

Comparison Between Hyaluronic Acid and Platelet-Rich Plasma, Intra-articular Infiltration in the Treatment of Gonarthrosis

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Background: Arthrosis is particularly prevalent in the knee. Infiltration treatment for gonarthrosis is among the most widely used techniques in orthopaedic practice.

Purpose: To compare the clinical response of hyaluronic acid (HA) and platelet-rich plasma (PRP) treatment in 2 groups of patients affected by gonarthrosis.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: A total of 120 patients affected by clinically and radiographically documented gonarthrosis were included in this study. The gonarthrosis was graded using the Kellgren-Lawrence radiographic classification scale. The 120 patients were randomized into 2 study groups in a 1:1 ratio: 60 patients received 4 intra-articular injections of PRP (specifically, autologous conditioned plasma [ACP], 5.5 mL), and 60 patients received 4 intra-articular injections of HA (20 mg/2 mL). An unblinded physician performed infiltration once a week for 4 weeks into the knee affected by clinically relevant gonarthrosis (in both groups). All patients were evaluated with the Western Ontario and McMaster (WOMAC) score before the infiltration and at 4, 12, and 24 weeks after the first injection.

Results: Treatment with a local injection of ACP had a significant effect shortly after the final infiltration and a continuously improving sustained effect up to 24 weeks (WOMAC score, 65.1 and 36.5 in the HA and ACP groups, respectively; $P < .001$), where the clinical outcomes were better compared with the results with HA. In the HA group, the worst results were obtained for grade III gonarthrosis, whereas the clinical results obtained in the ACP group did not show any statistically significant difference in terms of the grade of gonarthrosis. The mean WOMAC scores for grade III gonarthrosis were 74.85 in the HA group and 41.20 in the ACP group ($P < .001$).

Conclusion: Treatment with ACP showed a significantly better clinical outcome than did treatment with HA, with sustained lower WOMAC scores. Treatment with HA did not seem to be effective in the patients with grade III gonarthrosis.

Keywords: platelet-rich plasma; hyaluronic acid; gonarthrosis; intra-articular infiltration

Four million Italians suffer from arthrosis, which mostly affects the knee and can be quite debilitating.⁶ Men are more often affected than women in populations younger

than 50 years. Beyond 65 years of age, however, women are affected twice as much as men, a fact that may be attributable to menopause.²² Gonarthrosis is a condition that affects the articular cartilage, synovial membrane, and subchondral bone. Cartilage cells, called chondrocytes, occupy 1% of the overall volume and produce the extracellular matrix, which is mainly composed of collagen II, proteoglycans, and glycosaminoglycans. The subchondral bone tissue, synovial membrane, and cartilage are equally important and are responsible for the biochemical and biomechanical balance of the joints.²⁵ Previously, joint overloading and mechanical stress were considered to be the main etiopathogenetic factors in the development of arthrosis. However, during the past few decades, increased emphasis has been placed on the biochemical balance required for the health of the cartilage. This balance can be improved by controlling the biochemical factors that inhibit metalloproteases (interleukin-4, interleukin-10,

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interleukin-13, tissue inhibitor of metalloproteinases, insulin-like growth factor [IGF], and transforming growth factor- β [TGF- β]) and the biochemical elements that increase their synthesis (interleukin-1 β , tumor necrosis factor- α , interleukin-8, interleukin-6, interleukin-17, interleukin-18, leukemia inhibitory factor, and nitric oxide).^{10,17} Furthermore, special attention has been paid to synovial fluid and its primary component, hyaluronic acid (HA). The synovial fluid is important for lubrication of the articular surface, reduction of surface stress “extension” of the load zone, and transportation of chondronutritive substances from the synovia.

In the literature, synovial fluid in an arthritic joint has been described as having noticeably diminished HA concentration and lower viscosity, molecular weight, and elasticity.^{1,8,28,31}

As shown by numerous studies carried out over the past 2 decades, HA exercises its effect in 2 ways.⁴ These are *viscosupplementation*, characterized by the restoration of the mechanical and viscoelastic properties of the synovial fluid, and *viscoinduction*, characterized by the stimulation of the endogenous production of HA by synoviocytes and chondrocytes. Treatment with HA is advisable for treatment of advanced gonarthrosis before surgical intervention. It also can serve as an alternative to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and/or cortisone-based compounds when they are contraindicated, not tolerated, or ineffective.²⁹ The therapeutic scheme of HA supplementation varies according to the molecular weight of the drug. One injection per week for 3 to 5 weeks is the most commonly used approach in contemporary literature.^{3,32}

The use of growth factors has become increasingly popular to modulate the healing time of injured and damaged tissues. Platelet-rich plasma (PRP), a new type of growth factor treatment, is the product of autologous whole-blood centrifugation to obtain plasma with an increased platelet concentration compared with whole blood.^{20,26} Platelets contain growth factors in their alpha granules (such as insulin like growth factor-1 [IGF-1] basic fibroblast growth factor [BFGF], platelet-derived growth factor [PDGF], epidermal growth factor [EGF], vascular endothelial growth factor [VEGF], and transforming growth factor-beta [TGF- β]), which are involved in the process of inflammation reduction, necrotic cell removal, and tissue reconstruction.³³ Platelet-rich plasma has been used in maxillofacial and plastic surgery for more than a decade. Presently, it is increasingly accepted in orthopaedics and sports medicine for the treatment of tendinopathy, acute and chronic muscular lesions, muscular fibrosis, and capsular relaxation in the shoulder. It is also used for spinal fusion, pseudarthrosis, arthritis, synovitis, tendinous inflammation, and lesions of the meniscus and articular cartilage.^{13,14,23,24,30} The specific PRP used in this study was autologous conditioned plasma (ACP; Biocore, Arthrex Inc, Karlsfeld, Germany), which was chosen because of its high content of growth factors⁵ and significantly decreased quantity of white blood cells (WBCs). Other PRP systems contain WBCs, which may be detrimental to tissues because of the proinflammatory substances that they release.^{9,19,27} The primary objective of this study was to compare the

clinical response to HA and PRP treatment in 2 groups of patients affected by gonarthrosis grades I to III. The secondary objective was to evaluate whether there is any difference in clinical response between the 2 groups in relation to the grade of gonarthrosis.

MATERIALS AND METHODS

This study was a prospective, randomized, comparative, clinical trial.

Patient Selection

A total of 120 consecutive patients were enrolled between September 2009 and September 2010 (53 men and 67 women) with clinically and radiographically documented grades I, II, or III gonarthrosis, graded according to the Kellgren-Lawrence radiographic classification scale.¹⁷ Exclusion criteria included a history of previous knee operations, previous infiltrative treatment of the affected knee, documented rheumatoid or autoimmune abnormalities, and cases of grade IV gonarthrosis.

All the patients enrolled in the study had previously received physical therapy or pharmacological therapy with little benefit. Radiographic examination of the patients enrolled in the study included a radiogram of the lower limbs under load and 2 projections of the affected knee: anteroposterior in full extension and laterolateral in partial flexion. In the patients with bilateral arthrosis, only the side with significant symptoms for which the patient was referred to us was taken into consideration. The patients were consecutively randomized into the groups by their admission to our hospital. Groups allocated to the treatment with ACP underwent a hemochromocytometric examination to determine the platelet count. Patients with a platelet count less than 150,000/ μ L were excluded from the treatment, in accordance with the instructions for the use of ACP (Figure 1). All treatments and clinical checks were performed in our hospital.

All the patients gave their informed consent, and the study was approved by the local ethics committee.

Sixty patients received 4 intra-articular injections of ACP. The mean amount of blood drawn was 12 mL. The double syringe used for the infiltration contained 1 mL anticoagulant (sodium citrate). Sampling and the centrifugation of the ACP preparation were performed by the authors according to criteria established by the Authority Operational Office of Haematology of our hospital. Sixty patients received 4 intra-articular injections of HA (20 mg/2 mL; Hyalgan, Fidia, Abano Terme, Italy).

The injections were performed by the unblinded physician who had drawn the blood sample. Infiltration was performed once a week for 4 weeks on the knee affected by gonarthrosis. Before the injection, the skin was disinfected with alcohol or an iodine-based antiseptic solution.

The infiltration technique used for both groups was the superolateral approach, which has been shown to be the safest, ensuring intra-articular penetration of the drug in

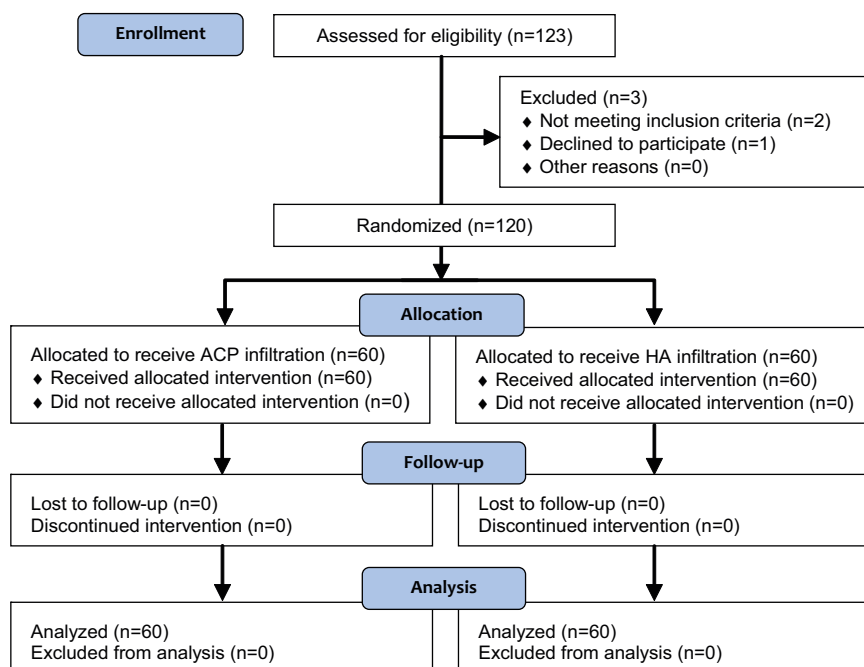


Figure 1. Flow diagram of the study. ACP, autologous conditioned plasma; HA, hyaluronic acid.

up to 93% of cases.¹⁵ The patient was placed in a supine position, the knee being slightly bent with the help of a popliteal cushion. The medial, lateral, and superior edges of the patella were always marked. After local anesthesia with lidocaine chlorohydrate, a superolateral approach was used whereby the needle was inserted at an angle of approximately 45° toward the medial joint line of the knee until reaching the “soft spot” between the patella and the femur, next to the junction of the line going through the lateral patellar edge and the line going through the superior pole of the patella. Before the drug was injected, the piston of the syringe was drawn back slightly to ensure that the needle was properly in the joint. The mean volume of ACP injected in our series was 5.5 mL for each infiltration.

After the infiltration, the patients were monitored for 10 minutes to ensure there were no adverse reactions. None were observed in our series. Postinjection protocol did not provide any restriction of physical activity. All the patients were evaluated before the infiltration and at 4, 12, and 24 weeks after the first injection. The Western Ontario and McMaster (WOMAC) osteoarthritis index questionnaire² was used, which assesses pain, articular stiffness, and functional limitation. This step was managed by the same operator. For WOMAC, the minimum score is zero and the maximum score, which represents the highest grade of debilitation, is 96.

The minimal detectable change was 1 and the minimal clinically important difference was 3.

Statistical Analysis

The significance of differences among the periods post-treatment (intragroup analysis) was tested by analysis of variance with Bonferroni correction. To test the

significance between the 2 types of treatment (intergroup analysis), we conducted a *t* test on groups of data belonging to the same level of pathologic changes and at the same posttreatment period.

With an anticipated effect size of 0.8 and a desired statistical power level of 0.8, we calculated a minimum sample size of 66 patients (33 patients per group).

RESULTS

No patients withdrew during the study period.

The ACP group consisted of 25 men and 35 women, with a mean age of 66.5 years (range, 31-90 years; standard deviation [SD], 11.3 years). Gonarthrosis was primary in 57 patients and was secondary to a trauma in 3 patients (lesion of cartilage due to repetitive traumas during sport in 2 patients; lesion of cartilage due to a fall in 1 patient). The pretreatment mean WOMAC score was 76.9 (range, 55-94; SD, 9.5). The patients were graded according to the Kellgren-Lawrence radiographic classification: 21 patients had grade I gonarthrosis, 24 had grade II, and 15 had grade III. The condition affected the right knee in 43 patients and the left knee in 17 patients.

The HA group consisted of 28 men and 32 women, with a mean age of 66.2 years (range, 36-87 years; SD, 10.6 years). In this group, gonarthrosis was primary in 59 patients and secondary to a trauma in 1 patient (fracture of the tibial plateau). The pretreatment mean WOMAC score was 75.4 (range, 54-91; SD, 10.7). The patients were graded again by the Kellgren-Lawrence classification: 25 patients had grade I gonarthrosis, 22 had grade II, and 13 had grade III. The condition affected the right knee in 48 patients and the left knee in 12 patients.

TABLE 1
Demographic Information^a

	ACP Group	HA Group
Average age (SD), y	66.5 (11.3)	66.2 (10.6)
Male patients, No. (%)	25 (42)	28 (47)
Female patients, No. (%)	35 (58)	32 (53)
Left knee, No.	17	12
Right knee, No.	43	48
Gonarthrosis, No. (%)		
Grade I	21 (35)	25 (42)
Grade II	24 (40)	22 (37)
Grade III	15 (25)	13 (21)

^aACP, autologous conditioned plasma; HA, hyaluronic acid; SD, standard deviation.

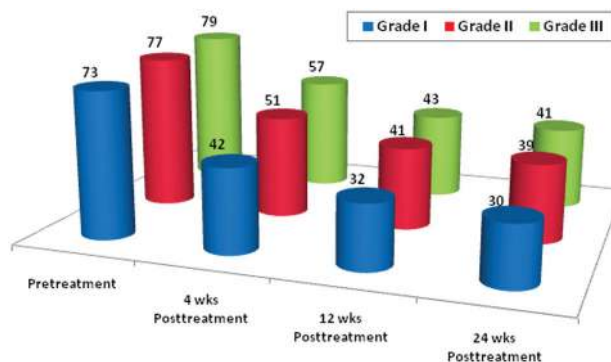


Figure 2. Mean Western Ontario and McMaster (WOMAC) scores for the autologous conditioned plasma (ACP) group in relation to degree of gonarthrosis.

There was no statistical difference in the age of the patients ($P > .05$). The percentage of men to women was similar between the 2 groups (ACP group: 42% men vs HA group: 47% men) with no statistically significant difference ($P > .05$). The distribution of gonarthrosis was also similar between the groups (ACP group: 35% grade I, 40% grade II, 25% grade III vs HA group: 42% grade I, 37% grade II, 21% grade III) with no statistically significant difference ($P > .05$). Demographic information is reported in Table 1. Finally, there was no statistical difference in pretreatment WOMAC scores ($P = .557$).

At week 4, both groups showed a significant reduction in the overall WOMAC score compared with baseline in both groups (Figure 2). The mean WOMAC score was 49.6 (range, 5-80; SD, ± 17.7) in the ACP group versus 55.2 (range, 25-78; SD, ± 12.3) in the HA group. The difference recorded between the ACP and the HA groups was statistically significant ($P < .001$) at this time point.

At week 12, a reverse trend was observed, with a continuous improvement in the patients treated with PRP and a slight worsening in patients treated with HA, as seen in Figure 3. The mean WOMAC score was 39.1 (range, 5-76; SD, ± 17.8) in the ACP group versus 57.0 (range, 32-78; SD, ± 11.7) in the HA group. The difference recorded between the groups was statistically significant ($P < .001$).

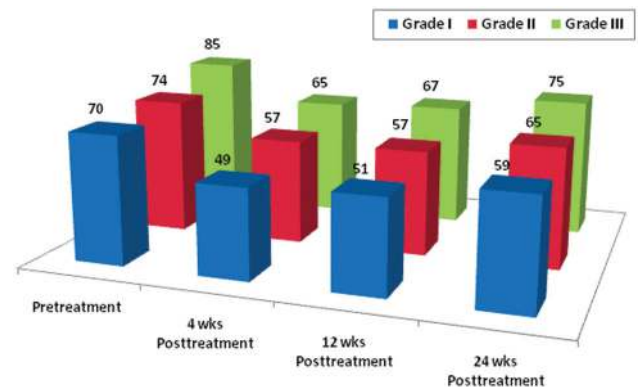


Figure 3. Mean Western Ontario and McMaster (WOMAC) scores for the hyaluronic acid (HA) group in relation to degree of gonarthrosis.

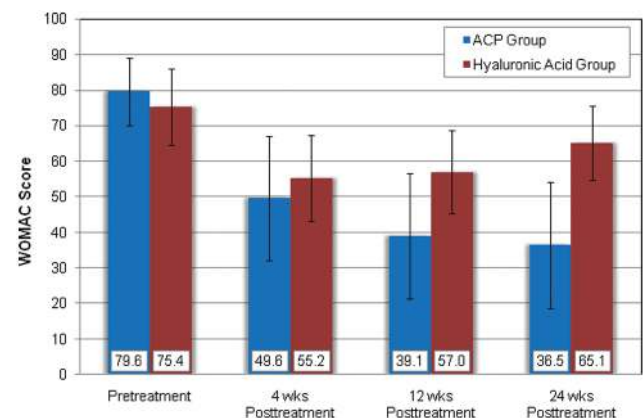


Figure 4. Mean Western Ontario and McMaster (WOMAC) scores for the autologous conditioned plasma (ACP) and hyaluronic acid (HA) groups.

In both groups the score was significantly better than baseline at week 12.

At week 24, the subjects treated with PRP showed a continuous improvement, whereas the subjects treated with HA showed a sharp worsening, as seen in Figure 4. Four subjects in the HA group regressed to their baseline WOMAC scores. Although the mean WOMAC score was 36.5 in the ACP group (range, 5-76; SD, ± 17.9), it was 65.1 in the HA group (range, 41-82; SD, ± 10.6). The difference recorded between the groups was statistically significant ($P < .001$).

In both groups, the score was significantly better than baseline at week 24.

In the ACP group, there were significant differences between pretreatment and all follow-up time points (4 weeks $P < .001$, 12 weeks $P < .001$, and 24 weeks $P < .001$). In addition, there were significant differences between 4 and 12 weeks ($P < .001$) and between 4 and 24 weeks ($P < .001$). There was no difference between 12 and 24 weeks ($P = .007$).

In the HA group, there were significant differences between pretreatment and all follow-up time points (4 weeks $P < .001$, 12 weeks $P < .001$, and 24 weeks $P < .001$). In addition, there were significant differences between 4 and 24 weeks ($P < .001$) and 12 and 24 weeks ($P < .001$). There was no difference between 4 and 12 weeks ($P = .196$).

At the end of week 24, the ACP group had 1 patient with no improvement in symptoms and with an unchanged WOMAC score in the 3 follow-ups; 2 patients showed a slight response and an overall improvement in their symptoms with a score reduction of 5 WOMAC points. Similarly, the HA group had 1 patient with a WOMAC score that remained unchanged in the 3 follow-ups.

We performed a statistical analysis to determine whether the clinical results depended on a difference in terms of the grade of gonarthrosis within the 2 groups.

In the group treated with ACP, the results obtained at weeks 4, 12, and 24 did not show a statistically significant difference in terms of the grade of gonarthrosis (Figures 2 and 3). In the group treated with HA, the worst results were obtained for grade III gonarthrosis, with statistically significant differences at week 12 ($P < .001$) and at week 24 ($P < .001$).

A statistically significant difference between grade III gonarthrosis treated with ACP and that treated with HA was observed at week 12 as well as at week 24, with a noticeable improvement that was greater in the patients treated with ACP ($P < .001$). The power t test for this subgroup was 0.92 and 0.99 for weeks 12 and 24, respectively.

A post hoc power analysis was performed on samples belonging to the same level of disease of different treatment groups. Where a difference of effect is expected (post 12 and post 24 weeks), the results show a good value of 1 beta (power index), which indicates a full sufficiency of sample size compared with the scale effect.

We tested the trend of differences (average $\pm$ standard error) between the value before treatment (pretreatment) and each of the values observed after 4, 12, and 24 weeks of treatment. For the HA group, the time that passed after treatment was related to a negative trend, whereas for the ACP group, the treatment effect continued to increase and approach the plateau.

DISCUSSION

The nonoperative treatment of gonarthrosis has been well documented in the literature over the past 5 decades. Treatment with HA restores the natural rheologic and metabolic homeostasis of the joints affected by the arthrotic process. The biochemical modifications induced by HA treatment improve the protective, lubricating, and shock-absorbing effect of the synovial fluid. Furthermore, this therapeutic approach does not cause side effects such as inflammatory and pseudoseptic reactions, a great advantage.²³

The pharmaceutical industry offers numerous types of HA. These substances differ from each other in terms of their production method, either extraction or

fermentation, and their molecular weight, which varies from 500,000 to 7,000,000 Da. The fermentation method has proved to be safe because it is not of animal origin and therefore not susceptible to viral infections. The CD44 receptor for HA on the synoviocyte membrane seems to have a higher affinity for substances with medium to low molecular weight (between 500,000 and 4,000,000 Da) because of stoichiometric reasons. Hyalgan, which was the HA used in this study, is a fermentative HA with a low molecular weight (500,000-750,000 Da).¹²⁻¹⁴

There are many PRP systems with a high concentration of growth factors, but without an additional concentration of WBCs, few of them are as effective as ACP. Treatment with PRP potentially could have an anti-inflammatory effect on soft tissues through the release of vital growth factors in both acute and chronic cases.^{7,11,12,21,26} In addition, there are no negative effects of reactive oxygen species, proteolytic enzymes, or matrix metalloproteinases released by WBCs when PRP is used.

Neutrophils are the most common type of WBC, constituting more than half of all WBCs in the body. Excessive neutrophil infiltration has been found to be responsible for the chronic inflammation seen in nonhealing wounds. Healing of the wound will not occur until the infiltration of neutrophils is reduced.⁹ Macrophages clear debris in the wound by a process of phagocytosis. However, macrophages must also clear particulate debris that was left behind by neutrophils after the activation and release of proteolytic enzymes.¹⁸ Because of this, the use of PRP that contains high levels of neutrophils could be questioned. The additional quantity of neutrophils can trigger increased tissue matrix degradation and diminish the body's ability to trigger the healing cascade. Macrophages may have a positive effect in terms of phagocytosis, but platelets release chemokines that activate and attract macrophages to the site of injury.²⁷ It is also becoming well established that platelets have an antibiotic effect attributable to their antimicrobial proteins.³⁰ Given the difference between ACP and other PRP products, it is unknown whether other PRP systems that contain a concentration of WBCs would show results similar to those found with the model presented here.

Few studies have evaluated the effectiveness of PRP in gonarthrosis. To our knowledge only one recent clinical trial¹⁶ compared the effectiveness of PRP and HA in a prospective design. Despite some differences in the assignment of the groups and the study protocol, the results of Kon et al¹⁶ were comparable with those obtained in our study, showing sustained efficacy of PRP.

Statistical analysis produced significant values. The subgroup of grade III gonarthrosis showed noteworthy differences, although it was of limited importance given the small number of patients with this grade of gonarthrosis in our series. Other limitations consisted of a relatively short-term follow-up and a lack of blinding.

However, the total number of patients treated and the homogeneity of the groups allow us to draw important considerations. Treatment with local infiltration of PRP has a significant effect shortly after the final injection and a continually improving sustained effect up to 24 weeks,

when the clinical outcomes are better compared with the results obtained with HA. This therapy can be administered easily and without any severe side effects for the patient. A treated patient can return to normal daily activity without any difficulty immediately after the infiltration.

Some of our patients reported benefits in terms of pain reduction within a few hours of the first treatment.

CONCLUSION

Treatment with PRP showed a significantly better clinical outcome compared with HA treatment; patients achieved lower WOMAC scores, which were subsequently maintained. In addition, the data indicated that this difference is greater in grade III gonarthrosis. In fact, in grade III patients, treatment with HA seemed decidedly less effective than treatment with PRP. Despite the relatively low number of patients in the subgroups, statistical analysis confirms the better result of the PRP, even in the highest degree of gonarthrosis. Treatment with HA did not seem to be effective in the patients with grade III gonarthrosis.

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