelbaum RI. A comparision of percutaneous radiofrequency trigeminal neurolysis and microvascular decompression of the trigeminal nerve for the treatment of tic douloureux. Neurosurgery 1977;1(1):16-21.

Baabor MG, Perez-Limonte L. Percutaneous balloon compression of the gasserian ganglion for the treatment of trigeminal neuralgia: personal experience of 206 patients. *Acta Neurochir Suppl*. 2011;108:251-4.

Barker FG, 2nd, Jannetta PJ, Bissonette DJ, Larkins MV, Jho HD. The long-term outcome of microvascular decompression for trigeminal neuralgia. *N Engl J Med.* 1996;334(17):1077-1083.

Bederson JB, Wilson CB. Evaluation of microvascular decompression and partial sensory rhizotomy in 252 cases of trigeminal neuralgia. *J Neurosurg*. 1989;71(3):359-367.

Bendtsen L, Zakrzewska JM, Abbott J, Braschinsky M, Di Stefano G, Donnet A, Eide PK, Leal PRL, Maarbjerg S, May A, Nurmikko T, Obermann M, Jensen TS, Cruccu G. European Academy of Neurology guideline on trigeminal neuralgia. *Eur J Neurol.* 2019;26(6):831-49.

Besi E, Boniface DR, Cregg R, Zakrzewska JM. Comparison of tolerability and adverse symptoms in oxcarbazepine and carbamazepine in the treatment of trigeminal neuralgia and neuralgiform headaches using the Liverpool Adverse Events Profile (AEP). *J Headache Pain*. 2015;16:563.

Beydoun A. Clinical use of tricyclic anticonvulsants in painful neuropathies and bipolar disorders. *Epilepsy Behav*. 2002;3(3S):S18-22.

Blom S. Trigeminal neuralgia: its treatment with a new anticonvulsant drug (G-32883). *Lancet*. 1962;1(7234):839-40.

Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lanteri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain*. 2005;114(1-2):29-36.

Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, Rostaing S, Lanteri-Minet M, Collin E, Grisart J, Boureau F. Development and validation of the Neuropathic Pain Symptom Inventory. Pain 2004;108(3):248-257.

Bowsher D. Trigeminal neuralgia: an anatomically oriented review. *Clin Anat.* 1997;10(6):409-415.

Brisman R. Microvascular decompression vs. gamma knife radiosurgery for typical trigeminal neuralgia: preliminary findings. *Stereotact Funct Neurosurg*. 2007;85(2-3):94-8.

Broggi G, Franzini A, Lasio G, Giorgi C, Servello D. Long-term results of percutaneous retrogasserian thermorhizotomy for "essential" trigeminal neuralgia: considerations in 1000 consecutive patients. *Neurosurgery.* 1990;26(5):783-7.

Brown JA, Chittum CJ, Sabol D, Gouda JJ. Percutaneous balloon compression of the trigeminal nerve for treatment of trigeminal neuralgia. Neurosurg Focus 1996;1(2):e4; discussion 1 p following e4.

Brown JA, Coursaget C, Preul MC, Sangvai D. Mercury water and cauterizing stones: Nicolas Andre and tic douloureux. J Neurosurg 1999;90(5):977-981.

Burchiel KJ, McCartney S. Trigeminal neuralgia. In: Burchiel K, editor. Surgical management of pain. New York: Thieme, 2015. p. 175-179.

Burchiel KJ. A new classification for facial pain. Neurosurgery 2003;53(5):1164-1166; discussion 1166-1167.

Campbell FG, Graham JG, Zilkha KJ. Clinical trial of carbazepine (tegretol) in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry*. 1966;29(3):265-7.

Casey KF. Role of patient history and physical examination in the diagnosis of trigeminal neuralgia. *Neurosurg Focus*. 2005;18(5):E1.

Cole CD, Liu JK, Apfelbaum RI. Historical perspectives on the diagnosis and treatment of trigeminal neuralgia. *Neurosurg Focus*. 2005;18(5):E4.

Cruccu G, Finnerup NB, Jensen TS, Scholz J, Sindou M, Svensson P, Treede RD, Zakrzewska JM, Nurmikko T. Trigeminal neuralgia: New classification and diagnostic grading for practice and research. *Neurology*. 2016;87(2):220-8.

Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, Nurmikko T, Zakrzewska JM. AAN-EFNS guidelines on trigeminal neuralgia management. *Eur J Neurol*. 2008;15(10):1013-28.

Dandy WE. Concerning the cause of trigeminal neuralgia. *Am J Surg*. 1934;24(2):447-55.

Dandy WE. Operation for cure of tic douloureaux; partial section of the sensory root at the pons. *Arch Surg*. 1929;18:687-734.

Dandy WE. Section of the sensory root of the trigeminal nerveat the pons: preliminary report of the operative procedure. *Bull Johns Hopkins Hosp*. 1925;36:105-6.

Dandy WE. The Treatment of trigeminal neuralgia by the cerebellar route. *Ann Surg*. 1932;96(4):787-95.

Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain 1983;17(2):197-210.

de Andrade DC, Ferreira KA, Nishimura CM, Yeng LT, Batista AF, de Sa K, Araujo J, Stump PR, Kaziyama HH, Galhardoni R, Fonoff ET, Ballester G, Zakka T, Bouhassira D, Teixeira MJ. Psychometric validation of the Portuguese version of the Neuropathic Pain Symptoms Inventory. Health Qual Life Outcomes 2011;9:107.

Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. *Psychol Med*. 1998;28(3):551-8.

Devor M, Amir R, Rappaport ZH. Pathophysiology of trigeminal neuralgia: the ignition hypothesis. Clin J Pain 2002;18(1):4-13.

Diggle P, Diggle PJ, Heagerty P, Heagerty PJ, Liang K-Y, Zeger S, al. e. *Analysis of longitudinal data*. Oxford: Oxford University Press, 2002.

Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, Kerns RD, Stucki G, Allen RR, Bellamy N, Carr DB, Chandler J, Cowan P, Dionne R, Galer BS, Hertz S, Jadad AR, Kramer LD, Manning DC, Martin S, McCormick CG, McDermott MP, McGrath P, Quessy S, Rappaport BA, Robbins W, Robinson JP, Rothman M, Royal MA, Simon L, Stauffer JW, Stein W, Tollett J, Wernicke J, Witter J. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113(1-2):9-19.

Eboli P, Stone JL, Aydin S, Slavin KV. Historical characterization of trigeminal neuralgia. *Neurosurgery*. 2009;64(6):1183-17.

Eller JL, Raslan AM, Burchiel KJ. Trigeminal neuralgia: definition and classification. *Neurosurg Focus*. 2005;18(5):E3.

Erdine S, Ozyalcin NS, Cimen A, Celik M, Talu GK, Disci R. Comparison of pulsed radiofrequency with conventional radiofrequency in the treatment of idiopathic trigeminal neuralgia. *Eur J Pain.* 2007;11(3):309-13.

Ferreira K, de Andrade DC, Teixeira MJ. Development and validation of a Brazilian version of the short-form McGill pain questionnaire (SF-MPQ). *Pain Manag Nurs.* 2013;14(4):210-19.

Ferreira KA, Teixeira MJ, Mendonza TR, Cleeland CS. Validation of brief pain inventory to Brazilian patients with pain. *Support Care Cancer*. 2011;19(4):505-11.

Fields HL. Treatment of trigeminal neuralgia. *N Engl J Med*. 1996;334(17):1125-6.

Fleck MP, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, Pinzon V. [Application of the Portuguese version of the abbreviated instrument of quality life WHOQOL-bref]. Rev Saude Publica 2000;34(2):178-183.

Frigyesi TL, Siegfried J, Broggi G. The selective vulnerability of evoked potentials in the trigeminal sensory root of graded thermocoagulation. *Exp Neurol*. 1975;49(1 Pt 1):11-21.

Gardner WJ, Miklos MV. Response of trigeminal neuralgia to decompression of sensory root; discussion of cause of trigeminal neuralgia. *J Am Med Assoc.* 1959;170(15):1773-6.

Gardner WJ. Concerning the mechanism of trigeminal neuralgia and hemifacial spasm. *J Neurosurg.* 1962;19:947-58.

Graf CJ. Trigeminal compression for tic douloureux: an evaluation. *J Neurosurg*. 1963;20:1029-32.

Gronseth G, Cruccu G, Alksne J, Argoff C, Brainin M, Burchiel K, Nurmikko T, Zakrzewska JM. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. *Neurology*. 2008;71(15):1183-90.

Hakanson S. Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. Neurosurgery 1981;9(6):638-646.

Harden RN, Weinland SR, Remble TA, Houle TT, Colio S, Steedman S, Kee WG. Medication Quantification Scale Version III: update in medication classes and revised detriment weights by survey of American Pain Society Physicians. J Pain 2005;6(6):364-371.

Harris W. An analysis of 1,433 cases of paroxysmal trigeminal neuralgia (trigeminal-tic) and the end-results of gasserian alcohol injection. *Brain*. 1940;63:209-40.

Härtel F. Die Behandlung der Trigeminusneuralgie mit intrakraniellen Alkoholeinspritzungen. *Deutsche Zeitschrift Für Chirurgie*. 1914;126(5-6):429-552.

Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018 Jan;38(1):1-211.

Holland M, Noeller J, Buatti J, He W, Shivapour ET, Hitchon PW. The cost-effectiveness of surgery for trigeminal neuralgia in surgically naive patients: a retrospective study. *Clin Neurol Neurosurg*. 2015;137:34-7.

Huibin Q, Jianxing L, Guangyu H, Dianen F. The treatment of first division idiopathic trigeminal neuralgia with radiofrequency thermocoagulation of the peripheral branches compared to conventional radiofrequency. *J Clin Neurosci.* 2009;16(11):1425-9.

Jannetta PJ. Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. *J Neurosurg*. 1967;26(1):Suppl:159-62.

Jannetta PJ. Microsurgical approach to the trigeminal nerve for tic douloureux. *Prog Neurol Surg*. 1976;7:180-200.

Jones MR, Urits I, Ehrhardt KP, Cefalu JN, Kendrick JB, Park DJ, Cornett EM, Kaye AD, Viswanath O. A comprehensive review of trigeminal neuralgia. *Curr Pain Headache Rep*. 2019;23(10):74.

Kalkanis SN, Eskandar EN, Carter BS, Barker FG, 2nd. Microvascular decompression surgery in the United States, 1996 to 2000: mortality rates, morbidity rates, and the effects of hospital and surgeon volumes. *Neurosurgery*. 2003;52(6):1251-62.

Kanpolat Y, Savas A, Bekar A, Berk C. Percutaneous controlled radiofrequency trigeminal rhizotomy for the treatment of idiopathic trigeminal neuralgia: 25-year experience with 1,600 patients. *Neurosurgery.* 2001;48(3):524-534.

Katusic S, Beard CM, Bergstralh E, Kurland LT. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984. *Ann Neurol*. 1990;27(1):89-95.

Killian JM, Fromm GH. Carbamazepine in the treatment of neuralgia. Use of side effects. *Arch Neurol*. 1968;19(2):129-36.

Kirschner M. Zur elektrochirurgie. *Areh Kiln Clair*. 1963;167:761-8.

Koopman JS, de Vries LM, Dieleman JP, Huygen FJ, Stricker BH, Sturkenboom MC. A nationwide study of three invasive treatments for trigeminal neuralgia. *Pain*. 2011;152(3):507-13.

Kundu B, Rolston JD. Nationwide shift from percutaneous rhizotomy to microvascular decompression for treatment of trigeminal and other cranial nerve neuralgias. *Headache*. 2018;58(10):1675-9.

Letcher FS, Goldring S. The effect of radiofrequency current and heat on peripheral nerve action potential in the cat. *J Neurosurg*. 1968;29(1):42-7.

Lewy F. The first authentic case of major trigeminal neuralgia and some comments on the history of the disease. *Ann Med Hist*. 1938;10:247250.

Lichtor T, Mullan JF. A 10-year follow-up review of percutaneous microcompression of the trigeminal ganglion. *J Neurosurg*. 1990;72(1):49-54.

Liebel JT, Menger N, Langohr H-D. Oxcarbazepine in the treatment of idiopathic trigeminal neuralgia. *Nervenheilkunde*. 2001;20(8):461-5.

Linskey ME, Ratanatharathorn V, Penagaricano J. A prospective cohort study of microvascular decompression and Gamma Knife surgery in patients with trigeminal neuralgia. *J Neurosurg*. 2008;109(Suppl):160-72.

Liu HB, Ma Y, Zou JJ, Li XG. Percutaneous microballoon compression for trigeminal neuralgia. *Chin Med J (Engl)*. 2007;120(3):228-30.

Maarbjerg S, Di Stefano G, Bendtsen L, Cruccu G. Trigeminal neuralgia - diagnosis and treatment. *Cephalalgia.* 2017;37(7):648-57.

MacDonald BK, Cockerell OC, Sander JW, Shorvon SD. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain.* 2000;123 (Pt 4):665-76.

McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. *BMJ*. 1995;311(7012):1047-52.

Melzack R. The short-form McGill Pain Questionnaire. *Pain*. 1987;30(2):191-7.

Montano N, Conforti G, Di Bonaventura R, Meglio M, Fernandez E, Papacci F. Advances in diagnosis and treatment of trigeminal neuralgia. *Ther Clin Risk Manag*. 2015;11:289-299.

Mullan S, Lichtor T. Percutaneous microcompression of the trigeminal ganglion for trigeminal neuralgia. *J Neurosurg*. 1983;59(6):1007-12.

Nicol CF. A four year double-blind study of tegretol in facial pain. *Headache*. 1969;9(1):54-57.

Noorani I, Lodge A, Vajramani G, Sparrow O. Comparing Percutaneous Treatments of Trigeminal Neuralgia: 19 Years of Experience in a Single Centre. *Stereotact Funct Neurosurg*. 2016;94(2):75-85.

Nurmikko TJ, Eldridge PR. Trigeminal neuralgia--pathophysiology, diagnosis and current treatment. *Br J Anaesth*. 2001;87(1):117-32.

Obermann M, Katsarava Z. Update on trigeminal neuralgia. Expert Rev Neurother 2009;9(3):323-329.

Pais-Ribeiro J, Silva I, Ferreira T, Martins A, Meneses R, Baltar M. Validation study of a Portuguese version of the Hospital Anxiety and Depression Scale. *Psychol Health Med* 2007;12(2):225-37.

Patel SK, Liu JK. Overview and history of trigeminal neuralgia. *Neurosurg Clin N Am*. 2016;27(3):265-76.

Pearce JMS. John Locke and the trigeminal neuralgia of the Countess of Northumberland. *J Neurol Neurosurg Psychiatry*. 1993;56(1):45.

Pollock BE, Schoeberl KA. Prospective comparison of posterior fossa exploration and stereotactic radiosurgery dorsal root entry zone target as primary surgery for patients with idiopathic trigeminal neuralgia. *Neurosurgery*. 2010;67(3):633-9.

Pollock LJ, Potter HE. Experimental studies of injection of the gasserian ganglion controlled by fluoroscopy. *JAMA*. 1916;67:1357-61.

Putnam TJ, Hampton AO. A technic of injection into the gasserian ganglion under roentgenographic control. Arch Neurol Psychiat 1936;35:92-98.

Rasmussen P, Riishede J. Facial pain treated with carbamazepin (Tegretol). *Acta Neurol Scand*. 1970;46(4):385-408.

Rocha R de O, Teixeira MJ, Yeng LT, Cantara MG, Faria VG, Liggieri V, Loduca A, Muller BM, Souza AC, de Andrade DC. Thoracic sympathetic block for the treatment of complex regional pain syndrome type I: a double-blind randomized controlled study. *Pain*. 2014;155(11):2274-81.

Rockliff BW, Davis EH. Controlled sequential trials of carbamazepine in trigeminal neuralgia. *Arch Neurol*. 1966;15(2):129-36.

Rose FC. Trigeminal neuralgia. *Arch Neurol.* 1999;56(9):1163-4.

Rutten-van Molken MP, van Doorslaer EK, van Vliet RC. Statistical analysis of cost outcomes in a randomized controlled clinical trial. Health Econ 1994;3(5):333-345.

Santos JG, Brito JO, de Andrade DC, Kaziyama VM, Ferreira KA, Souza I, Teixeira MJ, Bouhassira D, Baptista AF. Translation to Portuguese and validation of the Douleur Neuropathique 4 questionnaire. *J Pain*. 2010;11(5):484-90.

Schurmann K, Butz M, Brock M. Temporal retrogasserian resection of trigeminal root versus controlled elective percutaneous electrocoagulation of the ganglion of gasser in the treatment of trigeminal neuralgia. Report on a series of 531 cases. *Acta Neurochir (Wien)*. 1972;26(1):33-53.

Sehn F, Chachamovich E, Vidor LP, Dall-Agnol L, de Souza IC, Torres IL, Fregni F, Caumo W. Cross-cultural adaptation and validation of the Brazilian Portuguese version of the pain catastrophizing scale. *Pain Med*. 2012;13(11):1425-35.

Sengupta RP, Stunden RJ. Radiofrequency thermocoagulation of Gasserian ganglion and its rootlets for trigeminal neuralgia. *Br Med J.* 1977;1(6054):142-3.

Shelden CH, Crue BL, Coulter JA. Surgical treatment of trigeminal neuralgia and discussion of compression operation. *Postgrad Med* .1960;27:595-601.

Shelden CH, Pudenz RH, Freshwater DB, Crue BL. Compression rather than decompression for trigeminal neuralgia. *J Neurosur.g* 1955;12(2):123-6.

Siqueira SR, Alves B, Malpartida HM, Teixeira MJ, Siqueira JT. Abnormal expression of voltage-gated sodium channels Nav1.7, Nav1.3 and Nav1.8 in trigeminal neuralgia. *Neuroscience*. 2009;164(2):573-77.

Skirving DJ, Dan NG. A 20-year review of percutaneous balloon compression of the trigeminal ganglion. *J Neurosurg.* 2001;94(6):913-7.

Spatz AL, Zakrzewska JM, Kay EJ. Decision analysis of medical and surgical treatments for trigeminal neuralgia: how patient evaluations of benefits and risks affect the utility of treatment decisions. *Pain*. 2007;131(3):302-10.

Stookey B, Ransohoff J. Trigeminal neuralgia. In: Its history and treatment. Springfield: Charles C Thomas; 1959.

Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment* 1995;7(4):524-32.

Sweet WG. Proceedings: Analgesia dolorosa after differential retrogasserian thermal or mechanical rhizotomy: tactics employed to decrease its influence. *J Neurol Neurosurg Psychiatry*. 1975;38(4):407.

Sweet WH, Wepsic JG. Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers. 1. Trigeminal neuralgia. *J Neurosurg* 1974;40(2):143-56.

Taarnhøj P. Decompression of the trigeminal root. *J Neurosurg*. 1954;11(3):299-305.

Taarnhøj P. Trigeminal neuralgia and decompression of the trigeminal root. *Surg Clin North Am*. 1956:1145-57.

Taha JM, Tew JM, Jr. Comparison of surgical treatments for trigeminal neuralgia: reevaluation of radiofrequency rhizotomy. *Neurosurgery.* 1996;38(5):865-71.

Tatli M, Satici O, Kanpolat Y, Sindou M. Various surgical modalities for trigeminal neuralgia: literature study of respective long-term outcomes. *Acta Neurochir (Wien).* 2008;150(3):243-55.

Taylor JC, Brauer S, Espir ML. Long-term treatment of trigeminal neuralgia with carbamazepine. Postgrad Med J 1981;57(663):16-18.

Teixeira MJ, Siqueira SR, Almeida GM. Percutaneous radiofrequency rhizotomy and neurovascular decompression of the trigeminal nerve for the treatment of facial pain. *Arq Neuropsiquiatr*. 2006;64(4):983-9.

Teixeira MJ. Descompressão discal vascular no nervo trigêmeo no tratamento das algias faciais. 1984 (Mestrado em Ciências) - Faculdade de Medicina, Universidade de São Paulo; 1984.

Tew JM, Jr., Keller JT. The treatment of trigeminal neuralgia by percutaneous radiofrequency technique. *Clin Neurosurg*. 1977;24:557-8.

Tew JM, Jr., Taha JM. Percutaneous rhizotomy in the treatment of intractable facial pain (trigeminal, glossopharyngeal, and vagal nerves). In: Schmidek H, Sweet WG, editors. *Operative neurosurgical techniques*: indications, methods and results. Philadelphia: WB Saunders, 1996. p. 1409-1418.

Texakalidis P, Xenos D, Tora MS, Wetzel JS, Boulis NM. Comparative safety and efficacy of percutaneous approaches for the treatment of trigeminal neuralgia: A systematic review and meta-analysis. *Clin Neurol Neurosurg*. 2019;182:112-22.

Tibano AT, de Siqueira SR, da Nobrega JC, Teixeira MJ. Cardiovascular response during trigeminal ganglion compression for trigeminal neuralgia according to the use of local anesthetics. *Acta Neurochir (Wien)*. 2010;152(8):1347-51.

Tronnier VM, Rasche D, Hamer J, Kienle AL, Kunze S. Treatment of idiopathic trigeminal neuralgia: comparison of long-term outcome after radiofrequency rhizotomy and microvascular decompression. *Neurosurgery*. 2001;48(6):1261-8.

Tubbs RS, Loukas M, Shoja MM, Cohen-Gadol AA. John Murray Carnochan (1817-1887): the first description of successful surgery for trigeminal neuralgia. *J Neurosurg*. 2010;112(1):199-201.

van Kleef M, van Genderen WE, Narouze S, Nurmikko TJ, van Zundert J, Geurts JW, Mekhail N. 1. Trigeminal neuralgia. *Pain Pract.* 2009;9(4):252-9.

Wang DD, Raygor KP, Cage TA, Ward MM, Westcott S, Barbaro NM, Chang EF. Prospective comparison of long-term pain relief rates after first-time microvascular decompression and stereotactic radiosurgery for trigeminal neuralgia. *J Neurosurg.* 2018;128(1):68-77.

White JC, Sweet WH. *Pain and the neurosurgeon:* a forty year experience. Springfield: Charles C Thomas, 1969.

Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2014(4):CD005451.

Wilkins R. Trigeminal neuralgia: historical overview, with emphasis on surgical treatment. In: Burchiel K, editor. *Surgical management of pain*. New York: Thieme; 2002. p. 288-301.

Yao P, Deng YY, Hong T, Wang ZB, Ma JM, Zhu YQ, Li HX, Ding YY, Pan SN. Radiofrequency thermocoagulation for V2/V3 idiopathic trigeminal neuralgia: effect of treatment temperatures on long-term clinical outcomes: A Cohort Study. *Medicine (Baltimore)*. 2016;95(26):e4019.

Zakrzewska JM, Akram H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. *Cochrane Database Syst Rev.* 2011(9):CD007312.

Zakrzewska JM, Linskey ME. Trigeminal neuralgia. In: Zakrzewska JM, editor. *Orofacial pain*. Oxford: Oxford University Press; 2009.

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67(6):361-370

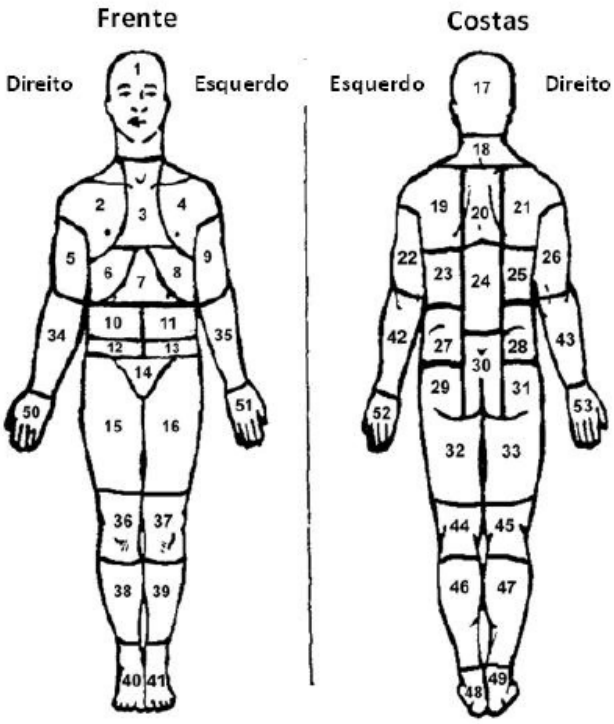
APPENDIX

Appendix A - Brief Pain Inventory

1) Durante a vida, a maioria das pessoas apresenta dor de vez em quando (dor de cabeça, dor de dente, etc.). Você teve hoje, dor diferente dessas?

1.Sim ☐ 2.Não ☐

2) Marque sobre o diagrama, com um X, as áreas onde você sente dor, e onde a dor é mais intensa.



3)Circule o número que melhor descreve a pior dor que você sentiu nas últimas 24 horas.

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

4) Circule o número que melhor descreve a dor mais fraca que você sentiu nas últimas 24 horas.

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

5) Circule o número que melhor descreve a média da sua dor.

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

6) Circule o número que mostra quanta dor você está sentindo agora (neste momento).

Sem dor O 1 2 3 4 5 6 7 8 9 10 Pior dor possível

7) Quais tratamentos ou medicações você está recebendo para dor?

Nome	Dose/ Freqüência	Data de Início

8) Nas últimas 24 horas, qual a intensidade da melhora proporcionada pelos tratamentos ou medicações que você está usando?

Circule o percentual que melhor representa o alívio que você obteve.

Sem alívio | 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% | alívio completo

9) Circule o número que melhor descreve como, nas últimas 24 horas, a dor interferiu na sua:

Atividade geral

Não interferiu | 0 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

Humor

Não interferiu | 0 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

Habilidade de caminhar

Não interferiu | 0 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

Trabalho

Não interferiu | 0 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

Relacionamento com outras pessoas

Não interferiu | 0 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

Sono

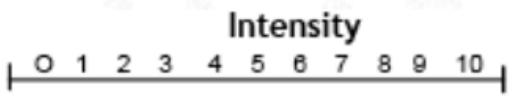
Não interferiu | 0 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

Habilidade para apreciar a vida

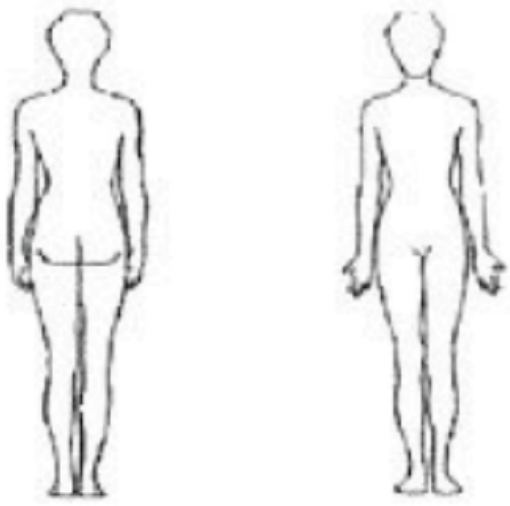
Não interferiu | 0 1 2 3 4 5 6 7 8 9 10 | interferiu completamente

Appendix B - McGill Pain Questionnaire Short-Form

Dimensão Sensitiva	Presente	Ausente
Latejante		
Pontada		
Choque		
Fina/agulhada		
Fisgada		
Queimação		
Espalha		
Dolorida		
Dimensão Afetiva		
Cansativa		
Enjoada		
Sufocante		
Apavorante		
Aborrecida		
Dimensão Avaliativa		
Que incomoda		
Insuportável		



Intensidade da dor



Localização da dor (marcar a localização)

Appendix C - Douleur Neuropatique 4

Por favor, nas quatro perguntas abaixo, complete o questionário marcando uma resposta para cada número:

ENTREVISTA DO PACIENTE

Questão 1: A sua dor tem uma ou mais das seguintes características?

	Sim	Não
1- Queimação		
2- Sensação de frio dolorosa		
3- Choque elétrico		

Questão 2: Há presença de um ou mais dos seguintes sintomas na mesma área da sua dor?

	Sim	Não
4- Formigamento		
5- Alfinetada e agulhada		
6- Adormecimento		
7- Coceira		

EXAME DO PACIENTE

Questão 3: A dor está localizada numa área onde o exame físico pode revelar uma ou mais das seguintes características?

	Sim	Não
8- Hipoestesia ao toque		
9- Hipoestesia a picada de agulha		

Questão 4: Na área dolorosa a dor pode ser causada ou aumentada por:

	Sim	Não
10- Escovação		

Appendix D - Neuropathic Pain Symptom Inventory

Você tem sofrido de dor devido a lesões ou doença do sistema nervoso. Esta dor pode ser de diversos tipos. Você pode ter dor espontânea, ex: dor na ausência de qualquer estímulo, que pode ser duradoura ou ocorrer em ataques breves. Você pode também ter dor provocada ou aumentada por leve toque, pressão, ou contacto com o frio na área dolorosa. Você pode sentir um ou mais tipos de dor. Este questionário foi desenvolvido para ajudar o seu médico a melhor avaliar e tratar diferentes tipos de dor que possa sentir.

*Nós queremos saber se você sente dor espontânea, isto é dor sem qualquer estímulo. Para cada das seguintes questões, por favor seleccione o número que melhor descreve a sua **gravidade média da dor espontânea durante as últimas 24 horas**. Seleccione o número 0 se você não sentiu tal dor (circule um número apenas).*

Q1. A sua dor dá a sensação de queimadura?

Não queima	0	1	2	3	4	5	6	7	8	9	10	A pior queimadura imaginável

Q2. A sua dor dá a sensação de apertar?

Não aperta	0	1	2	3	4	5	6	7	8	9	10	Aperta o pior imaginável

Q3. A sua dor dá a sensação de pressão?

Sem pressão	0	1	2	3	4	5	6	7	8	9	10	A pior pressão imaginável

Q4. **Durante as últimas 24 horas**, a sua dor espontânea tem estado presente:
Seleccione a resposta que melhor descreve o seu caso

Permanentemente	☐
Entre 8 e 12 horas	☐
Entre 4 e 7 horas	☐
Entre 1 e 3 horas	☐
Menos que 1 hora	☐

*Nós queremos saber se você teve ataques breves de dor. Para cada das seguintes questões, por favor seleccione o número que melhor descreve a **gravidade média dos seus ataques de dor durante as últimas 24 horas**. Seleccione o número 0 se você não sentiu tal dor (circule um número apenas).*

Q5. A sua dor dá a sensação de choque eléctrico?

Sem choque eléctrico	0	1	2	3	4	5	6	7	8	9	10	O pior choque eléctrico imaginável

Q6. A sua dor dá a sensação de apunhalar?

Sem punhalada	0	1	2	3	4	5	6	7	8	9	10 A pior punhalada imaginável

Q7. **Durante as últimas 24 horas**, quantos destes ataques de dor teve?

Seleccione a resposta que melhor descreve o seu caso

Mais de 20 ☐
Entre 11 e 20 ☐
Entre 6 e 10 ☐
Entre 1 e 5 ☐
Sem ataque de dor ☐

*Nós queremos saber se você sente dor provocada ou aumentada por leve toque, pressão, contacto com frio na área onde dói. Para cada das seguintes questões, por favor seleccione o número que melhor descreve a **gravidade média da dor provocada durante as últimas 24 horas**. Seleccione o número 0 se você não sentiu tal dor (circule um número apenas).*

Q8. A sua dor é provocada ou aumentada por um leve toque na área dolorosa?

Sem dor	0	1	2	3	4	5	6	7	8	9	10 A pior dor imaginável

Q9. A sua dor é provocada ou aumentada por pressão na área dolorosa?

Sem dor	0	1	2	3	4	5	6	7	8	9	10 A pior dor imaginável

Q10. A sua dor é provocada ou aumentada por contacto com algo frio na área dolorosa?

Sem dor	0	1	2	3	4	5	6	7	8	9	10 A pior dor imaginável

*Nós queremos saber se você sente sensações anormais **na zona onde dói**. Para cada das seguintes questões, por favor seleccione o número que melhor descreve a **gravidade média das sensações anormais durante as últimas 24 horas**. Seleccione o número 0 se você não sentiu tal dor (circule um número apenas).*

Q11. Sente alfinetes e agulhas?

Sem alfinetes nem agulhas	0	1	2	3	4	5	6	7	8	9	10 Os piores alfinetes e agulhas imagináveis

Q12. Sente dormente?

Sem dormência	0	1	2	3	4	5	6	7	8	9	10 O mais dormente imaginável

Appendix E - World Health Organization Quality of Life Brief-Form

Instruções:

Este questionário é sobre como você se sente a respeito de sua qualidade de vida, saúde e outras áreas de sua vida. **Por favor responda a todas as questões**. Se você não tem certeza sobre que resposta dar em uma questão, por favor, escolha entre as alternativas a que lhe parece mais apropriada. Esta, muitas vezes, poderá ser a sua primeira escolha.

Por favor, tenha em mente seus valores, aspirações, prazeres e preocupações. Nós estamos perguntando o que você acha de sua vida, tomando como referência as **duas últimas semanas**. Por exemplo, pensando nas duas últimas semanas, uma questão poderia ser:

Você recebe dos outros o apoio que necessita?

Nada	Muito pouco	Médio	Muito	Completamente
1	2	3	4	5

Você deve circular o número que melhor corresponde ao quanto você recebe dos outros o apoio que necessitou nestas duas últimas semanas. Portanto, você deve circular o número 4 se recebeu "muito" apoio. Você deve circular o número 1 se você não recebeu "nada" de apoio.

Por favor, leia cada questão, veja o que você acha e circule no número que lhe parece a melhor resposta.

1.Como você avaliaria a sua qualidade de vida?

Muito ruim	Ruim	Nem ruim nem boa	Boa	Muito boa
1	2	3	4	5

2.Quão satisfeito você está com sua saúde?

Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
1	2	3	4	5

As questões seguintes são sobre o quanto você tem sentido algumas coisas nas últimas duas semanas.

3.Em que medida você acha que sua dor (física) impede você de fazer o que você precisa?

Nada	Muito pouco	Mais ou menos	Bastante	Extremamente
1	2	3	4	5

4.O quanto você precisa de algum tratamento médico para levar a sua vida diária?

Nada	Muito pouco	Mais ou menos	Bastante	Extremamente
1	2	3	4	5

5.O quanto você aproveita a vida?

Nada	Muito pouco	Mais ou menos	Bastante	Extremamente
1	2	3	4	5

6.Em que medida você acha que sua vida tem sentido?

Nada	Muito pouco	Mais ou menos	Bastante	Extremamente
1	2	3	4	5

7.Quanto você consegue se concentrar?

Nada	Muito pouco	Mais ou menos	Bastante	Extremamente
1	2	3	4	5

8.Quão seguro você se sente em sua vida diária?

Nada	Muito pouco	Mais ou menos	Bastante	Extremamente
1	2	3	4	5

9.Quão saudável é o seu ambiente físico?

Nada	Muito pouco	Mais ou menos	Bastante	Extremamente
1	2	3	4	5

As questões seguintes perguntam sobre quão completamente você tem sentido ou é capaz de fazer certas coisas nas últimas duas semanas.

10.Você tem energia suficiente para o seu dia-a-dia?

Nada	Muito pouco	Médio	Muito	Completamente
1	2	3	4	5

11.Você é capaz de aceitar a sua aparência física?

Nada	Muito pouco	Médio	Muito	Completamente
1	2	3	4	5

12.Você tem dinheiro suficiente para satisfazer suas necessidades?

Nada	Muito pouco	Médio	Muito	Completamente
1	2	3	4	5

13.Quão disponíveis estão para você as informações que precisa no seu dia-a-dia?

Nada	Muito pouco	Médio	Muito	Completamente
1	2	3	4	5

14.Em que medida você tem oportunidade de atividades de lazer?

Nada	Muito pouco	Médio	Muito	Completamente
1	2	3	4	5

As questões seguintes perguntam sobre quão satisfeito você se sentiu a respeito de vários aspectos de sua vida nas últimas duas semanas.

15.Quão bem você é capaz de se locomover?

Muito ruim	Ruim	Nem ruim nem bem	Bem	Muito bem
1	2	3	4	5

16.Quão satisfeita você está com seu sono?

Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
1	2	3	4	5

17.Quão satisfeita você está com a sua capacidade de desempenhar as atividades do seu dia-a-dia?

Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
1	2	3	4	5

18.Quão satisfeito você está com a sua capacidade para o trabalho?

Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
1	2	3	4	5

19.Quão satisfeito(a) você está consigo mesmo?

Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
1	2	3	4	5

20.Quão satisfeito você está com suas relações pessoais (amigos, parentes, conhecidos, colegas)?

Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
1	2	3	4	5

21.Quão satisfeito você está com a sua vida sexual

Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
1	2	3	4	5

22.Quão satisfeito você está com o apoio que você recebe de seus amigos?

Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
1	2	3	4	5

23.Quão satisfeita você está com as condições do local onde mora?

Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
1	2	3	4	5

24.Quão satisfeita você está com seu acesso aos serviços de saúde?

Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
1	2	3	4	5

25.Quão satisfeita você está com o seu meio de transporte?

Muito insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito satisfeito
1	2	3	4	5

As questões seguintes referem-se a com que frequência você sentiu ou experimentou certas coisas nas últimas duas semanas.

26.Com que frequência você tem sentimentos negativos tais como mau humor, desespero, ansiedade, depressão?

Nunca	Algumas vezes	Freqüentemente	Muito freqüentemente	Sempre
1	2	3	4	5

Appendix F - Pain Catastrophizing Scale

Toda a gente passa por situações de dor em certos momentos da sua vida. Estas experiências podem incluir dores de cabeça, dores de dentes, dores articulares ou dores musculares. As pessoas estão muitas vezes expostas a situações que podem causar dor, tais como doenças, ferimentos, intervenções de dentista ou cirurgias.
Queremos conhecer os pensamentos e sentimentos que tem quando está a sentir dores. Em baixo encontra-se uma lista com treze afirmações que descrevem diferentes pensamentos e sentimentos que podem estar associados à dor. Usando a escala seguinte, por favor indique em que medida tem estes pensamentos e sentimentos quando está com dores.

0 – nunca **1** – ligeiramente **2** – moderadamente **3** – bastante **4** – sempre

Quando estou com dores …

1 ☐	Estou constantemente preocupado(a) em saber se a dor terá fim.
2 ☐	Sinto que não consigo continuar.
3 ☐	É terrível e penso que nunca mais vai melhorar.
4 ☐	É horrível e sinto que me ultrapassa completamente.
5 ☐	Sinto que já não aguento mais.
6 ☐	Fico com medo que a dor piore.
7 ☐	Estou sempre a pensar noutras situações dolorosas.
8 ☐	Quero ansiosamente que a dor desapareça.
9 ☐	Não consigo deixar de pensar nisso.
10 ☐	Estou sempre a pensar no quanto dói.
11 ☐	Estou sempre a pensar que quero muito que a dor passe.
12 ☐	Não há nada que eu possa fazer para reduzir a intensidade da dor.
13 ☐	Pergunto -me se poderá acontecer algo grave.

…Total

Appendix G - Hospital Anxiety and Depression Scale

ESCALA HOSPITLAR DE ANSIEDADE E DEPRESSÃO (HAD)	
ANSIEDADE	DEPRESSÃO
1) Eu me sinto tenso ou contraído: 3 ( ) A maior parte do tempo 2 ( ) Boa parte do tempo 1 ( ) De vez em quando 0 ( ) Nunca	2) Eu ainda sinto gosto pelas mesmas coisas de antes: 0 ( ) Sim, do mesmo jeito que antes 1 ( ) Não tanto quanto antes 2 ( ) Só um pouco 3 ( ) Já não sinto mais prazer em nada
3) Eu sinto uma espécie de medo, como se alguma coisa ruim fosse acontecer: 3 ( ) Sim, e de um jeito muito forte 2 ( ) Sim, mas não tão forte 1 ( ) Um pouco, mas isso não me preocupa 0 ( ) Não sinto nada disso	4) Dou risada e me divirto quando vejo coisas engraçadas: 0 ( ) Do mesmo jeito que antes 1 ( ) Atualmente um pouco menos 2 ( ) Atualmente bem menos 3 ( ) Não consigo mais
5) Estou com a cabeça cheia de preocupações: 3 ( ) A maior parte do tempo 2 ( ) Boa parte do tempo 1 ( ) De vez em quando 0 ( ) Raramente	6) Eu me sinto alegre: 3 ( ) Nunca 2 ( ) Poucas vezes 1 ( ) Muitas vezes 0 ( ) A maior parte do tempo
7) Consigo ficar sentado à vontade e me sentir relaxado: 0 ( ) Sim, quase sempre 1 ( ) Muitas vezes 2 ( ) Poucas vezes 3 ( ) Nunca	8) Eu estou lento para pensar e fazer as coisas: 3 ( ) Quase sempre 2 ( ) Muitas vezes 1 ( ) De vez em quando 0 ( ) Nunca
9) Eu tenho uma sensação ruim de medo, como um frio na barriga ou um aperto no estômago: 0 ( ) Nunca 1 ( ) De vez em quando 2 ( ) Muitas vezes 3 ( ) Quase sempre	10) Eu perdi o interesse em cuidar da minha aparência: 3 ( ) Completamente 2 ( ) Não estou mais me cuidando como deveria 1 ( ) Talvez não tanto quanto antes 0 ( ) Me cuido do mesmo jeito que antes
11) Eu me sinto inquieto, como se eu não pudesse ficar parado em lugar nenhum: 3 ( ) Sim, demais 2 ( ) Bastante 1 ( ) Um pouco 0 ( ) Não me sinto assim	12) Fico esperando animado as coisas boas que estão por vir: 0 ( ) Do mesmo jeito que antes 1 ( ) Um pouco menos do que antes 2 ( ) Bem menos do que antes 3 ( ) Quase nunca
13) De repente, tenho a sensação de entrar em Pânico: 3 ( ) A quase todo momento 2 ( ) Várias vezes 1 ( ) De vez em quando 0 ( ) Não sinto isso	14) Consigo sentir prazer quando assisto a um bom programa de televisão, de rádio ou quando leio alguma coisa: 0 ( ) Quase sempre 1 ( ) Várias vezes 2 ( ) Poucas vezes 3 ( ) Quase nunca
ESCORE ANSIEDADE:	ESCORE DEPRESSÃO:

Appendix H - Global Impression of Change

Impressão Clínica Global - ICG (versão do paciente)
Após o tratamento eu estou:

☐ 1) muito melhor;

☐ 2) melhor;

☐ 3) ligeiramente melhor;

☐ 4) sem alterações;

☐ 5) ligeiramente pior;

☐ 6) pior;

☐ 7) muito pior.

Impressão Clínica Global (versão do avaliador)
Após o tratamento, o paciente está:

☐ 1) muito melhor;

☐ 2) melhor;

☐ 3) ligeiramente melhor;

☐ 4) sem alterações;

☐ 5) ligeiramente pior;

☐ 6) pior;

☐ 7) muito pior.