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The effect of platelet concentrates on graft maturation and graft-bone interface healing in ACL reconstruction in human patients:

A systematic review of controlled trials

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Abstract

Purpose—To systematically review the current evidence for effects of platelet concentrates on (1) graft maturation and (2) graft-bone interface healing in ACL reconstruction in human, controlled trials, and for ensuing differences in clinical outcomes.

Methods—A systematic search of PubMed, CINAHL, EMBASE, CCTR and CDSR was performed for controlled trials of human ACL reconstruction with and without platelet concentrates. Data validity was assessed and data were collected on graft maturation, graft-bone interface healing and clinical outcome.

Results—Eight studies met the inclusion criteria. Seven studies reported on graft maturation with significantly better outcomes in the platelet groups in four, and large differences in means in two (underpowered) studies. Five studies report on tunnel healing, but four found no difference between groups. Three studies assessed clinical outcome but found no differences, regardless whether they had shown a benefical (1/3) or no effect (2/3) of platelets on graft and tunnel healing.

Conclusion—The current best evidence suggests that the addition of platelet concentrates to ACL reconstruction may have a beneficial effect on graft maturation and could improve it by 20–30% on average, but with substantial variability. The most likely mode of action is that treatment with platelets accelerates graft repopulation and remodeling, and this interpretation is supported by the existing data and biologically plausible. However, the current evidence also shows only a very limited influence of platelet concentrates on graft-bone interface healing and no significant difference in clinical outcomes.

Clinical Relevance—This systematic review collected evidence that the use of platelet concentrates may be a safe and inexpensive way to optimize graft maturation after ACL reconstruction, but there is no evidence for improved graft-bone interface healing or a significant difference in clinical outcomes.

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Level of Evidence—Level IV, systematic review of Level II, III, and IV studies.

1. Introduction

1.1. Rationale

Platelet concentrates are popular tool in clinical orthopedics and orthopedic research(1, 2). As a rich source of a plethora of growth factors, platelets are used in fracture healing, spine fusion, as local injections in tendinopathies, and as adjuncts in tendon repair procedures(3–10). One promising fields of platelet concentrate use, however, is sports medicine(1, 2). Platelets, often in combination with scaffolds, are employed in the management of anterior cruciate ligament ruptures and rotator cuff tears(11, 12). A number of new tissue engineering-based regenerative treatments, such as bio-enhanced ACL repair, are being investigated (11, 12), but in this study we want to focus on the effectiveness of clinically available platelet-based treatments for the ACL.

The current gold standard for treating ACL tears is ACL reconstruction, using autogeneic or allogeneic tendon grafts(13, 14). While a number of techniques for tendon preparation and fixation are available, all methods share a common postoperative scenario consisting of two main biologic processes: graft-to-bone healing in the femoral and tibial tunnels(15, 16), and ligamentization of the intra-articular portion of the tendon graft(17, 18). The success of ACL reconstruction depends heavily on these processes, and to improve their outcomes and assure optimal clinical results, platelet concentrates are being used. The rationale behind the use of platelets is the assumption of improved tunnel healing and faster and/or better graft remodeling due to the growth factors released from activated platelets(1, 19, 20). It was the aim of this study to systematically review the current literature for evidence that would substantiate this assumption.

1.2. Objective

The primary objective of this study was to systematically accrue evidence for effects of platelet concentrates on (1) graft maturation and (2) graft-bone interface healing in ACL reconstruction in human, controlled trials. Our primary hypothesis was that the addition of platelet concentrates improves both graft maturation and graft-bone interface healing,

Furthermore, data were collected for clinical outcomes, if provided in the same studies, to assess associations between of differences in clinical outcome with differences in maturation and interface healing based on platelet use. We hypothesized that the improvement in graft maturation and graft-bone interface healing would reflect in improved clinical function in the immediate postoperative phase.

2. Materials and Methods

This systematic review was performed following the PRISMA (*P*referred *R*eporting *I*tems for *S*ystematic reviews and *M*eta-*A*nalyses) statement (21). The PRISMA statement (www.prisma-statement.org), put forward by the CONSORT group (www.consort-statement.org) is a evidence-based guideline for conducting and reporting systematic reviews, and was formerly known as the QUOROM (*Q*uality *O*f *R*eporting *O*f *M*eta-analysis) statement(22).

2.1 Eligibility criteria

Studies were included if they reported on graft maturation and/or graft-bone interface healing in human patients undergoing ACL reconstruction augmented with platelet concentrates. All types of ACL reconstruction were eligible. Platelets could be applied as a

liquid or gel, with or without a carrier scaffold to the graft or tunnel(s) or both at the time of surgery. Repeated applications, postoperative injections or combination of platelets with other chemicals or bioactive reagents (growth factors, cytokines, etc) were not eligible. Animal studies were not eligible. No limit was set for minimum follow-up duration since it is sensible to assume the effects of platelet concentrates to be strongest in the short-term and plateau in the long-term. Reporting of clinical data was searched for, but not an inclusion criterion.

2.2 Data sources

The online databases PubMed, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews (CDSR) were searched for relevant publications. All dates and languages were included. The last search was performed on May 1st, 2011.

2.3 Search Strategy

The search algorithm was "**(((ACL)OR (anterior cruciate ligament))AND (reconstruction))OR (ACL reconstruction)) AND platelets"** and was replicated using the keywords as MeSH terms as well. The search algorithm was intentionally kept fairly general to maximize return. All searches were unlimited, i.e., considering publications in all languages and regardless of publication date. In addition to the online searches, the bibliographies of the included studies were reviewed to identify additional publications.

2.4 Study selection

Studies were excluded if title and abstract clearly refuted eligibility. Full texts were obtained for all studies matching the inclusion criteria and all with unclear eligibility. The obtained full texts were reviewed to re-confirm eligibility. All study selections were done independently in duplicate and cross-referenced. Disagreement was resolved by consensus.

2.5 Data items and collection process

Data were extracted for the endpoints maturation and graft-bone interface healing. Eligible methods for assessment of graft maturation were radiological imaging and histology of graft biopsies. Eligible methods for assessment of graft-bone interface healing were histology, MRI, and CT. For the secondary endpoint, clinical outcome, all reported endpoints (clinical scores, AP laxity, subjective patient evaluation, etc) were admitted. All data were extracted independently and in duplicate. Duplicate data extractions were compared for difference and disagreement was resolved by consensus.

2.6 Risk of bias in individual studies

The risk of bias was assessed through categorization by level-of-evidence. Additionally a modified Jadad Score was used(23–25). This score gives one point each for randomization, concealed allocation, and reporting of sample size calculation/attrition. Three points (pts) is the best possible outcome, zero the worst (26).

2.7 Data synthesis

We did not perform a quantitative data analysis because of the clinical heterogeneity, such as different types of platelet concentration systems (with different anticoagulants), different platelet concentrations, different ACL techniques, and different methods of outcome assessment. However, all studies used a platelet concentrate in a human ACL autograft model with imaging (MRI/CT) assessment of graft maturation and/or tunnel healing between 3 and 24 months, which is sufficient similarity to allow direct, descriptive comparison.

3. Results

3.1 Study selection

Our online search produced 57 results in total. All 57 publications were obtained and reviewed based on the criteria described above. One paper was published in a Chinese medical journal and could not be obtained for this study(27). One additional paper was identified by cross-referencing the bibliographies of the included papers. Finally, 8 papers reporting on a total of 380 patients (198 ACL reconstructions with platelets, 182 ACL reconstructions without platelets) were included in this analysis(28–35). (Figure 1) These papers were published between 2005 and 2010 in English.

3.2 Characteristics of the included studies

The average patient age across all studies was 28.9 ± 3.4 years, the patients in the control group were slightly younger by 1.5 ± 2.9 years on average (p=0.451). A average of 26 ± 12 patients were included per study. 23 ± 13% of patients were female. The longest follow-up was at, on average, 10.5±9.5 (range 1.5 to 24) months after ACL reconstruction. Table 1 summarizes the characteristics of these studies. All reports used bone-tendon-bone or hamstring autografts. (Table 2) Four papers report the use of a GPS® system (Gravitational Platelet Separation System, Biomet, Warsaw, IN)(30, 31, 33, 35), two used the Magellan® system (Medtronic, Minneapolis, MN)(28, 34), one used the BTI system II® (BTI Biotechnology Institute, Vitoria, Spain)(32) and one group did not use a commercial system but a Beckman (J-6B, Beckman Coulter Spain, Madrid Spain) centrifuge to create a platelet concentrate of 4.9-fold concentration(29). The concentration of platelets in the concentrates relative to whole blood was approximately 9× for the GPS®, 12× for the Magellan®, and 3× for the BTI® system. Throughout this paper, these platelet concentrations will be referred to as 3×, 5×, 9×, and 12×. (Table 3)

The earliest study by far was published by Ventura et al in 2005(35). 20 patients were randomly assigned to ACL reconstruction with (n=10) or without (n=10) a 9× platelet concentrate (level-II evidence). All patients received a quadrupled hamstring autograft that was fixed with BioTransFix (Arhtrex, Naples, FL) proximally and interference screws (BioRCI, Smith and Nephew, Andover, MA) distally. 3mL of platelet concentrate were placed in both tunnels directly with autologous thrombin and KOOS, KT-1000, Tegner and CT were used for outcome assessment at 6 months. A limited number of patients was assessed with MRI additionally.

Orrego et al, in 2008 level-II study, prospectively assessed 108 patients randomly allocated to receive ACL reconstruction alone (n=27), or ACL reconstruction with a platelet concentrate of 9× (n=26) placed on the graft (5mL) and into the femoral tunnel (1mL) after the graft was placed and secured (30). Another 55 patients were treated with a bone-plug and therefore excluded from this study. ACL reconstruction was done by four different surgeons using a quadrupled semitendinosus-gracilis graft fixed with biodegradable pins (Biotransfix, Arthrex, Naples, FL) proximally and biodegradable interference screws (Biodelta, Arthrex, Naples, FL) distally. The concentrate was added between the strands of the hamstring graft and once a firm adhering clot had formed, the graft was pulled into the tunnel. At 6 months MRI imaging was done to blindly assess graft maturation and tunnel healing, as well as clinical assessment using the Lysholm and IKDC scores.

Silva et al published a prospective level-II comparison of ACL reconstruction with and without 9× platelet-rich plasma (PRP) of 10 and 10 patients in 2009.(33) Another 20 patients received PRP three times over 4 weeks or with thrombin and were therefore not eligible for this review. They used a double-bundle technique (semitendinous AM, gracilis PL) with Endobutton (Smith and Nephew, Andover, MA) fixation proximally and bioabsorbable

interference screws (Smith and Nephew, Andover, MA) distally. The platelet concentrate was placed between the strands of the implant after it had been placed and secured. Outcome assessment was done at 3 months with MRI to establish the graft signal intensity relative to surrounding tissue as measure of ligamentization.

During that same year, a randomized controlled study of 100 patients undergoing ACL reconstruction (bone-tendon-bone with femoral RigidFix (DePuy Mitek, Raynham, MA) and tibial biodegradable interference screw fixation) with and without a platelet concentrate (n=50 each) was published by Nin et al.(29) The 5× platelet concentrate was allowed to gel and placed on the graft before it was folded and tubularized, so that the gel would remain at the center of the implant during passage. The remaining gel was placed in the tibial tunnel after the graft had been placed. This level-I study presented blinded MRI assessment as well as clinical evaluation at 24 month as endpoints.

In 2010, Vogrin et al compared 20 ACL reconstructions with 21 ACL reconstructions with 4mL of a 12× platelet concentration on the graft and 1 mL in both tunnels in a level-I randomized, controlled, double-blind study(34). The surgical technique used was a double-looped semitendinosus-gracilis graft with crosspins and a tibial bioscrew (both Mitek), all prodcedures were performed by the same surgeon. The graft was covered with platelet gel before being pulled into the tunnels. After graft fixation the remaining gel was placed in the tunnels. Outcome was assessed by MRI 3 months post-operatively.

Three more studies were published in 2010, all of level-III evidence. Radice et al present a prospective, single-blinded study of two groups of 50 athletes each(31). As a multi-center study, different types of ACL reconstruction were used: Bone-tendon-bone (metallic interference screws) for rugby and soccer players and hamstrings (TransFix and tibial screws with metallic staples, both Arthrex, Naples, FL) for skiing, hockey, tae kwan do, and volleyball. For the experimental group, 5mL of platelet concentrate were soaked in a absorbable, porcine, gelatin sponge (Gelfoam, Pfizer, New York, NY) which was either wrapped around the bone-tendon-bone graft or placed in-between strands of hamstrings before implantation. MRI assessment was performed monthly from 3 to 9 month by a blinded radiologist.

Figueroa et al report on a non-randomized comparison of MRI results 14 month after ACL reconstruction in 20 patients with ACL reconstruction with a platelet concentrate in 30 controls(28). Hamstring grafts fixed with TransFix (Arthrex, Naples, FL) and Delta screws (Arthrex, Naples, FL) were used by two different surgeons and, in the experimental group, augmented with 4mL of a 12× concentrate on the graft and 3mL in the femoral and tibial tunnel each using, under arthroscopy, a long needle after the graft was placed and fixed. This is the only study that reports a formal sample size assessment.

The only study without imaging results was published by Sanchez et al, who instead focused on gross morphology and histology of biopsies (3mm × 5–10 mm from proximal end) from second look arthroscopies after hamstring ACL reconstruction with screw fixation proximally and distally(32). 22 patients had received a 12× platelet concentrate by injection of 6 mL into the graft and letting it soak in platelet concentrate before implantation, 15 patients without such treatment served as controls. All second look procedures were done between 6 and 24 months after reconstruction.

3.3 Risk of bias in the included studies

Two studies were blinded, randomized controlled trials with less than 20% attrition and narrow confidence intervals and thus qualify as level-I evidence(29, 34). Three studies were classified as level-II(30, 33, 35), and the remaining three as level-3 comparative studies(28,

31, 32). The average Jadad score was 1.6±1.1 points. No other reasons, such as potential selection bias or attrition bias, for a systematic deviation from the truth were observed. (Table 1)

3.4 Graft Maturation

Six publications provide data on MRI assessment of maturation, assuming that homogenously low signals, similar to native ligaments, are a sign of a maturing graft. Orrego et al classified the graft as high-intensity (similar to synovial fluid) or low-intensity (similar to native posterior cruciate ligament) and found 100% low-intense grafts in the platelet group but only 78% in the control group (p=0.036) at 6 months(30). Figuero et al compared the graft to the semitendinous 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 without platelets (p=0.316)(28). Nin et al found a 21% lower intensity on PD- and 23% lower intensity on T2-weighted MRI images in the platelet group at 24 months (p=0.454 and 0.100) (29). These papers show a consistent 20–30% difference between ACL reconstruction with and without platelets, even though this difference was not always statistically significant, most likely because of the rather small sample sizes and considerable variability.

Radice et al focused on the time course of graft homogenization and showed that the addition of platelet concentrates reduced this time from 369 days to 177 days on average(31). Vogrin et al, in turn, focused on vascularization in their MRI analysis but found no differences of the intra-articular portion of ACL grafts treated with platelets and without such treatment at 12 weeks(34).

Sanchez et al assessed ACL grafts in gross morphology and histologically. Arthroscopic gross evaluation based on synovium coverage, thickness, and tension revealed excellent ratings for 57.1% of platelet treated ACL grafts, but only 33.3% in the control group (p=0.051)(32). Histological assessment revealed a significantly better maturity index for ACL grafts (12 pts vs 14 pts, p=0.024), and more newly developed synovial tissue enveloping the platelet treated grafts (77% of cases) compared to the control grafts without platelets (40%), which is consistent with a statistically significant difference (p=0.023). Also, in the platelet group, the maturation of this synovial envelope was correlated with healing time (p=0.014 for correlation with follow-up duration), but haphazard in the control group (p=0.674 for correlation with follow-up duration).

Ventura et al presented CT data, which showed a significant difference between groups (p<0.01) with platelet treated ACL graft similar to native PCL tissue, while untreated grafts showed a more heterogeneous nature(35).

3.5 Graft-Bone Interface Healing

Five studies present data on the effect(s) of platelet concentrates on tunnel healing. Silva, in a double-bundle study with 6 months follow-up found no significant difference between PD-weighted and T1-weighted tunnels and showed 31% hypointense interfaces for both groups in the posterolateral tunnels and 28.6%, again for both groups, in the anteromedial tunnels at the earliest follow-up of 3 months(33). The study by Orrego and coworkers showed no osteoligamentous interface in 67% of controls and 88% of platelet treated knees (p=0.107) at 6 months(30). There was no difference in the occurrence of tunnel widening at the same follow-up (p=0.452). Figueroa et al. found no synovial fluid at the tendon-bone interface in 86.8% of patients receiving platelets and 94.7% of the controls (p=0.720) at 6 months of follow-up(28). Vogrin et al assessed vascularization of the interface and found a significantly better score for the group treated with platelets (p<0.001)(34). Ventura et al

were not able to assess the interface on CT because of artifacts from bony sclerosis about the tunnels(35).

3.6 Clinical results

Three studies report clinical evaluations in addition to graft and tunnel assessment(29, 30, 35). Ventura et al found no differences in KOOS (83 vs 84 pts), KT-1000 (0.8 mm vs 1.2 mm) or Tegner scores (0.9 pts vs 0.8 pts difference pre- to postoperative) between the platelet treated group and controls at 6 months but had seen a significant difference in graft homogeneity on CT (35). Orrego et al, at 6 months post-operatively, found no difference in Lysholm or IKDC scores either, although they did find a difference in graft maturation(30). Nin et al found no difference in inflammatory markers in peripheral blood, nor differences in range of motion, VAS, KT-1000, or IKDC score, in analogy with no difference seen in radiological outcomes at 24 months of follow-up(29).

4. Discussion

4.1 Summary of evidence

This systematic review assessed the effects of platelet concentrates on graft maturation and graft-bone interface healing in ACL reconstruction in human patients. The, somewhat limited, evidence from the current literature suggests that platelet concentrates may improve the rate at which grafts achieve a low signal on T2 imaging and histologic evidence of graft remodeling but have only little to no effect on tunnel healing. (Table 4)

Currently, it is estimated that 125,000 ACL reconstructions are performed per year in the US alone(36, 37). The outcome of such a procedure depends on two biological events that occur after the implantation–maturation of the graft and integration and secure fixation of the graft into the osseous tunnel. After implantation, the tendon graft matures by changing into a more ACL-like structure by changes in ultrastructure(38–40), vascularization(41, 42), and innervation(43–47). During the first two weeks after implantation there is histological evidence for central necrosis and subsequent hypocellularity in the graft, followed by a phase of vascularization and repopulation by host cells from week 4 to 10. Finally, the graft becomes more similar to the native ACL over 4 to 6 months. During this time the biomechanical strength of the graft is significantly compromised, but recovers over 6 to 12 months. At the same time, a fibrous interface develops between the implant and the surrounding bone. Weiler et al defined this interface as a disorganized, highly cellular and vascular granulation tissue(15, 16). Over time this tissue matures into a hypocellular and hypovascular dense connective tissue with Sharpey-like collagen fibres. Platelet concentrates are being used to stimulate both processes.

The first outcome for which we collected evidence in this study was graft maturation. Seven studies report on this outcome, but use different methods, different scores, and different follow-up time points. For those that use MRI, it is noteworthy that a healthy ligament shows a homogenous, low intensity signal in T2- and PD-weighted images. Generally, four out of seven studies observed positive effects of platelets on the intra-articular grafts. Such effects included reaching a higher level of tissue homogeneity on MRI or in histology, or reaching such a state earlier. Maybe more interesting is taking a look at three studies that did not find a difference in graft maturation. Nin et al measured graft intensity on proton density-weighted (PD) and T2-weighted images. While they found no significant differences, the mean scores were 230 vs 190 on PD and 75 vs 61 on T2 images for platelet treated grafts and controls, respectively, consistent with a 20–25% improvement based on platelet use. This numbers suggest the possibility of a type-II error, or “not seeing what truly is there”, based on insufficient sample size(48, 49). Figueroa et al found generally low

numbers of hypotense grafts on MRI for both groups (63.2% in the platelet group, 42.11% in the control group) despite the relatively long follow-up of 6 months, but again found a 20% difference and the same argument of low power made for Nin et al above can be made here.(28). Vogrin et al, in turn, focused specifically on difference in vascularization, not overall graft maturation, and found no significant difference in this parameter between ACL reconstructions with or without platelets(34). Interestingly, the studies that did not find a difference had various lengths of follow-ups (3, 6, and 24 months) and high concentrations of platelets (12× and 5×), ruling these parameters out as reasons for different outcomes. One explanation that is in agreement with all the available evidence and biologically plausible is that the addition of platelet concentrates, i.e. a source of growth factors, speeds up the maturation process, including cellular repopulation and remodeling, as shown by Orrego, Radice, and Ventura, as well as animal studies(30, 31). However, the beneficial effect of platelets wears off rapidly and no difference can be seen at later time points, as reported by Figueroa and Nin, other than on the microscopic level as demonstrated by Sanchez et al(32). Also, some (late stage) ligamentization processes, such as vascularization, seem not to be affected by platelets, as Vorgin and coworkers observed at 3 and 6 months(34).

The second determinant of success of ACL reconstruction studied herein was graft-bone interface healing. Data are available from 5 studies, but only two found a beneficial effect of platelets. Vogrin et al saw a higher level of interface vascularization, which is essential for bone remodeling, at 3 months, but not 6 months(34). This “early stage” effect is consistent with the mode of action posited above. Orrego et al found a borderline significant positive effect of platelets at six months postoperatively, while all other studies reporting on tunnel healing found no differences (30). All studies but Vogrin et al assess tunnel healing at 6 months of follow-up, which is an interesting fact because earlier studies have suggested that graft integration is largely complete by 12 weeks(50).

Finally, we were interested in assessing whether differences in graft and tunnel healing, or the lack thereof, would translate into differences in clinical outcomes. The three studies that evaluated clinical outcomes used different assessment tools but uniformly reported no differences between groups. Two issues should be considered when interpreting these data. First, the rationale for the use of platelets is to improve (the speed of) graft maturation, which is not necessarily visible in clinical scores focusing on pain, range of motion, and activities-of-daily-living. Second, considering that the most likely “clinical” effect of improved graft and tunnel healing is reduced rates of clinical graft failure, the current studies would be critically underpowered to assess differences in this rare outcome (even if they had included assessment of such outcomes). However, the current best evidence indicates no difference in clinical outcomes between ACL reconstruction with or without platelet concentrates.

After summarizing the findings from the included studies, we also want to focus on the second, no less important task of a good systematic review, identifying blank spots in the literature and describing ways to address them and to improve and expand the available evidence. One of the most obvious differences and the most commonly raised question in the included primary studies was the concentration of the used platelet concentrate. On the one hand, if a beneficial effect is to be assumed, one could also assume a dose-response relationship and opt for higher dosages to maximize the treatment effect. On the other hand, overdosing of platelet-released growth factors can be detrimental for two reasons, first, because of an over stimulation of cells leading to a poorly differentiated, chaotic scar, and second, because some of the released growth factors might precipitate adverse events, such as suppression of osteoclast generation (51). While, to the best of our knowledge, there are no human studies to assess the dose-response relationship of platelet concentrates and ACL healing, data is available from large animal models, suggesting that 3× and 5× concentrates

lead to equivalent biomechanical outcomes(52). Thus reducing platelet concentrations would be a safe way to minimize the potential for detrimental effects and the volume of blood needed from the patient without jeopardizing mechanical outcomes.

4.2 Limitations

This study has potential shortcomings. Like any systematic review the quality of this study depends on the quality of the primary data. We assessed the validity of these 8 studies based on levels-of-evidence and the Jadad score. Both methods are composite scores that focus on study design, such as randomization, concealed allocation, and attrition. The included studies scored in the middle to high range, which is representative for orthopedic research studies. However, neither score gives a comprehensive assessment of study validity, as they do not include parameters such as sample size estimation.

Beyond study design, another potential shortcoming is the clinical heterogeneity of the included studies. While age and gender distribution were uniform among all groups, as were postoperative rehabilitation algorithms, there were considerable differences in the used surgical techniques as well as the choice and placement of platelet concentrates. While some of these differences are only little, some might very well have major implications on healing, such as adding the platelet concentrate by injecting it on the graft under arthroscopy versus wrapping the graft in a biomaterial soaked in a platelet gel. As a matter of fact, these differences spurred a number of letters criticizing the lack of clarity when it comes to the description of the platelet concentrates uses (53)–after some authors have used platelet concentrates but referred to them as, for example, PDGF(29, 54). Interestingly, the authors of the included studies wrote letters commenting on the methods used in other studies, also included here, showing the extent of disagreement among investigators as what platelet concentration to use, and how to assess its effects(54). These differences stopped us from conducting a formal quantitative data synthesis, but it is still possible and valid to deduce evidence for a general, overall effect of platelet concentrates.

5. Conclusion

The current best evidence suggests that the addition of platelet concentrates to ACL reconstruction may have a beneficial effect on graft maturation and could improve it by 20–30% on average, but with substantial variability. The most likely mode of action is that treatment with platelets accelerates graft repopulation and remodeling, and this interpretation is supported by the existing data and biologically plausible. However, the current evidence also shows only a very limited influence of platelet concentrates on graft-bone interface healing and no significant difference in clinical outcomes.

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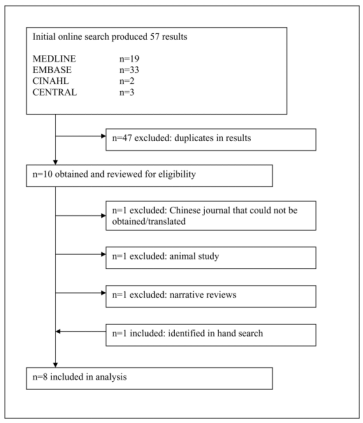

Figure 1.
Trial flow

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Table 1

Characteristics of the included studies

Author	randomized*	blinded assessment*	power calculation*	Jadad Score	LoE	follow- up (mo)	Mean Age Platelet Group	Mean Age Control Group	% female	n Platelet Group	n Contro Group
Ventura et al. 2005	yes	no	no	1	2	6	36.6	30.2	0.1	10	10
Orrego et al. 2008	yes	yes	yes	3	2	6	30	30	0.15	26	27
Nin et al. 2009	yes	yes	no	2	1	24	26.1	26.6	0.22	50	50
Silva et al. 2009	yes	no	no	1	2	3	26.8	26.8	0.05	10	10
Vogrin et al. 2010	yes	yes	no	2	1	3	37.2	32.6	0.43	25	25
Figueroa et al. 2010	yes	yes	yes	3	3	6	26.8	23.6	0.34	30	20
Sanchez et al. 2010	no	no	no	0	3	24	28	28	0.3	22	15
Radice et al. 2010	no	yes	no	1	3	9	30	32	0.22	25	25

* whether reported in paper.

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Table 2

Surgical Parameters

Author	Graft	Femoral Fixation	Tibial Fixation	Rehabilition Program*
Ventura et al. 2005	Quadrupled Hamstring	Cross Pin	Bioabsorbable Interference Screw	immediate mobilization w/o brace, protected weight bearing for 3 weeks, return to sports @ 6 months
Orrego et al. 2008	Quadrupled Hamstring	Cross Pin	Bioabsorbable Interference Screw	accelerated rehab protocol
Nin et al. 2009	Bone-Patellar Tendon-Bone	Cross Pin	Bioabsorbable Interference Screw	immediate mobilization w/o brace, cycling @ 2–3 months, runnning @ 4 month, return to sports @ 6 months
Silva et al. 2009	Hamstring - Double Bundle	Extracortical Button	Bioabsorbable Interference Screw	Immobilization with brace for 1st week, progressive ROM and protected weight bearing until 5th week
Vogrin et al. 2010	Double-looped Hamstring	Cross Pin	Bioabsorbable Interference Screw	immediate mobilization w/o brace, closed kinetic chain exercises, runnning @ 12 weeks, return to sports @ 6 months
Figueroa et al. 2010	Hamstrings	Cross Pin	Bioabsorbable Interference Screw	accelerated rehab protocol
Sanchez et al. 2010	Hamstrings	Screw	Staples	not reported
Radice et al. 2010	Bone-Patellar Tendon-Bone OR Hamstring	Metallic Interference Screw OR Cross Pin	Metallic Interference Screw ± Staples	not reported

* abbreviated,

Table 3

Platelet Concentrate Parameters

Author	PRP Technique	PRP Concentration	PRP location (volume)	Volume Blood Drawn	Anticoagulant	Comments
Vogrin et al. 2010	Magellan	12×	graft (4mL) and both tunnels (1mL)	52 mL	Calcium Citrate (8 mL)	
Figueroa et al. 2010	Magellan	12×	graft (4 mL) both tunnels(3 mL)	55 mL	Citrate (5 mL)	
Nin et al. 2009	5× home made	5×	graft and tibial tunnel	40 mL	?	
Silva et al. 2009	Mini GPS III	9×	femoral tunnel (1.5m)l	27 mL	Citirc Acid (3mL)	
Orrego et al. 2008	GPS II	9×	graft (5 mL) and femoral tunnel (1 mL)	57 mL	unknown 3 mL	
Sanchez et al. 2010	BTI System II	3×	graft (6 mL) and both tunnels	65 mL	Sodium Citrate(3.8%)	
Radice et al. 2010	GPS	9×	graft (5 mL)	60 mL	?	with biomaterial
Ventura et al. 2005	GPS	9×	both tunnels	54 mL	Citirc Acid(6 mL)	

Table 4

Conclusion presented in included studies

Authors	Imaging - Graft	Imaging - Tunnel	Histology - Graft
Vogrin et al. 2010	…without a statistically signficance between both groups.	…enhances early revascularization in the interface…	
Figueroa et al. 2010	… with MRI at 6 months after reconstruction, we did not find any statistically significant benefit in the APC group in terms of integration assessment and graft maturation		
Nin et al. 2009	… use of PDGF i[…] has no discernable clinical or biomechanical effect at 2 years' follow-up.		
Silva et al. 2009		…use of PRP […] does not seem to accelerate tendon integration.	
Orrego et al. 2008	…enhancing effect on the graft maturation process…	…without showing a significant effect in the osteoligamentous interface or tunnel widening…	
Sanchez et al. 2010			…resulting in more remodeling compared with untreated grafts…
Radice et al. 2010	… a time shortening of 48%…		
Ventura et al. 2005	…transformation from autologous QHTG to new ACL was faster in the GF-treated group than in controls		