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Intra-articular injection with platelet-rich plasma compared to triamcinolone hexacetonide or saline solution in knee osteoarthritis: A double blinded randomized controlled trial with one year follow-up

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Abstract

Objectives: To compare the effectiveness of intra-articular injection (IAI) of Platelet-Rich Plasma (PRP) with Triamcinolone Hexacetonide (TH) and Saline Solution (SS), in patients with knee osteoarthritis (OA).
Design: A randomized controlled trial, with blinded patients and assessor.
Setting: Outpatient rheumatology service.
Subjects: Patients with knee osteoarthritis grades II and III.
Interventions: Patients received IAI with PRP, 40 mg TH, or SS.
Methods: Patients were assessed at baseline and after 4, 8, 12 e 52 weeks with: visual analogue scale (VAS) for pain at rest and movement, WOMAC questionnaire, Timed to Up and Go test, 6-min walk test, percentage of improvement, goniometry, quality of life SF-36 questionnaire, Likert scale and Kelgreen & Lawrence (KL) radiographic scale (only at baseline and 52 weeks).

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Results: 100 patients were studied, with a mean age of 67.13(6.56) years. The TH group was superior for: percentage of improvement (versus SS group from 4 to 52 weeks); WOMAC total and pain (versus PRP group at 4 weeks); and WOMAC stiffness (versus SS group at 12 weeks). The SS group was inferior for WOMAC function (from 8 to 52 weeks). The PRP group showed lowest radiographic progression [TH 17 (51.51%) to 24 (72.72%); SS 17 (51.51%) to 30 (90.90%); PRP 20 (58.82%) to 21 (61.76%)].
Conclusion: The Triamcinolone Hexacetonide group was superior for percentage of improvement and WOMAC, pain and stiffness. For the WOMAC function, the Platelet-Rich Plasma group and Triamcinolone Hexacetonide group were superior to the Saline group. The Platelet-Rich Plasma group showed the lowest radiographic progression at 52 weeks of follow-up.

Keywords
Intra-articular injection, osteoarthritis, knee, platelet-rich plasma, corticosteroid

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Introduction

Osteoarthritis is the most frequent in the group of musculoskeletal diseases.[1] The knee is the major joint affected, with a prevalence of 6-17%, present in approximately 10% of the population over 55 years old, of which 25% might become severely disabled.[2] This disease affects the joint globally including cartilage, subchondral bone, the synovial membrane, the ligaments, and the meniscus.[3]

The intra-articular injection with corticosteroid is recommended for the osteoarthritis treatment to reduce local pain. This action is fast, with a maximum peak of effect in less than one week but only lasting around four.[4] Triamcinolone hexacetonide has been considered more suitable for this procedure due to its longer length in the joint.[5]

Platelet-rich plasma is an autologous concentration of platelets in a small volume of plasma[6] and has been considered in the treatment of knee osteoarthritis.[7] This beneficial effect is supported by systematic reviews and meta-analyzes,[8–10] however, the few studies comparing Platelet-rich plasma with 0,9% saline solution in knee osteoarthritis patients showed conflicting results.[11–13]

To date, we are unaware of any study comparing simultaneously the use of intra-articular platelet-rich plasma versus triamcinolone hexacetonide which has also included a third group with saline solution.

The primary aim of this study was to compare the effectiveness of intra-articular injection with platelet-rich plasma versus triamcinolone hexacetonide versus saline for pain relief in the short, medium, and long term in patients with symptomatic primary knee osteoarthritis. Our secondary aims were to compare these three groups regarding the following parameters: perception of improvement, function, quality of life and radiographic progression according to the Kellgren and Lawrence[14] scale.

Methods

This study was carried out between March 2015 and September 2018. It had no funding source and was carried out in the discipline of Rheumatology of the *Universidade Federal de São Paulo*, in Brazil. Before starting the allocation of patients, the study was approved by the institutional ethical review board (protocol number: 965,920 on 02/25/2015/ CAAE: 36673814.1.0000.550), registered in ClinicalTrials.gov (Identifier: NCT03086759) and no changes in study methods occurred during its realization. This was a prospective, controlled, randomized and double-blind study involving three parallel groups of intra-articular injection in knee osteoarthritis patients:

Platelet-Rich Plasma versus Triamcinolone Hexacetonide and versus Saline. The patients

included were from an outpatient clinic of a tertiary hospital.

Patients with primary bilateral knee osteoarthritis according to the diagnostic criteria of the American College of Rheumatology were included.[15] The patients were recruited and selected by the study's principal investigator (JCNT), who was not involved in the randomization, intervention, or assessment of the study.

The inclusion criteria for the study were: age over 40 and less than 85 years; diagnosis of primary and symptomatic bilateral knee osteoarthritis, by clinical[15] and radiographic criteria (Kellgren & Lawrence classification of II-III);[14] with pain for more than three months; pain on movement in the knee between 4 and 8 cm on the visual analogue scale (VAS from 0 to 10 cm), which interfered with the function on most days of the week; agreement and signature of the Informed Consent Form of the study.

The exclusion criteria were: secondary knee OA; cutaneous knee injury; intra-articular injection with corticosteroids or hyaluronic acid in the knee in the last 6 months; use of corticosteroids in the last 30 days; inflammatory arthritis, gout or pseudogout; presence of oncologic disease; previous surgery on the knee; cardiovascular or respiratory disease interfering with functional status; pregnancy; breast-feeding; severe clotting disorder; suspected bacterial infection of any kind; any condition interfering with gait; use of antiplatelet agents and/or non-steroidal anti-inflammatory drugs, 14 days before the intervention; presence of thrombocytopenia (platelet dosage less than 150,000/mm^3).

All patients who met the inclusion criteria for the study underwent a blood test on the day of inclusion to exclude thrombocytopenia. Only patients with platelet results above 150,000/mm^3 were included and randomized.

The intervention, an intra-articular knee injection, was performed at the same time of day, around 4 PM, with the patient in the supine position and with the lower limb in extension in the three groups. Only a single intra-articular injection was performed on the most symptomatic knee according to the patient perception. The procedure was performed by the same rheumatologist with extensive experience in interventional rheumatology (RNVF) and who did not participate in the study's uptake, randomization, or evaluation phases. The 40×8 mm needle inlet was 2 centimeters from the superolateral angle of the patella. Two syringes were used. In the first syringe, 2% lidocaine without vasoconstrictor was used for anesthesia, only if there was difficulty in intra-articular approach to the knee. Arthrocentesis was systematically performed on the knees with joint effusion, and then the medication was injected according to the group. Visualization of the material injected by the patient was systematically avoided.

All material used in the intra-articular injection procedure was sterile and handled away from the patient's visual range. In the Triamcinolone Hexacetonide group, 40 mg (2 mL) of the corticosteroid was injected. In the Saline group, 2 mL of the saline solution (0,9%) was injected.

The injected knee was bandaged with a crepe bandage. Joint rest 48 h and the use of acetaminophen 750 mg up to 8/8 h, on demand, were recommended.

The intra-articular injections in the three groups were performed in a specific room in the outpatient rheumatology service, not in an operation theatre.

The preparation of the platelet-rich plasma was performed by a previously trained biomedical (FMH), according to the modified Arun K. Garg protocol, as described below[16,17]: it was collected 45 to 50 mL of venous blood in the antecubital fossa, with the patients comfortably lying on the stretcher where they received the intra-articular injection. A green 25×8 BD vacuum needle was used in the venipuncture to prevent irritation or trauma of the platelets and the collection was performed directly into a sterile flask.

The blood was then centrifuged in a tube with anticoagulant (ACD = citric acid + dextrose + sodium citrate) for 10 min at 1200 revolutions per minute (rpm) with an acceleration time of 30 s and a stop time of 55 s. The centrifuge used was the FANEN, Model Excelsa 2206. The tube used in the centrifugation was the "BD Vacutainer® ACD Solution A" REF 364606, sterile, produced by BD Franklin Lakes NJ USA. At the end of the

centrifugation, the blood was separated into red blood cells (which were deposited at the bottom), leukocytes (whitish layer just above the red blood cells), platelet-poor plasma (most superficial layer) and platelet-rich plasma (layer between leukocytes and platelet-poor plasma). The intention was to obtain a platelet value of 2.5 to 5 times the number of platelets in the blood collected.

The platelet-rich plasma was then carefully removed from the tube using a sterile, disposable, and plastic Pasteur pipette so that platelet aggregation and adhesion would not occur. The material was deposited on a sterile Petri dish from where the platelet-rich plasma was very carefully aspirated by a sterile syringe without a needle. A small sample of this material was separated to measure the number of platelets after the preparation of the platelet-rich plasma. To count the number of platelets, automated examination by fluorescent flow cytometry and impedance was used, with confirmation of counts and morphological analysis performed by microscopy, when applicable. In the technique of the Platelet-Rich Plasma preparation used in this study, no specific coagulants such as thrombin or calcium chloride (platelet activators) were used to obtain the platelet gel. Platelet activation, therefore, was endogenously induced. Immediately after its preparation the Platelet-Rich Plasma was injected very carefully into the intra-articular space of patients of the Platelet-rich plasma group (Figure 1). The platelet-rich plasma was carefully placed on the Petri dish only after the knee had already been punctured. In this study, the leukocyte count in platelet-rich plasma was not performed.

For all three groups of patients, venipuncture was performed to maintain the patients blinded (in the Triamcinolone Hexacetonide and Saline groups, only 1 mL was collected), and they were instructed to not use non-steroidal anti-inflammatory drugs for 14 days after the procedure. This last measure aimed to avoid platelet inhibition caused by such drugs. For the three groups of patients, it was impossible to visualize the amount of blood collected.

During this study, patients were instructed to avoid any other type of treatment such as exercise program, physical modalities, or knee brace.

The patients underwent five assessment times: at baseline, four weeks, eight weeks, twelve weeks, and fifty-two weeks. The assessments were carried out and the assessment instruments were applied by trained and blinded evaluators (JGM and SRT).

The patients underwent clinical and radiographic assessments. The clinical assessment was performed by a rheumatologist (JGM) and a nurse (SRT), and the radiographic assessment by a radiologist with more than 20 years of experience in musculoskeletal radiology (AR).

The outcomes measurements were:

- Primary outcome:
  - VAS of pain on movement in the studied knee (0-10 cm);
- Secondary outcomes:
  - VAS of pain at rest in the studied knee (0-10 cm);
  - Western Ontario and McMaster Universities (WOMAC) questionnaire with four domains (pain, stiffness, function and total) containing 17 questions, where the patient was asked to rank from 0 (none) to 4 (marked) the degree of difficulty in the last 72 h. The score can vary from 0 to 68 with higher scores representing worse function;[18]
  - Short Form - 36 (SF-36) quality of life questionnaire, consisting of eight domains (functional capacity, limitation due to physical aspects, pain, general health, vitality, social aspects, emotional aspects, and mental health). The score can vary from 0 to 100 with higher scores representing better quality of life;[19]
  - 6-min walk test: distance in meters the patient can travel on a 20 meter track within 6 min;[20]
  - Timed to up and go test: time (in seconds) the patient takes to get up from a chair, walk 3 meters without stopping, go back and sit down;[21]
  - Range of motion for flexion and extension of the studied knee, measured with a manual goniometer;

- Likert improvement scale of 5-point assessment: much worse, slightly worse, unchanged, slightly better, and much better;[22]
- Percentage of improvement (0 to 100%) – patient self-perceived improvement after the procedure;
- Radiographic assessment: conventional radiographs of the knee studied were performed on the same day of the week and by the same radiology technician at baseline and at 52 weeks. All participants underwent bilateral knee radiography using anteroposterior and lateral incidences with load, axial patella with 45 degrees of flexion and posteroanterior with load and 45° of knee flexion. These images were assessed by a "blinded" radiologist (AR) according to the Kellgren & Lawrence radiological classification.[14] This analysis was used for the radiographic characterization of the sample at baseline and for the comparison between groups for the radiographic evolution of the knee studied from the baseline to 52 weeks.

For sample calculation the visual analogue scale of pain on movement (0 to 10 cm) was used as the primary parameter, with a standard deviation of 2.0 cm. The analysis of variance (ANOVA) of repeated measures test was used as a statistical method for sample calculation. Considering a power of 80%, significance of 5% and a 2.0 cm difference in the mean values of VAS of pain on movement between the 3 groups in five assessment times, an N of 33 patients in each group was necessary.

Patients were randomized using a randomization sequence generated by the program Minitab 16 in three groups: Platelet-Rich Plasma versus Triamcinolone Hexacetonide and versus Saline. Sequentially numbered opaque envelopes were created and a strip of paper indicating the group was placed inside the envelope, and then these envelopes were sealed. As soon as the patient received an allocation number, the envelope with that number was opened by the principal investigator (JCNT) immediately before the intervention. The researcher responsible for the randomization and allocation of patients (JN) was not involved in their recruitment, intervention, or assessment. The evaluators and the patient remained blinded to the allocation group.

Statistical analysis

SPSS software version 15.0 (Chicago, IL) was used to perform the statistical analysis. Descriptive statistics (mean, standard deviation, 95% confidence interval) were used to characterize patients. At baseline, the 3 groups were compared using one way ANOVA test (for continuous variables with normal distribution), the Kruskall-Wallis test (for continuous variables with not normal distribution) and chi-square test (for categorical variables).

In intergroup groups analysis, the Generalized Linear Models test with a Negative Binomial link log was used.

Inter-observer reliability analysis was performed for the radiographic assessment according to the Kellgren & Lawrence radiological classification[14] in 30% of the sample. This analysis was performed by a radiologist (AR) and a rheumatologist (RNVF) who were blinded to patients' group. The images were independently evaluated in isolated rooms at 52 weeks. For this analysis, the Kappa coefficient was used. According to the Kappa test, inter-observer reliability was considered excellent if > 0.81; substantial between 0.61 to 0.80; moderate between 0.41 to 0.60; good between 0.21 to 0.40; minimum between 0.20–0, and not agreeing if the value is zero or less than zero.

This was initially meant to be an intention-to-treat study. However, since there were no dropouts or absences, data for all patients were analyzed at all assessment times. The level of statistical significance adopted in this study was 5%.

Results

Two hundred eighty-seven patients were assessed for eligibility and 187 were excluded of which 177 did not meet the inclusion criteria and 10 had thrombocytopenia. Therefore, 100 patients were

included in this study, 33 in the Triamcinolone Hexacetonide group, 33 in the Saline group and 34 in the Platelet-Rich Plasma group. All included patients underwent the intervention. All included patients attended and were evaluated at all assessment times. There were no losses in the present study. Figure 2 shows the study flowchart according to CONSORT 2010.[23,24]

The sample consisted of 100 patients with 10 men (10%) and 90 women (90%), 83 (83%) of whom were white, with a mean age of 67.13 (6.56) years, mean body mass index of 29.68 (3.9) and mean symptom time of 8.13 (5.9) years. The Kellgren & Lawrence radiographic classification[14] at baseline was 46% for grade II and 54% for grade III. These data were presented in table 1.

There was no significant difference between the three groups at baseline regarding age, sex, skin color, profession, education, body mass index, symptom length, time of diagnosis, Kellgren & Lawrence radiographic classification[14] and medication. The only difference observed between the groups at baseline was the use of simvastatin for the treatment of dyslipidemia (table 1).

In the analysis of the number of platelets contained in the Platelet-Rich Plasma, we found an average increase of 4.61 (0.37) times as high as the number of platelets measured in the blood of patients in the platelet-rich plasma group before the intervention (table 1).

Table 2 shows the inter-group comparisons for all outcomes of this study, except for Likert scale and radiographic evolution. Inter-group comparisons were performed using the Generalized Linear Models statistical test that compares all times of the three groups simultaneously.

Regarding pain on movement, our primary outcome, no significant differences were found in the inter-group comparison over time. Its analysis showed no statistical difference over time also for pain at rest, knee range of motion, Timed Up and Go test, 6-min walk tests, and SF-36 questionnaire domains (table 2). For all these outcomes, significant improvement was observed at assessment times following the intervention in relation to the baseline (p intra-group <0.001, valid for the three groups).

The outcome percentage of improvement was assessed from 4 weeks to 52 weeks. The Triamcinolone Hexacetonide group had better results compared to Saline group at all assessment times to this variable (table 2).

The Triamcinolone Hexacetonide group was superior to the Platelet-Rich Plasma group at 4 weeks for WOMAC total and pain and was superior to the Saline group at 12 weeks for WOMAC stiffness. The Triamcinolone Hexacetonide did not differ from Platelet-Rich Plasma and both groups showed better results compared to the Saline group for the WOMAC function at 8, 12 and 52 weeks (table 2).

On the Likert improvement scale, no significant differences were found in the inter-group comparison over time (table 3). Significant intra-group differences were found in the three groups as regards the perception of "improvement" or "much improvement" between 4 weeks and the others assessment times with intra-group $p = 0.001$, valid for the three groups.

Table 4 shows the inter-group comparisons for radiographic progression according to the Kellgren and Lawrence classification[14] from baseline to 52 weeks. A significantly statistical difference was observed. The number of patients with grade III of Kellgren and Lawrence classification at 52 weeks increased in the Triamcinolone Hexacetonide group, and in the Saline group in comparison to the baseline. The smallest radiographic progression for Kellgren and Lawrence grade III at 52 weeks was found in the Platelet-Rich Plasma group. Significant differences were found in the Triamcinolone Hexacetonide and Saline groups over time. On the other hand, the Platelet-Rich Plasma was the only group with no statistical difference in the radiographic progression between baseline and 52 weeks.

The analysis of inter-observer reliability for the assessment of radiographic progression according to Kellgren and Lawrence classification[14] was performed in 30% of the patients, in the anteroposterior and lateral positions. According to the Kappa test, a strong agreement was observed (Kappa = 0.850 and p <0.001). The agreement index between the two "blinded" observers was 93.33%.

Table 1. Sample characteristic at baseline.

	Triamcinolone Hexacetonide Group	Saline Group	Platelet- Rich Plasma Group	* inter-group p
Gender				
Female	30(90.9)	30 (90.9)	30 (88.2)	0.915
Male	3 (9.1)	3 (9.1)	4 (11.8)	
Race				0.213
White	27 (81.8)	30 (90.9)	26 (76.5)	
Nonwhite	6 (18.2)	3 (9.1)	8 (23.5)	
Knee injected				0.472
Right	17 (30.9)	21 (38.2)	17 (30.9)	
Left	16 (35.6)	12 (26.7)	17 (37.8)	
Age (Years)	65.8 (6.1)	68 (6.2)	67.6 (7.4)	0.262
BMI (Kg/m^2)	29.59 (4.5)	30.23 (4.1)	29.22 (3.2)	0.583
Time of onset of symptoms (years)	6.3 (5.7)	7.8 (4.9)	10.3 (7.1)	0.029
Time since diagnostic (years)	4.4 (4.7)	5.5 (3.5)	6.9 (5.6)	0.084
Work				0.676
Manual	11 (33.3)	7 (21.2)	9 (26.5)	
Non manual	6 (18.2)	8 (24.2)	10 (29.4)	
Housework	16 (48.5)	17 (51.5)	15 (44.1)	
Retired	0 (0.0)	1 (3.0)	0 (9.9)	
Education				0.480
Complete elementary school	18 (54.5)	22 (66.6)	21 (61.8)	
Complete high school	12 (36.4)	6 (18.2)	8 (23.5)	
Complete higher education	3 (9.1)	5 (15.2)	5 (14.7)	
Radiographic classification (Kellgren & Lawrence)				0993
Grade II	16 (48.5)	16 (48.5)	14 (41.2)	
Grade III	17 (51.5)	17 (51.5)	20 (58.8)	
Drugs				
Diacerein	0 (0.0)	1 (3.0)	1 (2.9)	0.605
Chloroquine (diphosphate / hydroxy)	0 (0.0)	0 (0.0)	0 (0.0)	1
Chondroitin	4 (12.1)	0 (0.0)	1 (2.9)	0.062
Glucosamine	3 (9.1)	1 (3.0)	0 (0.0)	0.155
Corticosteroid	0 (0.0)	0 (0.0)	1 (2.9)	0.375
Antihypertensive	11 (33.3)	7 (21.2)	17 (50.0)	0.046
Anxiolytic	1 (3.0)	0 (0.0)	1 (2.9)	0.605
Antidepressant	1 (3.0)	2 (6.1)	2 (5.9)	0.817
Hypoglycemic or Antidiabetic	2 (6.1)	2 (6.1)	5 (14.7)	0.359
Insulin	1 (3.0)	1 (3.0)	0 (0.0)	0.591
Levothyroxine	1 (3.0)	2 (6.1)	5 (14.7)	0.187
Statin	1 (3.0)	0 (0.0)	7 (20.6)	0.004
Analgesic	15 (45.5)	15 (45.5)	12 (35.3)	0.622
Platelet dosage				
Pre centrifugation (blood sample) (per mm^3)	--	--	244,000 (43,400)	
Post centrifugation (PRP) (per mm^3)	--	--	1,119,588 (152,930)	

Data presented as N (%) or mean (± SD); BMI: body mass index;; Kg/m^2: Kg per square meter; * Statistical tests: chi-square, Kruskall-Wallis and 1-way ANOVA.

Table 2. Long-term intergroup comparison.

	Triamcinolone Hexacetonide Ggroup					Saline Group					Platelet Rich Plasma Group					
	Baseline	4 weeks	8 weeks	12 weeks	52 weeks	Baseline	4 weeks	8 weeks	12 weeks	52 weeks	Baseline	4 weeks	8 weeks	12 weeks	52 weeks	[a] inter-group p
Pain-moviment (VAS 0-10 cm)	6.1 ± 2.2	2.1 ± 2.4	2.8 ± 2.8	2.8 ± 2.8	3.5 ± 3.1	5.6 ± 2.2	3.1 ± 3.0	3.8 ± 3.0	3.5 ± 2.8	3.5 ± 2.8	6.7 ± 1.5	3.8 ± 2.6	3.9 ± 2.5	3.6 ± 3.1	3.7 ± 3.2	0.433
Pain – rest (VAS 0-10 cm)	4.2 ± 2.7	1.2 ± 2.3	1.8 ± 2.8	1.7 ± 2.9	1.3 ± 1.8	4.2 ± 2.9	2.0 ± 2.5	2.4 ± 3.0	2.2 ± 2.8	1.7 ± 2.3	4.4 ± 3.0	1.7 ± 2.3	1.3 ± 2.1	2.1 ± 2.9	1.6 ± 2.7	0.641
Percentage of improvement	--	83.5 ± 21.4	75.8 ± 28.9	77.3 ± 25.3	74.3 ± 24.2	--	62.8 ± 64.8	64.8 ± 33.5	61.1 ± 35.1	66.2 ± 33.7	--	63.7 ± 30.9	74.4 ± 23.3	74.0 ± 27.3	65.0 ± 34.9	0.032[b]
Range of Motion																
Flexion	115.5 ± 3.5	115.9 ± 8.1	116.8 ± 10.4	115.3 ± 9.2	122.5 ± 10.5	119.7 ± 12.0	115.5 ± 10.6	117.2 ± 11.5	117.6 ± 11.5	124.5 ± 14.2	114.4 ± 12.3	116.5 ± 18.1	118.1 ± 7.9	119.3 ± 16.7	125.6 ± 13.0	0.584
Extension	10.1 ± 7.6	9.4 ± 9.3	9.9 ± 7.4	12.0 ± 9.3	17.8 ± 6.9	8.1 ± 6.5	9.8 ± 8.0	10.1 ± 7.8	10.0 ± 5.0	16.5 ± 7.4	11.1 ± 6.5	10.1 ± 6.7	9.3 ± 5.9	11.5 ± 9.9	19.0 ± 7.4	0.709
WOMAC																
Pain	9.45 ± 3.24	3.24 ± 2.92	4.15 ± 3.10	4.09 ± 3.75	4.09 ± 3.96	9.03 ± 3.64	5.06 ± 3.30	6.03 ± 4.36	5.67 ± 4.07	5.55 ± 3.50	9.62 ± 3.81	5.38 ± 3.05	4.41 ± 3.52	4.24 ± 3.35	3.68 ± 3.44	0.008[c]
Stiffness	3.36 ± 2.09	1.15 ± 1.37	1.3 ± 1.61	1.12 ± 1.34	1.73 ± 2.04	3.27 ± 3.2	1.79 ± 2.9	2.21 ± 2.7	2.39 ± 2.6	2.64 ± 3.4	3.50 ± 1.71	2.18 ± 1.78	1.50 ± 1.62	1.41 ± 1.60	1.26 ± 1.40	<0.001[d]
Function	31.5 ± 10.8	13.1 ± 10.6	15.0 ± 11.4	12.1 ± 10.3	14.2 ± 12.1	33.8 ± 9.8	23.9 ± 11.5	24.3 ± 10.1	24.2 ± 11.5	24.6 ± 12.2	32.4 ± 11.1	20.0 ± 11.1	14.4 ± 11.6	13.5 ± 10.5	12.0 ± 10.8	<0.001[e]
Total	5.29 ± 2.06	2.04 ± 1.75	2.69 ± 2.25	2.38 ± 2.18	2.91 ± 2.73	5.25 ± 1.97	2.99 ± 1.91	3.44 ± 2.21	3.12 ± 2.30	2.62 ± 2.15	5.39 ± 1.96	3.73 ± 2.04	2.95 ± 2.41	2.71 ± 2.27	2.57 ± 2.52	0.003[f]
Timed up and go Test	13.9 ± 4.2	11.4 ± 2.4	12.0 ± 3.0	11.5 ± 2.5	12.3 ± 3.0	13.7 ± 3.2	12.5 ± 2.9	12.0 ± 2.7	12.0 ± 2.6	12.5 ± 3.4	13.2 ± 5.0	12.3 ± 3.9	12.2 ± 3.6	12.1 ± 3.6	11.7 ± 4.3	0.109
6 min walk test	244.9 ± 45.7	265.2 ± 40.1	263.5 ± 44.4	267.8 ± 43.9	251.7 ± 51.8	245.6 ± 46.2	254.3 ± 42.5	254.2 ± 39.7	260.6 ± 42.6	260.0 ± 49.6	243.5 ± 59.2	255.7 ± 45.4	268.1 ± 45.4	260.2 ± 54.2	259.9 ± 42.6	0.235
SF-36 Questionnaire																
FC	40.5 ± 19.6	58.6 ± 27.0	55.0 ± 28.0	61.7 ± 27.5	50.0 ± 31.7	42.3 ± 21.0	52.9 ± 24.9	52.4 ± 22.0	56.4 ± 19.7	61.2 ± 26.2	39.0 ± 18.7	47.3 ± 21.1	55.1 ± 21.5	61.2 ± 25.5	59.3 ± 27.1	0.103
RF	33.3 ± 37.8	59.8 ± 42.4	56.1 ± 37.0	65.2 ± 36.9	45.5 ± 39.8	55.3 ± 36.3	59.2 ± 36.6	60.6 ± 35.9	59.1 ± 37.4	68.2 ± 35.5	39.0 ± 28.9	58.1 ± 37.2	63.3 ± 36.4	59.6 ± 34.7	58.1 ± 37.7	0.093
Pain	39.8 ± 19.4	55.9 ± 25.2	52.3 ± 24.0	50.9 ± 22.0	45.3 ± 21.4	44.9 ± 16.9	50.8 ± 19.4	53.3 ± 22.3	51.6 ± 21.7	50.5 ± 18.5	43.5 ± 18.7	54.1 ± 17.8	54.6 ± 20.4	58.5 ± 23.0	49.3 ± 26.3	0.683
GH	60.6 ± 18.9	61.0 ± 18.4	66.2 ± 19.5	65.7 ± 15.2	63.5 ± 15.5	67.1 ± 18.7	69.5 ± 17.0	64.5 ± 15.6	68.8 ± 15.1	71.0 ± 16.9	65.3 ± 17.8	65.6 ± 16.8	65.8 ± 16.8	67.1 ± 19.9	65.9 ± 16.3	0.419
VIT																0.661

(Continued)

Table 2. (Continued)

	Triamcinolone Hexacetonide Ggroup					Saline Group					Platelet Rich Plasma Group					
	Baseline	4 weeks	8 weeks	12 weeks	52 weeks	Baseline	4 weeks	8 weeks	12 weeks	52 weeks	Baseline	4 weeks	8 weeks	12 weeks	52 weeks	[a] inter-group p
	46.5 ± 19.1	57.6 ± 27.0	53.8 ± 24.8	59.7 ± 18.5	47.9 ± 24.9	54.1 ± 18.5	58.2 ± 20.7	58.0 ± 18.2	62.3 ± 15.8	57.4 ± 21.7	54.5 ± 21.9	63.5 ± 16.2	63.7 ± 17.4	67.8 ± 19.7	58.9 ± 19.5	
SA	64.5 ± 27.8	72.0 ± 21.7	70.9 ± 28.8	72.0 ± 23.4	57.6 ± 25.8	63.3 ± 20.2	74.2 ± 20.7	75.0 ± 20.0	71.1 ± 24.1	68.6 ± 28.5	65.4 ± 26.7	73.5 ± 21.5	77.6 ± 21.7	74.3 ± 22.8	68.8 ± 23.1	0.563
EA	75.8 ± 30.4	80.8 ± 28.9	75.8 ± 31.5	74.7 ± 31.2	75.7 ± 31.5	61.6 ± 26.5	73.7 ± 28.6	77.8 ± 28.5	76.8 ± 29.4	78.8 ± 28.6	65.7 ± 31.2	74.5 ± 29.7	78.4 ± 28.3	83.3 ± 27.5	73.5 ± 30.5	0.084
MH	58.3 ± 25.1	69.6 ± 21.7	65.8 ± 24.0	66.5 ± 22.8	58.9 ± 23.5	61.1 ± 22.3	68.7 ± 16.6	68.4 ± 20.9	70.5 ± 21.0	65.6 ± 19.3	65.1 ± 18.6	68.6 ± 18.2	73.2 ± 14.8	75.3 ± 16.3	68.1 ± 19.7	0.209

Data presented as mean ± standard deviation; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities questionnaire; SF-36 questionnaire: SF-36 quality of life questionnaire; FC = functional capacity; RF = role function; GH = general health; VIT = vitality; SA = social aspects; EA = emotional aspects; MH = mental health; [a] Statistical test: GLM (Generalized Linear Models);[b] : superiority of the Triamcinolone Hexacetonide group over the Saline group at 4, 8, 12 and 52 weeks; [c, f]: superiority of the Triamcinolone Hexacetonide group over the other two groups at 4 weeks; [d]: superiority of the Triamcinolone Hexacetonide group over the Saline group at 12 weeks; [e:] superiority of the Platelet-Rich plasma and Triamcinolone Hexacetonide groups over the Saline group at 8, 12 e 52 weeks.

Table 3. Intergroup comparison according to Likert scale of improvement .

	Triamcinolone Hexacetonide Group					Saline Group					Platelet-Rich Plasma Group					
	Much worse	Little worse	Unchanged	Little better	Much better	Much worse	Little worse	Unchanged	Little better	Much better	Much worse	Little worse	Unchanged	Little better	Much better	* inter-group p
4 weeks	0 ± 0.0	1 ± 3.0	0 ± 0.0	8 ± 24.2	24 ± 72.7	1 ± 3.0	1 ± 3.0	2 ± 6.1	8 ± 24.2	21 ± 63.6	0 ± 0.0	0 ± 0.0	2 ± 5.9	12 ± 35.3	20 ± 58.8	0.178
8 weeks	1 ± 3.0	0 ± 0.0	2 ± 6.1	7 ± 2.2	23 ± 69.7	1 ± 3.0	5 ± 15.2	0 ± 0.0	8 ± 24.2	19 ± 57.6	0 ± 0.0	1 ± 2.9	2 ± 5.9	9 ± 26.5	22 ± 64.7	
12 weeks	1 ± 3.0	0 ± 0.0	2 ± 6.1	2 ± 6.1	28 ± 84.8	1 ± 3.0	3 ± 9.1	3 ± 9.1	6 ± 18.2	20 ± 60.6	0 ± 0.0	2 ± 5.9	1 ± 2.9	12 ± 35.5	19 ± 55.9	
52 weeks	1 ± 3.0	3 ± 9.1	2 ± 6.1	11 ± 33.3	16 ± 48.5	3 ± 9.1	2 ± 6.1	1 ± 3.0	12 ± 3.4	15 ± 45.5	4 ± 11.8	2 ± 5.9	3 ± 8.8	6 ± 17.6	19 ± 55.9	

Data presented as mean ± standard deviation; * : Statistical test: GLM (Generalized Linear Models).

Table 4. Analysis according to the Kellgren & Lawrence radiographic classification from baseline to 52 weeks for the injected knee.

	Kellgren & Lawrence radiographic classification Grade 2		Kellgren & Lawrence radiographic classification Grade 3		% of increase of Kellgren & Lawrence grade III at 52 weeks compared to baseline	* p
Groups	**Baseline N (%)**	**52 weeks N (%)**	**Baseline N (%)**	**52 weeks N (%)**		
Triamcinolone Hxacetonide Group	16(48.48)	9(27.27)	17(51.51)	24(72.72)	41.17%	0.003 #
Saline Group	16 (48.48)	3(9.09)	17(51.51)	30(90.90)	76.47%	<0.001&
Platelet-Rich Plasma Group	14 (41.17)	13(38.23)	20(58.82)	21(61.76)	5%	0.311 ¶

Data presented as N (%); *statistical test: GLM (Generalized Linear Models); #, &, ¶: analysis from baseline to 52 weeks.

No adverse effects were observed in any patients of the three groups.

Discussion

Intra-articular injection with Platelet-Rich Plasma has been considered a therapeutic option for the treatment of knee osteoarthritis. In this study, the Triamcinolone Hexacetonide group was superior to the Saline group for perceiving improvement post-intervention at all times of assessment and for the WOMAC stiffness at 12 weeks. The Triamcinolone Hexacetonide was also superior to the Platelet-Rich Plasma group for the WOMAC pain and WOMAC total at 4 weeks. For the WOMAC function, the Triamcinolone Hexacetonide and Platelet-Rich Plasma groups were superior to the Saline group from 8 to 52 weeks. In the radiographic assessment, the Platelet-Rich Plasma group was the only group with no statistical progression according to Kellgren and Lawrence classification from baseline to 52 weeks. There was no difference among the three groups for the other variables assessed, including our primary outcome, VAS score of pain on movement.

There is a lack of drugs for the treatment of osteoarthritis. Studies suggest that growth factors and bioactive proteins contained in platelet alpha granules of Platelet-Rich Plasma may influence a decrease in cartilage catabolism and synovial inflammation,[7,8,25–27] in pain[28] and in the shear stress of the joint with OA.[29,30] As far as we know, ours is the only study comparing Platelet-Rich Plasma with Triamcinolone Hexacetonide simultaneously with a third group of Saline solution.

Six studies in the literature compared an intra-articular injection with corticosteroids versus Platelet-Rich Plasma in knee osteoarthritis patients[31–36] of which only one used Triamcinolone Hexacetonide.[36] The intra-articular injection with Platelet-Rich Plasma in these studies was superior to the corticosteroid for some clinical and functional variables, especially in the study by Forogoh et al.,[31] whose intervention was superior to the use of methylprednisolone for pain, walking time, duration of symptoms, difficulty in daily activities and quality of life. In our study, Platelet-Rich Plasma did not outperform Triamcinolone Hexacetonide. Unlike ours, there was no third group (control) in these six studies.

In the studies where Platelet-Rich Plasma was compared to Saline, the superiority of the former was observed in the first two[11,12] for functional variables. In the last one[13] intra-articular knee injections of Platelet-Rich Plasma did not result in a significant difference in symptoms or joint structure, assessed by magnetic resonance imaging, at 12 months, when compared to Saline.[13] In the present study, the unexpected similar evolution of

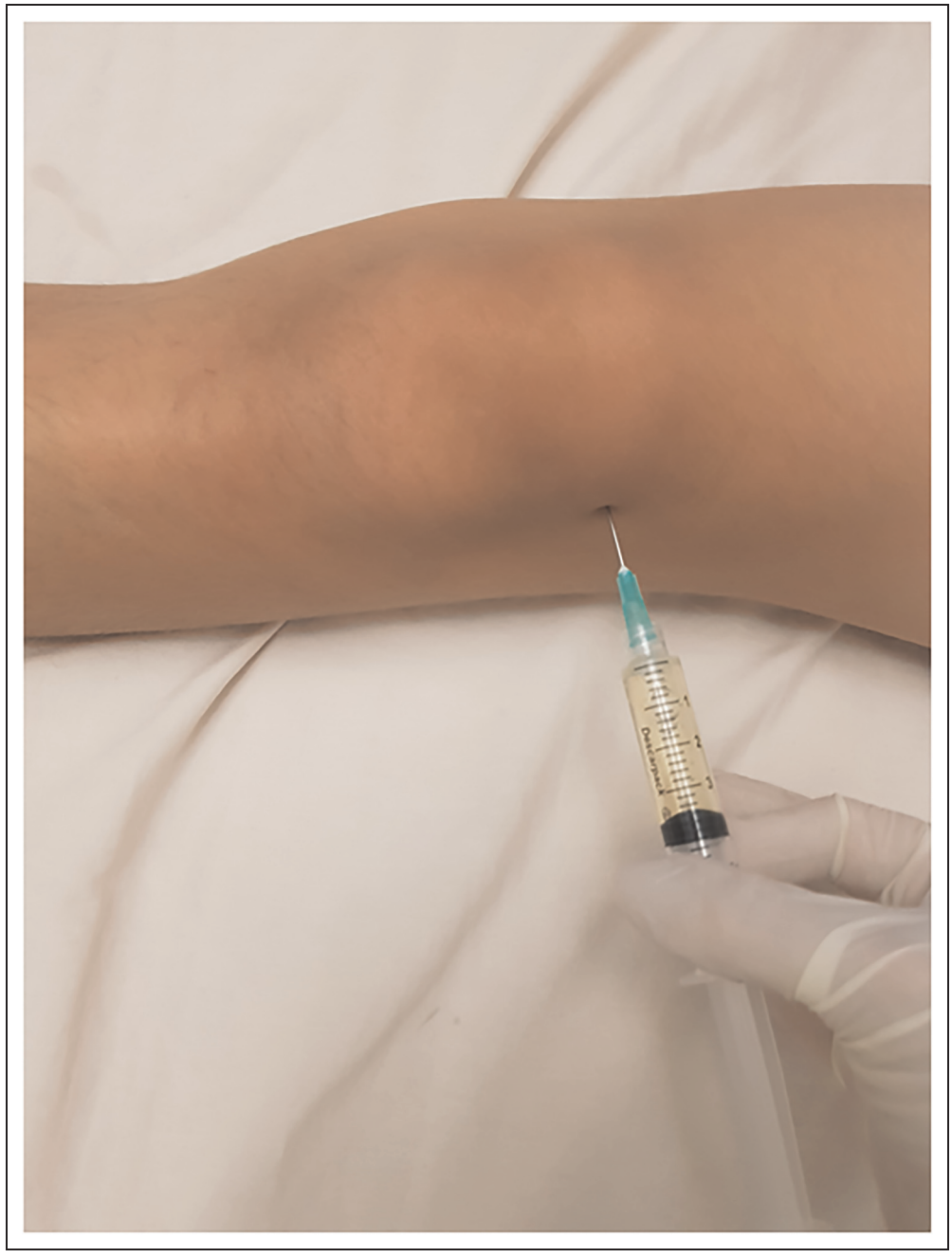

Figure 1. Intra-articular injection with Platelet-Rich Plasma.

the Saline group and the other two "treatment" groups is noteworthy. Also, the Triamcinolone Hexacetonide group was superior to the Saline group only for perceived improvement post-procedure from 4 to 52 weeks and for the WOMAC stiffness punctually at 12 weeks.

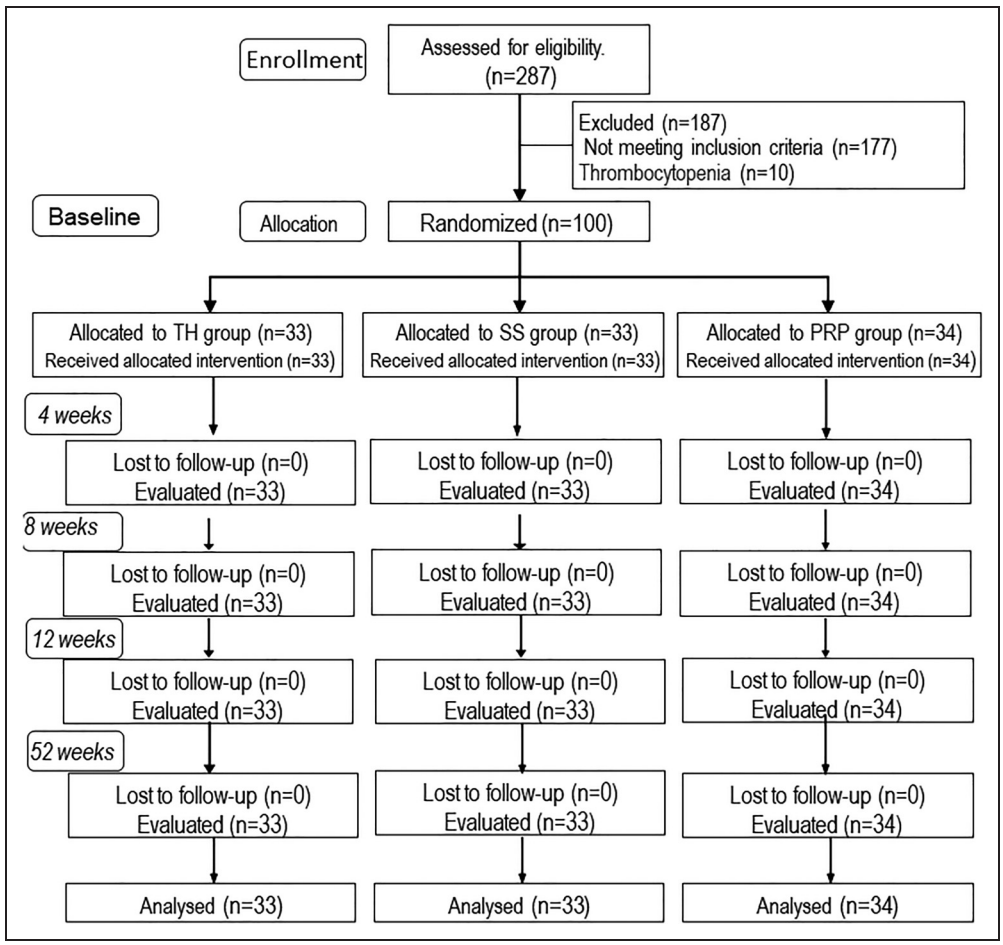

Figure 2. Study flowchart according to CONSORT 2010.

A similar therapeutic effect of Triamcinolone Hexacetonide and Platelet-Rich Plasma groups was expected, but the small difference in evolution compared to the Saline group did come as a surprise. There are studies suggesting that the Saline solution has a possible biological intra-articular effect.[37–39] It is still unknown whether Saline has any analgesic or anti-inflammatory effects *per se*. The analgesic effects of a placebo may occur by descending inhibitory mechanisms induced by expectation, such as the release of endogenous opioids. A placebo is also believed to cause a reduction in local inflammation through activation of the hypothalamic-pituitary-adrenal axis, promoting descending pain inhibition.[38] These effects should be strongly considered when a group of intra-articular injections with Saline behaves similarly to the other two treatment groups, with one as potent as Triamcinolone Hexacetonide.

In our study, an intra-articular injection in the knee with a higher dose of Triamcinolone Hexacetonide or repeated intra-articular use of Platelet-Rich Plasma might have been more effective than the intra-articular injection with Saline. Or, if our sample had been composed of patients with early osteoarthritis, intra-articular injections of Platelet-Rich Plasma might have been most effective in the long term.

The radiographic progression of the treated knee was the most important of our results. We observed

that the Platelet-Rich Plasma was the only group that did not progress radiographically according to the Kellgreen and Lawrence grade III radiographic classification from T0 to T52 (Saline group from 51.51% to 90.90%; Triamcinolone Hexacetonide group from 51.51% to 72.72%; and Platelet-Rich Plasma group from 58.82% to 61.76%). This is the only study to date with three groups of intra-articular injection simultaneously involving Triamcinolone Hexacetonide versus Platelet-Rich Plasma versus Saline solution with radiographic assessment before the intervention and after 52 weeks (1 year) of follow-up. Our results differ from the result of a recent study that showed no difference between the effect of intra-articular Platelet-Rich Plasma and Saline injection on magnetic resonance image of knees with osteoarthritis followed up for 12 months.[13] According to our work, a single intra-articular knee injection with Platelet-Rich Plasma influenced the radiographic progression of the knee even after 52 weeks of follow-up. This finding suggests that with only one intra-articular injection, the Platelet-Rich Plasma may have had a long-term chondroprotective effect on knee osteoarthritis patients. In a disease as prevalent as osteoarthritis, the intra-articular use of endogenous drugs with a possible chondroprotective effect can be a good therapeutic alternative, especially in individuals with initial disease or those with contraindications to other options of intra-articular injections.

This study has some limitations. Although calculated, the "n" may have been small for a study with three groups. The small percentage of males in our sample makes our results better applicable to female patients. In this study, the interventionist was not blinded to the volume of the syringe, higher in some patients of the Platelet-Rich Plasma group than that of the other groups. If more than one intra-articular injection with Platelet-Rich Plasma had been used, the effectiveness of this treatment group could have been increased. The 40 mg dose of Triamcinolone Hexacetonide may have been small for a large joint such as the knee. In this study, randomization was done on patients rather than randomization of knees; if knees were randomized and the same patient would have received different treatments in their two knees, maybe the result would have been different.

The use of a more sensitive method, such as magnetic resonance imaging, could have differentiated the three groups in terms of the radiological assessment better.

The practical applicability of the present study was to have demonstrated that although similar in terms of several assessment variables including pain, the effect of the intra-articular injection with Triamcinolone Hexacetonide, Platelet-Rich Plasma or Saline solution was different for the percentage of improvement and for the WOMAC questionnaire. When there was a clinical difference inter-groups, the intra-articular use of Triamcinolone Hexacetonide stood in superiority and the Saline in inferiority. However, the intra-articular use of Platelet-Rich Plasma stood as the only one to influence the radiographic progression in the injected knee at 52 weeks of follow-up.

Osteoarthritis is the most prevalent joint disease, it relies on the fewest therapeutic drugs though. An endogenous therapy with simple preparation, local application, good tolerance, low cost, and long-term effect, as it seems to be the intra-articular injection with Platelet-Rich Plasma, can be very interesting for the treatment of such a disease. The intra-articular injection with Platelet-Rich Plasma should be tested in comparison to drugs already established such as corticosteroids, and even saline solution, with its apparent therapeutic effect within the joint. Studies with a larger sample, a longer follow-up time and more sensitive radiological methods should be carried out to prove our results.

With up to one-year follow-up assessment after a single intra-articular injection, this study showed that patients with knee osteoarthritis injected with Triamcinolone Hexacetonide evolved better than those injected with Saline for the percentage of improvement and WOMAC stiffness, and better than those with Platelet-Rich Plasma for the WOMAC pain and total. For the WOMAC function, the Platelet-Rich Plasma and Triamcinolone Hexacetonide groups evolved similarly and were superior to the Saline group. For the assessment

according to the Kellgreen and Lawrence radiographic classification, the knees injected with Platelet-Rich Plasma showed less radiographic progression than the other two groups at 52 weeks of follow-up. There was no difference between the three groups for the other variables evaluated.

Clinical messages

- The effectiveness of the intra-articular knee injection with Triamcinolone Hexacetonide, Platelet–Rich Plasma or Saline was similar to pain, range of motion, quality of life, and functional tests at 52 weeks of follow-up.
- The knees injected with Platelet–Rich Plasma showed less radiographic progression than Triamcinolone Hexacetonide and Saline at 52 weeks of follow-up.

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