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Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial

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Abstract

Objective: Aim of this trial was to compare efficacy of activated platelet-rich plasma against hyaluronic acid as intra-articular injections to people with osteoarthritis of the knee.

Design: Phase-2 randomized controlled trial, with blind patients and outcome assessors.

Setting: Outpatient rehabilitation service; years 2011–2013.

Subjects: Patients with knee osteoarthritis grades 2–3 at magnetic resonance imaging (MRI) were included after consent and randomized. Target sample size was 25 patients per group.

Interventions: Patients received three activated platelet-rich plasma (intervention group) or hyaluronic acid (controls) intra-articular injections at 4-week intervals.

Main measures: Main outcome measure was proportion of patients with >1 grade improvement at six months from last injection, as assessed by a radiologist blind to study group. Patients were evaluated over time clinically and with functional scales (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lysholm, Tegner, American Knee Society Score (AKSS), Lequesne, visual analogue scale (VAS) for pain).

Results: Overall, 30 patients were randomized to intervention and 28 to control group. For primary outcome, 28 patients (29 knees) in the intervention and 22 (25 knees) in the control group were available. Patients with at least 1 grade improvement at repeat MRI were 14 (48.3%) in the intervention and 2 (8%) in the control group ($P < 0.003$). Improvement in symptoms and functional scales was consistently higher in the intervention group. No side-effects were observed in either group.

Conclusion: Activated platelet-rich plasma reduces articular damage as evident at MRI, as soon as six months after treatment; it reduces pain and improves patient's function and overall quality of life.

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Introduction

Pathogenesis of osteoarthritis is complex and is linked to the limited ability of cartilage to repair, given its limited vascularisation.[1,2] The knee is the most commonly involved joint.[1]

Many pharmacological and non-pharmacological treatments have been proposed.[3,4] Intra-articular injections of hyaluronic acid are effective in improving symptoms and slow disease progression, but are not able to reverse the damage mechanism and trigger cartilage healing.[5,6] Biological, regenerative, minimally invasive treatments such as platelet-rich plasma have been investigated.[7,8] Growth factors included in platelet-rich plasma could stimulate cartilage repair, normalize synovial fluid viscoelasticity, induce a correction in tissue damage, improve articular function, control pain and ameliorate quality of life.[8,9] Recently, a stable cartilage damage was demonstrated in 73% of patients 1 year after the treatment with platelet-rich plasma, thus suggesting that this treatment might be able to stop the damage mechanism.[10] This treatment also appears safe.[11]

Primary aim of this trial was to assess, among patients with grade II/III osteoarthritis of the knee, efficacy (as determined by improvement at magnetic resonance imaging (MRI) six months after the first injection) of three intra-articular injections of platelet lysate when compared to hyaluronic acid. Additional objectives were to compare the treatment groups in terms of several functional scales and of number of adverse events.

Methods

This study was designed as a Phase-2, two-parallel-arm, randomized controlled trial, where patients, radiologist, clinical outcome assessors and statistician were blinded to study treatments. Prior to starting patients' enrolment, the study was approved by the institutional ethic review board (protocol number: 28914/2009). The anticipated study duration was three years (January 2011–December 2013). No change in study methods intervened during study conduct (ClinicalTrials.gov, Identifier: NCT02958761). Full protocol is available upon request.

All consecutive patients referred to the Physical Medicine and Rehabilitation Unit of Policlinico San Matteo Foundation for osteoarthritis of the knee in the study period were screened for inclusion. Eligibility criteria were as follows:

- Grade II/III osteoarthritis of the knee demonstrated at MRI, according to Shahriaree Classification System – Modified[12] (Table 1, web only);
- Age >18 years;
- No previous osteoarthritis treatment with local hyaluronic acid or steroid injections;
- Life expectancy >1 year (i.e. no cancer, no end-stage liver disease, no-end-stage kidney disease, no heart failure New York Heart Association (NYHA) class III or IV);
- No ongoing pregnancy;
- Ability to understand and complete clinical and functional scales;
- No known allergy to hyaluronic acid;
- No acute bacterial skin and soft structure infection of the knee;
- Written consent.

Patients were then randomized into one of the treatment groups; if a patient had both knees affected, both were treated with the allocated study treatment. The patient's allocation ratio was 1:1. The randomization list was prepared by means of the ralloc procedure in Stata (version 10), with blocks (dimension of blocks 4-6-8). Concealment of allocation was obtained by maintaining the randomization list at the Clinical Epidemiology Unit

Table 1. Baseline patients' and knees' characteristics.

Characteristic	Category/ description	Platelet lysate ($n = 30$ patients, 31 knees)		Hyaluronic acid ($n = 28$ patients, 31 knees)	
Gender[a]	Males	20	67%	16	57%
Age (years)[a]	Mean (SD)	53.5	(15.1)	57.1	(10.0)
Laterality	Right	17		13	
VAS	Mean (SD)	6.28	(0.59)	5.40	(0.36)
WOMAC pain	Mean (SD)	6.6	(0.81)	5.04	(0.51)
WOMAC rigidity	Mean (SD)	2.6	(0.45)	2.32	(0.28)
WOMAC ADL	Mean (SD)	27.80	(2.45)	21.16	(1.65)
Overall WOMAC	Mean (SD)	36.96	(3.33)	28.48	(2.22)
AKSS	Mean (SD)	73.04	(3.22)	77.08	(2.03)
Lysholm	Mean (SD)	61.96	(3.44)	70.28	(2.17)
Tegner	Mean (SD)	3.04	(0.32)	3.6	(0.23)
Lequesne	Mean (SD)	11.16	(0.85)	9.00	(0.58)
Flexion (angle degrees)	Mean (SD)	123.4	(2.98)	126.8	(1.97)
Complete extension	Yes	31	100%	31	100%

VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; ADL: activities of daily living; AKSS: American Knee Society Score.
Data are *n* (%) unless otherwise specified.
[a]Data at patient's level.

by the study statistician, who allocated each consecutive patient to treatment A or B. The clinicians administering the injections were unblinded; in case of bilateral knee osteoarthritis, both knees were treated with the treatment to which the patient had been allocated.

Patients in the intervention group received three autologous platelet-rich plasma plus calcium gluconate (as activator) intra-articular injections at four-week intervals. Briefly, at the Immunohaematology and Transfusion Service, on each scheduled visit, 20 mL of autologous whole blood was sampled from each patient and 2 mL Anticoagulant Citrate Dextrose Solution, Solution A was added directly through the syringe as anticoagulant; finally, the vial was gently centrifuged at 900 r/min for seven minutes. Platelet-rich plasma was collected. The platelet-rich plasma vial plus activator was immediately shipped to the rehabilitation unit, where intra-articular injection was performed by an experienced physiatrist.

Patients in the control group received three intra-articular hyaluronic acid (20 mg/2 mL; Hyalgan; Fidia, Abano Terme, Italy) injections at the same intervals by the same study staff. It was not possible to blind injectors for the different look of the treatments being compared. The infiltration technique used for both groups was the superolateral approach into the suprapatellar pouch.[13,14] After iodopovidone-base disinfection, a 21-gauge needle is ideal for knee injections with a 5-mL syringe was used.

For the superomedial approach, the patient lies supine with the knee almost fully or fully extended with a thin pad support underneath the knee to facilitate relaxation. Under ultrasound guidance in longitudinal section at the quadriceps tendon, the suprapatellar receps is localized; the clinician's thumb is used to gently rock and then stabilize the patella, the probe is rotated 90° and the needle is inserted laterally between the iliotibial band and the vastus lateralis muscle, directed to the centre or the probe.

Active flexion and extension of the knee was recommended after the injection, and the patient was observed in a supine position for 10–15 minutes, to ensure there were no adverse reactions, and was then discharged home without further recommendations or limitations. Patients were also allowed to take their pharmacological treatment for pain.

Six months after the last infiltration, MRI was repeated and assessed by a radiologist blind to study group. The radiologist scored each articular component (patellar front, patellar rear, tibial medial and tibial lateral) according to Shahriaree Classification System–modified (Table 1, web only).[12] For each knee at each time, the maximum grade was used. Primary end-point for each knee was improvement, from baseline, by at least one grade the maximum MRI score at six months.

At baseline (prior to treatment), at 15 days from the last injection, at six months from the last infiltration and at one year, all patients were clinically evaluated by a clinician blind to treatment group for articular angle, visual analogue scale (VAS) for pain and a number of functional scales: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; which measures pain, stiffness and disability in osteoarthritis),[15,16] Lequesne Scale (which measures the impairment in function, caused by pain),[17,18] Lysholm and Tegner Scales (which measure pain, joint block, instability and activity) and American Knee Society Score (AKSS) scale[19,20] (which allows a global evaluation specifically for the knee).

All study data were recorded on a paper case report form and then imputed into a database build with Microsoft Access by dedicated medical personnel. The target sample size was 25 patients per group and was calculated on the basis of a 50% patients improving at least one grade at the six-month MRI in the treatment group vs. a 10% improvement in the control group, to be detected with power 90% and alpha error 5% by means of a two-tailed chi-square test. No interim analyses were planned.

Descriptive statistics were produced for demographic, clinical and laboratory characteristics of enrolled patients and knees. Mean and standard deviation are presented for normally distributed variables, median and interquartile range for non-normally distributed variables and number and percentages for categorical variables. Groups were compared with parametric or nonparametric tests, according to data distribution, for continuous variables and with Fisher exact test for categorical variables. Also, to compare groups, taking into account that some patient had two knees treated, logistic regression models with clustering per patient were used. Multilevel mixed models were used to assess trend over time of secondary end-points (clinical and functional scales); random effects were patient, knee and slope over time, and interaction of group with time was the fixed effect. To achieve normality, Box–Cox transformation was applied whenever relevant (however, for readability, plots were produced in the original scale). In all cases, two-tailed tests were used. Statistical significance was set at 0.05. Whenever relevant, 95% confidence intervals (CIs) were calculated.

Results

Of the 30 patients randomized to treatment group and the 28 to control group, 28 (1 with bilateral involvement, that is, 29 knees) and 22 patients (3 with bilateral involvement, that is, 25 knees) received the allocated intervention (Figure 1). No patient switched between treatment groups. Complete data at six months (primary end-point) were available for all knees. Therefore, 29+25 knees (28+22 patients) were evaluated in the primary analysis.

No relevant baseline differences between the two groups were observed (Table 1).

The number of patients (and knees) with at least 1 grade improvement at the MRI six months after last injection was 14 (48.3%, 95% CI: 29.4–67.5) in the treatment group and 2 (8%, 95% CI: 1.0–26.0) in the control group ($P<0.003$; Table 2 and Figure 2). Some patients even achieved complete *restitution ad integrum* of cartilage (Figure 3, web only).

Changes over time in terms of symptoms and functional scales were consistently better in the treatment group than the control group, reaching statistical significance for activity of daily living and total WOMAC, AKSS and Lequesne scale (Table 3; Figure 4, web only). No side-effects were observed in either group.

Discussion

We found that activated platelet-rich plasma reduces articular damage as evident at MRI, as soon as six months after treatment. To our knowledge, this is the first study demonstrating efficacy of activated platelet-rich plasma on a strong clinical end-point such as

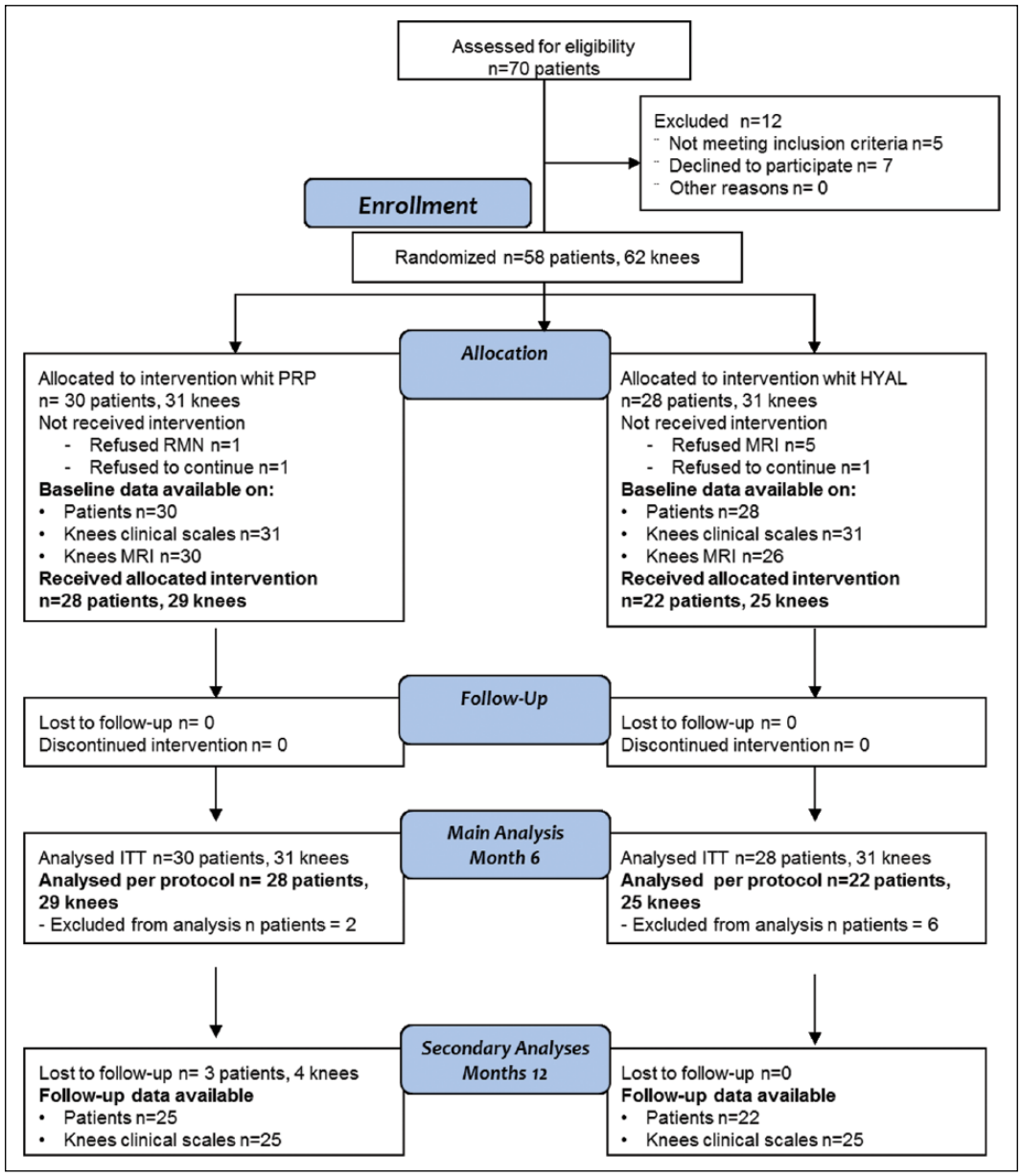

Figure 1. Patients' and knees' flowchart.
PRP: platelet-rich plasma; Hyal: hyaluronic acid; ITT: intention to treat; MRI: magnetic resonance imaging.

imaging. Besides, it reduces pain, improves function and ameliorates quality of life for at least one year.

In the past decade, many studies have been published on the intra-articular use of platelet products (usually platelet-rich plasma); advantages are the limited invasiveness of the procedures, the relatively low costs, the low infectious risk, thanks to the autologous blood, and the direct delivery on the poorly vascularized cartilage tissues. Preliminary in vitro studies showed effect of platelet-rich plasma on

Table 2. Primary outcome (improving at least one grade at the six-month magnetic resonance imaging)[12,21] comparison.

Analysis	Category	Platelet lysate (knees $n = 31/29$)	% (with 95% CI)	Hyaluronic acid (knees $n = 31/25$)	% (with 95% CI)	*P*-value
Number of knees with missing primary outcome data		2		6		
Intent-to-treat, missing = no improvement	Number of knees with >1 grade improvement	14/31	25.8 (27.3–64.0)	2/31	6.45 (0.8–21.4)	0.002
Intent-to-treat, missing = improvement	Number of knees with >1 grade improvement	16/31	51.6 (33.0–69.8)	8/31	25.8 (11.8–41.6)	0.038
Per protocol analysis	Number of knees with >1 grade improvement	14/29	48.3 (29.4–67.5)	2/25	8 (1.0–26.0)	0.003

CI: confidence interval.

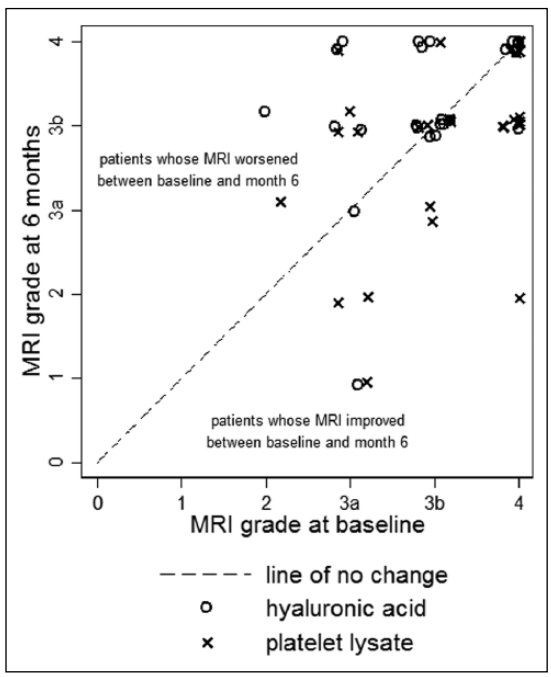

Figure 2. Change in magnetic resonance imaging grade from baseline to six months in the two groups.

fibroblasts, subsequently confirmed in animal studies.[22] It has been suggested that the favourable effect of platelet-rich plasma injections on symptoms does not exceed one year duration.[22,23] Among 50 patients treated with nine injections of platelet-rich plasma, no relevant improvement at MRI was seen at one year, despite improvement in functional and quality-of-life scales.[24] In our study, we found improvement in functional and quality-of-life indices in both groups: pain (in VAS and WOMAC) and articular range of movement. For some scales (Activities of Daily Living, WOMAC, Lysholm, Lequesne and AKSS), improvement was more evident (and statistically significantly so) in the activated platelet-rich plasma group and was still evident at the one year visit.[24,25]

Platelet-rich plasma also appear to have a role in the modulation of inflammation and in analgesia.[26] Therefore, repeat intra-articular platelet lysate injections can have a clinical role in modifying clinical evolution of osteoarthritis and delaying the need for surgery.

Research and theoretical implications

Many important proteomic studies demonstrated that platelets contain hundreds of proteins able to induce numerous modifications for more than 1500 protein-based bioactive factors. The physiologic actions of many of these proteins have been clarified including growing factors, peptide hormones, chemoattractants

Table 3. Secondary outcomes comparison.

Scale	Time	Hyaluronic acid ($n = 25$)			Platelet lysate ($n = 29$)			*P*-value
		Median	IQR	Min-max	Median	IQR	Min-max	
VAS	Baseline	6	(5–7)	3–8	6	(5–7)	0–8	0.78
	15 days	2	(1–4)	0–7	1	(0–4)	0–7	
	6 months	2	(0–3)	0–7	1	(0–2)	0–6	
	12 months	1	(0–3)	0–4	0	(0–2)	0–6	
WOMAC pain	Baseline	7	(4–9)	3–13	4	(3–6)	1–13	0.91
	15 days	4	(2–5)	0–8	1	(1–3)	0–9	
	6 months	3	(2–5)	0–9	0	(0–3)	0–12	
	12 months	3	(1–5)	0–11	0	(0–1)	0–10	
WOMAC rigidity	Baseline	3	(1–3)	0–5	2	(0–4)	0–6	0.58
	15 days	1	(0–2)	0–4	1	(0–1)	0–6	
	6 months	1	(0–2)	0–3	0	(0–1)	0–5	
	12 months	0	(0–2)	0–5	0	(0–1)	0–4	
WOMAC ADL	Baseline	21	(15–24)	9–44	21	(10–30)	2–46	0.002
	15 days	11	(6–16)	1–33	5	(3–10)	0–34	
	6 months	11	(7–20)	0–24	4	(2–9)	0–33	
	12 months	10	(4–19)	0–31	3	(1–5)	0–26	
WOMAC total	Baseline	29	(25–35)	16–61	27	(13–38)	4–59	0.16
	15 days	17	(8–22)	2–45	9	(4–13)	0–44	
	6 months	14	(10–27)	0–35	6	(2–12)	0–50	
	12 months	14	(6–28)	0–43	3,5	(1–8)	0–40	
AKSS	Baseline	85	(70–87)	39–90	80	(64–85)	40–95	0.29
	15 days	90	(85–95)	69–100	90	(85–95)	63–100	
	6 months	90	(85–95)	70–100	95	(90–100)	58–100	
	12 months	90	(85–100)	71–100	100	(95–100)	70–100	
Lysholm	Baseline	73	(67–79)	20–90	73	(64–78)	36–88	0.22
	15 days	86	(78–91)	35–100	92	(85–97)	61–100	
	6 months	83	(77–90)	68–100	94	(85–99)	63–100	
	12 months	88	(76–95)	65–100	95	(90–100)	76–100	
Tegner	Baseline	3	(2–3)	1–5	3	(3–4)	2–7	0.63
	15 days	3	(3–4)	1–5	4	(3–4)	2–7	
	6 months	4	(2–4)	1–6	4	(3–5)	2–7	
	12 months	4	(3–4)	2–5	5	(3–6)	2–6	
Lequesne	Baseline	7.5	(6–9.5)	3.5–13.5	8.5	(6–12.5)	2.5–15.5	0.04
	15 days	4.5	(3–6.5)	0–10.5	4	(1.5–5.5)	0–11.5	
	6 months	5	(3–6)	0–10	2	(0.5–4)	0–12	
	12 months	3.5	(1–5.5)	0–11.5	1.5	(0.5–3)	0–9.5	
Flexion	Baseline	125	(120–130)	70–140	130	(120–130)	110–140	0.81
	15 days	135	(120–140)	110–160	140	(130–140)	125–145	
	6 months	140	(130–140)	105–150	140	(135–140)	120–145	
	12 months	140	(130–140)	105–150	140	(138–140)	128–150	

IQR: interquartile range; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; ADL: activities of daily living; AKSS: American Knee Society Score.

for stem cells, macrophages, neutrophils, and a wide range of other proteins, such as fibrinogen and fibrin. In particular, fibrin could work as a temporary scaffold for stem or primary cell migration and differentiation and functions as a biological glue. Platelet dense granules also retain an antibacterial and antifungal effect together with the capacity of releasing adenoside diphosphate, adenoside triphosphate, dopamine, calcium ions and histamine that are active in tissue homeostasis and healing processes in concurrence with a broad spectrum of growth factors and other active molecules to the site of injury. Growth factors secreted by platelets include platelet-derived growth factor, epidermal growth factor, insulin-like growth factor, transforming growth factor-β1, vascular endothelial growth factor and hepatocyte growth factor. This wide variety of growth factors, acting in a synergistic way, definitely contributes to the broad spectrum of biological functions of platelet-rich plasma regarding enhancement of anabolism, bone remodeling, proliferation and angiogenesis. Especially, transforming growth factor-β1 is widely deemed one of the most important enhancers of matrix production, cell proliferation and chondrogenic differentiation. Hence, both the quantitative and qualitative components of platelet-rich plasma are substantial in mimicking or enhancing the natural processes of tissue repairing and facilitating the neoformation of cartilage.[27,28]

There is in vitro evidence that activated platelet-rich plasma is more rich in platelet-derived growth factor, epidermal growth factor and transforming growth factor-β than serum and that it stimulates growth of corneal epithelial cells.[29] This mechanism is triggered by the cooperation of platelet-derived growth factors (such as epidermal growth factor and platelet-derived growth factor A-B, promoting in particular cell proliferation) and the inhibitors of inflammation (e.g. interleukin-1 receptor antagonist and inhibitors of metalloproteinases).[29,30]

We did not find an association between platelet-derived growth factor concentration or number of platelets in peripheral blood and response. The high inter-patient variability in individual platelet-derived growth factors may explain this finding, since our study was insufficiently powered to detect this effect.[31] Also, our study confirms the good patient compliance with this technique and the safety of the three procedures.[22,32]

Limitations of the study

We must acknowledge a number of limitations. The small sample size is the most obvious and precludes detection of statistically significant differences between groups in terms of pain and selected functional scales; however, we were able to detect difference in some important scales such as total WOMAC, AKSS and Lequesne.

Also, we could not determine the long-term radiological improvement. Longer-lasting effects, evident at MRI, might require a higher number of injections and a longer follow-up.[33]

More studies, larger and with a longer follow-up, are needed to standardize the procedures for platelet-rich plasma preparation, the number of necessary infiltrations, the interval between injections, the local anaesthesia, the long-term clinical effectiveness, the risk of short- and long-term adverse events and type and severity of the underlying osteoarthritis to be treated.[32]

Clinical messages

- Intra-articular-activated platelet-rich plasma reduces articular damage more than hyaluronic acid.
- It also reduces pain and improves patient's function and quality of life.
- It may have a role in delaying the need for surgery.
- Unresolved issues are the number of necessary infiltrations, the interval between injections, and others.

Author contributions

The manuscript has been read and approved by all named authors and there are no other persons who satisfied the criteria for authorship.

Contributors

C.L., G.D.N. and L.S. equally contributed to the authorship: designing the study, initiating it, monitoring progress, deciding on the analytic strategy and writing the paper itself. C.P. is the guarantor.

Declaration of Conflicting Interests

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Studies involving humans or animals

In this study, animals are not involved.

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