

Intra-articular hyaluronic acid vs platelet-rich plasma in the treatment of hip osteoarthritis

Luca Di Sante¹, Ciro Villani^{3,4}, Valter Santilli^{1,2}, Massimo Valeo^{3,4}, Emmalisa Bologna², Luca Imparato⁴, Marco Paoloni¹, Annamaria Iagnocco⁵

¹Physical Medicine and Rehabilitation Unit, Azienda Policlinico Umberto I, ²Department of Physical Medicine and Rehabilitation, Sapienza Università di Roma, ³Orthopaedic Clinic Azienda Policlinico Umberto I, ⁴Department of Orthopedic Science, Sapienza Università di Roma, ⁵Dipartimento Scienze Cliniche e Biologiche – Reumatologia, Università degli Studi di Torino, Turin, Italy

Abstract

Aim: To compare the efficacy of ultrasound-guided intra-articular (IA) treatment with platelet-rich plasma (PRP) versus viscosupplementation (hyaluronic acid [HA]) in hip osteoarthritis. **Material and methods:** A total of 43 patients affected by monolateral severe hip osteoarthritis (OA) were included in the study. Patients were randomized to receive either intra-articular PRP (3 ml) or HA (30 mg/2 ml; 1,000-2,900 kDa), 3 injections in total – 1/week. Clinical assessments for each patient were made at baseline (T0), 4 (T1), and 16 weeks (T2) of follow-up. The primary efficacy outcome was pain reduction as measured by VAS and by WOMAC pain subscale. **Results:** Data analysis revealed that, compared to T0, in the PRP-treated group VAS scores significantly decreased at T1 but not at T2, thereby indicating an early effect on pain which was not maintained at a longer term follow-up. In the HA group a significant decrease of both VAS and WOMAC values was registered only between T0 and T2. **Conclusions:** Intra-articular PRP had an immediate effect on pain that was not maintained at longer term follow-up when, on the contrary, the effects of intra-articular HA were evident.

Keywords: hip osteoarthritis, Platelet-Rich Plasma, Hyaluronic Acid, ultrasound-guided injection.

Introduction

Osteoarthritis (OA) is a degenerative disease of the synovial joints with global articular involvement, including hyaline cartilage and subchondral bone. It is the most common cause of chronic pain in the elderly. Particularly, hip OA is one of the main causes of functional disability and joint pain in adults older than 55 years [1-5]. Current treatment strategies with either non-pharmacologic or pharmacologic therapies aim to reduce pain and physical disability and, possibly also, to limit structural deterioration of the affected joints. In the last decade the use of intra-articular (IA) injections of hyaluronic acid (HA) has become more and more popular, and recently a number

of studies have addressed the efficacy of this therapeutic intervention on pain and function in hip OA [6,7]. IA injections have many effects: primarily restoration of elastic and viscous properties of synovial fluid, but also anti-inflammatory and anti-nociceptive effects, as well as normalization of hyaluronan synthesis by synoviocytes [8].

Current research in the field is aimed at investigating new methods for stimulating the repair of damaged cartilage. The most recent acquisitions regarding tissue biology highlighted the complex regulation of growth factors (GFs) for the normal tissue structure and the reaction to tissue damage. In addition, the influence of these growth factors on cartilage repair has been widely investigated in vitro and in vivo [9-12].

Platelet-rich plasma (PRP) therapy is a feasible, minimally invasive and relatively inexpensive treatment that allows a natural concentrate of autologous growth factors to be obtained from the blood. This therapy is widely experimented in different fields of medicine to test its potential role to enhance tissue re-generation [13-17]. In a recent non-controlled prospective trial, the safety, toler-

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Corresponding author: Annamaria Iagnocco, MD

Sapienza Università di Roma, Rome, Italy

Viale del Policlinico 155 – 00161 Rome, Italy

Phone: +39-6-49973062

E-mail: annamaria.iagnocco1@gmail.com

ability and efficacy of PRP IA injections have been the subject of a preliminary report on 40 hip OA patients at 7 weeks' and 6 months' follow-up [18]. More recently, ultrasound-guided injection of platelet-rich plasma and HA were used separately and in combination in hip OA patients in a randomized controlled study [19]. Moreover, the efficacy of ultrasound-guided intra-articular injections of PRP versus HA was assessed in another study focused on hip OA [20].

Based on the previously reported researches in the field, the **aim** of the present study is to test the efficacy of PRP IA therapy as compared to HA IA treatment in terms of pain relief and functional recovery in a population of hip OA patients.

Material and methods

Consecutive patients of both genders with a diagnosis of hip OA, according to American College of Rheumatology criteria [21], were enrolled in the study. Exclusion criteria were the following: I and IV Kellgren and Lawrence scores [22]; clinical evidence of hip joint instability; previous open or arthroscopic hip surgery; history of systemic or local infectious, neoplastic and/or other rheumatic diseases; haematological diseases (coagulopathy); severe cardiovascular diseases; infections; immunodepression; patients in therapy with antiplatelet drugs; and patients with Hb values <11g/dl and platelet values <150,000/mm³.

The study protocol was approved by the local Ethics Committee. The experimental protocol was carefully explained to the patients participating in the study, and their informed consent was obtained by signing a detailed form in accordance with the Declaration of Helsinki. Participants were randomly assigned to either the HA group or PRP group by an independent person who selected a sealed envelope 30 minutes before the intervention was due to start.

Clinical outcome measures

Self-rated pain intensity at the moment of the evaluation was measured on a 10-cm horizontal visual-analogue scale (VAS), with 0 cm labeled as "no pain" and 10 cm labeled as "worst pain I have ever had". The Italian version of the Western Ontario and McMaster Universities (WOMAC) OA index [23], a self-assessment multidimensional instrument that evaluates 17 functional activities, 5 pain-related activities, and 2 joint stiffness categories in 3 different subscales, was used to measure dysfunction and pain.

Platelet-rich plasma preparation

PRP was obtained following the instructions for the use of the Regen Kit® in the preparation of the Autologous Platelet Gel. The procedure entailed a 8-ml venous blood sample for each hip treated. A complete peripheral

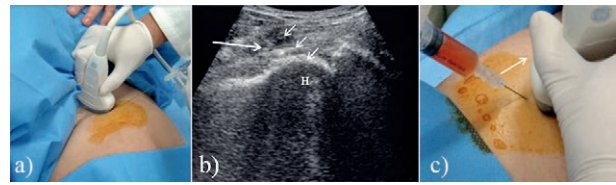


Fig 1. a) Free-hand technique with US probe placed parallel to the femur neck; b) sagittal US showing synovium/capsule (long arrow), the needle situated in the articulation (three short arrows), and the femoral head (H); c) PRP ultrasound-guided IA injections

blood count was also collected at the time of the initial blood donation. The samples were centrifuged twice at 3100 rpm (for 9 min) in order to produce 4 ml of PRP. After turning the test-tube upside down repeatedly, so as to achieve a homogeneous distribution, we linked the test-tube to the transferral and aspirated the content.

All procedures were performed in the same laboratory setting. All of the open procedures were performed in an A-class sterile hood. Randomly one PRP unit was sent to the laboratory for quality analysis (platelet count and bacteriological test). The total number of platelets/ml in the PRP without leukocytes represented a mean increase of around 100-150% compared with whole blood values.

Therapeutic Procedure

By using a computer-generated 1:1 allocation sequence, patients were randomized to either receiving Na-HA (30 mg/2 ml of HA with molecular weight 1,000 to 2,900 kDa) or PRP (3 ml) injections (3 injections in total – 1/week). For patients who satisfied the inclusion criteria the procedure entailed a 8-ml venous blood sample (see above). Ultrasound (GE Healthcare, Logiq P5 pro) was used as guidance for performing the IA procedure in all cases [24]. The injection was performed under sterile conditions by means of a 3.5 MHz convex probe. The patients laid supine with the hip in 15°–20° internal rotation, and previously to the injection, the hip region was scanned in order to localize the most relevant local landmarks such as the femoral neurovascular bundle, the femoral neck, the hip joint capsule, and the anterior synovial recess (fig 1). The probe was then aligned with the long axis of the femoral neck, including the acetabulum and the femoral head and, by a freehand technique, a 20-gauge (9 cm) spinal needle was then advanced under direct ultrasound guidance into the anterior synovial recess at the junction of the femoral head and neck. Once the needle touched the bone it was retracted by 1 mm and a synovial fluid aspiration was performed previously to the IA injection in order to decrease dilutions of the injected therapy [25]. Subsequently the injection was performed under sonographic guidance. As an additional confirmation of the correctly performed procedure and

IA therapy placement, a distension of the joint capsule was registered. After a few minutes of rest, the patients were allowed to walk and leave the clinic. They were also advised to rest until the next morning and during the follow-up period (16 weeks); the use of any anti-inflammatory or analgesic medication was not allowed. In addition, all patients were monitored for any side effects due to the IA injections.

Follow-Up

All patients underwent clinical evaluation at baseline (T0), 4 weeks (T1) and 16 weeks (T2) after the therapeutic procedure (fig 2). As a primary outcome measure, we considered pain reduction as measured by VAS. As secondary outcome measures, we considered pain reduction as measured by the WOMAC pain subscale (WOMAC A), and functional improvement as measured by WOMAC joint stiffness (WOMAC B) and disability (WOMAC C) subscales. All questionnaires were answered before the physical examination performed in the out-patient clinic.

Statistical analysis

Sample size was calculated for the primary end point. Assuming from a pilot study a mean difference from baseline of 3-points of the VAS score at T2 with an α error of 0.05, a β error of 0.2 the minimum sample size was 17 for each group. Assuming a dropout of 15%, 20 patients per group were required. The statistical analysis was performed using the MedCalc version 10.2.0.0 for Windows. All primary and secondary outcome analyses were performed according to the principle of intention-to-treat [22]. The chi-square or 2-sample t-tests were ap-

plied to compare the differences of the baseline data. A 2-way ANOVA with group (experimental versus control) as the between-subjects factor, and time (T0, T1 and T2) as the within-subjects factor was used to detect any significant differences between the experimental and control groups and within each group. A Tukey post-hoc comparison was used to detect any significant differences between the mean values when a significant main effect and interaction were found. The level of significance was set at $p < 0.05$ for all analyses.

Results

A total of 43 patients were randomized into two groups: HA group (n=22) or PRP group (n=21). Demographic and clinical characteristics of the patients at baseline were well balanced among groups, and are summarized in Table I. No complications related to the IA injections were registered during the treatment and follow-up period and all patients completed the treatment and performed the post-treatment assessment.

Two-way ANOVA showed a significant group (F=5.529; p=0.02) and time (F=7.491; p=0.001) effect for VAS score, and a significant group and time interaction (F=5.174; p=0.007). Particularly, post hoc analysis revealed that VAS scores were significantly lower than T0 values at T1, but not at T2 in the PRP group, thereby indicating an immediate effect on pain of PRP which was afterward lost (at T2 VAS value was further reduced but this reduction was not statistically significant). In contrast, in the HA group the significance between VAS values was reached only between T0 and T2 values. At T2, patients in the HA group had lower VAS values than those in the PRP group, the difference being significant at the 2-sample t-test (p=0.0004). Two-way ANOVA showed a significant group (F=32.070; p<0.0001) and time (F=6.036; p=0.003) effect for WOMAC A, while no significant group x time

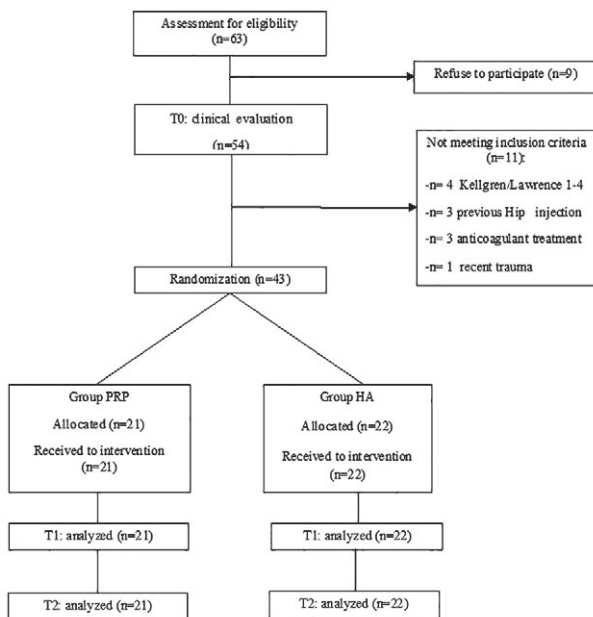


Fig 2. Flow-chart of the patients selection.

Table I. Patient baseline characteristics.

	Platelet-rich plasma group (n=21)	Hyaluronic acid group (n=22)	p
Age (year)	71.37±6.03	73.62±7.87	>0.05
Sex			
Female	10	13	>0.05
Male	11	9	
K-L			
Grade II	5	7	>0.05
Grade III	16	15	>0.05
VAS	6.3 (1.56)	7.08 (2.04)	>0.05
WOMAC a	55.6 8 (21.2)	46.7 (22.1)	>0.05
WOMAC b	53.7 (22.7)	57.6 (26.2)	>0.05
WOMAC c	59.8 (22.5)	45.9 (21.7)	>0.05

K-L: Kellgren and Lawrence scores, VAS: visual-analogue scale, WOMAC: Western Ontario and McMaster Universities index.

Table II. Visual-Analog-Scale (VAS) and WOMAC scores at baseline (T0), 4-week (T1) and 16-weeks (T2) evaluations in the analysed groups.

Hyaluronic acid group		Platelet rich plasma group	
Mean \pm SD (95% CI)	p-value ^a	Mean \pm SD (95% CI)	p-value ^a
VAS			
T0	6.32 \pm 1.7 (5.527-7.113)	T0 vs T1	NS
T1	5.27 \pm 1.6 (4.538-6.002)	T0 vs T2	<0.01
T2	3.63 \pm 2.1 (2.624-4.636)	T1 vs T2	NS
WOMAC A			
T0	42.36 \pm 20.5 (32.757-51.963)	T0 vs T1	NS
T1	29.6 \pm 13.4 (23.333-35.867)	T0 vs T2	<0.01
T2	19.9 \pm 11.4 (14.553-25.247)	T1 vs T2	NS
WOMAC B			
T0	57.65 \pm 26.2 (45.365-69.935)	T0 vs T1	NS
T1	47.69 \pm 21.2 (37.787-57.593)	T0 vs T2	<0.01
T2	32.91 \pm 20.6 (23.249-42.567)	T1 vs T2	NS
WOMAC C			
T0	45.83 \pm 21.7 (35.663-55.991)	T0 vs T1	NS
T1	39.13 \pm 17.2 (31.096-47.158)	T0 vs T2	<0.01
T2	28.39 \pm 17.2 (20.360-36.420)	T1 vs T2	NS

^aBonferroni corrected, NS: not significant, VAS: visual-analogue scale, WOMAC: Western Ontario and McMaster Universities index, SD: standard deviation.

interaction effect was found ($F=2.488$; $p=0.09$). Post hoc analysis revealed that WOMAC A scores were significantly lower than T0 values at T2 but not at T1 in the HA group (Table II). No differences between T0, T1 and T2 values were discernible in the PRP group.

As regards to secondary outcome measures, a significant time ($F=4.436$; $p=0.01$) effect was found for WOMAC B, while no significant group ($F=0.471$; $p=0.49$) or group \times time interaction ($F=1.653$; $p=0.20$) effects were found. Significant differences at post-hoc analysis were found only in the HA group between T0 and T2 values. A significant group ($F=14.177$; $p<0.0001$) and time ($F=3.680$; $p=0.03$) effect was found for WOMAC C, while no group \times time interaction effect was found ($F=0.789$; $p=0.457$). Again, post-hoc analysis revealed a significant difference between T0 and T2 values in the HA group. All these results are detailed in Table II.

Discussions

The efficacy of PRP IA therapy as compared to HA on pain relief and functional recovery in patients with hip OA was tested in the present study which demonstrated an early effect (4 weeks) of PRP treatment on hip joint pain that however, was not maintained at follow-up. On the contrary, HA produced a long term (16-weeks) pain relief and not a short term response. Interestingly, for all the other outcome measures, no significant effect could be demonstrated.

To our knowledge, only a few studies have aimed at comparing the response to IA treatments with PRP or

HA in hip OA patients. Particularly, a preliminary non-controlled prospective study supported the safety, tolerability and efficacy of PRP injections for pain relief and improved function in a limited number of patients with OA of the hip [20]. The main difference between that study and our research was the patients' age that was significantly higher in our study.

More recently, ultrasound-guided injection of PRP and HA were used separately and in combination in hip OA patients in a randomized controlled study which demonstrated that intra-articular PRP injections offered a significant clinical improvement in patients with hip OA with a benefit that was significantly more stable up to 12 months. Those results are partially in agreement with our study which showed an early effect of PRP that was not maintained at long term follow-up [19].

Furthermore, the efficacy of ultrasound-guided intra-articular injections of PRP versus HA in hip OA was previously assessed in another study and injections of PRP proved to be efficacious in terms of functional improvement and pain reduction but were not superior to HA in patients with symptomatic hip OA at 12-month follow-up [20]. The results of this study are partially in agreement with our research.

Moreover, the response to multiple PRP injections has been evaluated also in patients with knee degenerative conditions [26] showing a statistically significant improvement on symptoms at 2 and 6 months' follow-up in early knee OA and in the younger subjects group, with the worst results obtained in older patients and especially in

those with advanced cartilage degeneration. This finding may explain why the PRP injections had only a short term efficacy in our group of patients. Contrarily, IA HA injection demonstrated significant reduction in pain scores, disability scores and analgesic use also in advanced hip OA [27]. Better results are thus expected in young patients with a low degree of cartilage degeneration treated with HA and that can easily be explained by the mechanism of action hypothesized for the PRP treatment.

The rationale for the use of PRP in tissue regeneration is simply based on the activity of GFs carried in the blood. Autologous PRP is a volume of plasma having platelet concentration above normative baseline values [28]. Depending on the method used to process the PRP, it may also contain white blood cell concentrations above baseline values [29]. Platelets and white blood cells are sources of high concentrations of cytokines, which are well documented as regulating a number of processes related to healing and tissue regeneration [30]. These processes include cell migration, cell proliferation, angiogenesis, inflammation mediation, and collagen synthesis [31]. Several *in vitro* and *in vivo* models show that all kinds of cells involved in tissue regeneration are sensitive to growth factors, in particular chondrocytes, osteoblasts and periosteal cell growth is up-regulated by platelet-derived factors such as PDGF and bFGF [30-32] and, what is more, TGF- β . TGF- β is one of the most important factors involved in the process of cartilage regeneration, as it induces chondrogenic differentiation of mesenchymal stem cells as well as matrix deposition [32]. Many studies suggest an important role for these potent biologic regulators of chondrocytes in cartilage repair. Obviously, the potential for GFs action is the presence of a residual number of chondrocytes sensitive to their stimulation. On the other hand, the role of PRP in improving the proliferation of chondrocytes has been recently demonstrated in a controlled laboratory study [33]. Advanced OA is difficult to treat and presents a challenge for clinicians and orthopedic surgeons because of the distinctive structure and function of hyaline cartilage and its inherently low healing potential [34]. Older and more degenerated joints present a low percentage of living and vital cells and, therefore, a low response potential to the GFs. These considerations are, however, only speculative and hypotheses should be confirmed by studies addressed to understanding the influence of age and cartilage degeneration in response to PRP IA injections.

It should also be noted that in previously performed studies PRP injected into the knees of OA patients was characterized by a high platelets' concentration (500%-600%) [35]. In our case, the concentration of platelets per milliliter in the PRP represented a mean increase around

of 100-150% compared with whole blood values, and this may have limited the potential therapeutic effect.

The main limitation of the present study is its lack of a control group without therapy. However, we aimed to compare PRP injections directly with HA injections by means of a non-inferiority study, considering the HA injections as a "gold standard" IA therapy [36,37]. The sample size was limited to 43 patients. However, with this sample size, we had a β error of at least 0.2, so that the study demonstrated a good power. Finally, the key point in OA is long-term outcomes (1 year to 2 year) as opposed to a 3-month follow-up especially if the mechanism of regeneration is proposed.

In **conclusion**, the treatment with IA injection of PRP or HA, in elderly patients with OA of the hip, has been proven to be safe and without risks. However, the functional WOMAC and VAS score in the HA has shown to be more effective in the long-term (T2) than the PRP group which presents only significant improvement in VAS scores 4 weeks after treatment (T1). Further studies are needed to confirm these results with longer follow-ups especially if the mechanism of regeneration is proposed and in order to understand the mechanism of action, particular with a view to finding different platelet concentrations and injection timing.

Conflict of interest: none

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