Efficacy of Autologous Platelet-Rich Plasma Use for Orthopaedic Indications: A Meta-Analysis

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Background: The recent emergence of autologous blood concentrates, such as platelet-rich plasma, as a treatment option for patients with orthopaedic injuries has led to an extensive debate about their clinical benefit. We conducted a systematic review and meta-analysis to determine the efficacy of autologous blood concentrates in decreasing pain and improving healing and function in patients with orthopaedic bone and soft-tissue injuries.

Methods: We searched MEDLINE and Embase for randomized controlled trials or prospective cohort studies that compared autologous blood concentrates with a control therapy in patients with an orthopaedic injury. We identified additional studies by searching through the bibliographies of eligible studies as well as the archives of orthopaedic conferences and meetings.

Results: Twenty-three randomized trials and ten prospective cohort studies were identified. There was a lack of consistency in outcome measures across all studies. In six randomized controlled trials (n = 358) and three prospective cohort studies (n = 88), the authors reported visual analog scale (VAS) scores when comparing platelet-rich plasma with a control therapy across injuries to the acromion, rotator cuff, lateral humeral epicondyle, anterior cruciate ligament, patella, tibia, and spine. The use of platelet-rich plasma provided no significant benefit up to (and including) twenty-four months across the randomized trials (standardized mean difference, -0.34; 95% confidence interval [CI], -0.75 to 0.06) or the prospective cohort studies (standardized mean difference, -0.20; 95% CI, -0.64 to 0.23). Both point estimates suggested a small trend favoring platelet-rich plasma, but the associated wide confidence intervals were consistent with nonsignificant effects.

Conclusions: The current literature is complicated by a lack of standardization of study protocols, platelet-separation techniques, and outcome measures. As a result, there is uncertainty about the evidence to support the increasing clinical use of platelet-rich plasma and autologous blood concentrates as a treatment modality for orthopaedic bone and soft-tissue injuries.

Level of Evidence: Therapeutic Level II. Please see Instructions for Authors for a complete description of levels of evidence.

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A utologous blood concentrates, which include platelet-derived products such as platelet-rich plasma, have been gaining popularity among professional and recreational athletes as a result of the increasing attention that these products have received in the mainstream media. In addition to orthopaedic injuries, the application of these products is well documented for use in cardiovascular, plastic, dental, and craniofacial surgical procedures. The market for platelet-rich plasma, which was valued at $45 million in 2009, is expected to be worth more than $1.20 billion by 2016.

In the body's natural response to injury, a complex healing process is initiated at the site of tissue damage and platelets participate in this process. Platelets are responsible for stopping bleeding and for hemostasis, and once they are activated by mediators at the site of injury they undergo degranulation and release bioactive proteins or growth factors that aid in wound-healing. These growth factors include transforming growth factor-beta, platelet-derived growth factor, insulin-like growth factors I and II, fibroblast growth factor, epidermal growth factor, vascular endothelial growth factor, and endothelial cell growth factor, all of which have been shown in experimental settings to promote healing and the formation of new tissue.

Platelet-rich plasma is harvested from a patient's own peripheral blood, centrifuged to obtain a concentrated amount of platelets, placed in a small volume of plasma, and readministered at the site of injury. Other platelet-containing preparations, such as autologous whole blood, are not obtained by centrifuging peripheral blood and therefore contain only baseline levels of platelets. Ultimately, the rationale for the use of the platelet-rich preparations is the belief that the additional platelets will substantially increase the concentration of growth factors at the site of injury and augment the natural healing process.

With the emergence of platelet-rich plasma as a treatment modality for orthopaedic injuries, there is a growing debate regarding its clinical efficacy. Several uncontrolled studies have shown benefit for a variety of indications. However, recent controlled studies have demonstrated less favorable results. Given this uncertainty, we undertook a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies to assess the clinical results, with regard to decreasing pain and improving healing and function, of autologous blood concentrates compared with control therapy in the treatment of orthopaedic injuries.

Materials and Methods

Eligibility Criteria

We identified studies, written in the English language, fulfilling the following eligibility criteria: (1) the study compared platelet-rich plasma or a similar product containing platelets (e.g., autologous blood injection, autologous platelet concentrate, autologous conditioned plasma, osteoinductive gel, platelet-leukocyte gel, autologous platelet-derived growth factor, or platelet gel) with a control (e.g., placebo, corticosteroid, or a standard procedure) in patients with orthopaedic injuries, and (2) the study was a published or unpublished (presented at a society meeting) randomized controlled trial or prospective cohort study.
ICC yields values identical to a weighted kappa with quadratic weights. An a priori \( k \geq 0.65 \) was chosen to represent adequate agreement.

**Data Analysis**

Prior to reviewing the data, we specified a priori that only outcomes that were common to three or more studies would be pooled. We grouped studies using low platelet levels and high platelet levels for these outcomes. An intervention was considered to have low platelet levels if centrifugation was not used in the production process (e.g., autologous blood injections), while interventions employing at least one cycle of centrifugation were deemed to have high platelet levels (i.e., platelet-rich plasma).

We calculated the standard mean difference and 95% confidence interval (CI) for all continuous outcomes. Where appropriate, outcome measures were pooled with use of the random-effects model of DerSimonian and Laird. All pooled estimates were weighted by study size.

To assess for publication bias, we constructed funnel plots for each outcome to examine the magnitude of the effect against the sample size. A symmetrical, inverted, funnel-shaped scatterplot suggests an absence of bias.

**Evaluation of Heterogeneity**

Large differences in effect size between studies define important heterogeneity of the study results. Before analyzing the data, we hypothesized that heterogeneity may be due to differences in platelet-rich-plasma preparation (e.g., number of centrifugations or use of anticoagulation or activating agents), dose of platelet-rich plasma (volume and number of applications), outcome measures (subjective versus objective outcomes), study populations (e.g., elderly versus athletes), clinical use (e.g., spinal fusion versus lateral epicondylitis), duration of follow-up (e.g., three months versus two years), or methodological features (low quality versus high quality).

Heterogeneity between studies was quantified with use of the \( I^2 \) statistic. We chose an \( I^2 \) value of <25% to represent low heterogeneity and an \( I^2 \) value of >75% to indicate high heterogeneity. Tests for significance were two-tailed, and \( p < 0.05 \) was deemed to be significant.

**Source of Funding**

Dr. Bhandari holds a Canada Research Chair in Orthopaedics. However, no funders played a role in the study design, collection, analysis, interpretation of data, writing of the report, or decision to submit the paper for publication.

**Results**

Our literature search generated 895 relevant citations. Of these, thirty-three studies, including twenty-three randomized controlled trials and ten prospective cohort studies, proved eligible for inclusion (Fig. 1). The title of one of the eligible studies stated that it was a randomized trial; however,
after review of the full article, it was deemed to be a prospective cohort study. One study was a conference presentation of a published article that contained important data not reported in the published article. This study was used solely as an adjunct, and was therefore not evaluated as a separate study. The weighted kappa for overall agreement between reviewers for final eligibility was 0.85 (95% CI, 0.75 to 0.95).

**Study Characteristics and Outcomes**

A table in the Appendix describes the characteristics of the eligible studies. The sample sizes of these studies ranged from ten to 165 patients and the duration of follow-up ranged from five days to two years. The efficacy of platelet-rich plasma was examined for a wide range of orthopaedic indications (e.g., anterior cruciate ligament [ACL] reconstruction, reconstruction, total knee arthroplasty, humeral epicondylitis, and Achilles tendinopathy). A variety of primary outcome measures were reported, including an assortment of functional parameters (e.g., knee stability, tenderness threshold, visual analog scale [VAS]), and Disabilities of the Arm, Shoulder and Hand [DASH] score) and imaging parameters (radiographs, computed tomography [CT], and magnetic resonance imaging [MRI]) used to define healing and patient-reported quality of life.

Details of the study protocol and the platelet separation system used by each study can be found in the Appendix. An activating agent, such as autologous thrombin or calcium chloride, was used in the platelet preparation process in twenty-six (79%) of the thirty-three studies. More than one application of platelet product was used in two studies (7%), one evaluating platelet-rich plasma use in ACL reconstruction and the other evaluating it for patellar tendinopathy. The final volume of platelet product used in each study ranged from 2 to 70 mL. The manufacturer of the platelet separation system used was reported in twenty-two studies (61%) but not reported in eight studies (30%); a platelet separation system was not used in three studies (9%). Of the twenty studies in which a platelet separation system was used, only one utilized white-blood-cell-poor platelet-rich plasma, while the remaining studies used white-blood-cell-rich platelet-rich plasma. The authors of five studies reported receiving funding from the manufacturer of the platelet separation system used. All studies evaluating plantar fasciitis therapy utilized autologous, or whole blood injections.

**Study Quality**

We found twenty studies to be of high methodological quality, thirteen studies to be of moderate quality, and no studies to be of low quality (see Appendix). The level of agreement between reviewers in evaluating methodological quality was excellent for randomized controlled trials (ICC, 0.93; 95% CI, 0.91 to 0.94) and prospective cohort studies (ICC, 0.99; 95% CI, 0.97 to 0.99).

The quality of available evidence for the use of platelet-rich plasma and autologous blood injections as per the GRADE system is summarized for tendon, bone, and soft tissue healing indications in Table I.

**Functional Outcomes**

A total of twenty-seven different functional outcome measures were used, eleven of which served as the primary outcome of the study. Of the twenty-three randomized controlled trials included in this review, six showed that platelet-rich plasma provided a significant functional benefit, fifteen demonstrated no difference...
TABLE 1 GRADE Quality Assessment of Evidence for Platelet-Rich Plasma and Autologous Blood Injections

<table>
<thead>
<tr>
<th>Study Design*</th>
<th>No. of Studies (Participants)</th>
<th>Methodological Limitations†</th>
<th>Consistency‡</th>
<th>Directness§</th>
<th>Precision#</th>
<th>Quality of the Evidence (GRADE)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet-rich plasma ACL reconstruction</td>
<td>4 (298)</td>
<td>Serious limitations (-2) No important inconsistency</td>
<td>Indirect (-1)</td>
<td>Uncertain (-1)</td>
<td>+ Very low</td>
<td>Uncertain (-1) + Very low</td>
</tr>
<tr>
<td>PCS</td>
<td>3 (140)</td>
<td>Serious limitations (-1) Unexplained heterogeneity (-1)</td>
<td>Indirect (-1)</td>
<td>Uncertain (-1)</td>
<td>+ Very low</td>
<td>Unexplained heterogeneity (-1)</td>
</tr>
<tr>
<td>Spinal fusion RCT</td>
<td>3 (157)</td>
<td>Serious limitations (-2) No important inconsistency</td>
<td>Indirect (-2)</td>
<td>Uncertain (-1)</td>
<td>+ Very low</td>
<td>No important inconsistency</td>
</tr>
<tr>
<td>PCS</td>
<td>2 (72)</td>
<td>Serious limitations (-1) No important inconsistency</td>
<td>Direct</td>
<td>Uncertain (-1)</td>
<td>+ Very low</td>
<td>No important inconsistency</td>
</tr>
<tr>
<td>Tibial osteotomy RCT</td>
<td>3 (68)</td>
<td>Serious limitations (-1) No important inconsistency</td>
<td>Indirect (-1)</td>
<td>Uncertain (-1)</td>
<td>+ Very low</td>
<td>Unexplained heterogeneity (-1)</td>
</tr>
<tr>
<td>Total knee arthroplasty RCT</td>
<td>2 (142)</td>
<td>Serious limitations (-1) No important inconsistency</td>
<td>Indirect (-1)</td>
<td>Uncertain (-1)</td>
<td>+ Very low</td>
<td>No important inconsistency</td>
</tr>
<tr>
<td>PCS</td>
<td>1 (165)</td>
<td>Serious limitations (-1)</td>
<td>N/A</td>
<td>N/A</td>
<td>+ Very low</td>
<td>N/A</td>
</tr>
<tr>
<td>Rotator cuff repair RCT</td>
<td>2 (141)</td>
<td>Minimal limitations</td>
<td>Direct</td>
<td>Certain</td>
<td>+++ Moderate</td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>1 (42)</td>
<td>Minimal limitations</td>
<td>N/A</td>
<td>N/A</td>
<td>+ Very low</td>
<td></td>
</tr>
<tr>
<td>Achilles tendon rupture RCT</td>
<td>1 (30)</td>
<td>Minimal limitations</td>
<td>N/A</td>
<td>N/A</td>
<td>+ Very low</td>
<td></td>
</tr>
<tr>
<td>Achilles tendinopathy RCT</td>
<td>1 (54)</td>
<td>Minimal limitations</td>
<td>N/A</td>
<td>N/A</td>
<td>+ Very low</td>
<td></td>
</tr>
<tr>
<td>Lateral epicondylitis RCT</td>
<td>1 (100)</td>
<td>Serious limitations (-2)</td>
<td>N/A</td>
<td>N/A</td>
<td>+ Very low</td>
<td></td>
</tr>
<tr>
<td>Total shoulder arthroplasty RCT</td>
<td>1 (40)</td>
<td>Minimal limitations</td>
<td>N/A</td>
<td>N/A</td>
<td>+ Very low</td>
<td></td>
</tr>
<tr>
<td>Total hip arthroplasty RCT</td>
<td>1 (120)</td>
<td>Serious limitations (-2)</td>
<td>N/A</td>
<td>N/A</td>
<td>+ Very low</td>
<td></td>
</tr>
<tr>
<td>Long bone nonunions RCT</td>
<td>1 (120)</td>
<td>Serious limitations (-2)</td>
<td>N/A</td>
<td>N/A</td>
<td>+ Very low</td>
<td></td>
</tr>
</tbody>
</table>
between platelet-rich plasma and the control, and one showed that the control provided a significant functional benefit; the authors of the remaining study did not evaluate functional outcomes (see Appendix). Of the ten prospective cohort studies, three showed that platelet-rich plasma provided a significant functional benefit, six demonstrated no difference between platelet-rich plasma and the control, and one study showed that the control provided a significant functional benefit.

**Visual Analog Scale—Pain**

The most common outcome measure across all studies was the visual analog pain scale. Of the thirty-three eligible studies, twelve (N = 662 patients) provided VAS scores. Nine of the studies used platelet-rich plasma, while the three remaining studies used autologous blood injections. Of the nine studies evaluating platelet-rich plasma, six were randomized trials (n = 358 patients) and three were prospective cohort studies (n = 88 patients). Each study used platelet-rich plasma in a different setting: open subacromial decompression, ACL repair, ribial osteotomy, rotator cuff repair, lateral humeral epicondylitis, chronic elbow tendinosis, spinal fusion, and patellar tendinopathy. Our decision to pool the VAS scores across the different indications was based on the assumption that it is a consistent and general measure of pain assessed in the same way across any indication.

There was no significant difference in VAS scores between the platelet-rich plasma and control groups across randomized trials (standardized mean difference, -0.34; 95% CI, -0.75 to 0.06; p = 0.10; and I² = 70%) (Fig. 2) or prospective cohort.
自动血浆使用对骨科应用的疗效：一项元分析

- 我们收集了15篇随机对照试验和5篇前瞻性队列研究，评价了血小板富集血浆（PRP）的疗效。
- 我们使用随机效应模型对数据进行了池化。
- 在6周、6个月和1年或以上的不同时间点，血小板富集血浆和对照组在视觉模拟评分（VAS）上有显著差异。
- 在6周时，血小板富集血浆的VAS评分比对照组低0.62（95% CI，-1.25至0.02；p = 0.03）。
- 在6个月时，血小板富集血浆的VAS评分比对照组低0.24（95% CI，-0.85至0.35；p = 0.55）。
- 在1年或以上的数据中，血小板富集血浆和对照组的VAS评分相似。

- 三个研究（n = 206患者）评估了对趾筋膜炎患者使用自体血液注射的效果。
- 作者报告了使用自体血液在6个月内VAS评分的提高。
- 池化结果表明使用自体血液的VAS评分在6个月后更高。

- 一项敏感性分析完成，以确定治疗对骨科应用的影响。
- 在15篇随机对照试验和5篇前瞻性队列研究中，血小板富集血浆和对照组的VAS评分相似。
- 心脏病和下肢骨的影像学结果。”
unexplained heterogeneity, variability in study characteristics, and uncertainty surrounding the precision of the results demonstrated that the overall body of evidence for platelet-rich plasma use was of very low quality according to the GRADE criteria.

Neither platelet-rich plasma nor autologous blood appeared to reduce pain compared with that in controls in the studies included in this review. In addition, there is inadequate evidence to definitively conclude that platelet-rich plasma provides a benefit for patients treated with spinal fusion or with respect to healing of the graft, as seen on advanced imaging studies; in the setting of ACL reconstruction. An analysis of the three studies in which autologous blood (non-concentrated) had been utilized for the treatment of plantar fasciitis demonstrated a nonsignificant trend that favored the control group. The effect of concentrated platelet-rich plasma on this condition remains unknown. Of note, a recent randomized trial by Creaney and colleagues was the first to directly compare platelet-rich plasma and autologous whole blood. They demonstrated that the results at six months may be slightly superior with the use of autologous whole blood in patients with refractory elbow tendinopathy, thereby suggesting "less is more."

Two systematic reviews evaluating the use of platelet-rich plasma or autologous blood within the field of orthopedics were recently published. De Vos et al. focused on the use of autologous blood in patients with chronic tendinopathy. Although the scope of their review was limited in comparison with ours, the results are similar. De Vos et al. also found evidence against the use of autologous blood injections as a treatment option for chronic tendinopathies, including plantar fasciitis. In the other systematic review, Griffin et al. concluded that there was no evidence to support the routine use of platelet-rich plasma to improve fracture-healing. Previous reviews were largely limited by a lack of randomized trials to guide their recommendations.

**Strengths and Limitations**

Historically, randomized controlled trials have represented only 3% of the reports in the orthopaedic literature, and many of the published trials have been undermined by methodological deficiencies. In contrast, most of the trials included in our analysis of autologous blood concentrates in orthopaedics are, individually, of moderate-to-high quality. Of note, no other of the studies meeting our inclusion criteria has been published since 2006. The dramatic surge in clinical trials on this topic reflects the enormous interest and growing use of autologous blood concentrates in orthopaedics.

For the current systematic review, we developed explicit inclusion and exclusion criteria, utilized a comprehensive search strategy involving a variety of resources, assessed the methodological quality of the studies, demonstrated the reproducibility of the study selection, conducted a quantitative analysis, and explored potential causes for differences between study results. We minimized selection bias by conducting the selection and data extraction process in duplicate.

While this review included twenty-three randomized controlled trials and ten prospective cohort studies, our analysis was limited by marked variability among the studies with respect to the preparation and dosage of blood concentrates and outcome measures as well as the large number of orthopaedic indications for which the use of the autologous blood concentrates was examined. Furthermore, there was variability across all pooled outcomes in terms of follow-up because of a lack of consistent study time frames. There is also the potential for additional biases in the observational, nonrandomized data presented in this review. In order to minimize sources of bias, we limited the inclusion criteria to prospective cohort studies, as retrospective observational studies are typically subject to both recall and selection bias and have been shown to overestimate treatment effects.

**Implications for Future Studies**

Future trials should be conducted to address the shortcomings of the current body of evidence. The trials in the current review ranged from ten to 165 patients; however, detection of minimally important differences in patient outcomes such as pain and function will require sample sizes that are at least fourfold larger.

Authors of new trials should also use validated, disease-specific, and patient-important outcome measures that can be consistently applied for similar indications. In addition, basic science and clinical studies are needed to clarify the optimal preparation and dosage of autologous blood concentrates. Specifically, questions regarding the optimal platelet concentration, platelet separation technique (use of activating agents), volume of concentrate, number of applications, and inclusion of leukocytes need to be addressed.

Additionally, a head-to-head comparison of platelet separation systems in an experimental model would be quite helpful in determining optimal platelet-rich plasma preparation. In fact, Castillo et al. recently conducted a study in which they compared the composition of platelet-rich plasma produced by three commercially available platelet separation systems (Cascade, Musculoskeletal Transplant Foundation, Edison, New Jersey; GPS III, Biomet Biologies, Warsaw, Indiana; and Magellan, Arteriocyte Medical Systems, Technology Innovation Center, Rogers, Minnesota). There was a significant difference among all three with regard to the concentrations of white blood cells, platelet-derived growth factor, and vascular endothelial growth factor. Future research should determine the clinical relevance of this finding.

Current literature demonstrates that use of platelet-rich plasma in animal and in vitro studies has a positive effect on healing. However, these studies were of healthy tendons and acute traumatic lesions, and their results may not apply well to degenerative diseases. Future trials should focus on determining whether platelet-rich plasma functions optimally in the early phase of an acute injury and the duration of its effect.

In conclusion, current evidence is insufficient to discern whether autologous blood concentrates provide a clinical benefit
in the treatment of orthopaedic conditions. Large and carefully designed randomized clinical trials are needed to draw definitive conclusions on the potential risks and benefits of autologous blood concentrates, such as platelet-rich plasma, in orthopaedics.

Appendix


References