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RESEARCH ARTICLE

# Rehabilitation in Patients with Anterior Cruciate Ligament Reconstruction Using Auxiliary Platelet-Rich Plasma Therapy

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**Background**: The main target after successful AnteriorCruciate Ligament (ACL) reconstruction is early rehabilitation. New options such as PRP (platelet rich plasma) may improve clinical outcomes. **Objective**: The aim of our study was to evaluate two consecutive series of patients who underwent ACL reconstruction, one with PRP treatment and one without it. **Material and method**: Two groups of consecutive patients underwent arthroscopic ACL reconstruction, using the SemiT and BPTB techniques. Postoperatively all patients included in this study followed the same standardized rehabilitation protocol. In addition, patients in the first group received three intraarticular PRP injections as auxiliary therapy. Injections were performed at week two, four and six. The patients were evaluated at enrolment and every four and twelve weeks using the Tegner Lysholm Knee Scoring Scale (Scoring Scale: poor <65/ fair 65-83 / good 84-90 / excellent > 90). Each patient was operated on and evaluated afterwards by the same team of surgeons. **Results**: At 12 weeks interval, Group A had a higher mean clinical score than Group B (94.67 vs 92.50) although marginally not statistically significant (p=0.0503, 95% CI:-4.336 to 0.002911). Regarding pain in patients from Group A compared with patients from Group B, we saw a statistically significant difference at 4 weeks interval (16.90 vs. 18.89, p=0.0370, 95% CI: 0.1260 to 3.842) and no significant difference at 12 weeks interval (21.19 vs. 21.94, p=0.3744, 95%CI: -0.9452 to 2.453). In terms of swelling points scored between the two groups, there was no statistically significant difference at 4 week interval (5.048 vs. 4.00, p=0.1979, 95% CI: -2.667 to 0.5714) but there is a significant difference in favor of patients from Group A at 12 weeks interval (8.475 vs. 5.556, p=0.0002, 95% CI: -4.323 to -1.159). **Conclusions**: In the short term, the local treatment showed improvement on the overall clinical status of the patients (less pain, improved mobility, less swelling) undergoing rehabilitation after ACL reconstruction, although further studies are required.

**Keywords**: platelets, plasma, cruciate ligament, rehabilitation

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## Introduction

One of the most common knee injury among patients is the anterior cruciate ligament (ACL) rupture, which usually results in the loss of knee stability. This type of injury is generally found among young patients who participate in sports and professional athletes. To restore knee stability, surgical ACL reconstruction is perfomed using different techniques, one of them being autologous graft transplant [1,2]. The most commonly used grafts in this procedure are bone-patellar (BPTB) and hamstrings (Semitendinosum and Gracillis) tendons. While BPTB offers the strongest healing potential (bone to bone integration), it has a higher donor-site morbidity. Autologous hamstring grafts have less donor-site morbidity yet they rely solely on tendon-to-bone healing, meaning a slower healing process and delayed recovery for the patient [3,4,5].

A systematic review on return to sports showed that around 82% of the patients rebound to some form of physical activity and only 63% of the operated patients returned to their pre-injury level of sports. The overall success rate in terms of mid-term clinical outcome does not exceed 85-90% [6]. Based on that data, the main goal after ACL reconstruction, beside secure graft attachment and integration, is early rehabilitation. Achieving high range of motion and activity as soon as possible is imperative especially among professional athletes [7].

Intense early rehabilitation may cause pain and swelling to the knee while prolonged recovery may cause range of motion deficiency and muscle atrophy preventing patients to resume full physical activity [8].

During recent years, the use of growth factors has been thought to quicken tissue healing, therefore allowing an earlier return to unrestricted activity [9]. Platelet-rich plasma (PRP) is defined as an autologous concentration of human platelets in a small volume of plasma [10,11]. These platelets, once activated, are proven to be actively and progressively secreting protein growth factors (such as TGF-β1, PDGF and VEGF) that initiate mesenchymal tissue healing, cell proliferation and osteogenesis thus contributing to the acceleration of postoperative tissue repair and reduce local inflammation [10-13].

Regarding these facts, the use of platelet-rich-plasma (PRP) could be an effective, cost-efficient adjuvant therapy in the rehabilitation process among patients with ACL reconstruction.

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The purpose of our study was to test whether the inclusion of an auxilliary PRP treatment to the standardized rehabilitation protocol may improve recovery and clinical outcomes.

## Material and method

A prospective, interventional study was carried out in the Orthopedic Surgery and Traumatology Clinic I, County Emergency Clinical Hospital, Târgu-Mureş, România. This study was conducted in accordance to the recommendations of the local ethics committee and the informed consent was obtained from all off our patients before starting treatment. Thirty-nine patients were included in our study, with two patients excluded due to refusal to continue the treatment. The patients were divided into two groups: one with PRP treatment added during rehabilitation phase and one following the standard recovery protocol. The inclusion criteria were: acute primary total tear of the ACL, diagnosed by clinical examination (Lachman and Gravity Drawer instability test) and MR imaging, without previous history of ligament tears, surgery at least sixty days before trauma and healthy contralateral knee. The exclusion criteria were: multi-ligament lesions, infective knee disease and chondral defect graded Outerbridge III or IV in any knee compartment.

Even if MRI scans and clinical test were positive, a first arthroscopic step was performed to observe and confirm the ACL total tear, before graft harvesting.

Patients from both groups underwent arthroscopic ACL reconstruction and the same surgical team (1 senior surgeon M. R. and 1 resident A.D.) performed all the interventions. BPTB and SemiTwas used alternatively. All the patients on whom we used the BPTB method were professional athletes due to proven faster graft integration times. Notch plasty and treatment of the concomitant pathologies were addressed as necessary. Partial meniscectomy was performed when considered required. All the Outerbridge IIchondral defects were treated using Pridie microfractures.

ACL reconstruction utilizing BPTB method was done using a single incision technique with bioabsorbable interference screw fixation (provided by Arthrex) in both the femoral and tibial tunnel. The allografts were fashioned in similar manner to create 8 to 10 mm bone plugs. The femural tunnel (corresponding with the bone plug offset) was placed at 10 respectively 2 o'clock position while the tibial tunnel was placed at the anatomic footprint using an aiming guide set at 55˚. A negative pressure intra-articular drain was positioned and left for 24 hours. The SemiT method involved a longitudinal skin incision above the hamstring insertion. Semitendinosus and gracilis tendon were isolated and harvested using a blunt tendon stripper. The graft was prepared over a work station using a ,,roman sandal" suture. Tibial tunnel was drilled at 55˚ in sagittal plane. A 40-45 mm femoral tunnel was drilled transtibial in 12 cases while in the other 24 we used a medial parapatellar incision (standard arthroscopic portal). The offset for the tunnel diameter was inconstant, depending on graft size. Bioabsorbable interference screws were also used to fix the graft (with the knee hold at 45˚ of flexion). A compressive antithrombotic bandage was applied and maintained for 24-48 hours. Anticoagulation therapy (Fraxiparine 0,4 ML 1x1/day) started promptly after surgery and was carried 7 to 14 days afterwards. Pain relieving protocols consisted in painkillers (Algocalmin 1g/2ml IM injection 1x1/day the first two days followed by PO treatment) and NSAID (Dicloreum 150 mg 1x1/day) therapy. Local ice was applied when needed. All medication was halted after the second week.

Each group underwent the same standardized rehabilitative protocol with the mention that patients on whom we used the BPTB technique underwent a less aggressive and more conservative rehabilitation process, mainly due to anterior knee pain and higher donor site morbidity. Further, we took into consideration the fact that the patellar tendon is more rigid in composition than the semitendinosus. Passive mobilization exercises of the lower operated limb were started the next postoperative day. Knee was protected for 2 weeks with a knee brace (fixed in full extension the first week with progressive range of motion increase so that that the patient reaches 90˚ of flexion on the forth week). Among patients without chondral defects, partial load bearing was allowed from day one with crutches. Patients who have undergone microfracture surgery were allowed partial weight bearing at 14 days postoperatively. Full load bearing was allowed at four weeks. Closed kinetics chain exercises were progressively introduced. Patients started open kinetic exercises at 1.5 to 2 months after surgery to improve extensor strength. Isokinetic rehabilitation was reserved before returning to sport activities. Running was allowed at 3.5-4 months and patients will be allowed to resume unrestricted sports activity at 6 months.

Patients in Group A were treated with PRP intraarticular injections at two, four and six weeks interval after surgery while Group B were considered as control group and followed the recovery program without PRP treatment.

The procedure for preparing PRP, described in this paper, was modified after several trials and according to the international literature[11,14-16]. The blood sample (16 –18 ml of autologous venous blood) was drawn into two 9-ml vacutainer tubes (BD Vacutainer for plasma) each containing Sodium Heparin (17 UI/ml of blood). The obtained samples were gently agitated to thoroughly mix the blood with the anticoagulant and then centrifuged at 1500 rpm for 5 minutes at room temperature (Hettich Zentrifugen EBA 20) resulting in three following layers: inferior layers composed of erythrocytes, the intermediate layer composed of leukocytes (the buffy coat) and the superior layer made up of plasma (PRP). The superior layers were then aspirated with two 5 ml syringe, obtaining a final PRP product (5-6 ml) used for the intra-articular injection within the first 30 minutes*;* regarding the fact that the platelets secrete 70% of their stored growth factors in

the first 10-15 minutes and close to 100% in the first hour and can go on for about 8 days until they are depleted and die [17,18]. The injection was performed through a lateral approach of the knee joint, after disinfection of the skin, using sterile instruments and consumables. We repeated the procedure at two week interval for a total of three injections, all procedures being performed in the same office setting and by the same personnel. Considering the various positive effects of PRP treatment in different clinical applications, we opted to use nonactivated PRP (it is shown that thrombin activated PRP inhibits osteogenesis while nonactivatet PRP favorized bone formation in vitro and in vivo) [10,19].

The total time needed to prepare the platelet concentrate and performing the injection was approximately 7 to 10 minutes.

Before surgery and rehabilitation, all patients underwent base-line clinical evaluation, using the Tegner Lysholm Knee Scoring Scale (Scoring Scale: poor<65/fair 65-83/good 84-90/excellent>90) [20]. The Tegner Lysholm Knee Scoring Scale evaluates the existence of limp, the need of support, the locking sensation, the instability acquired, the pain resented by the patient, the swelling of the knee, the possibility of stair – climbing and squatting. The outcome was then measured at four weeks and at three months afterwards. We took special interest in ,,pain" and ,,swelling" points, taken into consideration that these are the key factors to an efficient clinical rehabilitation and recovery. Swelling was evaluated by direct inspection and palpation (temperature, skin colorant ,,puffy" aspect) and by performing clinical tests such as the patellar tap test (tapping down the to create an upward and downward movement; the test is considered positive if a palpable click is felt by the examiner when the patella hits the underlying femur) and the stroke test (when the knee is rested in full extension the examiner creates a movable fluid wave which can be displaced in different joint areas). Furthermore we used measuring tape to determine the joint circumference (placing the tape around the superior border of the patella) bilaterally. Differences greater than 1,5 cm were noted. Presence of swelling was correlated with the intensity of movements performed by the patients (severe or ordinary exertion).

Range of motion (ROM) assessment was done at 4 and 12 weeks interval (noting that we limited knee flexion at 90˚ on the first evaluation). We used a simple three point score to evaluate the joint functional status as follows: Score 1–no changed condition, passive ROM/Score 2–increased joint ability to perform tasks but not complete, assisted ROM/Score 3 –complete functional recovery, active ROM.

MRI scans were considered useful among patients that were professional athletes and optional for the rest and not all the patients were referred to this examination.

The data obtained from the clinical examination was analyzed using the ANOVA test using the GraphPrism 6.0 software.

## Results

The study population consisted of 39 consecutive patients (from a total of 41) with confirmed complete ACL rupture. Two patients were excluded due to refusal on taking part in every phase of the research and their data and evolution was not included in this study. All surgical interventions performed were successful and there were no noted complications afterwards.

Group A consisted of 21 patients, 4 female and 17 male, with ages between 17 and 43 yrs. old (mean age of 39 yrs old). Seven of the patients were professional athletes (2 male basketball players, 1 male wrestler, 1 male rugby player, 1 female basketball player and 2 female handball players), five semi-professional athletes ( 5 male Sunday-league football players) and nine patients with normal physical activity. Group B consisted of 18 patients, 2 female and 16 male, with ages between 25 and 45 yrs. old (mean age of 35 yrs. old). Two of the patients were professional athletes (2 B-league football players).

BPTB was used in two patients from Group A and 1 patient in Group B while SemiT was used on 19 patients from Group A and 17 patients in Group B. Partial meniscectomy was necessary in 7 cases while in 10 other cases we diagnosed focalchondral defects (8 cases OuterbridgeII and 2 cases Outerbridge I). Pridie microfractures were required in 8 of the mentioned cases. We had twenty-three cases which required surgical intervention on the left knee and sixteen on the right knee. Three patients from each group (5 professional athletes and 1 semi-professional athlete), underwent MRI scans at 12 weeks postoperatively.All the patients from Group A scored 3 points in range of motion assessment; this outcome remained unchanged at 12 weeks evaluation period. From Group B, at 4 weeks evaluation, 15 patients scored 3 points in the ROM test while 3 patients scored 2 points. All the patients from Group B scored maximum points at 12 weeks ROM evaluation. Every patient included in this study finished the standard rehabilitation protocol.

Clinical evaluation using the TegnerLysholm Knee Scoring Scale was performed on all patients and the results are presented in Table 1.

In Group A we observed an improvement in the clinical score from baseline examination to 4 weeks (75.76 vs. 84.95, p<0.0001, 95% CI: 6.889 to 11.49), from 4 weeks to 12 weeks (84.95 vs. 94.67, p<0.0001, 95% CI: 7.370 to 12.06) and from baseline to 12 weeks (75.76 vs. 94.67, p<0.0001, 95% CI: 11.69 to 19.87). Improvements from 4 to 12 weeks were also recorded in pain scores (16.90 vs. 21.19, p<0.0001, 95% CI: 2.631 to 5.940) and swelling scores (5.048 vs. 8.476, p<0.0001, 95% CI: 2.105 to 4.752) *(Fig. 1 and Fig. 2)*

Improvements in clinical score were also noted in Group B from baseline to 4 weeks (76.72 vs. 84.72, p=0.0004, 95% CI: 4.114 to 11.89), from 4 to 12 weeks (84.72 vs. 92.50, p<0.0001, 95% CI: 5.976 to 9.579) and from baseline to 12 weeks (76.72 vs. 92.50, p<0.0001, 95% CI:

**Table 1. Tegner Lysholm Knee Scoring Scale (Values are expressed as mean +/- SD)**

| Group | Score | Value |
|---|---|---|
| Group A | Clinical score baseline | 75.76 +/- 6.693 |
| | Clinical score at 4 weeks | 84.95 +/- 5.572 |
| | Clinical score at 12 weeks | 94.67 +/- 3.322 |
| | Pain points at 4 weeks | 16.90 +/- 2.948 |
| | Pain points at 12 weeks | 21.19 +/- 2.695 |
| | Swelling points at 4 weeks | 5.048 +/- 2.801 |
| | Swelling points at 12 weeks | 8.476 +/- 1.990 |
| Group B | Clnical score baseline | 76.72 +/- 7.737 |
| | Clinical score at 4 weeks | 84.72 +/- 4.625 |
| | Clinical score at 12 weeks | 92.50 +/- 3.348 |
| | Pain points at 4 weeks | 18.89 +/- 2.742 |
| | Pain points at 12 weeks | 21.94 +/- 2.508 |
| | Swelling points at 4 weeks | 4.00+/- 2.058 |
| | Swelling points at 12 weeks | 5.556 +/- 2.332 |

11.69 to 19.87). Pain score (18.89 vs. 21.94, p<0.0001, 95% CI: 1.808 to 4.303) and swelling score (4.00 vs. 5.556, p=0.0043, 95% CI: 0.5577 to 2.553) were also improved *(Fig. 3 and Fig. 4)*

Using multiple analysis of variance testing (ANOVA test) we observed a significant improvement of global clinical score from baseline to 12 weeks (p<0.0001) in both Group A and B.

Comparing the two groups, we found no significant difference between baseline clinical scores (75.76 vs. 76.72 p=0.6800, 95% CI:-3.720 to 5.641). However at 12 weeks interval, Group A had a higher mean clinical score than Group B (94.67 vs. 92.50) although marginally not statistically significant (p=0.0503, 95% CI:-4.336 to 0.002911) *(Fig. 5 and Fig. 6).*

Regarding pain in patients from Group A compared with patients from Group B, we saw a statistically significant difference at 4 weeks interval (16.90 vs. 18.89, p=0.0370, 95%CI: 0.1260 to 3.842) and no significant difference at 12 weeks interval (21.19 vs. 21.94, p=0.3744, 95% CI: -0.9452 to 2.453).

In terms of swelling points scored between the two groups, there was no statistically significant difference at 4 week interval (5.048 vs. 4.00, p=0.1979, 95% CI: -2.667 to 0.5714) but there is a significant difference in favor of patients from Group A at 12 weeks interval (8.475 vs. 5.556, p=0.0002, 95% CI: -4.323 to -1.159).

## Discussion

The treatment of joint and musculoskeletal injuries using platelet concentrates, as a source of growth factors, are very popular tools in regenerative medicine and generally appreciated by patients reporting an overall recovery benefits. We expected an improvement regarding clinical scores in both groups, with improved ,,stability" and ,,stair-climbing" scores in all the patients, which is due to the suc-

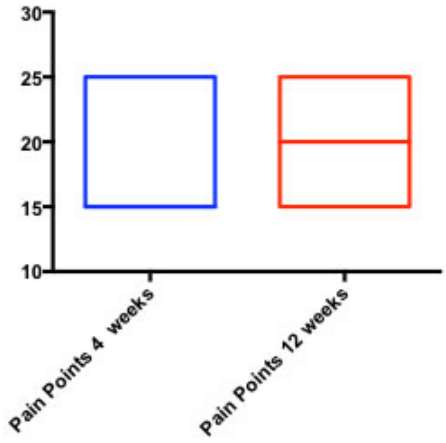


Fig.1. Pain Points Group A

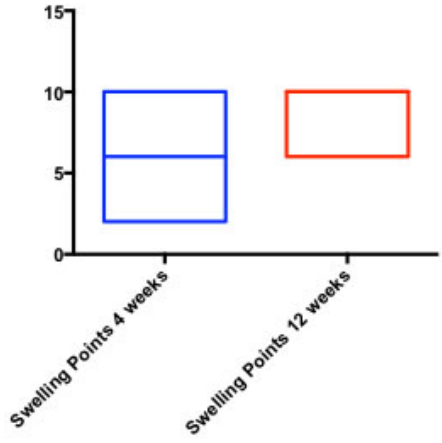


Fig.2. Swelling Points Group A

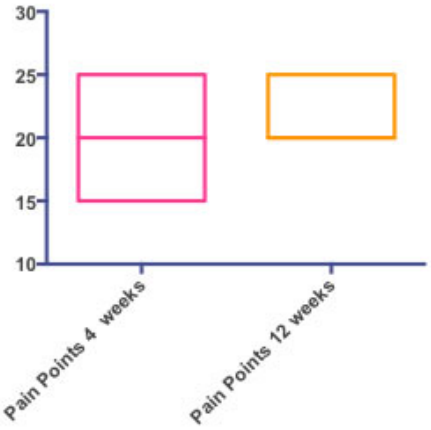


Fig. 3. Pain Points Group B

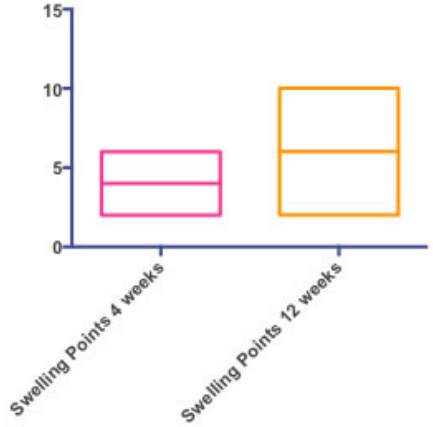


Fig. 4. Swelling Points Group B

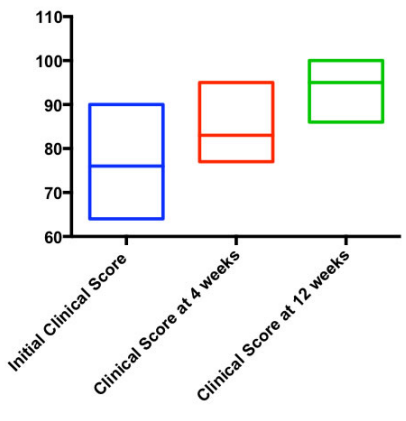


Fig. 5. Clinical scores Group A

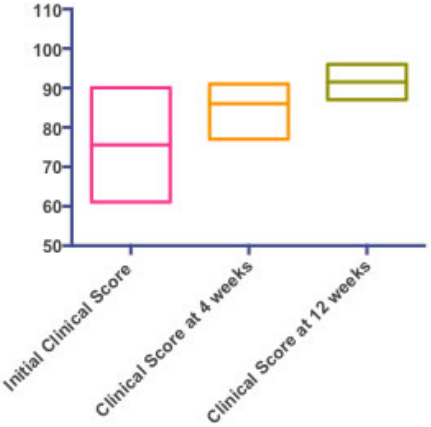


Fig. 6. Clinical scores Group B

cessful surgical intervention, graft positioning and fixation. With this fact in mind, we took special interest in development of pain and swelling especially among patients in Group A. We found that a statistically significant improvement in the clinical outcome was obtained after PRP treatment in terms of subjective function. Patients who were treated with PRP injections showed a fast relief regarding pain at 4 weeks follow-up compared with patients from Group B. If there was no significant difference in pain at 12 weeks evaluation period, we see that there is a big improvement among patients from Group A in terms of swelling at 12 weeks evaluation period, with 13 of the total 21 patients scoring maximum points. Range of motion assessment showed improved results in Group A compared with Group B at 4 weeks interval. This can be attributed to the pain relief described by patients during clinical investigations, although correct graft positioning during surgery has a major impact on joint function afterwards.

From a psychological point of view, patients from Group A performed better during rehabilitation protocol, notably from week 4 onwards. The absence of swelling at 12 weeks interval means that the patients can emphasis on muscle strength recovery and specific sport related exercises.

Most patients from Group B presented slight swelling of the operated knee at 3 month interval and they will be submitted to a more conservative recovery protocol until swelling if fully gone.

Our study revealed that intra-articular injections of PRP mainly showed a reduction in pain, limp and swelling, accelerating the recovery function of the knee joint in patients who were treated with ACL tear and allowing a less conservative rehabilitation protocol. The improvement in terms of subjective function in patients with PRP was not limited to the postoperative phase and it was stable over time (4 weeks to 3 months) which suggests that it may not just be a pain modulation mediated by platelets, but it is likely that PRP may play a role in the healing mechanisms. The trauma causing ACL tear can be also responsible for damaging other tissues and therefore can cause an altered joint homeostasis, which is further maintained by the surgical trauma itself. The reduced swelling observed at 12 weeks in patients from Group A can suggest that PRP acts favoring a better joint homeostasis through the release of growth factors and bioactive molecules. Indirectly it can limit further intra-articular bleeding from the tunnels. However, these are just hypothesis, since the design of this study does not determine the mechanism of action of PRP [4,9,21,22]. One thing to note is that according to the international literature, microfracture surgery using Pridie drillings has, at some point, similar effects as PRP treatment. Although only eight such surgical interventions were performed, we did not see any improvement or worsening concerning the evolution of patients but further studies will be carried to compare these two treatments and their effect on bone and cartilage regeneration.

We were unable to find any improvements or worsening concerning the graft integration on MRI investigations during these 3 months, although 3 patients from each group are clearly a small number to draw any conclusions at this point. There were no cases of graft slippage and the improved stability of the knee was rather due to the mechanical factors such as graft positioning and fixation mechanism.Further studies of PRP therapy should be carried to see if there is the possibility to accelerate and improve the graft integration process which at this point is questionable.

PRP was prepared from autologous blood, so any concerns of allergic reactions and transmissible diseases were eliminated.

These preliminary results showed that treatment with PRP injections is safe and has the potential to reduce pain and swelling therefore improving life quality among patients and has the potential to speed up the rehabilitation process, a key factor among professional athletes and the return to previous sport activity.

Improved clinical scores, reduction in pain and swelling at 3 months interval may be considered a success and can indicate that PRP therapy is a viable low-cost solution and can be used as an auxiliary treatment in the rehabilitation process among patients with ACL reconstruction.

Our study is one of the first in our clinic, which is focused on the use of autologous therapy in patients treated with complete ACL tear, but at this point it has some limitations including the lack of standardization and relative short follow-up period.

Implementation of a standard protocol is problematic at this point because PRP has an autologous origin which means that blood from one patient may have a different composition from another and in the same time blood from an individual can also vary greatly between each draw.

Furthermore, the outcome should be evaluated at six months after surgical intervention because from then on the rehabilitation period is over and patients are able to return to sports.

## Conclusions

In the short term, the local treatment showed improvement on the overall clinical status of the patients (less pain, improved mobility, less swelling) undergoing rehabilitation after anterior-cruciate ligament reconstruction.

Platelet-rich plasma could be regarded as an additional and integrative therapy to support conventional treatments and recovery protocols based on our early findings.

The role of autologous plasma products regarding graft healing and integration is questionable and further studies are required in order to prove or deny this hypothesis.

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## Conflict of interest

None to declare.

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