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

Ujash Sheth, BHSc, Nicole Simunovic, MSc, Guy Klein, DO, Freddie Fu, MD, Thomas A. Einhorn, MD, Emil Schemitsch, MD, Olufemi R. Ayeni, MD, and Mohit Bhandari, MD, PhD

Investigation performed at the Center for Evidence-Based Orthopaedics, Division of Orthopaedic Surgery, McMaster University, Hamilton, Ontario, Canada

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.

Disclosure: None of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of any aspect of this work. One or more of the authors, or his or her institution, has had a financial relationship, in the thirty-six months prior to submission of this work, with an entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. No author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete **Disclosures of Potential Conflicts of Interest** submitted by authors are always provided with the online version of the article.

JBJS | *Express*

This article was chosen to appear electronically on January 11, 2012, before publication of the final, definitive version.

A commentary by Matthew J. Matava, MD, is linked to the online version of this article at jbjs.org.

Autologous 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 craniomaxillofacial surgical procedures[1-4]. The market for platelet-rich plasma, which was valued at $45 million in 2009, is expected to be worth more than $120 million by 2016[5].

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[6], 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[7]. 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[8].

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[6,8]. 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[9-11]. However, recent controlled studies have demonstrated less favorable results[12,13]. 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.

Literature Search

A comprehensive literature search was conducted for all relevant articles with use of the electronic databases MEDLINE and Embase from 1996 and 1947, respectively, up to and including July 25, 2011. The complete search strategies are shown in the Appendix. Presentations and abstracts from the annual meetings of the American Academy of Orthopaedic Surgeons (2005 to 2010), the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (2009), and the Canadian Orthopaedic Association (2009) were hand searched for any relevant unpublished literature. Additional studies were identified by consulting with experts, reviewing the reference lists of eligible studies, and using the "related articles" feature in PubMed.

Study Selection

One reviewer screened the titles and abstracts of all studies identified in our initial search. Hand searches of orthopaedic conference proceedings conducted by the same reviewer revealed nine potentially relevant abstracts/presentations. Two reviewers independently assessed the eligibility of the retrieved full-text articles and abstracts/presentations for final inclusion. Discrepancies were resolved through discussion until a consensus was reached.

Data Extraction

Two investigators collected all relevant information regarding the study design, population, intervention, control, primary outcome, methodological quality, and duration of follow-up. The investigators also made note of whether the authors of the study reported key features of the intervention and control protocols, such as the manufacturer of the platelet separator system, the use of an anticoagulant, the use of an activating agent, the number of applications of platelet-rich plasma, and the final volume of platelet-rich plasma used.

Methodological Quality Assessment

Two investigators independently graded the methodological quality of each eligible study using the Detsky scale[14] for randomized controlled trials and the Newcastle-Ottawa Scale[15] for prospective cohort studies. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[16] was used to evaluate the quality of available evidence for all indications for the use of platelet-rich plasma assessed in our study.

The Detsky scale is a 21-point scale used to evaluate the methodological quality of randomized trials on the basis of randomization (present and concealed), blinding (patients and outcome assessors), outcome measures (objective), eligibility criteria (inclusion and exclusion criteria defined), and statistical analysis (appropriate analysis). All quality scores obtained with use of the Detsky scale were converted into a percentage for ease of interpretation. A quality score of ≥75% was chosen a priori to indicate high quality. Studies with a score of ≥50% and <75% were considered to be of moderate quality, while those with a score of <50% were deemed to be of low quality.

The Newcastle-Ottawa Scale is a 9-point scale used to grade prospective cohort studies with regard to their methodological quality of selection, comparability, exposure, and outcome of the study participants. A quality score of ≥7 was chosen a priori to represent high quality. Studies with a score of 5 or 6 were considered to be of moderate quality, and those with a score of ≤4 were deemed to be of low quality[17].

The GRADE system was developed to classify the strength of clinical recommendations on the basis of the quality of evidence and the balance of benefit versus harm. The GRADE system works on the principle that "all relevant clinical studies and observations provide evidence, the quality of which varies."[16] Quality of evidence is determined on the basis of four key factors: methodological limitations, heterogeneity, directness, and precision. The basic study design is the most important determinant of how the evidence is graded. Randomized trials are assumed to be of higher quality than observational studies and are downgraded on the basis of analysis of the four previously mentioned factors. The quality of the evidence is graded as high, moderate, low, or very low.

Assessing Investigator Agreement

The kappa statistic was used to evaluate the agreement between the investigators who determined study eligibility. The intraclass correlation coefficient (ICC) was used to assess the interobserver agreement on methodological quality scores. The

ICC yields values identical to a weighted kappa with quadratic weights[18]. An a priori $\kappa \geq 0.65$ was chosen to represent adequate agreement[17].

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[19]. 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[20]. We chose an I^2 value of <25% to represent low heterogeneity and an I^2 value of >75% to indicate high heterogeneity[21]. 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

Literature Search

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[12,13,22-53] (Fig. 1). The title of one of the eligible studies stated that it was a randomized trial; however,

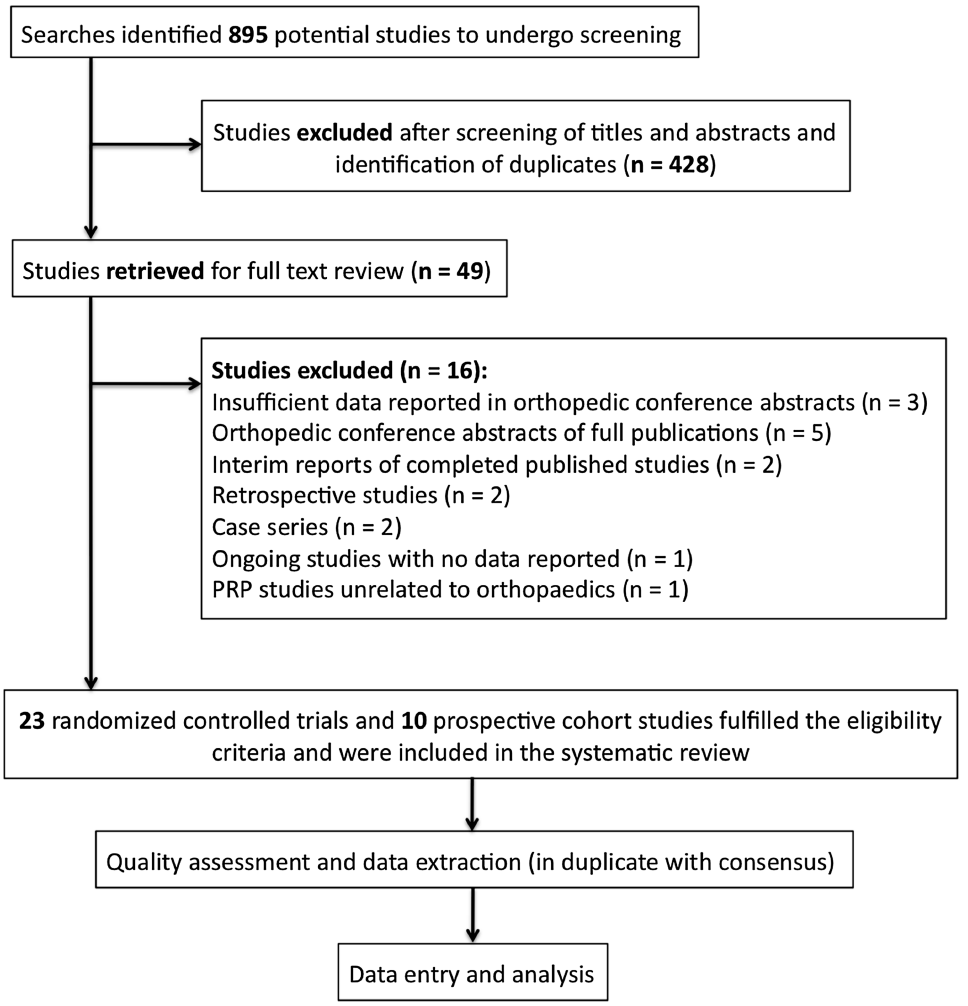

Fig. 1

Flowchart of studies through the systematic review. PRP = platelet-rich plasma.

after review of the full article, it was deemed to be a prospective cohort study[22]. One study was a conference presentation[30] of a published article[29] 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, spinal fusion, 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[47] and the other evaluating it for patellar tendinopathy[53]. 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[50], 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[20,28,36,38,51]. 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

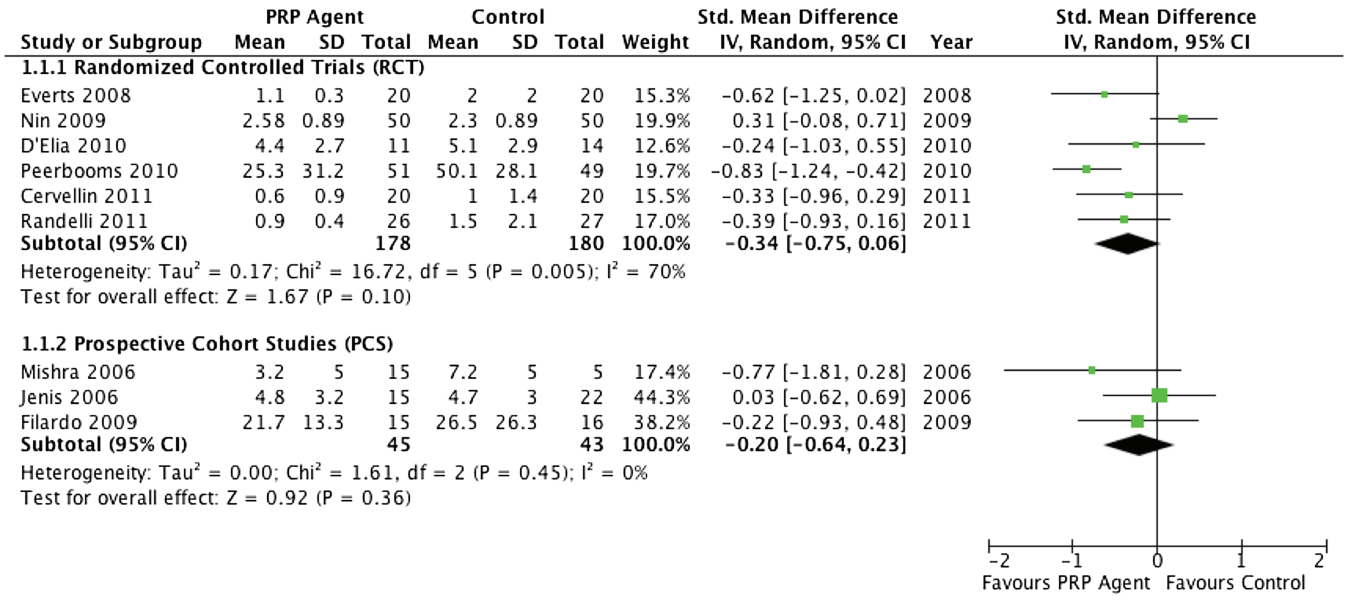

Fig. 2

The effect, on pain scores, of platelet-rich plasma (PRP) treatment compared with treatment for control patients. Forest plot of standardized mean difference for the effect of platelet-rich plasma on pain (visual analog scale) scores up to (and including) twenty-four months. Diamonds indicate the pooled relative risk estimates. Squares represent point estimates around which 95% confidence intervals (CI) are denoted by a horizontal line. ''Random'' indicates that a random-effects model was used to pool the data. IV = inverse variance.

TABLE I GRADE Quality Assessment of Evidence for Platelet-Rich Plasma and Autologous Blood Injections

Study Design*	No. of Studies (Participants)	Methodological Limitations†	Consistency†	Directness§	Precision#	Quality of the Evidence (GRADE)**
Platelet-rich plasma						
ACL reconstruction						
RCT	4 (298)	Serious limitations (−2)	Unexplained heterogeneity (−1)	Indirect (−1)	Uncertain (−1)	+ Very low
PCS	3 (140)	Serious limitations (−1)	Unexplained heterogeneity (−1)	Indirect (−1)	Uncertain (−1)	+ Very low
Spinal fusion						
RCT	3 (157)	Serious limitations (−1)	No important inconsistency	Indirect (−1)	Uncertain (−1)	+ Very low
PCS	2 (72)	Serious limitations (−1)	No important inconsistency	Direct	Uncertain (−1)	+ Very low
Tibial osteotomy						
RCT	3 (68)	Serious limitations (−1)	No important inconsistency	Indirect (−1)	Uncertain (−1)	+ Very low
Total knee arthroplasty						
RCT	2 (142)	Serious limitations (−1)	No important inconsistency	Indirect (−1)	Uncertain (−1)	+ Very low
PCS	1 (165)	Serious limitations (−1)	N/A	N/A	N/A	+ Very low
Rotator cuff repair						
RCT	2 (141)	Minimal limitations	Unexplained heterogeneity (−1)	Direct	Certain	+++ Moderate
PCS	1 (42)	Minimal limitations	N/A	N/A	N/A	+ Very low
Achilles tendon rupture						
RCT	1 (30)	Minimal limitations	N/A	N/A	N/A	+ Very low
Achilles tendinopathy						
RCT	1 (54)	Minimal limitations	N/A	N/A	N/A	+ Very low
Lateral epicondylitis						
RCT	1 (100)	Serious limitations (−2)	N/A	N/A	N/A	+ Very low
Total shoulder arthroplasty						
RCT	1 (40)	Minimal limitations	N/A	N/A	N/A	+ Very low
Total hip arthroplasty						
RCT	1 (120)	Serious limitations (−2)	N/A	N/A	N/A	+ Very low
Long-bone nonunions						
RCT	1 (120)	Serious limitations (−2)	N/A	N/A	N/A	+ Very low

TABLE I *(continued)*

Study Design*	No. of Studies (Participants)	Methodological Limitations†	Consistency†	Directness§	Precision#	Quality of the Evidence (GRADE)**
Open subacromial decompression						
RCT	1 (40)	Minimal limitations	N/A	N/A	N/A	+ Very low
Chronic elbow tendinosis						
PCS	1 (20)	Serious limitations (−1)	N/A	N/A	N/A	+ Very low
Chronic refractory patellar tendinopathy (jumper's knee)						
PCS	1 (31)	Serious limitations (−1)	N/A	N/A	N/A	+ Very low
Autologous blood injections						
Plantar fasciitis						
RCT	2 (106)	Serious limitations (−1)	Unexplained heterogeneity (−1)	Direct	Uncertain (−1)	+ Very low
PCS	1 (100)	Minimal limitations	N/A	N/A	N/A	+ Very low

*RCT = randomized controlled trial, and PCS = prospective cohort study. †Randomized controlled trials are assumed to be of high quality and are downgraded accordingly (−1 or −2), while prospective cohort studies are assumed to be of low quality and are upgraded (+1 or +2) or downgraded accordingly (−1 or −2). Limitations that result in downgrading include lack of blinding with subjective outcomes, lack of concealment, failure to use intention-to-treat analysis, a large loss to follow-up, or early cessation of the study. †The quality of evidence is diminished when studies with vastly differing estimates of treatment effect are unexplained. When heterogeneity exists, the quality rating of the studies is downgraded (−1). This is not applicable (N/A) for subgroups with only one study available for analysis. §The population, intervention, comparison, and outcomes measured should be similar between studies in order to directly apply the results. If a discrepancy exists between studies, then the quality rating is downgraded (−1 or −2). #When there is a lack of patients and events, the results are uninformative and therefore deemed to be imprecise. Data are also imprecise if the confidence intervals are not reported or they are so wide that the estimate is consistent with conflicting recommendations. If imprecise data are detected, then the quality rating is downgraded (−1). This is not applicable (N/A) for subgroups with only one study available for analysis. **Randomized controlled trials (RCT) are deemed to be of high quality (++++), a downgraded RCT or an upgraded prospective cohort study (PCS) is considered to be of moderate quality (+++), a well-done PCS is considered to be of low quality (++), and a downgraded RCT or PCS is considered to be of very low quality (+). Note that the quality of evidence was evaluated only for full publications (not abstracts). All results classified as not applicable (N/A) received a reduction in the quality rating (−1).

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[44], ACL repair[13,23], tibial osteotomy[30], rotator cuff repair[36], lateral humeral epicondylitis[38], chronic elbow tendinosis[51], spinal fusion[49], and patellar tendinopathy[53]. 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[54].

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 I^2 = 70%) (Fig. 2) or prospective cohort

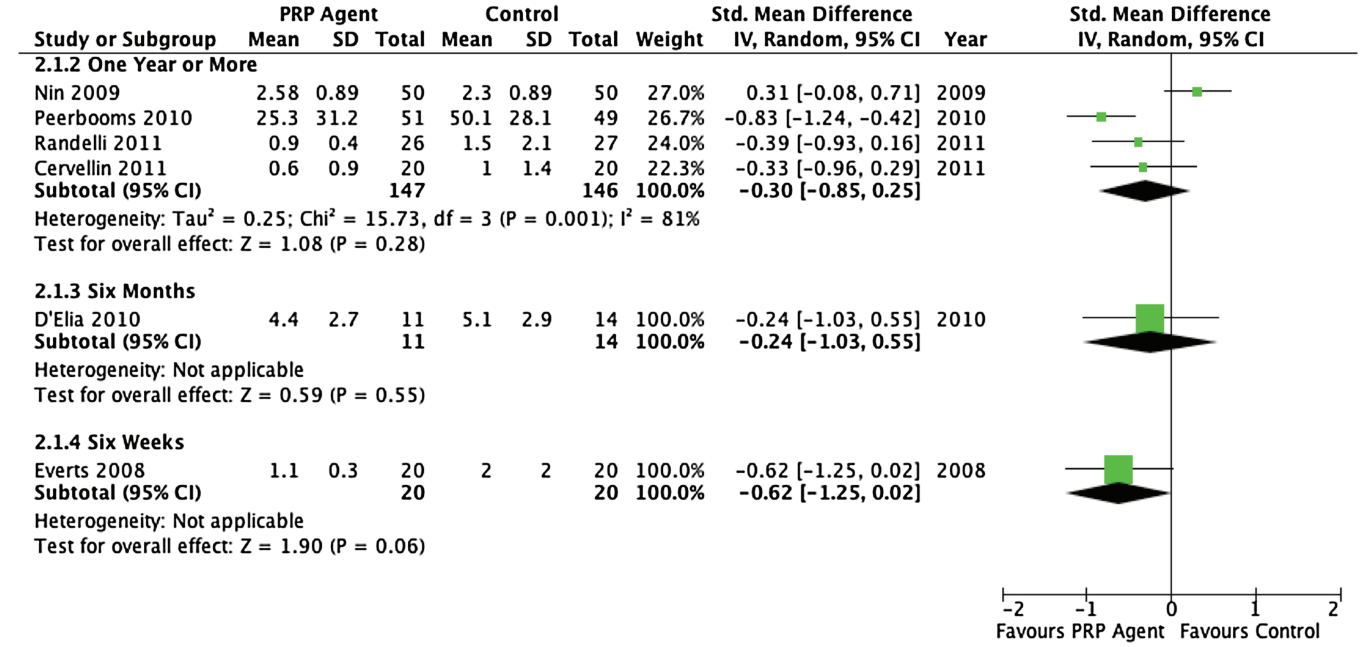

Fig. 3

Temporal effect, on pain scores, of platelet-rich plasma (PRP) treatment compared with treatment for control patients. Forest plot of standardized mean difference for the effect of platelet-rich plasma on pain (visual analog scale) scores up to (and including) twenty-four months. Diamonds indicate the pooled relative risk estimates. Squares represent point estimates around which 95% confidence intervals (CI) are denoted by a horizontal line. ''Random'' indicates that a random-effects model was used to pool the data. IV = inverse variance.

studies (standardized mean difference, –0.20; 95% CI, –0.64 to 0.23; p = 0.36; and I^2 = 0% (Fig. 2). Because of the small number of studies available for comparison, the funnel plot was inconclusive regarding publication bias, but it did suggest a possible absence of negative studies.

A sensitivity analysis was completed to determine the effect of time on the efficacy of platelet-rich plasma. We pooled VAS scores at six weeks, six months, and one year or more after platelet-rich plasma administration for the six randomized trials. One study assessed pain at six weeks; another study, at six months; and the remaining four studies, at one year or more. The pooled estimates demonstrated no significant difference between the platelet-rich plasma and control groups at six weeks (standardized mean difference, −0.62; 95% CI, −1.25 to 0.02; p = 0.06), six months (standardized mean difference, −0.24; 95% CI, −1.03 to 0.55; p = 0.55), or one year or more (standardized mean difference, –0.30; 95% CI, –0.85 to 0.25; p = 0.28) (Fig. 3).

In one study[38], the authors reported VAS scores at multiple time points (one, two, three, six, and twelve months) in patients with lateral humeral epicondylitis. We pooled those scores to determine if there was a potential effect of platelet-rich plasma over time. There was a trend favoring the use of platelet-rich plasma over corticosteroids for this particular condition over the course of one year.

Three studies (n = 206 patients) evaluated the effect of autologous blood injections in patients with plantar fasciitis at six months[22,33,34]. The pooled results suggested that the VAS scores after use of autologous blood were higher than those in either control group (anesthetic or corticosteroid) (standardized mean difference, 0.41; 95% CI, –0.01 to 0.83; p = 0.05; and I^2 = 33%).

Imaging Outcomes

The authors of three studies[27,28,48] (n = 152 patients) reported on the number of solid spinal fusions at one year. The platelet-rich plasma and control groups were similar with regard to solid fusion, with a risk ratio of 1.06 (95% CI, 0.93 to 1.22; p = 0.33; I^2 = 0%).

No significant difference was found in the number of patients with low MRI signal intensity of the autograft used in ACL reconstruction between the platelet-rich plasma and control groups[25,45,47] (n = 198 patients; risk ratio, 0.76; 95% CIs, 0.50 to 1.15; p = 0.19; I^2 = 0).

Discussion

Our systematic review and meta-analysis suggest considerable uncertainty about the evidence regarding a clinical benefit of the use of autologous blood concentrates, such as platelet-rich plasma, for a variety of disorders in orthopaedics. Fifteen randomized controlled trials and five prospective cohort studies showed no clinical benefit with platelet-rich plasma. On the basis of GRADE criteria, the overall quality of evidence was graded as very low for thirteen of the fourteen indications for which platelet-rich plasma was used. Nine of the fourteen proposed indications for use of platelet-rich plasma were evaluated in only one study each. As for the remaining five indications, evaluated in two studies or more, serious methodological limitations,

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[55] 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 orthopaedics were recently published[56,57]. De Vos et al.[56] 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.[57] 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[58-60]. 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, all of the studies meeting our inclusion criteria had 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 lines. 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[61].

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.[62] 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 Biologics, 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[61]. 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[63-65]. 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

eA Tables showing the characteristics of all eligible studies, the characteristics of study protocol and platelet separation systems, and the electronic search strategies used are available with the online version of this article as a data supplement at jbjs.org. ■

Ujash Sheth, BHSc
Nicole Simunovic, MSc
Mohit Bhandari, MD, PhD
Center for Evidence-Based Orthopaedics,
Division of Orthopaedic Surgery, McMaster University,
293 Wellington Street North, Suite 110,
Hamilton, ON L8L 8E7, Canada.

E-mail address for U. Sheth: usheth@qmed.ca.
E-mail address for M. Bhandari: bhandam@mcmaster.ca

Guy Klein, DO
University Hospitals Richmond Medical Center,
27100 Chardon Road, Richmond Heights, OH 44143

Freddie Fu, MD
UPMC Center for Sports Medicine,
3200 South Water Street, Pittsburgh, PA 15203

Thomas A. Einhorn, MD
Boston University Orthopaedic Surgical Associates,
725 Albany Street, Shapiro 4th Floor, Suite 4B,
Boston, MA 02118

Emil Schemitsch, MD
St. Michael's Hospital, 55 Queen Street East, Suite 800,
Toronto, ON M5C 1R6, Canada

Olufemi R. Ayeni, MD
McMaster University Medical Centre, 1200 Main Street West,
Room 4E17, Hamilton, ON L8N 3Z5, Canada

References

1. Khalafi RS, Bradford DW, Wilson MG. Topical application of autologous blood products during surgical closure following a coronary artery bypass graft. Eur J Cardiothorac Surg. 2008;34:360-4.
2. Welsh WJ. Autologous platelet gel-clinical function and usage in plastic surgery. Cosmetic Dermatol. 2000;51:13-8.
3. Hanna R, Trejo PM, Weltman RL. Treatment of intrabony defects with bovine-derived xenograft alone and in combination with platelet-rich plasma: a randomized clinical trial. J Periodontol. 2004;75:1668-77.
4. Wiltfang J, Schlegel KA, Schultze-Mosgau S, Nkenke E, Zimmermann R, Kessler P. Sinus floor augmentation with beta-tricalciumphosphate (beta-TCP): does platelet-rich plasma promote its osseous integration and degradation? Clin Oral Implants Res. 2003;14:213-8.
5. GlobalData. Platelet rich plasma: a market snapshot. http://www.docstoc.com/docs/47503668/Platelet-Rich-Plasma-A-Market-Snapshot. Accessed 2010 Sep 16.
6. Woodell-May JE, Pietrzak WS. Platelet-rich plasma in orthopedics. In: Pietrzak WS, editor. Musculoskeletal tissue regeneration: biological materials and methods. New York, NY: Springer-Verlag; 2008. p 547-68.
7. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost. 2004;91:4-15.
8. Lopez-Vidriero E, Goulding KA, Simon DA, Sanchez M, Johnson DH. The use of platelet-rich plasma in arthroscopy and sports medicine: optimizing the healing environment. Arthroscopy. 2010;26:269-78.
9. Franchini M, Dupplicato P, Ferro I, De Gironcoli M, Aldegheri R. Efficacy of platelet gel in reconstructive bone surgery. Orthopedics. 2005;28:161-3.
10. Hee HT, Majd ME, Holt RT, Myers L. Do autologous growth factors enhance transforaminal lumbar interbody fusion? Eur Spine J. 2003;12:400-7.
11. Sánchez M, Azofra J, Anitua E, Andía I, Padilla S, Santisteban J, Mujika I. Plasma rich in growth factors to treat an articular cartilage avulsion: a case report. Med Sci Sports Exerc. 2003;35:1648-52.
12. de Vos RJ, Weir A, van Schie HT, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Tol JL. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. JAMA. 2010;303:144-9.
13. Nin JR, Gasque GM, Azcárate AV, Beola JD, Gonzalez MH. Has platelet-rich plasma any role in anterior cruciate ligament allograft healing? Arthroscopy. 2009;25:1206-13.
14. Detsky AS, Naylor CD, O'Rourke K, McGeer AJ, L'Abbé KA. Incorporating variations in the quality of individual randomized trials into meta-analysis. J Clin Epidemiol. 1992;45:255-65.
15. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Tugwell P, Losos M. Ottawa Hospital Research Institute. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Presented at 3rd Symposium on Systematic Reviews: Beyond the Basics. Oxford, England; 2000. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.
16. Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, Fahy BF, Gould MK, Horan KL, Krishnan JA, Manthous CA, Maurer JR, McNicholas WT, Oxman AD, Rubenfeld G, Turino GM, Guyatt G; ATS Documents Development and Implementation Committee. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. Am J Respir Crit Care Med. 2006;174:605-14.
17. Simunovic N, Devereaux PJ, Sprague S, Guyatt GH, Schemitsch E, Debeer J, Bhandari M. Effect of early surgery after hip fracture on mortality and complications: systematic review and meta-analysis. CMAJ. 2010 Sep 13. [Epub ahead of print].
18. Fleiss JL, Cohen J. The equivalence of weighted kappa and the intraclass correlation coefficient as measures of reliability. Educ Psychol Measur. 1973;33:613-9.
19. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88.
20. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-58.
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60.
22. Kalaci A, Cakici H, Hapa O, Yanat AN, Dogramaci Y, Sevinç TT. Treatment of plantar fasciitis using four different local injection modalities: a randomized prospective clinical trial. J Am Podiatr Med Assoc. 2009;99:108-13.
23. Cervellin M, de Girolamo L, Bait C, Denti M, Volpi P. Autologous platelet-rich plasma gel to reduce donor-site morbidity after patellar tendon graft harvesting for anterior cruciate ligament reconstruction: a randomized, controlled clinical study. Knee Surg Sports Traumatol Arthrosc 2011 Jun 16. [Epub ahead of print].
24. Vogrin M, Rupreht M, Crnjac A, Dinevski D, Krajnc Z, Recnik G. The effect of platelet-derived growth factors on knee stability after anterior cruciate ligament reconstruction: a prospective randomized clinical study. Wien Klin Wochenschr. 2010;122 Suppl 2:91-5.
25. Orrego M, Larrain C, Rosales J, Valenzuela L, Matas J, Durruty J, Sudy H, Mardones R. Effects of platelet concentrate and a bone plug on the healing of hamstring tendons in a bone tunnel. Arthroscopy. 2008;24:1373-80.
26. Sys J, Weyler J, Van Der Zijden T, Parizel P, Michielsen J. Platelet-rich plasma in mono-segmental posterior lumbar interbody fusion. Eur Spine J. 2011 Jul 10 [Epub ahead of print].
27. Tsai CH, Hsu HC, Chen YJ, Lin MJ, Chen HT. Using the growth factors-enriched platelet glue in spinal fusion and its efficiency. J Spinal Disord Tech. 2009;22:246-50.
28. Feiz-Erfan I, Harrigan M, Sonntag VK, Harrington TR. Effect of autologous platelet gel on early and late graft fusion in anterior cervical spine surgery. J Neurosurg Spine. 2007;7:496-502.
29. D'Elia CO, de Rezenda MU, Bitar AC, Tatsui N, Pecora JR, Hernandez AJ, Camanho GL. Comparison between platelet-rich plasma and autologous iliac grafts for tibial osteotomy. Cartilage. 2010;1:320-7.

30. D'Elia CO, Uchoa MR, Bitar AC, Tatsui N, Pecora JR, Hernandez AJ, Camanho GL. A comparative study of the use of platelet-rich plasma and autologous iliac crest as graft sources in opening wedge high tibial osteotomy. Presented at the 7th Biannual Meeting of the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine; 2009 Apr 5-9; Osaka, Japan. E-poster no.1002.

31. Dallari D, Savarino L, Stagni C, Cenni E, Cenacchi A, Fornasari PM, Albisinni U, Rimondi E, Baldini N, Giunti A. Enhanced tibial osteotomy healing with use of bone grafts supplemented with platelet gel or platelet gel and bone marrow stromal cells. J Bone Joint Surg Am. 2007;89:2413-20.

32. Savarino L, Cenni E, Tarabusi C, Dallari D, Stagni C, Cenacchi A, Fornasari PM, Giunti A, Baldini N. Evaluation of bone healing enhancement by lyophilized bone grafts supplemented with platelet gel: a standardized methodology in patients with tibial osteotomy for genu varus. J Biomed Mater Res B Appl Biomater. 2006;76:364-72.

33. Lee TG, Ahmad TS. Intralesional autologous blood injection compared to corticosteroid injection for treatment of chronic plantar fasciitis. A prospective, randomized, controlled trial. Foot Ankle Int. 2007;28:984-90.

34. Kiter E, Celikbas E, Akkaya S, Demirkan F, Kiliç BA. Comparison of injection modalities in the treatment of plantar heel pain: a randomized controlled trial. J Am Podiatr Med Assoc. 2006;96:293-6.

35. Castricini R, Longo UG, De Benedetto M, Panfoli N, Pirani P, Zini R, Maffulli N, Denaro V. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: a randomized controlled trial. Am J Sports Med. 2011;39:258-65.

36. Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. J Shoulder Elbow Surg. 2011;20:518-28.

37. Horstmann WG, Slappendel R, van Hellemondt GG, Wymenga AW, Jack N, Everts PA. Autologous platelet gel in total knee arthroplasty: a prospective randomized study. Knee Surg Sports Traumatol Arthrosc. 2010 July 18. [Epub ahead of print].

38. Peerbooms JC, Sluimer J, Bruijn DJ, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. Am J Sports Med. 2010;38:255-62.

39. Schepull T, Kvist J, Norrman H, Trinks M, Berlin G, Aspenberg P. Autologous platelets have no effect on the healing of human Achilles tendon ruptures: a randomized single-blind study. Am J Sports Med. 2011;39:38-47.

40. Peerbooms JC, de Wolf GS, Colaris JW, Bruijn DJ, Verhaar JA. No positive effect of autologous platelet gel after total knee arthroplasty. Acta Orthop. 2009;80:557-62.

41. Zavadil DP, Satterlee CC, Costigan JM, Holt DW, Shostrom VK. Autologous platelet gel and platelet-poor plasma reduce pain with total shoulder arthroplasty. J Extra Corpor Technol. 2007;39:177-82.

42. Thomas W, Tafuro L, Thomas S. Osteoinductive gel in cementless hip joint replacement: a randomized prospective study. Curr Orthop Prac. 2009;20:655-9.

43. Calori GM, Tagliabue L, Gala L, d'Imporzano M, Peretti G, Albisetti W. Application of rhBMP-7 and platelet-rich plasma in the treatment of long bone non-unions: a prospective randomised clinical study on 120 patients. Injury. 2008;39:1391-402.

44. Everts PA, Devilee RJ, Brown Mahoney C, van Erp A, Oosterbos CJ, Stellenboom M, Knape JT, van Zundert A. Exogenous application of platelet-leukocyte gel during open subacromial decompression contributes to improved patient outcome. A prospective randomized double-blind study. Eur Surg Res. 2008;40:203-10.

45. Figueroa D, Melean P, Calvo R, Vaisman A, Zilleruelo N, Figueroa F, Villalón I. Magnetic resonance imaging evaluation of the integration and maturation of semitendinosus-gracilis graft in anterior cruciate ligament reconstruction using autologous platelet concentrate. Arthroscopy. 2010;26:1318-25.

46. Radice F, Yánez R, Gutiérrez V, Rosales J, Pinedo M, Coda S. Comparison of magnetic resonance imaging findings in anterior cruciate ligament grafts with and without autologous platelet-derived growth factors. Arthroscopy. 2010;26:50-7.

47. Silva A, Sampaio R. Anatomic ACL reconstruction: does the platelet-rich plasma accelerate tendon healing? Knee Surg Sports Traumatol Arthrosc. 2009;17:676-82.

48. Hartmann EK, Heintel T, Morrison RH, Weckbach A. Influence of platelet-rich plasma on the anterior fusion in spinal injuries: a qualitative and quantitative analysis using computer tomography. Arch Orthop Trauma Surg. 2010;130:909-14.

49. Jenis LG, Banco RJ, Kwon B. A prospective study of Autologous Growth Factors (AGF) in lumbar interbody fusion. Spine J. 2006;6:14-20.

50. Jo CH, Kim JE, Yoon KS, Lee JH, Kang SB, Lee JH, Han HS, Rhee SH, Shin S. Does platelet-rich plasma accelerate recovery after rotator cuff repair? A prospective cohort study. Am J Sports Med. 2011 Jul 7 [Epub ahead of print].

51. Mishra A, Pavelko T. Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. Am J Sports Med. 2006;34:1774-8.

52. Everts PA, Devilee RJ, Oosterbos CJ, Mahoney CB, Schattenkerk ME, Knape JT, van Zundert A. Autologous platelet gel and fibrin sealant enhance the efficacy of total knee arthroplasty: improved range of motion, decreased length of stay and a reduced incidence of arthrofibrosis. Knee Surg Sports Traumatol Arthrosc. 2007;15:888-94.

53. Filardo G, Kon E, Della Villa S, Vincentelli F, Fornasari PM, Marcacci M. Use of platelet-rich plasma for the treatment of refractory jumper's knee. Int Orthop. 2010;34:909-15. 2009 Jul 31 [Epub ahead of print].

54. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med. 1988;18:1007-19.

55. Creaney L, Wallace A, Curtis M, Connell D. Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: a prospective, single-blind, randomised trial of autologous blood injections versus platelet-rich plasma injections. Br J Sports Med. 2011 Mar 15. [Epub ahead of print].

56. de Vos RJ, van Veldhoven PL, Moen MH, Weir A, Tol JL, Maffulli N. Autologous growth factor injections in chronic tendinopathy: a systematic review. Br Med Bull. 2010;95:63-77.

57. Griffin XL, Smith CM, Costa ML. The clinical use of platelet-rich plasma in the promotion of bone healing: a systematic review. Injury. 2009;40:158-62.

58. Bhandari M, Richards RR, Sprague S, Schemitsch EH. The quality of reporting of randomized trials in the Journal of Bone and Joint Surgery from 1988 through 2000. J Bone Joint Surg Am. 2002;84:388-96.

59. Poolman RW, Struijs PA, Krips R, Sierevelt IN, Lutz KH, Bhandari M. Does a ''Level I Evidence'' rating imply high quality of reporting in orthopaedic randomised controlled trials? BMC Med Res Methodol. 2006;6:44.

60. Poolman RW, Struijs PA, Krips R, Sierevelt IN, Marti RK, Farrokhyar F, Bhandari M. Reporting of outcomes in orthopaedic randomized trials: does blinding of outcome assessors matter? J Bone Joint Surg Am. 2007;89:550-8.

61. Hulley SB, Cummings SR, Browner WS, Grady D, Newman TB. Designing clinical research. 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2006.

62. Castillo TN, Pouliot MA, Kim HJ, Dragoo JL. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. Am J Sports Med. 2011;39:266-71.

63. de Mos M, van der Windt AE, Jahr H, van Schie HT, Weinans H, Verhaar JA, van Osch GJ. Can platelet-rich plasma enhance tendon repair? A cell culture study. Am J Sports Med. 2008;36:1171-8.

64. Virchenko O, Aspenberg P. How can one platelet injection after tendon injury lead to a stronger tendon after 4 weeks? Interplay between early regeneration and mechanical stimulation. Acta Orthop. 2006;77:806-12.

65. McCarrel T, Fortier L. Temporal growth factor release from platelet-rich plasma, trehalose lyophilized platelets, and bone marrow aspirate and their effect on tendon and ligament gene expression. J Orthop Res. 2009;27:1033-42.