Systematic Review

Platelet-Rich Plasma Use in Anterior Cruciate Ligament Surgery: Systematic Review of the Literature

David Figueroa, M.D., Francisco Figueroa, M.D., Rafael Calvo, M.D., Alex Vaisman, M.D., Ximena Ahumada, M.D., and Sergio Arellano, M.D.

Purpose: To systematically review the current literature for evidence that would substantiate the use of platelet-rich plasma (PRP) in the treatment of anterior cruciate ligament (ACL) ruptures. **Methods:** We performed a systematic search in PubMed and Embase of studies written in the English and Spanish languages that compared the use of PRP with a control group in patients with ACL injuries assessing graft-to-bone healing, graft maturation, and/or clinical outcomes and were randomized controlled trials or prospective cohort studies. **Results:** Eleven studies fulfilled the inclusion criteria, comprising 516 patients (266 ACL reconstructions using PRP and 250 ACL reconstructions without PRP). Six studies reported a statistically significant difference (4 studies) or tendency toward faster graft maturation in the platelet group (2 studies). One study found no differences. Regarding tunnel healing/widening, 1 study showed faster healing in the PRP group and 5 studies showed no differences between the 2 groups. Considering clinical outcomes, 1 study showed better clinical outcomes with PRP use and 5 studies showed no benefits with the use of PRP. **Conclusions:** Concerning ACL graft maturation, there is promising evidence that the addition of PRP could be a synergic factor in acquiring maturity more quickly than grafts with no PRP, with the clinical implication of this remaining unclear. Regarding tunnel healing, it appears that there is not an improvement with the addition of PRP. There is no proof that clinical outcomes of ACL surgery are enhanced by the use of PRP. **Level of Evidence:** Level III, systematic review of Level I through III studies.

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Over the past few years, tissue-engineering and new technologies have been introduced in orthopaedic surgery daily practice with encouraging results in different pathologies. Within this group is platelet-derived growth factor, which though known for more than 30 years, started to be used in orthopaedic surgery in the 1990s, reaching recognition in the 21st century.[1]

The platelet-derived growth factor that is used today in medical practice is obtained from autologous blood centrifugation, leading to a concentrate with 3 to 5 more platelets than normal blood. This centrifugate is known as platelet-rich plasma (PRP).[1] One promising field of PRP use is sports medicine,[2,3] and important research has been performed regarding anterior cruciate ligament (ACL) ruptures,[4-7] assuming that the success of ACL reconstruction depends heavily on biological processes that could improve the outcomes and ensure optimal clinical results.

The aim of this study was to systematically review the current literature for evidence that would substantiate the use of PRP in the treatment of ACL ruptures. We hypothesized that PRP could reduce the maturation and integration time of the graft in ACL reconstruction but, besides that, PRP use does not change clinical or arthrometric results in ACL reconstruction patients.

Methods

Eligibility Criteria

We searched studies, written in the English and Spanish languages, fulfilling the following eligibility criteria: (1) The study compared the use of PRP with a

From the Knee Unit, Orthopaedics Department, Facultad de Medicina, Clínica Alemana, Universidad del Desarrollo, Santiago, Chile.

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Address correspondence to David Figueroa, M.D., Knee Unit, Orthopaedics Department, Facultad de Medicina, Clínica Alemana, Universidad del Desarrollo, Vitacura 5951, Santiago, Chile. E-mail: dhfigueroa@gmail.com

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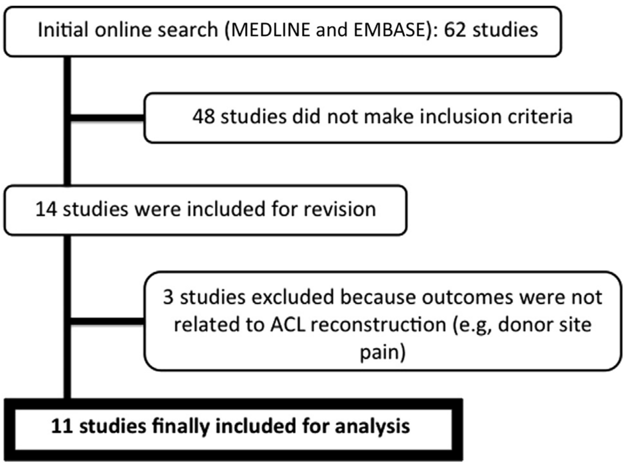

Fig 1. Flowchart of studies through systematic review. (ACL, anterior cruciate ligament.)

control group (standard reconstruction) in patients with ACL injuries. (2) The main study outcome was to assess whether there were any differences in graft-to-bone healing, graft maturation, and/or clinical outcomes in ACL-reconstructed patients with or without the use of PRP. (3) The study was a published randomized controlled trial or prospective cohort study.

Literature Search

A comprehensive literature search was conducted for all relevant articles using the electronic databases Medline and Embase. We used the terms "anterior cruciate ligament [AND] platelet rich plasma," "ACL [AND] platelet rich plasma," "anterior cruciate ligament [AND] PRP," and "ACL [AND] PRP." The last search was performed on February 1, 2014.

Study Selection

Full texts were obtained for all studies matching the previously listed inclusion criteria. The obtained full texts were reviewed to reconfirm eligibility. The study selection was performed independently by all the investigators of this review. Disagreement was resolved by consensus.

Data Items and Collection Process

We collected all relevant information regarding the study design, population, intervention group, control group, outcomes, methodologic quality, and duration of follow-up. Regarding PRP, we noted the use of an anticoagulant, the use of an activating agent, the number of applications of PRP, and the final volume of PRP used.

Methodologic Quality Assessment

We graded the methodologic quality of each eligible study using the Detsky scale[8] for randomized controlled trials and the Newcastle-Ottawa Scale[9] for prospective cohort studies.

Data Synthesis

We did not perform a quantitative analysis because of the clinical heterogeneity of the studies reviewed. There were different PRP concentrations, different ACL reconstruction techniques, and different methods of outcome assessment, among several additional reasons.

Results

Study Selection

A total of 62 studies were found. Eleven articles with a total of 516 patients (266 ACL reconstructions with PRP and 250 ACL reconstructions without PRP) were included in this study. They were all published between 2005 and 2013 (Fig 1).

Study Quality

We found 6 studies to be of high methodologic quality, 5 studies to be of moderate quality, and no studies to be of low quality according to the Detsky scale[8] for randomized controlled trials and the Newcastle-Ottawa Scale[9] for prospective cohort studies.

Study Characteristics

The general characteristics of the studies reviewed are summarized in Table 1. The data regarding ACL

Table 1. Characteristics of Included Studies

						Mean Age, yr		No. of Patients	
Authors	Randomized	Blinded Assessment	Power Calculation	Level of Evidence	Follow-up, mo	PRP Group	Control Group	PRP Group	Control Group
Ventura et al.[10] (2005)	Yes	No	No	II	6	36.6	30.2	10	10
Orrego et al.[13] (2008)	Yes	Yes	Yes	II	6	30	30	26	27
Nin et al.[16] (2009)	Yes	Yes	No	I	24	26.1	26.6	50	50
Silva et al.[17] (2010)	Yes	No	No	II	3	26.8	26.8	10	10
Vogrin et al.[18] (2010)	Yes	Yes	No	I	3	37.2	32.6	25	25
Vogrin et al.[19] (2010)	Yes	No	No	III	6	35.4	33	25	25
Figueroa et al.[21] (2010)	Yes	Yes	Yes	III	6	26.8	23.6	30	20
Sánchez et al.[22] (2010)	No	No	No	III	24	28	28	22	15
Radice et al.[20] (2010)	No	Yes	No	III	9	30	32	25	25
Vadalà et al.[24] (2013)	Yes	No	Yes	II	14.7	34.5	34.5	20	20
Mirzatolooei et al.[23] (2013)	Yes	No	No	I	3	26.4	26.9	23	23

Table 2. Surgical Parameters

Authors	Graft	Femoral Fixation	Tibial Fixation	Rehabilitation Program
Ventura et al.[10] (2005)	Quadrupled hamstring	Cross pin	Bioabsorbable interference screw	Immediate mobilization without brace, protected weight bearing for 3 wk, return to sports at 6 mo
Orrego et al.[13] (2008)	Quadrupled hamstring	Cross pin	Bioabsorbable interference screw	Accelerated rehabilitation protocol
Nin et al.[16] (2009)	Bone–patellar tendon–bone	Cross pin	Bioabsorbable interference screw	Immediate mobilization without brace, cycling at 2-3 mo, running at 4 mo, return to sports at 6 mo
Silva et al.[17] (2010)	Quadrupled hamstring	Extracortical button	Bioabsorbable interference screw	Immobilization with brace for first week, progressive range of motion and protected weight bearing until fifth week
Vogrin et al.[18] (2010)	Double-looped hamstring	Cross pin	Bioabsorbable interference screw	Immediate mobilization without brace, closed kinetic chain exercises, running at 12 wk, return to sports at 6 mo
Vogrin et al.[19] (2010)	Double-looped hamstring	Cross pin	Bioabsorbable interference screw	Immediate mobilization without brace, closed kinetic chain exercises, running at 12 wk, return to sports at 6 mo
Figueroa et al.[21] (2010)	Hamstring	Cross pin	Bioabsorbable interference screw	Accelerated rehabilitation protocol
Sánchez et al.[22] (2010)	Hamstring	Screw	Staples	Not reported
Radice et al.[20] (2010)	Bone–patellar tendon–bone	Metallic interference screw or cross pin	Metallic interference screw with or without staples	Not reported
Vadalà et al.[24] (2013)	Hamstring	Swing-Bridge device*	Evolgate*	Immediate weight bearing and isometric exercises with brace for 2 wk, return to sports at 6 mo
Mirzatolooei et al.[23] (2013)	Quadrupled hamstring	Cross pin	Bioabsorbable interference screw	Not reported

*Citieffe, Bologna, Italy.

reconstructions are summarized in Table 2. Finally, the PRP parameters used in the different studies are summarized in Table 3.

The first study regarding PRP in ACL surgery was published by Ventura et al.[10] in 2005. They randomly assigned 20 patients to ACL hamstring reconstruction with or without PRP. Three milliliters of PRP was placed in both tunnels directly with autologous thrombin. Clinical outcomes were assessed with the Knee Injury and Osteoarthritis Outcome Score,[11] KT-1000 arthrometer (MEDmetric, San Diego, CA) testing, and the Tegner score.[12] Tunnel widening was measured with computed tomography (CT) at 6 months.

Orrego et al.[13] published a prospective randomized study in 2008 in which 53 patients underwent ACL hamstring reconstruction alone or ACL reconstruction with PRP placed on the graft (5 mL) and into the femoral tunnel (1 mL) after the graft was placed and secured. At 6 months, magnetic resonance imaging (MRI) was performed to assess graft maturation and tunnel healing. Clinical outcomes were assessed using the Lysholm score[14] and International Knee Documentation Committee (IKDC) score.[15]

In 2009 a randomized controlled study of 100 patients undergoing ACL bone-tendon-bone reconstruction with or without a platelet concentrate was published by Nin et al.[16] The PRP was placed on the graft and in the tibial tunnel. This study presented blinded MRI assessment and clinical evaluation at 24 months as endpoints.

Silva et al.[17] in 2010 published a prospective comparison of ACL double-bundle hamstring reconstruction with and without PRP. PRP was placed between the strands of the implant. Outcome assessment was performed at 3 months with MRI to establish the graft signal intensity relative to surrounding tissue as a measure of ligamentization.

In 2010 Vogrin et al.[18] compared ACL hamstring reconstruction without PRP and ACL reconstruction with PRP on the graft and in both tunnels in a randomized controlled, double-blind study. Outcome was assessed by MRI at 3 months postoperatively. In the same year Vogrin et al.[19] published another article in which anteroposterior knee stability with the KT-2000 arthrometer (MEDmetric) was evaluated before surgery and at 3 and 6 months after surgery in ACL-reconstructed patients with and without PRP.

Radice et al.[20] presented a prospective, single-blind, multicenter study of 100 patients in 2010. They used different surgical techniques (bone-tendon-bone for contact sports and hamstring for noncontact sports). PRP was placed on the graft. MRI assessment was performed monthly from 3 to 9 months by a blinded radiologist.

Table 3. PRP Parameters

Authors	PRP Technique	PRP Concentration	PRP Location (Volume)	Volume of Blood Drawn	Anticoagulant
Ventura et al.[10] (2005)	GPS*	9×	Both tunnels	54 mL	Citric acid (6 mL)
Orrego et al.[13] (2008)	GPS II*	9×	Graft (5 mL) and femoral tunnel (1 mL)	57 mL	Unknown (3 mL)
Nin et al.[16] (2009)	Noncommercial system	5×	Graft and tibial tunnel	40 mL	Not reported
Silva et al.[17] (2010)	Mini GPS III*	9×	Femoral tunnel (1.5 mL)	27 mL	Citric acid (3 mL)
Vogrin et al.[18] (2010)	Magellan†	12×	Graft (4 mL) and both tunnels (1 mL)	52 mL	Calcium citrate (8 mL)
Vogrin et al.[19] (2010)	Magellan	12×	Graft (4 mL) and both tunnels (1 mL)	52 mL	Calcium citrate (8 mL)
Figueroa et al.[21] (2010)	Magellan	12×	Graft (4 mL) both tunnels (3 mL)	55 mL	Citrate (5 mL)
Sánchez et al.[22] (2010)	BTI System II‡	3×	Graft (6 mL) and both tunnels	65 mL	Sodium citrate (3.8%)
Radice et al.[20] (2010)	GPS	9×	Graft (5 mL)	60 mL	Not reported
Vadalà et al.[24] (2013)	PRP Fast Biotech kit (MyCells)§	3×	Graft (5 mL) and both tunnels	10 mL	10% calcium gluconate
Mirzatolooei et al.[23] (2013)	Arthrex, Naples, FL	7×	Graft, femoral tunnel (2 mL), tibial tunnel (1.5 mL)	10 mL	Not reported

*Biomet, Warsaw, IN.
†Medtronic Biologic Therapeutics and Diagnostics, Minneapolis, MN.
‡BTI Biotechnology Institute, Vitoria, Spain.
§Kaylight Technologies Ltd., Holon, Israel.

In 2010 Figueroa et al.[21] reported a randomized, prospective study with a single-blinded evaluator that was performed in 2 consecutive series of patients who underwent hamstring ACL reconstruction with and without the use of PRP over a 14-month period. PRP was placed on the graft and in both tunnels. At 6 months, an MRI evaluation was performed, with observation of the graft's maturation and presence or absence of synovial fluid at the tunnel-graft interface. To facilitate interpretation, a scoring scale was designed to evaluate graft integration and maturation.

Sánchez et al.[22] focused on the morphology and histology of biopsy specimens from second-look arthroscopies after hamstring ACL reconstructions with and without PRP. PRP was placed on the graft. All second-look procedures were performed between 6 and 24 months after reconstruction.

In 2013 Mirzatolooei et al.[23] presented a study consisting of patients undergoing ACL reconstruction with a hamstring graft who were randomly allocated either to have PRP introduced into the tunnels perioperatively or not. CT of the knees was carried out on the day after surgery and at 3 months postoperatively, and the width of the tunnels was measured. Patients were also evaluated clinically at 3 months, when laxity was also measured.

Vadalà et al.[24] published a prospective randomized study in 2013 in which patients with both femoral and tibial 9-mm tunnels were enrolled. The patients were randomly assigned to a PRP group and a control group. All patients were followed up at a median of 14.7 months, with physical examination; the Tegner, Lysholm, and objective IKDC scoring scales; and KT-1000 arthrometer testing. Moreover, they underwent a CT evaluation to assess the amount of tunnel enlargement.

Outcomes

The main findings of the different studies analyzed are summarized in Table 4. Ventura et al.,[10] regarding graft maturation, presented CT data that showed a significant difference between groups ($P < .01$), with PRP ACL graft similar to native ACL tissue, whereas untreated grafts showed a more heterogeneous nature. From the clinical aspect, they found no differences in Knee Injury and Osteoarthritis Outcome Score, KT-1000 measurement, or Tegner score between the PRP group and control group at 6 months.

Orrego et al.[13] found no differences 3 months after surgery between the groups regarding MRI maturation criteria. At 6 months after surgery, 78% of the patients in the control group had low-intensity signal, whereas in the PRP group, low-intensity signal was present in 100% of the patients, with a statistically significant difference ($P = .036$). No statistical differences were observed regarding the osteoligamentous interface between groups. There was also no statistical difference in tunnel widening between the PRP and control groups. At 6 months postoperatively, Orrego et al. found no difference in Lysholm or IKDC scores.

The results of Nin et al.[16] did not show any statistically significant differences between the groups for

Table 4. Studies' Main Findings

Authors	Graft Maturation	Tunnel Healing/Widening	Clinical Evaluation
Ventura et al.[10] (n = 20)	CT highlighted a significant difference ($P < .01$) between ACL density of the 2 groups and showed that ACL density was similar to that of the posterior cruciate ligament in the PRP-treated group.[*]	NE	There were no significant differences concerning KOOS, IKDC score, KT-1000 testing, Tegner score rating, and clinical examination between the 2 groups 6 mo after ACL surgery.
Orrego et al.[13] (n = 53)	At 3 mo after surgery, no differences were found between the groups regarding MRI maturation criteria. At 6 mo after surgery, 78% of the patients in the control group had low-intensity signal, whereas in the PRP group, low-intensity signal was present in 100% of the patients ($P < .036$).[*]	No statistical differences were observed regarding the osteoligamentous interface between the groups.	There were no statistical differences between the groups regarding the functional results.
Nin et al.[16] (n = 100)	The results did not show any statistically significant differences between the groups for MRI appearance of the graft (although there was 20% to 25% improvement based on PRP use)	NE	The results did not show any statistically significant differences between the groups for inflammatory parameters (perimeters of the knee and C-reactive protein level) and clinical evaluation scores (visual analog scale, IKDC score, and KT-1000 arthrometer testing).
Silva et al.[17] (n = 20)	NE	There were not any differences between the groups when comparing the signal intensity in the fibrous interzone of the femoral tunnels on MRI.	NE
Vogrin et al.[18] (n = 50)	After 4-6 wk, in the intra-articular part of the graft, there was no evidence of revascularization in either group. At 10-12 wk, the results suggested initiation of revascularization in the PRP group, but without a statistical significance between the groups.	After 4-6 wk, the PRP-treated group showed a significantly higher level of vascularization at the osteoligamentous interface than the control group ($P < .001$).[*]	NE
Vogrin et al.[19] (n = 50)	NE	NE	Patients treated with PRP showed significantly better anteroposterior knee stability than patients in the control group ($P = .011$).[*]
Figueroa et al.[21] (n = 50)	The final mean maturation score was 4.45 points in the PRP group and 4.2 points in the control group ($P > .05$). There was a tendency toward a more hypointense signal of the graft evaluated by MRI in the PRP group (20% benefit in PRP group).	Good integration was found in 97.37% of patients in the PRP group and 94.74% in the control group ($P = .784$).	NE
Sánchez et al.[22] (n = 37)	Findings of arthroscopic evaluations were not statistically different between the PRP and control groups ($P = .051$). PRP treatment influenced the histologic characteristics of the tendon graft, resulting in tissue that was more mature than in control patients ($P = .024$).[*]	NE	NE

(continued)

Table 4. Continued

Authors	Graft Maturation	Tunnel Healing/Widening	Clinical Evaluation
Radice et al.[20] (n = 50)	The mean time to obtain a completely homogeneous intra-articular segment on MRI was 177 d after surgery in the PRP-added group and 369 d in the control group. The PRP-added group needed only 48% of the time that the control group required to achieve the same MRI findings ($P < .001$).*	NE	NE
Vadalà et al.[24] (n = 40)	NE	Femoral tunnel diameter increased with no statically significant differences between groups ($P = .043$). Tibial tunnel diameter increased with no statically significant differences between groups ($P = .028$).	Physical examination findings, as well as the evaluation scales used, showed no differences between the 2 groups.
Mirzatolooei et al.[23] (n = 46)	NE	Despite slightly less tunnel widening in the PRP group, there was no significant difference between the groups at the femoral opening and mid tunnel ($P = .370$ and $P = .363$, respectively) or at the tibial opening and mid tunnel ($P = .333$ and $P = .177$, respectively).	Arthrometric results had improved significantly in both groups.

ACL, anterior cruciate ligament; CT, computed tomography; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; MRI, magnetic resonance imaging; NE, non-evaluated; PRP, platelet-rich plasma.

*Positive results.

inflammatory parameters (perimeters of the knee and C-reactive protein level), MRI appearance of the graft (although there was an improvement consistent with 20% to 25% based on platelet use), and clinical evaluation scores (visual analog scale, IKDC, and KT-1000 arthrometer). Silva et al.[17] found no significant difference between proton density–weighted and T1-weighted tunnels and showed 31% hypointense interfaces for both groups in the posterolateral tunnels and 28.6% for both groups in the anteromedial tunnels at the earliest follow-up of 3 months.

Vogrin et al.[18] focused on vascularization in their MRI analysis but found no differences in the intra-articular portion of ACL grafts with PRP treatment and without such treatment at 12 weeks. They also assessed vascularization at the bone-ligament interface and found a significantly better score for the group treated with PRP ($P < .001$). In addition, Vogrin et al.[19] noted significantly better anteroposterior knee stability in patients treated with PRP than in patients in the control group ($P = .011$).

Radice et al.[20] focused on the time course of graft homogenization and showed that the addition of PRP reduced this time from 369 to 177 days on average. This means that ACL reconstructions with PRP needed only 48% of the time of controls to achieve the same MRI findings ($P < .001$).

Figueroa et al.[21] compared grafts with semitendinosus muscle tissue at 6 months postoperatively and found 63.2% hypointense grafts in the platelet group but only 42.11% hypointense grafts in the control group with no PRP (20% benefit but with no statistical significance between groups). They also found no synovial fluid at the tendon-bone interface in 86.8% of patients receiving platelets and 94.7% of the control patients (with no statistical significance between groups) at 6 months of follow-up.

Sánchez et al.[22] performed an arthroscopic macroscopic evaluation based on synovial coverage, thickness, and tension of the ACL reconstruction and showed excellent ratings for 57.1% of PRP ACL grafts and 33.3% in the control group (with no statistical significance between groups). Histologic assessment showed a significantly better maturity index for ACL grafts and more newly developed synovial tissue enveloping the PRP grafts (77% of cases) compared with the control grafts without PRP (40%) ($P = .024$).

Mirzatolooei et al.[23] found that despite slightly less tunnel widening in the PRP group, there was no significant difference between the groups at the femoral opening or the mid-femoral tunnel or at the tibial opening or mid-tibial tunnel. Clinical results were similar between the 2 groups.

Vadalà et al.[24] found no differences in tunnel enlargement between the PRP group and non-PRP group. Physical examination findings, as well as the evaluation scales used, showed no differences between the 2 groups.

Discussion

This systematic review assessed the effects of PRP on different outcomes in ACL reconstruction. Regarding ACL graft maturation, there is some promising evidence that the addition of PRP to the graft or tunnels could be a synergic factor in acquiring maturity more quickly than grafts with no PRP.[10,13,20,22] There were 2 studies that showed a tendency toward this outcome, but the small sample size numbers probably made it difficult to obtain statistically significant differences between the groups.[16,21] There was 1 study that showed no differences regarding maturation when using or not using PRP in ACL reconstruction.[18]

If we consider tunnel healing and tunnel widening, it seems that PRP offers little or no benefit.[13,17,21,23,24] All studies showed similar results between groups with and without PRP, with only 1 study (Vogrin et al.[18]) showing better vascularization at the bone-ligament interface in the PRP group. In fact, Vogrin et al.[19] were the only authors who found a clinical benefit with the addition of PRP in a subsequent study, in which they showed more anteroposterior stability in ACL reconstructions with PRP. The other studies showed no benefit in clinical outcomes with the use of PRP in ACL reconstruction.[10,13,16,23,24]

Limitations

Most of the limitations of this study are related to the studies reviewed. We assessed the quality of the 11 studies reviewed using the Detsky scale[8] for randomized controlled trials and the Newcastle-Ottawa Scale[9] for prospective cohort studies. We found 6 studies to be of high methodologic quality, 5 studies to be of moderate quality, and no studies to be of low quality.

The considerable heterogeneity of the studies is another problem when attempting to find valuable results or conclusions. (1) The volume and concentration of PRP, (2) the location of the injection, (3) the presence of anticoagulants and triggers, (4) the different surgical techniques, and (5) the different rehabilitation schemes affect the results and make them less comparable. Because of this, we did not perform a quantitative analysis of the studies reviewed, a fact that limits the conclusions made by this systematic review.

Conclusions

Using the best current evidence available on the use of PRP in ACL reconstruction, we can conclude that regarding ACL graft maturation, there is some promising evidence that the addition of PRP to the graft or tunnels could be a synergic factor in acquiring maturity more quickly than grafts with no PRP, with the clinical implication of this remaining unclear. Considering tunnel healing and tunnel widening, it seems that PRP offers little or no benefit.

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