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The effects of repeated intra-articular PRP injections on clinical outcomes of early osteoarthritis of the knee

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Abstract
Purpose To assess the outcome of intra-articular platelet-rich plasma (PRP) injections into the knee in patients with early stages of osteoarthritis (OA) and to determine whether cyclical dosing would affect the end result.
Methods This is a prospective, randomized study in which 93 patients (119 knees) were followed up for a minimum of 2 years. Fifty knees were randomly selected prior to the first injection, to receive a second cycle at the completion of 1 year. A cycle consisted of three injections, each given at a monthly interval. The outcome was assessed using Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analogue Scale (VAS), Tegner and Marx scoring systems, recorded prior to the first injection and then at 12, 18 and 24 months.
Results There was a significant improvement in all scores over time compared to the pre-treatment value ($p < 0.001$). At 12 months, both groups showed similar and significant improvement. At 18 months, except for KOOS (Symptoms) and Tegner score, all other parameters showed a significant difference between the two groups in favour of the patients who had received the second cycle ($p < 0.001$). At 2 years, the scores declined in both groups but remained above the pre-treatment value with no significant difference between the groups despite the patients with two cycles showing higher mean values for all the scores.
Conclusion Intra-articular PRP injections into the knee for symptomatic early stages of OA are a valid treatment option. There is a significant reduction in pain and improvement in function after 12 months, which can be further improved at 18 months by annual repetition of the treatment. Although the beneficial effects are ill sustained at 2 years, the results are encouraging when compared to the pre-treatment function.
Level of evidence II.

Keywords Platelet-rich plasma · Osteoarthritis · Knee · Dosage · Cyclic treatment

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Introduction

Osteoarthritis (OA) has a major impact on function and independence and was estimated to affect 27 million Americans in 2012 [41]. Orthopaedic surgeons, physicians and rheumatologists around the globe have been concerned regarding management of early stage OA in a population which is now too young or too fit to undergo a total knee replacement.

In 2007, platelet-rich plasma (PRP) was defined by the Medical Subject Heading Database as a limited volume of plasma containing concentrated platelets (minimum 200,000 platelets/μL), growth factors of which enhance wound healing and regeneration. Intra-articular injections of autologous PRP for chondral lesions have been used for many years now with encouraging preliminary results [17, 33, 42]. It is based on the intra-articular delivery of autologous platelet-rich preparations containing a large pool of growth factors (GFs) and proteins stored in the alpha granules of platelets. These GFs and proteins have been implicated in tissue repairing mechanisms and have

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been found to take part in the regulation of articular cartilage [40]. They are directed at stimulating repair and replacing damaged cartilage, which is incapable of repair, given its avascular, aneural and hypocellular nature.

Various growth factors (platelet-derived growth factor, transforming growth factor beta, vascular endothelial growth factors), endostatins, platelet factor 4, angiopoietins, and thrombospondin 1 are secreted upon activation of platelets, and these are involved in the healing process [2]. Moreover, platelets have been identified to have analgesic properties by releasing protease-activated receptor 4 peptides [3]. However, PRP contains not only platelets but also plasma with fibrin and other growth factors that influence healing. The 'therapeutic dose' of PRP is considered at a range of at least 2–6 times higher than the normal platelet count [12, 26].

Almost all earlier published data regarding PRP injections for early stages of OA have had short follow-up periods up to 12 months. Studies having longer follow-ups are necessary and a more defined therapeutic dosing schedule must be established. Dosing is important in order to understand the true potential of PRP, which is a promising treatment in early stages of OA and a potential means of delaying or avoiding altogether a metal resurfacing procedure. No previous studies have looked into the clinical outcomes of cyclical administration of intra-articular autologous PRP injections into the knee for early stages of OA.

The aim of this study was to assess the clinical effects of intra-articular PRP injections into knees with early stages of OA with respect to pain, quality of life and return to activity and to determine whether annual repetition of treatment with intra-articular autologous PRP injections into the knee could improve the final outcome.

The hypothesis was that three intra-articular PRP injections at monthly intervals, repeated annually would improve the outcome at final follow-up when compared to a group in whom the treatment was not repeated.

Materials and methods

This is a prospective, randomized study initiated in 2009. Of 319 patients, 93 (119 knees) that met the inclusion criteria received intra-articular autologous platelet-rich plasma (PRP) injections (Regen ACR-C, Regen Lab, Switzerland) into the knee for early stages of OA (Kellgren–Lawrence Grade 1–2) [21] and were systematically followed up for a minimum of 2 years from the start of treatment. All the patients were involved with a recreational sport (jogging, swimming, skiing, bicycling, walking or trekking) at a non-professional level and had onset of symptoms within the previous 3 years.

Inclusion criteria

Patients with symptomatic OA of the knees (Kellgren–Lawrence Grade 1–2 on radiographs) between the ages of 40 and 65 years, having a body mass index (BMI) <30, with stable knees without malalignment or maltracking of the patella were included in the study. Additional inclusion criteria were patients having severe pain without relief with anti-inflammatory agents even after 3 months, normal blood results and coagulation profile (platelets between 150,000 and 450,000/μL), patients who had not undergone any surgery on the affected knee within 2 years prior to the first injection and zero, trace or 1+ effusion on the grading scale based on the Stroke test [37].

Exclusion criteria

Patients diagnosed with tricompartmental OA, rheumatoid arthritis, or concomitant severe hip OA were not included in the study. A previous high tibial osteotomy or cartilage transplantation procedure, Grade 2+ and 3+ effusion in the knee joint (requiring aspiration) based on the Stroke test, blood diseases, systemic metabolic disorders, immunodeficiency, Hepatitis B or C, HIV positive status, local or systemic infection and ingestion of anti-platelet medications within 7 days prior to the injection and treatment with intra-articular or oral corticosteroids in the 3 months prior to the first injection were considered criteria for exclusion.

Those patients that met the inclusion criteria received a minimum of 1 cycle of intra-articular PRP injection into the affected knee. A cycle consisted of three injections, each given at a monthly interval. Thirty-eight patients (50 knees) were randomly selected using computer generated random numbers (Research Randomizer © 1997–2013 G. Urbaniak and S. Plous) prior to the first injection, to receive a second cycle at the completion of 1 year. Between the cycles, the patients would receive no other intra-articular injections or oral medications for the knee with the exception of acetaminophen on an 'as required' basis. Patients were questioned regarding analgesic consumption and alternative treatments at each follow-up. All patients underwent physiotherapy at the same centre, with the same protocol for 4 weeks beginning 1 week after the first injection to improve quadriceps muscle strength and range of motion.

Pre-treatment radiographic evaluation included a standing anteroposterior long-leg radiograph (including hips and ankles), standing anteroposterior/lateral views of the knees, skyline patellofemoral and standing 45° flexion knee views and magnetic resonance imaging.

Routine blood investigations were carried out before treatment, including complete blood count, coagulation

profile and screening for transmittable diseases (HIV, HBsAg).

PRP preparation

Eight millilitre of blood was obtained from the cubital vein and centrifuged for 5 min at 1,500*g* centrifugal force (RCF) and 3,500 revolutions per minute as per the recommendations of the manufacturer. This system did not use a second centrifugation process. Centrifugation of whole venous blood takes advantage of differing density gradients of the components in blood to concentrate platelets. Erythrocytes, which are most dense, remain as the packed cell layer at the bottom of the centrifuge container. The buffy coat of white blood cells is above this while the platelets are at the highest concentration in the plasma just above the buffy coat and decrease in concentration towards the top of the plasma layer. After centrifugation, platelet recovery was >80 % (twofold increase) and total leucocyte concentration was below the normal level-specific granulocyte depletion >95 % (mostly mononuclear cells being recovered 75 % lymphocytes; 50 % monocytes) in 4 mL of PRP. Leucocyte poor-PRP (LP-PRP) was obtained according to Dohan Ehrenfest classification [11] while it was P2 Bβ as per the PAW classification [9]. The PRP was aspirated into a syringe and a topical anaesthetic skin refrigerant was applied locally before intra-articular infiltration by a supra-patellar approach using sterile aseptic precautions. The PRP was activated in vivo when the platelets were exposed to collagen or von Willebrand factor, leading to their aggregation. After treatment, patients were allowed weight bearing, and local ice application was recommended for 20 min every 2–3 h for 24 h. Vigorous activities of the knee were not recommended for 48 h.

Outcome measures

Outcome following treatment was assessed using Knee Injury and OA Outcome Score (KOOS) [32], Visual Analogue Scale (VAS) (0 = no pain to 10 = worst possible pain) [7], Tegner [38] and Marx [25] scoring systems which were recorded through questionnaires filled by the patients themselves prior to the first injection and then at 12, 18 and 24 months follow-up. Data were recorded in SOCRATES™ (2012 Ortholink PTY Ltd.) orthopaedic outcomes software.

An institutional review board approved the study (San Raffaele AISPO at Milan, Italy, with protocol number 20081203/14) and date of approval November 12, 2008. All patients gave a written informed consent prior to inclusion in the study.

Statistical analysis

Statistical analysis was performed by an independent statistician using the SPSS software (SPSS 17.0, SPSS, Chicago, IL, USA). The general linear model for repeated measure test was performed to investigate within time variations for the continuous variables (KOOS, Marx, VAS) for all patients and each evaluated subgroup. The evaluated factors were 'number of cycles' and the Greenhouse-Geisser p value is reported. Post hoc test with Bonferroni adjustment for pair-wise comparisons within time was performed to investigate the improvement and deterioration for each variable and between subgroups. The nonparametric Friedman test was performed to detect within time differences in ordinal variable (Tegner), and the nonparametric Wilcoxon rank test as post hoc was used with a Bonferroni adjustment of the significant level. To investigate difference in improvement between the evaluated subgroups, the nonparametric Mann–Whitney U test was performed. The modified intention to treat analysis was performed on the originally randomized treatment groups to rule out bias due to crossover. Reported p values are two-tailed with an alpha level of 0.05 indicating significance.

Results

The two groups based on cyclical treatment were homogeneous by gender (n.s.), age (n.s.), BMI (n.s.) and follow-up (n.s.). Demographic data are described in Table 1. Seventy-nine patients (102 knees) were available at final follow-up: 51 patients (69 knees) in the single cycle group (group 1) and 28 patients (33 knees) in the two cycles group (group 2). At 1 year follow-up, 14 patients (17 knees) from group 2 showed significant symptomatic improvement; these patients did not feel the need for a second cycle. Since they had received a complete cycle of injections, they were retained in the study group but results are reported with patients in group 1. In order to eliminate any bias generated by this crossover, a modified intention to treat analysis was performed. No difference was found between the results reported and the estimated findings (n.s.). Fourteen patients (17 knees) from group 1 were lost to follow-up or were excluded. Other than the 10 patients who crossed over to group 1, no patients were lost to follow-up from group 2 (Fig. 1).

There was a significant improvement in all scores (KOOS, VAS, Tegner and Marx) at each follow-up compared to the pre-treatment value ($p < 0.001$). When comparing the effect of cyclical treatment, at 12 months, both groups showed similar and significant improvement. Results at 18 months, however, showed a significant difference between the two groups with a greater

Table 1 Demographic data

Groups	No. of males (knees)	No. of females (knees)	Age (range 40–65 years)	BMI	Follow-up (in years)
1 Cycle	30 (41)	21 (28)	54.8 ± 1.1	24.3 ± 0.2	2.1 ± 0.2
2 Cycles	20 (24)	8 (9)	54.3 ± 1.4	24.7 ± 0.3	2.2 ± 0.2

Values represented as mean ± SD

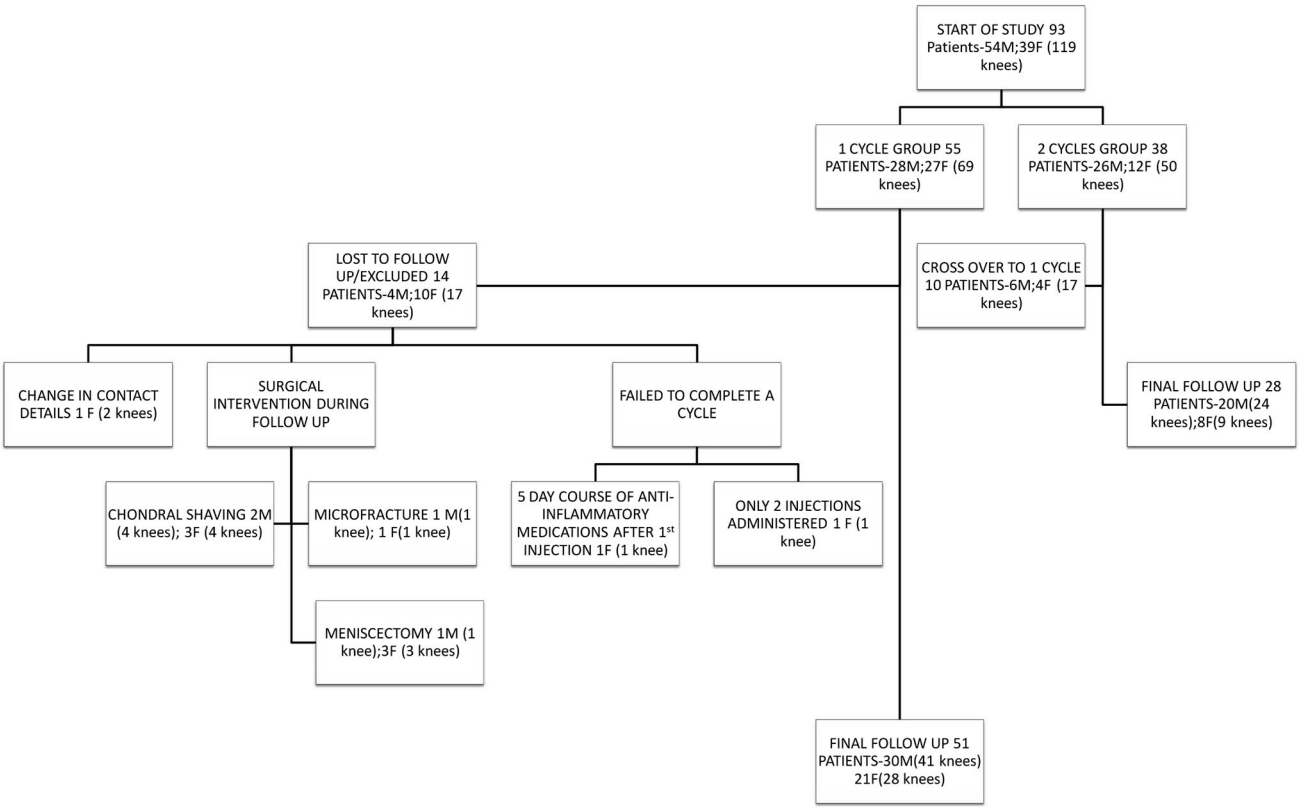

Fig. 1 Flow chart showing the patient population included in the study and their distribution along with the lost and excluded cases. *M* males, *F* females

improvement in results in the patients who had received the second cycle of injections ($p < 0.001$). The only two values which did not vary significantly between the groups at 18 months were KOOS symptoms subscale and Tegner score.

At 2-year follow-up, the scores had declined from the 18-month value in both the groups. The mean value in both groups, however, remained significantly above the pre-treatment value, and no significant difference was found between the scores in the two groups despite the patients in group 2 having higher mean values for all the scores (Fig. 2; Table 2).

Discussion

The most important results of this study are that intra-articular PRP injections can improve functional outcomes and reduce pain in patients with early stages of OA of the knee, and annual repetition of three such injections can better the results. The beneficial effects of the treatment peak within 6 months of the injections and subsequently reduce, and the outcome measures remain significantly higher than pre-treatment values even 24 months after treatment.

In many cases, PRP is administered together with other biological augmentation methods, such as mesenchymal stem cells [6, 15, 16, 18] or bio-engineered scaffolds [10, 35], making it difficult to assess the net contribution made by PRP to the outcome. This study investigated PRP as an isolated entity in the treatment of early stages of OA. Numerous in vitro and in vivo studies have investigated the effect of PRP on articular cartilage [1, 4, 5, 24, 27, 28, 30, 34, 36], but no studies have looked into the outcome following cyclical treatment with PRP. Conflicting results have been seen even in in vivo studies. Serra et al. [34]

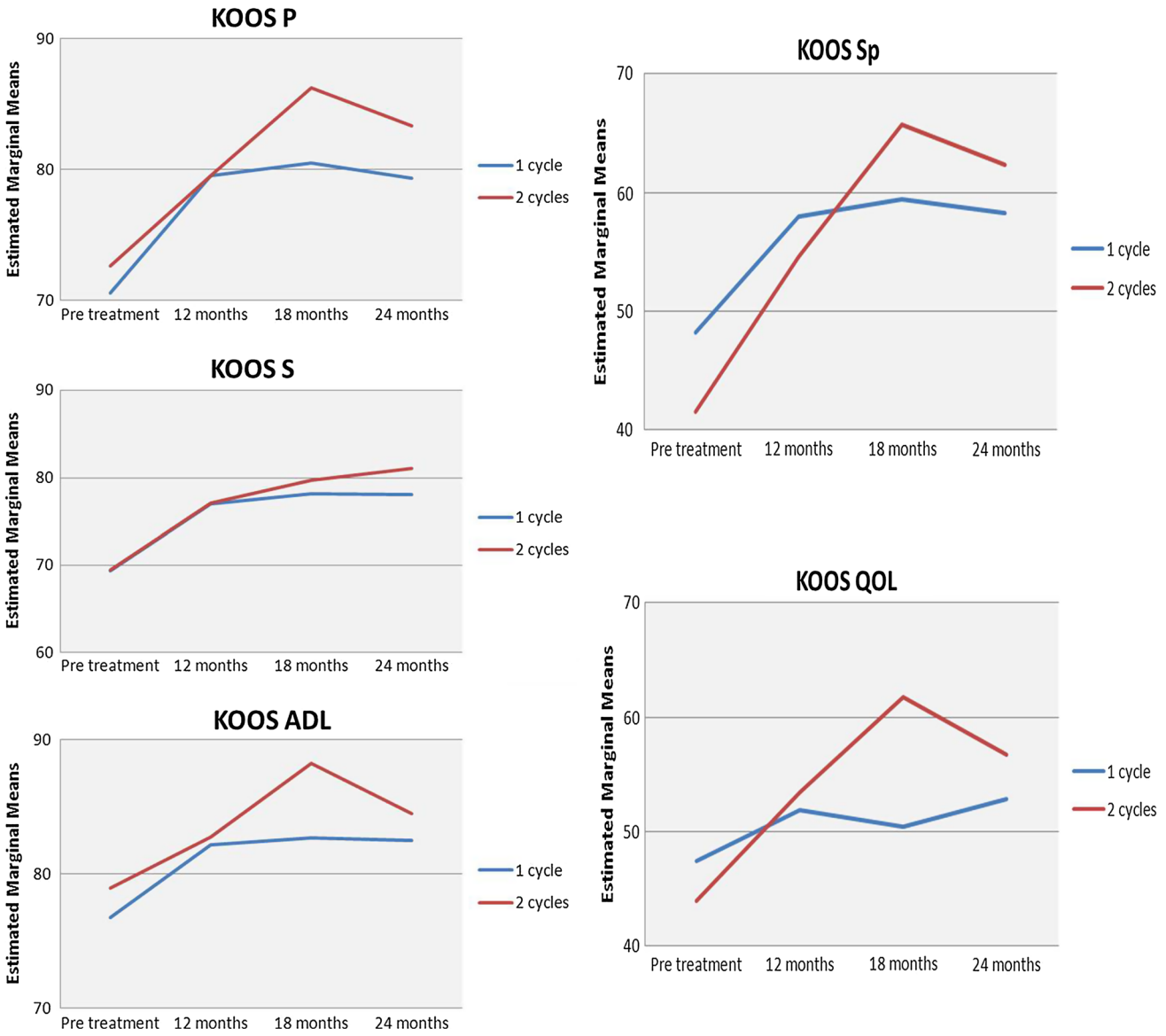

Fig. 2 Variation in KOOS score over the course of study at each follow-up. A significant improvement in scores is evident in the 1st year in both groups, which continues to improve until 18 months for those patients who received the 2nd cycle. By 2 years, even these patients show deterioration in results although the final mean is above the pre-treatment and 1 year mean. KOOS: *P* pain; *S* symptoms; *ADL* activity of daily living; *Sp* sports; *QOL* quality of life

using 24 New Zealand white rabbits in a control study failed to show any significant difference when PRP was used to treat full-thickness cartilage lesions. On the other hand, histological evidence of cartilage repair has been demonstrated after just 4 weeks in immunodeficient rats and sheep [27, 28] with improved cartilage stiffness, justifying further research into the method of clinical use of PRP.

Previous clinical studies suggest that PRP is an effective short term (6 weeks up to 6 months) treatment for chondral lesions, but there are very few randomized control trials (RCT). Amongst the clinical studies, in a recently published RCT, Patel et al. [31] compared the outcome following single and double PRP injections compared to a control group for early OA at 6 weeks, 3 and 6 months. They concluded that there was a significant improvement in WOMAC score at all follow-ups when PRP was administered, with no difference between single and double injections. Hart et al. [19] in a prospective study of 50 patients administered nine injections in 1 year to assess if PRP can increase tibiofemoral cartilage regeneration in the knee. They reported improvement in all scores at 12 months but with no significant cartilage regeneration. Torrero et al. [39] in a prospective study included patients aged 18–65 years and reported significant improvement in the KOOS and VAS score after a single injection up to

Table 2 Mean values ± SD of VAS, Marx and Tegner scores through the follow-up

Score	Group	Pre-treatment	12 months	*p* value	18 months	*p* value	24 months	*p* value
VAS	1	4.2 ± 1.8	2.8 ± 1.7	n.s.	2.9 ± 1.8	<0.001	2.6 ± 1.8	n.s.
	2	4.3 ± 2.2	3.2 ± 2.2		1.9 ± 1.6		2.1 ± 1.7	
Marx	1	3.7 ± 3.6	4.0 ± 3.6	n.s.	5.07 ± 4.2	<0.001	5.96 ± 4.8	n.s.
	2	4.7 ± 3.7	5.8 ± 4.3		6.03 ± 3.9		6.88 ± 4.2	
Tegner	1	2.9 ± 1.5	3.1 ± 1.3	n.s.	3.44 ± 1.3	n.s.	3.68 ± 1.4	n.s.
	2	3.4 ± 1.6	3.2 ± 1.4		3.63 ± 1.2		3.87 ± 1.3	

Values are represented as mean ± SD

Groups 1: single cycle; 2: two cycles

VAS Visual Analogue Scale, *n.s.* not significant

Significant improvement ($p < 0.001$) in all the scores at the end of 12 months. The *p* values are of the comparison between the cycles

6 months after the treatment. In our previous study [17], significant improvement was demonstrated in IKDC, KOOS, VAS, Tegner and Marx scores at 12-month follow-up after two injections administered a month apart. We also found that patients who had undergone previous cartilage surgery (such as shaving or microfracture) and presented with persisting symptoms, showed favorable results, indicating that PRP could be an effective additional therapy. Preliminary reports and results of treatment with PRP have been encouraging in almost all the studies. However, the follow-up period has been as short as 5 weeks to 12 months in most studies. Filardo et al. [14] compared a single spin and double spin method of preparation of PRP in 144 patients, demonstrating a significant clinical improvement in both groups with better results in younger patients. In a comparative study to assess the efficacy of PRP and hyaluronic acid in 150 patients over 6 months, Kon et al. [23] showed improved IKDC and VAS scores in both groups after 2 and 6 months with better results in the PRP group. In a prospective study including 91 patients, a follow-up of 24 months has been reported [13, 22]; patients received three intra-articular PRP injections at monthly intervals, and all parameters worsened at 2 years with significantly lower levels of IKDC objective, subjective and EQ-VAS scores with respect to the 12-month evaluation (IKDC objective fell from 67 to 59 % of normal and nearly normal knees; IKDC subjective score reduced from 60 to 51 %, though they remained higher than the basal level). Jang et al. [20] showed deterioration in scores within the 1st year itself. Unlike the above studies, our results showed a plateau in the results after 1 year for patients receiving a single cycle of treatment and deterioration after 18 months of the 1st injection when the treatment was repeated annually. The final follow-up results, however, continued to remain higher than the baseline pre-treatment values in both groups and were also higher that the values obtained by group 1. This difference, however, was not statistically significant. These findings could be explained on the following grounds: the factors contained within PRP may act to inhibit the most notable catabolic cytokines acting on articular cartilage: interleukin 1β (IL-1β) and tumour necrosis factor α (TNF-α). The production of these enzymes is under the control of transcription factor nuclear factor κβ (NF-κβ). Although PRP does not act directly on NF-κβ, the factors stored within α-granules and released with platelet activation may counteract the effects of NF-κβ mediated cartilage degradation [1, 8]. As the injections were administered at monthly intervals, the anti-cytokinetic effect could have been prolonged and potentially compounded explaining the improved scores even after 12 months. The cartilage breakdown having been potentially slowed down, and the administration of the second cycle of injections may have further improved the symptomatic response.

The strengths of this study lie in the fact that it is a prospective, randomized study of a topic which has not yet been investigated. The study group is large, with a homogenous patient population and strict inclusion and exclusion criteria were laid down to eliminate any bias. Although the results were entirely subjective, all efforts have been made to eliminate confounding factors which may have arisen. When reviewing the literature, it was evident that there was no uniformity in the indications for which PRP has been used. Although intra-articular PRP injections have been administered in the knee for degenerative cartilage lesions, the age group included in previous studies has been as wide as 18–81 years [29, 39]. This study only included patients between the age of 40 and 65 years, who are non-professional athletes in order to eliminate bias which could occur due to extremes of age. A detailed description of the PRP and its preparation technique have been described, to enable further future investigation and comparison between different types of PRP and preparation methods.

The limitations of the study are that it was not possible to have post treatment MRI images for every patient and a

post treatment arthroscopy and biopsy to assess the status of cartilage healing could not be obtained. At the start of the study, 50 knees were assigned to receive a second cycle of injections, but 10 patients (17 knees) crossed over from group 2 to group 1 at the end of 1 year, greatly reducing the patient population in group 2. This could have generated a bias in the findings but was found to be insignificant on the intention to treat analysis. A placebo control group would have provided a key ingredient in this study. However, as it was proposed as a 2-year study period for patients with symptomatic, early stages of OA, it was considered unethical by the review board to leave a certain patient population in a placebo group untreated.

Conclusion

Intra-articular PRP injections into the knee for symptomatic early stages of OA are a valid treatment option. There is a significant reduction in pain and improvement in function after 12 months, which can be further improved at 18 months by annual repetition of the treatment. Although the beneficial effects are ill sustained at 2 years, the results are encouraging when compared to the pre-treatment function.

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Conflict of interest The authors have no conflict of interests to declare.

References

1. Abrams GD, Frank RM, Fortier LA, Cole BJ (2013) Platelet-rich plasma for articular cartilage repair. Sports Med Arthrosc 21:213–219
2. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT (2004) Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost 91:4–15 (Review)
3. Asfaha S, Cenac N, Houle S, Altier C, Papez MD, Nguyen C, Steinhoff M, Chapman K, Zamponi GW, Vergnolle N (2007) Protease-activated receptor-4: a novel mechanism of inflammatory pain modulation. Br J Pharmacol 150:176–185
4. Bendinelli P, Matteucci E, Dogliotti G, Corsi MM, Banfi G, Maroni P, Desiderio MA (2010) Molecular basis of anti-inflammatory action of platelet-rich plasma on human chondrocytes: mechanisms of NF-κB inhibition via HGF. J Cell Physiol 225:757–766
5. Browning SR, Weiser AM, Woolf N, Golish SR, SanGiovanni TP, Scuderi GJ, Carballo C, Hanna LS (2012) Platelet-rich plasma increases matrix metalloproteinases in cultures of human synovial fibroblasts. J Bone Joint Surg Am 94:e1721–e1727
6. Buda R, Vannini F, Cavallo M, Grigolo B, Cenacchi A, Giannini S (2010) Osteochondral lesions of the knee: a new one-step repair technique with bone-marrow-derived cells. J Bone Joint Surg Am 92(Suppl 2):2–11
7. Carlsson AM (1983) Assessment of chronic pain. I. Aspects of the reliability and validity of the Visual Analogue Scale. Pain 16:87–101
8. Chen LX, Lin L, Wang HJ, Wei XL, Fu X, Zhang JY, Yu CL (2008) Suppression of early experimental osteoarthritis by in vivo delivery of the adenoviral vector-mediated NF-kappaBp65-specific siRNA. Osteoarthr Cartil 16:174–184
9. DeLong JM, Russell RP, Mazzocca AD (2012) Platelet-rich plasma: the PAW classification system. Arthroscopy 28:998–1009
10. Dhollander AA, De Neve F, Almqvist KF, Verdonk R, Lambrecht S, Elewaut D, Verbruggen G, Verdonk PC (2011) Autologous matrix-induced chondrogenesis combined with platelet-rich plasma gel: technical description and a five pilot patients report. Knee Surg Sports Traumatol Arthrosc 19:536–542
11. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T (2009) Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol 27:158–167
12. Everts PA, Knape JT, Weibrich G, Schönberger JP, Hoffmann J, Overdevest EP, Box HA, van Zundert A (2006) Platelet-rich plasma and platelet gel: a review. J Extra Corpor Technol 38:174–187 (Review)
13. Filardo G, Kon E, Buda R, Timoncini A, Di Martino A, Cenacchi A, Fornasari PM, Giannini S, Marcacci M (2011) Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. Knee Surg Sports Traumatol Arthrosc 19:528–535
14. Filardo G, Kon E, Pereira Ruiz MT, Vaccaro F, Guitaldi R, Di Martino A, Cenacchi A, Fornasari PM, Marcacci M (2012) Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. Knee Surg Sports Traumatol Arthrosc 20:2082–2091
15. Giannini S, Buda R, Vannini F, Cavallo M, Grigolo B (2009) One-step bone marrow-derived cell transplantation in talar osteochondral lesions. Clin Orthop Relat Res 467:3307–3320
16. Gobbi A, Bathan L (2009) Biological approaches for cartilage repair. J Knee Surg 22:36–44 (Review)
17. Gobbi A, Karnatzikos G, Mahajan V, Malchira S (2012) Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis: preliminary results in a group of active patients. Sports Health 4:162–172
18. Gobbi A, Karnatzikos G, Sankineani SR (2014) One-step surgery with multipotent stem cells for the treatment of large full-thickness chondral defects of the knee. Am J Sports Med 42:648–657
19. Hart R, Safi A, Komzák M, Jajtner P, Puskeiler M, Hartová P (2013) Platelet-rich plasma in patients with tibiofemoral cartilage degeneration. Arch Orthop Trauma Surg 133:1295–1301
20. Jang SJ, Kim JD, Cha SS (2013) Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis. Eur J Orthop Surg Traumatol 23:573–580
21. Kellgren JH, Lawrence JS (1957) Radiological assessment of osteo-arthrosis. Ann Rheum Dis 16:494–502
22. Kon E, Buda R, Filardo G, Di Martino A, Timoncini A, Cenacchi A, Fornasari PM, Giannini S, Marcacci M (2010) Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surg Sports Traumatol Arthrosc 18:472–479
23. Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, Fornasari PM, Giannini S, Marcacci M (2011) Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy 27:1490–1501
24. Krüger JP, Hondke S, Endres M, Pruss A, Siclari A, Kaps C (2012) Human platelet-rich plasma stimulates migration and

chondrogenic differentiation of human subchondral progenitor cells. J Orthop Res 30:845–852
25. Marx RG, Stump TJ, Jones EC, Wickiewicz TL, Warren RF (2001) Development and evaluation of an activity rating scale for disorders of the knee. Am J Sports Med 29:213–218
26. Mazzucco L, Balbo V, Cattana E, Guaschino R, Borzini P (2009) Not every PRP-gel is born equal. Evaluation of growth factor availability for tissues through four PRP-gel preparations: fibrinet, RegenPRP-Kit, Plateltex and one manual procedure. Vox Sang 97:110–118
27. Mifune Y, Matsumoto T, Takayama K, Ota S, Li H, Meszaros LB, Usas A, Nagamune K, Gharaibeh B, Fu FH, Huard J (2013) The effect of platelet-rich plasma on the regenerative therapy of muscle derived stem cells for articular cartilage repair. Osteoarthr Cartil 21:175–185
28. Milano G, Deriu L, Sanna Passino E, Masala G, Manunta A, Postacchini R, Saccomanno MF, Fabbriciani C (2012) Repeated platelet concentrate injections enhance reparative response of microfractures in the treatment of chondral defects of the knee: an experimental study in an animal model. Arthroscopy 28:688–701
29. Napolitano M, Matera S, Bossio M, Crescibene A, Costabile E, Almolla J, Almolla H, Togo F, Giannuzzi C, Guido G (2012) Autologous platelet gel for tissue regeneration in degenerative disorders of the knee. Blood Transfus 10:72–77
30. Park SI, Lee HR, Kim S, Ahn MW, Do SH (2012) Time-sequential modulation in expression of growth factors from platelet-rich plasma (PRP) on the chondrocyte cultures. Mol Cell Biochem 361:9–17
31. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A (2013) Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med 41:356–364
32. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD (1998) Knee Injury and Osteoarthritis Outcome Score (KOOS)—development of a self-administered outcome measure. J Orthop Sports Phys Ther 28:88–96
33. Sampson S, Reed M, Silvers H, Meng M, Mandelbaum B (2010) Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study. Am J Phys Med Rehabil 89:961–969
34. Serra CI, Soler C, Carillo JM, Sopena JJ, Redondo JI, Cugat R (2013) Effect of autologous platelet-rich plasma on the repair of full-thickness articular defects in rabbits. Knee Surg Sports Traumatol Arthrosc 21:1730–1736
35. Siclari A, Mascaro G, Gentili C, Cancedda R, Boux E (2012) A cell-free scaffold-based cartilage repair provides improved function hyaline-like repair at one year. Clin Orthop Relat Res 470:910–919
36. Spreafico A, Chellini F, Frediani B, Bernardini G, Niccolini S, Serchi T, Collodel G, Paffetti A, Fossombroni V, Galeazzi M, Marcolongo R, Santucci A (2009) Biochemical investigation of the effects of human platelet releasates on human articular chondrocytes. J Cell Biochem 108:1153–1165
37. Sturgill LP, Snyder-Mackler L, Manal TJ, Axe MJ (2009) Interrater reliability of a clinical scale to assess knee joint effusion. J Orthop Sports Phys Ther 39:845–849
38. Tegner Y, Lysholm J (1985) Rating systems in the evaluation of knee ligament injuries. Clin Orthop Relat Res 198:43–49
39. Torrero JI, Aroles F, Ferrer D (2012) Treatment of knee chondropathy with platelet rich plasma. Preliminary results at 6 months of follow-up with only one injection. J Biol Regul Homeost Agents 26(2 Suppl 1):71S–78S
40. Ulrich-Vinther M, Maloney MD, Schwarz EM, Rosier R, O'Keefe RJ (2003) Articular cartilage biology. J Am Acad Orthop Surg 11:421–430 (Review)
41. Van Manen MD, Nace J, Mont MA (2012) Management of primary knee osteoarthritis and indications for total knee arthroplasty for general practitioners. J Am Osteopath Assoc 112:709–715 (Review)
42. Wang-Saegusa A, Cugat R, Ares O, Seijas R, Cuscó X, Garcia-Balletbó M (2011) Infiltration of plasma rich in growth factors for osteoarthritis of the knee short-term effects on function and quality of life. Arch Orthop Trauma Surg 131:311–317