Available online at **www.ijmrhs.com**

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2016, 5, 7S:539-546

The Comparison between Two Methods for the Relief of Knee Osteoarthritis Pain: Radiofrequency and Intra-Periarticular Ozone Injection: A Clinical Trial Study

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ABSTRACT

Knee osteoarthritis is not always well controlled by usual treatments, therefore new therapeutic methods such as radiofrequency and ozone injection should be investigated. Comparing the efficacy of two methods: radiofrequency and intra-periarticular ozone injection. This randomized clinical trial study was performed in an academic Pain Clinic of Guilan University of Medical Sciences in Iran from September 2014 to June 2015. The research was carried out on seventy-two patients, were randomly allocated in two groups by triple blocks. thirty-six patients in ozone group received intra-periarticular ozone injection and 36 patients in RF group, after a positive diagnostic genicular nerve blocks received Conventional Radiofrequency(CRF)and then intra articular Pulse Radiofrequency(PRF). The evaluation was based on Visual Analog Scale (VAS) and Oxford Knee Score (OKS) before and 12 weeks after the procedure. The analysis was performed by paired t-test, Fisher, Chi square and Mann-Whitney-U tests in SPSS version18. In Ozone group the mean of initial OKS was 38.77±7.75 compare to 41.22±7.44 in RF group. After 12 weeks, it diminished to 21.77±7.78 and 22±6.21 respectively (p=0.0001). In Ozone group VAS decreased from 9±1.43 to 3.38±1.79 (p=0.0001) while in RF group from 9.44±0.85 to 2.77 ±1.06 (p=0.0001). Comparing two methods, there was no significant difference between two groups based on OKS(p=0.23) and VAS (p=0.202). Also RF resulted in more acceptable pain relief based on OKS among subjects older than 65 years (p=0.0001). Both radiofrequency and intra-periarticular ozone injection have good clinical effects on knee osteoarthritis with superiority of radiofrequency in age above 65 years old.

Keywords: Knee osteoarthritis, Ozone, Radiofrequency, Pulse Radiofrequency

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INTRODUCTION

Osteoarthritis is the most common type of arthritis.[1] It is a cause of significant disability and decreased quality of life in persons older than 65 leading to an economic impact.[2]Knee osteoarthritis contributes 23% of all osteoarthritis which 27% of people under 70 are affected by.[3] More than one-third of people above 65 known as elderly are affected by knee osteoarthritis among which 80 percent have some movement limitations.[4, 5]It is a joint failure, wherein all the structures undergo pathologic changes.[1]The risk factors are advanced age, female gender, genetic, diet, obesity, previous damages, smoking, occupation and metabolic diseases, among which age and obesity are the two major ones. [3, 6] To alleviate pain and restore the joint function, treatments can be pharmacologic including oral analgesics, topical agents and nutritional supplements or non-pharmacologic including weight loss, social support, orthotics, appropriate footwear, knee bracing and exercise and in the end stage patients with uncontrolled pain, total joint replacement can be considered. However these treatments are sometimes disappointing and may cause dangerous complications.

It is important to note that 53% of patients continue to have knee pain after surgery.Since knee joint has a complex anatomy of the nerve supply, invasive treatments are difficult to perform. Therefore it is necessary to investigate new therapeutic methods with more effectiveness and less side effects.[1, 4, 7-12]

Two new therapeutic methods to manage kneeosteoarthritis are Radiofrequency and intra-periarticular Ozone injection. Studies have shown that these methods are effective with no serious side effects. Those patients who cannot take medication or their symptoms are refractory to conservative treatments and are not appropriate surgical candidates because of co-morbidities, benefit from these treatments.[4, 6-10, 13-16]For Conventional Radiofrequency [CRF] a high frequency alternating current is used. An electrode is placed on the target nerve and thermo-coagulation induces tissue destruction by producing heat up to 60-80$^{\circ c}$. CRF is safer than chemical neurolysis. Pulse Radiofrequency [PRF] is an alternative to CRF in which temperature remains below 45-50$^{\circ c}$ so the tissue injury will not develop.[10, 17]

Ozone therapy is another method which induces anti-inflammatory and analgesic effects and within its therapeutic concentrations, can relieve pain and improves knee function without serious adverse effects. [9] Ozone is also bacteriostatic, fungicidal and virucidal, therefore with minimal infection risk. It also stimulates the oxygen metabolism and activates the immune system. Detoxification effect of ozone is performed by activation of metabolic processes in liver and kidney. [18, 19]

This study compares the effectiveness of these two methods on the knee osteoarthritis pain relief and function improvement.

MATERIALS AND METHODS

This clinical trial study was conducted at an academic pain clinic of Guilan University of Medical Science (GUMS), in Iran from September 2014 to June 2015on the patients with knee osteoarthritis which was diagnosed based on ACR (American College of Rheumatology) criteria.(4, 20)It was registered in Iranian Registry of Clinical Trials (IRCT) with the number of 12156186N6.This study was carried out after acquisition of permission from the Ethics Committee of Research & Technology of Vice-chancellorship of GUMS.

Sample Size:
To determine the required sample size, with α=0.05,β=10% , Z1-β= 1.28 and a power of 90%, the minimum sample size required in each group was calculated to be 36 cases .Allowing for losses, we finally estimated a sample size of 40 cases in each group.

A total of 72 patients in the age range of 30 to 80 year participated in this study after filling out a written informed consent. These patients were randomly allocated to two groups intervened by Ozone and Radiofrequency in triple blocks. The patients had moderate to severe knee pain at least for 3 months with no response to usual conservative treatments. Their radiologic K/L (Keller-Lawrence Grading Scale) scores were between 2 to 3.[21]We excluded the patients with acute knee pain, prior knee surgery, other connective tissue diseases affecting the knee, secondary osteoarthritis, serious neurologic or psychiatric disorders, sciatic pain or any other neuropathic pain, anticoagulant

medications, having pacemaker, steroids injection in the last three months, and prior electro acupuncture treatment. (7, 9)One physician performed all procedures.

Ozone group patients received intra articular ozone injection (10^{cc} O_2-O_3 mixture 40µg/ml) and periarticular injection (5^{cc} O_2-O_3 mixture 10µg/ml) by Ozone Generator HERRMANN. The patients were required to rest for 30 minutes in functional position after the procedure. This procedure was performed three times during the first week and twice during the second week and once in every next three weeks. Articular branches of various nerves such as femoral, common peroneal, saphenous, tibial and obturator nerves which are known as genicular nerves innervate the knee joint.[15]

In Radiofrequency (RF) group the first step was to perform diagnostic genicular nerve blocks under fluoroscopic guidance. The targets were superior-lateral, superior-medial and inferior-medial genicular nerves that pass periosteal areas connecting the shaft of the femur to bilateral epicondyles and the shaft of the tibia to the medial epicondyle. If a decrement of 50% was achieved in VAS that lasted for more than 6 hours, responses were considered positive, after injection of 1 ml of Bupivacaine 0.5%. After diagnostic nerve blocks, the patient received conventional RF by Diros3AP RF generator. 1ml of Lidocain1% under sterile condition in a supine position was injected to anesthetize the skin and soft tissue.

After making the knee joint visible antero-posteriorly under fluoroscopy guidance, a 10 cm, 22 gauge sharp RF cannula with a 10 mm active tip was advanced towards the target sites, areas connecting the shaft to the epicondyle until the cannula contacts to the bone(tunnel technique).

To identify the correct needle position, we used a 50 Hz sensory stimulation above a threshold 0.4 Volt (sensory test), and then a 2Hz stimulation above a threshold 0.8 Volt (motor test) was used to avoid motor nerve injury. After assuring the correct needle placement in anterior-posterior and lateral view, 1ml of Lidocain1% was injected and afterwards RF generator was activated, rising electrode tip temperature to $70^{°c}$ for 90 seconds.

The procedure was carried out for each genicular nerve and then intra-articular PRF having a pulse width of 10 milliseconds at 2 Hz and 65 Volt, using a 15 mm active tip SMK-C15 blunt needle was performed for 10 minutes.(Fig1)

The evaluation of pain severity and knee function was based on Visual Analog Scale (VAS) and Oxford Knee Score (OKS) carried out once prior and once 12 weeks after the treatment. OKS is a short, simple, practical, valid and sensitive scoring system, containing12 questions each scored from 1 to 5. [7, 22] The questionnaires for all the patients were filled out by one physician. The patients were also asked to report any side effects like bleeding, paresthesia, numbness, motor weakness, and thermal injuries within the 12 weeks of the follow up. Medical attention and other means were available for the patients subjected to the study.

Statistical Methodology:
To test all scale variables normality, Kolmogorov-Smirnov test was used. Based on the normality of variables the appropriate statistic tests were chosen. To compare patients' characteristics variables, Chi-square test and Fisher test were used. The differences of VAS and OKS between the two groups at baseline were compared by using paired-t-test. Also Mann-Whitney-U test to compare the changes of VAS from baseline until 12 weeks after treatment and paired t-test to compare the changes of VAS from baseline until 12 weeks after treatment were used. The data analysis was performed in SPSS software version 18. The values were estimated as mean ± standard deviation(SD). P value of <0.05 was considered significant in all analysis.

RESULTS

The patients for the study were selected from a hundred forty-seven patients with knee pain during the study period. Among them,56 did not meet the inclusion criteria and11of them refused to enter the study for personal reasons. The remaining 80 patients were enrolled in this clinical trial and were divided into Ozone and RF groups. Four patients allocated to Ozone group, lost the follow up and therefore were deleted from the study. One had an accident and was referred to an orthopedic surgeon for the broken knee at one week post-procedure. Another patient had a similar accident at the second week. The other two did not come to complete the questionnaire after 12 weeks.

In RF group, four patients did not complete the protocol. One was pain free after diagnostic nerve blocks and the other three did not have a positive response to diagnostic nerve blocks. A total of 72 patients (in the age range of 51-78 year), half in each group with similar distribution of gender, age and BMI (Body Mass Index) completed the study, which the mean of BMI of participants in Ozone and RF groups was 28.64± 4.98 and 26.13±3.03 (p= 0.06).Also the mean of age was 66.69±8.95 and 68.33±3.48 (p= 0.459) respectively. Twenty patients (66.7%) in ozone group and 32 patients (88.9%) in RF group were above 65 years old. Considering the gender distribution, females have formed 86.1% and 77.8% of contributors of mention groups respectively (p=0.461)

No severe side effects were reported. We recorded only a tolerable mild to moderate swelling around the joint in some patients that was not considered a serious complication.

Based on both VAS and OKS we found that both groups responded well to treatments and the pain severity decreased significantly after 12 weeks compared with baseline.(Fig 2&3) (Table 1)

By comparing the two methods, although relief of pain based on VAS and OKS was more prominent in RF group but not significant (p>0.05). (Table 2).Having studied patients in two different age groups, below and above 65 years, RF resulted in more acceptable pain relief based on OKS among subjects older than 65 years(p=0.0001) (Table 3)**.**

DISCUSSION

The study focused on comparing radiofrequency and ozone injection in making relief of the knee osteoarthritis pain, due to lack of profound findings in the related studies. We hope this study promises further studies. According to the results, both proposed procedures were acceptable and tolerable for the patients, inducing analgesia and improved knee function, which agrees with the previous findings of others. These methods are relatively new and therefore, their real mechanisms of action are not completely known. However, the findings of the current study as well as those of the others confirm their effectiveness and therapeutic role.[3, 7-10], [23-25]

Our present understanding from Ozone therapy and RF indicates that the mechanisms of action of these methods are different from each other and as well as from conventionally available methods. For example, the mechanism of CRF action is based on the theory that the heat induced lesion in the nerve supply to a painful structure, such as knee joint, can relieve pain and restore function[7].In large joints such as knee, PRF takes effect on immune cells. The electrical field affects these cells, and consequently the production of pro-inflammatory cytokines, interleukin-B, Tumor necrosis factor and interleukin-6 occurs. This method does not cause neuronal or tissue damage; therefore can be applied for peripheral nerves.[10] In ozone therapy, a soluble gas mixture with oxidization activity is used. When pure oxygen passes through a high voltage gradient [5-13V] in a generator, ozone is produced. Ozone increases antioxidant capacity and oxygen delivery to tissues by neo-angiogenesis.[26, 27]It blocks phosphodiasterase-A2 and therefore can induce anti-inflammatory and analgesia effects. The mechanism which ozone can raise the pain threshold is probably the stimulation of the anti-nociceptive apparatus mediated by endogenous serotonin and opioids.[9, 13, 28]

In this study 86.1% of the patients in ozone group and 77.8% in RF group were female. Likewise 66.7%of patients in ozone group and 88.9% in RF group were above 65 years old. Considering the selection strategy of patients in this study and the above statistics, the two factors of female gender and advanced age are confirmed to be the major ones. [1, 6]The evaluation was based on VAS and OKS, considering that VAS and OKS are different types of scales for evaluation. So that VAS only measures pain intensity while OKS measures disability due to pain. It is the reason for the difference observed in our results by VAS and OKS. Bellini M et al. used cooled RF as a novel technology for knee OA. They demonstrated that this technique had the potential to significant improve in pain and function of the knee joint.[15]

Pattnaik M et al. reported that PRF of the sensory and motor nerves of the knee joint is a minimally invasive and effective modality in improvement of knee function.[29] Schianchi PM Recommended Intra-articular PRF as a minimal invasive method with encouraging success rate in articular pain.[30]

Eyigor C *et al.*in 2014 studied the efficacy of Intra-articular PRF application in knee OA. They found this intervention safe and effective for this purpose.[31] A study by Karman H et al. in 2010 focused only on intra-

articular PRF showed the reduction of knee osteoarthritis pain. The pain severity by VAS score changed from 6.1±1.9 to 4.1±1.9 after 6 months. [10]In comparison, by our data the change of VAS of 9.44±0.85 to 2.77±1.06 after 12 weeks showed better consequences. It is believed that the reason is the CRF performed after diagnostic nerve blocks additionally to PRF. It is worthwhile to mention that the follow up duration in our study was shorter than the work done by Karman H et al. If we could have evaluated our patients after 6 months, we might have had different results.

Jong Choi W et al.in 2010 found that CRF reduces chronic pain of knee osteoarthritis. The average age in their study was 67.9±7.1 and 62.22±7.59 years in our study. Both studies had the same follow up duration of 12 weeks. In their study VAS diminished from 78.2±13.8 to 42.4±25.4 and OKS from 27.4±10.2 to 39.8±6.5.(7)In our study the initial VAS was 9.44±0.85 and 2.77±1.06, 12 weeks after procedure and OKS diminished from 41.22±7.44 to 22±6.21. It seems that our results were better by VAS and OKS due to the differences between two methods.After diagnostic nerve blocks, we followed CRF by performing intra-articular PRF.

Morreti M et al. in 2010 showed that intra-articular ozone injection was effective for the function and symptoms of knee osteoarthritis. Their patients with the average age of 54 years old received intra articular ozone injection (5^{cc} O_2-O_3 mixture 15µg/ml) and hyaluronic acid, we had a superior improvement by VAS because of the difference of methods.(3)In various conditions, different concentrations of oxygen-ozone mixture have been recommended. For example inozone therapy for lumbar disc herniation ozone is administrated in the form of an oxygen-ozone mixture at a concentration of 27 µg/ml, in degenerative disease like knee osteoarthritis it has been used in a range of 3-11µg/ml peri-articular and 30-40µg/ml intra-articular. Even in metastatic tumors a concentration of 90µg/ml is used. But nontoxic concentrations vary from 1µg/ml to 40µg/ml.(23, 32) Several studies indicate that peri-articular injections(local anesthetics, steroids, ozone) are easy to use, cost effectiveness, safe with no major complications and have agood efficacy in knee pain control. By the way we know that stimulation of fibers in the joint and surrounding tissues produces nociception, therefore the source of knee osteoarthritis pain is related to peri-articular structures in additional to articular.(33-36) We used a mixture with concentration of 40µg/ml intra-articular. Additionally we performed peri-articular injection,$5^{cc}$of mixture in mediolateral sides of knee, whereas in study by Morreti only a solution with 15µg/ml concentration was used intra-articular. Although the average age of patients was less than ours and received hyaluronic acid in addition to ozone injection, but we had better results. It seems that more concentration of (O_2-O_3) mixture and more treatment sessions together with peri-articular injection in addition to intra- articular injection give better results.(3)

The limitations of the present study were: first we do not know whether the effectiveness of our treatment will continue in the long term or not, second we cannot be sure enough about the safety of these procedures in the long term, third in RF group we denervated only three branches innervating knee joint, the results could have been different with denervating other branches.

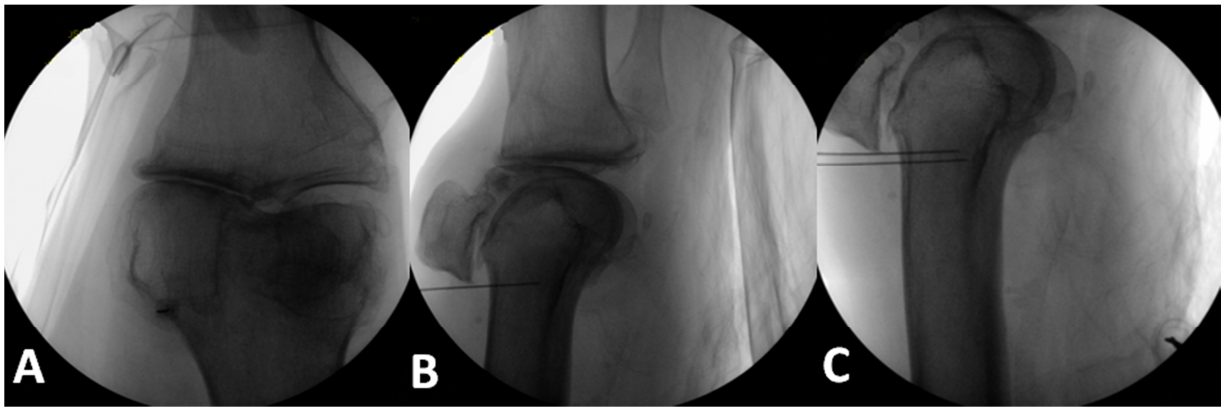

Figure 1: radiofrequency neurotomy of genicular nerves (A&B), Intra-articular pulsed radiofrequency(C)

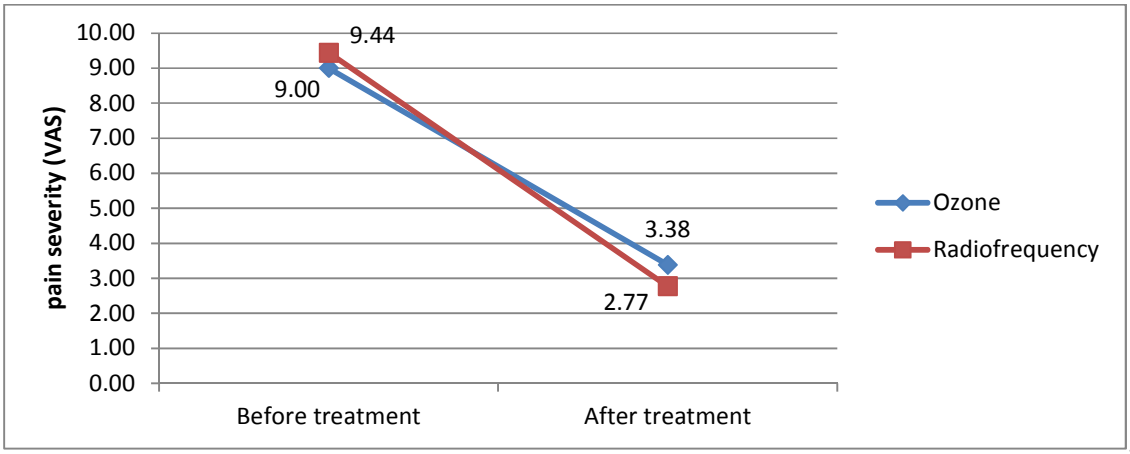

Figure 2 :VAS changes after 12 weeks compared with baseline

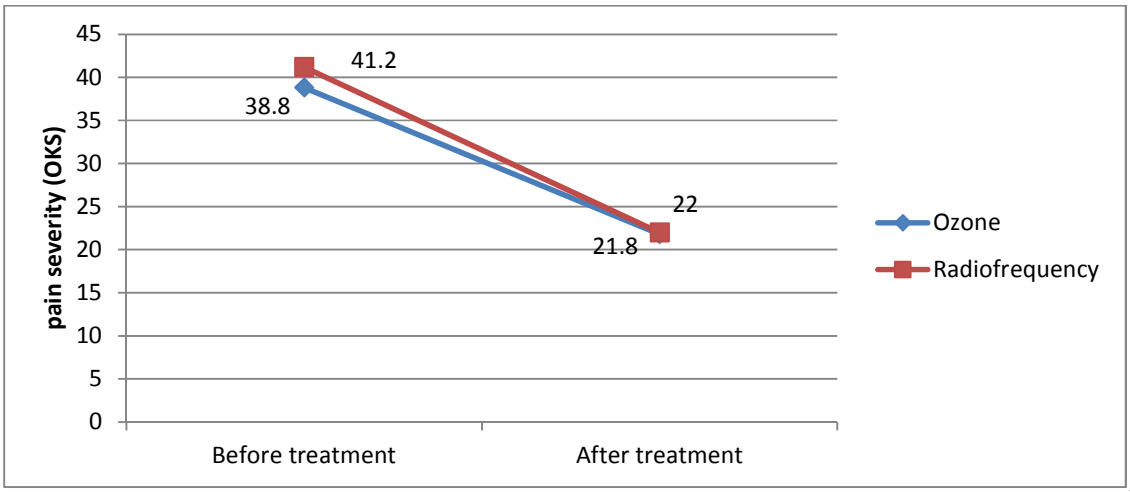

Figure 3: OKS changes after 12 weeks compared with baseline

Table 1: The means of pain severity in RF and Ozone groups before and after treatment and its changes (by VAS & OKS)					
	Before treatment	After treatment	P-Value	Mean of changes± SD	P-Value
Ozone (VAS)	9 ±1.43	3.38±1.79	0.0001	5.61±2.14	0.202
Radiofrequency (VAS)	9.44±0.85	2.77±1.06	0.0001	6.66±0.84	
Ozone (OKS)	38.77 ± 7.75	21.77 ± 7.78	0.0001	17±6.89	0.23
Radiofrequency (OKS)	41.22 ± 7.44	22 ± 6.21	0.0001	19.22±4.98	

Table 2: The means of changes of pain severity in RF and Ozone groups (by VAS & OKS)		
	Mean of changes± SD	P-Value
Ozone (VAS)	5.61±2.14	0.202
Radiofrequency (VAS)	6.66±0.84	
Ozone (OKS)	17±6.89	0.23
Radiofrequency (OKS)	19.22±4.98	

Table 3: The means of changes of pain severity in RF and Ozone groups (by VAS & OKS) according to age				
Age(year)	Group	Number	Mean of changes± SD	P-Value
<65	Ozone (VAS)	12	5.66±1.3	0.549
	Radiofrequency(VAS)	4	6±0	
	Ozone(OKS)	12	16.2±6.18	0.423
	Radiofrequency(OKS)	4	20±2.3	
≥65	Ozone(VAS)	24	5.58±2.48	0.623
	Radiofrequency(VAS)	32	6.75±0.85	
	Ozone(OKS)	24	17.37±7.32	0.0001
	Radiofrequency(OKS)	32	30.37±3.93	

CONCLUSION

It seems that both radiofrequency and intra-periarticular ozone injection have good clinical effect on reliving knee osteoarthritis pain. But it is interesting to note that in patients older than 65 years, Radiofrequency resulted in a superior improvement. Of course further studies and more experience are essential to establish the role of these methods in management of knee osteoarthritis.

Acknowledgments
With thanks to Research and Technology Vice- Chancellorship of Guilan University of Medical Science (GUMS).

Financial Disclosure: The authors declare that they have no conflicts of interest

Funding/Support: This study was financially supported by the vice-chancellorship of research and technology at Guilan university of medical sciences.

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