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Intraarticular Injectıon Selection in Gonarthrosis Treatment: Platelet Rich Plasma, Ozone or Combined Treatment

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Abstract: *The aim of this study is to compare the efficacy of intraarticular platelet-rich plasma (PRP), ozone therapy (OT) and PRP + OT applied for therapeutic purposes in patients diagnosed with gonarthrosis.In the study made as prospective, randomized controlled study (RCT), by obtaining consent, 75 patients diagnosed with stage 2 or 3 gonarthrosis according to Kellgren-Lawrence scoring system were included in the study. In the first group (n = 25) OT, in the second group (n = 25) PRP, in the third group (n = 25) PRP + OT (n = 25) injections were administered intraarticularly for a total of 3 sessions one week apart. Visual pain scale (VAS) and severity of pain were compared with Western Ontario Mc Master Osteoarthritis Index (WOMAC).In the PRP + OT group, WOMAC pain, physical function, and WOMAC total score were significantly (p< 0.05) lower after treatment than those treated with OT or PRP only. WOMAC hardness score was not showed significant (p> 0.05) difference. Although the VAS score showed decreasing significantly(p < 0.05) compared to pre- treatment after treatment in all three groups, the VAS score of the PRP+ OT group was significantly more lower (p < 0.05) than the OT or PRP group.PRP and OT, which have been used frequently in medicine in recent years, confirm that it is beneficial in the treatment of gonarthrosis in terms of pain and functional recovery,however, when the two are used together, their efficacy is better than when used alone. Most importantly, our study contributes to the literature in terms of the limited number of publications on this subject.*

Keywords: *Osteoarthritis, Ozone Therapy, Platelet Rich Plasma*

INTRODUCTION

Knee pain is one of the most common reasons for presenting in orthopedic outpatient clinics and gonarthrosis is the most common cause of knee pain in societies over 50 years [1]. When we put aside trauma-induced pain, the increase in life expectancy and intense sporting activities lead to an increase in joint cartilage problems, triggering an increasing amount of gonarthrosis formation. In gonarthrosis cases under the age of fifty, males are affected more frequently, whereas in patients over 65 years of age, the number of female patients is 2 times more than in males [2]. Gonarthrosis is a condition in which joint cartilage, synovial membrane and subchondral bone are affected.In the past, addition, although overload and mechanical stress were thought to played a major role in the development of arthrosis, but it has been shown to play active role in the formation of gonarthrosis in metabolic disorders along with many different inflammatory processes. Today, it is focuses on that intra-articular biochemical balance has an important role in maintaining joint health and it is aimed to treat gonarthrosis with the way by correcting this biochemical balance which was corupted in gonarthrosis joints [3]. The primary goal of gonarthrosis treatment is to reduce pain. Although the mechanism of pain in gonoarthrosis is very complex, many non-surgical treatment methods are available. First recommendations that will made, patient information and education; if obese, are weight loss and exercises.Varus or valgus deformity in the knee is a risk factor for gonarthrosis and osteoarthritis (OA) progression. Knee bracing is a logical method of correcting biomechanical imbalance and may help to correct symptoms [4]. In Gonarthrosis, treatments are arranged according to the stage of the disease. Staging is performed according to radiological standards along with the clinical status of the patient [5,6]. Physical therapy applying to the knee reduces pain and the Mc Ontario Osteoarthritis Index (WOMAC) score in Western Ontario [7]. Other treatments applying in symptomatic gonarthrosis are oral or topical nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, intraarticular steroid injection.However, since these agents do not have curative efficacy, they are only used to suppress acute exacerbations and their potential side effects limit their long-term use [8]. Hyalunoric acid (HA), radioisotopes, botilinumtoxin A, tropisetron are synthetic agents aimed at healing by regeneration. Recently, the nerve growth factor tanezumab has also been shown to reduce inflammation in OA. Although many studies have been published examining the efficacy of these agents, no clear conclusions have been reached as to how effective they are [3,9]. The use of agents containing growth factors of autologous origin is therefore becoming increasingly common. Platelet-rich plasma (PRP) is the leading one [10].Besides PRP, plasma rich in growth factors (PRGF), platelet-rich fibrin (A-PRF), concentrated growth factor (CGF), bone marrow-derived chondrogenic stem cell (BMSAC), non-fractionated bone marrow (WBM) are agents that obtained from patient's own blood or bone marrow and injected into the joint. Likewise, by using these

autologous agents, it is aimed to stop intraarticular damage and improve the resulting damage. Although studies which was made, have shown that these products are superior to the synthetic products, there is no clear literature information about which product should be used in which patient [11-12]. Intraarticular medical ozone is a long been applied treatment, but the number of literature on this issue is limited. ozone therapy (OT) is thought that, by increasing blood flow and oxygenation in tissues with inflammation and pain, provides better joint mobility by cleaning metabolic wastes in the affected joints.Again, it has anti-inflammatory, immunomodulatory, anti-edemic and antioxidant effects. In patients who has gonarthrosis, there are studies shown that with intraartricular OT, pain reduces and quality of life improves. Intraartricular OT is a minimally invasive and well-tolerated procedure in patients with could not be get sufficient clinical response to conservative treatments or with patients whose physiotherapy is contraindicated [13-15]. In patients with gonarthrosis, there are very limited studies in the literature comparing the efficacy of PRP and OT or, where there were combined application . In this study, we published our results by examining the effects of PRP and OT, that are more easier to obtain compared to the other autologous products mentioned above, on gonarthrosis when used alone in the short term and applied in together.

MATERİALS AND METHODS

In our study, 75 patients admitted to the physical medicine and rehabilitation clinic between September 2019 and December 2019 with knee pain and diagnosed as stage 2-3 gonarthrosis according to Kellgren-Lawrence classification were included.In study which was made prospectively, patients were randomizely divided into 3 groups. The first group was injected intraarticular OT a total of 3 sessions one week apart(n = 25), PRP (n = 25) in the second group, and injected PRP+OT together in the third group (n = 25). Each patient was evaluated with VAS score in terms of pain, WOMAC score in terms of functional, before and 1 month after treatment. by giving Information to the patients about the study, patients informed consent and ethical committee approval of our study were obtained (02.09.2019-015). The individual rights of the patients were respected throughout the study, adhering to the principles of the Helsinki Declaration. Inclusion criteria were defined as; according to the Kellgren-Lawrence classification, to be stage 2 or 3 primary gonarthrosis, to be between the ages of 35-65, and th pain did not go away with NSAID. Patients with stage 1 or 4 gonarthrosis; and steroid, HA, PRP, OT treatment have been taken before; who have previous history of knee surgery; who have autoimmune disease, who have thrombocytopenia, history of malignancyand who have active infection was not included in the study.

Procedures:

OT was applied to the first group to inside the knee joint under sterile conditions for a total of 3 weeks, once a week. After 2 ml 2% lidocaine lelocal anesthesia was provided by the aseptic technique from the lower outer edge of the patella, by entering to the joint space with a 22 G needle and after 15 ml 20 µg / ml OT was applied, flexion and extension movements to the knee joint have it made and distribution of the ozone that is given was provided into the joint.The second group received PRP treatment once a week for a total of 3 weeks. preparing and administrationing of PRP was made in all patients under the same conditions. A total of 10 cc of peripheral blood taken from the antecubital region was taken into 3.2% sodium citraticeren tubes. Samples were centrifuged at 3200 rev/ min for 10 minutes at room temperature (Eppendorfcentrifuge 5702, Hamburg Germany). The resulting 2 ml PRP was injected into the joint after local anesthesia was provided with 2 ml 2% lidocaine with aseptic technique from the lower outer edge of the patella in the sterile conditions. To the third group, in the same syringe 2 ml PRP with 15 ml 20 µg / ml ozone were applied simultaneously.

Evaluation Criteria:

Pain assessment: VAS was used for pain assessment. A 10 cm non-segmented line was used to determine the severity of pain. Zero value was reported to indicate absence of pain and the value of 10 indicates the unbearability of pain. The measured value was recorded in the patient follow-up form.

Functional Assessment: Functional assessment was performed with WOMAC. In this index, the pain, stiffness and daily life activities of the patients in the last 48 hours have questioned by using a five point likert scale. The total score is 0-20 for pain, 0-8 for stiffness, 0-68 for difficulties in daily living activities. Lower score expressed the better functional level, while the higher the scores are indicate that the disease activity is more. Tüzün et al. have shown the Turkish validity and reliability of the index [16].

Ethical Informations: Patients informed consent and ethical committee approval of our study were obtained (02.09.2019-015). The individual rights of the patients were respected throughout the study, adhering to the principles of the Helsinki Declaration.

Statistical Methods: For descriptive statistics, mean, standard deviation, median, minimum, maximum value frequency and percentage were used.The distribution of variables was checked with kolmogorov-simirnov test. For the comparison of quantitative data, Kruskal-wallis and Mann-Whitney U test were used. For the repeated measurement analysis Wilcoxon test were used. For the comparison of the qualitative data, Chi-Square test was used. For statistical analyses SPSS 26.0 was used.

RESULTS

In the OT, PRP, PRP + OT groups, the age of the patients did not show differ significantly ($p > 0.05$). In the OT, PRP, PRP + OT groups, gender distribution did not differ significantly ($p > 0.05$). (Table 1)

The WOMAC pain score of all three groups decreased significantly ($p < 0.05$) after treatment compared to the pre-treatment. In the PRP + OT group, the WOMAC pain score was significantly more lower than in the OT and PRP group (p P 0.05) (Table 1).

In all three groups, WOMAC stiffness score decreased significantly ($p < 0.05$) after treatment compared to the pre-treatment. In the OT, PRP and PRP + OT groups, the decrease in WOMAC stiffness score after treatment did not show differ significantly ($p > 0.05$) (Table 1).

In all three groups, WOMAC physical function score after treatment showed significant($p < 0.05$) decrease compared to the pre-treatment. The WOMAC physical function score after treatment in the PRP + OT group was significantly ($p<0.05$) more lower than the OT and PRP group (Table 1).

WOMAC total score after treatment of all three groups decreased significantly ($p < 0.05$) compared to the pre-treatment. The WOMAC total score after treatment in the PRP + OT group was significantly($p < 0.05$) more lower than the OT and PRP group (Table 1) (Figure 1).

The VAS pain score after treatment of all three groups showed decrease significantly ($p < 0.05$) compared to the pre- treatment. The VAS pain score after treatment in the PRP + OT group was significantly($p < 0.05$) more lower than the OT and PRP group (Table 1) (Figure 1).

DISCUSSION

In our study which was made with 75 patients diagnosed with gonarthrosis who is evaluated prospectively, although in all three groups WOMAC subgroup and in the total scores and VAS scores improved significantly compared to pre-treatment, the improvement in PRP + OT applied group is seen more higher than the other groups.

Different treatment options are applied according to gonarthrosis stages. Intra-knee injections, physiotherapy and NSAIDs are frequent used conservative treatment methods. Using Intra-knee injection applications in the clinic are increasing. It has been reported that steroid injections which have been applied for many years may have negative effects on articular cartilage [17]. It has been recommended that treatments should be symptomatic, due to the damage to the intraarticular in gonarthrosis until recently was irreversible qualification. The discovery that growth factors, stem cells, and various cytokines have positive effects on regeneration has break down this taboo. However, it continues to remain an enigma that which agent should be used to which patient and how, and how much [18].PRP is the easiest autologous biological agent to obtain. PRP include factors such as platelet-derived insulin-like growth factor, fibroblast growth factor, epidermal growth factor. These factors suppress inflammation, help tissue regeneration by stimulating the removal of necrotic cells. Because of these properties which it have, in medicine it is used not only in musculoskeletal problems but also in many different specialty areas and positive results have been reported [19]. With the effect of growth factors which it include, PRP stimulates local stem cells and with circulation, activates the repairing cells in the bone marrow. In addition, it provides improvement by increasing tenocyte proliferation and collagen proliferation by providing re-vascularization with the growth factors it contains in tendon problems [20]. In the studies which was made have been seen that in order to be effective of PRP should be over 300,000 / µl [21].PRP obtained using manual or ready-made kits is activate by adding bovine or human thrombin or calcium chloride. However, there are also authors who use it without activating. In our study, PRP has been prepared with ready kit (PRP S & M, STR Bio Medical Technologies, Çorum / Turkey).In the analysis of the prepared PRP, it has determined that it was 5 times higher than the platelet count in the peripheral blood, calcium chloride has not added to the prepared PRP for activation.

Although PRP has been started to use quite frequently in different areas in recent years, there is no definite consensus on the total number of sessions to be applied, frequency, amount, and activation [22]. Güler et al. in the study which they compared PRP and HA injections with the 175 patients, they administered total of 2 ml plasma and buffycoat compound the obtained after the procedure, 3 injections with one week apart in and reported that they achieved a significant improvement in PRP and VAS scores compared to the HA patients [1]. Cerza et al. in the study which they compared PRP and HA injections with the 120 patients; to the patients, they administered total of 5,5 ml plasma and buffycoat compound the obtained after the procedure, 4 injections with one week apart in and reported that they obtained more improvement in pain and function with PRP [23].Ozone (O3) is that consisting of three oxygen atoms an unstable, strong oxidizing gas with antiseptic, immune modulator, analgesic and anti-inflammatory properties. Ozone, a colorless, pungent fragrant gas, is also a chemical derivative of oxygen [24,25]. The first use of ozone in medicine was carried out by Fisch in 1932. In 1935, Payer examined the contribution of OT to surgical treatment. In todays, OT can be used in different branches with different indications. In the inflammatory and degenerative diseases which are about with of the musculoskeletal system, activation of anti-inflammatory and anti-oxidative capacity of ozone injection, and utilized from the effects of immuno-modulation. Clinical studies evaluating the effects of ozone on the musculoskeletal system are increasingly. OT is increasingly used in musculoskeletal disorders

due to reducing in inflammation, ensuring the rapid pain control and associated early mobilization effects [26,27]. Dissolved ozone in body fluids reacts immediately with the antioxidants and polyunsaturated fatty acids, and emerges that the fast-acting (half-life is short) reactive oxygen compounds (ROS) (most importantly H2O2) and lipid peroxidation products which have a longer half-life (LOPs). In the first phase, H2O2 spreads to the cell cytoplasm and acts as trigger. It causes different chemical pathways acoording to the cell types it affects. Reactive oxygen products act as short-acting messengers and are removed by antioxidants in a very short time, but the complex pharmacodynamics that lipid peroxidase products have, by minimizing their potential toxicity enable them to become long-term messenger [28].Ozone is soluble in the water component of synovial fluid by intraarticular application, and by reacting with biomolecules, pioneers to the formation of ROS and LOP. Result; inhibition of the release of proinflammatory cytokines and proteolytic enzymes, besides, ıt is the reduction of inflammation level with the release of transforming growth factor beta 1 (TGF-b1) and interleukin 10 (IL-10), which are immunosuppressive cytokines. Increased TGF-b1 regulates the expression of integrins and stimulates the synthesis of matrix proteins such as collagen and glycosaminoglycans. chondrocytes which stimulated with the H2O2 way, and matrix proliferation lead to increased synthesis of articular cartilage [29].Intraarticular applications can be preferred most often in the knee joint, hip, shoulder, ankle and other peripheral joints. It can be used in inflammatory / degenerative diseases and after the sports injuries. Although there is no consensus on ozone / oxygen concentrations and doses, in line the studies which was made, in the knee and shoulder joints in 10-20 µg / mL concentration of 5-20 mL and in the smaller joints1-2 mL weekly injections have been recommended [30]. In our study similar with the literature, we applied ozone at a dose of 15ml 20 µg/ ml. In recent years, there have been publications both comparing OT in the gonarthrosis treatment with other agents which was applied intra-articular, and oral treatments. Cardelli et al. in the study result that they investigated the effects of OT and HA combination on hip OA, found a 30% increase in functionality and a significant decrease in pain levels in all patients in the first month after treatment [31]. Xufeng et al. in the study that they performed in 76 patients with gonarthrosis, half of the patients underwent intraarticular OT, and the other half have been examined after the treatment in terms of pain and functional by giving oral glucosamine and celecoxib, in the group that OT applied, pain and functional improvement were seen statistically better than the other group [32].Although there are studies comparing PRP treatment with different agents in gonarthrosis, there are very few reports comparing OT in the literature.In 2018, Gaballa et al. In one study that they done, in patients with detected gonarthrosis, a total of 2 doses of PRP injections to the one group every two week; and to the other group 4 doses OT once a week received, and at the first and third months after treatment and both VAS and WOMAC scores improved in both groups, and in the PRP group, a more significant improvement was detected compared to the OT group [33]. There are other studies supporting this result [34-36].Duymus et al. in a study that they made with 102 patients with mild to moderate gonarthrosis, intraarticular PRP was applied to the first group, HA to the second group and OT to the third group; and while VAS and WOMAC scores were improved in three groups in the first month, at the 12th month, it was observed that the improvement continued only in the group treated with PRP [37]. Shen et al. Similarly, in a study performed by him,PRP injection was seen to be superior to placebo, OT, HA and corticosteroid injections in terms of functional recovery [38]. In this study, according to the similar studies we found healing in the pain and functional scores in every three groups compared to the pre-treatment. However, we found more improvement in the PRP + OT applied group.When we scan the literature in terms of studies where PRP and OT were administered simultaneously and that was investigating the superiority of its efficacy compared to the their alone application, we saw that there was a single publication.Yeprem et al. in a study that they conducted in 2018, they divided 120 patients diagnosed with stage 2-3 gonarthroses equally into 3 groups, and to the first group twice a week 12 sessions of OT in 5 ml 10 µg / ml concentration, total 3 sessions 3 ml PRP once a week to the second group; a total of 3 sessions of PRP + OT performed to the third group once a week as combinely,VAS scores was observed that there were reduced in all three groups, but the best improvement in the combined treatment group [39]. This result carries similarity with our study. In our study, we did not come across any other publications other than this study similar to our study. In the community, in the treatment of gonarthrosis, which is mostly seen in obese patients, while beneficial in reducing the level of pain in patients that couldn't be taken adequate clinical response to intraartricular PRP and OT conservative treatments but its effectiveness in long-term is not known. Prospective long-term follow-up studies are needed to be better demonstrate their efficacy.

CONCLUSION

This study confirms that PRP and OT, which have been used frequently in medicine in recent years, are beneficial for pain and functional recovery in the treatment of gonarthrosis; but is show that when the two are used together, their efficacy is better than when used alone. Most importantly, as there have been very few publications which was made on this subject, it contributes to the literature from this respect.

Limitations of our study can countable as; limited number of patients, and limitation of follow-up time

after the treatment to as little as 1 month, and no comparison of long-term effects.

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Table-1

		Ozone[1]		PRP[2]		Ozone+PRP[3]		p
		Mean±sd/n-%	Median	Mean±sd/n-%	Median	Mean±sd/n-%	Median	
Age		52,8 ± 7,9	54,0	53,6 ± 8,2	55,0	52,8 ± 7,9	52,0	0,897 K
Gender	Female	13 52,0%		12 48,0%		14 56,0%		0,852 X^2
	Male	12 48,0%		13 52,0%		11 44,0%		
WOMAC Pain								
Before Treatment		12,0 ± 3,6	12,0	11,3 ± 3,6	10,0	11,5 ± 3,7	10,0	0,747 K
After Treatment		7,0 ± 3.2[23]	7,0	1,9 ± 1.4[3]	2,0	0,9 ± 0,9	1,0	***0,000*** K
Before/After Difference		5,0 ± 4.5[23]	4,0	9,4 ± 3,7	9,0	10,6 ± 3,4	9,0	***0,000*** K
Intra Group p Value		***0,000*** w		***0,000*** w		***0,000*** w		
WOMAC Stifness								
Before Treatment		2,2 ± 0,9	2,0	1,9 ± 1,2	2,0	2,0 ± 1,2	2,0	0,678 K
After Treatment		0,8 ± 0,7	1,0	0,4 ± 0,6	0,0	0,5 ± 0,5	0,0	0,153 K
Before/After Difference		1,4 ± 0,9	1,0	1,5 ± 1,0	2,0	1,5 ± 1,1	1,0	0,984 K
Intra Group p Value		***0,000*** w		***0,000*** w		***0,000*** w		
WOMAC Physical Function								
Before Treatment		40,1 ± 9,0	39,0	40,4 ± 11,2	44,0	40,3 ± 11,2	43,0	0,993 K
After Treatment		10,1 ± 5.9[23]	11,0	5,8 ± 5,7	4,0	3,3 ± 2,3	3,0	***0,000*** K
Before/After Difference		30,0 ± 8.7[3]	30,0	34,6 ± 12,9	38,0	37,0 ± 10,0	40,0	***0,045*** K
Intra Group p Value		***0,000*** w		***0,000*** w		***0,000*** w		
WOMAC Total								
Before Treatment		56,6 ± 12,2	55,2	55,9 ± 14,1	58,3	56,0 ± 14,3	58,3	0,999 K
After Treatment		18,5 ± 6.4[23]	20,8	10,0 ± 9,6	7,3	4,9 ± 2,6	5,2	***0,000*** K
Before/After Difference		38,0 ± 9.6[3]	39,6	45,8 ± 16,6	52,1	51,1 ± 12,9	56,3	***0,008*** K
Intra Group p Value		***0,000*** w		***0,000*** w		***0,000*** w		
VAS								
Before Treatment		6,0 ± 1,7	6,0	6,9 ± 1,0	7,0	6,5 ± 1,0	7,0	0,117 K
After Treatment		3,0 ± 1.3[23]	3,0	1,1 ± 0.7[3]	1,0	0,4 ± 0,6	0,0	***0,000*** K
Before/After Difference		3,0 ± 1.6[23]	3,0	5,8 ± 1,3	6,0	6,1 ± 1,2	6,0	***0,000*** K
Intra Group p Value		***0,000*** w		***0,000*** w		***0,000*** w		

K Kruskal-wallis (Mann-whitney u test) / X^2 Chi-square test

[2] Difference with PRP group $p < 0.05$ / [3] Difference with Ozone+PRP group $p < 0.05$

Figure 1

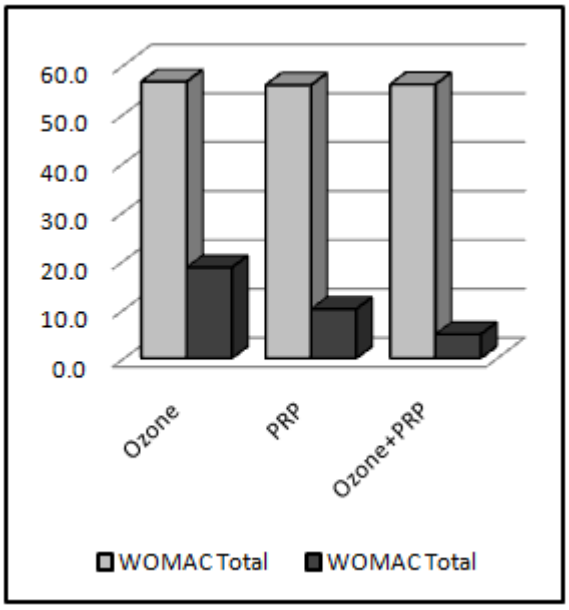

Figure 2