Eur J Orthop Surg Traumatol
DOI 10.1007/s00590-014-1517-x

ORIGINAL ARTICLE

Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients

O. Guler · S. Mutlu · M. Isyar · A. Seker · M. E. Kayaalp · M. Mahirogullari

Received: 25 March 2014 / Accepted: 21 July 2014
© Springer-Verlag France 2014

Abstract The present study aimed to compare short-term clinical outcomes between intraarticular platelet-rich plasma (PRP) and hyaluronic acid (HA) treatments in early-stage gonarthrosis patients. Data of gonarthrosis patients, who were stage 1 or stage 2 according to Kellgren–Lawrence classification and underwent intraarticular PRP or HA treatment, were obtained retrospectively. The patients received treatment for three times at one-week intervals (intraarticular PRP or HA). They were evaluated using the Knee Society's Knee Scoring System (KSS) and the visual analog scale (VAS) scoring system before treatment and at the second and sixth months of treatment. The study included 132 patients (mean age, 55.06 ± 8.41 years). Sixty-three patients (86 knees) were in the HA group and 69 patients (89 knees) were in the PRP group. Changes in KSS and VAS scores over time and the differences between the treatment groups in terms of changes in KSS and VAS scores over time were significant. In conclusion, PRP appears to be an appropriate option for intraarticular treatment in patients with early-stage knee osteoarthritis.

Keywords Platelet-rich plasma · Intraarticular treatment · Early-stage gonarthrosis · Hyaluronic acid

O. Guler (✉) · M. Isyar · A. Seker · M. E. Kayaalp · M. Mahirogullari
Orthopedics and Traumatology Department, Medical Faculty, Medipol University, Ataturk Bulvarı, No:27, 34083 Unkapanı-Fatih, Istanbul, Turkey
e-mail: olcay_gler@yahoo.com; olcayguler77@gmail.com

S. Mutlu
Orthopedics and Traumatology Department, Kanuni Sultan Suleyman Training Hospital, Istanbul, Turkey

Introduction

Osteoarthritis is the most frequent joint disease in adults. Knee osteoarthritis is the most common type and encountered in 6 % of adults, with a prevalence reaching to 40 % in advanced age (>70 years) [1]. Currently, osteoarthritis is not a curable disease; therefore, prevention is important. Treatment focuses on alleviating the signs and symptoms and slowing the progression down. Treatment includes physical treatment modalities, orthoses, medical therapy, and surgical methods [1]. Intraarticular injection is an option among pharmacological therapies and it has been shown to be efficient particularly in knee osteoarthritis [1, 2]. Corticosteroids and hyaluronic acid (HA) are the agents commonly used in intraarticular treatment [2]. In addition, autologous growth factors [3], radioisotopes, botulinum toxin type A, tropisetron, tanezumab [4], and platelet-rich plasma (PRP) [5, 6] are also administered via intraarticular route and successful results of various degrees have been reported. Nevertheless, there is an opinion that further researches are needed on intraarticular treatments [7].

The present study aimed to compare short-term clinical outcomes between intraarticular PRP and HA treatments in early-stage gonarthrosis patients.

Materials and methods

Patients

Data of gonarthrosis patients, who were stage 1 or stage 2 according to Kellgren–Lawrence classification and underwent intraarticular PRP or HA treatment in our clinic between February 2011 and November 2012, were obtained retrospectively from hospital records. Patients

Published online: 02 August 2014

with diabetes mellitus, rheumatoid disease, hematological disease (coagulation disorder), major lower extremity axis disorder (varus >5, valgus >5°), severe cardiovascular diseases, infection, and immunosuppressive diseases, those receiving anticoagulant therapy, those who received anti-inflammatory drugs until 5 days before blood sampling, those with abnormal complete blood count, and those who could not be evaluated by scoring systems were excluded.

The patients received treatment for three times at one-week intervals (intraarticular PRP or HA). They were evaluated using the Knee Society's Knee Scoring System (KSS) and the visual analog scale (VAS) scoring system before treatment and at the second and sixth months of treatment. Demographic characteristics of the patients as well as complications and adverse events during treatment were recorded.

Sixty-three patients (86 knees) were in the HA group and 69 patients (89 knees) were in the PRP group. Two groups were compared in terms of VAS and KSS scores before and after treatment.

Scales

The KSS was used for pre- and post-treatment clinical and functional evaluation [8]. The VAS scoring system was used to assess pre- and post-treatment degree of pain, which was scored from 0 (no pain) to 10 (extremely severe).

Platelet-rich plasma preparation

A peripheral blood sample of 15 mL was obtained from the upper extremities of patients, and 1.5 mL of the sample was used for platelet count before centrifugation. The remaining 13.5 mL venous blood was mixed in a 15-mL sterile centrifuge tube containing 1.5 mL of 3.2 % sodium citrate, and then, centrifugation was performed at 4,000 rpm for 10 min in a centrifuge device (Rotofix 32, Hettich, Germany). After centrifugation, a total of 2.5 mL PRP was obtained from the middle part of the blood sample between the erythrocytes at the bottom and the plasma at the top of the tube. Then, a PRP sample of 0.5 mL was separated for platelet count. Approximately 2 mL PRP was administered into the knee joint. No specific kit was used to obtain PRP.

The mean platelet count was 238 $\times$ 10^3/μL (minimum 156 $\times$ 10^3/μL and maximum 351 $\times$ 10^3/μL) before centrifugation and 987 $\times$ 10^3/μL (minimum 685 $\times$ 10^3/μL and maximum 1,373 $\times$ 10^3/μL) after centrifugation. The mean change in platelet count was determined to be 4.3 (minimum 3.6 and maximum 4.6). The mean leukocyte count in PRP was calculated to be 6.77 $\times$ 10^3/μL (minimum 5.25 $\times$ 10^3/μL and maximum 10.25 $\times$ 10^3/μL) before centrifugation and 30.5 $\times$ 10^3/μL (minimum 22.1 $\times$ 10^3/μL and maximum 44.4 $\times$ 10^3/μL) after centrifugation. The mean change in leukocyte count was determined to be 4.7 (minimum 4.1 and maximum 5.4).

Hyaluronic acid preparation

Osteonil® plus 40 mg/2.0 mL (Bio-gen, TRB CHEMEDICA SA, Switzerland), which is HA preparation, was administered.

Administration of injection

After the knee that would undergo injection was prepared using a sterile cover, intraarticular HA or PRP was arthroscopically administered through anterolateral portal using a proper needle. Following administration, passive flexion and extension of the knee was performed for a short term. The patient was sent home after injection. Limited movement was allowed for 24 h and resting was recommended in case of pain. The patient was recommended not to receive non-steroidal inflammatory drugs (NSAIDs) or not to apply local ice for a week after injection in order not to reduce efficacy of PRP. In addition, an exercise program was given to the patients and performing normal daily activities was recommended when tolerable.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, Il, USA; version 15.0) for Windows program. Descriptive statistics were expressed as number and percentage for categorical variables and as mean, standard deviation, median, minimum, and maximum for numerical variables. Chi-square test was used for paired group comparison of categorical variables. For the comparison of two independent groups, Mann–Whitney *U* test was used for non-normally distributed numerical variables. Repeated measures analysis was used to determine the differences between the groups over time for dependent numerical variables. A *p* value smaller than 0.05 was considered statistically significant.

Results

The present study comprised 132 patients with a mean age of 55.06 ± 8.41 years. While knee involvement was unilateral in 89 patients, it was bilateral in 43 patients. Of the patients, 69 (89 knees) was administered with PRP and 63 (86 knees) was administered with HA. General characteristics of the patients are demonstrated in Table 1.

Table 1 General characteristics of the patients in the treatment groups

Characteristics	HA Group ($n = 63$)	PRP Group ($n = 69$)	p
Gender			
Male	7 (11.1)	14 (20.3)	0.150
Female	56 (88.9)	55 (79.7)	
Age	55.14 ± 9.63	54.99 ± 7.19	0.433
BMI	28.56 ± 2.71	28.44 ± 3.24	0.745
Stage			
Stage 1	20 (31.7)	31 (44.9)	0.120
Stage 2	43 (68.3)	38 (55.1)	
Knee involvement			
Unilateral	40 (63.5)	49 (71.0)	0.357
Bilateral	23 (36.5)	20 (29.0)	

Values are demonstrated as mean ± SD or number (%), where appropriate

HA hyaluronic acid, *PRP* platelet-rich plasma

Table 2 Knee Society's Knee Scoring System scores in the knees of treatment groups

KSS score, mean ± SD	HA Group ($n = 86$)	PRP Group ($n = 89$)	p
Pre-treatment	60.36 ± 5.69	60.51 ± 5.76	0.930
Post-treatment second month	70.37 ± 5.69	78.11 ± 7.24	<0.001
Post-treatment sixth month	79.15 ± 6.30	88.97 ± 5.60	<0.001
p	<0.001		

HA hyaluronic acid, *PRP* platelet-rich plasma, *KSS* the Knee Society's Knee Scoring System, *SD* standard deviation

No significant difference was determined between the treatment groups in terms of gender, age, body mass index (BMI), distribution among stages, and unilateral/bilateral involvement.

Any intraarticular injection-related major complication (infection, deep venous thrombosis, muscular atrophy, etc.) was not detected in any of the patients over the course of treatments. Temporary swelling occurred in 5 knees in the PRP group and in 8 knees in the HA group.

Post-treatment second month and sixth month KSS scores are demonstrated in Table 2.

While there was no difference between the groups in terms of pre-treatment KSS score, the PRP group had significantly higher KSS scores at the post-treatment second month and sixth month.

Change in KSS score over time and the difference between treatment groups in terms of change in KSS score over time were significant ($p < 0.001$ and $p < 0.001$, respectively).

Table 3 Visual analog scale scores in the knees of treatment groups

VAS score	HA Group ($n = 86$)	PRP Group ($n = 89$)	p
Pre-treatment	7.92 ± 0.74	7.46 ± 1.06	0.006
Post-treatment second month	6.09 ± 0.86	4.45 ± 1.17	<0.001
Post-treatment sixth month	5.02 ± 0.84	3.35 ± 0.92	<0.001
p	<0.001		

HA hyaluronic acid, *PRP* platelet-rich plasma, *VAS* the visual analog scale, *SD* standard deviation

Increase in KSS score from baseline to post-treatment second month was significant ($p < 0.001$). This increase was higher in the PRP group than in the HA group (difference between the scores in the HA group: 10.01 ± 0.11; difference between the scores in the PRP group: 17.61 ± 5.61; $p < 0.001$).

Increase in KSS score from post-treatment second month to post-treatment sixth month was significant ($p < 0.001$). This increase was higher in the PRP group than in the HA group (difference between the scores in the HA group: 8.78 ± 3.28; difference between the scores in the PRP group: 10.85 ± 5.17; $p = 0.008$).

Visual analog scale (VAS) scores before treatment and at the post-treatment second and sixth months are demonstrated in Table 3.

Pre-treatment and post-treatment second month and sixth month VAS scores were significantly lower in the PRP group than in the HA group.

Change in VAS scores over time and the difference between treatment groups in terms of change in VAS scores over time were significant ($p < 0.001$ and $p < 0.001$, respectively).

Decrease in VAS scores from baseline to post-treatment second month was significant ($p < 0.001$). The decrease was higher in the PRP group than in the HA group (difference between the scores in the HA group: −1.83 ± 0.56; difference between the scores in the PRP group: −3.01 ± 1.01; $p < 0.001$).

Decrease in VAS score from post-treatment second month to post-treatment sixth month was significant ($p < 0.001$). This decrease did not differ in the groups (difference between the scores in the HA group: −1.07 ± 0.61; difference between the scores in the PRP group: −1.10 ± 1.07; $p = 0.161$).

Discussion

Intraarticular injection is one of the options preferred in the symptomatic treatment of osteoarthritis. There are

numerous intraarticular treatment protocols such as corticosteroids, HA, NSAIDs, and PRP [9]. In the present study, both HA, which is one of the traditional medications, and PRP, which has attracted increasing attention recently, were used and the results were compared. The lack of a statistical difference between the treatment groups in terms of gender, age, BMI, distribution among stages, and unilateral/bilateral involvement indicated that the groups were comparable.

Hyaluronic acid is a glycosaminoglycan complex extensively found in human tissues, particularly in extracellular matrix and body fluids. HA is the main component of synovial fluid and cartilage and has a molecular weight ranging from 100 to 10,000 kDa depending on the tissue [10]. In randomized, placebo-controlled, multi-center studies, HA has been reported to be effective when administered via intraarticular route in patients with knee osteoarthritis [10, 11]. In addition, it has been reported that HA therapy is more effective in the treatment of early-stage osteoarthritis as compared to advanced stage [12]. There are various HA formulations in different compositions and molecular weights for intraarticular administration. Nevertheless, based on randomized controlled studies, there is no difference between HA products in terms of efficacy [13].

Thrombocytes are small anucleated cytoplasmic particles of megakaryocytes. Thrombocytes play a role in hemostasis, coagulation cascade, and tissue healing [14]. It is thought that fibrin and high-concentration growth factors found in the thrombocyte content contributes to wound healing [15]. PRP is obtained from patient's own blood and contains higher amount of thrombocyte as compared to whole blood. PRP has higher concentrations of growth factors and cytokines due to its higher thrombocyte content than physiological level [16]. Because of its regenerative effect on tissues, PRP attracts attention in the clinical practice in numerous fields, primarily in orthopedics and plastic surgery [17]. PRP contributes to local healing in damaged tissues by increasing concentrations of growth factors and other bioactive molecules [18]. Intraarticular PRP administration has been studied in patients with osteoarthritis, and it is benefited from its modulating effects on platelet inflammation, angiogenesis, chondroprotection, synovial cell modulation, and cell differentiation [19]. Fields of clinical PRP application include maxillofacial surgery, plastic surgery, cardiac by-pass surgery dermatology, orthopedics, and sports surgery [14]. In recent years, PRP is being widely used in the treatment of knee osteoarthritis, together with bone grafts, in rotator cuff repair, anterior cruciate ligament reconstruction, patellar tendinopathy, plantar fasciitis, and lateral epicondylitis [16].

Platelet-rich plasma (PRP) can be easily prepared by centrifugation in laboratories, outpatient clinics, radiology clinics, and in similar units. The facts that study protocols are not standard, PRP is prepared using different techniques, and the contents are not the same make the comparison of studies difficult [20]. Various factors that affect the characteristics of prepared PRP product and thereby its potential efficacy include volume of whole blood sample, efficacy of platelet recovery, final plasma volume in which the platelets are suspended, the presence or absence of red and/or white blood cells, addition of thrombin or calcium chloride to stimulate fibrin formation, and addition of pH-altering compounds [18].

In a limited number of available studies comparing outcomes of intraarticular PRP and HA administration in the treatment of gonarthrosis, better outcomes have been reported with PRP [21–23]. Cerza et al. [21] conducted a study in 120 patients and assigned the patients to PRP or HA groups as 1:1 randomization and compared the groups at the 4th, 12th and 24th weeks after 4 intraarticular administrations. They reported lower Western Ontario and McMaster (WOMAC) scores and better clinical outcomes in the PRP group. While no difference was found between the outcomes according to the stage of gonarthrosis in the PRP group, HA was found to be ineffective in stage III. Filardo et al. [22] evaluated patients receiving PRP ($n = 54$) or HA ($n = 55$) (3-week injections) at the post-treatment second, sixth and 12th months. They determined clinical improvement, which was evaluated by scoring systems, in both groups and reported a trend in favor of PRP group only in patients with low-grade articular degeneration (Kellgren–Lawrence score up to 2), although the difference was not significant between the groups. Spakova et al. [23] administered PRP and HA for three times at weekly intervals in two groups (each including 60 patients) and evaluated the outcomes at the third and sixth months. While there was no difference between the groups in terms of baseline WOMAC scores, it was found to be significantly lower in the PRP group than in the HA group after 3 months. Above-mentioned studies have reported no significant complication or adverse event associated with PRP administration. In the present study, based on the evaluation by KSS and VAS scores, better outcomes were obtained with PRP as compared to HA and none of the patients developed major complication. Indeed, it has been reported that no adverse event, except for local reactions at the injection site, is expected with PRP due to its autologous nature [16].

There are some limitations of this study. First of all its retrospective nature had less scientific significance. And the second is fewer case quantity and short follow-up time.

In conclusion, PRP appears to be an appropriate option for intraarticular treatment in patients with early-stage knee osteoarthritis.

Conflict of interest None.

References

1. Michael JW, Schlüter-Brust KU, Eysel P (2010) The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. Dtsch Arztebl Int 107(9):152–162
2. Sinusas K (2012) Osteoarthritis: diagnosis and treatment. Am Fam Physician 85(1):49–56
3. Sánchez M, Anitua E, Azofra J, Aguirre JJ, Andia I (2008) Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: a retrospective cohort study. Clin Exp Rheumatol 26(5):910–913
4. Cheng OT, Souzdalnitski D, Vrooman B, Cheng J (2012) Evidence-based knee injections for the management of arthritis. Pain Med 13(6):740–753
5. Frizziero A, Giannotti E, Ferraro C, Masiero S (2012) Platelet rich plasma intra-articular injections: a new therapeutic strategy for the treatment of knee osteoarthritis in sport rehabilitation. A systematic review. Sport Sci Health 8:15–22
6. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A (2013) Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med 41(2):356–364
7. Jevsevar DS (2013) Treatment of osteoarthritis of the knee: evidence-based guideline, 2nd edition. J Am Acad Orthop Surg 21(9):571–576
8. Canale ST, Beaty JH (eds) (2008) Campbell's operative orthopaedics. Knee arthroplasty, 11th edn, 6th chap, 263 p
9. Hameed F, Ihm J (2012) Injectable medication for osteoarthritis. PM&R 4((5 Suppl)):S75–S81
10. Curran MP (2010) Hyaluronic acid (Supartz®): a review of its use in osteoarthritis of the knee. Drugs Aging 27(11):925–941
11. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM (2004) Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. J Bone Joint Surg Am 86-A(3):538–545
12. Migliore A, Granata M (2008) Intra-articular use of hyaluronic acid in the treatment of osteoarthritis. Clin Interv Aging 3(2):365–369
13. Das A, Neher JO, Safranek S (2009) Clinical inquiries. Do hyaluronic acid injections relieve OA knee pain? J Fam Pract 58(5):281c–281e
14. Lee KS (2013) Platelet-rich plasma injection. Semin Musculoskelet Radiol 17(1):91–98
15. Martinez-Zapata MJ, Martí-Carvajal AJ, Solà I, Expósito JA, Bolíbar I, Rodríguez L, Garcia J (2012) Autologous platelet-rich plasma for treating chronic wounds. Cochrane Database Syst Rev17(10):CD006899
16. Saucedo JM, Yaffe MA, Berschback JC, Hsu WK, Kalainov DM (2012) Platelet-rich plasma. J Hand Surg Am 37(3):587–589 (quiz 590)
17. Alsousou J, Ali A, Willett K, Harrison P (2013) The role of platelet-rich plasma in tissue regeneration. Platelets 24(3):173–182
18. Arnoczky SP, Delos D, Rodeo SA (2011) What is platelet-rich plasma? Oper Tech Sports Med 19(3):142–148
19. Andia I, Sánchez M, Maffulli N (2012) Joint pathology and platelet-rich plasma therapies. Expert Opin Biol Ther 12(1):7–22
20. Sheth U, Simunovic N, Klein G, Fu F, Einhorn TA, Schemitsch E, Ayeni OR, Bhandari M (2012) Efficacy of autologous platelet-rich plasma use for orthopaedic indications: a meta-analysis. J Bone Joint Surg Am 94(4):298–307
21. Cerza F, Carnì S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora A, De Biasi G, Ciuffreda M (2012) Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. Am J Sports Med 40(12):2822–2827
22. Filardo G, Kon E, Di Martino A, Di Matteo B, Merli ML, Cenacchi A, Fornasari PM, Marcacci M (2012) Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord 23(13):229
23. Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A (2012) Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. Am J Phys Med Rehabil 91(5):411–417