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Review article

Platelet-rich plasma for osteoarthritis treatment

*Eduardo Knop**, *Luiz Eduardo de Paula*, *Ricardo Fuller*

Rheumatology Service, Hospital das Clínicas, School of Medicine, Universidade de São Paulo (USP), São Paulo, SP, Brazil

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ABSTRACT

We conducted a comprehensive and systematic search of the literature on the use of platelet-rich plasma (PRP) in the treatment of osteoarthritis, using the Medline, Lilacs, Cochrane and SciELO databases, from May 2012 to October 2013.

A total of 23 studies were selected, with nine being controlled trials and, of these, seven randomized, which included 725 patients. In this series, the group receiving PRP showed improvement in pain and joint function compared to placebo and hyaluronic acid. The response lasted up to two years and was better in milder cases.

However it was found that there is no standardization in the PRP production method, neither in the number, timing, and volume of applications. Furthermore, the populations studied were not clearly described in many studies. Thus, these results should be analyzed with caution, and further studies with more standardized methods would be necessary for a more consistent conclusion about the PRP role in osteoarthritis.

Plasma rico em plaquetas no tratamento da osteoartrite

Palavras-chave:
Plasma rico em plaquetas
Cartilagem
Osteoartrite

RESUMO

Fez-se uma pesquisa abrangente e sistemática da literatura sobre o uso de plasma rico em plaquetas (PRP) no tratamento da osteoartrite nas bases de dados do Medline, Lilacs, Cochrane e SciELO, de maio de 2012 a outubro de 2013.

Foram selecionados 23 estudos, entre eles nove ensaios controlados e, desses, sete randomizados, os quais incluíram 725 pacientes. Nessa casuística, o grupo que recebeu PRP apresentou melhoria na dor e na função articular quando comparado ao que recebeu placebo e ácido hialurônico. A resposta durou até dois anos e foi melhor nos casos mais leves.

Entretanto, verificou-se que não há uma padronização no método de obtenção do PRP, bem como no número, intervalo e volume de aplicações. Além disso, as populações estudadas

* *Corresponding author.*
E-mail: eduardo_knop@hotmail.com (E. Knop).
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também não foram claramente descritas em muitos estudos. Desse modo, esses resultados devem ser analisados com cautela e seriam necessários novos estudos com métodos mais padronizados para uma conclusão mais consistente sobre o papel do PRP na osteoartrite.

Introduction

Although osteoarthritis (OA) is one of the most prevalent musculoskeletal diseases in the world, its treatment is still relatively limited.[1] The Osteoarthritis Research Society International notes that there is little evidence that the currently used drugs have effective action against the progression of the disease.[2]

A relatively new strategy for the treatment of OA is the use of cell elements and biomediators of tissue response. In this context, the platelet-rich plasma (PRP) has been configured as a perspective for improving clinical and structural outcomes by delivering a high concentration of growth factors that mediate cartilage healing and remodeling. Its potential has been shown in vitro and in vivo studies, however its real efficacy in OA is not well established.[3]

Thus, this study has the purpose to present some technical aspects for obtaining PRP, possible mechanisms of action and a review of its use in knee osteoarthritis.

Methods

We conducted a comprehensive and systematic literature search using MEDLINE, LILACS, Cochrane and SciELO databases, from May 2012 to October 2013. The key words used were "platelet-rich plasma," "platelet-rich growth factor", "osteoarthritis", "hip", "knee", "ankle", "human" and "cartilage". The studies found in the initial search were reviewed and additional references were also evaluated and included where relevant. The search was limited to studies performed in humans. The selected articles were read in full by two reviewers for analysis of their methods and their limitations. Disagreements were discussed for a consensus, with the mediation of a third author.

The quality of the studies analyzed was initially classified according to randomization. Then we proceeded to the evaluation of the following items: type of control group (active controller – hyaluronic acid – or placebo), double-blind evaluation (with description of SHAM procedure), number of treated patients, definition of radiographic and level of pain in the inclusion criteria, definition of exclusion criteria, description of blinding and randomization process, intention to treat analysis, assessment tools (whether including OMERACT criteria or not), description of the process to obtain PRP, platelet concentration, volume injected, guided-injection performance, number of injections in the treated and control groups, and report of adverse events.

A total of 23 studies (Fig. 1 and Tables 1 and 2) were selected, with nine being controlled trials, and of these, seven randomized, which included 725 patients. In this review some results of other 13 non-controlled studies, and also a retrospective cohort were also listed.

Mechanism of action of PRP

When PRP is injected into the injured site, platelets are activated by endogenous thrombin and/or intra-articular collagen.[4] Once activated, there is secretion of growth factors by degranulation of the α-granules.[5] Among secreted substances we can find: platelet-derived growth factor (PDGF), interleukin-1 receptor antagonist (IL-1RA), soluble receptor of tumor necrosis factor α (TNF-RI), transforming growth factor β (TGF-β), platelet factor 4 (PF4), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), osteocalcin (Oc), osteonectin (On), fibrinogen, vitronectin, fibronectin and thrombospondin-1 (TSP-1).[6]

Many of these mediators act as anti-catabolic and anti-inflammatory agents. The antagonist of IL-1 receptor inhibits activation of NFκB gene, cytokine involved in apoptosis and inflammation process.[4,7] Moreover, the soluble receptors of the tumor necrosis factor bind to TNF-α, preventing its interaction with cellular receptors and its pro-inflammatory signaling. TGF-β1 also acts as a factor inhibiting cartilage degradation, regulating and enhancing gene expression of tissue inhibitors of metalloproteinases (TIMP-1).[8] Other factors such as IGF-1, PDGF and TGF-β1 favor the stabilization of cartilage by controlling the metabolic functions of chondrocytes and subchondral bone, maintaining the homeostasis between the synthesis and degradation of proteoglycans, and stimulating the proliferation of chondrocytes.[9,10] It was also found that platelet growth factors stimulate synovial fibroblasts to synthesize hyaluronic acid.[9] These mechanisms are illustrated in Fig. 2.

Technical aspects for obtainment of platelet-rich plasma

PRP is obtained by centrifuging the autologous venous blood, causing a high concentration of platelets in a small volume of plasma.[11] There is no standardization regarding the speed, duration and number of centrifugations needed, neither which layer exactly is removed from the precipitate after this process.[3]

After the separation of the blood component rich in platelets, platelet activation can be stimulated artificially. The most commonly used activator is calcium chloride, which stimulates the production of thrombin, leading to release of growth factors. Other activators described are bovine thrombin and type I collagen. It is believed that the latter leads to a more gradual and durable release of the platelet granules, in

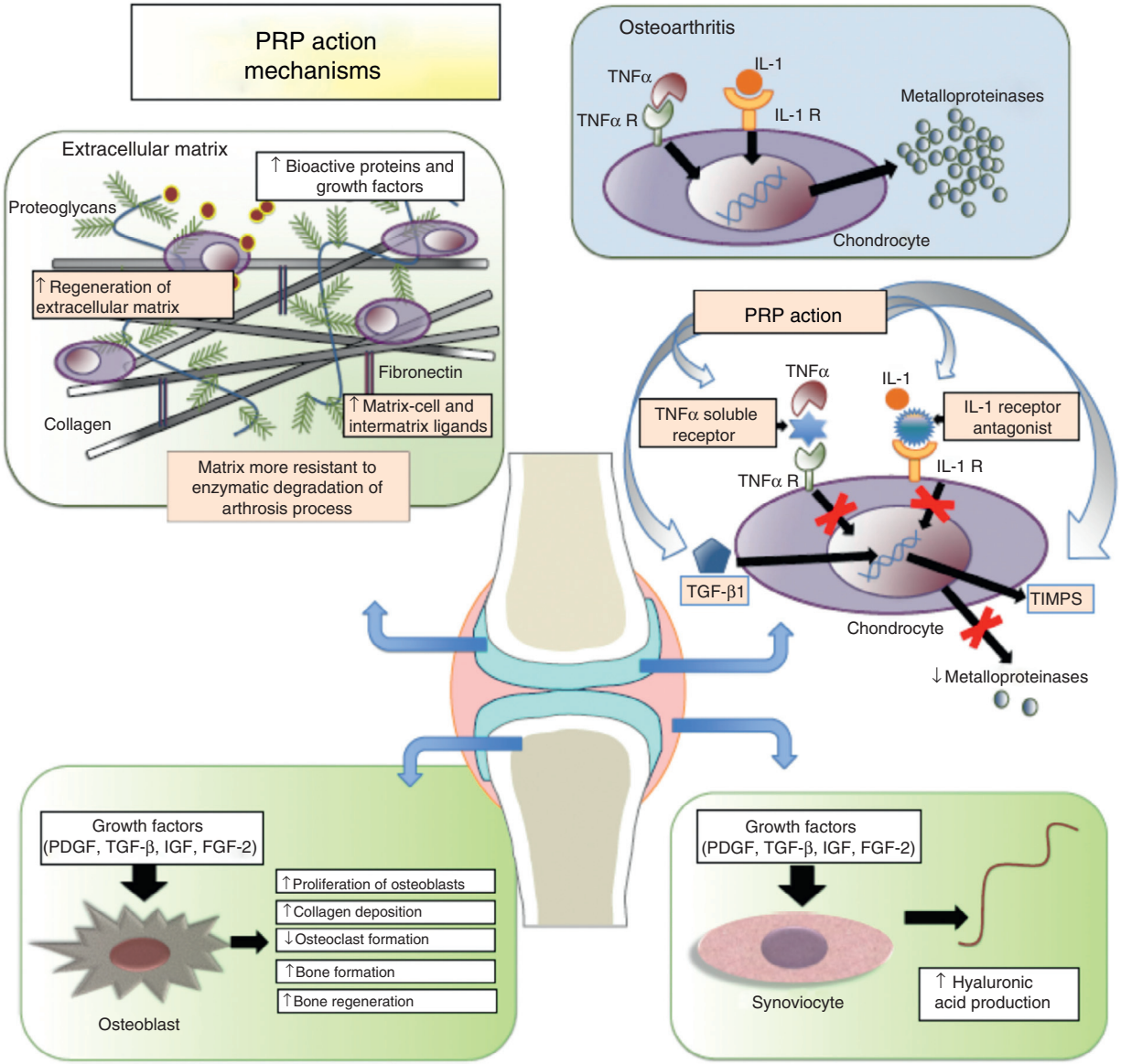

Fig. 1 – PRP action mechanisms. TNF, tumor necrosis factor α; TNFαR, tumor necrosis factor α receptor; IL-1 interleukin-1; IL-1R, interleukin-1 receptor; TGF β, transforming growth factor β; TIMP, tissue inhibitor of metalloproteinases; PDGF, platelet-derived growth factor; IGF, insulin-like growth factor; FGF-2, fibroblast growth factor-2.

Table 1 – Platelet-rich plasma for the treatment of knee osteoarthritis – prospective, randomized and controlled trials.

Study	Mean age (years)	Aspects related to PRP				Study design							Assessments	Results
		Centrifugation	Injections interval	Volume (ml)	Platelet count	Radiographica grade	Randomization/ Method	Double-blind/ SHAM procedure	Intention to treat	Treated (N)	Controls (N)	Analyzed parameters		
Sánchez 2012[25]	60.5 ± 7.9 (PRP) 58.9 ± 8.2 (HA)	Single 580 g (8 min)	3 injections Weekly (PRP and HA)	2	NS	1–3 (Ahlbäck)	Yes Patients were identified by numbers	Yes Yes	Yes	89	87 HA	WOMAC Lequesne	0 and 24 weeks	PRP reduced WOMAC by 50%. Secondary outcomes with no difference.
Vaquerizo 2013[26]	62.4 ± 6.6 (PRP) 64.8 ± 7.7 (HA)	Single 580 g (8 min)	3 Injections Weekly (PRP) Single (AH)	2	NS	2–4 (K-L)	Yes Through software	No No	Yes	48	48 HA	WOMAC Lequesne OMERACT-OARSI	0, 24 and 48 weeks	PRP better than HA at 24 and 48 weeks.
Li 2011[28]	57.6 (PRP) 58.2 (H)A	Double 2000 rpm (10 min each)	3 Injections Every 3 weeks (PRP and HA)	3.5	(819.4 ± 136,3) $\times 10^6$ ml^{-1}	1–4 (K-L)	Yes NS	NS No	Yes	15	15 HA	IKDC WOMAC Lequesne	3, 4 and 6 months	PRP e HA showed benefit. PRP showed to be better in the final evaluation at 6 months.
Spaková 2012[29]	52.8 ± 12.4 (PRP) 53.2 ± 14.5 (HA)	Triple 3200 rpm (15 min) 1500 rpm (10 min) 3200 rpm (10 min)	3 Injections Weekly (PRP e HA)	3	680 ± 132 $\times 10^6$ ml^{-1}	1–3 (K-L)	Yes NS	NS Yes	NS	60	60 HA	WOMAC NRS	3 and 6 months	PRP better than HA. Side effects (level of pain) more evident in the PRP group, which remitted in 2 days.

Table 1 – (*Continued*)

Study	Mean age (years)	Aspects related to PRP				Study design							Assessments	Results
		Centrifugation	Injections interval	Volume (ml)	Platelet count	Radiographica grade	Randomization/ Method	Double-blind/ SHAM procedure	Intention to treat	Treated (N)	Controls (N)	Analyzed parameters		
Cerza 2012[30]	66.5 ± 1.3 (PRP) 66.2 ± 10.6 (HA)	Double NS	4 Injections Weekly (PRP e HA)	5.5	NS	1–3 (K-L)	Yes NS	No No	Yes	60	60 HA	WOMAC	4, 12 and 24 weeks	PRP better than HA, regardless of grade of osteoarthritis.
Filardo, 2012[31]	55 (PRP) 58 (HA)	Double 1480 rpm (6 min) 3400 rpm (15 min)	3 Injections Weekly (PRP e HA)	5	NS	1–3 (K-L)	Yes NS	Yes Yes	Yes	55	54 HA	IKDC EQ-VAS Tegner KOOS	2, 6 and 12 months	No difference between PRP and HA. Tendency of superiority of PRP in lower grades of osteoarthritis
Patel 2013[33]	53.1 ± 11.6 (Group A) 51.6 ± 9.2 (Group B) 53.7 ± 8.2 (Group C)	Single 1500 rpm (15 min)	Group A: Single (PRP) Group B: 2 ijections, one every 3 weeks (PRP) Group C: Single (placebo)	8	31,014 $\times 10^6$ L^{-1}	1–2(Ahlbäck)	Yes Through software	Yes Yes	No	26 (Group A) 25 (Group B)	23 saline	WOMAC	6; 12 and 24 weeks	PRP superior to placebo No difference between one or two Injections

N, number of individuals; PRP, platelet-rich plasma; HA, hyaluronic acid; OA, osteoarthritis; BMI, body mass index; K-L, Kellgren-Lawrence; NE, not specified; WOMAC, Western Ontario and McMaster Universities index; OMERACT-OARSI, Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative; NRS, Numeric Rating Scale; KOOS scale, Knee injury and Osteoarthritis Outcome Score; EQ-VAS, EuroQol visual analog scale; IKDC, International Knee Documentation Committee; min, minutes; rpm, rotations per minute; g, unit of centrifugal force.

Table 2 – Platelet rich plasma for the treatment of human osteoarthritis – nonrandomized, non-controlled, cohort trials.

Studies	Type of study	Joint	Centrifugation	Treated (N)	Controls (N)	Injections (N) interval	Analyzed parameter	Assessment	Results
Say[27]	Prospective Controlled Non-randomized	Knee	Single	45	45 HA	Injection Single	KOOS VAS	0, 3 and 6 months	PRP superior to HA. Better cost-benefit of PRP
Kon[32]	Prospective Controlled Non-randomized	Knee	Double	50	50 HAAP 50 LWHA	3 injections Biweekly	IKDC EQ-VAS	2 and 6 months	PRP showed benefit; Better results in young people and lower degree of degeneration
Sánchez[34]	Retrospective	Knee	Single	30	30 HA	3 injections Weekly	WOMAC	8 weeks	PRP superior to HA
Kon[35]	Prospective	Knee	Double	100	None	3 injections Every 3 weeks	IKDC EQ-VAS	2, 6 and 12 months	PRP showed benefit; Better results in young people and lower degree of degeneration
Filardo[36]	Prospective	Knee	Double	91	None	3 injections Every 3 weeks	IKDC EQ-VAS	2, 6, 12 and 24 months	PRP showed benefit; Decrease in response after 12 months, but higher than the initial scores
Sampson[37]	Prospective	Knee	Single	14	None	3 injections Monthly	Brittberg- Peterson VAS KOOS Thickness	2, 5, 11, 18 and 52 weeks	PRP showed benefit; No increase in thickness of cartilage
Ana Wang-Saegusa[38]	Prospective	Knee	Single	261	None	3 injections Biweekly	VAS SF-36 WOMAC Lequesne	6 months	PRP showed benefit
Napolitano[39]	Prospective	Knee	Single	27	None	3 injections Weekly	WOMAC NRS	7 days and 6 months	PRP showed benefit
Sanchez[40]	Prospective	Hip	Single	40	None	3 injections Weekly	WOMAC VAS HHS	6–7 weeks and 6 months	PRP showed benefit
Jang[41]	Prospective	Knee	Double	65	None	Injections single	WOMAC	1, 3,6 9 and 12 months	PRP showed benefit
Battaglia[42]	Prospective Pilot study	Hip	Not specified	20	None	3 injections Biweekly	HHS WOMAC	3, 6 and 12 months	PRP showed benefit; Decrease in response after 3 months, but higher than the initial scores. Better results in young people.

Table 2 – (*Continued*)

Studies	Type of study	Joint	Centrifugation	Treated (N)	Controls (N)	Injections (N) interval	Analyzed parameter	Assessment	Results
Halpern[43]	Prospective Pilot Study	Knee	Not specified	17	None	Injections Single	VAS WOMAC MRI de knee	1, 3, 6 and 12 months	PRP showed benefit There was no reduction in cartilage thickness in MRI
Gobbi[44]	Prospective	Knee	Single	50	None	2 injections Monthly	KOOS, VAS Tegner IKDC Marx scores	0, 6 and 12 months	PRP showed benefit; There was no difference between patients that were previously approached and patients with no previous intervention.
Hart[45]	Prospective	Knee	Double	55	None	6 injections Weekly. After maintenance with 3 quarterly injections	Lysholm Tegner IKDC Cincinnati Knee MRI	0 and 12 months	PRP showed benefit There was no reduction in cartilage thickness in MRI
Filardo[46]	Prospective	Knee	Double	72 PRGF 72 PRP	None	3 injections Each 3 weeks	IKDC EQ-VAS Tegner scores	2, 6 and 12 months	Similar benefit between methods; Double centrifugation shows more side effects
Dhollander[47]	Prospective	Knee	Double	5	None	Injections Single	VAS KOOS Tegner Score MOCART	0, 12 and 24 months	Procedure leads to clinical improvement; No response in the analysis of cartilage in MRI

N, number of individuals; WOMAC, Western Ontario and McMaster Universities index; NRS, Numeric Rating Scale; KOOS scale, Knee injury and Osteoarthritis Outcome Score; EQ-VAS, EuroQol visual analog scale; VAS, visual-analog scale; IKDC, International Knee Documentation Committee; SF-36, Short Form (36) Health Survey; HHS, Harris Hip Score; AOFAS, American Orthopaedic Foot and Ankle Society; AHFS, Ankle-Hindfoot Scale; MOCART, Magnetic Resonance Observation of Cartilage Repair Tissue; PRP, platelet-rich plasma; HA, hyaluronic acid; LWHA, low molecular weight hyaluronic acid; HWHA, High molecular weight hyaluronic acid; SF, saline; MRI, resonance magnetic imaging.

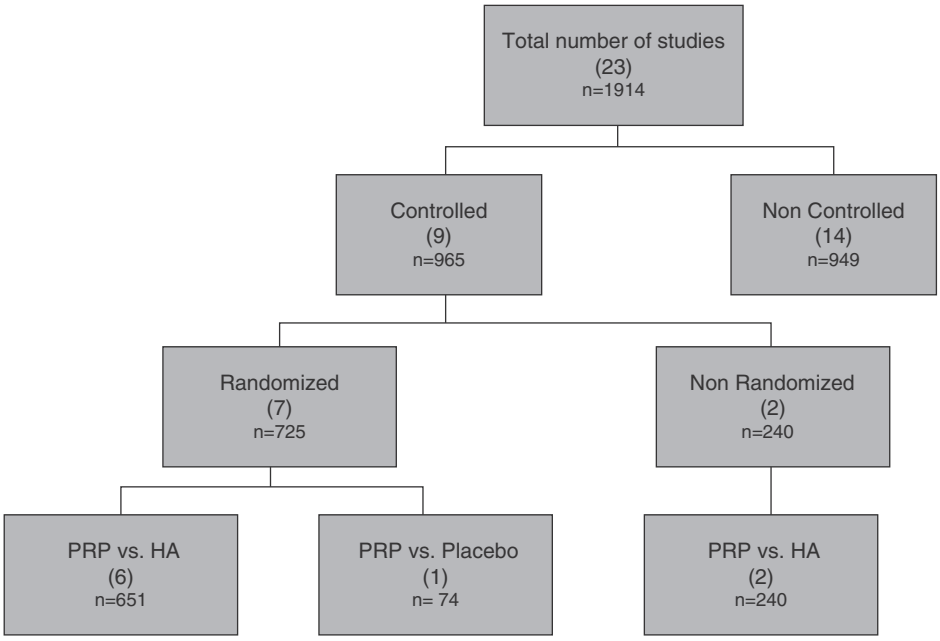

Fig. 2 – Platelet-rich plasma (PRP) in the treatment of human osteoarthritis. PRP, platelet-rich plasma; HA, hyaluronic acid; n, total number of patients evaluated in all studies; in brackets, number of studies.

contrast to the path of thrombin, which induces an immediate release of growth factors.[12] Regardless of the activator used, it is recommended that the component is applied immediately after platelet activation.[13]

Recently some authors[14] developed a classification of the different types of PRP, according to the platelet count, the activator used, and the presence of white blood cells. This system was called PAW (Platelets, Activation and White Blood Cells). The classification, however, is complex and its practical significance has not been established yet.

In general, there are two basic types of platelet-rich plasma compounds: the platelet-rich plasma, obtained by double centrifugation of blood together with an anticoagulant (citrate in general); and platelet rich in growth factors (PRGF) obtained through a single centrifugation, also with an anticoagulant agent. However, there is no standardization for its obtainment, and each study has its own method.

Clinical applications of platelet-rich plasma

PRP has been utilized in various clinical situations in order to regenerate tissues. It is currently used in the treatment of soft tissue lesions, such as repair of chronic ulcers,[15] tendinopathies and fasciitis.[16] Its use in dental procedures, such as periodontal regeneration in dental implants,[17] bone regeneration in grafts[18] and fractures, is also noteworthy.[19]

The action of the PRP began to be studied in osteoarthritis in order to increase the anabolic activity of chondrocytes. The platelet-rich plasma is capable of inducing proliferation of mesenchymal cells, as demonstrated in vitro by Huang et al.[20] and Kilian et al.[21] PRP can regulate the action of metalloproteinases and activate mechanisms of matrix regenerators such as the synthesis of collagen and proteoglycans.[22] Nakagawa et al.[23] demonstrated the in vitro efficacy of PRP stimulating chondrocyte proliferation and synthesis of collagen. Mishra et al.[24] showed that the platelet-rich plasma can lead to proliferation of fibroblasts in vitro, as well as stimulate the expression of genes responsible for the chondrogenic and osteogenic differentiation.

PRP controlled trials versus hyaluronic acid or placebo

Sánchez et al.[25] in 2012, in a double-blind, randomized trial, compared the PRP and hyaluronic acid in 176 patients with knee OA. The scores used for the analysis were WOMAC (Western Ontario McMasters Universities Osteoarthritis Index) and Lequesne. Treatment with PRP reduced by 50% the WOMAC index (primary outcome) and showed a trend of improvement in secondary outcomes, however with no statistical significance. The limitations mentioned by the author were no comparison between the level of physical activity before and after treatment, the short follow-up, the lack of a placebo group and the exclusion of cases considered to be severe on radiographic examination.

Vaquerizo et al.[26] published in 2013 a study with similar design to the study by Sanchez, where 96 patients were evaluated for 48 weeks. The PRP showed better responses in all parameters analyzed, both in 24 and in 48 weeks, including the percentage of responders of OMERACT-OARSI (Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative).

Another study published in 2013 conducted by Say et al.,[27] compared a single PRP injection with three hyaluronic acid (HA) injections in individuals with knee osteoarthritis. Clinical evaluation was made by KOOS (Knee injury and Osteoarthritis Outcome Score) and VAS (Visual Analog Scale) scores.

The study showed clinical improvement with both treatments after three and six months of the procedures, however, with a better response in patients treated with PRP. Furthermore, the cost of treatment was lower in the group treated with PRP. The limitations mentioned by the author were no patients randomization and the exclusive use of clinical parameters in the results analysis.

Li et al.[28] in 2011, conducted a randomized study comparing the use of PRP and HA in 30 patients with knee osteoarthritis. Both groups showed improvement in WOMAC and IKDC indicators (International Knee Documentation Committee), maintaining similar efficacy up to the fourth month of follow-up and superiority of PRP in the sixth month. The short follow-up period does not allow the evaluation of the duration of the response, but points to the trend of a more sustained response of platelet-rich plasma.

Spaková et al.[29] in 2012, in a randomized study, followed 120 patients for six months with knee osteoarthritis: 60 received PRP and 60 HA. The group receiving PRP presented better improvement compared to HA when assessed by WOMAC and the NRS (Numerical Rating Scale).

Cerza et al.[30] compared PRP and HA in 120 patients with knee osteoarthritis followed for 24 weeks. The assessment by the WOMAC showed better responses with PRP, regardless of the degree of joint damage (assessed by the Kellgren-Lawrence classification), contrasting with HA which was ineffective in treating osteoarthritis grade III.

In 2012, Filardo et al.[31] also compared PRP with HA in 109 patients with osteoarthritis of the knee through a randomized double-blind study. The patients were evaluated by IKDC, EQ-VAS (visual analog scale EuroQol), Tegner and KOOS scores over a period of 12 months. Both groups showed clinical improvement, with no difference between them. When comparing the groups regarding the degree of osteoarthritis in the scale of Kellgren-Lawrence, only a trend toward better response from PRP in milder degree (degrees $\leq$ II) was found.

Kon et al.[32] in 2011 treated three groups of 50 patients with knee osteoarthritis who received PRP, high and low molecular weight HA respectively. A random distribution of patients was not carried out among the three groups, since the treatment performed was dependent on the center where the injections were performed, with each institution being responsible for the application of a single substance. Clinical response measured by the IKDC and EQ-VAS scores was higher in patients that received PRP injections compared to HA. The low molecular weight HA performed better than the high molecular weight; however, still lower than the response obtained by PRP.

Patel et al.[33] in 2013 selected 74 patients with knee osteoarthritis and divided them randomly into three groups: those that received a single PRP injection ($n = 26$); those who received two PRP injections 3-weeks apart ($n = 25$) and the third group ($n = 23$) who received a single placebo injection of normal saline. The groups were assessed by WOMAC score by an observer blinded to treatment status for 24 weeks. There was a significant improvement in both groups receiving intervention, with a tendency to decrease in the last assessment at six months. Regarding the number of injections, there was no increase in response to treatment with an additional application.

Non-controlled studies and retrospective cohort

In a retrospective cohort study, Sánchez et al.[34] evaluated two groups of 30 patients with knee OA who were treated with PRP and HA infiltrations, respectively. Patients were evaluated by WOMAC (pain domain as the primary outcome), comparing baseline data with those obtained after five weeks of injections. There was a better response of patients treated with PRP compared to HA. As this was a retrospective study and based on data reviewed in the medical records, the lack of some information, such as mean disease duration and use of analgesics, may have jeopardized the analysis of the data.

Kon et al.[35] conducted a prospective study in 2010 in which 100 patients with knee osteoarthritis were treated with PRP and evaluated at six and twelve months through IKDC and EQ-VAS scales. There was a favorable response in the first six months, not sustained after twelve months, despite remaining significantly above the initial scores. Another study by the same group, with similar methods, published in 2010 by Filardo et al.[36] demonstrated a positive response in the first twelve months, which was not sustained until the end of the second year of follow-up.

Sampson et al.[37] in 2010 evaluated the use of PRP in knee OA in 14 patients using the KOOS and Brittberg-Peterson VAS scores, and followed them for 52 weeks. There was a significant clinical improvement in patients treated with PRP.

Ana Wang-Saegusa et al.[38] conducted a study with 216 patients with knee OA that received PRP injection, assessed by VAS scores, SF-36 (Short Form 36 Health Survey), WOMAC and Lequesne for six months. All indexes showed improvement in clinical parameters evaluated.

Napolitano et al.[39] injected PRP in 27 patients with degenerative diseases of the knee, divided into two groups: those with osteoarthritis and those with cartilage diseases (not specified). Using the WOMAC and NRS questionnaires, there was an early and sustained response for six months follow up in both groups. As limitations, the author does not specify the selection criteria and the study lacks statistical analysis, which prevents the interpretation of results.

Sanchez et al.[40] studied the effect of PRP injection in 40 patients with unilateral hip OA. The indices used for evaluation were WOMAC, VAS and HHS (Harris Hip Score). There was a positive response to PRP and the patients who did not respond had more severe osteoarthritis on radiographic examination.

In 2012, Jang et al.[41] studied the effect of a single application of PRP in 65 patients with knee osteoarthritis. The patients showed a favorable response in the VAS for pain, and IKDC up to six months after treatment, which was not sustained after one year of the injection.

In a pilot study, Battaglia et al.[42] checked the effect of PRP in 20 patients with hip OA, assessed by HHS and WOMAC for 12 months. There was a significant improvement between the first and third months, with a progressive decrease in the response thereafter. After one year, the indices remained above baseline.

In another pilot study conducted by Halpern et al.,[43] the responses to a single PRP injection in 17 patients with knee osteoarthritis were assessed by VAS and WOMAC. Both pain

and functional indices were significantly reduced at six and twelve months compared to baseline.

Use of PRP in previous surgical interventions

Gobbi et al.[44] in 2012 studied the PRP application on the knee of 50 individuals, subdividing them also in patients who had undergone surgery in this joint and others with no prior approaches. Surgical procedures considered in this study were the arthroscopic debridement and microfractures. The instruments used were KOOS, VAS, Tegner, IKDC and Marx. A clinical improvement was observed in the patients after injection of PRP regarding pain, function and return to usual activities, regardless of surgery performed.

In 2013, Hart et al.[45] performed a sequence of nine PRP applications after undergoing arthroscopy in 50 patients with knee OA. The assessment tools were Lyshcolm, Tegner, IKDC and Cincinnati scores. There was an improvement of the indices after six months of treatment, which was not maintained after 12 months.

PRP obtained from single versus double centrifugation

Regarding the technique for obtaining platelet-rich plasma, Filardo et al.[46] in 2011 conducted a study with 144 patients with knee osteoarthritis, comparing the acquisition of platelets concentrate by single (plasma rich in growth factors – PRGF) or double centrifugation (PRP). It was found that the benefit was similar in both groups using the IKDC, EQ VAS and Tegner scores. However, adverse events (especially local arthritis) occurred more often in the PRP obtained by double centrifugation, due to higher leukocyte concentration produced by this method.

PRP efficacy evaluation through imaging methods

There is no consistent evidence regarding the effectiveness of PRP measured by imaging methods. Some non-controlled series point to a possible stabilization of cartilage loss.

Sampson et al.[37] in 2010, in addition to clinical response assessment previously described, performed a joint ultrasound to measure the articular cartilage thickness one year after PRP injection in 14 patients studied. The results showed no benefit in increasing the thickness of the articular cartilage, which does not mean a negative result, since the method sensitivity is low for the detection of small changes.

Dhollander et al.[47] in 2011 treated five patients with chondral lesions of the patella with cartilage debridement, followed by placement of a collagen membrane and PRP. The patients were evaluated by magnetic resonance imaging (MRI) before the procedure and after 12 and 24 months. Benefits were observed in clinical scores (VAS, KOOS subscale), except for the Tegner score. However, there was no difference in MOCART score (Magnetic Resonance Observation of Cartilage Tissue Repair), and only stability of the lesions took place.

Hart et al.[45] in 2013 evaluated PRP response in 50 patients with knee OA by MRI before and one year after the injection. The degree of cartilage damage was measured by modified Outerbridge Grading Scale. Cartilage thickness remained unchanged in 94% of cases and a slight increase (less than 1 mm) was recorded in three cases (6%). There was no control group.

In a pilot study, Halpern et al.[43] also evaluated, in a non-controlled manner, the articular cartilage of 17 patients undergoing PRP injection, using knee MRI. There was no reduction in cartilage thickness during the year analyzed. Considering that there is an annual fall of 4% to 6% in the volume of articular cartilage in osteoarthritis,[47] the authors conclude that PRP can have a chondroprotective action.

Side effects

Side effects related to injection of platelet-rich plasma are considered uncommon and, when present, usually manifest in a mild and self-limited form.

Local symptoms are the most common adverse events, ranging from pain at the injection site to signs of arthritis. Filardo et al.[46] in 2011 showed that the way of obtainment of PRP influences the degree of intra-articular inflammatory response, with this effect being attributed to the number of leukocytes present in the infiltrate. Allergic reactions are possible but rare effects since it is an autologous product. The most feared complication is the intra-articular infection that can be prevented by performing the aseptic procedure.

In the studies selected from this review, the most frequently reported adverse events were arthralgia in the injected joint, whose intensity varied from mild to moderate, and its resolution occurred in days, extending to weeks in the most severe cases. Dhollander et al.[47] reported a case of hypertrophy of the regenerated cartilage tissue diagnosed by an arthroscopy performed because of the patient's symptoms, and was resolved by local debridement. Sánchez et al.[40] reported a case of rash after the injection, the resolution of which was spontaneous, with no need for specific treatment. Filardo et al.[31] demonstrated that higher post-injection pain was noted in those patients injected with PRP compared to HA. Systemic symptoms and infections were not reported in the analyzed studies.

Final considerations

In this review seven randomized controlled trials were found, which showed a great methodological diversity, both in design and in procedure for obtainment and injection of PRP. Of these, only one[33] used the placebo comparison. The other control groups received intra-articular hyaluronic acid, although there is no consensus in the literature about its effectiveness in the treatment of osteoarthritis.[48] Only one of the controlled studies[25] defined the degree of pain in the sample selection, which is a significant methodology gap, considering the frequent clinical-imaging dissociation in osteoarthritis. In addition, some studies included patients with minimal and maximal radiographic grade (grades 1 and 4 Kellgren-Lawrence respectively). However, level 1 is not completely specific to osteoarthritis, and grade 4 corresponds to the terminal illness. In 3 studies there was no concern with the correct blinding mode, which would only be possible with the

adoption of an appropriate SHAM procedure. There were differences or lack of data in the range and number of injections, administered volume and platelet concentration. The assessment tools also varied, and only one study[26] used OMERACT. There are numerous other differences among the studies, as shown in Table 1. This large variability was also recently appointed in an interesting review,[3] with the conclusion that more controlled studies about the subject are necessary.

Despite the methodological heterogeneity and gaps in the designs, Chang et al.,[49] in 2013, published a meta-analysis on the use of PRP in patients with knee osteoarthritis. The quality of the work was measured by Jadad score, with the selection of 16 papers. The analysis was based on the choice of only one of the scores used in each article, establishing the following priority: IKDC, KOOS and WOMAC. The results showed higher efficacy and durability of treatment with PRP comparison with the control group. The author exposes the limitations of the meta-analysis, highlighting the lack of standardization in methods for PRP obtainment, the different scores used in the work, resulting in a heterogeneous data analysis; and the inclusion of patients with Kellgren-Lawrence scale of zero in some studies.

In the same year a systematic review by Khoshbin et al. was published.[50] Their assessment was based in scales that consider randomization, blinding, results, measurements, inclusion and exclusion criteria, description of treatment and statistical analysis. In the end, six studies were selected. A benefit of PRP was observed compared to control groups (hyaluronic acid and saline) in WOMAC score in four studies and IKDC in three studies, but no benefits in other criteria such as visual scale of pain and patient satisfaction scores. Adverse events were more frequent in the group receiving PRP.

We conclude that, based on randomized controlled studies, PRP seems to produce improvement in pain and joint function in knee osteoarthritis, both compared to placebo and hyaluronic acid. The response can be sustained for a period of up to two years, and seems to be more evident in milder cases of OA. There is no consistent evidence of the action of PRP on the cartilage measured by imaging.

Although PRP seems to be an effective option, caution is required in interpreting the results. In most studies the sample is small, the period of observation short and OA characteristics have not been fully described. The comparison of the results is complicated by the lack of standardization in the collection and application of PRP regimen.

Thus, more randomized, prospective studies with appropriate design are needed to confirm the actual PRP role in osteoarthritis.

Conflicts of interest

The authors declare no conflicts of interest.

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