

Assesment of pulsed radiofrequency's effect on level of tnf- α as a proinflammatory cytokin

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ÖZET

Pulse radyofrekans uygulamasının pro-inflamatuar sitokin olan tnf- α üzerine etkisinin değerlendirilmesi

Pulse Radyofrekans kronik ağrı sendromlarının tedavisinde etkin bir yöntemdir. Pulse radyofrekansın çalışma mekanizması bilinmemektedir ve halen araştırılmaktadır.

Biz, kronik ağrı sendromu olan 20-75 yaşları arasındaki pulse radyofrekans tedavisi uygulanan otuz hastaya bu prospektif klinik çalışmayı planladık. Tümör nekroz faktörü-alfa (TNF- α), görsel analog skala ve kategorik ağrı skalası düzeyleri tüm olgularda pulse radyofrekans tedavisi öncesi ve tedavi sonrası üçüncü hafta sonuçları ile karşılaştırıldı.

TNF- α 'nın tedavi öncesi değerleri $5,230 \pm 3,858$ iken, tedavi sonrası üçüncü hafta sonuçları $12,763 \pm 3,322$ idi. Biz TNF- α düzeyleri arasında istatistiksel olarak anlamlı bir artış bulduk ($p < 0.05$).

İkinci kontroldeki TNF- α düzeyindeki artış, inflamatuvar sürecin artırılmış olduğunu gösterebilir. Hasta sayısının artırılması ve/veya diğer anti-inflamatuar sitokinlerinde ölçülerek çalışmanın geliştirilmesini düşünmekteyiz.

Anahtar Kelimeler: Pulse Radyofrekans, TNF- α , Kronik Ağrı

SUMMARY

Pulsed Radiofrequency is a efficient method in chronic pain syndrome therapies. Working mechanism of pulsed radiofrequency is unknown and is currently being investigated.

We studied thirty 20-75 year-old patients with chronic pain syndrome and scheduled for pulsed radiofrequency in a prospective clinical trial. Tumor necrosis factor-alpha (TNF- α) levels, visual analogue scale scores and categorical pain scale scores before pulsed radiofrequency therapy were compared with results of third weeks after pulsed radiofrequency therapy in all cases.

Mean level of TNF- α before a procedure is 5.230 ± 3.858 and means level of TNF- α three weeks after procedure is 12.763 ± 3.322 . We found a statistically significant increase between TNF- α levels ($p < 0.05$).

Increase in second control of TNF- α levels may demonstrate that we aggravated inflammatory process. We also devise to develop this study by increasing number of patient and/or measuring other anti-inflammatory cytokines.

Key words: Pulsed Radiofrequency, TNF- α , Chronic Pain

Introduction

Pulsed radiofrequency (PRF) is a relatively new developed technique that is a variation of conventional radiofrequency treatment. PRF treatment does not allow temperatures above 42°C at the tip of the electrode. PRF provides advantage avoiding thermal tissue destruction and pain sequelae in management of pain. Recently, it has been recommended for treatment of chronic pain (1). Electromagnetic field which is thought to be responsible for the clinical effect of pulsed RF spread from active tip of electrode to around the electrode. The most intense part of the electromagnetic field is pointed tip of the electrode (2). It is a minimally invasive technique that involves application of electric fields to nerves to inhibit nociceptive stimuli and prevent pain transmission. PRF can be considered when conventional treatments have intolerable side effects or do not sufficiently relieve pain (3).

The immune system and circulating cytokines play an important role in treatment of chronic pain. Levels of the pro-inflammatory cytokines IL-1 β , IL-6, and Tumor necrosis factor-alpha (TNF- α) have been directly linked to pain intensity of chronic pain patients (3). TNF- α is one of main mediators in pro-inflammatory process including necrosis, apoptosis and proliferation. It is usually produced by macrophage and T-lymphocyte as a response to injured tissue or stress. Therefore, it can be used as a systemic marker in tissue injury. It is often accompanied by increased serum levels in inflammation in autoimmune diseases and the complications. Tissue damage and inflammation is also considered in pain formation. Inflammatory process in tissue damage seems to be generally accepted responsibly in developing chronic nociceptive signaling and pain formation. Therefore, increased level of TNF- α seems to be a possible link between the inflammatory process, chronic pain, and PRF treatment (4).

Working mechanism of PRF which is recently more preferred technique to treat chronic pain due to not forming tissue damage and less painful procedure is not exactly known but it is considered to act neuromodulation (4-10).

We investigated whether PRF has anti-inflammatory effect by measuring level of TNF- α before and after procedure.

Material and Methods

A prospective study was planned by taking the local ethics committee approval and patients' written consent. Between 20-75 years of age, thirty patients suffering more than 3 months long chronic pain syndrome were planned for pulsed radiofrequency procedure.

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Patients were informed about the technique, at the level of cooperation that can provide this information to understand and work with patients who have the level of cooperation that can provide this information to understand and agree to participate in work were included in the study. Patients included in the study were given an appointment for the procedure.

In all cases taken to the operating room, routine monitoring was conducted. ECG, noninvasive blood pressure and peripheral arterial saturation (SpO₂) was monitored. After the monitoring, patients were taken the convenient position for the procedure. The C-arm fluoroscopy and/or ultrasonography was used for imaging during process.

The needle puncture site determined by fluoroscopy and ultrasound probe was cleaned with an antiseptic solution for sterilization. The Radiofrequency (RF) application was performed to all patients as detailed below: following subcutaneous local anesthetic infiltration, Cosman RFG-1A Lesion Generator (Cosman Medical, Inc., Burlington, Massachusetts, USA) was used for RF thermo-ablation. RF cannula (22 g, 10 cm, 5 mm active electrode tip or 5 cm, 2 mm active electrode tip) was placed in a determined puncture site before processing and then the electrode was placed into the cannula. Electrical stimulation at a frequency of 50 Hz was given for sensory testing after 300 to 700 ohms of impedance values were observed. Paresthesia was questioned asking patients whether there is any pressure, compression or increase in pain where the needle tip was while testing. We accepted that the cannula is in the right place when paresthesia occurs below 0.5V. Motor stimulation was given with a frequency of 2 Hz. Motor response did not occur above 1.5 V. RF procedure was started after our location also confirmed by fluoroscopy or ultrasound. Pulse RF current at 42 °C at 20 ms 2 times per second was performed to patients for 360 seconds. The electrode was removed and needle entry site was closed with a sterile spunch after procedure completed. Patients were discharged within 1 hour following the procedure.

The demographic characteristics, pain duration and characteristics and previously treatment methods of patients, visual analogue scale (VAS) scores and categorical pain scale (CPS) scores before procedure were saved. Patients were invited again after 3 weeks later and a blood samples were gathered again for evaluating their condition. VAS and CPS scores of the patients and degree of satisfaction were saved.

Blood samples were centrifugated by the device (NÜVE NF 1200 brand) turning 4000 rpm/min. Thus shaped elements of the blood and plasma was separated. These serums were stored at -80 degrees centigrade. After serum collected from all patients, we tested TNF- α values with Bender Medsystems brand instant ELISA BMS223INST human TNF- α kit by ELISA method.

Statistical analysis were made with the SPSS for Windows 15.0 (Chi, IL, USA) statistical package program. Descriptive statistics were given as frequency, mean, SD, and proportions. Comparisons were made using the Pearson chi-square or linear by linear association chi-square test for categorical variables. The Kruskal Wallis test was used for comparisons of continuous variables. For comparison of methods, the paired t-test was used. Statistical significance was set at $p < 0.05$ for all other comparisons.

Results

When assessing demographic characteristics age and gender were taken into consideration. The mean age of the patients was 51.00 ± 20.155 . Analysing gender, 66.7 % of patients were female.

The study included 30 patients performed PRF procedure in different approaches according to diagnosed chronic pain syndrome. When all patients evaluated, 5 different PRF techniques were performed. PRF caudal was the most widely applied (Table I).

Table I. PRF procedures performed.

Diagnoses	Procedures	n (%)
Postherpetic neuralgia	Thoracal DRG PRF	1 (3,3)
Morton neuroma	Interdigital PRF	8 (26,7)
Coccygodynia	Caudal PRF	15 (50)
Occipital neuralgia	Occipital PRF	1 (3,3)
Frozen shoulder	Supraclavicular PRF	5 (16,7)
Total		30 (100)

DRG: dorsal root ganglion, PRF: pulsed radiofrequency, n: number of patients

VAS scores before the procedure and 3 weeks after the procedure were compared in all patients. The reduction of VAS scores after 3 weeks were found statistically highly significant when compared to VAS scores before process ($p < 0.001$) (Table II).

Table II. Comparing of Pain scores.

Pain Scores	Before procedure	After procedure (3rd weeks)	p
VAS	$8.00 \pm 1,531$	3.40 ± 2.417	< 0.001
CPS (1/2)	5/25	23/7	< 0.001

VAS: visual analogue scale, CPS: categorical pain scale

In all cases, CPS scores before and three weeks after the procedure were compared. Mild and moderate pain were considered as 1, severe and very severe pain were considered as 2 when comparing. CPS scores are seen at table II. 3rd weeks' CPS scores was found to be statistically significant reduced when compared CPS scores before the procedure ($p < 0.001$).

Patient satisfaction for treatment 3 weeks after the procedure were questioned subjectively. It was found that the majority of patients (63.3 %) were satisfied with procedure performed.

The average values of TNF- α were given at table III. The TNF- α values 3 weeks after the procedure were found to be statistically significant increased when compared the TNF- α values before procedure ($p < 0.001$).

Table III. Evaluating of TNF- alpha levels.

	Before procedure	After procedure (3rd weeks)	p
TNF- alpha	5.230 ± 3.858	12.763 ± 3.322	< 0.001

Discussion

In our study, we performed different PRF methods according to diagnosis of 30 patients. When we compared VAS scores of the patients before the procedure and 3 weeks after the procedure, we found a statistically significant reduction. When we compared the CPS values, the number of patients with mild and moderate pain before procedure was 5. 3 weeks after the procedure this number was 23. CPS results 3 weeks after the procedure as compared to the CPS results before procedure was found to be statistically significant reduced. As we considered in terms of patient satisfaction, we found that 63.3 % of patients who underwent procedure remained satisfied with the treatment of pain. The TNF- α values 3 weeks after the procedure were found to be statistically significant increased when compared the TNF-alpha values before procedure.

Pain management is a combined treatment included pharmacological treatments, interventional procedures, physical therapies and psychological treatments (1). In recent years interventional techniques has become widespread in the treatment of pain (2). One of these is the application of radiofrequency (1,2). PRF is a newer RF method to treat pain that was defined by Sluijter et al (2) and RF signals which came from the generator in the form of short pulses is administered to the neural tissue by RF electrodes. PRF treatment consists of two explosion causing the changing currents each of which is 20 milliseconds per second. Changing current frequency is 500 kHz. 480 ms-silent phase follows 20 ms-active phase. Thus, the detachment of the heat generated is allowed. Current is usually 45 to 50 volts. Higher RF voltage than conventional RF without reaching the average tissue temperature "lethal temperature range" (45-50 °C) is used for PRF. Therefore, PRF is defined as a non-thermal or nondestructive process (5).

Many clinical studies have investigated the effect of PRF in various types of pain. Some clinical trials reported reduction in pain within weeks or months. These publications mentioned treatment of neuropathic pain which include PRF administered to DRG or peripheral nerves. It has been accepted by the authorities that PRF treatment is clinically effective without causing tissue damage (6).

PRF's action mechanism varies between cellular dysfunction, high electromagnetic field, the heat explosion and neuromodulation (2, 6-10). The experimental studies showed that PRF caused neuronal activation (6, 9, 10). The study done by Erdine et al (8) also showed that PRF could cause the cellular structure damage.

PRF's analgesic efficacy mechanisms are still accurately unknown. Higuchi et al (9) reported that PRF caused the electromagnetic field during its acute phase. Thus PRF reduced the transmission of pain signals by causing neuromodulation at molecular and cellular level. In another study, Hagiwara et al (6) reported that analgesic effect of PRF are inhibited by three drugs including α 2-adrenoceptor antagonists, selective 5-HT 3 serotonin receptor antagonist and non-selective 5-HT serotonin receptor antagonist and consequently PRF made analgesic effect by strengthening noradrenergic and serotonergic descending pain inhibitory pathway.

Cell stress markers was measured after PRF administration in several studies. In a study of Higuchi et al (9), PRF was

performed to DRG of rat models and number of cells expressing c-fos gene in superficial laminae of the spinal dorsal horns was observed in significant increase when measured. In an experimental study made recently by Van Zundert et al (10), number of cells expressing the c-fos gene was shown to be increased in both PRF and CRF. Intense c-fos gene expression has been shown to cause sustained activation of some pain inhibitor mechanism.

Göksal et al (11) examined levels of IL-13 showing the anti-inflammatory activity in patients with fibromyalgia, one of the chronic pain syndrome, in a their study. In this study, serum IL-13 levels of patients with fibromyalgia symptoms for less than 2 years, were found low. As a result, it was thought to be an indirect indicator for an increase in proinflammatory cytokines and that no compensatory mechanisms work.

Several cytokines contribute to the perception of pain and pathogenesis of the disease (12,13). TNF- α , one of these, is thought to act as a regulator in the induction of pain in the peripheral and central nervous system (13). It is a powerful inducer for increased sensitivity to pain (hyperalgesia), when administered exogenously (14). Levels of TNF- α expression in nerve biopsies from patients with painful neuropathy in particularly schwann cells were found high (15). Administered intra-sciatic TNF- α injection to rats resulted in pain hypersensitivity which is similar to neuropathic pain in humans (16).

TNF- α has been shown to induce directly neuronal production of neuropeptide and inflammatory agents such as substance P and calcitonin gene related peptide (CGRP) in the spinal cord and dorsal root ganglia. Substance P and CGRP's effects in neuropathic pain are well-known (17). Moreover it has been published that TNF-alpha sensitizes nociceptive neurons by inducing the proinflammatory cytokine cascade indirectly including IL-1beta, IL-6 and IL-8. This cytokine cascade leads to the release of prostaglandin and other inflammatory mediators from immune cells. TNF- α also may induce pain directly. The proof of that is creating painful neuropathy, when injected into the sciatic nerve (18). Maretto et al (3) investigated a possible role of PRF-induced modulation of TNF- α secretion by differentiated monocytes in chronic pain management. They determined that PRF does significantly increase TNF- α secretion of differentiated monocytes that have not been stimulated with LPS. This may clarify a possible role of PRF treatment in increasing TNF- α production of non-stimulated monocytes.

Conclusion

In our present study, we investigated the mechanisms of PRF's effect from a different aspect by investigating whether PRF used for treatment of many chronic pain syndromes affect impact levels of TNF-alpha which is one of the most important proinflammatory cytokines and plays a key role in the pain formation. We found statistically significant increase of TNF- α levels 3 weeks after procedure when compared the TNF- α levels before procedure.

As it is known, anti-inflammatory cytokines are involved in inflammatory response process, of which the most important finding is pain as proinflammatory cytokines. According to results of our study, we found out an increase in TNF- α values as a result of the inflammatory response. Measuring serum levels of all anti-inflammatory cytokines would me

more helpful in understanding the relationship between inflammation and pain because due to our study results increase in anti-inflammatory cytokines might have responded with an induction in increase of inflammatory cytokines.

Finally, the PRF is an effective method in the treatment of chronic pain syndromes and it provides high advantages like being non-destructive and causing no nerve damage. PRF's known effect mechanism is neuromodulation created by electromagnetic field formed. At the beginning of our study, our aim was to assess whether PRF method has the anti-inflammatory activity. We found that PRF provoked TNF- α as a proinflammatory cytokine. According to these results, we determined that we cause an inflammatory process contrast to our expectations. We think that to assess an anti-inflammatory cytokine (exp. IL-13) in patient's serum is the missing point of our study. Therefore we believe that we will take the study a step further, when we assess whether PRF impact the anti-inflammatory process.

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