# Is platelet-rich plasma effective for osteoarthritis?

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## Abstract

### Introduction

Despite varied non-surgical alternatives for the treatment of osteoarthritis, many patients remain symptomatic. In the last decade, the use of intra-articular platelet-rich plasma (PRP) has been proposed as an option. However, there is controversy about its clinical benefit and safety.

### Methods

To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

### Results and conclusions

We identified twelve systematic reviews including four studies overall, of which all corresponded to randomized trials. We concluded that intra-articular injection of platelet-rich plasma might slightly decrease joint pain and improve patient satisfaction,vut it is not clear whether it has any effect on functionality because the certainty of the evidence is very low. As for the adverse effects, if they exist, they would be non-severe and self-limited.

## Problem

Osteoarthritis is a highly prevalent condition and an important cause of consultation in both primary and secondary care. The persistence of its symptoms, particularly pain, leads patients to repeated consultation, generally looking for non-surgical alternatives.Platelet-rich plasma is a blood product prepared through the centrifugation of autologous blood to increase the concentration of platelets and therefore the level of growth factors. The regenerative and anti-inflammatory potential of platelet-rich plasma is being studied in multiple musculoskeletal conditions, including osteoarthritis. Additionally, adverse effects would be mild, mainly secondary to arthrocentesis. However, the costs associated to this intervention are substantial, so it is important to have a clear estimation of benefits and harms.

## Key messages

- Intra-articular injection of platelet-rich plasma might slightly decrease joint pain, and improve patient satisfaction, but the certainty of the evidence is low.
- It is not clear whether it improves knee function, because the certainty of the evidence is very low.
- Most patients probably do not experience adverse effects, and if they present them, these are not severe and self-limited.

## About the body of evidence for this question

| | |
|---|---|
| What is the evidence.<br>See evidence matrix in Epistemonikos later | We found twelve systematic reviews [1,2,3,4,5,6,7,8,9,10,11,12] that included four primary studies [13,14,15,16], all corresponding to randomized trials. |
| What types of patients were included* | All of the trials focused on osteoarthritis of the knee.<br>Average age of patients ranged between 50.1 and 56.4 years [13,14,15,16].<br>The proportion of women was between 55.1 and 93.5 in the different trials. |
| What types of interventions were included* | The number of platelet-rich plasma injections was one or two [13], two [14] and three [15,16].<br>The volume injected in each trial was 5 ml [16], 4 to 6 ml [14], between 3 to 8 ml [15] and 8 ml [13].<br>The platelet activating agent was calcium chloride in two trials [13,16] and none in the rest of the trials [14,15].<br>The platelet-rich plasma was centrifuged once [13,15] or twice [14,16].<br>The leukocyte concentration of the platelet-rich plasma was poor in two trials [13,15] and rich in the other two [14,16], depending on the concentration of leukocytes in the blood of the patient.<br>All of the trials compared against placebo. Three of them used saline as placebo [13,15,16] and the fourth did not use intra-articular injections in the control group. |
| What types of outcomes were measured | The outcomes reported in the systematic reviews were pain (measured with WOMAC pain scale) [4,5,6,10,12], functionality (measured with WOMAC function scale)[4,5,6,10], total WOMAC [3,5,6,8,10], patient satisfaction[5,8] and adverse effects [3,4,5,6,10].<br>Follow-up was 6 months in three trials [13,14,16] and 12 months in one trial [15]. |

## Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

## Summary of Findings

The information on the effects of platelet-rich plasma was based on three randomized trials that included 140 participants [13,14,15]. One trial did not contribute to the meta-analysis [16].

All the trials measured the outcomes pain (WOMAC), functionality (WOMAC) and adverse effects. Only one trial [13] reported patient satisfaction (48 participants).

The summary of findings is as follows:

- Intra-articular injection of platelet-rich plasma might slightly decrease joint pain in patients with osteoarthritis, but the certainty of the evidence is low.
- It is not clear whether an intra-articular injection of platelet-rich plasma improves knee functionality because the certainty of the evidence is very low.
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- Intra-articular injection of platelet-rich plasma probably improves patient satisfaction. The certainty of the evidence is low.
- Most patients probably do not experience adverse effects, and if they present them, these are not severe, self-limited and directly related to the number of intra-articular injections. The certainty of this evidence is moderate.

**Platelet-rich plasma for osteoarthritis**

**Patients** Individuals with osteoarthritis
**Intervention** Intra-articular platelet-rich plasma (PRP)
**Comparison** Placebo

| Outcome | Absolute effect* | | Relative effect (95% CI) | Certainty of Evidence (GRADE) |
|---|---|---|---|---|
| | **WITHOUT platelet-rich plasma** | **WITH platelet-rich plasma** | | |
| | Difference: patients per 1000 | | | |
| Pain** (WOMAC pain scale: 0-20) | 7.9 points | 4.7 points | -- | ⨁⨁◯◯ Low[1,2] |
| | Difference: 3.2 points less (Margin of error: 1.84 to 4.55 less) | | | |
| Functionality *** (WOMAC functionality scale: 0-68) | 26.2 points | 16.3 points | -- | ⨁◯◯◯ Very low[1,3] |
| | MD: 9.9 points less (Margin of error: 5.82 to 13.99 less) | | | |
| Patient satisfaction **** | 87 per 1000 | 680 per 1000 | RR 7.82 (2.02 to 30.20) | ⨁⨁◯◯ Low[1,4] |
| | Difference: 593 more (Margin of error: 89 to 1000 more) | | | |
| Adverse effects ***** | Reported in 11 of 71 patients with platelet-rich plasma and in 0 of 69 patients without platelet-rich plasma | | -- | ⨁⨁⨁◯ Moderate[5,6] |

**Margin of error**: 95% confidence interval (CI).
**RR**: Risk ratio.
**MD**: Mean difference.
**GRADE**: Evidence grades of the GRADE Working Group (see later).

*The risk **WITHOUT platelet-rich plasma** is based on the risk in the control group of the trials. The risk **WITH platelet-rich plasma** (and its margin of error) is calculated from relative effect (and its margin of error).
** Pain: evaluated with WOMAC pain scale which is a sub-item of WOMAC (*Western Ontario and McMaster Universities Osteoarthritis Index*). It was used the Likert version in which each item is classified in none, mild, moderate, severe and extreme pointing a maximum of 4 points per item [17,18]. WOMAC pain scale presents 5 items so is scored between

0 and 20. The MID (*Minimally Important Difference*) for improve is between 0.67 and 0.75 for the different sub-items (pain, stiffness, functionality) [19].
***Physical functionality: evaluated with WOMAC functionality scale which is a sub-item of WOMAC (*Western Ontario and McMaster Universities Osteoarthritis Index*). It was used the Likert version in which each item is classified in none, mild, moderate, severe and extreme pointing a maximum of 4 points per item [17,18]. WOMAC functionality scale presents 17 items so is scored between 0 and 68. The MID (*Minimally Important Difference*) for improve is between -9.1 and -7.9 for WOMAC functionality scale [20].
*** Patient satisfaction: included in the patient's global assessment, represents the number of patients satisfied at 6 months of follow-up. (The systematic review does not provide more information).
*****Adverse effects: pain, stiffness, syncope, dizziness, headache, nausea, gastritis, sweating, tachycardia. All self-limited in days.

[1] The certainty of the evidence was downgraded in one level due to moderate risk of bias reported in the reviews.
[2] The certainty of the evidence was downgraded in one level for inconsistency because an $I^2$ of 82% in the meta-analysis.
[3] The certainty of the evidence was downgraded in two levels for inconsistency because an $I^2$ of 92% in the meta-analysis.
[4] The certainty of the evidence was downgraded in one level for indirect outcome
[5] The certainty of the evidence was downgraded in one level for imprecision.
[6] Although some studies found adverse effects and other did not, it was decided not to downgrade the certainty of the evidence for imprecision because the decision does not change since adverse effects are infrequent and transient.

## About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
**High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
**Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
**Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
**Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

## Other considerations for decision-making

### To whom this evidence does and does not apply

This review applies to adults with symptomatic osteoarthritis of the knee. Nevertheless, it seems reasonable to extrapolate the results of this review to other affected joints because the mechanism of action of the intervention are similar regardless of the affected joint.

On the other hand, the use of platelet-rich plasma is being discussed in other musculoskeletal conditions that were not included in this review. However, we think it is not reasonable to apply the results of this review to such conditions.

This evidence does not apply to patients with previous surgical treatment because the reviews did not include such population.

### About the outcomes included in this summary

The outcomes included in this summary are those considered critical for decision-making by the authors of this summary and agree with the Core Outcome Measures in Effectiveness Trials (COMET) [21] which states that the most relevant outcomes in osteoarthritis are: joint pain, functionality, patient satisfaction, quality of life in relation to health, work situation, mortality, reoperation and hospital readmission.

### Balance between benefits and risks, and certainty of the evidence

Although platelet-rich plasma injections reduce joint pain, it is not over the minimally important difference reported in the literature [19] so the clinical relevance is not clear. On the other hand, it might improve patient satisfaction, but is not clear whether it improves physical functionality because the certainty of the evidence is very low.

In terms of safety: three trials analyzed intra-articular platelet-rich plasma adverse effects [13,14,15]. One trial [13] described self-limiting adverse effects (days) and directly related them to the number of intra-articular injections. None of the other two trials [14,15] described adverse effects neither in the intervention group nor in the control group, thus it was not possible to estimate the safety of the intervention.

Regarding the certainty of the evidence, it is low for pain because serious risk of bias and inconsistency. Something similar occurs with the outcome physical functionality, as the certainty of the evidence is very low due to serious risk of bias and very serious inconsistency. The certainty of the evidence for the outcome patient satisfaction is low since this is and indirect outcome and serious risk of bias was reported in the systematic reviews. For the adverse effects, the certainty of the evidence is moderate due to imprecision.

### Resource considerations

Considering that obtaining platelet-rich-plasma requires personnel, infrastructure and time to extract blood and process it, it is a relatively expensive intervention for the patient.

Furthermore, if we add there are small benefits, the balance between costs and benefits is probably not favorable.

### What would patients and their doctors think about this intervention

There is high expectations among patients respect this kind of interventions, given the current non-surgical treatments are mainly symptomatic and require multiple lifestyle changes.

Currently, most clinicians do not routinely suggest intra-articular platelet-rich plasma due to insufficient evidence about the benefits and the high economic costs.

### Differences between this summary and other sources

The conclusion of our summary agrees with most reviews included in this summary in terms of the small benefits associated with pain reduction and functionality when comparing intra-articular injections of platelet-rich plasma against placebo [2,3,4,5,6,7,8,9,10,11]. It must be taken into consideration that several reviews mentioned the poor methodology of the included studies and substantial heterogeneity in the intervention [3,4,5,6,7,8,9,10,11,12]. It is concluded that more studies with better methodology and homogenization in the intervention are needed to improve the certainty of the evidence, until now insufficient [2,3,5,7,9,11].

This summary agrees with the NICE guideline 2014 [22] for osteoarthritis, in which the use of intra-articular platelet-rich plasma as an alternative non-surgical treatment for knee osteoarthritis is not recommended.

### Could this evidence change in the future?

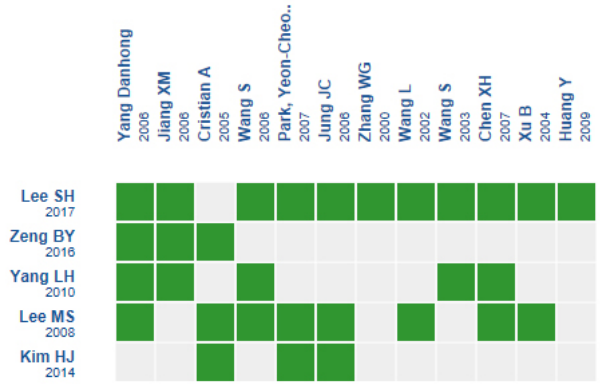
The probability that the conclusions of this summary change with future research is high, due to the existing uncertainty of the evidence.

We searched in PROSPERO (International Prospective Register of Systematic Reviews) where we found eight ongoing reviews [23,24,25,26,27,28,29,30] which could change the results of this summary in the future.

We searched in the International Clinical Trial Registry Platform of the World Health Organization and we found seven ongoing trials which could provide relevant information for our topic of interest [31,32,33,34,35,36,37].

## How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.




An evidence matrix is a table that compares systematic reviews that answer the same question.
Rows represent systematic reviews, and columns show primary studies.
The boxes in green correspond to studies included in the respective revisions.
The system automatically detects new systematic reviews including any of the primary studies in the matrix, which will be added if they actually answer the same question.

Follow the link to access the **interactive version:** Acupuncture for Parkinson's disease

## Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

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