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Intra-articular Infiltration of Platelet-Rich Plasma versus Hyaluronic Acid in Patients with Primary Knee Osteoarthritis: Preliminary Results from a Randomized *Clinical Trial**

Infiltração intraarticular de plasma rico em plaquetas versus ácido hialurônico em pacientes com osteoartrose primária do joelho: Ensaio clínico randomizado com resultados preliminares

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Abstract

Objective The present study aimed to compare the effects of intraarticular infiltration of platelet-rich plasma with those of hyaluronic acid infiltration in the treatment of patients with primary knee osteoarthritis.

Methods A randomized clinical trial was conducted with 29 patients who received an intraarticular infiltration with hyaluronic acid (control group) or platelet-rich plasma. Clinical outcomes were assessed using the visual analog scale for pain and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire before and after the intervention. In addition, the posttreatment adverse effects were recorded. Categorical variables were analyzed using the chi-square and Fisher exact tests, whereas continuous variables were analyzed using the Student *t* test, analysis of variance, and the Wilcoxon test; all calculations were performed with the Stats package of the R software.

Results An independent analysis of each group revealed a statistical difference within the first months, with improvement in the pain and function scores, but worsening on the 6th month after the procedure. There was no difference in the outcomes between the groups receiving hyaluronic acid or platelet-rich plasma. There was no serious adverse effect or allergic reaction during the entire follow-up period.

Keywords
- osteoarthritis, knee
- hyaluronic acid
- infiltration

* *Study developed at the Orthopedics and Traumatology Department, Instituto Prevent Senior, São Paulo, Brazil.*

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Conclusion Intraarticular infiltration with hyaluronic acid or platelet-rich plasma in patients with primary knee gonarthrosis resulted in temporary improvement of functional symptoms and pain. There was no difference between interventions.

Resumo

Objetivo Comparar o efeito da infiltração intraarticular do plasma rico em plaqueta com a do ácido hialurônico no tratamento de pacientes com osteoartrose primária de joelho.

Métodos Realizou-se um ensaio clínico randomizado com 29 pacientes, sendo um grupo submetido à infiltração com ácido hialurônico (controle) e o outro com plasma rico em plaquetas. Os desfechos clínicos avaliados foram a escala visual analógica da dor; o questionário *Western Ontario and McMaster Universities Arthritis Index* (WOMAC), antes e depois da intervenção; e os efeitos adversos após as aplicações. Utilizou-se os testes do qui-quadrado e exato de Fisher para as variáveis categóricas, e o teste t de Student, análise de variância, e Wilcoxon para as variáveis contínuas, através do software de estatística R.

Resultados A análise independente de cada grupo revelou uma diferença estatística nos meses iniciais, com melhora dos escores de dor e função; porém, com piora no 6° mês após o procedimento. Não houve diferença dos desfechos avaliados entre os grupos que foram submetidos à infiltração com ácido hialurônico ou com plasma rico em plaquetas. Não houve efeito adverso grave ou reação alérgica durante todo o seguimento.

Conclusão A infiltração intraarticular com ácido hialurônico ou plasma rico em plaquetas nos joelhos dos pacientes com gonartrose primária apresentou melhora temporária dos sintomas de função e dor. Não houve diferença entre as duas intervenções.

Palavras-chave
- osteoartrite do joelho
- ácido hialurônico
- infiltração

Introduction

Knee osteoarthritis (OA) is a degenerative disease affecting mostly females and resulting in progressive joint cartilage destruction. Osteoarthritis leads to joint deformity, potentially with muscle and ligament imbalance, and most abnormalities occur in regions subjected to greater load. Its typical radiographic signs include bone sclerosis, cysts, and osteophytes.[1–3]

Knee OA has a great impact on physical performance, and it is considered one of the 10 main causes of disability around the world. Standard conservative treatments for knee OA include weight loss, exercise, non-steroidal antiinflammatory drugs (NSAIDs), analgesic agents, intraarticular injection of hyaluronic acid (HA) and glucocorticoids.[4]

Hyaluronic acid is used in the treatment of degenerative joint diseases. It is a glycosaminoglycan that acts on the extracellular matrix providing greater joint lubrication and protection.

Recently, however, orthobiologic injections have emerged as a potentially safe and effective option for knee OA treatment. These injections include bone marrow concentrate (BMC), mesenchymal stem cells (MSC), and platelet-rich plasma (PRP).

Platelet-rich plasma consists in plasma with a high platelet concentration.[5] Depending on the method used for PRP processing, it may also contain white blood cells in abnormally high concentrations.[6] Platelets and white blood cells are sources of high cytokines levels, which play a well-documented role in controlling a number of tissue regeneration processes, including cell movement and proliferation, angiogenesis, inflammation regulation, and collagen synthesis.[6]

In addition to their role in local hemostasis, platelets contain an abundance of growth factors and cytokines, which are crucial in soft-tissue healing and bone mineralization.[7] Moreover, they release a number of proteins that attract macrophages, mesenchymal stem cells, and osteoblasts, resulting in necrotic tissues removal and faster tissue regeneration.[4]

Recently, some studies investigated the potential beneficial effects of PRP in chronic diseases, including lateral epicondylitis and plantar fasciitis.[4] However, most studies using PRP in the literature are non-randomized and have insufficient samples.

The present study aims to determine the effect on pain and function outcomes of an intraarticular application of PRP in comparison to HA to treat knee OA patients.

Method

This is a randomized clinical trial with 29 consecutively included patients. All patients participating in the present study agreed and signed an informed consent form.

This study complied with the Helsinki Declaration and Guideline for Good Clinical Practice. The research protocol

was approved by the local ethics committee (Opinion at *Plataforma Brasil*, number 3.293.253).

Patient selection

The total sample included 29 patients of both genders, aged between 49 and 75 years old, who met the clinical and radiographic diagnostic criteria of the American College of Rheumatology (ACR) for knee OA and categorized as grade II or III according to the Kellgren-Lawrence classification.[2]

The exclusion criteria were the following: previous surgery on the affected knee at any time or orthopedic surgery on the lower limbs within the 12 months prior to the study; previous HA or steroid infiltration within 3 months prior to the study; advanced OA cases (grades IV and V); diagnosis of autoimmune or rheumatological diseases; body mass index (BMI) $\geq$ 35; secondary OA (i.e., fractures, neoplasms); history of acute or chronic communicable diseases; difficult-to-control or insulin-dependent type I or II diabetes; coxarthrosis diagnosed at the physical or radiographic examination; active infection or history of infection at the affected joint; axial deviation in 10º varus, 15º varus or 1 cm discrepancy in lower limbs; use of anticoagulants or immunosuppressants; discontinuation of oral chondroprotective therapy within the last 3 months; and abnormal renal and/or liver function.

All included patients had a confirmed diagnosis of knee OA and underwent conservative treatment with physical therapy, stretching exercises, and analgesic agents for at least 6 months before the start of the study. Osteoarthritis was evaluated with knee radiographies in two views (anteroposterior and lateral) under load.

Tests requested during preselection visits were the following: biochemical blood tests (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, fasting blood sugar, creatinine, sodium, potassium, hemoglobin A1C, complete blood count), serology for communicable diseases, magnetic resonance imaging (MRI) of the affected knee, bilateral knee radiography, and panoramic radiography of lower limbs.

Randomization

Patients were randomized using the Research Randomizer System.[8] Thus, the study had two arms: a study group, submitted to an intraarticular application of PRP, and a control group, receiving a HA application.

Application method

Patients from both study arms were scheduled on an outpatient basis for infiltration at the following week. Control group patients underwent a single knee intra-articular infiltration with Synvisc One Hylan G-F20 (Lancaster, Pennsylvania, United States) following specific asepsis and antisepsis protocols.

Upon arrival at the hospital, subjects from the study group were directed to the blood collection sector, where a sample of 15 mL of blood was sterilely collected by peripheral access in a specific tube. The sample was then transported at a controlled temperature for processing at a laboratory from the same hospital.

The sample was centrifuged at 1,500 rotations per minute for 5 minutes at room temperature. Next, the sample was quantified and considered acceptable if it presented a two-fold increase in the number of platelets when compared with the baseline value.

After obtaining approximately 5 mL of PRP, the knee infiltration procedure was performed in a small surgical room. Platelet-rich plasma was applied through an intra-articular puncture on the knee. The entire process was carried out using the Arthrex Autologous Conditioned Plasma system (Arthrex Inc., Naples, FL, USA). The application process was repeated over the next 2 weeks, at 7 and 14 days, respectively, totaling 3 PRP infiltrations.

Clinical follow-up and outcomes evaluation

The subjects' data were collected by the researchers, including age, laterality, BMI, edema, and stiffness in the affected knee. Both groups were followed-up at the same frequency after the control group received the 3rd application, for a total period of 6 months.

The standardized follow-up consisted in 5 outpatient medical visits over a 6-month period: the 1st visit occurred after 1 week, and the following visits were at 2 weeks, 1, 3, and 6 months after the treatment. In addition, there were 2 telephone contacts with the patient, at 2 and 4 months after the procedure.

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) score was obtained at the following times: preinfiltration, 1, 3, and 6 months after treatment. The visual analog scale (VAS) for pain was used 2 and 4 months after the procedure.

Statistical analysis

Statistical analysis was performed using the Stats package of the R software (R Foundation for Statistical Computing, Vienna, Austria).[9] Continuous variables were descriptively analyzed using means and standard deviations, followed by a normal distribution evaluation using the Shapiro test.[10] Categorical variables were presented as proportions.

For intra-group comparison, the analysis of variance (ANOVA) and Fisher's least significant difference tests were used[11] to determine any difference at WOMAC scores, whereas the VAS results were analyzed using a Student paired *t* test.

Intergroup differences were assessed using the Student *t* tests[12] for parametric variables, and the Mann-Whitney test[13] for non-parametric variables. Categorical variables were assessed between the study and the control groups using the chi-squared test[14] or Fisher exact test.[15]

Results

No patient was lost at follow-up. Both the control and study groups were homogeneous, with no statistical difference between parameters, as shown in ►**Table 1**.

Regarding functional outcomes (WOMAC scores), there was no statistical differences between the study and control groups from the preintervention level to 6 months after treatment (►**Table 2**).

Table 1 Patients characteristics

	Platelet-rich plasma	Hyaluronic acid	*P*-value
Number of patients	14	15	–
Body mass index	28.3 (2.9*)	28.1 (3.9*)	0.60
Age (years), Mean (SD)	62.78 (6.10*)	63.40 (4.99*)	0.77
Gender	11 females 3 males	13 females 2 males	0.93
Affected side	Right = 7 Left = 7	Right = 11 Left = 4	0.36
Radiological Classification	Grade II = 9 Grade III = 5	Grade II = 9 Grade III = 6	1
Knee swelling	Yes = 1 No = 13	Yes = 2 No = 13	1
Knee stiffness	Yes = 1 No = 13	Yes = 2 No = 13	1

Abbreviation: SD, standard deviation.
Source: Prevent Senior São Paulo.

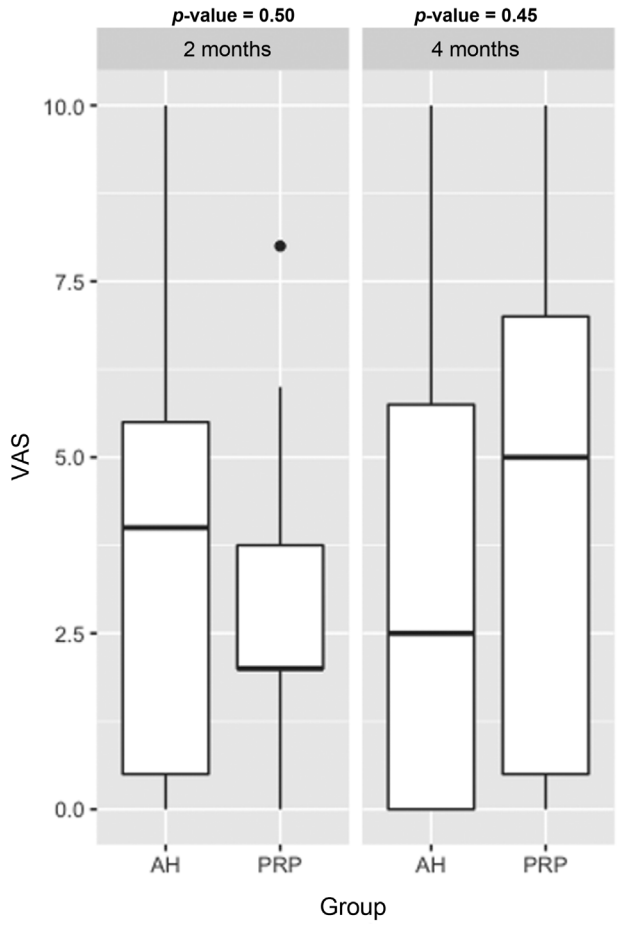

Fig. 1 Distribution of the visual analog scale (VAS) for pain score in subjects treated with hyaluronic acid (HA) or platelet-rich plasma (PRP).

In addition, the VAS score for pain revealed no statistical difference at the 2nd ($p = 0.50$) and 4th ($p = 0.45$) month after the treatment, as shown in ►**Figure 1**.

In the intragroup evaluation, function improved after the procedure, but worsened at the last month of evaluation. For the PRP group, there was a statistical difference between the WOMAC score at baseline and 3 months after the procedure ($p < 0.05$). In addition, there was a difference between scores from the 1st and 6th month after the procedure due to an increased score ($p < 0.05$). Pain was also influenced, with a mean difference in VAS score of 1.64 between the 2nd and 4th months after the treatment ($p < 0.05$). ►**Figure 2** shows WOMAC scores from the study group at different times.

Regarding the HA group, there was a statistical difference in WOMAC scores from baseline and 1 month ($p < 0.05$) and baseline to 3 months after treatment ($p < 0.05$). There was no statistical difference in the VAS score for pain at the 2nd and 4th months after the treatment ($p = 0.49$). ►**Figure 3** shows this distribution.

No infections or allergic reactions were reported during the 6-month follow-up. Pain cases were treated with analgesic agents, cryotherapy, and rehabilitation.

Discussion

The main finding of our study was the lack of difference in functional outcomes and pain assessment at a medium-term follow-up (6 months) between patients undergoing intraarticular infiltration with HA and PRP. However, both treatment methods were effective in improving pain and function over the study period and proved to be safe.

Table 2 Western Ontario and McMaster Universities Osteoarthritis Index score in subjects treated with platelet-rich plasma or hyaluronic acid

		WOMAC, baseline	WOMAC, 1 month	WOMAC, 3 months	WOMAC, 6 months
PRP	Mean	42.5	29.0	23.7	41.1
	Standard deviation	17.9	16.0	22.0	24.8
HA	Mean	41.1	24.0	26.0	35.7
	Standard deviation	15.5	14.6	22.0	35.7
	p-value	0.82	0.39	0.78	0.73

Abbreviations: HA, hyaluronic acid; PRP, platelet-rich plasma; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
Source: Prevent Senior São Paulo.

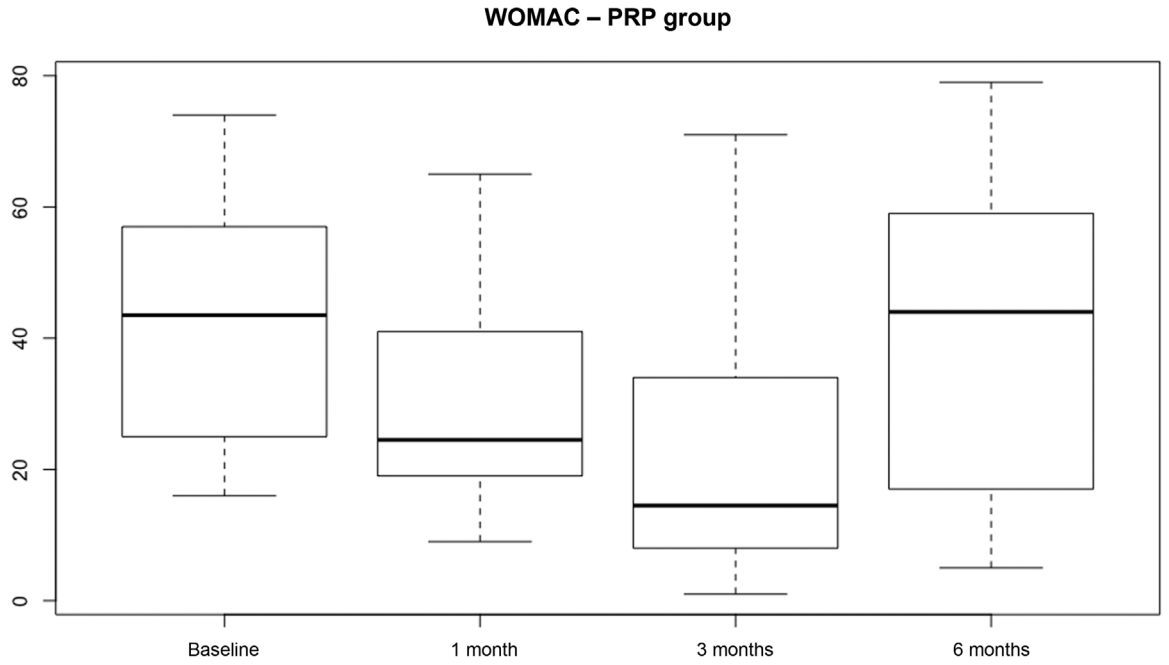

Fig. 2 Distribution of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score in subjects treated with platelet-rich plasma (PRP).

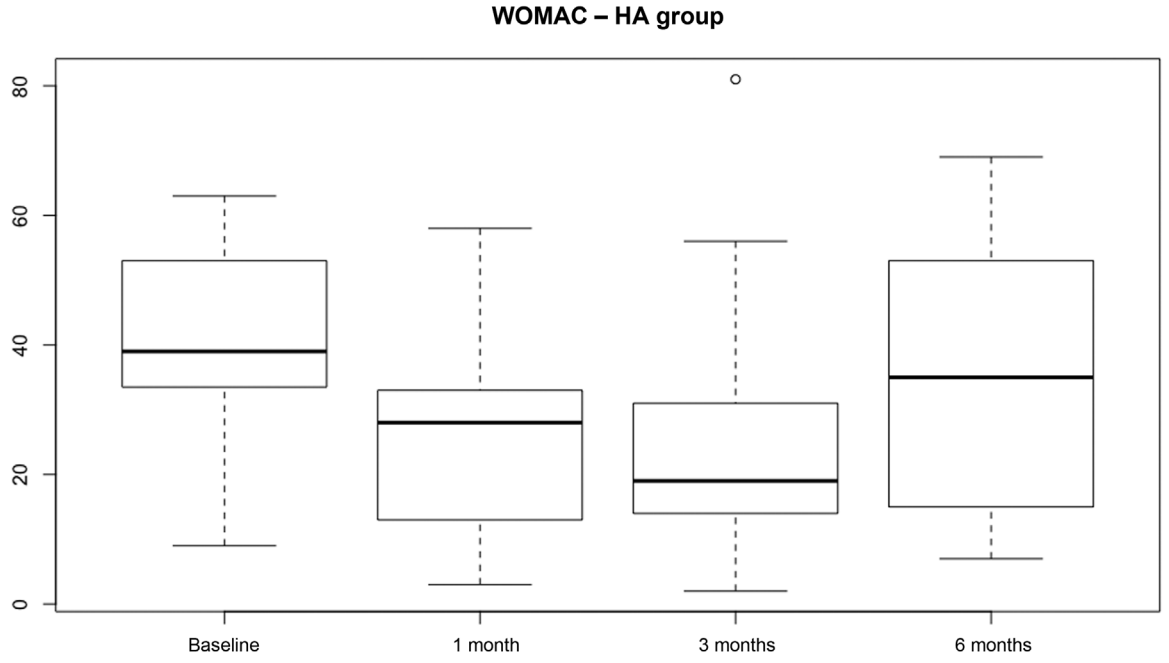

Fig. 3 Distribution of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score in subjects treated with hyaluronic acid (HA).

Functional assessment was performed using the WOMAC questionnaire, revealing no differences between the two groups over the 6-month follow-up. The literature is still controversial regarding this outcome. A recently published systematic review using the total WOMAC score for functional assessment concluded that PRP is superior to HA in the medium term (3–6 months). However, the same study found no differences between groups when analyzing fractional WOMAC scores for stiffness and physical function.[16]

Another meta-analysis demonstrated the superiority of PRP over HA in pain improvement as assessed by the WOMAC score. However, the study concluded that there is no obvious superiority between PRP and HA in knee OA treatment.[17]

Some randomized clinical trials comparing these two methods for OA treatment also found no differences in functional scores after 6 months of follow-up.[18,19]

We found no differences regarding pain between the PRP and HA groups. Similarly, these outcomes are quite divergent

to the literature. Zhang et al.[17] found no differences in the VAS for pain between both treatments 3 and 6 months after infiltrations. However, Cole et al.[19] demonstrated significant pain improvement according to the VAS in patients treated with PRP 6 and 12 months after the infiltration.

Most systematic reviews on the subject report the challenge in comparing the several published studies due to major variations in the PRP preparation and composition, the number of infiltrations performed, small samples, short follow-up times, and different inclusion and evaluation criteria.[20]

Our study used a standardized kit for PRP preparation; in addition, samples were homogeneous, and infiltrations were performed once a week for 3 weeks. Previous studies had shown advantages of multiple PRP applications when compared to a single infiltration, including longer PRP effects when more than one application was performed.[21,22]

Our study demonstrated that both PRP and HA were effective in treating pain and improving function. However, their effects deteriorate over time and virtually disappear 5 to 6 months after the treatment. Di Martino et al.[23] found similar outcomes in a randomized clinical trial. According to these authors, patients reported symptom improvement up to 9 months after HA application and up to 12 months after intraarticular PRP infiltration, but with progressive effect loss.

Filardo et al.[18] also observed similar outcomes in a randomized clinical trial with 1 year of follow-up. These authors showed an improvement in pain and function in patients treated with PRP or HA, but these outcomes remained virtually stable 2 months after treatment.

Regarding adverse effects, both PRP and HA proved to be safe in our study. None of the drugs caused severe, lasting side effects. In a meta-analysis, Han et al found no differences between treatment groups regarding adverse effects.[24] Other studies have also concluded that both treatments are safe, and have few side effects during follow-up.[25,26]

The study has some limitations. First, despite being a preliminary report, the sample size is small. Second, the follow-up period is relatively short (6 months), and some studies have shown that PRP effects last longer than those of HA. The absence of a sham group (placebo or steroid infiltration) and the lack of group blinding are other limitations from our study.

Conclusion

Knee intraarticular infiltration with HA or PRP in patients with primary gonarthrosis resulted in transient improvement of pain and function. Both treatments proved to be safe. There was no difference between these interventions.

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Conflict of Interests
The authors declare no potential conflict of interests.

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