

# Effects of Platelet Rich Plasma on Pain in Adult and Elderly Patients with Knee Osteoarthritis: a Systematic Review

## Efeitos do Plasma Rico em Plaquetas na Dor em Pacientes Adultos e Idosos com Osteoartrite de Joelho: uma Revisão Sistemática

Caroline Hammerschmitt Eduardo<sup>a</sup>; José Fernando Baumgartner Maciel<sup>a</sup>; Camila Amaral Coracini<sup>a</sup>; Alberito Rodrigo de Carvalho<sup>a</sup>; Gladson Ricardo Flor Bertolini<sup>\*a</sup>

<sup>a</sup>Universidade Estadual do Oeste do Paraná, Stricto Sensu Graduate Program in Bioscience and Health. PR, Brazil.

\*E-mail: gladsonricardo@gmail.com

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### Abstract

Platelet-rich plasma (PRP) has been shown to be a promising treatment for osteoarthritis (OA) of the knee in adult and elderly patients, acting in the repair of joint tissues damaged by OA - a degenerative disease that mainly affects articular cartilage. This process of degradation of joint components leads to an increase in the level of pain in these patients. Therefore, this study aimed to evaluate the effectiveness of intra-articular injection of PRP in knee OA in relation to pain. For this systematic review, five databases were used: PubMed, Lilacs, PEDro, Cochrane Library and Google Scholar. Search strategies included the keywords Osteoarthritis, Knee, Platelet-rich plasma, and Pain. In order to be included in this review, the studies had to be of the randomized clinical trial type; use as a sample people between 18 and 80 years old diagnosed with knee OA; use intra-articular PRP treatment compared to placebo; and assess pain intensity. After completion of the selection phase, 5 studies were included in this review. These showed positive results in reducing pain in patients with lower-degeneration OA, and less effective in advanced OA. Furthermore, few side effects were reported after the application of PRP. Therefore, the intra-articular application of PRP can be an important tool for the treatment of knee OA, as it is an effective therapy in decreasing pain levels in patients affected by this pathology.

**Keywords:** Orthopedics. Platelet-Derived Growth Factor. Pain Measurement. Knee Joint.

### Resumo

*O plasma rico em plaquetas (PRP) tem se mostrado um tratamento promissor na osteoartrite (OA) de joelho de pacientes adultos e idosos, atuando no reparo dos tecidos articulares lesados pela OA - doença degenerativa que afeta principalmente a cartilagem articular. Esse processo de degradação dos componentes articulares leva ao aumento do nível de dor nesses pacientes. Sendo assim, este estudo objetivou avaliar a eficácia da injeção intra-articular de PRP na AO de joelho em relação a dor. Para esta revisão sistemática, cinco bases de dados foram utilizadas: PubMed, LILACS, PEDro, Cochrane Library e Google Scholar. As estratégias de busca incluíram as palavras-chave Osteoarthritis, Knee, Platelet-rich plasma e Pain. Para serem incluídos nesta revisão, os estudos deveriam ser do tipo ensaio clínico randomizado; utilizar como amostra pessoas entre 18 e 80 anos diagnosticadas com AO de joelho; utilizar o tratamento com PRP intra-articular comparado ao placebo; e avaliar a intensidade da dor. Após o término da fase de seleção, 5 estudos foram incluídos nesta revisão. Estes apresentaram resultados positivos na redução da dor em pacientes com OA de menor grau de degeneração, e menor efetividade na OA avançada. Ademais, poucos efeitos colaterais foram relatados após a aplicação do PRP. Portanto, a aplicação intra-articular do PRP pode ser um importante instrumento para o tratamento da OA de joelhos, visto que é uma terapia eficaz na diminuição dos níveis dor dos pacientes acometidos por tal patologia.*

**Palavras-chave:** Ortopedia. Fator de Crescimento Derivado de Plaquetas. Medição da Dor. Articulação do Joelho.

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### 1 Introduction

Osteoarthritis (OA), also known as osteoarthrosis<sup>1</sup>, is an orthopedic disease that affects 4.14% of the Brazilian population, affecting mainly adults and the elderly<sup>2</sup>. Because it is a progressive degenerative disease, it mainly damages the articular tissue (in the case of knee OA, the tibial and patellofemoral joints), as well as the adjacent soft tissues<sup>3</sup>. Its clinical manifestations include joint pain, sensitivity alteration, stiffness, joint edema, movement restriction and joint deformities<sup>4</sup>.

The most common form of treatment for AO is drug therapy, which, despite promoting pain relief and inflammation, induces significant side effects, especially in

the gastrointestinal tract<sup>5</sup>. Previous studies have demonstrated the need for research that seeks strategies that aim to improve the efficacy of treatments for AO<sup>1,6-8</sup>. Thus, studies that address other forms of therapy with fewer side effects are necessary.

One of the therapies that proved promising for treatment of OA is the application of platelet-rich plasma (PRP). It consists of a concentrate of multifunctional blood platelets, which can be applied through intra-articular injection to reduce clinical manifestations and damage caused by OA, in addition to speeding up the recovery process of the damaged joint<sup>9</sup>. Studies that used PRP in the treatment of knee OA demonstrate that, after the application, there was repair of the injured articular tissues and reduction of inflammation and pain, presenting only mild side effects after injection, such as

pain and limitations in joint function<sup>8,10</sup>.

One of the forms of PRP action is to reduce the levels of proinflammatory cytokines (interleukin 1 and tumor necrosis factor- $\alpha$ ) that have exacerbated action in AO. This generates an increase in the expression of metalloproteinases (MMP) and a decrease in the synthesis of macromolecules, such as type II collagen and aggrecan proteoglycan. Since these macromolecules are responsible for maintaining the joint structure, reducing the levels of cytokines in the synovial fluid improves not only the inflammatory signs, but also the repair of joint tissues – advocating the use of PRP therapy in OA<sup>4,11</sup>.

In general, PRP has been evolving as a promising solution for several orthopedic conditions, with favorable effects on pain and joint function<sup>1</sup>. However, although there are many studies on PRP, the number of randomized clinical trials and placebo-controlled studies is limited. In addition, no consensus was reached on the efficacy and application of this treatment method in knee OA<sup>12</sup>. Thus, the present study aimed to evaluate the efficacy of intra-articular PRP injection in knee OA in relation to pain when compared to saline injection.

## 2 Material and Methods

The following databases were used to carry out this systematic review: PubMed, Latin American and Caribbean Health Science literature (LILACS), Physiotherapy Evidence Database (Pedro), Cochrane Library and Google Scholar, as gray literature. Search strategies were elaborated using the keywords: Osteoarthritis, Knee, plasma platelet-rich and pain; with the definitive search being carried out on June 12th, 2021.

Studies published in any language and year were considered. The eligibility criteria were elaborated using PICO strategy – Population, Intervention, Comparison and Results. Therefore, to be included in this review, the studies should be: Randomized Clinical Trial (RCT); use as a sample individuals diagnosed with knee OA, aged between 18 and 80 years; use PRP as a single intra-articular therapy; use as a comparative study a placebo group submitted to saline injection; and evaluate pain intensity. Studies that did not meet all of these criteria were excluded.

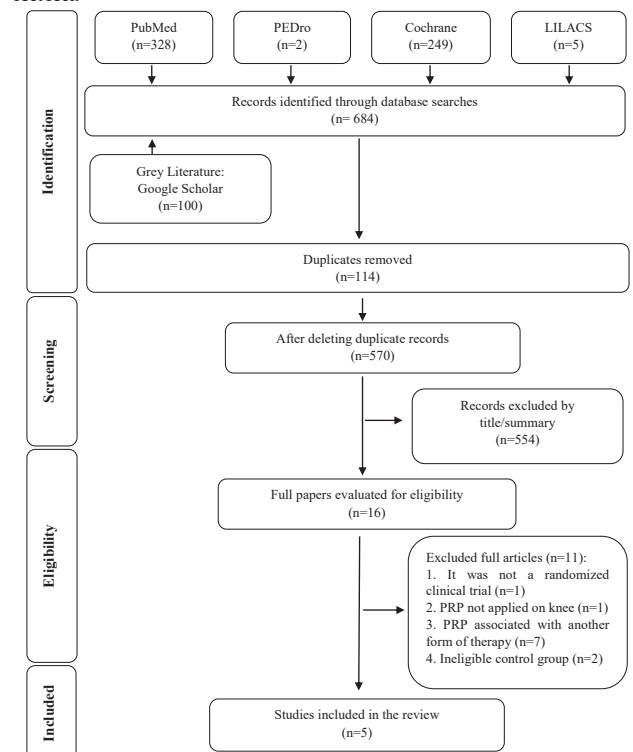
Data analysis was performed as follows: in the first stage, the final search was performed with the keywords in the databases mentioned above. Then, duplicate articles were removed and two independent evaluators selected studies based on titles and abstracts to identify those that met the selection criteria. In the sequence, the studies were carefully read in full to identify those that fit within all the inclusion criteria proposed by the present study. In case of divergence among the reviewers, a third reviewer was requested to perform the analysis and determine its inclusion or exclusion. Finally, the data of the articles included were extracted by tools elaborated by the reviewers themselves, and the methodological quality of the clinical trials was evaluated using the PEDro scale. This consists of 11 criteria, and only 10 of them receive scores. Each criterion is scored according to its

presence or absence in the study, and the final score is obtained by the sum of all the positive responses.

## 3 Results and Discussion

After the definitive search was performed in the databases, 648 studies were found. Of these, 144 was removed because they were duplicated, and another 554 was excluded after reading the title and summary. Sixteen studies were read in full and 5 were included in the present review (Figure 1). Among those included, the sample size ranged from 30 to 148 knees with OA, the age of the participants ranged from 27 to 84 years, and most of them were female (67.92 %). The affected joints varied between uni or bilateral, and OA degrees varied from initial to advanced.

**Figure 1** - Flow chart of the literature search and the selection criteria



Source: Based on the PRISMA<sup>13</sup> model.

Two articles evaluated pain through *Western Ontario e McMaster Universities Osteoarthritis* (WOMAC) questionnaire, two others evaluated through the WOMAC and *Visual Analogue scale* (VAS), and one evaluated through the VAS and *the International Knee Documentation Committee* (IKDC) questionnaire. Four studies followed up until the 6th month after the PRP was applied, and one study followed up for 12 months. All of them presented positive results in pain reduction, with few side effects after the application of PRP. Regarding the methodological quality of the studies evaluated through the PEDro scale, scores ranged from 07 to 08 points, being considered articles of good methodological quality<sup>14</sup>. The specific characteristics of each study included were described in Tables 1 and 2.

**Table 1 - Summary of the studies included**

Author	Methods					Results
	Sample / Pathology	Interventions	Comparisons	Pain-related outcomes	Follow-up time	
Ghai et al. <sup>15</sup>	20 patients, of both sexes, aged between 30-65 years  Bilateral knee OA (ASA I and II classification) for more than 4 months, without significant deformity (Kellgren radiological classification – Lawrence grade I and II)	PRP Single application performed with ultrasound 6ml of concentrated platelet solution ( 2ml CaCl <sub>2</sub> ) were injected into the suprapatellar pouch, via a superolateral approach with an 18G needle Average amount of platelets injected per knee: 238.56×10 <sup>7</sup> /μL The knees were immobilized for 10 minutes after injection Acetaminophen (500 mg) and Tramadol were recommended after intervention	Control Group (CON): received saline solution, n=20 knees  Group treated with PRP (PRP): received platelet-rich plasma, n=20 knees	Pain scale (VAS)  Osteoarthritis Questionnaire (WOMAC)	After 2 weeks After 6 weeks After 3 months After 6 months	Reduction between PRP <i>versus</i> CON at all times  Reduction between PRP <i>versus</i> CON at all times
Görmeli et al. <sup>16</sup>	162 patients, of both sexes, aged between 27-84 years  OA for more than 4 months, being subdivided into initial OA (Kellgren – Lawrence grade 0 with cartilage degeneration or grade I – III) and advanced OA (Kellgren – Lawrence grade IV)	PRP 5ml of concentrated platelet solution ( + 1ml CaCl <sub>2</sub> ) were injected into the suprapatellar pouch, via a superolateral approach with an 22G needle Average quantity of injected platelets: ? The knees were immobilized for 10 minutes after injection Cryotherapy and paracetamol were recommended after intervention The 3 injections were administered every 7 days in all groups  Hyaluronic acid 2ml of solution was prepared from 30mg of high molecular weight hyaluronic acid It was injected in the suprapatellar pouch, via a superolateral approach with a 22G needle 3 injections were administered every 7 days in all groups	Control Group (CON): received 3 saline injections, n=40 Group treated with hyaluronic acid (AH): received 3 injections of hyaluronic acid, n=39 Group treated with 1 PRP dose (PRP1): received 1 PRP injection and 2 saline injections, n=44 Group treated with 3 PRP doses (PRP3): received 3 PRP injections, n=39 Each group was divided into 2 subgroups (initial OA and advanced OA)	Pain scale (EQ-VAS)  Knee reported pain Questionnaire (IKDC)	After 6 weeks After 3 months After 6 months	Reduction between groups treated <i>versus</i> CON (initial and advanced OA); reduction between PRP3 <i>versus</i> PRP1 and AH (initial OA); SDE between PRP1 and AH (initial OA); SDE between groups treated (advanced OA) - at all times for all outcomes
Patel et al. <sup>17</sup>	78 patients, of both sexes, aged between 33-80 years  Initial bilateral OA, diagnosed by the criteria of the American College of Rheumatology, without significant deformity (Ahlback Grade I and II radiological classification)	PRP 6ml of concentrated platelet solution ( 2ml CaCl <sub>2</sub> ) were injected into the suprapatellar pouch, via a superolateral approach with an 18G needle Average quantity of injected platelets: 238.56×10 <sup>7</sup> /μL The knees were immobilized for 10 minutes after injection Paracetamol was recommended after intervention The 2 injections were administered, with an interval of 3 weeks between them	Control Group (CON): received 1 saline injection, n=46 knees  Group treated with 1 PRP injection (PRP1): n=52 knees  Group treated with 2 PRP injections (PRP2): n=50 knees	Pain scale (VAS)  Osteoarthritis Questionnaire (WOMAC)	After 6 weeks After 3 months After 6 months	SDE between groups (at all times)  Reduction between PRP1 and PRP2 <i>versus</i> CON at all times
Smith <sup>18</sup>	30 patients, of both sexes, aged between 30-80 years  OA for more than 6 weeks, with moderate pain, without significant deformity (Kellgren radiological classification – Lawrence grade II and III)	PRP 3-8mL of concentrated platelet solution were injected into the suprapatellar pocket, via a superolateral approach with an 18G needle Average amount of platelets injected per knee: ? Paracetamol was recommended post intervention 3 injections were administered in the 1 week period	Control Group (CON): received saline solution, n=15  Group treated with PRP (PRP): received platelet-rich plasma, n=15	Osteoarthritis Questionnaire (WOMAC)	After 1 week After 2 weeks After 2 months After 3 months After 6 months After 12 months	Reduction between PRP <i>versus</i> CON from 2 weeks to 12 months

Author	Methods					Results
	Sample / Pathology	Interventions	Comparisons	Pain-related outcomes	Follow-up time	
Wu et al. <sup>19</sup>	20 patients, of both sexes, aged between 50-75 years  Bilateral OA for more than 6 months, with moderate pain (VAS ≥ 4), without significant deformity (Ahlback Grade I and II radiological classification)	PRP - Single application of 4ml of concentrated platelet solution was injected into the suprapatellar pouch, via a superolateral approach Average amount of platelets injected per knee: ? Paracetamol was recommended post intervention	Control Group (CON): received saline solution, n=20 knees  Group treated with PRP (PRP): received platelet-rich plasma, n=20 knees	Osteoarthritis Questionnaire (WOMAC)	After 2 weeks - After 1 month After 3 months After 6 months	Reduction between PRP versus CON at all times

Acronyms: EQ-VAS= EuroQol *Visual Analogue Scale*; IKDC = International Knee Documentation Committee; OA: Osteoarthritis; PRP = platelet-rich plasma; SDE = no statistical difference; VAS = *Visual Analogue scale*; WOMAC = Western Ontario and McMaster Universities Osteoarthritis. Source: Research data.

**Table 2** - Presentation of PEDro scale, according to the study and the study country of origin

Author	Country	PEDro scale
Ghai et al. <sup>15</sup>	Brazil	8
Görmeli et al. <sup>16</sup>	Turkey	7
Patel et al. <sup>17</sup>	India	7
Smith <sup>18</sup>	USA	8
Wu et al. <sup>19</sup>	Taiwan	8

Source: research data

The results of this systematic review address the efficacy of platelet-rich plasma compared to saline solution in the treatment of pain in knee osteoarthritis. Montañez-Heredia et al.<sup>20</sup> in their study show that the increasing evidence highlighted the efficacy of intra-articular injection with PRP, presenting promising clinical results.

This efficacy results from when PRP contacts the knee, releasing a group of biologically active proteins that bind to its cellular target, promoting cell recruitment, development and morphogenesis, and also regulating inflammation<sup>21</sup>. Since inflammatory cytokines have a critical role in OA induction and development, and PRP contains highly concentrated platelets and high levels of cell growth factors, after therapy there is promotion of proliferation and differentiation of synovial cells, recovering the cartilage morphology<sup>4</sup>.

To Aurégan et al.<sup>22</sup>, the results vary according to the type of PRP, as the autologous plasma conditioned in one study showed that this type of plasma contained significantly less platelets and growth factors than other PRPs. According to Elik et al.<sup>12</sup>, due to the remarkable results obtained in animal or in vitro studies, the number of clinical studies evaluating the various types of PRPs in musculoskeletal pathologies has been growing in recent years, and in studies involving osteoarthritis, a form of evaluation among the ones used is the Western Ontario and McMaster Universities Arthritis Indices (WOMAC).

Of the selected articles, four used the WOMAC scale, which is according to Copsey et al.<sup>23</sup>, an evaluation measure

listed by the patient for the analysis of osteoarthritis of the lower limbs. WOMAC measurement has been used for decades and is recommended as a result parameter of better performance for knee and hip osteoarthritis in terms of validity, interpretation, reliability and responsiveness. It mainly evaluates pain, since pain is a limiting factor in the functional activities of these patients<sup>3</sup>.

Studies and evaluations are carried out in both genders, but most of the participants in the present study were female, because according to Primorac et al.<sup>24</sup>, men are less likely to develop OA, because women have thinner patellas, narrow femurs, and differences in the size of tibial condyles, more likely to develop OA. And for Hame and Alexander<sup>25</sup>, in addition to the different anatomical part, women commonly point at more advanced stages when compared to men and report more disabilities and pain.

Patel et al.<sup>17</sup> analyzed in men and women the difference in treatment with 1 PRP injection or 2 PRP injections and presented results without statistical difference between the groups, leading to the questioning of why an injection is apparently as effective as two injections. At the end of the follow-up by Patel et al.<sup>17</sup>, in their 6-month follow-up, both treatment groups with PRP presented a significant increase in pain level. As in the study by Kon et al.<sup>26</sup>, which also had pain worsening after 6 and 12 months of the intervention, and the 6-month interval between injections for pain control was suggested.

Görmeli et al.<sup>16</sup>, report that there is a need to clarify the quantity and frequency of injections for adequate efficacy in different stages of knee osteoarthritis. They also concluded that only one injection of PRP or AH did not show statistical improvement with OA at an advanced stage. Chang et al.<sup>27</sup>, in their systematic review and meta-analysis, also found that patients with less degree of degeneration achieved higher results than those with advanced OA. To Görmeli et al.<sup>16</sup>, this occurs due to the greater amount of living cells and high response of growth factors in less degenerated joints.

## 4 Conclusion

In short, this systematic review revealed that the use of intra-articular PRP injection, compared to placebo of saline solution, was effective in decreasing pain levels in patients with knee OA with lower degeneration degree, being less effective in patients with advanced AO. Therefore, it is an efficient treatment option for such pathology.

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