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Infiltration of plasma rich in growth factors for osteoarthritis of the knee short-term effects on function and quality of life

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Abstract
Purpose Osteoarthritis (OA) is a highly prevalent, chronic, degenerative condition that generates a high expense. Alternative and co-adjuvant therapies to improve the quality of life and physical function of affected patients are currently being sought.
Methods A total of 808 patients with knee pathology were treated with PRGF (plasma rich in growth factors), 312 of them with OA of the knee (Outerbridge grades I–IV) and symptoms of >3 months duration met the inclusion criteria and were evaluated to obtain a sample of 261 patients, 109 women and 152 men, with an average age of 48.39. Three intra-articular injections of autologous PRGF were administered at 2-week intervals in outpatient surgery. The process of obtaining PRGF was carried out following the Anitua Technique. Participants were asked to fill out a questionnaire with personal data and the following assessment instruments: VAS, SF-36, WOMAC Index and Lequesne Index before the first infiltration of PRGF and 6 months after the last infiltration.
Results Statistically significant differences ($P < 0.0001$) between pre-treatment and follow-up values were found for pain, stiffness and functional capacity in the WOMAC Index; pain and total score, distance and daily life activities in the Lequesne Index; the VAS pain score; and the SF-36 physical health domain. There were no adverse effects related to PRGF infiltration.
Conclusion At 6 months following intra-articular infiltration of PRGF in patients with OA of the knee, improvements in function and quality of life were documented by OA-specific and general clinical assessment instruments. These favourable findings point to consider PRGF as a therapy for OA.

Keywords Osteoarthritis · Chondropathy · Platelet-rich plasma · PRP

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Introduction

Osteoarthritis (OA) is a highly prevalent, chronic, degenerative illness, the most frequent cause of pain and a major cause of disability and dependence, which generates a high expense. Currently, there is no curative treatment for OA. The therapy used may be a conservative approach or surgery and varies depending on the affected joint. Non-steroidal anti-inflammatory drugs (NSAIDs) have been the main pharmacological OA treatment, but the elderly have a high risk of showing side effects. Studies show that 5 IA injections of hyaluronic acid (HA) produce an extended symptomatic improvement in patients with OA [17].

In the past, arthritis therapy did not taken into account, the true causes and underlying pathogenic mechanisms of the condition, focusing mainly on treating the symptoms, rather than interfering with the progression of cartilage damage. This approach is now changing [15] with the

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development of drugs that delay cartilage degeneration and enhance the repair process [20]. In recent years, autologous plasma rich in growth factors (PRGFs) has been considered as a regenerative treatment for chondral tissue and a potential biologic tool to treat soft tissue lesions [13, 23, 29]. PRGF isolated from autologous blood could be useful as a source of growth factors (GFs) to stimulate chondrocytes to produce cartilage. A marked increase to the proteoglycan and collagen synthesis is observed in chondrocytes treated with PRGF [2]. The repair tissue created after PRGF treatment has similar histological characteristics [29] similar to hyaline articular cartilage. This repair tissue and healthy articular cartilage show biomechanical behaviour typical of a viscoelastic material. After PRGF treatment, the mechanical behaviour of full-thickness chondral injuries is similar to that of immature healthy articular cartilage [32, 34].

Embryogenesis and reparation are very similar. In both processes, precursor cells, GFs and bone morphogenetic proteins are important elements [35].

GFs are soluble, diffusible, polypeptidic macromolecules which are produced by a great variety of cells. They have potent specific actions on the growth, differentiation and the genotype of numerous cell types, including chondrocytes. Each GF has one or several specific activities and actions in a concrete cell, depending on the particular circumstances of the environment. GFs are multifunctional and participate in tissue repair and healing. They regulate key processes, such as mitogenesis, chemotaxis, cellular differentiation and metabolism [4].

Studies performed in molecular biology have localised the chromosome and its segment containing the genes that codify PDGF (platelet-derived GF), TGF-β1 (transforming GF β1), as well as their receptors [10]. Platelets play a central role in haemostasia and wound healing, which is mediated by protein release during platelet activation. It directly or indirectly influences all aspects of healing [24]. Anitua described a technique for obtaining PRGF®, a plasmatic fraction acquired by simple slow spinning (BTI PRGF® System), which is characterised for having a high concentration of platelets and GFs [32], including anabolic factors for cartilage, such as TGF-β1 (transforming GF β1), PDGF (platelet-derived GF) and IGF-I (insulin-like GF-I) [4]. Composition correlates with the number of platelets [30] and it is as follows: TGFβ-1 (29.15 $\pm$ 12.88 ng/ml), PDGF (17.41 $\pm$ 9.66 ng/ml), VEGF (vascular endothelial GF) (212 pg/ml), IGF-I (54.85 $\pm$ 18.41 ng/ml) and HGF (hepatocyte GF) (522 $\pm$ 253 pg/ml) [31].

The synergetic actions of other factors with PDGF are important for modulation of the wound healing process. The physiological homeostasis is fundamental in the performance of GFs, producing feedback with which they regulate themselves and each other for their optimal performance [4].

This study intends to show that PRGF intra-articular treatment in OA of the knee can improve patients′ quality of life and functional capacity.

Hypothesis. Infiltration of plasma rich in growth factors (PRGF) will improve the quality of life and physical function of patients with OA of the knee.

Materials and methods

A non-randomized, prospective, longitudinal study was carried out, to evaluate the effectiveness of a cycle of three intra-articular injections of autologous PRGF, 1 every 2 weeks, in patients with OA of the knee and clinical symptoms for at least 3 months. The follow-up period was 6 months. All patients signed an informed consent form to participate.

Sample selection was performed by non-probabilistic sampling of consecutive cases. A total of 808 patients with knee pathology were treated with PRGF, 312 of them with OA of the knee met the inclusion criteria (Table 1). After strictly applying the exclusion criteria (Table 1), the study group comprises 261 patients, 109 women and 152 men, average age 48.39 (SD 16.65), with OA in one or both knees, categorised as Outerbridge grades I–IV by magnetic resonance imaging [7].

Current work status was active in 67.8% of the sample and it had a mean BMI of 25.91 (SD 3.90) at the start of the study and 25.92 (SD 3.92) at 6-month follow-up. The chondropathy grade distribution was as follows: grade I 13.1%, grade II 30.8%, grade III 19.2% and grade IV 36.9%. PRGF infiltration was performed in 88 right knees (33.72%), 75 left knees (28.73%) and 98 bilateral knees (37.55%).

A questionnaire was designed to record the characteristics of the patient sample, such as: age, body mass index (BMI), current work status (active/passive/retired), dominant extremity and to administer four tests: the visual analogue scale (VAS), SF-36 Health Survey (Spanish version 1.4, June 1999), Western Ontario and McMaster Universities Index of Osteoarthritis (WOMAC) and Lequesne Algofunctional Index. Participants were asked to fill out the questionnaire before the first infiltration of PRGF and again at 6 months after the last infiltration.

Blood extraction was performed in the pre-surgical area using a vacuum system. A total of 20 ml of blood (4 samples of 5 ml) per patient was collected in sterile sodium citrate tubes. PRGF was obtained following Anitua′s technique. The tubes with citrated blood were centrifuged at 1,800 rpm for 8 min to obtain a concentrate of platelets suspended in plasma, which was separated into three fractions. Pipetting was carried out with extreme care in all steps, particularly in the last fraction where, to avoid

Table 1 Inclusion and exclusion criteria applied

Inclusion criteria	Exclusion criteria
Three consecutive intra-articular PRGF® injections	Questionnaires not completed
Radiological diagnosis of OA	Three injection cycle not completed
OA severity, Outerbridge grades I–IV by MRI	Questionnaires completed or injections received outside predetermined study period
Patello-femoral and/or tibio-femoral chondropathy	Difficulties in comprehension and/or reading and writing
Clinical symptoms >3 months	Physical impediments to answer the questionnaire
Both sexes	Informed consent not provided
Body mass index between 18 and 35	Body mass index <18 or body mass index >35
	Polyarticular disease
	Pseudogout/hyperuricemia
	Intra-articular HA injection in the last 6 months
	Steroid treatment in the last 3 months
	Systemic autoimmune rheumatic disease
	Blood dyscrasia
	Immunosuppressive or dicoumarin treatment
	Immunodepressive disease
	Infectious disease
	Cancer/malignant lesions

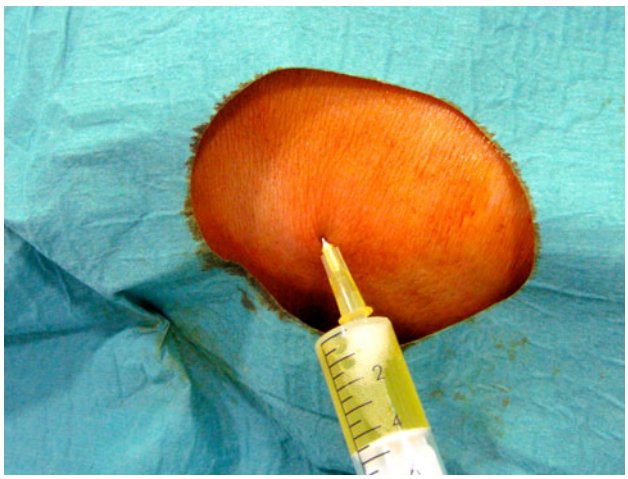

Fig. 1 PRGF injection is done in outpatient surgery applying asepsia measures

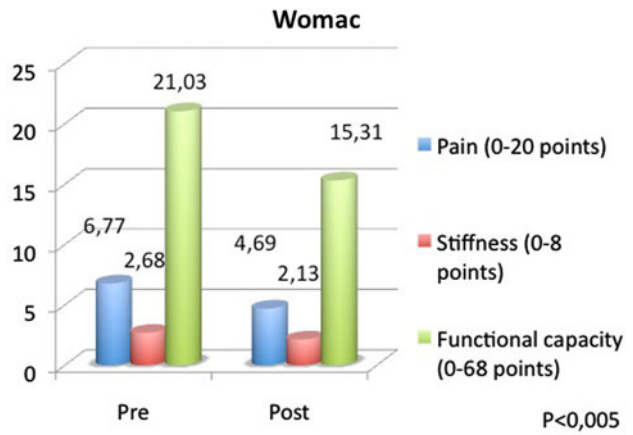

Fig. 2 WOMAC Index: pre and post-treatment marks for pain, stiffness and functional capacity (FC). All results show improvement with statistical significance rates

inflammation, leukocytes present in the lowermost portion of the centrifuged plasma were not aspirated.

PRGF was activated by adding calcium chloride 10%, immediately before infiltration (Fig. 1). The proportion required for PRGF activation is 50 ml of activator per 1,000 ml of PRGF. Separation of plasma into three fractions and subsequent activation of the fractions for injection was performed in a laminar flow chamber.

The means of paired samples were compared for VAS with the Student's *t* parametric test. SF-36, WOMAC Index and Lequesne Index were tested by the nonparametric Wilcoxon's rank sum test. Significance was set at $P < 0.05$.

Results

The chondropathy grade distribution was as follows: grade I 13.1%, grade II 30.8%, grade III 19.2% and grade IV 36.9%. PRGF infiltration was performed in 88 right knees (33.72%), 75 left knees (28.73%) and 98 bilateral knees (37.55%).

Scores for pain, stiffness and functional capacity were 6.77, 2.68 and 21.03, respectively, on the pre-treatment WOMAC Index and 4.69, 2.13 and 15.31, respectively, on the 6-month follow-up assessment, with significant differences for all three items ($P < 0.0001$). The patients′ follow-up improvement was 65.5, 48.2 and 67.4% for pain, stiffness and functional capacity, respectively (Fig. 2).

The Lequesne Index showed pre-treatment values of 3.93 for pain, 1.92 for distance walked, 3.58 for daily life activities and 9.43 for total score. The post-treatment values were 2.97 for pain, 1.58 for distance walked, 2.94 for daily life activities and 7.50 for total score. Pre-treatment and follow-up values were statistically different: $P < 0.0001$ for pain, daily life activities and total score and, $P = 0.001$ for distance walked. The percentages of improvement for the

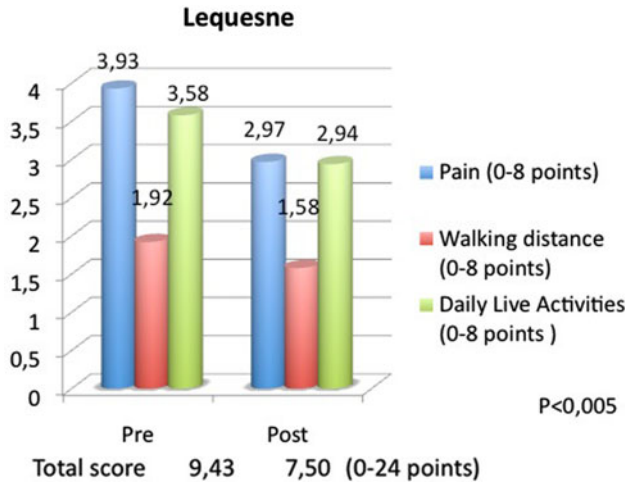

Fig. 3 Lequesne Index: pre and post-treatment marks for pain, distance walked, daily life activities (DLA) and total score. All results show improvement with statistical significance rates

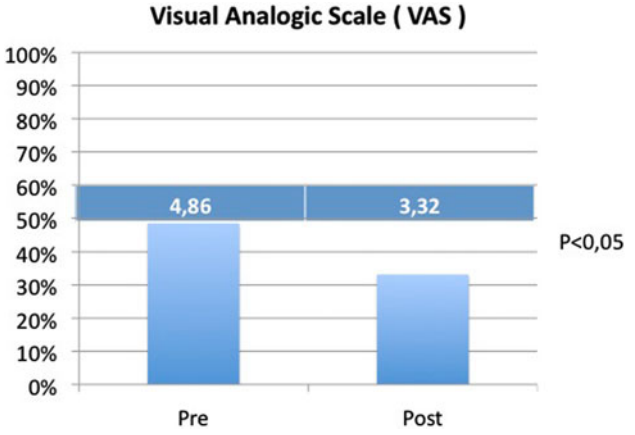

Fig. 4 VAS: pre and post-treatment marks for pain. The results show statistical significant rates

three items and total score were 59.8, 36.6, 53.7 and 67.2%, respectively. On the distance scale, 42.8% of patients showed no changes; therefore, 79.4% of the patients treated with PRGF either showed no changes or were able to walk farther (Fig. 3).

The VAS score for pain was 4.86 pre-treatment and 3.32 follow-up, with statistically significant differences ($P < 0.0001$). An improvement was documented in 73.4% of patients (Fig. 4).

The pre-treatment results of the standard SF-36 test were 51.94 for the mental health domain and 38.87 for the physical health domain. Follow-up results were 52.85 for mental health domain and 42.28 for physical health domain. Differences were statistically significant ($P < 0.0001$) for the SF-36 physical and non-significant ($P = 0.096$) for the SF-36 mental. An improvement was attained in 52.0% of patients

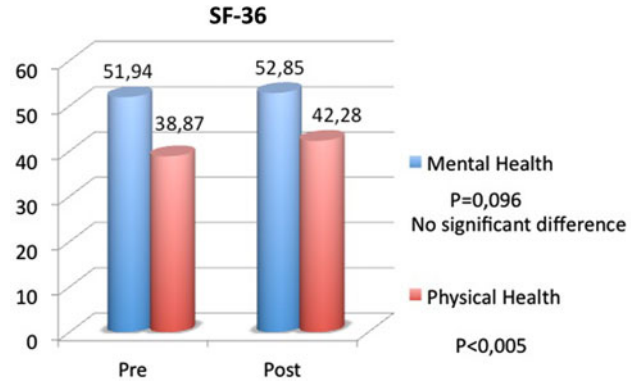

Fig. 5 SF-36 test: pre and post-treatment marks for the mental health domain and the physical health domain. Physical health rates improve with statistical significance. Mental health domain no show significant difference rates

in the mental domain and 64.6% of patients in the physical domain (Fig. 5).

All results are shown in Table 2.

There were no local or superficial infections, allergic reactions, or any other complications related to intra-articular PRGF infiltration during the study period.

Discussion

Osteoarthritis is mainly an alteration of the chondral tissue and the most common reason for consultation is pain. In the present study, intra-articular injection of PRGFs in OA of the knee improved the quality of life and functional capacity of the patients treated.

Cartilage tissue engineering is an emerging technique for cartilage regeneration, in which important advances have been made in recent years [1, 8, 26, 27]. Ochi et al. [25] point to minimally invasive tissue engineering techniques, as the future direction for cartilage repair and consider injection of cytokines or GFs and cells as the optimal procedure for cartilage repair.

Platelet-derived GFs obtained from autologous blood are proteins with the capacity to stimulate chondrocytes to regenerate cartilage. PRGF-treated chondrocytes showed markedly increased synthesis of proteoglycans and collagen. Plasma rich in GFs is an excellent vehicle for GFs, especially PDGF and TGFβ. GFs released from activated platelets initiate and modulate wound healing in both soft and hard tissue [9]. A recent strategy to promote the healing cascade is to apply a concentrate of autologous platelets obtained from plasma and containing GFs (PRGF) to the injury [12]. Its autologous nature gives it a significant advantage in tissue engineering applications which can be improved with the addition of adjuncts that increase the proliferation and differentiation of progenitor or stem cells

Table 2 Global results: pre/post-treatment average values, percentage of improvement, statistical significance rates

Test	Subtest	Pre	Post	Percentage of improvement	*P*
WOMAC	Pain	6.77	4.69	65.5	<0.0001
	Stiffness	2.68	2.13	48.2	<0.0001
	Functional capacity	21.03	15.31	67.4	<0.0001
SF-36	Mental	51.94	52.87	52.0	0.096
	Physical	38.87	42.28	64.6	<0.0001
VAS		4.86	3.32	73.4	<0.0001
Lequesne	Pain	3.93	2.97	59.8	<0.0001
	Distance	1.92	1.58	36.6	0.001
	DLA	3.58	2.94	53.7	<0.0001
Total		9.43	7.50	67.2	<0.0001

[23]. The effectiveness of autologous bone marrow stromal cell therapy was shown in articular cartilage defect repair [1, 36], restoring knee stability and function in acute incomplete anterior cruciate ligament lesions in athletes [16]. The results obtained in a cell culture experiment devised in mesenchymal stem cells (MSCs) confirm that PRP (platelet-rich plasma) enhances MSC proliferation and suggest that PRP causes chondrogenic differentiation of MSC in vitro [23] providing a promising alternative to surgery by promoting safe and natural healing [28]. The therapeutic use of platelets in a fibrin clot has a positive influence in clinical situations requiring rapid healing [24]. It has been safely used and documented in the last 20 years in many fields, including [28]: orthopaedics, sports medicine, odontology, periodontal, cosmetic medicine, plastic and cosmetic surgery and maxillofacial surgery, amongst others. The efficacy of this treatment resides in the continuous, local release of a wide range of GFs and proteins necessary for healing in a process that imitates physiological tissue repair [4, 24].

In an experimental study in an animal model, Soler [33] reported that administration of intra-articular PRGF is effective for repair of full-thickness cartilage injuries in rabbit and reduces healing time of these injuries when compared with conventional treatments, such as chondroitin sulphate and HA. In addition, the synergy between PRGF and HA resulted in a more pronounced effect when the two were used together. In another animal model, Serra found that the repair tissue created following PRGF treatment has histological characteristics similar to hyaline articular cartilage. The biomechanical behaviour of this repair tissue and the healthy articular cartilage is typical of a viscoelastic material. The mechanical properties of full-thickness chondral injuries that have healed after PRGF application are similar to that of healthy immature articular cartilage [32]. The improvements that occurred in the status of the joint cartilage can explain the statistically significant differences found on all the scales to assess the patients' quality of life and physical function used in this work.

HA is found naturally in the synovial fluid and cartilage. The viscoelastic and lubricant characteristics of synovial fluid, which are deteriorated in patients with OA, depend to a great part on HA. This substance improves the quality of fluid production by synoviocytes and seems to influence the presence and status of the inflammatory and receptor cells [17]. The clinical benefits of autologous PRGF infiltration in OA are in consonance with the results obtained after HA infiltration. This classic treatment for the symptoms of OA was used in the clinical trials conducted by Altman et al. and Husskison et al. [3, 17]. The VAS results for pain after PRGF show a higher percentage of improved patients (73.4%) than that achieved with the use of HA (56%), Altman et al. (1998) and statistical significance was higher in the group receiving PRGF than in the groups treated with HA. The WOMAC test results in the PRGF group were more significant ($P < 0.0001$) than the results in the groups treated with HA ($P < 0.041$). In a clinical trial by Husskison et al. the difference between HA infiltration and placebo for pain reduction at 4 months measured by the Lequesne pain item approached borderline significance ($P = 0.0528$). In the present study, the results were statistically significant ($P < 0.0001$), indicating a considerable improvement in this item with the use of PRGF. In a clinical trial, Kon et al. showed that autologous PRGF injections have more and longer efficacy than HA injections reducing pain and symptoms and recovering articular function in patients affected by severe chondropathies of the knee [19]. PRGF could balance angiogenesis and restore HA concentration in the joint [6].

Many of the treatments applied in OA to date have systemic repercussions. Intra-articular infiltration of autologous PRGF was well tolerated over the entire study period. The only secondary effects were local and infrequent at the injection site. A systematic review of 20 clinical trials investigating the efficacy and safety of PRGF in healing

and regenerating hard and soft tissue in medical and surgical procedures concluded that there were no complications related to the use of PRGF [22]. Safety is provided by the anti-bactericidal secretion of proteins by platelets which participate directly in the elimination of bacteria during sepsis. Platelets ability to reduce pain is due to a suppression of the inflammatory phase and a relatively low level of interleukins [14, 24]. It has been reported that the cells remain phenotypically stable in the presence of PRGF [2]. The safety of PRGF and the low incidence of adverse effects [28] make it an appropriate treatment for patients with OA, particularly the elderly, those intolerant to NSAIDs and those in whom NSAIDs are contraindicated. It could also be used to treat other joints, although the effect and outcome of this approach on the evolution of OA should be investigated.

The search for safe and effective therapeutic and co-adjuvant treatment for such a common condition generates considerable interest; platelet-rich plasma application has been showing promising results [21]. Sánchez et al. performed a retrospective observational cohort study ($n = 60$) to evaluate the effectiveness of 3 weekly intra-articular injections of autologous PRGF preparation for OA of the knee, with hyaluronan injections used as a control. The results obtained on WOMAC questionnaires prior to treatment and at 5 weeks after treatment showed a 33.4% success rate on the pain subscale for the PRGF group and 10% for the hyaluronan group. The difference was attributed exclusively to the treatment modality, $P = 0.004$. The improvements in the functional capacity subscale and overall WOMAC at 5 weeks in favour of PRGF were also associated only with the treatment modality ($P = 0.043$ and $P = 0.010$, respectively) [31]. The authors' results are also consistent with those obtained by Kon et al. after treating knee degenerative cartilage lesions with intra-articular PRP in a series of 100 patients (115 knees treated) [18].

Radiographically, OA is present in 15–30% of the population >45 years [17], which is in keeping with the mean age of the patients studied, 48.39 years (SD 16.65).

The most important modifiable risk factor of OA is obesity and having a BMI >25 significantly increases the risk of symptomatic knee OA in women [11]. The difference between pre and post-BMI was not significant; hence, the results obtained are not considered relevant.

This study shows that PRGF intra-articular infiltration in OA of the knee according to the established protocol is safe, tolerable and effective, resulting in a reduction in pain at short term. The mean interval between the two questionnaires was 191 days (range 160–200). It is not surprising that the reduction in pain was associated with a functional improvement, as documented with the Lequesne Index and WOMAC.

Regarding the PRGF obtaining technique used in this study [5], it can be highlighted that plasma rich in platelets is obtained without leucocytes and retaining all proteins and plasma coagulation factors. The technique is performed with very small volumes of blood, and clotting is achieved by adding calcium chloride without using thrombin, thereby avoiding the illnesses that can be caused by the use of this substance. The PRGF technique uses platelets as bearers of GFs and other proteins that are important for bone biology. The release of these proteins from the platelet alfa granules, and the concentration and deposit at the site of injury can be controlled. Thus, the lesion is exposed to a physiologic concentration of proteins that accelerates and favours the process of repair and regeneration [4].

An objective limitation of this study is the lack of control group, which is an obstacle in reaching definitive conclusions. However, we can say that intra-articular infiltration of autologous PRGF under the conditions described in this study seems to be a safe, effective treatment for OA, with no associated systemic repercussions or complications.

Conclusions

The results obtained in this study indicate that intra-articular infiltration of autologous PRGF in patients with OA of the knee has local, effective and temporal effects reducing pain and restoring function, without provoking local or systemic adverse events. PRGF may be particularly useful in elderly OA patients who may not tolerate NSAIDs and in patients in whom this treatment is contraindicated. The simplicity of autologous PRGF use makes it an attractive option for clinicians and researchers. Nonetheless, further study and clinical trials are needed to confirm the results observed. It may be an error to limit the application of PRGF as a single treatment. It can be applicable as a carrier or co-adjuvant of other therapeutic methods.

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