Original Article

Retrogasserian radiofrequency thermocoagulation: A repeatable treatment in trigeminal neuralgia unresponsive to drug therapy

ABSTRACT

Background: Trigeminal neuralgia present an incidence rates ranging between 5.9 and 12.6 per 100.000 persons; although not frequent, it is a pathology often characterized by intense pain, an extremely significant reduction in quality of life and medical therapy is not always effective or tolerated. In these cases, the patient can undergo interventional treatments including radiofrequency thermocoagulation. There are still doubts regarding the effectiveness over time, the injury parameters and the repeatability of the procedure.

Materials and Methods: We analyze patients with trigeminal pain undergo retrogasserian radiofrequency in a single center over a period of 8 years. The procedure was performed with the following parameters: Lesion time 60 sec, lesion temperature 70°C for first thermolesion 72°C for subsequent thermolesions. Duration of benefit, number of repetitions of the maneuver, and incidence of adverse events were assessed.

Results: Totally, 122 patients with essential trigeminal neuralgia and 20 patients with trigeminal neuralgia secondary to multiple sclerosis were analyzed; almost all patients (96.5%) showed a significant reduction in pain after one or more procedures over time; 96.5 of the patients showed excellent pain relief after 1 (40%) or more procedures (60%). The average time between one procedure and the next was 26 months.

Conclusion: The use of time and temperature parameters chosen shows excellent efficacy, in line with the literature, with very low incidence of adverse events. The pain-free time between one procedure and the next does not seem to be a significant prognostic criterion which may or may not indicate the repetition of the procedure.

Key words: Interventional pain treatment; neurolesion; neurosurgery; radiofrequency; trigeminal neuralgia

Introduction

Trigeminal neuralgia (TN) is a neuropathic pain condition affecting the facial area characterized by sudden brief and excruciating facial pain attacks in the territory of one or more of the branches, with a severe reduction of the quality of life of affected patients. TN has been defined by the International Association for the Study of Pain as "a sudden, usually unilateral, severe, brief, stabbing, recurrent pain in the distribution of one or more branches of the fifth cranial nerve."[1]

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This pain is often triggered by non-noxious stimuli or normal activities such as talking, chewing, swallowing, and brushing teeth, and is considered intractable or difficult to treat. Functional limitations maybe extreme, as patients may avoid eating, chewing, or oral hygiene for fear of precipitating an attack. The most common distribution involves V3 (60-70%), followed by V2, and least frequently, V1 (less than 5%). A correlation with multiple sclerosis has been claimed in approximately 2% to 3% of patients, but no satisfactory unifying pathophysiology has yet been advanced.[2]

Diagnostic criteria for classical TN are defined by International Headache Society (IHS)[3]:

Although among the most debilitating of chronic pain conditions, trigeminal neuralgia is fortunately successfully treated in the majority of patients. The antiepileptic drugs carbamazepine (CBZ) and oxcarbazepine (OXC) are the first-line pharmacological treatments. Other drugs (gabapentin, pregabalin, lamotrigine, phenytoin, baclofen) may be useful for pain control and generally are co-administered with CBZ or OXC to improve treatment efficacy.[4,5]

Carbamazepine is a well established and effective drug in managing TN and currently remains the medicine of choice[6] also if there are reported risks of severe mucocutaneous reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN) in patients taking carbamazepine.[4]

Surgical interventions should be reserved for those patients with debilitating pain refractory to pharmacological therapies. Percutaneous techniques to the Gasserian ganglion are all destructive and consist mainly of percutaneous glycerolrhizolysis, radiofrequency thermocoagulation, and balloon compression. The open surgical method (suboccipital craniotomy with microvascular decompression or MVD) is performed with the objective to resolve the neurovascular conflict between an abnormal vessel and the trigeminal nerve.[7]

Sensory loss (50%) is the most common side effect with high impact on quality of life for these patients, followed by dysesthesias (6%), corneal numbness with risk of keratitis (4%), and anesthesia dolorosa (4%).[8] Gasserian ganglion treatments are generally minor, overnight procedures with very low mortality.[6,9]

Materials and Methods

We analyzed 142 patients affected by essential Trigeminal Neuralgia (n. 122) and by secondary neuralgia in multiple sclerosis (n. 20), involving V2 and/or V3, unresponsive to drug therapy or with disabling side effects and with a severe reduction of the quality of life treated with Retrogasserian Radiofrequency Thermocoagulation in the last nine years (2011-2019) in our Pain Unit.

We considered percutaneous RF Gasserian rhizotomy (PRFGR) only in patients with intractable trigeminal neuralgia who have failed, or cannot tolerate high dosages of pharmacologic therapies.

We explain to the patients that the treatment could not be definitive and that it could be repeated after the symptoms reappeared. It is also explained that we try to avoid serious sensory loss but that it is not always possible. The aim of percutaneous treatment is to reduce the drugs and, if possible, to stop them. Drug therapy could be taken after the procedure if pain is not completely controlled or whenever pain reappears. We consider invasive procedure as a part of a multimodal treatment of TN where drugs are fundamental but not always effective.

The aim of the treatment was to obtain pain relief reducing the number of active fibers in the retrogasserian area without destroying all them in order to avoid the risks of a complete sensory loss and the dramatic condition of “anesthesia dolorosa”.

The procedures were done in the operating room. Intravenous access was obtained, prophylactic antibiotic was administered within 30 min before the procedure, standard monitoring was applied.

Deep sedation by intravenous propofol 1 mg/kg was obtained for needle insertion; the patient was woken up and able to collaborate when test stimulation was performed. Deep sedation with fentanyl (1 mcg/kg) and propofol (1 mg/kg) was performed for radiofrequency ablation.

A Neurotherm NT 1100 RF generator and TSS 100 DTCS 20-gauge 10 cm needles with an active tip of 5 mm were used.

The procedure was performed under fluoroscopic guidance with the patient in the supine position and head extended.

The C-arm was rotated to obtain, at the beginning, a lateral view of the skull and, when the needle reaches the skull base, an oblique submental view to visualize the foramen ovale. We defined the skin entry point according to Hartel technique 3 cm lateral to the commissura labialis (angle of the mouth) on the affected side. The needle trajectory followed a straight-line directed toward the pupil and passing 3 cm anterior to the external auditory meatus in depth.[10]

During the first part of procedure a finger was placed in the oral cavity to make sure that the buccal mucosa was not perforated. After entering the foramen ovale, the depth of the needle inside the Meckel's cavity was ascertained on the lateral fluoroscopic view. The needle was advanced up to ~2–4 mm from the junction of the petrous ridge of the temporal bone and the clivus. The stilet was removed to check for CSF leakage and the thermocouple was inserted.

The procedure was performed in two successive moments:

(a) Trial stimulation. Motor stimulation was performed using 2 Hz with 0.1–1.0 V in order to observe the masseter muscle contraction. Keeping verbal contact with patient sensory stimulation was given at 50 Hz, from 0.1 to 0.5 V to evoke a tingling sensation in the affected area.

(b) Radiofrequency lesioning. RF lesioning was performed at 70°C for the first procedure in patient's life and at 72°C for the following ones; the time of the lesion was fix in 60 s. If more than one branch was affected, another lesions was performed by repositioning the needle. After each repositioning, the stimulation test was repeated to search for paresthesia at the desired area. Thereafter, the sensitivity of the face and cornea were tested.

The day after the procedures we evaluate the disappearance of trigeminal pain attacks and we explain how to reduce drug therapy and how to behave in the event of a return of pain. We define as good pain control the absence of pain attacks by eating, speaking or other trigger factors.

Side effects and complications related to the technique were evaluated.

Statistical methods

All data analysis are performed with R (ver. 3.5.3).

Patient demographics were summarized using mean and SD or percentage.

The differences in time to relapse after second and third lesions were tested using the Student t test for unpaired data.

The correlation about time of pain relief and number of lesions was tested with Pearson's test.

Results

The first study group (G1) included 122 patients with primary TN (65 men and 57 women), 1 patient had a concomitant peripheral nervous system disease. The second study group (G2) included 20 patients with secondary TN due to multiple sclerosis (10 men and 10 women). We treated a total of 142 patients.

The mean ages were 68 (d.s. 12) and 54 (d.s. 10) years respectively. In G1 86 patients reported pain in the territory of one branch (70,5%), in 36 (29,5%) two branches (V2 and V3) were involved. The V2 branch was affected in 82 pts (67, 2%) and V3 in 72 pts (59%). 58 pts had pain in the right side and 64 in left side. In G2, 12 pts (60%) suffered pain in the territory of one branch, 8 pts (40%) in two branches (V2 and V3), The V2 branch was affected in 13 pts (65%) and V3 in 15 pts (75%). 9 pts had pain in the right side and 11 in left side.

137(96,5%) patients had good pain control without drugs or with a drug reduction after one or more close treatments, in 5 (3, 5%) patients of G1 (4%) the treatment failed. In 2 patients the procedure failed probably due to anatomical variation in Gasserian ganglion position because we couldn't evoke paresthesias in the affected area [Figure 1].

Number of procedures in G1 patients

47 (40%) patients had undergone only one procedure during the period 2011-2019 with persisting pain relief.

70 (60%) patients had undergone more than one procedure: 36 (30,8%) had two procedures, 28 patients (24%) three; 4 (3, 4%) four and 2 (1, 7%) five.

The duration of pain control varies between the procedures: 37 months (d.s. 27 mm) after the first procedure, 24 months (d.s 19) after the second, 19 months (d.s. 17 mm) after the third and 24 months (d.s. 29 mm) after the fourth procedure [Figure 2].

Analyzing the pain-free time between first and second lesions, there are no difference (p = 0,61) between the patients who underwent the third lesion and those who remained painless after the second.

The duration of the benefit does not therefore appear to be a predictive factor regarding the possibility of having to perform further lesions.

The duration of efficacy shows a trend in decrease with each further treatment, this trend does not have a statistically correlation (r = -0.32) [Figure 3].

Number of procedures in G2 patients

Totally, 8 (40%) patients had undergone only one procedure during the period 2011-2019 with good pain control without drugs or with well-tolerated dosages.

12 (60%) patients had undergone more than one procedure: 5 (25%) two procedures, 4 (20%) three, 3 (15%) four [Figure 4].

The duration of pain control varies between the procedures: 22 months (d.s. 21) after the first procedure, 15 months (d.s. 8) after the second, 18 months (d.s. 7) after the third [Figure 5].

Hypoestesia in the territory of the treated branch was frequent, usually improving with time and sometimes accompanied by well-tolerated dysesthesia. More severe side effects were reported in 4 (3,3%) patients in the first group. Two patients reported keratoconjunctivitis due to corneal reflex impairment for the unwanted involvement of the first trigeminal branch. In one patient, treated with radiofrequency of the second branch a spasm of facial mimic muscles was observed. The last one presented a trophic lesion of the nasal mucosa.

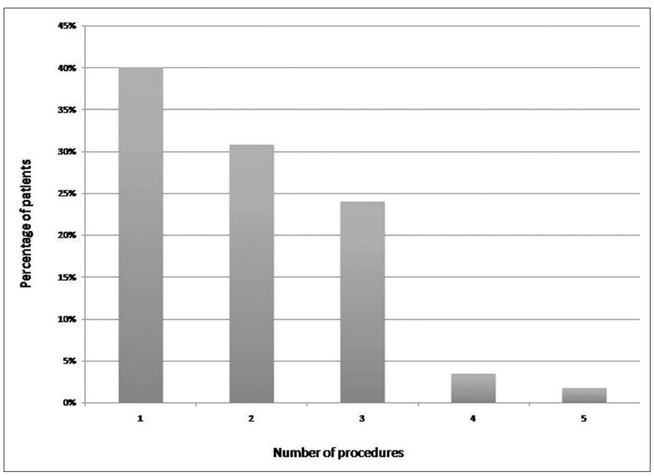

Figure 1: Number of procedure per patient in group 1

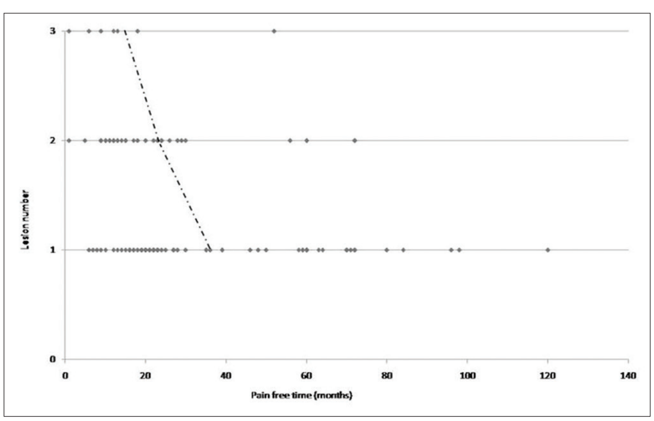

Figure 3: Relation between number of lesion and pain free time

Discussion

It is widely accepted that TN is a neuropathic type pain even if no sensory deficits can be detected. The etiology of TN has been suggested to be vascular compression of the central axons of the trigeminal nerve at the level of the pons, resulting in focal demyelination.[7] Demyelization of the trigeminal nerve also appears to account for the 2 ± 4% of TN patients with multiple sclerosis.[11] The etiological roles of compression and demyelization are, however, only inferred from clinical observations rather than from experimental manipulations.[12]

Thus, a foremost research question is to confirm compression and demyelization in the etiology of TN. Confirmation of etiology and identification of pathophysiological mechanisms have been hampered by the lack of an animal model with key features of TN.[13,14]

The peripheral pathophysiological mechanism described as relevant is the ephaptic transmission or the cross excitation of

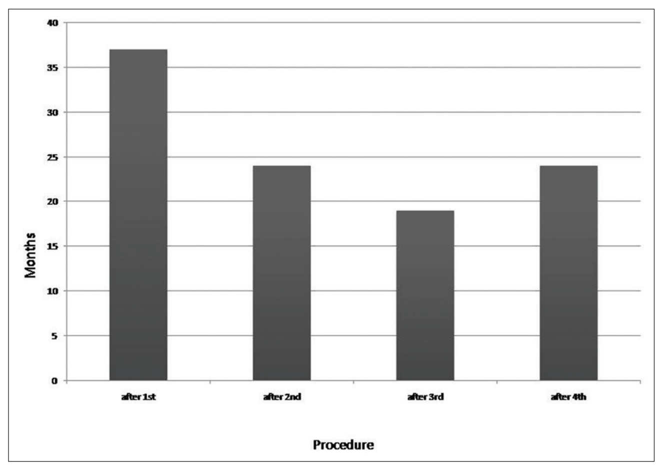

Figure 2: Duration of pain relief (months) in patients treated with more than one procedures in the group 1

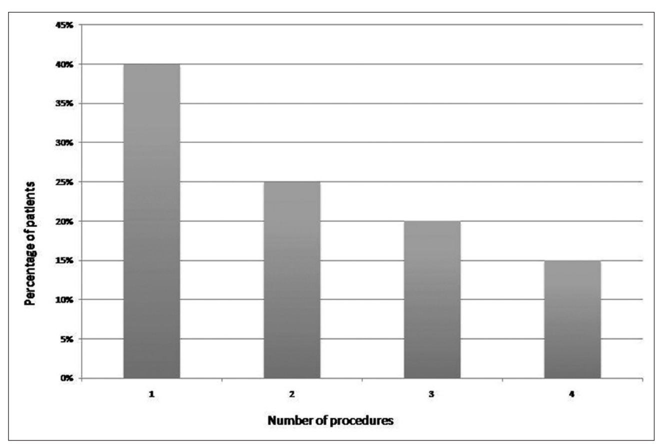

Figure 4: Number of procedure per patient in group 2

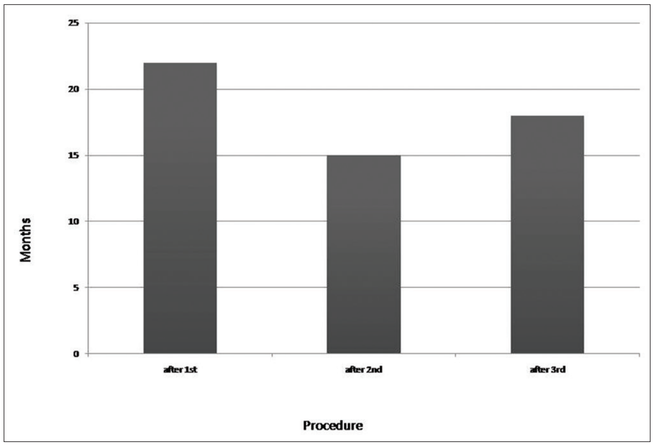

Figure 5: Duration of pain relief (months) in patients treated with more than one procedures in the group 2

nervous fibers. This phenomenon involves the transmission of action potentials from injured and hyperexcitable afferent peripheral sensory fibers to adjacent sensory fibers not stimulated.[15] The electromagnetic field generated in a fiber induces depolarization of neighbor fibers, causing cross excitation, and contributes to allodynia and hyperalgesia.[16] Some studies with surgical biopsies of TN patients have observed significant demyelization of trigeminal sensory fibers.[17]

Recognized hypothesis explaining the pathophysiology of TN is the "ignition hypothesis" as described by Devor.[18] It suggests that TN is precipitated by injury to the trigeminal axons in the nerve root or ganglion. The injury in most cases is related to compression of the nerve in the root entry zone by vascular structures. Imaging has shown there to be evidence of demyelization and remyelization of the nerve in this area.[17] Devor *et al*.[18] suggest the stop mechanism, or refractory period, is a consequence of post-burst potassium influx hyperpolarization, which renders the neuron refractory to further stimuli.

The prognosis of trigeminal neuralgia following percutaneous RF gasserian rhizotomy is good. In our experience 137 (96,5%) patients had good pain control without drugs or with a drug reduction after one or more close treatments; in 5 (3,5%) patients of the G1 the treatment failed.

Regarding efficacy of the procedures we find different results in literature. A comparative evaluation of radiofrequency thermocoagulation[19] reports an immediate pain relief varying from 78,8% to 97,6%, while the pain free duration from 12 to 61 months. A recurrence rate of 15% to 20% can also be expected within the 1st year.[20] It is general opinion that if symptoms recur, repeat rhizotomy may be considered and has been demonstrated to be effective. In patients with recalcitrant trigeminal neuralgia who have failed repeat RF neurotomy, microvascular decompression may be considered.

If we consider the extent of the thermal lesion we believe that RF should reduce Aδ afferents from the trigger area and not necessarily destroy all nociceptive fibers. A reduction in tactile and proprioceptive input can be enough to inhibit "ephaptic cross-talk" with the limit of temporary efficacy when sensitivity recovers but a larger lesion, involving also small fibers is to be avoided for the risk of the severe side effect of "anesthesia dolorosa". It is essential for success to research, during surgery, the paresthesia coverage of the trigger zone.

Although RF has been common for over 40 years, there is limited literature on the effects of RF parameters on the surgical outcome. Selection of ablation temperature is often empiric. In literature we found different temperature values from 55 to 9020. Based on previous experience, we performed RF lesioning at 70°C or 72°C (according to number of previous treatments) for 60 seconds.

Regarding ablation duration, we found in literature variations from 60 to 120 seconds. Some Physicians perform multiple lesions until loss of pain sensitivity in affected area. It is difficult to establish whether the extent of the lesion in terms of number and type of injured fibers is mainly due to temperature or duration of the RF lesion.

In a recent article Xie *et al*.[21] assert that higher temperatures may be necessary to achieve pain relief in some patients, given the progressive nature of the facial pain, but they are not associated with longer duration of pain relief in patients who have recurrent pain. Modulation of the ablation duration does not seem to affect the short-term or long-term outcomes. The duration of pain control varies between the procedures. In our experience it is difficult to identify the reason why pain relief in some patients is long lasting (and in other patients it is temporary and the patients need more radiofrequency procedures.

There are no correlations between the number of procedure and branch/branches involved. There were no significant differences between the groups regarding age, gender, duration, and the site of pain. We expected an increase of the interval between the procedures by the greater damage related to repeated lesions but the contrary was demonstrated.

The temperature and the duration of the lesions did not cause serious neural damages but probably explain the different neurological deficits but not the duration of pain relief.

This study included a proportion of participants with MS (14%) as is reported in literature,[22] although rates as low as 1% have been reported in some populations.[23] The pathophysiologic relationship between MS and TN remains uncertain,[24] but TN associated with MS is generally understood to be more difficult to treat than in patients without MS, with a shorter duration of pain relief after treatments and a greater number of treatments required.[25,26] Xie *et al*.[21] assert that the duration of pain relief was generally shorter in patients with multiple sclerosis and in repeated procedures. We observed the same data but without any statistical significance.Post-. procedural pain relief was not different in patients with and without MS. This would suggest that when it comes to ablation parameters in MS patients, similar consideration should be made as in non-MS patients.

In our study the incidence and the severity of side effects are limited, In literature we find heterogeneous data[27] for side effects reported as follow: Sensory loss >50%, dysesthesia <6%, anesthesia dolorosa 4%, eye complications 4%, meningitis 0.2%. In an older article[28,29] side effects related to the different procedures (radiofrequency rhizotomy RR, balloon compression BC, glycerol injection GI and microvascular decompression MD) are reported. The incidence of facial numbness is high in RR (98%) and BC (72%), while is very low (2%) in MD. Anesthesia dolorosa is rarely encountered but mostly in GI (1,8%) in comparison with other procedures (0,2 in RR - 0,1 in BC – 0 in MD). Corneal anesthesia is found in the procedures RR, BC and GI respectively in 3%, 1,5%, and 3.7%.

Conclusion

Retragasserian radiofrequency thermorhizotony is an effective and safe procedure for primary or secondary TN in well-selected patients when drugs failed to control pain attacks. We consider candidates to radiofrequency only patients with evoked shock like pain independently if essential TN or TN in MS. The procedure can be effectively repeated when pain returns. The fear of this sudden and dramatic pain prompted patients to ask for help as soon as symptoms reappear. From a physiopathological point of view the hypothesis of electrical cross-over between demyelinated neurons can explain the results obtained with the reduction of Adelta fibers. our study supports the idea that a protocol that limits the treatment time to 60 seconds and the temperature to 70°C can obtain satisfactory results in terms of pain reduction (with percentages similar to those present in the literature), significantly limiting the effects side.

The use of these parameters exposes some patients to the need for repetition of the procedure, this procedure often proves to be just as effective although there is a trend in reduction of pain-free time. A complete sensory loss is not indicative of success but virtually responsible of anesthesia dolorosa as we observed in patients treated elsewhere. We can conclude that retrogasserian radiofrequency applied, as we have proposed, does not have the ambition to eliminate drugs but to make them effective on a low and well tolerate dosage.

Highlights

Retrogasserian radiofrequency is a safe and effective therapy for trigeminal neuralgia both of essential origin and secondary to multiple sclerosis.

Retrogasserian radiofrequency is safe with a very low incidence in adverse effects if first branch is ruled out.

The aim of the retrogasserian radiofrequency is to reduce (not necessarily suspend) medication intake at the same time as better pain control

Retrogasserian radiofrequency is a repeatable procedure that can guarantee efficacy even after several times.

Sixty seconds for each termolesion can be considered a good safe and effective choice.

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Author contributor: L. Demartini, C. Bonezzi and M. Marchesini were involved in data collection, data interpretation, data analysis, literature review, manuscript preparation including figures and writing, prepared the first draft of the manuscript and contributed equally to the article.

G. Conversa and R. Bettaglio contributed to data collection.

All the authors performed the retrogasserian thermocoagulation during their clinical practice and performed the follow up of their patients.

All authors read and approved the final manuscript.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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