Relationship between Sensory Stimulation and Side Effects in Percutaneous Radiofrequency Treatment of the Trigeminal Ganglion

Mark V. Koning, MD*; Nick J. Koning, BSc†‡; Henk M. Koning, MD, PhD§; Maarten van Kleef, MD, PhD¶,**

*Department of Anesthesiology, Erasmus University Medical Center, Rotterdam; †Departments of Anesthesiology and Cardiothoracic Surgery, Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, The Netherlands; ‡Department of Integrated Neurovascular Biology, INSERM U1083, CNRS UMR 6214, LUNAM University, Université d’Angers, Angers, France; §Department of Pain Therapy, Medical Center Jan van Goyen, Amsterdam; ¶Department of Anesthesiology and Pain Management, Maastricht University Medical Center, Maastricht; * Department of Anesthesiology and Pain Management, VU University Medical Center, Amsterdam, The Netherlands

Abstract

Introduction: The objective of this study was to determine the efficacy of percutaneous radiofrequency (RF) treatment of the trigeminal ganglion for treating patients with trigeminal neuralgia, to determine which patients have a long-term benefit, and to evaluate the effect of RF parameters.

Methods: A retrospective study in 28 consecutive patients in combination with a follow-up questionnaire (n = 26, 93% response).

Results: An initial treatment effect of 89% was observed, 60% sustained at 12-month follow-up. Major side effects were hypesthesia (56%), dry eye (20%), and masseter muscle weakness (12%). A lower sensory stimulation threshold during treatment was associated with better patient satisfaction (P = 0.016), improved pain relief (P = 0.039), and trended toward more hypesthesia (P = 0.077).

Discussion: This low-volume study reported treatment effects in an older population that were similar to previous studies. Only a higher incidence of hypesthesia was detected by long-term follow-up. This study supported the high efficiency of RF treatment, but there was a high level of side effects. Most notable, low sensory stimulation was associated with increased hypesthesia, whereas higher stimulation levels yielded less effectiveness. Further investigation of an optimal sensory stimulation range for percutaneous RF treatment of the trigeminal ganglion was found to be warranted.

Key Words: percutaneous radiofrequency treatment, sensory stimulation threshold, trigeminal neuralgia, idiopathic

INTRODUCTION

Trigeminal neuralgia (TN) is the most common form of cranial neuralgia; however, little is known about the exact pathophysiology of classical TN. Several types of noninvasive (medicinal, radiation) and invasive (percutaneous treatments, surgical procedures) treatments are available. None of these treatments have been shown to
be superior due to a lack of well-designed randomized controlled trials and conflicting results in the literature on observational studies regarding TN.²⁻⁴

A frequently used percutaneous treatment is radiofrequency (RF) treatment, which is a minimally invasive, low-risk technique with a high rate of initial efficacy for treating TN. The minimally invasive nature of this technique makes it the preferred form of treatment for elderly patients.⁵ Its disadvantages, however, include a large variability of effects and side effects, and a high rate of long-term failure. The procedure can be repeated if pain recurs, which emphasizes the importance of gaining more knowledge regarding the effects and side effects of RF treatment.²,⁶

Empirical data on sensory stimulation thresholds, lesion time, and temperature during RF treatment, which could support making the most effective selection from the treatment options currently available, are lacking. Moreover, nothing is known regarding the relationship between technical parameters used during RF treatment of the trigeminal ganglion, the initial success rate, the long-term effectiveness, or the side effects.

The objective of this study is to elucidate on determinants of outcome in percutaneous RF treatment of the trigeminal ganglion. In particular, the aim is to investigate the effects that the technical aspects of RF treatment have on success rate, long-term effectiveness, and side effects.

**METHODS**

The Medical Research Ethics Committee of the Jan van Goyen Medical Centre approved the present observational study. The participants were 28 consecutive patients with classical TN who were treated with percutaneous RF treatment on the trigeminal nerve at our medical center during a period of 3 years between November 2008 and November 2011.

**Patient Evaluation**

The diagnosis of classical TN was in accordance with The International Headache Society classification.¹ Medical treatment with carbamazepine in dosages up to 1,800 mg daily was started after exclusion by MRI of any significant neurovascular conflict and any lesion or tumor in the pontocerebellar angle, petrous apex, cavernous sinus, or cranial base. Indication for percutaneous rhizolysis was classical TN unresponsive to medical treatment or intolerance of medical treatment.

**Percutaneous Radiofrequency Treatment of the Trigeminal Ganglion**

An experienced anesthesiologist performed all RF interventions of the trigeminal ganglion in a routine manner, on an outpatient basis. The procedure was performed with the patient in the supine position. No premedication was used, and a peripheral intravenous line was placed. The procedure took place with intravenous sedation in incremental doses of propofol under respiratory and cardiovascular monitoring. After disinfecting the puncture site with chlorhexidine 60% in alcohol, the skin was injected 2 cm lateral from the angle of the mouth at the site of the TN with a 1% or 2% solution of xylocaine. A 22 gauge SMK needle with a 2 or 5 mm nonisolated tip was inserted at the same point as the anesthetic infiltration and advanced slowly under intermittent fluoroscopic control in anteroposterior, lateral, and oblique submental position toward the foramen ovale. Once the needle was positioned in the trigeminal cavity, manual control of oral mucosal perforation took place.

Electric stimulation of the electrode at 50 Hz was increased from 0.1 to 0.8 V in increments of 0.1 V until the patient felt a tingling-like sensation or electric-like paresthesias in the affected painful area. Following stimulation higher than 0.5 V, the electrode was redirected to obtain paresthesias at a lower voltage. The electrode was then stimulated at 2 Hz from 1.0 V down to 0.1 V in steps of 0.1 V to check absence of a motor response of the masseter muscle. When motor response was absent at voltages lower than 0.4 V, the needle position was considered acceptable.

Lesions were made for 60 seconds at 65°C when sensory stimulation was < 0.4 V, or at 70°C when sensory stimulation was > 0.4 V. After each lesion, the response to pinprick was assessed in each division if the trigeminal nerve is on both sides. Adequate hypalgiesia was defined as a diminished mimic response of the patient to pinprick in the nerve division that was to be treated. If the patient had a positive pinprick response, additional 60-second lesions were made and up to 3 consecutive RF lesions were administered in 1 session. The ciliary reflex at the affected facial area was cautiously monitored during the lesions.

The patients were observed and monitored in the recovery room and discharged home after 1 to 2 hours. All medications previously provided for pain control were discontinued when the patient experienced pain relief. Patients were re-evaluated 6 weeks after treatment by the interventionist.
Data Assessment

Patient charts were retrospectively reviewed by an independent observer to identify patient characteristics (age, sex), pain characteristics (left side or right side, affected branch, triggers, duration of complaints, previous treatments), treatment parameters, reported benefit, and side effects from treatment after 6 weeks, period of pain relief, and, if applicable, relapse.

In August 2012, a different independent observer conducted a long-term follow-up assessment of the therapy through a telephone interview with each patient. A letter announced the telephonic interview, 2 weeks in advance. The standardized questionnaire was used to evaluate treatment results (current pain status, time of recurrence of the original pain, need for additional therapy), the presence of surgical or other sequelae after the RF treatment of the trigeminal ganglion, and the presence of side effects (facial hypesthesia, ocular complications, masseter muscle weakness). Each possible side effect was asked for specifically, to prevent under-reportage. The questionnaire was followed by an open question, allowing patients to provide information regarding procedural complications that were not included in the above list.

Definitions

The primary outcome is the success rate, defined as an initial positive effect reported by patients after 6 weeks. Patients were considered to have an initial positive effect when oral medication could be stopped within 6 weeks after RF treatment or when patients reported any pain relief following RF treatment. Conversely, failure was defined as no report of pain relief and continuation of pain medication. At the time of the questionnaire, patients were asked to describe their initial extent of pain relief on a 4-point scale (none, moderate, good, and very good). They were asked how long their pain-free period (duration of effect) lasted. The effect was considered no longer present when patients reported needing retreatment with either medication or an invasive treatment. This was cross-checked with their charts to check for conflicts. When there was a difference between the patient’s report and the information on the charts, we regarded the documented patient’s chart as a superior source of information than the self-reported effect because the retrospective nature of the questionnaire depends on the patient’s memory. Additionally, patients were asked to rate the sustainability of the treatment on a 4-point scale (easy, moderate, hard, and intolerable), whether treatment was painful, and whether they would repeat the treatment if symptoms returned.

Statistical Methods

Statistical analysis was performed with Minitab 16 (State College, PA, U.S.A.) and SPSS version 20.0 (IBM, Armonk, NY, U.S.A.). Chi-square test and Fisher’s exact test were used for dichotomous data, and Student’s t-test was used for continuous variables. The duration of effect for the treatment was investigated using the Kaplan–Meier survival analysis. Side effects and treatment sustainability were presented in proportions. Discriminant analysis was used to evaluate the relation that technical treatment parameters had with the initial effect, the extent of effect, and the side effects. Data are presented as mean (standard deviation) unless otherwise specified. A P value under 0.05 was considered statistically significant.

RESULTS

A total of 28 patients who underwent percutaneous RF treatment of the trigeminal ganglion for TN were included in this study. Twenty-six patients were interviewed by telephone for long-term follow-up; 1 patient died during the follow-up period from a cause unrelated to this procedure, and 1 patient could not be located at the time of this evaluation. Twenty-five of 28 patients (89%) experienced significant initial pain relief following percutaneous RF treatment of the trigeminal ganglion. The median length of follow-up was 32 months (20 to 43) after a patient’s initial procedure. The survival curve of 25 patients with initial treatment effect demonstrated that the percentage of pain-free patients was 60% at 12 months and 50% (10 out of 20 patients) at 24 months (Figure 1). No further recurrence of TN was observed after 24 months.

Patients were divided into groups based on the median duration of their pain-free period to identify characteristics associated with long-term effect of treatment (Table 1). No differences were found between groups with short-term and long-term benefit following percutaneous RF treatment of the trigeminal ganglion.

The effects and side effects of percutaneous RF treatment of the trigeminal ganglion as assessed by the questionnaire are presented in Table 2. Pain relief was qualified as good or very good in 72% of the patients.
However, facial hypesthesia, dryness of the eye, and masseter muscle weakness were reported in 56%, 20%, and 12% of the patients, respectively. In 1 patient, treatment was complicated by the development of streptococcal meningitis within 2 days after treatment. This patient was administered antibiotics, recovered, and did not develop any sequelae. The percentage of patients who would repeat the procedure if necessary is presented in the column “Repeat treatment”. The more a patient reported pain relief, the more a patient would choose to repeat the treatment if needed. However, the presence of side effects did not seem to alter patients’ choice concerning repeat treatment.

Table 3 shows the effects of technical aspects of RF treatment on the results of the procedure. Most notable was that the self-reported quality of result (“good result”) following treatment was associated with lower sensory stimulation levels at 50 Hz during treatment as compared to patients without good treatment result. In contrast, a trend toward the assumption that treatments complicated by hypesthesia were performed with lower sensory stimulation thresholds was observed. In addition, patients with good treatment effect were treated with lower lesion times than nonresponsive patients, although it was nonsignificant ($P = 0.074$).

Figure 2 demonstrates discriminant analysis for self-reported (very) good treatment results, a positive result following treatment and hypesthesia vs. the sensory stimulation threshold at 50 Hz. High prevalence of hypesthesia (71%) at sensory stimulation levels lower than 0.32 Hz was found, vs. 33% reported hypesthesia at stimulation levels above 0.32 Hz. Moreover, a high prevalence of self-reported (very) good treatment results was detected at sensory stimulation threshold under 0.38 V, whereas higher sensory stimulation voltages were associated with lower percentages of satisfactory results (83% vs. 40%, respectively). No significant relations between the number of lesions or lesion temperature and outcome were identified. Moreover, no associations between the number of lesions, lesions temperature, and sensory stimulation were found.

DISCUSSION

The present study shows that there may be an optimum of sensory stimulation levels at 50 Hz during RF treatment of the trigeminal ganglion. At lower sensory stimulation levels ($< 0.32$ V), we observed an increased prevalence of facial hypesthesia as a side effect. Higher sensory stimulation levels ($> 0.38$ Hz), however, were
related to reduced treatment effect, despite the lower lesion temperatures used at stimulation thresholds under 0.4 V. We found no association between lesion time or temperature and clinical outcome. Moreover, no clinical or treatment parameter was associated with long-term positive effect of RF treatment. Finally, this study contributes more patient information regarding side effects that could be underestimated if the patient has not thoroughly inquired about them.

The majority of our knowledge and recommendations are based on observational or retrospective studies, as there are only a few well-designed RCTs.\(^3,4,8\) These studies report that RF treatment is a minimally invasive, low-risk technique with a high rate of efficacy for treating TN, which is associated with high rates of side effects.\(^2\) Between 85% and 97% of patients report an initial effect of the RF ablation of the trigeminal ganglion.\(^2,6,9,10\) Pain recurrence rates are between 25% and 60%, and recurrence occurs after a mean of 24 to 68 months.\(^2,6,10\)

We demonstrate an initial positive effect of 89%, a mean duration of 20 months, and a recurrence rate of 50%. The lower mean duration of effect could be explained by the lower follow-up time, which limits detecting higher durations of successful treatment. In this study, patient characteristics are similar to previously published studies regarding sex, co-morbidity, and pain characteristics.\(^6,9\) However, the patient populations of Udupi et al. and Kanpolat et al. are younger than the patient population in this study (mean patient ages of 53, and 56 vs. 68 years, respectively).\(^6,10\) Overall, our treatment effect and recurrence rates are well within the aforementioned range.

The self-reported side effects are facial hypesthesia (56%), masseter muscle weakness (12%), and dry eyes (20%). Although the subjective burden of these side effects is unknown, the side effects are not important regarding the patient’s decision to undergo repeated treatment. Altogether, our results emphasize that percutaneous RF treatment of the trigeminal ganglion represents a high rate of efficacy for treating TN, but there are high rates of side effects.

The objective of RF ablation is hypalgesia in the trigger zone of the neuralgia.\(^10\) However, both the level of hypalgesia as the method of testing remains to be an issue of debate.\(^10,12\) Interestingly, in our study, the presence of facial hypesthesia as side effect was not related to a superior or prolonged effect of therapy, in contrast to the previously mentioned sensory stimulation threshold. Therefore, 1 can consider using the sensory stimulation threshold as a sole indicator for the RF lesion when aiming for good treatment result with reduced incidence of post-treatment facial hypesthesia.

Table 3. Radiofrequency (RF) Treatment Parameters Lesion Time, Temperature, and Sensory Stimulation Used During RF Treatment in Patients with Presence or Absence of Self-Reported (Very) Good Result, Positive Treatment Result, or Post-Treatment Facial Numbness

<table>
<thead>
<tr>
<th></th>
<th>(Very) good result</th>
<th>Positive result</th>
<th>Facial numbness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion Time (Seconds)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>107 (33)</td>
<td>111 (35)</td>
<td>116 (45)</td>
</tr>
<tr>
<td>No</td>
<td>137 (45)</td>
<td>132 (50)</td>
<td>115 (33)</td>
</tr>
<tr>
<td>Temperature (65:70 °C)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>100:56%</td>
<td>100:73%</td>
<td>57:53%</td>
</tr>
<tr>
<td>No</td>
<td>0.44%</td>
<td>0.27%</td>
<td>43:47%</td>
</tr>
<tr>
<td>Stimulation at 50 Hz (V)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.18 (0.18)</td>
<td>0.18 (0.12)</td>
<td>0.45 (0.52)</td>
</tr>
<tr>
<td>No</td>
<td>0.58 (0.55)</td>
<td>0.62 (0.66)</td>
<td></td>
</tr>
</tbody>
</table>

Continuous data are expressed as mean (SD) and tested with Student’s t-tests. The temperature column is presented as the proportion per temperature and tested with Fisher’s exact test.
The current rationale is that RF lesions lead to unselective heat destruction of all fibers in the center of the lesion. In the periphery of the lesion, there is a selective destruction of more vulnerable, small fibers (Aβ fibers and C fibers) with preservation of the larger fibers.\textsuperscript{13,14} It is assumed that sensory stimulation levels under 0.2 V are associated with needles placed intraneurally, destroying all types of fibers unselectively. Nerve destruction by heat might only be a part of the explanation, as RF treatment additionally exposes tissue to an electrical field, which independently induces a change in gene expression.\textsuperscript{15,16} Its effect has yet to be determined, but this could be an explanation for the fact that in some patients, pain relief lasts longer than hypesthesia.

At higher sensory stimulation thresholds, indicating increased nerve-to-needle distance, it might be assumed that the only effects of the electrical field and the selective heat destruction of small fibers will occur. Our results could fit well in the theory of an optimal needle-to-nerve distance for effective and selective pain fiber lesions. Noteworthy is that the sensory stimulation threshold is influenced by many factors (eg, diabetes, previous rhizotomies) and thus has a high intra- and interperson variance, although we could not reproduce these alterations in our current study.\textsuperscript{14,17,18} In conclusion, the current results may provide an indication for increased importance of sensory stimulation levels for needle placement during treatment; however, prospective investigation of an optimal level is still required.

In the present study, we could not objectify relations between lesion time, lesion temperature, and number of lesions with outcome. This might be explained by small variations in these parameters in our database or by small sample size. However, the current rationale underlying these treatment parameters is scarce, leaving room for prospective investigation of optimal technical settings during RF treatment of the trigeminal ganglion. The addition of antidromal responses to the sensory stimulation levels might be valuable, and should be evaluated.\textsuperscript{19}

The current study is limited by its small sample size, which hinders detection of associations between patient characteristics or treatment parameters and outcome. However, our database yields patient characteristics similar to what is reported in the literature. Nevertheless, there are significant differences, which are likely to be reflected in a larger sample. Another limitation is our questionnaire by telephone, which disabled testing patients for corneal anesthesia and sensory loss. On the other hand, we might not have an equally high number of respondents (currently 93%), when aiming for follow-up at the outpatient clinic. Additionally, regarding the sensory stimulation levels, this retrospective study was not designed to find actual cutoff values for optimal stimulation threshold.

In conclusion, the RF treatment of TN has a high initial pain relief rate, but long-term effects are moderate and side effects have high incidences, in the current older patient cohort. Furthermore, the present study shows that low sensory stimulation is associated with increased hypesthesia, whereas higher stimulation levels yield less effectiveness. To our knowledge, we are the first to report a correlation with the sensory stimulation threshold and the effects or the side effects of the treatment. This relation is well fitted in the current knowledge that the effects of RF are not solely based on heat-induced nerve destruction. We propose that needle placement during treatment occurs on sensory stimulation alone, and optimal levels for sensory stimulation are identified in prospective studies.

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