

Has Platelet-Rich Plasma Any Role in Anterior Cruciate Ligament Allograft Healing?

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Purpose: The aim of this study was to evaluate and compare the clinical and inflammatory parameters with the addition of platelet-derived growth factor (PDGF) in primary anterior cruciate ligament (ACL) reconstruction with bone–patellar tendon–bone allograft. **Methods:** We prospectively randomized 100 patients undergoing arthroscopic patellar tendon allograft ACL reconstruction to a group in whom platelet-enriched gel was used ($n = 50$) and a non-gel group ($n = 50$). The platelet concentration was $837 \times 10^3/\text{mm}^3$, and the gel was introduced inside the graft and the tibial tunnel. Demographic data were comparable between groups. The mean follow-up was 24 months for both groups and included a history, clinical evaluation with the International Knee Documentation Committee score, radiographs, and magnetic resonance imaging. **Results:** There were no differences in the number of associated injuries. The results did not show any statistically significant differences between the groups for inflammatory parameters (perimeters of the knee and C-reactive protein level), magnetic resonance imaging appearance of the graft, and clinical evaluation scores (visual analog scale, International Knee Documentation Committee, and KT-1000 arthrometer [MEDmetric, San Diego, CA]). **Conclusions:** At this time, the therapeutic role of PDGF in ACL reconstruction remains unclear. The use of PDGF, on the graft and inside the tibial tunnel, in patients treated with bone–patellar tendon–bone allografts has no discernable clinical or biomechanical effect at 2 years' follow-up. More clinical studies will be needed to show the efficacy and use of these factors in daily practice in ACL reconstruction. **Level of Evidence:** Level I, prospective, randomized, double-blind study. **Key Words:** Platelet-derived growth factor—Anterior cruciate ligament—Allograft.

The anterior cruciate ligament (ACL) plays an important role in maintaining the normal motion and stability of the knee joint¹; it is the primary stabilizer against anterior translation, and it is a stabilizer for rotation of the knee.²

ACL disruption occurs with a relatively high incidence and has the potential to cause functional instability and decreased function,³ which subsequently lead to injuries of other ligaments, cartilage, and meniscus and development of degenerative joint disease from recurrent episodes of instability.⁴

Treatment options should consider the patient's age, knee instability, and type and intensity of sports activities among other factors. Nonsurgical options make it difficult to continue participating in aggressive twisting sports. Surgical treatment is widely accepted as the therapy of choice and is recommended especially for young athletes who need to promptly return to their preinjury level of sports activities.⁵⁻⁷ There are several graft alternatives in ACL reconstruction, including bone–patellar tendon allograft, autograft, hamstrings, fascia lata, Achilles, and tibial posterior tendon.

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In recent years tissue engineering has emerged, and new technology and techniques are being introduced in the orthopaedic field. Gradually, the results of grafts have been improving, shortening the length of recovery.⁸

Since the 1990s, basic science has shown that there are several components within blood constituents (e.g., platelet-derived growth factor [PDGF], transforming growth factor β , fibrin, and fibronectin) that are part of the natural healing process, which can be modified or accelerated by concentrating these factors. These proteins set the stage for tissue healing, chemotaxis, proliferation, differentiation, angiogenesis, and removal of tissue debris.^{9,10}

Growth factors such as PDGF have been thought to accelerate ligament and tendon healing⁹ and to allow for an earlier return to unrestricted activity.^{11,12} Growth factors have been reported for a wide variety of applications, most predominately for wound and maxillofacial pathologies.^{13,14} One of the first clinical applications was in maxillofacial surgery, where PDGF was added to cancellous bone with good results in bone consolidation.¹⁵

The use of PDGF is increasing in orthopaedics to enhance the treatment of different pathologies, such as bone repair, including acceleration of fracture healing (particularly in patients who are at high risk for non-union); enhancement of primary spinal fusion; treatment of established pseudarthrosis; wound and ligament healing; tissue repair; and even treatment of degenerative osteoarthritis.^{9,11,13} These studies try to provide a foundation for its use. However, many reports are predominantly case studies or limited case series. No Level I studies with a control group comparison are available to definitively determine the role of platelet-rich plasma. There is little consensus in the literature regarding established standards that are necessary to indicate the use of PDGF.^{16,17}

Our purpose was to analyze the effect of platelet-enriched gel, obtained with our laboratory's method, on the inflammatory process during the days after ACL reconstruction with bone-patellar tendon-bone allograft and the clinical results at 2 years' follow-up. We want to offer information about the use of platelet-rich concentrate in a reproducible surgery to provide orthopaedic surgeons with evidence-based guidelines for the correct use of platelet concentrates. We hypothesized that the addition of platelet-rich plasma would accelerate graft incorporation and improve clinical stability measurements.

METHODS

The study design was prospective, randomized, and double blind. A randomized controlled trial was designed to compare 2 methods with the agreement of the ethics committee. Patient inclusion criteria were as follows: diagnosis of ACL disruption established by an orthopaedic surgeon, including laxity assessment by the Lachman test, pivot-shift test, and magnetic resonance imaging (MRI) studies; no prior knee surgery; and normal contralateral knee. Patients with previous knee pathology or symptoms before ACL rupture, which could modify the functional results, were excluded. All patients were informed about the purpose of the study and provided informed consent, and no patient refused to participate.

Using a computer program, we prospectively randomized 100 patients undergoing arthroscopic ACL reconstruction into 2 groups: group 1 (control group) comprised 50 patients with patellar tendon allograft reconstruction and group 2 (gel group) comprised 50 patients with patellar tendon allograft reconstruction and platelet-enriched gel (as a carrier of growth factors).

Platelet-Derived Growth Factor

One hour before surgery, we obtain 40 mL of blood from all patients in both groups (for every 10 mL of blood, we obtain 1 mL of platelet-enriched gel). Patients have a baseline blood platelet count of approximately $178 \times 10^3/\text{mm}^3$. Platelet-rich concentrate should achieve a 3- to 5-fold increase in platelet concentration over baseline.¹⁷ The method we used was described previously in the literature, with some variation in centrifugation.¹⁸ With our method, we have a mean platelet concentration of $837 \times 10^3/\text{mm}^3$ (469% increase) with platelet recovery of 63.8% from patient blood. The rest of the platelets are destroyed during processing and centrifugation.

Forty milliliters of citrated blood are drawn from the patient into Vacuettes (Becton, Dickinson and Company, Franklin Lakes, NJ) and centrifuged for 8 minutes at 3,000 rpm (2,217*g*) by use of a standard centrifuge (Beckman J-6B, Beckman Coulter Spain, Madrid, Spain). This results in 2 fractions: the blood cell component, consisting of red and white blood cells and platelets forming a red, opaque lower fraction, and a second upper straw-yellow turbid fraction with plasma and platelets, called the serum component. The top yellow serum is the platelet-poor plasma, which contains autologous fibrinogen and is poor in platelets. The level around the transition be-

tween the serum component and blood cell component has the highest concentration of platelets.

To maximize the platelet concentration, we pipetted out material into a fresh sterile Vacurette without citrate around the dividing line (buffy coat) between these 2 phases. This pipetted material is again centrifuged for 6 minutes at 1,000 rpm (380g) at room temperature. After the second centrifugation, we obtained 2 levels. The top fraction is yellow serum with fibrinogen and has a very low concentration of platelets (platelet-poor plasma). The remaining substance is the available platelet concentrate, rich in platelets with autologous fibrinogen.

We obtain one pipette with platelet-rich plasma and other with platelet-poor plasma. The whole process lasts 45 minutes. Thereafter, in the operating room we add 10% calcium chloride (0.05 mL of calcium chloride for each milliliter of platelet-rich plasma) to activate platelets to release their growth factors. Within approximately 15 minutes, the coagulum has solidified and the gel is obtained (Fig 1A).

Surgical Technique

All ACL reconstructions were performed by the same surgical team, using the same anesthetic technique, that is, general anesthesia with a laryngeal mask and with tourniquet ischemia of 300 mm Hg. We started arthroscopy repairing associated lesions, and afterward, we reconstructed the ACL with patellar tendon allograft with a RigidFix technique (DePuy Mitek, Raynham, MA)¹⁹ with 2 biodegradable cross pins to fixate the femoral bone and a tibial biodegradable interference screw.

Partial meniscectomy was performed when the meniscal lesions were irreparable; these included degenerated or radial tears. All meniscal repairs were performed for fresh lesions and those involving the vascular region with all-inside methods. The Smith & Nephew FasT-Fix Meniscal Repair System (Smith & Nephew Endoscopy, Andover, MA) was the only all-inside suture used. No inside-out methods were used.

In the gel group the ligament was covered with gel and sutured over itself with gel in its interior (Fig 1B).

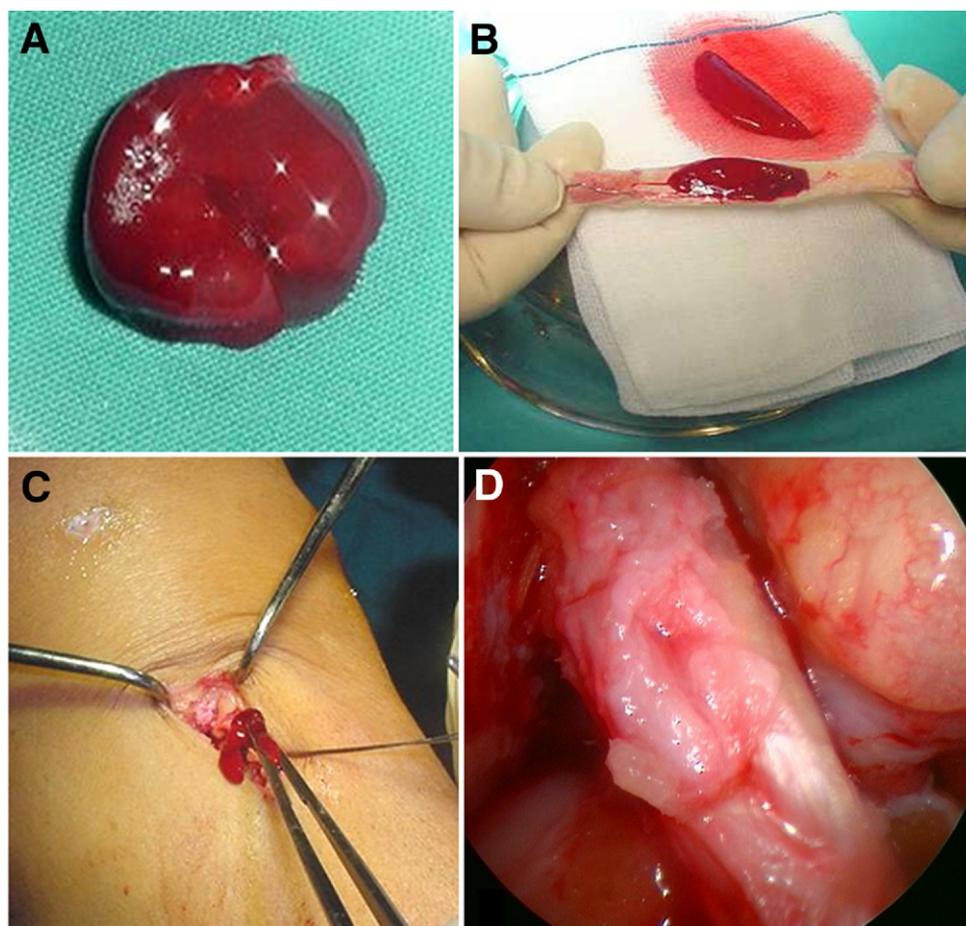


FIGURE 1. (A) Gel activated after addition of 10% calcium chloride. (B) Gel introduced into ligament. (C) Gel placed in tibial tunnel. (D) Intra-articular view of allograft with gel.

The rest of the gel was introduced after implantation of the graft inside the tibial tunnel, after shutting off the water (Figs 1C, 1D). No technical variation was needed at any time. Multiple growth factor delivery options exist; we selected direct transfer of the clot to the region of interest (ROI).

Postoperative Protocol

Patients were immobilized with a knee brace immediately postoperatively and were allowed to move the knee through the whole range of movement after 10 days, at which time we removed the sutures. We applied ice bags to all knees in the ward, and patients were treated with nonsteroidal anti-inflammatory drugs. No steroids and opioid drugs were prescribed or administered after surgery. Patients were discharged from the hospital at less than 48 hours postoperatively. Cycling was allowed at 2 to 3 months after surgery, straight-line running was allowed at 4 months, and sports were allowed at 6 months, always with normal knee motion, muscle torque, and proprioception.

Clinical Evaluation

Follow-up visits were scheduled preoperatively and occurred postoperatively at 3, 6, and 12 months and yearly thereafter. Clinical and inflammatory measurements were performed by a physician who was not involved in the study and did not know whether gel was used.

A pain visual analog scale was used to serially assess postoperative pain the day after surgery. Scores ranged from 0 (no pain) to 10 (maximum pain). Anterior laxity was measured with a KT-1000 arthrometer (MEDmetric, San Diego, CA). The objective questionnaire-based International Knee Documentation Committee scale was included to compare the functional state in both groups.²⁰

Inflammatory Parameters

The C-reactive protein (CRP) level was measured 24 hours after surgery (CRP 1) and 10 days after surgery (CRP 2). With a metric tape, we measured the perimeter in the middle of the kneecap before and 24 hours after surgery and determined the difference (PER 1). At 5 cm above the top edge of the kneecap, we measured a second perimeter before surgery and 24 hours postoperatively and obtained the difference (PER 2).

Radiology Evaluation

Anteroposterior and lateral standardized radiographs were evaluated to verify healing of the graft in the femur and tibial bone at 6 months. A double-blind study of MRI with an independent radiologist was performed at 6 months after surgery, evaluating the status of the ACL grafts using routine knee MRI. The MRI examinations included orthogonal proton density-weighted axial, sagittal, and coronal images and T1- and T2-weighted images, which were oriented parallel to the course of the femoral intercondylar roof. The ACL grafts in both groups were evaluated by MRI by use of direct signs, such as thickness, intensity, and uniformity of the graft and tunnel direction, as well as indirect signs, including tibial anterior translation and position of the posterior cruciate ligament (PCL).²¹ These results were compared between both groups.

Anterior tibial displacement can be measured by drawing a vertical line that is tangential to the posterior cortex of the lateral femoral condyle and by measuring the distance from this line to the posterior cortex of the lateral tibial plateau. This measurement is normally less than 5 mm, with greater than 7 mm indicating abnormality and 5 to 7 mm being an equivocal finding.²²

Tunnel placement and graft position in the tibia and femur were evaluated with the method of McCauley.²¹ The tunnel in the tibia should be behind a line drawn along the roof of the femoral notch (oblique line), and the center of the graft tunnel should be one quarter to one half of the distance from the anterior tibial cortex to the posterior tibial cortex. The femoral tunnel should be behind a point formed by a line drawn along the posterior femoral cortex and a line drawn along the roof of the intercondylar notch. We evaluated tunnels as correctly placed, anterior, or posterior.

Intensity, uniformity, and thickness were measured at the center of the graft with proton density-weighted and T2-weighted images. A normal ACL has low signal intensity on either image. The intensity of the graft was measured with an ROI.

The PCL angle was the angle measured between a line through the center of the distal portion of the ligament and a vertical perpendicular line through the tibial plateau.

Statistical Analysis

Statistical analysis of our results was performed with SPSS software, version 14.0 (SPSS, Chicago, IL). We performed a Kolmogorov test to verify statistical normality of the variables. Thereafter a Student

TABLE 1. Associated Procedures in Both Groups

	Control Group (n = 50)	Gel Group (n = 50)
ACL reconstruction (without associated lesions)	22	20
Partial meniscectomy	14	13
Meniscal repair	10	14
Microfractures	4	3

t test was used to determine the results of normal parameters, and a Mann-Whitney *U* test was used for nonparametric values and categorical variables.

RESULTS

Group 1 (control group) comprised 50 patients with patellar tendon allograft reconstruction. The mean age of these patients was 26.6 years (range, 15 to 59 years), with 12 female and 38 male patients.

Group 2 (gel group) comprised 50 patients with patellar tendon allograft reconstruction and platelet-enriched gel (as a carrier of growth factors). The mean age of these patients was 26.1 years (range, 14 to 57 years), with 10 female and 40 male patients.

No patients were lost to follow-up. Demographic data were comparable between groups, and the mean age of all patients was 26 years. The minimum follow-up of the patients was 18 months, with a mean of 24.3 months (range, 18 to 36 months).

There were no differences in the number of associated injuries. In the control group there were 28 injuries (meniscal repair in 10, partial meniscectomy in 14, and microfractures due to osteochondral lesions in 4), and 22 patients did not require any other procedure. In the gel group there were 30 associated injuries (meniscal repair in 14, partial meniscectomy in 13, and microfractures in 3), and 20 patients did not require other procedures (Table 1).

Statistical analysis was performed with the Student *t* test and Mann-Whitney *U* test to determine different results.

All laboratory and clinical parameters of both groups are shown in Table 2. Statistical analysis obtained did not show any significant difference between both groups: CRP 1 ($P = .742$), CRP 2 ($P = .086$), PER 1 ($P = .934$), PER 2 ($P = .194$), and visual analog scale ($P = .379$). There were no significant differences in the range of knee motion, muscle torque, or International Knee Documentation Committee score. The pivot-shift test was negative in 94% of all patients.

Radiology Results

An independent radiologist evaluated the intensity, thickness, and uniformity of graft; the direction of the tibial and femoral tunnels; tibial anterior translation; and other parameters described in the "Methods" section; no statistical differences were found between both groups ($P > .05$).

The surgical technique was comparable between groups because we did not find statistically significant differences in the graft angle, direction of tunnels, tibial translation, or associated injuries.

In our control group the mean angle of the ACL was 66° (range, 39° to 75°), and in the gel group the graft angle was 67° (range, 43° to 73°), with no significant difference ($P = .734$). When we compared the thickness of the graft between both groups, we found no differences, with a mean diameter of 8 mm (range, 5 to 12 mm) in the control group and 9 mm (range, 5 to 12 mm) in the gel group.

Tibial anterior translation in the control group was normal in 16 patients, between 5 and 7 mm in 7, and over 7 mm in 2. The mean anterior displacement of the tibia in the control group was 4.5 mm (range, -2 to 9 mm). In the gel group tibial translation was normal in 18 patients, between 5 and 7 mm in 6, and

TABLE 2. Comparative Laboratory and Clinical Parameters Between Groups

	Age (yr)	Sex	CRP 1 (mg/dL)*	CRP 2 (mg/dL)*	VAS	PER 1 (cm)	PER 2 (cm)	KT-1000 Before Surgery (mean)	KT-1000 After Surgery (mean)	IKDC
Control group	26.6 (15 to 59)	12 F and 38 M	1.22 (0.1 to 4.4)	0.85 (0.07 to 3.8)	2.30 (1 to 7)	2.6	2.3	5 (2 to 7)	0.5 (-2 to 3)	70% A, 26% B, and 4% Cr
Gel group	26.1 (14 to 57)	10 F and 40 M	1.14 (0.1 to 4.8)	0.88 (0.03 to 5.5)	2.58 (1 to 7)	2.6	1.9	4 (2 to 7)	0.5 (-2 to 3.5)	70% A and 30% B

NOTE. No statistically significant differences ($P < .05$) were found for comparisons.

Abbreviations: VAS, visual analog scale; IKDC, International Knee Documentation Committee.

*The normal value is less than 1 mg/dL.

over 7 mm in 1. In this group the mean was 4.2 mm (range, -3 to 8 mm), with no statistically significant differences when we compared both groups ($P > .05$).

There were no significant differences in the PCL angle ($P = .457$). It was 11° in the control group (range, 0° to 27°) and 14° in the gel group (range, 3° to 27°).

Signal intensity of the ACL graft on proton density-weighted images showed a mean of 190 ROIs in the control group and 230 ROIs in the gel group, with no differences between both groups ($P = .454$). On T2-weighted images, the mean number of ROIs was 61 in the control group and 75 in the gel group ($P = .10$).

All tunnel directions were correctly placed in the control group, whereas 1 femoral tunnel in the gel group was placed anteriorly, with no statistically significant difference.

DISCUSSION

Although mechanical solutions have been the mainstay of orthopaedic interventions for musculoskeletal pathologies, the search for alternative treatment strategies is currently under way. The placement of a supraphysiologic concentration of autologous platelets at the site of tissue injury is supported by basic science studies. Platelets are rapidly deployed to sites of injury, quickly degraded, and potentially modulate inflammatory processes by interacting with leukocytes and by secreting cytokines, chemokines, and other inflammatory mediators.^{23,24} PDGF is secreted by platelets and is one of the numerous growth factors that regulate cell growth proliferation, migration, and division. It plays a significant role in blood vessel formation (angiogenesis), bone formation, soft-tissue healing, and stimulation of cellular replication.²⁵

The biology and the interactions are not well known, and at this time, the therapeutic role of PDGF in ACL reconstruction remains unclear; however, its application seems promising in the healing process. Many different experimental studies in animals, some anecdotal oral presentations, and numerous publications have established that PDGF has an important role in ligament healing and in the repair of other musculoskeletal tissues,²⁶⁻²⁸ but few randomized prospective clinical studies (Level I) are available to show the role of these factors in patients. The only published cohort study in tendons was a study with a small number of patients and without a randomized control group.²⁹ Regardless, these growth factors are being used in daily practice.

The available preclinical data on the efficacy of PDGF in the treatment of ligament healing are insufficient to make predictions regarding the future clinical utility of these factors. At present, we need more information about PDGF. It is important that orthopaedic surgeons understand the mechanisms of action, functions, targets, doses, and possible adverse effects of PDGF before widespread use of this technology in clinics.

The aim of this article was to evaluate whether local administration of PDGF has any benefit on clinical, analytic, or radiologic results. We must point out that these factors, without a suitable surgical technique and correct graft stability, do not have any benefit.

We have used fresh-frozen allograft because we have a great amount of experience with good results using ACL grafts and other musculoskeletal allografts. The efficacy and results of fresh-frozen allografts have been well established in multiple studies.³⁰⁻³³ It is possible that PDGF could have more action in autologous graft, but no clinical studies could confirm this point.

Regarding the method of obtaining platelets, there are many commercially available systems to prepare platelet concentrate. Large variations exist; each system needs to be tested individually for growth factor expression.

Each procedure has different concentrations, different aseptic preparations, and most importantly, different efficacy. We cannot include all types of platelet concentrations in one general concept.³⁴

Our procedure was performed in our hospital's laboratory under aseptic conditions, with a 3- to 5-fold increase in platelet concentration over baseline as has been previously described.^{17,35} There are commercial systems to concentrate platelets with a relatively atraumatic filtration system as opposed to a centrifuge. We cannot confirm whether our procedure is better than other procedures because there are no studies to establish this.

A limitation of our study could be that no significant differences were found because of the limited number of patients, although there are no other randomized studies using gel in these conditions. Even if differences had been found in our results, these would probably be clinically irrelevant.

The strong points of this study include that we used a reproducible method, using the same anesthetic procedure, operative technique, and postoperative management protocol. Both groups had similar de-

mographic backgrounds and associated lesions, with a blind observer. The only difference was the use of the gel.

We continue to have many questions about the role of PDGF in orthopaedics. Proper clinical use and a good understanding of the role that platelet-rich factors can play in orthopaedics are key to achieving desired outcomes. Platelets may have potential and could be a promising tool in improving healing after ACL reconstruction and therefore sports recovery, but nothing has been definitively shown clinically at present. Perhaps, in the future, the development of appropriate and effective delivery concentrations over a long period of time will yield better results after ACL reconstruction.

CONCLUSIONS

The use of PDGF in patients treated with bone-patellar tendon-bone allografts has no discernable clinical or biomechanical effect at 2 years' follow-up. At this time, the therapeutic role of PDGF in ACL reconstruction remains unclear. More clinical studies will be needed to show the efficacy and use of these factors in daily practice in ACL reconstruction.

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