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The Effects of Biological Augmentation with Platelet-Rich Plasma on Graft Healing and Clinical Outcomes in Arthroscopic Assisted Anterior Cruciate Ligament Reconstruction

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ABSTRACT

Objective: To evaluate the clinical and radiological effects of platelet-rich plasma on graft maturation applied during anterior cruciate ligament reconstruction with bone–patellar-tendon–bone autograft.

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Orthopedic Surgery, Combined Military Hospital Rawalpindi, Pakistan from Oct 2022 to Sep 2023.

Methodology: A total of 40 patients, aged 18 to 50 years, with unstable symptomatic knee and complete anterior cruciate ligament tear, were sequentially enrolled into two groups. Arthroscopic anterior cruciate ligament reconstruction with patellar tendon autograft was conducted on all knees using the same protocol with the addition of platelet-rich plasma to the graft in Group A (PRP Group), and no PRP was added in Group B (control group). Follow-up visits occurred postoperatively every 4 weeks. The IKDC Scoring Scale and Lysholm Knee Scoring Scale were included to compare functional status, and an MRI was conducted 3 and 6 months after surgery to assess graft maturation.

Results: Anterior cruciate ligament reconstruction with the use of platelet-rich plasma achieves more diffusely hyperintense grafts assessed by MRI at 3 and 6 months, compared to anterior cruciate ligament reconstruction without platelet-rich plasma. At 3 and 6 months, 5(25%) and 9(45%) grafts were diffusely hyperintense in PRP group (p=0.03. p=0.04). Moreover, the platelet-rich plasma group showed a statistically significant improvement in clinical score at 3-month intervals only with mean IKDC Score being 66.9±4.8 (p=0.001) and mean Lysholm Score being 70.0±6.8 (p=0.01).

Conclusion: Patellar tendon graft remodeling seems to be accelerated by platelet-rich plasma, but has only short-term functional enhancement. More clinical trials will be needed to establish the efficacy and use of platelet-rich plasma in daily practice during platelet-rich plasma reconstruction.

Keywords: Anterior cruciate ligament; Anatomic reconstruction, Graft remodeling; MRI; Patellar tendon graft; Platelet-rich plasma.

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INTRODUCTION

The pivotal role of the anterior cruciate ligament (ACL) in maintaining the knee joint's stability and range of motion is well known. It prevents anterior tibial translation and renders rotatory stability to the knee as well.[1] The anterior cruciate ligament (ACL) is one of the most often injured ligaments in athletic competitions (75,000–100,000 cases/year in USA),[2] and its incidence has shown a rising trend in the last decade. Disruption of ACL causes functional instability and suboptimal function of the joint, which eventually steer towards injuries of other ligaments, cartilage, and menisci and culminate in the degenerative joint disease from repetitive events of instability.[3]

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Complete ACL tears causing knee instability are usually treated surgically but the regime is always tailored according to the patient's age and extent of instability, type, and intensity of sports activities besides other factors. Various surgical techniques are established for the reconstruction of the ACL using autologous tendons, and they offer positive clinical outcomes with the return to athletic activity. Because it primarily depends on bone-to-bone integration between the graft bone plug and the tunnel wall, autologous bone-patellar tendon-bone grafting has the highest potential for healing.[4]

Despite the various aspects of the procedure being revised repeatedly to make the reconstruction as anatomic as possible, the process of graft healing is extremely complex and not yet fully understood.[5] The clinical outcome of the procedure can be enhanced with a quick return to sports if the healing process of

the graft can be augmented. Two biological processes occur following anterior cruciate ligament (ACL) reconstruction: ligamentization of the graft's intra-articular portion and bone tunnel osteointegration.[6]

The recovery time needed after undergoing surgical treatment of an ACL tear is often very long taking up to a year. For professional athletes, who frequently suffer these injuries, this extended "away from the game" period has adverse effects on their careers. Thus, in an effort to reduce the time needed for the graft to develop biomechanical qualities similar to those of the original ACL, many techniques have been tested.[7]

Platelet-rich Plasma (PRP) is one of many bio-augmentative materials that can proposedly hasten the maturation of the graft in ACL reconstruction. Platelet-rich Plasma (PRP) is a potent source of a wide array of growth factors such as Platelets derived growth factors (PDGFs), transforming growth factors (TGFs), insulin-like growth factors, epidermal growth factors, vascular endothelial growth factors, and fibroblast growth factors.[8] Most parts of biological remodeling processes taking place in vivo are attributable to these factors.[9]

Consequently, strong clinical interest has been observed in researchers for the use of PRP for bioaugmentation in ACL reconstruction. Using various PRP preparations, some studies on ACL reconstructions have indicated positive clinical results.[10]

We postulated that graft remodeling would proceed more quickly with the addition of platelet-rich plasma, facilitating a quicker return to sports and an earlier postoperative recuperation. This prospective study aimed to compare the clinical and MRI results after ACL Reconstruction with Bone-Patellar Tendon-Bone (BTB) graft with bioaugmentation using Platelet-rich plasma (PRP).

METHODOLOGY

The quasi-experimental study was conducted at the author's institution, Combined Military Hospital, Rawalpindi Pakistan from October 2022 to September 2023 after obtaining approval from the Institutional Ethical Review Board (IRB # 466). Written consent was obtained from every participant of the study before enrollment.

The sample size was calculated using SPSS Version 28, considering the mean of Group A as 71.18±9.23 and that of Group B as 63.11±10.83 for a two-tailed hypothesis.[11]

Inclusion Criteria: Patients between 18 to 50 years old, with a complete ACL tear and unstable symptomatic knee, diagnosed by an orthopedic surgeon, and confirmed by MRI studies as an ACL injury, with no prior knee pathology were included.

Exclusion Criteria: Individuals who had previously undergone any knee surgery or suffered any pathology before the ACL rupture, or who had any illness that prohibited the use of PRP, were not eligible.

Two groups were established: Group A included 20 patients (18 men and 2 women), with a mean age of 28.4 years (range, 18-47 years), with ACL reconstruction plus PRP; Group B also included 20 patients (19 men and 1 women), with a mean age of 28.7 years (range: 18-41 years), with ACL reconstruction without PRP (Figure). Patients were allocated groups according to the odd-even order of their enrollment in the study.

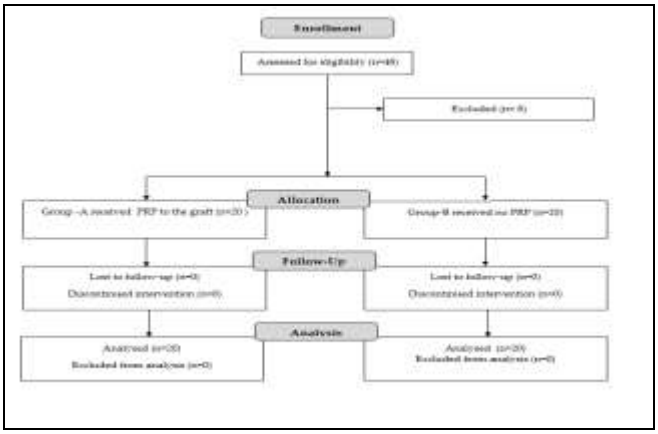

Figure: Patient Flow Diagram (n=40)

The concentration of platelets should be 2 to 5 times greater in the platelet-saturated concentrate than baseline, according to the literature.[12] A baseline blood platelet count of 210×106/ml was observed in the patients involved in this study. We were able to attain a 403% increase utilizing our usual centrifugation process employing Hettich EBA 280. It indicates 60.8% platelet recovery from patient blood, the rest were eliminated during the process. Just before inculcating on the graft, 7ml of platelet-rich plasma (for every 9ml of blood, we obtain 1ml of PRP) was actuated with the incorporation of 10% calcium chloride in the liquid aliquot (0.05 ml of calcium chloride per ml PRP). It

took 15 for the coagulum to solidify and the PRP gel was ready to use.

All patients enrolled in the study underwent arthroscopic assisted ACL reconstruction with autologous patellar tendon grafts. Each surgery was performed under general anesthesia with a tourniquet inflation pressure of 300 mm Hg after exsanguinating the limb with elevation. After arthroscopy, conducted for synovectomy and debridement or repair of associated lesions, the graft was harvested via an anterior midline incision. Ten millimeters from the posterior cortex of the femur, the drilling of the femoral tunnel was done utilizing an anteromedial portal. With an articular outlet located behind the anterior horn of the lateral meniscus as well as the anterior tibial spine, the tibial tunnel was fashioned using a guide at a 55^{o} angle. The graft was placed at 10 or 2 o'clock depending upon the side of the limb. The diameter of both the tibial and femoral plugs was 8mm and both ends of the graft were secured by Titanium interference screws.

In Group A, utilizing a method that prevents concentrate loss during graft passage via bone tunnels and standardizes the dosage of concentrate employed, PRP was delivered. Preoperatively, 60ml of the patient's blood was taken into sterile sodium citrate tubes 3.8% (wt/vol) and centrifuged to yield autologous activated platelet gel in the operating room aseptically. The graft's ligamentous portion of the graft was sutured over itself with gel being inside of it after being coated in platelet-rich gel. After autograft positioning into its place, a spinal needle was used to introduce gel femoral and tibial tunnels, after draining the water out. The whole process demanded no technical changes in the apparatus. There are various methods for delivering PRP gel; to prevent the wastage of gel while setting up the graft in bony tunnels, we decided to apply the clot directly to the area of interest.

Postoperatively, both groups followed the same supervised standardized recovery scheme. Knee immobilizer was applied to keep the knee restrained. Within 1st week, passive mobilization of the knee was allowed. During the intermediate post-op period, the whole range of motion was encouraged in the physiotherapy program. Progressive weight-bearing ambulation was permitted at 4th week four as long as the pain was bearable. Swimming was authorized in 6th week, outdoor cycling at the end of 3rd month, progressive running by 4th month, and restoration of unrestrained athletics by 6th month.

Monthly follow-up of patients was ensured, with average follow-up duration being 8 months (range 6–10 months). An independent orthopedic consultant, blinded to treatment, assessed the patients for the arc of motion, Lachman, and anterior draw tests on every visit. Moreover, they were equitably assessed with the "Lysholm Knee Scoring Scale,[13] and "International Knee Documentation Committee (IKDC) Score,[14] questionnaires at 3 and 6 months post-op for functional outcomes. These are patient-reported rating systems that consist of subscales for knee symptoms, function, and sports activities. Scores range from 0 (worst disability/ least function) to 100 (least disability/highest function). Graft healing was evaluated using MRI at 3 and 6 months after surgery, specifically the ligamentous component with the synovial cavity. Based on signal intensity, remodeling phases of the graft were rated into four grades by a radiologist, uninformed of allotment of intervention.[15] Grade I indicates the homogeneously hypointense graft, while Grade II indicates that >50% graft is still hypointense with areas of enhanced signals. Grade III depicts more than 50% graft is hyperintense and Grade IV denotes the diffusely hyperintense graft without any hypointense patches. Higher grades demonstrate advanced remodeling and healing stages of graft.[16]

Statistical analysis was performed using SPSS software version 26 [Chicago, IL: SPSS, Inc.; 2019]. For continuous variables, Mean±SD was calculated while frequency and percentage were calculated for categorical variables. To analyze statistically significant difference between variables of PRP vs Control groups, Chi Square and Independent sample t test were used. The paired t-test was run to determine whether there was a statistically significant mean difference between the functional scores after ACL reconstruction, irrespective of with PRP or with PRP. The *p*-value of 0.05 or less was taken as significant.

RESULT

None of the patients in either group had any complications during or after surgery. After ACL reconstruction, all patients had stable knees with negative Anterior draw and Lachmann tests.

There was marked improvement noted in the IKDC and Lysholm scores at 3 and 6 months postoperatively in 2 groups in comparison with preoperative values (IKDC Score $p<0.001$, Lysholm

Score p<0.001). Though, At 3 months, the PRP group's scores were considerably higher than those of the control group (IKDC Score p=0.001, Lysholm Score p=0.01), but at 6 months, the two groups did not exhibit any appreciable differences. (IKDC Score p=0.08, Lysholm Score p=0.15) [Table-I: Mean IKDC Score in PRP and Control Groups at 3 and 6 months] [Table-II: Mean Lysholm Score in PRP and Control Groups at 3 and 6 months].

After both the 3rd and 6th month post-op MRI, it was observed that more patients in the PRP group than in the control group attained higher phases of remodelling (p=0.03 and p=0.04 respectively) [Table - III].

Table-I: Mean International Knee Documentation Committee (IKDC) Score in Platelet-Rich Plasma (PRP) and Control Groups at 3 and 6 months (n=40)

	PRP Group (n=20)	Control Group (n=20)	*p*-value
IKDC Score			
Pre-Operative	38.17±7.87	36.19±8.22	
3rd Month	66.97±4.84	60.20±6.61	p=0.001
6th Month	83.51±4.30	80.79±5.28	p=0.08
p-value	p<0.001	p<0.001	

Platelet-Rich Plasma : PRP, International Knee Documentation Committee (IKDC) Score

Table-II: Mean Lysholm Score in Platelet-Rich Plasma and Control Groups at 3 and 6 Months (n=40)

	PRP Group (n=20)	Control Group (n=20)	*p*-value
Lysholm Score			
Pre-Operative	29.69±6.35	30.77±5.09	
3rd Month	70.03±6.80	65.00±4.82	p=0.01
6th Month	84.81±6.14	82.59±3.08	p=0.15
p-value	p<0.001	p<0.001	

Platelet-Rich Plasma : PRP, International Knee Documentation Committee (IKDC) Score

Table-III: Comparison of Graft Remodelling Stage on MRI at 3rd and 6th months Post-Operative between the Two groups (n=40)

Graft Remodeling	PRP Group (N=20)	Control Group (N=20)	*p*-value
3rd Month			
Diffusely Hypointense	4(20%)	9(45%)	0.03
Mildly Hyperintense	5(25%)	8(40%)	
Moderately Hyperintense	6(30%)	3(15%)	
Diffusely Hyperintense	5(25%)	0(0%)	
6th Month			
Diffusely Hypointense	2(10%)	5(25%)	0.04
Mildly Hyperintense	3(15%)	8(40%)	
Moderately Hyperintense	6(30%)	5(25%)	
Diffusely Hyperintense	9(45%)	2(10%)	

Platelet-Rich Plasma : PRP, International Knee Documentation Committee (IKDC) Score

DISCUSSION

Knee stability and functional restoration can only be achieved by ACL reconstruction.[17] Over the years, various grafts have been put to test in reconstruction but for elite athletes, reinjury attributable to trauma in early phases after return to physical activity demonstrates that the time of osteointegration in the bone tunnels and maturation of the ligamentous portion is not reduced despite advancements. This results in lengthier rehabilitative periods as for patellar tendon graft, it takes around 9 to 12 months to gain close to normal strength.[18,19]

After implantation, the patellar tendon graft goes into a phase of avascular necrosis with hypocellularity and collagen fragmentation, before remodeling in terms of vascularisation, cellularity, collagen fiber pattern, and metaplasia sets into action. Over the last few years, the mainstay of research has been looking for breakthroughs in basic sciences that can accelerate soft tissue healing and remodeling. Though the interactions by which it plays its role are unclear at the moment, the application of PRP has shown promising results in the healing of ACL grafts, in both animal and human clinical trials. The effects of Platelet-derived growth factors (PDGF) on patellar grafts in dogs analyzed by Yasuda *et al.*,[20] showed enhanced fibroblasts and collagen synthesis by 40%. PRP has also been reported to stimulate enhanced collagen Type-I and III production in horse tendons.

The period needed by the graft to attain biological maturity showing as complete homogenization on MRI was significantly shortened (by at least 48%) when PRP was used in a study.[21] In a human trial, Orrego *et al.*,[11] reported enhanced graft maturation with PRP as measured by MRI signal intensity, but had no discernible impact on the osteoligamentous interface within the tunnel. Our study also showed accelerated graft maturation in the PRP group. Moreover, there are no published studies at present that relate the signal intensity of graft on MRI with histological ligamentization or mechanical strength testing in humans, al biet, Weiler *et al.*,[22] showed a correlation between the homogeneity of the graft on MRI, maturation, and strength in sheep models.

Though multiple clinical trials have shown accelerated graft maturation on MRI with the application of PRP, so far available literature has failed to prove any positive influence of PRP on clinical outcomes.[12,23] It is partly because, with the variations

in the process of obtaining PRP and its constituents ultimately, its efficiency varies greatly.[24] In our series, functional scoring systems showed statistically significant improvement initially (at 3 months), but no perceptible influence was noted at 6 months.

The function of PRP in orthopedics continues to be a subject of much debate. Firstly, current technologies do not allow us to specifically isolate the growth factors related to the process, so presently, it's conceivable that we're using a combination in the form of PRP.[25] Which growth factor has the greatest influence on ACL maturation? Moreover, what is the optimum technique and time for introducing PRP? It is also unclear to us if applying these components repeatedly during the postoperative recovery and rehabilitation process would be even more helpful than doing so alone at the time of surgery. Is the quantity we're applying enough? How much time does their impact last? These are questions for which we still lack a consensus, so further extensive trials should be carried out.

LIMITATIONS OF STUDY

Despite the comparative nature, limited sample size, absence of randomization, and brief follow-up period were some of the study's shortcomings. The fact that the MRIs were examined by just one radiologist was also one of the study's limitations. The inter-observer reproducibility might have been assessed by many radiologists. On the other hand, the strengths of this study are the correlation between remodeling stages on MRI with functional outcome analyzed by Lysholm and IKDC Score at every 3-month interval post-op.

CONCLUSION

PRP can only be considered adjuvant in ACL reconstruction once we have more data from well-conducted studies regarding its positive outcomes in the field of sports medicine. In our study, PRP enhanced the functional parameters in the short-term postoperative tenure. Although we have been able to demonstrate accelerated graft maturation analyzed by MRI, it remains to be seen if this translates into an earlier return to sports or a quicker overall recovery.

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

BAQ : Data acquisition, critical review, approval of the final version to be published.

MOR & AMH: Conception, study design, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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