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Original Article

Association of Neuropathic Pain Improvement and hs-CRP Changes among Trigeminal Neuralgia Patients Experienced Radiofrequency Ablation 60° and 65° Celcius: 6 Months Follow Up

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Abstract

Background : Trigeminal neuralgia (NT) is a neuropathic pain that involves the trigeminal nerve in the face. The first-line medical management of patients with NT is Carbamazepine (CBZ). Radiofrequency ablation (RFA) procedure is a minimally invasive procedure using a high-frequency current-generating device that produced heat ablate of C-fibers with effectiveness around 76% for 10 yeas follow-up. Inflammed trigeminal nerve (TG) or the branch(es) might be one of the underlying mechanisms unless vascular compression is a common etiology. The heat effects might be according to the temperature set up varies recently from 60°C to 95°C.
Methods : This observational study enrolled 75 severe NT subjects without satisfactory improvement of treatments, divided into 3 groups: analgesics prescription (Control), RFA 60, and RFA 65 Groups. The LANSS scores and hs-CRP levels were followed-up before (baseline), 2 weeks, 3, and 6 months experienced the treatments. Subjects ages in the range of 48.32 ± 12.73 to 50.88 ± 14.59 years old, and the duration of illness from 4.48 to 10.32 months.
Results : The LANSS score >12 before treatments showed significance improvements ($p<0.001$), as in the Control (64% with neuropathic pain), RFA 60 (100% with neuropathic pain), and RFA 65 group (92% with nociceptive pain) at 2 weeks followed-up. At 3 and 6 months observed 100% subjects with nociceptive pain but without significancies. Even though the hs-CRP levels observed reduced for all groups, especially RFA 60 and RFA 65, but have no significances.
Conclusion : The LANSS scores changes observed significant improvement in all groups, which mentioned if the neuropathic pain syndromes might be better under each treatment. The Hs-CRP levels improvement is better in the neuro ablation groups than analgesic drugs treatment. Even though the Hs-CRP are following of systemic nonspecific inflammation, NT is a focal inflammation.

Keywords : Trigeminal neuralgia, neuropathic pain, inflammation, LANSS score, Hs-CRP

INTRODUCTION

Trigeminal neuralgia (NT) or tic douloureux is a neuropathic pain that involves the trigeminal nerve in the face. Based on existing studies, the prevalence of neuropathic pain in NT in France and England is around 6% to 8%, while data from 13 hospitals in Indonesia ranges from 21.8%. Several epidemiological studies show that the prevalence of NT sufferers in the European region ranges from 0.16 to 0.3%, in Asia it ranges from 0.3 to 0.4%, and the prevalence rate in the world ranges from 12.6 to 27.0 per 100,000 people per year. From several studies, it can be concluded that female sufferers are more often affected (60%) than men (40%) with a ratio of 1.5: 1.1. The age group between 50 and 70 years is a frequent case.[1]

According to The International Association for the Study of Pain (IASP), NT is defined as a recurrent, severe, brief, and sharp pain in one or more division of trigeminal nerves. While the International Headache Society (IHS) defines NT as unilateral facial pain, characterized by facial pain such as electric shock, which is brief and limited to the distribution of one or more divisions of the trigeminal nerve. NT can involve bilateral trigeminal nerve abnormalities although it is rare.[2] The pathophysiology of NT events is still unclear, but the theoretical basis behind the occurrence of NT which is most found around 80% is the theory that vascular compression by vascular tissue generally occurs around the area of entry of the trigeminal nerve to the pons. Trigeminal nerve compression is most caused by arteries (64% of cases), with the Superior Cerebellar Artery (SCA) in 75%, while the remaining 25% is compression of other small arteries and veins.[3,4]

Treatment of NT can be done in 2 ways, namely non-operative and operative. In non-operative management, intervention can be done through drugs or radiofrequency therapy. The first-line medical management of patients with NT according to the European Federation of Neurological Societies (EFNS) and the American Academy of Neurology (AAN), is Carbamazepine (CBZ) with an effectiveness of 70% to 80% with an initial dose of 200–300 mg/day with a maximum dose of 1200 mg/day.[5,6]

Radiofrequency ablation (RFA) procedure or can be called rhizotomy is a minimally invasive procedure using a high-frequency current-generating device that produces heat with the aim of making lesions on a tissue, including nerve tissue.[7,8] RFA is very relevant for the management of trigeminal neuralgia according to the 2019 EAN (European Academy of Neurology) guidelines. Radiofrequency energy utilization can use 2 methods, namely: pulsation or ablation. Pulsed radiofrequency (PRF) has a lower clinical improvement effectiveness than RFA, but the potential for side effects or complications is minimal. Based on case studies, RFA showed better effectiveness with greater potential for side effects. There is no specific standard for temperature selection in RFA. A literature shows that the temperature for RFA varies widely between studies (60°C to 95°C). The long-term analgesic effect of RFA at elevated temperatures (80°C) is not superior to those at relatively low temperatures (60–75°C). Therefore, we recommend a low temperature RFA (60–75°C) for the treatment of NT.[8,9]

The effectiveness of RFA reaches 3 to 10 years after the procedure, about 76% of subjects are pain free without medical therapy, 5% are on a reduced drug dose, and 15% of subjects require high doses of drugs or surgery.[8] Although there are some complications, RFA is still an effective procedure that can instantly relieve pain in 90–100% of NT cases. The proportion of patients who had no pain for 5 years and did not require oral treatment was 57.7%, after 15 years, 42.2% of patients still had no relapse, after 2 years the RFA was as high as 97.2%, after 8.8 years only 7.6%, and the rate of pain improvement after 11 years 52%.[8,10]

Clinical trials and effective pain management require valid and reliable assessments, one of which is using a measuring tool such as the Leedes Assessment of Neuropathic Symptoms and Sign Scale (LANSS), which is the first screening tool made for the diagnosis of neuropathic pain and consists of 5 aspects that describe symptoms and 2 aspects of clinical examination. LANSS has a sensitivity and specificity of 82–91% and 80–94%. If the score is 12 the patient suffers from neuropathic pain.[11]

Some recent studies have indicated the close relationship of inflammation with NT, and some inflammatory factors have been reported to induce neuropathic pain. Inflammation is suggested to exert a certain effect on nociceptor sensitization, and some studies have shown that the pro-inflammatory cytokines that have been produced at the time of inflammation can activate the nerve endings of polymodal nociceptor. Consequently, such kind of peripheral nociceptor sensitization will result indifferent pain quality and duration from the inflammatory tissues.[12]

High sensitivity C-Reactive Protein (Hs-CRP) is used as a marker of choice in monitoring the inflammatory response in the acute phase and can also be used in the chronic phase associated with depression, because in several studies the concentration of Hs-CRP increased thousands of times over time. 48 hours after the onset of inflammation compared to basal concentrations. The CRP test is not a specific test, it only shows inflammation in the body but cannot tell you exactly where it is.[13] The normal reference value for Hs-CRP is 0–0.30 mg/dL. Hs-CRP levels are influenced by proinflammatory cytokines, namely interleukin 1 (IL1), interleukin 6 (IL6), Tumor Necrosis Factor (TNFα), Substance P (SP) and Calcitonin Gene Related Peptide (CGRP).[14] In the study of Lakoski SG *et al*. said overall women had significantly higher median CRP levels than

men (2.56 mg/L: 1.43 mg/dL).[15]

This study aims to determine the effect of low-grade and high-grade RFA and medical therapy on changes in LANSS scores and Hs-CRP levels in NT patients.

METHODS

This is a cohort retrospective observational study with that conducted in the Department of Neurology Dr. Kariadi Hospital in Semarang that conducted for 5 months from May 2022 to September 2022. Participants were NT sufferers who received adequate analgesics prescription, but without any satisfaction of improvement. Subjects definitely carry out tumors, multiple sclerosis, or vascular malformation in regards to FIESTA 3D Head MRI examinations. The dropout criteria include patients who refer for surgeries or RFA re-intervention or died during the study. Seventy-five NT subjects were collected and divided into 3 groups: analgesics medication only (Control), RFA 60°C (RFA 60), and RFA 65°C (RFA 65). LANSS scores and Hs-CRP levels are measured before intervention and after undergoing RFA intervention (2 weeks, 3, and 6 months). RFA procedures were done by a Neurologist Pain and Minimally Invasive physician, who experienced more than 3500 cases of intractable pain. All procedures have done in Operation Theater of Dr. Kariadi Hospital Semarang, by guiding fluoroscope and under local anesthesia. Subjects will refer to the recovery room for 30 minutes to monitor post-intervention. They might monitor for 24 hours then, and be hospitalized for as long as 3 days. The LANSS score <12 means nociceptive pain, while a score >12 was neuropathic pain. The Hs-CRP level was assessed using a venous blood sample. Measurement results were grouped into normal (0–0.3 mg/dL) and high (> 0.3 mg/dL). This study has received ethical approval from the Ethics Commission with the number 1013/EC/KEPK-RSDK/2020.

The data were processed using SPSS statistical software version 26. Nominal data will be expressed as a distribution of frequencies and proportions. For each variable, a normality test was performed. Univariate analysis to see a description of all research data. Bivariate analysis was carried out to test each variable on the output results. Numerical data, consisting of age, are tested using the ANOVA test and Spearman correlation. Nominal data, consisting of gender, was tested using chi-square and Fischer exact. Ordinal data, consisting of long-time of suffering, LANSS score, and Hs-CRP levels, were tested using Kruskal Wallis. The significance result test results are said to be significant if $p < 0.05$.

RESULTS

The 75 subjects enrolled in this study with ages in the range of 48–56 years old, and the duration of illness from 4.48 to 10.32 months. There was no drop outed subject in this study until 6-month follow-up.

All subjects were considered for neuropathic pain concerning LANSS score with improvement at week 2, such is 36% of the Control group showed nociceptive pain, the RFA60 group still the same 100% still neuropathic pain, and in the RFA65 group 92% with nociceptive pain. Then months 3 and 6 showed 100% subjects in all groups with nociceptive pain, and no significant difference ($p = 1.000$).

Even though the Hs-CRP levels observed reduced for all groups, especially RFA 60 and RFA 65, but have no significance. Mild facial numbness gradually improve after RFA was performed, and no serious complications. Analgesics prescribed observed dose reduction, except

TABLE 1
Characteristics of research subjects

Variable	Control	RFA60	RFA65	p
Age (years)	50.88 ± 14.59; 56 (21–74)	50.56 ± 13.16;55 (27–72)	48.32 ± 12.73;48 (20–69)	0.767τ
≤ 50 years	11 (44%)	10 (40%)	13 (52%)	
> 50 years	14 (56%)	15 (60%)	12 (48%)	
Gender				1·000¥
Male	10 (40%)	10 (40%)	11 (44%)	
Female	15 (60%)	15 (60%)	14 (56%)	
Long-time of suffering (months)	4.48 ± 4.68; 3 (1–24)	5.88 ± 5.23;4 (1–24)	10.32 ± 15.84;5 (1–60)	0.123£
≤ 3 months	15 (60%)	8 (32%)	8 (32%)	
> 3 months	10 (40%)	17 (68%)	17 (68%)	

τ = ANOVA, £ = Kruskal wallis, ¥ = Chi Square, *significant p<0.05

TABLE 2
Differences in LANSS scores before and after the 2nd week of treatment, 3rd month and 6th month of the medical group, RFA60, and RFA65

	Control	RFA60	RFA65	p
Pre-treatment				1.000£
Nociceptive	0	0	0	
Neuropathic	25 (100%)	25 (100%)	25 (100%)	
2 weeks				<0.001£*
Nociceptive	9 (36%)	25 (100%)	23 (92%)	
Neuropathic	16 (64%)	0	2 (8%)	
3 months				1.000£
Nociceptive	25 (100%)	25 (100%)	25 (100%)	
Neuropathic	0	0	0	
6 months				1.000£
Nociceptive	25 (100%)	25 (100%)	25 (100%)	
Neuropathic	0	0	0	

£ = Kruskal wallis, *significant p<0.05

TABLE 3
Differences in Hs-CRP levels before and after the 2nd week, 3rd month and 6th month of treatment in the Medical, RFA60, and RFA65 groups

	Control	RFA60	RFA65	p
Pre-treatment				0.048£*
Normal	3 (12%)	10 (40%)	10 (40%)	
High	22 (88%)	15 (60%)	15 (60%)	
2 weeks				0.928£
Normal	5 (20%)	7 (28%)	7 (28%)	
High	20 (80%)	18 (72%)	18 (72%)	
3 months				0.686£
Normal	10 (40%)	16 (64%)	16 (64%)	
High	15 (60%)	9 (36%)	9 (36%)	
6 months				0.834£
Normal	20 (80%)	22 (88%)	23 (92%)	
High	5 (20%)	3 (12%)	2 (8%)	

£ = Kruskal wallis, *significant p<0.05

the Control group is remain analgesic doses.

Increased hsCRP levels correlated with an increase in the LANSS score before therapy, but no correlation was found after the intervention was given. It is suspected that the intervention given has more effect on reducing the LANSS score than reducing hsCRP levels.

DISCUSSION

The neuropathic pain syndromes might establish due to nociceptors activation both in peripheral and central nervous systems, although without clear trigeminal compression or lesions. Neurotransmitter and vasoactive

TABLE 4
The correlation of LANSS score and Hs-CRP levels among subjects

	Hs-CRP pre	Hs-CRP at week 2	Hs-CRP at month 3	Hs-CRP at month 6
Control Group				
LANSS pre	p= 0.230, r= 0.249			
LANSS at week 2		p= 0.217, r= -0.256		
LANSS at month 3			p= 0.195, r= 0.268	
LANSS at month 6				p= 0.973, r= 0.007
RFA60 Group				
LANSS pre	p<0.001, r= 0.692			
LANSS at week 2		p=0.783, r= 0.058		
LANSS at month 3			p=0.511, *r= -0.138	
LANSS at month 6				Not Definited
RFA65 Group				
LANSS pre	p= 0.002, r= 0.592			
LANSS at week 2		p= 0.992, r= 0.002		
LANSS at month 3			p= 0.67, *r= -0.285	
LANSS at month 6				Not Definited

substances lead to a threshold decreased, so both nociceptive and non-nociceptive impulses play a role in pain transmission generation. It continued to the higher centers that will interpret a pain sensation. Nerve injury or resonance vibration near the TG might promote nerve cell hyperexcitation and abnormal transmission. This can be caused by facial pain occurrence even though without noxious stimuli performed.[25] Our study with similarities to the recent that observed female NT subjects more find than males (3: 2.28. This could be associated with smaller TG volume in females than males, as 0.74 mm3 (range 0.35–1.71 mm3) in females and 0.88 mm3 (range 0.42–1.4 mm3) in males. By advancing ages the TG volumes might gradually shrink more related to the degeneration process or atrophy.[26,27] Persistent vascular compression to TG might lead to demyelinated changes, wherein myelin might act as an insulator to facilitate pain transmission.[27] Hormones state play an important role in pain intensity in women. As estrogen can stimulate both central and peripheral sensitization[28], progesterone reduces the pain threshold.[18,29] A common females suffering from NT is slightly more depressed and anxious[30], and tend to be more excessive to express pain than males.[31]

Recently the Numerical Rating Scale (NRS) showed significant improvement underwent RFA by setting the temperatures <70°C (0.88±2.21), 75°C (0.61±1.88), or >80°C (0.57±1.47) ($p < 0.05$). The 75°C set up of radiofrequency might be the optimal temperature set up, that reduced the pain intensity and minimal facial numbness or dysesthesia complications. When the temperature is slightly lower than 75°C, so can cause pain improvement while the long-term effectiveness could be shorter.[32] The successful outcomes described as the severity of pain might reduce at least 50% than before for more than 6 months follow up.[33]

Our study with similar results to the previous study presented a 70-year-old woman suffering from trigeminal neuralgia. She underwent 3 cycles of ablation that increased gradual temperature to 65°C, 70°C, and 75°C RFA for 60 seconds duration respectively, so she has lowering analgesics prescribed. And she gradually pains reduction, and it was completely free after 8 months.[34] The RFA set up at 60°C to 65°C for 90 seconds improved pain among NT patients (91.7%) within 10 days afterward. Only 2 patients (8.3%) showed delayed pain intensity reduction at 8 weeks later.[35] Another study's conclusion of immediate pain relief might reach approximately 91% o 94.8%, with a recurrence of around 18% to 22% after 2 to 9 years of follow-up, and reduced analgesics prescription. A three cycles RFA treatment at 70°C temperatures each for 60 seconds has shown improvement of pain around 67% at three months follow up.[36] The continuous low-grade RFA performed from 50°C to 68°C for 180 seconds for NT patients, observed gradual improvement on the next day with 95%, at 1 week and 1 month 100%, 1 month, 3 months, 6 months, and

1 year of action were 95%, 100%, 100%, 95%, 85%, and 85%.[37] The results are similar to this study that observed significance pain reduction when following up at 2 weeks, 3 months, and 6 months underwent RFA treatments. The reason for selecting the RFA intervention with low temperature is to create a lower degree of post-operative inflammation while still providing benefits similar to standard operational RFA in general.

Those, Control, RFA60, and RFA65 groups did not show significant differences in Hs -CRP levels before and after treatments (2 weeks, 3 and 6 months) (Table 3). NT disorders are associated with local nerve damage or inflammation than systemic events, but the hs-CRP might be following a nonspecific inflammation.[38] It is a non-systemic inflammatory mediator frequently analyzed of association between pain attack among migraine patients and Hs-CRP levels. Increasing levels of Hs-CRP (10.00–20.00 mg/l) correlate to the risks of a chronic migraine attack, but remais of controversy results. Increasing of Hs-CRP levels was associate to frequent attacks of migraine (≥7 days/month) but not for <7 days/month. The 11-years of follow-up mentioned of higher Hs-CRP levels are associated with the risk of chronic migraine. Thus elevation levels might affect on peripheral and/or central general pain sensitization.[39] It is in accordance to the oxidative stress, leukocyte activation, vasodilation, and inflammatory cytokines increased during migraine attacks.[21] The elevated hs-CRP (> 0.3 mg/L) could be related to other comorbidities, such are depression due to chronic pain or systemic inflammation due to advanced body mass index. Whereas this study observed no significant improvement in Hs-CRP levels, although the blood examination showed reduce. Subjects in this study observed no vascular offense to the TG, so the local inflammation from vessel compression is absent. Commonly Hs-CRP had been analyzed as mediators involved in migraine attacks that bring sensitivity (70%) and specificity (73%).[40,41]

In the Control group, there was no correlation between changes in the LANSS score and Hs-CRP levels before and after treatment. At week 2 observed of negative correlation as the LANSS score increased while Hs-CRP levels decrease. This can be understanding that the neuropathic pain syndrome is remains even though the inflammation states reduced. Whereas at months 3 and 6 after the intervention with a positive correlation, as increasing of LANSS score accompanied by Hs-CRP levels increase. The RFA60 and RFA65 groups showed a moderately positive correlation, which the LANSS scores in and Hs-CRP levels increased both at week 2 and month 3 (Table 4). It was might be following post-neuro ablation inflammation, as the performed of radiofrequency neuro ablation the temperature of the surrounding tissue might increase or the frictional heating happen too. Radiofrequency ablation is aimed to interfere with the pain impulses by forming denervating nerves, so immediately can lead to inflammation surrounded.[42] At week 2 observed only the RFA65 group remained with 2 subjects (8%) with neuropathic pain syndromes, even though the LANSS improvement was significant. Whereas after 6 months post neuro ablation the LANSS score showed of null or zero cause might be neuropathic pain syndromes are absented.

Moreover, NT might be an association with inflammation which the nociceptive sensitization activated. When the disorders get prolonged also the inflammation tends to chronic stages, so the polymodal nociceptor and peripheral sensitization activation might increase. By those events, the satellite glial cells and sensory ganglion release the pro-inflammatory mediators, then the nerve excitability might increase and chronic pain appears. The primary sensory trigeminal afferents near the entry zone will be demyelinated, then it can be baed on the NT etiology. The macrophage and mast cells can be found in trigeminal roots, and this with related to the inflammation and NT present.[43] Nonetheless, we realize that limitations remain in this study. We had not analyzed of patient's comorbidities, as they might play the role in the pain perceptions of each subject. NT might be underly by inflammation and degeneration process events, so might be analyzing of cytokines involvement or the neurophysiology examinations.

CONCLUSION

The decrease in LANSS scores and clinical improvement in postoperative pain was greatest in the RFA60 group, starting from the 2nd week. The decrease in postoperative Hs-CRP levels was greatest in the RFA60 dan RFA65 group.

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AUTHOR CONTRIBUTIONS

TB designed the study and proceed with the RFA, TB and YA collected and follow up with the subjects, DP and ED formally analyzed the results. YA wrote the original article draft, and TB write and edited the article.

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