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Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options

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Abstract
Purpose This study was performed to compare the efficacy of treatment in three groups of patients with knee osteoarthritis (OA) given an intra-articular injection of platelet-rich plasma (PRP), hyaluronic acid (HA) or ozone gas.
Methods A total of 102 patients with mild–moderate and moderate knee OA who presented at the polyclinic with at least a 1-year history of knee pain and VAS score ≥4 were randomly separated into three groups. Group 1 (PRP group) received intra-articular injection of PRP × 2 doses, Group 2 (HA group) received a single dose of HA, and Group 3 (Ozone group) received ozone × four doses. Weight-bearing anteroposterior–lateral and Merchant's radiographs of both knees were evaluated. WOMAC and VAS scores were applied to all patients on first presentation and at 1, 3, 6 and 12 months.
Results At the end of the 1st month after injection, significant improvements were seen in all groups. In the 3rd month, the improvements in WOMAC and VAS scores were similar in Groups 1 and 2, while those in Group 3 were lower ($p < 0.001$). At the 6th month, while the clinical efficacies of PRP and HA were similar and continued, the clinical effect of ozone had disappeared ($p < 0.001$). At the end of the 12th month, PRP was determined to be both statistically and clinically superior to HA ($p < 0.001$).
Conclusion In the treatment of mild–moderate knee OA, PRP was more successful than HA and ozone injections, as the application alone was sufficient to provide at least 12 months of pain-free daily living activities.
Level of evidence Therapeutic study, Level I.

Keywords Hyaluronic acid · Intra-articular injection options · Knee osteoarthritis · Platelet-rich plasma · Ozone

Introduction

Osteoarthritis (OA) is the most common joint disease, which is characterised by progressive loss of joint cartilage, subchondral bone sclerosis, changes in the synovial membrane and reduced viscosity of the synovial fluid [35].

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The most commonly affected joint is the knee, and the rate of knee OA has been reported as 30 % in subjects over 50 years of age examined by radiographic imaging [11].

There is no definitive treatment method to prevent progression of OA. However, a number of treatment methods, including modification of daily activities, medical treatment, physical therapy, intra-articular injections and joint replacement, have the primary aim of relieving pain and increasing joint functions [27]. The most appropriate treatment choice for the patient depends on the clinical history, contraindications to specific treatments and how well the patient would be able to tolerate the treatment being considered. Especially in cases where the target patient group is of advanced age and simple treatment methods have not been successful, physicians have increasingly preferred injections because of the potential side effects of non-steroidal anti-inflammatory drugs (NSAIDs) [27]. Topical medications are often used for short-term relief, but are not effective in cases of severe OA [36].

The knee joint cartilage is non-vascular. Given that nourishment is based on diffusion, as intra-articular injections are given at high concentrations, they have become the preferred method in cartilage regeneration. Various intra-articular agents have been developed for this purpose [16, 24, 26]. Among these developments, intra-articular hyaluronic acid (HA) injection, which is widely used in knee OA, is an important component of synovial fluid. HA plays a key role in lubrication of the articular surface, reduces the stress on weight-bearing surfaces and transports chondronutritive substances coming from the synovium. HA concentrations in the synovial fluid of osteoarthritic knees have been shown to be reduced [6]. HA injections have a role in the treatment of OA due to its viscoinduction properties, which stimulate endogenous HA expression from the synovium, and viscosupplementation increases the viscoelasticity [9].

Platelet-rich plasma (PRP), which is obtained at a higher concentration than full blood, is an encouraging treatment option. Biologically active proteins expressed by active platelets lead to gene expression by binding to the transmembrane receptors in the target cells. As a result, cellular recruitment, growth and morphogenesis are triggered and, at the same time, inflammation is reduced [4]. Thus, as a minimally invasive treatment option, it has been widely used in clinical studies [33]. PRP injection has been presented as a promising treatment option for cartilage damage associated with arthrosis or sporting injuries [20, 27]. In the treatment of knees with OA, it shows long-term clinical effectiveness [20].

In this prospective, randomised study, patients with knee OA were separated into three groups according to the type of intra-articular injection administered, i.e. PRP, HA and ozone gas, and comparisons were then performed between the groups with regard to the efficacy of the treatment.

Materials and methods

The study population consisted of 163 consecutive patients (132 women and 21 men) presenting at the polyclinic between February 2014 and September 2014 with complaints of pain that had been ongoing for at least 1 year and that worsened with weight-bearing (VAS score $\geq$4) and were classified as mild–moderate or moderate knee OA (Kellgren–Lawrence Grade 2 or 3) [23]. All radiographs (weight-bearing anteroposterior, weight-bearing lateral and Merchant's radiographs of both knees) were evaluated. To determine the presence of chondral lesions and effusion, magnetic resonance imaging (MRI) was performed in all patients prior to treatment. Patients with intra-articular effusion on MRI were not included in the study.

Inclusion criteria

Patients with symptomatic knee OA (Kellgren–Lawrence Grade 2 or 3), aged 47–80 years, body mass index (BMI) <30, with stable knees without malalignment, and normal blood results and coagulation profile were included in the study.

Exclusion criteria

The exclusion criteria were severe OA, age >80 years, recent history of knee trauma, rheumatic pathology, concomitant severe hip OA, systemic or metabolic disease, immunosuppressive or anticoagulant treatment, invasive procedure applied to the knee, intra-articular steroid injection to the knee within the previous 12 months or previous joint infection.

Study design and patient selection

The study population consisted of 163 consecutive patients (132 women and 21 men) who presented at the polyclinic with a 1-year history of pain that worsened with weight-bearing (VAS score $\geq$4). When a total of 120 participants fulfilling the inclusion criteria were reached, the patients were randomly assigned into three groups by a computer-based protocol. The patients were separated into three groups according to the type of treatment administered. The patients were returned to the clinic for intra-articular injections: Group 1 (PRP group, $n = 41$), PRP $\times$ 2/month; Group 2 (HA group, $n = 40$), HA single dose; and Group 3 (Ozone group, $n = 39$), ozone $\times$ 4/week. However, a total of 102 of the 120 participants were prospectively evaluated at the 12-month follow-up examination as 18 patients did not continue the treatment or were lost to follow-up (Fig. 1).

The injections were performed in all patients in the supine position. The skin of the injection site was prepared and draped. The PRP, HA or ozone gas injections were administered under sterile conditions using a needle through the classic suprapatellar approach for intra-articular injection. All patients were prohibited from using NSAIDs or any steroids. Paracetamol was permitted three times a day, along with application of an ice pack if there was pain at the injection site. In patients with bilateral symptoms, only the side with significant symptoms was taken into consideration.

Group 1: PRP preparation

To obtain 3–4 ml of PRP at a 9–13-fold concentration of normal blood mean platelet values, 2 ml of anticoagulant was withdrawn into a 20-ml injector. Then, 14 ml of blood was taken from the patients using an 18-gauge (G) needle. A total blood sample of 16 ml was carefully injected into a Ycellbio kit at an angle of 45°. To concentrate the platelets, the kit was centrifuged at 3700 rpm for 7 min. Using the lever on the base of the Ycellbio kit, by raising 3–4 ml of the leucocytes contained in the PRP to the midline, 5 ml was withdrawn into a sterile injector. The skin of the injection site was prepared and draped, and PRP was injected under sterile conditions using a 22G needle through the classic approach for intra-articular injection. There was no additional activator in the kit. Concentrated growth factors and platelets more effective than 1,500,000/μl were included. There were almost no red blood cells. The second dose was applied after an interval of 1 month.

Group 2: Hyaluronic acid

The Ostenil Plus® syringe is a pre-filled syringe containing 40 mg of fermentative HA and 10 mg of mannitol, which was sterilised after filling with a volume of 2 ml. The mean molecular weight of the fermentative HA in the Ostenil Plus® is 1.6 Million Daltons. These pre-filled syringes were individually sealed, placed in sterile packets and then autoclaved. Thus, both the contents and surfaces of the syringes were sterile.

Group 3: Ozone gas

The device was set to produce ozone (O_3) from O_2 at a concentration of 30 μg/ml. Aliquots of 15 ml were withdrawn into a sterile injector. Before the injection of ozone

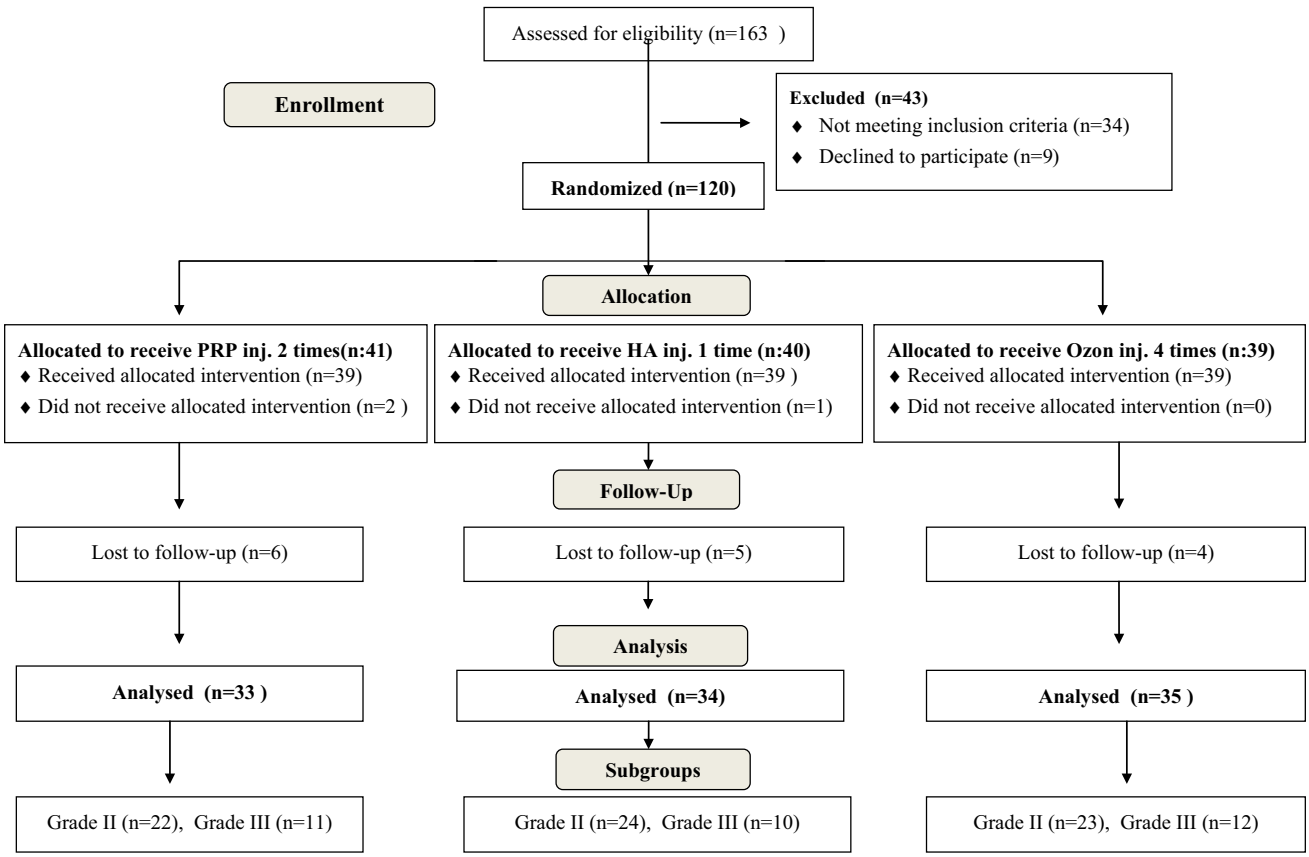

Fig. 1 Flow diagram of the study. *n* number of patients, *OA* osteoarthritis, *PRP* platelet-rich plasma, *HA* hyaluronic acid and ozone

gas, lidocaine (2 cc) was injected into the knee followed by 15 ml of 30 µg/ml O_3. Lidocaine was administered to reduce the burning pain felt in the knee during ozone gas injection, which lasted several minutes.

Outcome assessment

For inclusion in the study, routine haematological and blood biochemistry tests were applied to patients 1 week before the first injection. Clinical baseline parameters, such as weight, height, body mass index (BMI), age, gender and grade of knee OA, were also recorded. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) and visual analogue scale (VAS) scores were applied in all patients. Knee pain was primarily evaluated with VAS (on a scale of 0–10, where 0 = no pain and 10 = worst pain). Secondary evaluation was performed with WOMAC, which consists of three parts: pain, stiffness and physical function. WOMAC scores from 0 to 4 were recorded on a Likert scale (0 = no pain/restriction, 1 = mild pain/restriction, 2 = moderate pain/restriction, 3 = severe pain/restriction, 4 = very severe pain/restriction). The maximum scores for pain, stiffness and physical function were 20, 8 and 68, respectively, giving an overall total maximum of 96 [7]. Clinical measurements were performed through questionnaires completed by independent evaluators prior to the first injection and then at the 1-, 3-, 6- and 12-month follow-up examinations. Data were recorded using Excel software. As the WOMAC and VAS are well-validated assessment tools, measurement of test–retest reliability was not necessary. All of the participants provided written informed consent before this study, and the study was approved by the Local Ethics Committee, Istanbul Kanuni Sultan Suleyman Education and Research Hospital, Turkey (ID Number: 2014/2-18129).

Statistical analysis

The sample size estimation was calculated using GPower software. The minimum sample size was calculated by taking into account the effect size of results at 12 months among groups of more than 0.30 for a false-positive rate of 5 % ($\alpha = 0.05$) and a power of at least 80 % ($\beta = 0.2$) [30]. Using these parameters, and adjusting for multiple comparisons, we required a minimum sample size of 99 patients (33 per arm). A total of 40 patients per group were required, taking into consideration the estimated 20 % dropout rate (failure of follow-up), thus giving a total of 120 patients enrolled in the study (Fig. 1). Patient recruitment was stopped when the minimum number of patients was achieved in all groups.

Statistical analyses were performed using the R software package. Categorical variables are given with frequency and percentage and the descriptive statistics of continuous variables are shown with the median, minimum and maximum values. The Pearson Chi-square test was used for comparison of categorical variables between groups. The Kruskal–Wallis test was used for comparison of three or more independent groups of continuous variables, the Mann–Whitney *U*-test was used for comparison of two independent groups, and paired post hoc comparisons were performed with the Mann–Whitney *U*-test with Bonferroni correction. The Wilcoxon test was applied for intra-group comparison of dependent variables. In all analyses, a value of $p < 0.05$ was accepted as statistically significant.

Results

There were no statistically significant differences between groups with regard to age, gender, affected side or knee OA grade. There were no statistically or clinically significant differences between the groups with regard to VAS and WOMAC scores, except for a slight increase in the initial VAS score in the HA group (Table 1).

At the first follow-up examination after treatment, significant increases were determined in the VAS and WOMAC scores within each group compared to the initial scores when examined with Wilcoxon's test ($p < 0.001$). When the VAS scores were compared between the groups, no significant differences were observed between the HA and PRP groups, but the scores in both groups were better than those in the Ozone group. Compared to the initial scores, while there were improvements of 65 ± 0.13 % in the PRP group and 67 ± 0.16 % in the HA group, the improvement in the Ozone group was 52 ± 0.19 %. Effective clinical results were achieved in all groups at the first follow-up examination. At the end of the 3rd month, a significant difference was observed between the PRP, HA and Ozone groups with regard to VAS and WOMAC scores ($p < 0.001$). In the Ozone group, the mean VAS recovery rate compared to the initial value was 52 % ± 0.18 % at the end of the 1st month, and this decreased to 29 ± 0.20 % at the end of the 3rd month. The total WOMAC score reduced from 58 ± 0.18 to 28 ± 0.19 % and the clinical effectiveness was markedly decreased. There were no significant decreases in the PRP or HA groups compared to the initial values. There were no significant differences between these two groups, but both were superior to the Ozone group (Table 2).

In the 6th month, significant differences were seen among all three groups ($p < 0.001$). In the PRP and HA groups, although there were slight increases in the scores compared to the initial values, the clinical effect continued and there were no statistically significant differences. The

Table 1 Demographic distribution and comparison of the groups

	PRP group	HA group	Ozone group	*p*
No of cases[b]	33	34	35	n.s.
Age[b]	60.4 ± 5.1	60.3 ± 9.1	59.4 ± 5.7	n.s.
BMI (kg/m^2)[b]	27.6 ± 4.6	28.4 ± 3.6	27.6 ± 4.4	n.s.
Gender[a]				
Female	32 (97.0 %)	33 (97.1 %)	31 (88.6 %)	n.s.
Male	1 (3.0 %)	1 (2.9 %)	4 (11.4 %)	n.s.
Knee OA grade[a]				
Grade II	22 (66.7 %)	24 (61.8 %)	23 (65.8 %)	n.s.
Grade III	11 (33.3 %)	10 (38.2 %)	12 (34.2 %)	n.s.
VAS (initial)[b]	7.4 ± 1.0	8.3 ± 0.4	7.2 ± 1.1	<0.001
WOMAC (initial)[b]				
Pain	15.4 ± 2.0	16.6 ± 1.1	16.0 ± 2.7	n.s.
Stiffness	6.1 ± 0.9	6.0 ± 0.8	6.4 ± 1.0	n.s.
P. Function	54.5 ± 6.7	54.3 ± 1.8	53.5 ± 8.7	n.s.
Total	76.1 ± 9.4	77.0 ± 2.5	76.0 ± 11.9	n.s.

The initial pre-treatment VAS and WOMAC scores of the PRP, HA and Ozone groups

n.s. not significant

[a] Pearson Chi-square test (gender, knee OA grade).[b] Kruskal–Wallis test (no of cases, age, initial VAS, WOMAC). Significant improvement ($p < 0.001$) in all the scores

results in both the PRP and HA groups were better than those of the Ozone group. In the 6th month, the WOMAC and VAS scores of the Ozone group had completely reverted to the initial values and the clinical effect had disappeared. At the end of the 12th month, there were statistically significant differences among all three groups ($p < 0.001$). The treatment showed clinical effectiveness only in the HA and PRP groups. Compared to the initial value, the VAS score dropped to a mean of 29 ± 0.27 % in the PRP group, while that in the HA group was 18 ± 0.13 %. The total WOMAC score decreased to a mean of 27 ± 0.16 % compared to the initial value in the PRP group, while that in the HA group was 10 ± 0.07 %. The difference between PRP and HA was statistically significant, with PRP superior to HA (Table 2; Figs. 2, 3).

In the total 12-month follow-up period, there were no statistically significant differences between PRP and HA in the first 6 months, and the VAS and WOMAC scores were similar between the two groups. At the end of the 12th month, there was a difference between the two groups, and the clinical efficacy had reduced, but was seen to continue. This reduction was more evident in the HA group, and at the end of the 12th month PRP was found to be significantly superior to HA (Table 2).

Table 2 VAS and WOMAC scores of the PRP, HA and Ozone groups at the 1st, 3rd, 6th and 12th month after injection

	VAS[a]	WOMAC[a]			
		Pain	Stiffness	P. Function	Total
1st month					
PRP	2.5 ± 0.7	6.8 ± 1.8	2.8 ± 0.8	19.7 ± 7.1	26.4 ± 9.5
HA	2.6 ± 1.2	6.1 ± 2.4	2.7 ± 1.1	24.3 ± 9.5	33.2 ± 12.2
Ozone	3.5 ± 1.5	6.6 ± 3.5	2.7 ± 1.6	21.7 ± 8.6	31.1 ± 12.9
p value	<0.001	n.s.	n.s.	n.s.	n.s.
3rd month					
PRP	2.9 ± 0.7	7.24 ± 2.37	3.0 ± 1.1	22.0 ± 5.4	32.2 ± 7.8
HA	3.1 ± 0.9	7.00 ± 1.74	3.2 ± 1.0	25.1 ± 8.9	35.3 ± 10.5
Ozone	5.7 ± 1.2	11.1 ± 3.4	4.2 ± 1.3	387 ± 12.2	53.1 ± 15.9
p value	<0.001	<0.001	n.s.	<0.001	<0.001
6th month					
PRP	4.0 ± 1.3	9.4 ± 1.7	3.6 ± 0.7	29.6 ± 5.7	42.8 ± 7.1
HA	4.3 ± 1.3	9.7 ± 1.6	3.8 ± 1.1	30.1 ± 5.7	44.5 ± 6.6
Ozone	7.3 ± 1.03	16.0 ± 2.9	6.4 ± 1.0	54.1 ± 7.3	76.6 ± 10.7
p value	<0.001	<0.001	<0.001	<0.001	<0.001
12th month					
PRP	5.1 ± 1.3	11.4 ± 2.4	4.7 ± 1.2	38.6 ± 7.7	54.9 ± 10.8
HA	6.8 ± 0.1	14.2 ± 1.1	5.4 ± 0.7	49.6 ± 3.3	69.3 ± 4.3
Ozone	7.6 ± 1.1	16.2 ± 2.8	6.5 ± 0.1	54.2 ± 7.9	77.0 ± 10.1
p value	<0.001	<0.001	<0.001	<0.001	<0.001

n.s. not significant

[a] Kruskal–Wallis test (VAS and WOMAC). Significant improvement ($p < 0.001$) in all the scores

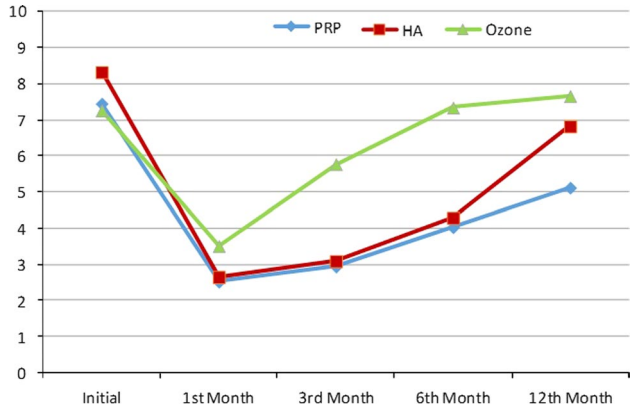

Fig. 2 VAS scores of the groups pre- and post-treatment

Fig. 3 Total WOMAC scores of the groups before and after treatment

Discussion

The most significant finding of this study was that better clinical results were achieved with PRP than with HA or ozone in the treatment of knees with OA. In particular, ozone gas injection was effective for only the first 3 months, whereas the effects of PRP injection lasted for at least 12 months. However, in the first 6 months of the study, there were no clinically significant differences between HA and PRP groups.

The application of PRP was developed based on studies demonstrating the physiological roles of several bioactive proteins expressed in platelets, which lead to tissue regeneration [28, 32]. In prospective studies, intra-articular PRP injection was reported to be effective in degenerative knees [15, 30]. Comparisons indicated that PRP is superior to HA and PRP in terms of efficacy [13, 22, 29]. In addition, a study of the mechanism underlying the effect of PRP emphasised that in synovium and cartilage tissue cultures obtained after knee prosthesis operations, HA production was stimulated and cartilage catabolism was reduced [34]. In the present study, PRP was shown to be significantly superior to HA. In contrast, there have been studies indicating no significant difference between PRP and HA [30]. However, these previous studies differed from the present study in the number of PRP applications. In other studies, the application was performed in a single session, while here PRP injections were administered twice at an interval of 1 month, as it was thought that better results would be obtained with multiple applications. In a prospective, randomised, placebo-controlled study, Gormeli et al. compared HA, multiple-dose PRP and single-dose PRP, and reported that although there were no differences in results between HA and single-dose PRP, multiple-dose PRP was significantly superior to both of these treatments [20]. The number of intra-articular injections applied to the groups in this study was different because, when defining the number of applications, rather than an equal number of injections, the aim was to achieve the optimal response with minimum intervention to the knee for each type of injection. There is no consensus in the literature regarding the optimal number of applications of PRP or HA, or intervals. Taking the manufacturer's opinion into consideration, ozone was applied in four doses, PRP in two doses and HA was applied as a single dose.

In a systematic review, Filardo et al. [18] concluded that PRP was beneficial to damaged cartilage in OA and was more effective in young patients with early or moderate stage arthrosis, but had a limited effect in cases of advanced OA. In another study conducted in the same year, Filardo et al. [17] reported that there was no difference with regard to clinical healing between HA and PRP with a 1-year follow-up period, but it was emphasised that in terms of viscosupplementation, PRP should not be selected. However, a significant disadvantage of the Filardo study was that all cases of knee OA with grades 0–3 were included. The differences in results and interpretations in the literature may have been due to the inclusion of patients with dissimilar grades of disease severity.

In the present study, the level of clinical efficacy of PRP gradually decreased and was shown to last for a mean of 1 year. Filardo et al. [15] reported that the estimated clinical efficacy and benefits were limited by time, and the estimated duration of effectiveness was similar to that in the present study at 1 year. Another report emphasised that the clinical effectiveness continued for 2 years [19]. However, that study was restricted to cases of early-stage knee OA. The duration of effectiveness can be considered to be shorter in advanced grades. Thus, for continued effectiveness of treatment and to achieve prolonged clinical relief, it is necessary to repeat the injections at specified intervals. This shows a need for further prospective studies related to

the dosage and number of sessions to obtain permanent or long-term clinical results.

As a major component of synovial fluid and joint cartilage, HA itself, which is synthesised by chondrocytes, is fully responsible for the viscoelasticity of synovial fluid [5]. In a study comparing oral NSAIDs alone, HA alone and a combination of both (oral NSAID + HA), while the results were similar in the first 3 months, it was reported that HA alone or in combination with NSAID on the 26th week was superior to oral NSAID alone [2]. In the results of the first 3 months in the present study, ozone gas treatment was seen to have a similar effect duration to corticosteroids. With regard to the mechanism of the effect, after injection of the gas, changes were detected in the levels of cytokines that lead to the formation of OA [10]. Based on these biochemical changes, ozone gas was recommended for use in the treatment of OA [31]. In the present study, especially within a short time after injection, clinical relief and rapid reduction in pain were observed. However, the duration of the effect was much shorter compared to HA and PRP, and the patients reverted to their initial status from the 3rd month after treatment. This short-term effect on symptoms was thought to be due to the relatively powerful anti-inflammatory properties of ozone rather than intra-articular structural improvement. The reduction in joint oedema and swelling via the anti-inflammatory effect is effective against pain [12]. Al-Jaziri et al. [3] reported a strong degree of pain killing due to the anti-inflammatory effect of ozone–oxygen applied intra-articularly in knee OA. In the present study, the clinical effect of ozone lasted for at least 3 months, but it had completely disappeared towards the 6th month. In contrast, Misha et al. [25] reported that the effectiveness lasted 6 months. This was considered to be due to the inclusion of young patients with OA $\leq$ Grade 2. As it has almost no side effects and a strong analgesic effect, ozone could be considered, at least, as a strong alternative to steroid injections. However, it should not be considered an alternative for HA as the results of this study showed the effect duration of HA to be significantly longer than that of ozone. In addition, HA injection has a good safety profile, no known interactions with medications, is a local treatment and is advantageous for use in patients with comorbidities [8, 21].

An important limitation of this study was the inclusion of Grade II and III patients together. Cerza et al. [13] reported that HA was effective in Grade II but not in Grade III OA, while PRP was concluded to be effective in both groups. Prospective multiple comparisons should be performed to obtain clearer results regarding efficacy in isolated Grade II or Grade III OA. Thus, a specific injection algorithm could be developed according to the stage of knee OA. A meta-analysis performed based on PRP only emphasised that PRP was effective in mild–moderate and moderate grades [14].

PRP provides structural recovery by activating regeneration in joint cartilage damaged as a result of OA in the knee or sporting injuries [24]. As a minimally invasive treatment option, it has been widely used in clinical studies [33]. When the side effects of anti-inflammatory drugs are taken into account, PRP injections are both safe and effective, as shown in this and similar studies. Apart from mild and very short-term side effects (pain, heat and redness) in a few patients, there are no side effects [1]. Therefore, PRP can be considered a useful therapeutic option in selected patients with mild–moderate or moderate degrees of OA who fail to respond to current treatments, including therapeutic exercise and physical modalities.

Conclusion

PRP is superior to HA and ozone in the treatment of mild–moderate and moderate knee OA and is an encouraging treatment option, use of which is becoming increasingly widespread. PRP injection alone was effective for achieving at least 12 months of pain-free daily activities.

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