Pain Medicine, 24(3), 2023, 234–243
https://doi.org/10.1093/pm/pnac132
Advance Access Publication Date: 27 August 2022
Original Research Article

OXFORD

HEADACHE & FACIAL PAIN SECTION

Percutaneous Radiofrequency Ablation for Trigeminal Neuralgia Management: A Randomized, Double-Blinded, Sham-Controlled Clinical Trial

André Marques Mansano, MD, PhD,* Thiago Nouer Frederico, MD,† Raquel Elisa B. Valentin,‡ Maria Jose Carvalho Carmona, MD, PhD,* Hazem Adel Ashmawi, MD, PhD*

*Anesthesiology Department, Faculdade de Medicina da Universidade de São Paulo, São Paulo, SP, Brazil; †Interventional Pain Management, Hospita Israelita Albert Einstein, São Paulo, SP, Brazil; and ‡Pontifícia Universidade Católica de Campinas, São Paulo, SP, Brazil

Correspondence to: André Marques Mansano, MD, PhD, Anesthesiology Department, Faculdade de Medicina da Universidade de São Paulo, Rua Joaquim Antunes, 479 ap 03, São Paulo, SP 05415011, Brazil. Tel: +5511986537000; E-mail: andremarquesmansano@gmail.com.

Funding sources: No funding.

Conflicts of interest: There are no conflicts of interest to report.

Human Subjects and Animals: Comitê de Ética em Pesquisa da Universidade de São Paulo, 55375616.7.0000.0065.

Clinical Trial Registry: https://ensaiosclinicos.gov.br/rg/RBR-3w29vx/.

Enrollment began April 5, 2020.

Received on 25 May 2022; revised on 19 August 2022; Accepted on 22 August 2022

Abstract

Trigeminal neuralgia, considered by many the worst pain that humankind can experience, has been called "the suicide disease." Neuroablative procedures are good options when conservative treatment fails to promote pain relief or in those whose side effects are unbearable.

The objective was to compare the effectiveness and safety of trigeminal percutaneous radiofrequency ablation in classical refractory trigeminal neuralgia in a prospective, randomized, double-blind, sham-controlled clinical trial. We included 30 consecutive patients with classical trigeminal neuralgia who had failed to respond to drug treatment. The patients were randomly assigned into two groups: a thermal radiofrequency and a sham group. The thermal radiofrequency group were submitted to a 75°C lesion for 60 seconds after proper sensory and motor stimulation. All steps were carried out in the sham group except the thermal lesion. Patients were evaluated using the Numerical Rating Scale (NRS), the 36-Item Short-Form Health Survey questionnaire, and anticonvulsant dose.

After 1 month, the mean NRS score decreased from 9.2 to 0.7 in the radiofrequency group and from 8.9 to 5.8 in the sham group. This significant reduction was measurable starting at day one after the procedure and remained significant throughout the first month. Changing groups was allowed after one month, after which the pain reduction was similar between the two groups. Percutaneous trigeminal radiofrequency ablation results in statistically and clinically significant greater pain relief than the sham procedure after 1 month of follow-up. These results support using radiofrequency nerve ablation as a treatment for refractory trigeminal neuralgia.

Key Words: Trigeminal; Neuralgia; Ablation; Radiofrequency; Percutaneous

Introduction

Trigeminal neuralgia (TN) is considered by many the worst pain humans can experience and has been called "the suicide disease." The disease is characterized by paroxysmal episodes of shock-like facial pain, usually unilateral, occurring in one or more trigeminal divisions,

frequently elicited by innocuous stimuli [1]. The cornerstone of conservative treatment is anticonvulsants, especially sodium channel blockers such as carbamazepine and oxcarbazepine, leading to pain relief in nearly 90% of patients [2]. Unfortunately, the incidence of side effects is high, and nearly 30% of patients need to discontinue or decrease doses due to unpleasant reactions [3]. Interventional management is an option for refractory patients. Examples include botulinum toxin intradermal infiltration, percutaneous radiofrequency or balloon compression ablation [4], gamma-knife surgery [5], or surgical microvascular decompression [6]. A small-gauge needle can be introduced into Meckel's cave in percutaneous radiofrequency ablation, allowing selective ablation of trigeminal divisions. The technique is used worldwide, although its level of evidence is still weak [7]. In a large but noncomparative series, Kanpolat et al. showed a 96% efficacy rate right after the procedure [8]. In this trial, we evaluated the efficacy of percutaneous radiofrequency ablation in trigeminal neuralgia management using a double-blind, randomized, controlled trial with a sham group.

Methods

Study Design

This trial was a sham-controlled, double-blind, randomized trial, previously registered at the Brazilian Registry of Clinical Trials (ReBEC—Registration Number: RBR-3w29vx). All participants were adequately informed of the study protocol and signed written informed consent to take part in the trial. The primary outcome was to determine the difference between groups in mean scores for the reduction of pain using the Numerical Rating Scale (NRS) during the study protocol period. Participants were evaluated at the following time points: before the procedure, each week after the procedure in the first two months, and once a month for the next ten months. The primary endpoint was pain intensity at one month, after one month all patients were allowed to change groups. The total study period was 12 months. The secondary outcomes determined the differences between groups in quality of life, physical functioning, and anticonvulsant consumption across one year. This study was explicitly limited to refractory classical trigeminal neuralgia [9]. After 1 month, we allowed the patients to move to the other arm of the study, keeping the patient and the evaluator blinded.

Participants

Inclusion Criteria

- Patient aged 50 years or more, presenting trigeminal neuralgia, characterized by recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli.
- Refractory disease, defined as severe pain (NRS >7) with the maximum dose of anticonvulsants or presence of severe side effects.
- V2 or V3 division involvement.
- Pain for more than 6 months
- The diagnosis of trigeminal neuralgia was established according to the International Classification of Headache Disorders [10].

Exclusion Criteria

Patients presenting secondary trigeminal neuralgia (i.e., multiple sclerosis), secondary trigeminal neuropathy (i.e., post-dental procedure nerve injury or post-herpetic neuralgia), and V1 involvement due to the risk of radiofrequency-induced corneal hypoesthesia; use of anticoagulants or antiplatelet agent, except acetylsalicylic acid; infection at the site of needle entry or systemic infection; and psychiatric disorders, except stable depression and/or anxiety.

Randomization and Blinding

Participants were randomized using the www.randomizer.org website, which generated a random sequence and allocation. After 1 month, due to ethical and moral issues, all patients were allowed to change groups. Participants, the pain interventionist, and health care professionals in charge of the follow-up were blinded and remained so throughout the entire study period.

Procedures

All participants received intravenous (IV) sedation (midazolam, fentanyl, and propofol) and skin infiltration with 2% lidocaine at the needle entry point. The *foramen ovale* was identified using fluoroscopic submental view; then a 20G, 10 cm, 5 mm active tip radiofrequency was placed inside Meckel's cave in a coaxial approach. At this moment, all patients were awakened to allow proper sensory and motor stimulation. After adequate needle position confirmation near the affected division, the patients were deeply sedated, and the sealed randomization envelope was opened after the operator left the room. In the radiofrequency group, at 75°C, 60 seconds of thermal radiofrequency was applied. The needle was left in place for 60 seconds in the sham group, after which it was removed. No local anesthetic was injected into Meckel's cave in any group. Additional analgesics were allowed for participants' comfort after the procedure. The same physician (AMS) performed all procedures.

Outcomes

Participants were assessed at baseline (day of the procedure), day 1 after the procedure, weekly during the first 2 months, and monthly during the first year after the procedure. The regimen of anticonvulsants was modified when appropriate during the study period.

All complications and adverse events during the procedure and until the last follow-up were reported. The primary objective was to determine the difference between groups in mean reduction of the NRS score during the first month, after which patients were allowed to change groups if they so desired. The NRS score ranged from 0 (no pain) to 10 (worst pain possible). We defined clinically relevant pain relief as a decrease of 2 points on the NRS from baseline in each group. The secondary outcomes were to compare the groups for quality of life and physical functioning. We measured quality of life using the 36-Item Short-Form Health Survey questionnaire (SF-36) [11], which consists of eight scales yielding two summary measures: physical and mental health. Higher scores indicate better health status, while a mean score of 50 is defined as a normative value for all scales; the Brazilian Portuguese validated questionnaire was used [12]. Anticonvulsant consumption was also evaluated in the time frame.

Statistical Analysis

Analyses were performed using R, version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). We defined P values $<.05$ as indicating statistical significance. G*Power was used to calculate the sample size. Based on a difference of at least 1.5 points on the NRS of 11 points (0 to 10), with a standard deviation of 2.0, balanced distribution between the groups ($r\_ = 1$), with 13 repeated measures (follow-ups) of the outcome, assuming a correlation coefficient between the repeated measures of 0.3 and taking 20% dropout, the equation described above suggested 24 individuals in total (12 in each group), at least, to ensure a significance level of 5% ($\alpha = 0.05$) and statistical power of 80% ($\beta = 0.2$; $1 - \beta = 0.8$; $0.8 \times 100 = 80\%$). To be more conservative and increase the probability of reaching the abovementioned level of significance and statistical power, considering the possibility of unexpected setbacks during the study, we included 30 patients, 15 in each group.

Analysis was by intention to treat—that is, we analyzed patients based on their initial treatment assignment. We used a mixed modeling approach to analyze our primary endpoint (the difference between groups in mean reduction of NRS score during the 12-month follow-up) and secondary endpoints (the difference between groups in mean increase of SF-36 during the 12-month follow-up). Using the custom hypothesis test command in R, we derived tests directly from the mixed model for differences between the groups at specific time points. A mixed model analysis makes use of all available data for each participant, thereby accounting for data missing at random. We used a first-order autoregressive covariance structure to model the repeated measurements. A Cox regression analysis was employed to determine the extent to which patients achieved statistically significant pain relief over time. We also carried out exploratory post hoc analyses to assess the proportion of patients with no, mild, moderate, and severe pain across the timeframe. We used generalized mixed modeling to investigate differences between groups in the use of analgesics during the 12-month follow-up.

Results

Patient Characteristics

Of 384 patients presenting facial pain screened for eligibility, 30 patients with classical trigeminal neuralgia were randomly allocated: 15 to the radiofrequency group and 15 to the sham procedure. During the 12 months of follow-up, one patient (radiofrequency group) died of unrelated causes (Figure 1). The median time from onset of symptoms to treatment was 65.7 weeks (interquartile range 58.1–75.3 weeks) in the radiofrequency group and 59.8 (53.0–70.5) days in the sham-procedure group. Suicidal ideation was present in eight (57.1%) in the radiofrequency group and nine (60%) in the sham-procedure group. Four patients (28.5%) attempted suicide at least once in the radiofrequency group and three (20%) in the sham-procedure group, all of them through anticonvulsant overdose. Thirteen patients chose to change groups after 1 month (one from the radiofrequency group and 12 from the sham-procedure group). Both groups had similar baseline characteristics (Table 1).

After 1 month, the mean NRS score decreased from 9.2 to 0.7 in the radiofrequency group and from 8.9 to 5.8 in the sham group. This significant reduction was measurable starting at day one after the procedure and remained significant throughout the first month. Participants were allowed to change groups after one month, after which the pain reduction was similar between the two groups (Figure 2 and Table 2). Three patients (20%) reported complete pain relief after the sham procedure.

Secondary Outcomes

A similar pattern of improvement was observed in the quality of life outcomes, measured by the SF-36 questionnaire. The radiofrequency group had a greater improvement in all SF-36 scales during the first-month follow-up, except general health perception. After the first month, both groups had a similar improvement of SF-36 outcomes until the last follow-up at 12 months. (Figures 3 and 4).

At baseline, all 30 patients were using a high dose of anticonvulsants (carbamazepine or oxcarbazepine). The mean reduction in anticonvulsant consumption was significantly greater in the radiofrequency group at one month (84.75%) than in the sham-procedure group (16.46%). After 1 month, both groups showed no statistically significant difference in analgesic use until the last follow-up at 12 months (Figure 5)

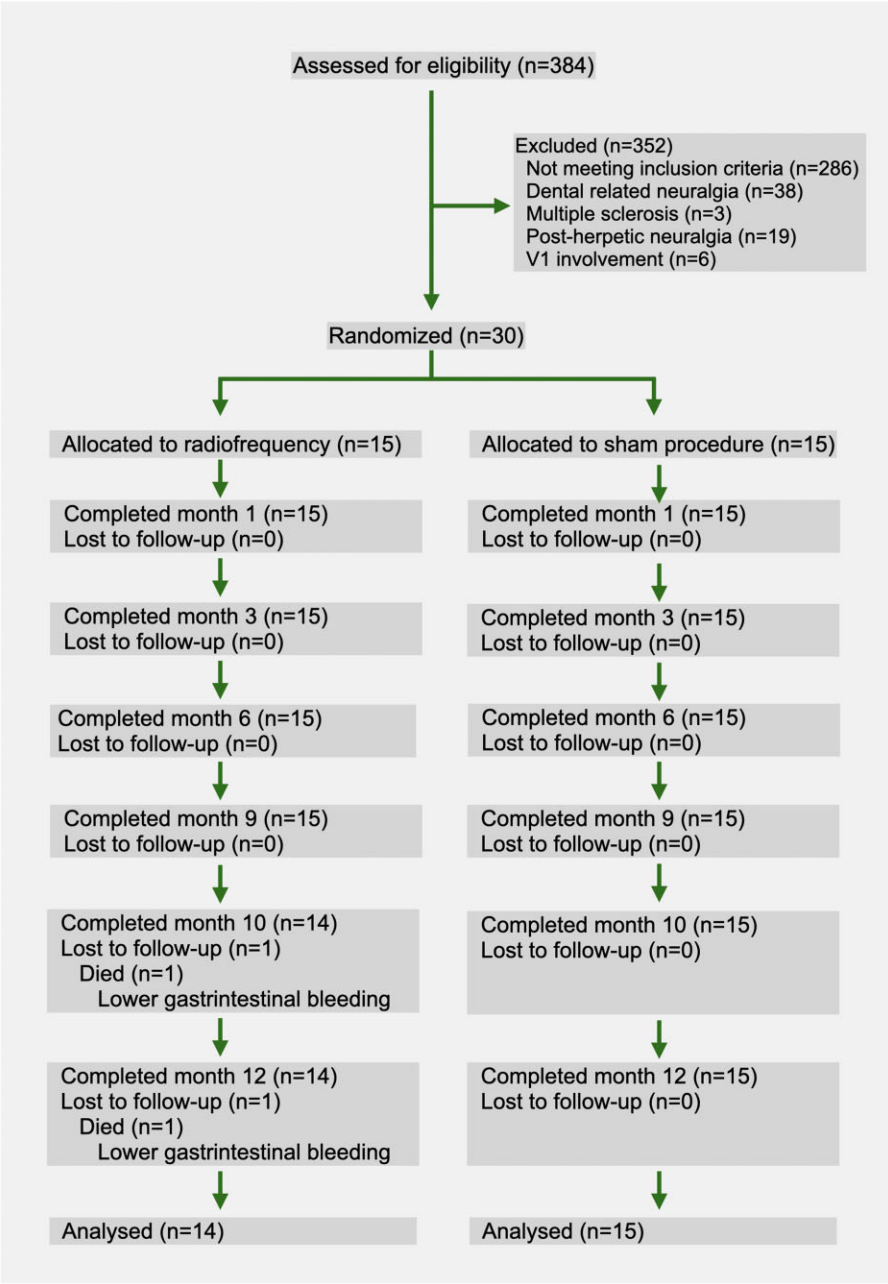

Figure 1. Flowchart of the study.

Procedure-Related Complications

The occurrence of numbness reached 40%, 3 months after radiofrequency application and decreased by 6.7% to 18.7% after 12 months. Paresthesia was less frequent, occurring in no more than 13.3% and dropping to less than 7% after 12 months (Figure 6). Six patients (three from the radiofrequency group and three from the sham-procedure group) had labial herpes simplex reactivation, and one patient, from the radiofrequency group, developed masseter muscle weakness. There was no occurrence of post-traumatic trigeminal neuropathy, previously known as anesthesia dolorosa.

Ancillary Analyses

Post hoc analysis showed that, during the first 4 weeks of follow-up, a significantly higher percentage of participants in the radiofrequency group had no pain or mild pain in contrast to members of the sham-procedure group, while more patients in the sham-procedure group had severe pain in the same timeframe (Figure 7).

Discussion

Trigeminal neuralgia remains the most excruciating pain known to humanity. The cornerstone of conservative treatment is sodium channel blockers, with good results

Table 1. Primary outcome

Characteristics	Radiofrequency	Sham
Mean (SD) age (years)	66.9 (10.7)	62.5 (10.50)
Women	12 (80)	10 (66.7)
Median (interquartile range) no. of weeks with back pain before procedure	65.7 (58.1–75.3)	59.8 (53.0–70.5)
Trigeminal branch involved		
V2	5 (35.7)	3 (20)
V3	6 (42.8)	6 (40)
V2/V3	4 (28.5)	6 (40)
Vascular conflict	5 (35.7)	7 (46.6)
Suicidal ideation	8 (57.1)	9 (60)
Suicide attempt	4 (28.5)	3 (20.0)
Mean initial NRS Score*	9.6 (0.7)	9.8 (0.4)
Anticonvulsant dose (DP)‡	1093.30 (438.30)	1133.30 (768.70)
Mean initial SF-36 Vitality Score (DP)†	42.0 (30.8)	45.3 (23.0)
Mean initial SF-36 Bodily Pain Score (DP)†	40.3 (31.3)	34.8 (23.8)
Mean initial SF-36 Physical Functioning Score (DP)†	31.7 (43.8)	35.0 (45.1)
Mean initial SF-36 General Health Perception Score (DP)†	48.6 (19.4)	50.9 (12.2)
Mean initial SF-36 Physical Role Functioning Score (DP)†	62.0 (27.8)	53.3 (33.1)
Mean initial SF-36 Emotional Role Functioning (DP)†	44.4 (49.9)	42.2 (44.5)
Mean initial SF-36 Social Role Functioning (DP)†	52.2 (33.9)	45.7 (17.5)
Mean initial SF-36 Mental Health (DP)†	57.9 (30.0)	52.3 (25.0)

Baseline characteristics of participants. Values are numbers (percentages) unless stated otherwise. *From 0 (no pain) to 10 (worst pain ever).
†From 0 to 100, with higher scores indicating worse quality of life.
‡Carbamazepina/oxcarbazepine—miligrams.
NRS = numerical rate scale; SF-36 = Short Form Health Survey.

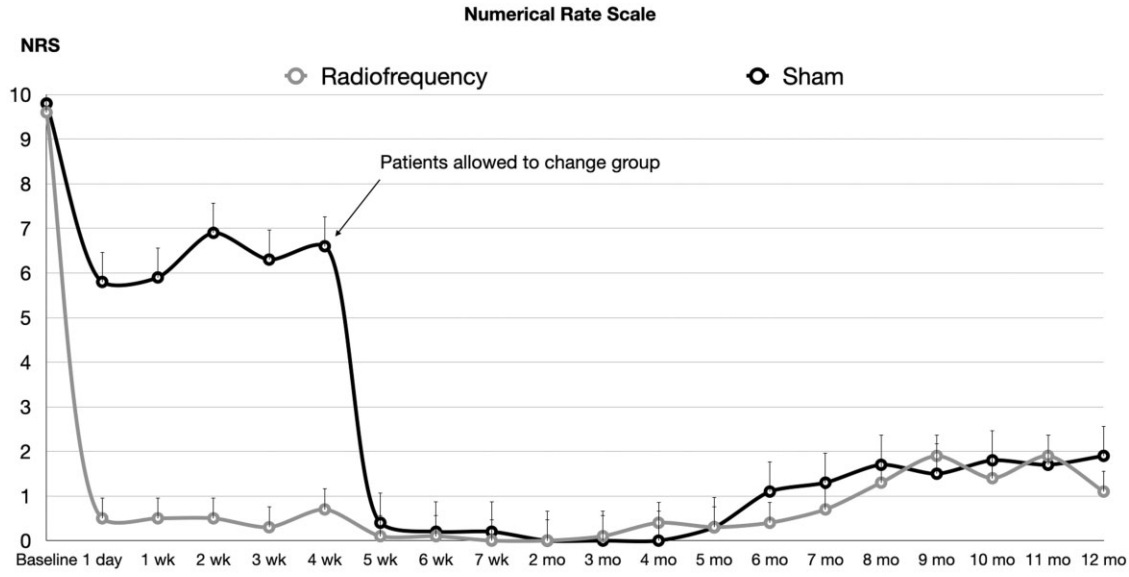

Figure 2. Mean Numerical Rating Scale scores for the trigeminal-radiofrequency and sham-procedure groups at each time point during 12-month follow-up. Whiskers represent 95% confidence intervals.

in 70% of patients [13]. Surgical and neuroablative interventions are reserved for patients who fail to respond to or adequately tolerate conservative therapies. Options include surgical decompression [6], percutaneous radiofrequency ablation [14], percutaneous balloon compression [15], or radiosurgery [16].

Although percutaneous trigeminal radiofrequency ablation is done worldwide with good reported results, its level of evidence is still weak [7] due to the of lack of controlled studies. Kanpolat published the study with the largest cohort treated with trigeminal radiofrequency ablation, with 1600 patients evaluated retrospectively for more than 20 years, demonstrating initial pain relief in 97.6% with sustained good results in 57.7%, 52.4%, 42.2%, and 41% in 5, 10, 15, and 20 years, respectively [8].

Erdine et al. compared conventional (70°C, 60 seconds) with pulsed radiofrequency (45 V, 2 Hz, 20

Table 2. Mean Numerical Rating Scale scores for trigeminal-radiofrequency and sham-procedure groups at each time point

Time Points	Mean NRS Scores Radiofrequency (n-15)	Mean NRS Scores Sham Procedure (n-15)	Group difference (IC 95%)	p value
Baseline	9.6	9.8	0,2 (−0,25 to 0.65)	
1 day	0.5	5.8	5.31 (3.75 to 6.87)	<0.001
1 week	0.5	5.9	5.4 (3.47 to 7.33)	<0.001
2 weeks	0.5	6.9	6.33 (4.28 to 8.39)	<0.001
3 weeks	0.3	6.3	6.07 (3.78 to 8.36)	<0.001
4 weeks	0.7	6.6	5.87 (3.57 to 8.17)	<0.001
5 weeks	0.1	0.4	0.27 (−0.25 to 0,78)	0.744
6 weeks	0.1	0.2	0.07 (−0.28 to 0.42)	0.953
7 weeks	0	0.2	0.2 (−0.10 to 0.50)	0.8124
2 months	0	0	0 (0.00 to 0.00)	0.9759
3 months	0.1	0	−0.13 (−0.41 to 0.14)	0.8347
4 months	0.4	0	−0.43 (−1.06 to 0.21)	0.5803
5 months	0.3	0.3	0 (−0.73 to 0.73)	0.9759
6 months	0.4	1.1	0.73 (−0.28 to 1.75)	0.3418
7 months	0.7	1.3	0.53 (−1.09 to 2.16)	0.4945
8 months	1.3	1.7	0.4 (−1.49 to 2.29)	0.6136
9 months	1.9	1.5	−0.4 (−2.62 to 1.82)	0.5718
10 months	1.4	1.8	0.37 (−1.51 to 2.25)	0.6629
11 months	1.9	1.7	−0.19 (−2.54 to 2.16)	0.7615
12 months	1.1	1.9	0.72 (−1.49 to 2.94)	0.3684

Mean numerical rate scale (NRS) scores for radiofrequency and sham procedure groups at each time point. NRS score ranging from 0 (no pain) to 10 (worst pain).

Between groups differences are contrast estimates at each point. Positive estimates favour the radiofrequency procedure, negative estimates favour sham procedure.

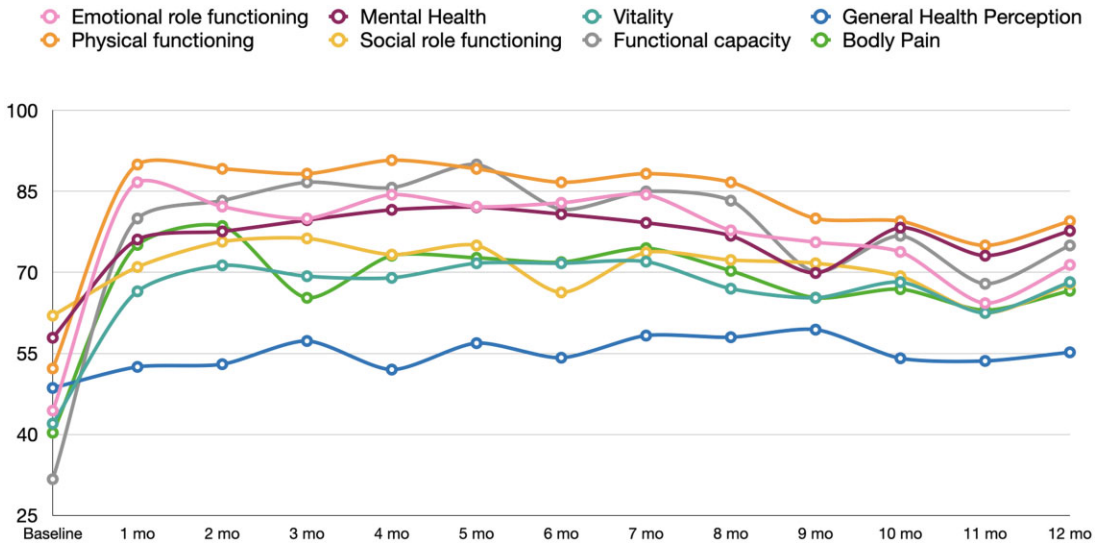

Figure 3. Mean SF-36 scores for participants in the radiofrequency group during the 12-month follow-up.

milliseconds/pulse, 120 seconds, maximum of 42°C) in the treatment of trigeminal neuralgia, showing better results for the thermal radiofrequency group [17], corroborating more recent data that showed satisfactory results in 25% and 83.3% of patients submitted to pulsed and thermal radiofrequency, respectively [18].

Our study was the first double-blind, randomized trial that compared the efficacy of trigeminal radiofrequency with a sham procedure. The NRS score decrease after trigeminal radiofrequency ablation was superior to that in the control group. The proportion of patients with mild or no pain was 92.8% in the treatment group and 26.7% in the sham group after the first month. The proportion of patients with severe pain was 0% in the treatment group and 46.7% in the sham group. All patients were completely pain-free two months after the radiofrequency ablation, and this number decreased to 78.6% by the end of the last follow-up at 12 months. Although completely pain free, one patient of the radiofrequency group decided to change groups, probably due to

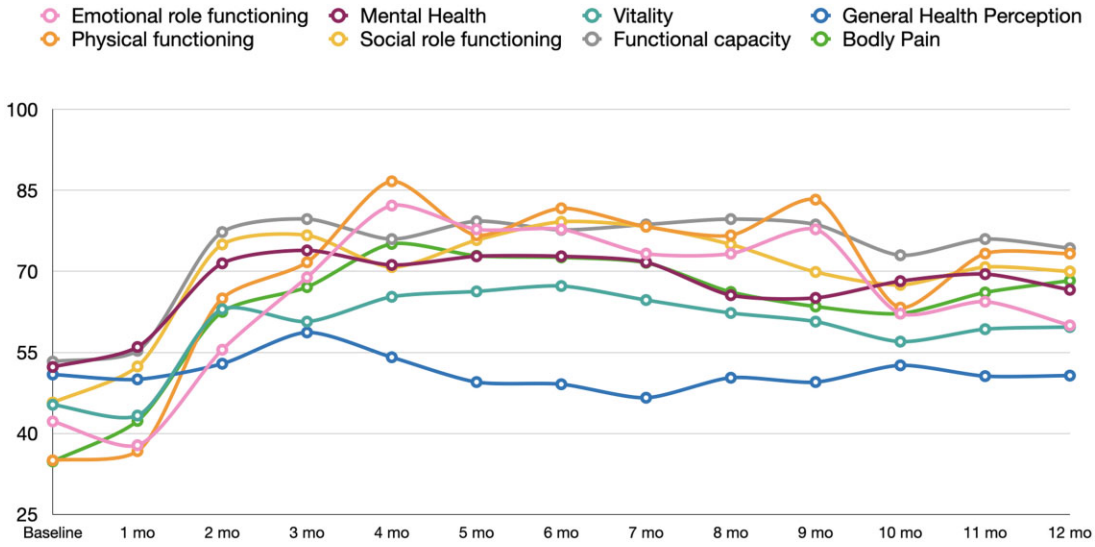

Figure 4. Mean SF-36 scores for participants in the sham-procedure group during the 12-month follow-up.

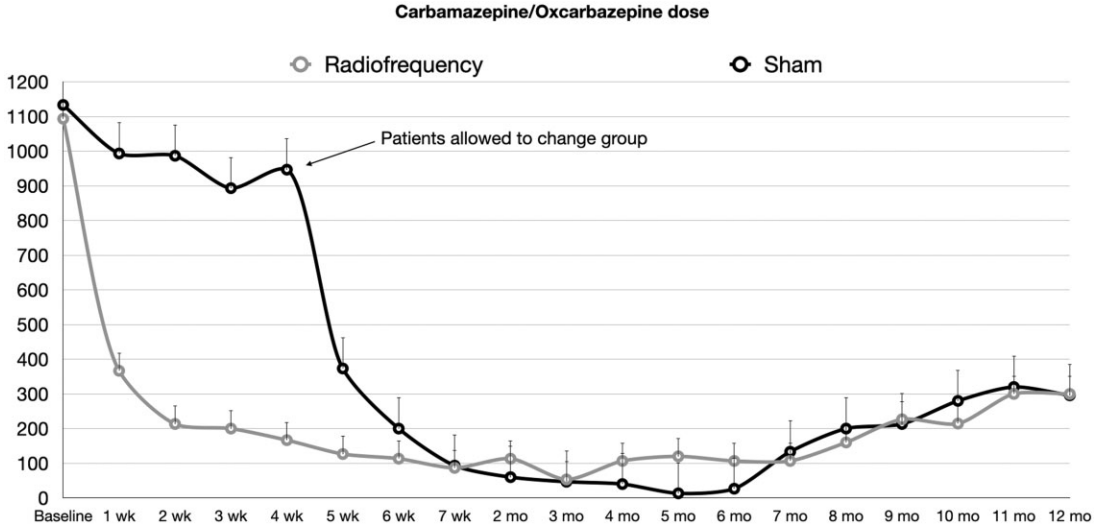

Figure 5. Mean anticonvulsant consumption (in mg) in the trigeminal-radiofrequency and sham-procedure groups at each time point during the 12-month follow-up. Whiskers represent 95% confidence intervals.

uncertainty about whether or not he had been submitted to RFA. We also showed that only 7.1% of patients were suffering from severe pain at 12 months. These findings corroborate the large retrospective series published by Kampolat [8].

More significant improvements were also observed in daily anticonvulsant consumption and in quality of life scores. It was reported that some patients without pain still preferred to keep a small dose of sodium channel blockers, maybe due to uncertainty regarding the procedure's efficacy or the possibility of pain relapse. This behavior was more common in those patients without facial numbness.

One of the most controversial issues was setting up the radiofrequency parameters. It is well accepted that larger lesions are associated with optimal nerve ablation but also with sensory complications. The needle bore, active tip size, temperature, and time are the main factors that influence lesion size [19]. We used a 20G needle and a 5 mm active tip at 75°C for 60 seconds. These parameters are supported by a retrospective cohort showing that 75°C was the optimal temperature to maximize pain relief and minimize facial dysesthesia [20].

In our cohort, 12 patients (five in the radiofrequency and seven in the sham-procedure group) had trigeminal vascular conflict detected by magnetic resonance imaging. Apparently, there is no difference in radiofrequency ablation outcomes between patients with or without vascular compression [21].

In our study, we inserted a 20G radiofrequency needle into Meckel's cave and performed sensory stimulation in both groups. Given that the use of the sham procedure is ethically and morally controversial, we allowed patients to change groups after a 1-month follow-up. The sham

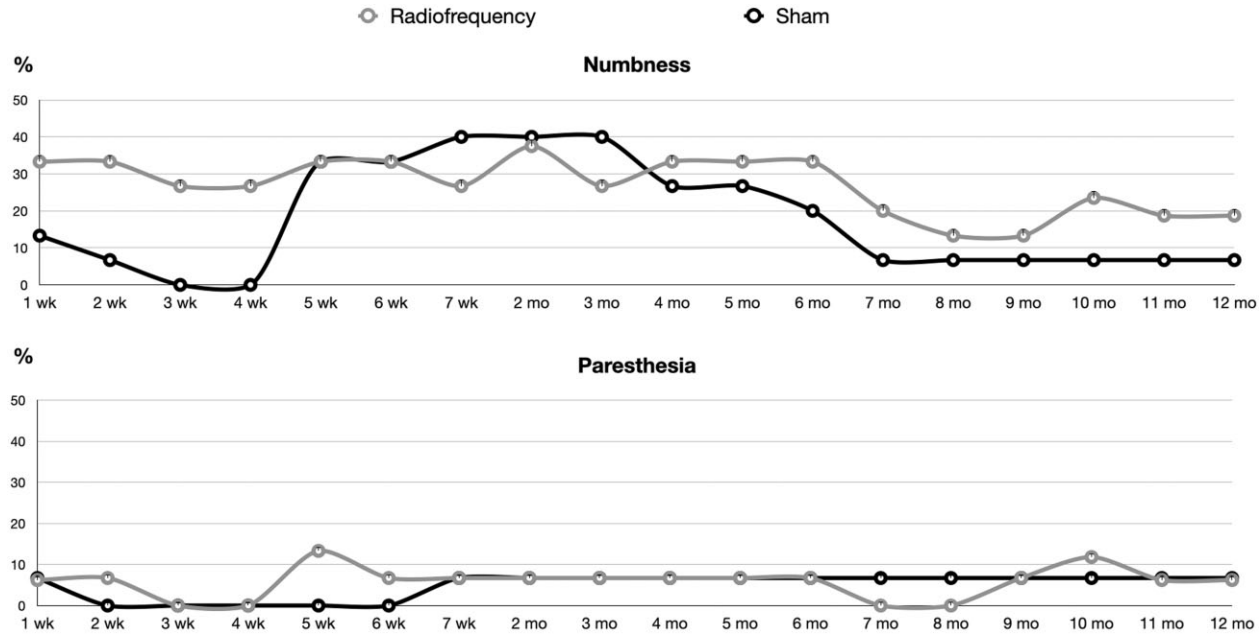

Figure 6. Occurrence of numbness and paresthesia in the trigeminal-radiofrequency and sham-procedure groups at each time point during the 12-month follow-up.

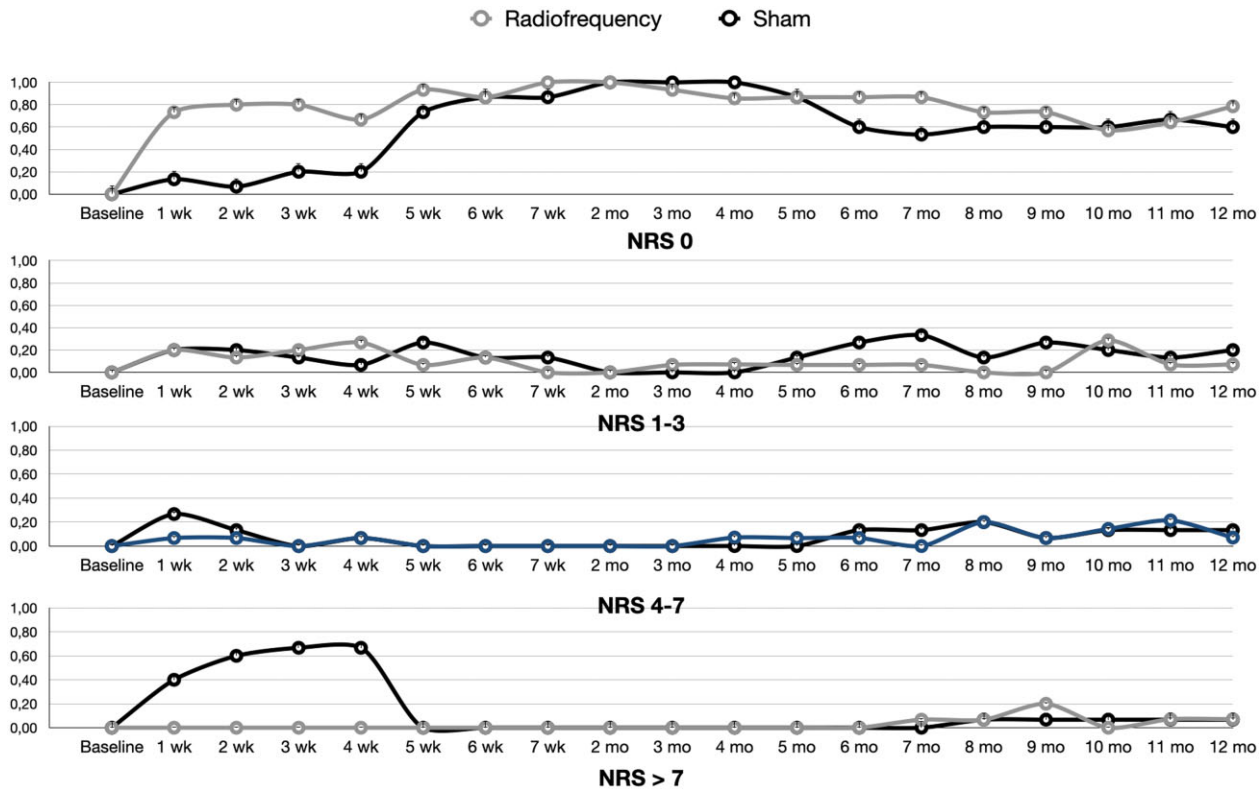

Figure 7. Proportion of patients with no pain, mild pain, moderate pain, and severe pain in the trigeminal-radiofrequency and sham-procedure groups at each time point during the 12-month follow-up.

procedure could be carried out only with skin puncture, but the ideal sham must guarantee patient and evaluator blindness while keeping the patient as safe as possible [22]. Three patients (20%) from the sham-procedure group had more than 70% pain relief during the entire follow-up period. We hypothesized that this was related to a placebo [23] or Hawthorne effect [24] or even local effects of needle trauma or sensory stimulation. Therefore, successful case reports should not be overestimated.

Facial sensory impairment remains the main drawback of ablative procedures. We had a high incidence of facial numbness and paresthesia that decreased over time. Fortunately, there were no cases of post-traumatic trigeminal neuropathy, whose incidence is less than 1% [8, 25]; the absence of such cases was perhaps due to the small number of patients enrolled.

Among the 30 patients enrolled in this study, 56.6% had suicidal ideation or thoughts before the procedures (57.1% in the radiofrequency group and 60% in the sham-procedure group). The incidence was higher than that published by Nieto RB et al., who found a small suicide risk of 3% [26]. This difference is probably due to different criteria and definitions used [27]. We defined suicide ideation or thoughts as any consideration of suicide during the course of the disease.

Radiofrequency ablation is probably the most performed percutaneous trigeminal treatment worldwide; other options include percutaneous balloon compression and glycerol rhizotomy. Although the head to head studies show the same efficacy [4], radiofrequency ablation has some advantages over balloon compression such as the use of small bore needles and selectiveness over trigeminal divisions. Both procedures have superior durability when compared with glycerol rhizotomy [28].

Limitations

This study did not compare different temperatures, needle bore, or active tip lengths. We carried out the sham procedure by inserting the needle into Meckel's cave and performing proper sensory and motor stimulation. This can be criticized not only because it is more invasive than merely sticking a needle a few centimeters through the skin, but also because the nerve needling can have direct or indirect neural effects. We preferred to ensure operator and patient blindness [29], which was only possible by submitting the patients to all steps except the true thermal lesion. We allowed patients to change groups after one month of follow-up due to ethical and moral questions. Although methodologically accurate, it would be unfeeling to keep patients untreated for 12 months. We did not include a control group that received only standard conservative medical treatment.

Conclusions

Percutaneous trigeminal radiofrequency ablation results in statistically and clinically significant greater pain relief than the sham procedure during one month of follow-up. These results support the use of radiofrequency nerve ablation as a treatment for refractory trigeminal neuralgia. More studies are necessary to help decide on the best therapy, especially a comparison between percutaneous trigeminal ablation and surgical decompression.

References

1. Jones MR, Urits I, Ehrhardt KP, et al. A comprehensive review of trigeminal neuralgia. Curr Pain Headache Rep 2019;23:74.
2. Di Stefano G, De Stefano G, Leone C, et al. Real-world effectiveness and tolerability of carbamazepine and oxcarbazepine in 354 patients with trigeminal neuralgia. Eur J Pain 2021;25(5):1064–71.
3. Di Stefano G, La Cesa S, Truini A, Cruccu G. Natural history and outcome of 200 outpatients with classical trigeminal neuralgia treated with carbamazepine or oxcarbazepine in a tertiary centre for neuropathic pain. J Head Pain 2014;15(1):34.
4. Sterman-Neto H, Fukuda CY, Duarte KP, et al. Balloon compression vs radiofrequency for primary trigeminal neuralgia: A randomized, controlled trial. Pain 2021;162(3):919–29.
5. Régis J, Tuleasca C, Resseguier N, et al. The very long-term outcome of radiosurgery for classical trigeminal neuralgia. Stereotact Funct Neurosurg 2016;94(1):24–32.
6. Gubian A, Rosahl SK. Meta-analysis on safety and efficacy of microsurgical and radiosurgical treatment of trigeminal neuralgia. World Neurosurg 2017;103:757–67.
7. Huygen F, Kallewaard JW, van Tulder M, et al. "Evidence-based interventional pain medicine according to clinical diagnoses": Update 2018. Pain Pract 2019;19(6):664–75.
8. 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):524–34. discussion 532–4.
9. 13.1.1.1 Classical Trigeminal neuralgia - ICHD-3. Available at: https://ichd-3.org/13-painful-cranial-neuropathies-and-other-facial-pains/13-1-trigeminal-neuralgia/13-1-1-classical-trigeminal-neuralgia/13-1-1-1-classical-trigeminal-neuralgia-purely-paroxysmal/ (accessed May 24, 2021).
10. 13.1.1 Trigeminal neuralgia - ICHD-3 The International Classification of Headache Disorders. 3rd edition. Available at: https://ichd-3.org/13-painful-cranial-neuropathies-and-other-facial-pains/13-1-trigeminal-neuralgia/13-1-1-classical-trigeminal-neuralgia/ (accessed August 18, 2020).
11. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: results from the medical outcomes study. JAMA J Am Med Assoc 1989;262(7):914–9.
12. Ciconelli RM, Ferraz MB, Santos W, Meinão I, Quaresma MR. Tradução para a língua portuguesa e validação do questionário genérico de avaliação de qualidade de vida SF-36 (Brasil SF-36). Rev Bras Reumatol 1999;39(3):143–50.
13. Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2014;2014(4):CD005451.
14. Liu P, Zhong W, Liao C, Yang M, Zhang W. The role of percutaneous radiofrequency thermocoagulation for persistent or recurrent trigeminal neuralgia after surgery. J Craniofacial Surgery 2016;27(8):e752–e755.
15. Bender MT, Bettegowda C. Percutaneous procedures for the treatment of trigeminal neuralgia. Neurosurg Clin North Am 2016;27:277–95.
16. Tuleasca C, Régis J, Sahgal A, et al. Stereotactic radiosurgery for trigeminal neuralgia: A systematic review. J Neurosurg 2019;130:733–57.
17. 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.
18. Agarwal A, Rastogi S, Bansal M, Kumar S, Malviya D, Thacker A. Radiofrequency treatment of idiopathic trigeminal neuralgia

(Conventional vs Pulsed): A prospective randomized control study. Anesth Essays Res 2021;15(1):14.
19. Cosman ER, Dolensky JR, Hoffman RA. Factors that affect radiofrequency heat lesion size. Pain Medicine (United States) 2014;15(12):2020–36.
20. Tang Y-Z, Yang L-Q, Yue J-N, Wang X-P, He L-L, Ni J-X. The optimal radiofrequency temperature in radiofrequency thermocoagulation for idiopathic trigeminal neuralgia: A cohort study. Medicine 2016;95(28):e4103.
21. Kao C-H, Lee M-H, Yang J-T, Tsai Y-H, Lin MH. C. Percutaneous radiofrequency rhizotomy is equally effective for trigeminal neuralgia patients with or without neurovascular compression. Pain Med 2022;23(4):807–14.
22. Ciccozzi M, Menga R, Ricci G, et al. Critical review of sham surgery clinical trials: Confounding factors analysis. Ann Med Surg 2016;12:21–6.
23. Turner JA. The importance of placebo effects in pain treatment and research. JAMA J Am Med Assoc 1994;271(20):1609.
24. Demetriou C, Hu L, Smith TO, Hing CB. Hawthorne effect on surgical studies. ANZ J Surg 2019;89(12):1567–76.
25. 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.
26. Nieto RG. Suicide risk in refractory chronic migraine, refractory chronic cluster headache, and refractory trigeminal neuralgia. Which is the "suicide disease"? In: International Headache Congress, Dublin, Ireland: IHC-PO-018; IHC 2019 Abstracts. Cephalalgia 2019;39(1_suppl):1–337. doi:10.1177/0333102419859835.
27. Harmer BL. Suicidal Ideation. Treasure Island, FL: StatPearls Publishing; 2021.
28. Noorani I, Lodge A, Vajramani G, Sparrow O. The effectiveness of percutaneous balloon compression, thermocoagulation, and glycerol rhizolysis for trigeminal neuralgia in multiple sclerosis. Neurosurg 2019;85(4):E684–92.
29. Cotton P, Pauls Q, Wood A, Durkalski-Mauldin V. Maintaining the blind in sham controlled interventional trials: Lessons from the EPISOD study. Endosc Int Open 2019;07 (11):E1322–6.