Original Article

# Comparison of the Analgesic Effects of Pulse Radiofrequency and Cryoablation in Rabbits with Mental Nerve Neuropathic Pain

*DG Canpolat, E Soylu[1], F Doğruel, N Kütük, F Uğur[2]*

Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, [2]Department of Anesthesiology, Faculty of Medicine, Erciyes University, Kayseri, [1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Gaziosmanpasa University, Tokat, Turkey

**Abstract**

**Purpose:** After mental nerve injury, several sensory disorders may occur. The alterations in sensation may differ from mild paresthesia to complete anesthesia, or neuropathic pain. Neuropathic pain is a difficult clinical condition to manage. The aim of this study was to compare the analgesic effects of pulsed radiofrequency (PRF) and cryoablation in an experimental mental nerve neuropathic pain model in rabbits. **Materials and Methods:** Fifteen rabbits were divided into three groups. One-third to one-half of the mental nerve was ligated with 4-0 silk sutures. In Group 1, a nonconducting PRF electrode was placed on the mental nerve for 6 min, whereas the mental nerve was exposed to PRF in Group 2. In Group 3, the cryoablation was processed. The responses to thermal and mechanical stimuli were measured at the 1st, 2nd, 3rd, and 4th weeks. **Results:** There were no statistically significant differences among the groups for thermal withdrawal latency to heat stimulation in any weeks ($P > 0.05$). However, a significant difference was found between the groups ($P < 0.05$) in the 3rd and 4th weeks for mechanical withdrawal latency values. **Conclusions:** Both PRF and cryoablation therapies are successful in the treatment of experimentally induced mental nerve neuropathic pain in rabbits.

**Keywords:** *Cryoablation, mental nerve, neuropathic pain, pulse radiofrequency*

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## Introduction

The International Association for the Study of Pain defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system." It generally presents with abnormal sensory signs such as allodynia or hyperalgesia and has a complicated mechanism, which is possibly caused by events in the peripheral, spinal, and central nervous system. Furthermore, the relationship between the etiology, symptoms, and mechanisms of neuropathic pain is complicated. The same symptom may be caused by different mechanisms in two different patients or the mechanism may introduce differences in the same patient over time.[1,2] Several medical treatments (antidepressants, anticonvulsants, membrane stabilizers) and invasive treatments (peripheral nerve blocks, ablation techniques) and alternative therapies (acupuncture) have been used for the management of neuropathic pain over the years. To improve methodologies for the treatment of neuropathic pain, the etiology, symptoms, and mechanisms of neuropathic pain should be properly understood.[2,3] Pulsed radiofrequency (PRF) application and cryoneuroablation are invasive specialized techniques that provide relief for neuropathic pain. It has been reported that the application of PRF may have a minimal destructive impact on neuronal tissue because it is applied for a short duration at a high voltage. Cryoneuroablation, also known as cryoanalgesia or cryoneurolysis, is another treatment method for pain management that provides long-term pain relief. It has been used for craniofacial pain such as trigeminal neuralgia, glossopharyngeal neuralgia, or mental neuralgia.[4,5]

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***Address for correspondence:*** Dr. E Soylu, Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Gaziosmanpaşa University, Tokat, Turkey.
E-mail: dtemrahsoylu@hotmail.com



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The mental nerve is a branch of inferior alveolar nerve that emanates from the foramen mentale. It provides sensory innervation to the lower incisor teeth together with the periodontium and lower lip. A traumatic local anesthetic injection or surgical procedure involving the anterior mandible can damage the mental nerve. Depending on the degree of nerve injury, several sensory disorders may occur. The alterations in sensation may differ from mild paresthesia to complete anesthesia, or neuropathic pain; the neuropathic pain may be either transient or permanent.[5,6] Neuropathic pain is a difficult clinical condition in which classical medical analgesics and treatment methods are often inadequate and requires a multidisciplinary approach for appropriate treatment. We hypothesized that both PRF and cryoablation can alleviate neuropathic pain caused by lesions of the mental nerve. The aim of the present study was to compare the analgesic effects of PRF and cryoablation in an experimental mental nerve neuropathic pain model in rabbits.

## Materials and Methods

The study protocol was approved by the Local Animal Experiments Ethics Committee of Erciyes University. The study was designed as a randomized experimental study and performed between June 2014 and January 2015. Fifteen females white New Zealand rabbits weighing 3000–3400 g were included in the study. The animals were housed 1 per cage on a 12-h/12-h light-dark cycle. The rabbits were allowed to consume food and water *ad libitum*.

The rabbits were randomly divided into three groups of five each. Before the procedure, the weights of the animals were measured. Two authors DGC and FD of this study were blinded to different treatment groups or sham. The left mental nerve dermatome area was shaved, and after a 30-min acclimation period, the responses of the rabbits to basal thermal and mechanical stimuli were measured 3 times at intervals of 2 min. To determine the basal thermal responses and the presence of hyperalgesia, the jaw withdrawal latency for heat stimulation was measured using the hot plate test (20°C–64°C, 220 V/50–60 Hz, with a digital time meter; Analgesic Hot Plate, AHP 9601; Commat Ltd, Ankara, Turkey) on the left side of the chin (cutoff time: 20 s, base temperature: 58.5°C). This technique was adapted from the model of Abbadie *et al*.[7] After 1 h of acclimation, the withdrawal latency for mechanical stimuli was measured by using an electronic algometer.[8]

The animals fasted for 12 h preoperatively and were anesthetized with intramuscular 35 mg/kg ketamine (Ketalar 50 mg/ml, Pfizer Inc., New York, USA) and 5 mg/kg xylazine (Rompun 23.32 mg/ml; Bayer, Mefar Ilac San AS, Istanbul, Turkey). The left mental nerve dermatome area was shaved and disinfected with iodine solution. Infiltrative anesthesia was administered to this area extraorally using 1 ml of articaine hydrochloride (Ultracaine DS, Sanofi Aventis, Istanbul, Turkey). The mental nerve was carefully dissected through a 2 cm length incision, and one-third to one-half of its diameter was ligated with 4-0 silk sutures. This model was adapted from the neuropathic pain model of Seltzer *et al*.[9] The skin incision was closed using 3-0 absorbable silk suture.

The control values of thermal and mechanical withdrawal thresholds of the rabbits were measured 10 days after the mental nerve ligation. The rabbits were anesthetized with the same protocol, and the mental nerve was exposed with a small incision. The presence of neuropathic pain was assessed using the hot plate test and the electronic algometer. After determining the presence of neuropathic pain, PRF (42°C) or cryoablation (−50°C) treatments were applied to the left proximal mental nerve of the rabbits. PRF applications were repeated 3 times at 2 min intervals with a lesion generator which produced RF waves[10] (Neurotherm, Morgan Automation, UK), a 22-gauge RF needle with a length of 5 mm as the active terminal point (Neurotherm 22 GA, Medipoint, Germany), and an electrocoter plate to provide grounding. The cryoablation was applied with a cryoablation device (Universal Cryo-Unit, Eren Medical, Erzurum, Turkey) which works at 600 psi pressure and has a $CO_2$-perfused, 2 mm cryoprobe at −50°C.

In Group 1 (sham group), a nonconducting PRF electrode was placed on the mental nerve for 6 min, whereas the mental nerve was exposed to PRF for 6 min in Group 2 (PRF group). In Group 3 (cryoablation group), the cryoablation probe was placed on the mental nerve and was processed for 120 s. The defrosting process was performed for 30 s after every frost cycle.[5]

The mechanical and thermal withdrawal thresholds were measured in the 1st, 2nd, 3rd, and 4th weeks after the treatments. All measurements were taken between 09:00 and 15:00 for the rabbits to adapt better. The animals were sacrificed at the end of the 4th week.

A power of 1.00 and a significance level of 0.05 (at 4th week) indicated the adequacy of five animals per group.

### Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY, USA: IBM Corp) statistical software package.

Normal distribution of the values was assessed using Shapiro–Wilk's normality test and Q–Q graphics. Descriptive statistics were expressed as mean ± standard deviation and median (25th–75th percentile). Comparisons between groups were analyzed using one-way analysis of variance. If there was a difference, the Student–Newman–Keuls test was used for multiple comparisons. Intergroup comparisons between succeeding times were analyzed using one-way repeated measures analysis of variance in the case of normally distributed differences and with Friedman analysis in the case of nonnormal distribution. If there was a difference, parametric and nonparametric Student–Newman–Keuls tests were used. The result $P < 0.05$ was considered statistically significant.

## Results

There were no significant differences between groups with regard to weight ($P = 0.275$). The mean weights of the rabbits were 3420 ± 496 g, 3020 ± 178 g, and 3300 ± 400 g, respectively, in Groups 1, 2, and 3.

### Thermal hyperalgesia

There were no statistically significant differences between groups with respect to basal, 10th day (Tc), and 1st ($T_1$), 2nd ($T_2$), 3rd ($T_3$), and 4th ($T_4$) week values of thermal withdrawal latency to heat stimulation [Table 1, $P > 0.05$]. Thermal withdrawal latencies significantly decreased after mental nerve ligation in all groups [Table 1, $P < 0.05$]. There were significant differences between the weeks in all groups ($P < 0.05$).

In Group 1, the thermal stimulation jaw withdrawal latency increased significantly at the 4th week when compared to Tc, $T_1$, and $T_2$ [Table 1, $P < 0.01$, 0.01, and 0.02, respectively]. In Groups 2 and 3, thermal withdrawal latencies significantly increased at $T_1$, $T_3$, and $T_4$ when compared to the control values (Tc) [Table 1, $P < 0.001$]. In Group 3, $T_3$ and $T_4$ values were significantly higher than $T_1$ values ($P = 0.04$).

### Evaluating mechanical hyperalgesia

There were no statistically significant differences among the groups with respect to basal ($M_0$), control ($M_C$), and 1st ($M_1$), and 2nd ($M_2$) week values [Table 2, $P > 0.05$]. A significant difference was found between the groups ($P < 0.05$) in the 3rd ($M_3$) and 4th ($M_4$) week values [Table 2, $P = 0.01$ and $P < 0.001$, respectively]. Mechanical withdrawal latencies significantly decreased after mental nerve ligation in all groups [Table 2, $P < 0.05$].

In the 3rd and 4th weeks, mechanical withdrawal latency values were significantly shorter in Group 1 when compared to Groups 2 and 3 [Table 2, $P < 0.05$]. However, no significant difference was found between Groups 1 and 2 ($P = 0.24$, $P = 0.53$, respectively). In Group 1, $M_4$ values showed a significant increase when compared to $M_C$, $M_1$, $M_2$, and $M_3$ values [Table 2, $P < 0.05$]. $M_3$ values were also significantly higher than $M_C$ values [Table 2, $P < 0.05$].

In Group 2, $M_0$ values were significantly shorter than $M_1$, $M_2$, $M_3$, and $M_4$ values [Table 2, $P < 0.05$]. Thermal withdrawal latencies were significantly longer in the $M_3$ and $M_4$ when compared to $M_C$, $M_1$, and $M_2$ values [Table 2, $P < 0.05$]. Furthermore, $M_4$ values were found to be higher than $M_3$ values [Table 2, $P < 0.001$].

In Group 3, $M_0$ values were significantly shorter than $M_1$, $M_2$, $M_3$, and $M_4$ [Table 2, $P < 0.05$]. $M_4$ values were significantly higher than $M_C$, $M_1$, and $M_2$ ($P < 0.05$). However, there was no difference between $M_3$ and $M_4$ [Table 2, $P > 0.05$].

**Table 1: Hot plate test latencies of groups**

| | Groups (mean±SD, s) | | | *P* |
|---|---|---|---|---|
| | Group 1 (sham) (*n*=5) | Group 2 (PRF) (*n*=5) | Group 3 (cryoablation) (*n*=5) | |
| $T_0$ | 10.5±0.8[a] | 11.3±1.7[a] | 11.1±0.9[a] | 0.606 |
| $T_c$ | 3.1±0.3[b] | 3.1±0.4[b] | 2.8±0.5[b] | 0.580 |
| $T_1$ | 4.3±0.3[b] | 4.5±0.4[c] | 4.1±0.4[c] | 0.431 |
| $T_2$ | 4.5±0.4[b,c] | 4.8±0.08[c] | 4.8±0.3[c,d] | 0.343 |
| $T_3$ | 4.9±0.5[b,d] | 5.0±0.4[c] | 4.9±0.4[d] | 0.922 |
| $T_4$ | 5.3±0.4[d] | 5.3±0.5[c] | 5.4±0.3[d] | 0.940 |
| *P* | □0.001 | □0.001 | □0.001 | |

[a,b,c,d]Different letters within each column indicate significant statistical differences among the rates. PRF=Pulsed radiofrequency; SD=Standard deviation

**Table 2: Mechanical withdrawal threshold values of groups**

| | Groups (mean±SD, g) | | | *P* |
|---|---|---|---|---|
| | Group 1 (sham) (*n*=5) | Group 2 (PRF) (*n*=5) | Group 3 (cryoablation) (*n*=5) | |
| $M_0$ | 10.6±1.6[a] | 10.8±1.3[a] | 11.4±2.6[a] | 0.798 |
| $M_c$ | 3.8±0.8[b] | 4.2±0.8[b] | 3.8±0.8[b] | 0.691 |
| $M_1$ | 5.2±0.8[c] | 6.4±1.3[c] | 6.2±0.8[c] | 0.187 |
| $M_2$ | 5.8±0.8[c,d] | 6.6±1.5[c] | 7.4±1.1[c] | 0.150 |
| $M_3$ | 6.2±0.8[d] | 8.2±1.6[d] | 9.2±1.3[d] | 0.01 |
| $M_4$ | 7.2±1.0[e] | 11.0±1.2[a] | 10.6±0.5[d,a] | <0.001 |
| *P* | □0.001 | □0.001 | □0.001 | |

[a,b,c,d,e]Different letters within each column indicate significant statistical differences among the rates. PRF=Pulsed radiofrequency; SD=Standard deviation

## Discussion

In the present study, antihyperalgesic and antiallodynic properties of PRF and cryoablation methods were observed in rabbits with experimentally induced neuropathic pain. Positive effects of both treatments methods were evident at the 3rd and 4th weeks of posttreatment. The effects of the two treatment methods were similar.

Neuropathic pain presents challenges for both physicians and patients. It has various etiologies, with varying complaints among patients. In the orofacial region, trigeminal neuralgia, phantom tooth pain, traumatic neuropathies, and complex regional pain syndrome are the most common types of neuropathic pain. They are often misdiagnosed by dentists, leading to unnecessary treatments, such as endodontic treatment or tooth extraction, which do not solve the problem.[11] Therefore, it should be noted that accurate diagnosis and a multidisciplinary approach is essential for the treatment of neuropathic pain.

Several experimental animal models have been used to induce neuropathic pain in the literature. Most of these models have focused on generating damage or disease on spinal or peripheral nerves. A neuropathic pain model by partial ligation of the sciatic nerve has been described in previous studies.[8,9] Seltzer *et al*.[9] ligated one-third to one-half of the sciatic nerves of rats. The rats showed allodynia and hyperalgesia to thermal and mechanical stimuli after the ligation. For orofacial neuropathic pain models, the trigeminal nerve and its branches have been ligated totally or partially in rats.[12,13] Xu *et al*.[13] ligated infraorbital nerve partially with 7-0 silk sutures to develop neuropathic pain in mice. The mice showed significant allodynia from day 1 that lasted for over 3 weeks. In the present study, we used the same neuropathic pain model, partial ligation of the mental nerve with 4-0 silk sutures, in rabbits.

The threshold values for mechanical stimulation have been determined using von Frey filaments,[14] Semmes-Weinstein esthesiometer monofilaments,[12] rigid electro-von Frey filaments,[15] or an electronic algometer.[8] To determine thermal hyperalgesia, hot plate or radiant heating tests[7] can be used. In the present study, mechanical hyperalgesia and allodynia were evaluated with an electronic algometer which was previously developed by Aksu *et al*.[8] This electronic algometer can measure pressure values ranging from 0 to 3000 g using a rigid needle and overcomes the limitations of von Frey filaments, in which the pressure range varies from 1 to 75 g. We also used a hot plate to induce heat stimulation and recorded the head withdrawal latencies at 58.5°C.

It is known that nerve injuries reduce the mechanical and thermal withdrawal latencies. Dong *et al*.[15] observed a decrease in baseline hind paw threshold values to mechanical stimulation from 60–80 g to 30–40 g. Xu *et al*.[13] showed that baseline paw withdrawal latencies were significantly decreased. Aksu *et al*.[8] also found a decrease in the baseline mechanical and thermal left paw withdrawal latencies from 63.50 ± 8.1 to 29.33 ± 9.1 g and 8.83 ± 0.7 to 4.50 ± 0.5 s, respectively. Using Semmes-Weinstein esthesiometer monofilaments, Seino *et al*.[12] found the preoperative mechanical touch thresholds of the mental and lip areas to be 0.075 ± 0.094 and 0.066 ± 0.086 g, respectively. In contradiction to the previous studies on the sciatic nerve, the threshold values increased in their study. In the present study, however, basal mechanical and thermal withdrawal latencies significantly decreased in all groups. This was interpreted as neuropathic pain development.

RF is a minimally invasive neurolytic technique that relieves pain by modulating pain transmission with controlled tissue destruction. It has been used to overcome several chronic pain conditions for years.[16] PRF is considered an alternative method to conventional radiofrequency[17] with the advantage of causing less neural damage.[4] The analgesic effect of PRF may be attributed to the inhibition of excitatory C-fiber responses by repetitive, burst-like stimulation of A-delta fibers.[18] Aksu *et al*.[8] applied PRF 4 times, for a total duration of 8 min, with each cycle having a duration of 120 s at 42°C and showed positive effects of this method in the treatment of neuropathic pain in the sciatic nerves of rabbits. However, Ozsoylar *et al*.[10] reported that an increased duration of percutaneous PRF did not have a more antiallodynic effect when compared the durations of 2 or 6 min. In contrast, Tanaka *et al*.[19] showed that 6 min is superior to 2 min and longer cycles may be more effective. Furthermore, Park *et al*.[20] found that using >1–2-min cycles resulted in better treatment outcomes when treating occipital neuralgia. Therefore, we applied PRF to the left mental nerves of the rabbits for a total of 6 min, at 42°C. Aksu *et al*.[8] reported that hyperalgesia began to diminish at the 2nd week and returned to basal levels in the 4th week after PRF treatment. In the present study, for thermal stimuli, although threshold levels after the treatment were lower than basal levels, they increased gradually after PRF treatment. Furthermore, hyperalgesia on mechanical stimuli reached basal levels in the 4th week. The fact that the thermal stimuli threshold levels increased from the control levels of 3.1 ± 0.4 s to 5.0 ± 0.4 s in the 3rd week and to 5.3 ± 0.5 s in the 4th week after the treatment within the PRF group was a significant finding. The threshold levels on mechanical stimuli showed an increase from the control level of 4.2 ± 0.8 g to 8.2 ± 1.6 g in the 3rd week and to 11.0 ± 1.2 g in the 4th week posttreatment. According to these results, hyperalgesia reduced significantly in the 3rd and 4th weeks after PRF.

Cryoanalgesia is a safe, simple, and rapid method that is used in the treatment of pain originating from sensory neurons, with an irreversible effect. To achieve

cryoanalgesia, a cold lesion of the nervous tissue is created using a cryoprobe with pressurized gas ($N_2O$ or $CO_2$) at very low temperatures.[5] The length of the frost cycle affects the duration and extent of the cryoanalgesia. Lower temperatures and a longer duration of application cause greater neural damage resulting in a longer recovery period. Zhou *et al*.[21] evaluated somatosensory evoked potentials and sensory conduction velocity by creating cryolesions in the rabbit sciatic nerve between −20 and −180°C and found that the temperatures between −60°C and −100°C would be optimal for postoperative pain management. In addition, below the temperatures of −60°C, plantar flexion or foot drop developed, and decreased activities were observed in these extremities. Fasano *et al*.[22] applied cryoablation to the sciatic nerves of rabbits and rats at −60°C for 3 min and examined improvements in frozen nerves with electron microscopy up to 28 days after the treatment. They determined that degeneration was particularly in myelin fibers, and regeneration began on the 8th day. In the present study, we preferred −50°C to provide cryoablation to avoid neural damage as much as possible. It is known that applications longer than 3 min do not provide any additional benefit; also, sufficient defrost cycles that are longer than 20 s and shorter than 40 s enable more of an area to become affected in the next cycle.[5] In the present study, the frost cycles were determined to be 2 min, and defrost cycles lasted for 30 s. We applied cryoablation 3 times with 2 min intervals. This regime provided a significant decrease in hyperalgesia and allodynia. The significant increase in thermal and mechanical stimulation threshold levels in the cryoablation treatment group indicated some improvement. Moreover, the levels in the 4th week were significantly higher than at all other times, which suggested that they returned to basal levels. In this group, treatment effectiveness was more profound in the 3rd and 4th weeks.

Successful results with cryoablation of the trigeminal nerve for the management of craniofacial pain conditions have previously been reported.[23,24] For mental neuralgia, a 1.4 mm cryoprobe is recommended through percutaneous or intraoral applications.[5] Pradel *et al*.[25] froze infraorbital or mandibular nerves in 19 patients without exposing the nerve by surgical methods. The equipment was used was a nitrogen-perfused cryoprobe and had an outer diameter of 2.7 mm. With this technique, they achieved improvement in sensory processing and pain within 4–8 months. In our study, we were able to use a 2 mm cryoablation probe comfortably, by exposing the mental nerve surgically. Although the mental nerve was exposed through an extraoral incision, it can be approached transmucosally with a very simple surgical procedure in outpatient settings. This method extends the application field of the probe without the risk of damaging the adjacent tissues.

In a long-term follow-up study, Zakrzewska *et al*.[24] compared the effects of thermal RF ablation to cryoablation and microvascular decompression, in the treatment of patients with paroxysmal trigeminal neuralgia. As a result, complications rarely developed after cryotherapy, whereas prolonged sensory deprivation (88%), anesthesia dolorosa (8%), and ocular problems (15%) were seen in patients treated with RF. As for the patients treated with microvascular decompression, 11% had problems with the 8th cranial nerve, and there was 1% mortality. None of the patients in the cryoneuroablation group developed anesthesia dolorosa, and sensory deprivation areas were quite restricted. To the best of our knowledge, there have been no studies comparing the effects of cryoanalgesia and PRF in the treatment of mental nerve-related neuropathic pain. According to the results of our experimental study, there were no significant differences between the clinical effects of cryoablation and PRF methods.

## Conclusions

Both PRF and cryoablation therapies are successful for the treatment of experimentally induced mental nerve neuropathic pain in rabbits. Therefore, both techniques can be suggested to provide relief in neuropathic pain resulting from trauma or injuries to the mental nerve during oral and maxillofacial procedures. Further studies histologically evaluating the mental nerve condition are needed, and clinical studies with long-term results may elucidate the complications and satisfaction rate of the patients after the treatment of neuropathic pain with PRF and/or cryoablation.

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### Conflicts of interest

There are no conflicts of interest.

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