

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH



EFFECTIVENESS OF ULTRASOUND-GUIDED PLATELET-RICH PLASMA INJECTION IN COMPARISON WITH DEXTROSE PROLOTHERAPY ON IMPROVING PAIN AND FUNCTION AMONG THE ATHLETES WITH PARTIAL TEAR OF ANTERIOR CRUCIATE LIGAMENT: A RANDOMIZED CONTROL TRIAL.

Medicine

Dr Laimujam Sobhasini Devi	Post Graduate Student, Department of Sports Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India, Pin No. 795004
Dr Akoijam Joy Singh*	Nodal Officer, Professor and i/c Head Department of Sports Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India, Pin No. 795004 *Corresponding Author
Dr Yumnam Nandabir Singh	Professor, Department of Sports Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India, Pin No. 795004
Dr Yumnam Ningthemba Singh	Assistant Professor, Department of Sports Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India, Pin No. 795004
Dr Pheiroijam Bhupes	Assistant Professor, Department of Sports Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India, Pin No. 795004
Dr Kongkham Purnimala Chanu	Senior resident, Department of Sports Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India, Pin No. 795004
Dr Lisham Ranjankumar Singh	Senior resident, Department of Sports Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India, Pin No. 795004
Dr Sagolsem Adarsh Singh	Post Graduate Student, Department of Sports Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India, Pin No. 795004
Dr Ramkumar R	Post Graduate Student, Department of Sports Medicine, Regional Institute of Medical Sciences, Imphal, Manipur, India, Pin No. 795004

ABSTRACT

Background: Anterior Cruciate Ligament (ACL) injuries are one of the most common ligamentous injuries of knee. Multiple emerging therapies like PRP, prolotherapy are being explored to hasten the healing process of the ligaments which may have positive effect on the treatment of partial tear of ACL. The objective is to determine the effectiveness of PRP injection versus dextrose prolotherapy on improving pain and function among athletes with partial tear of ACL. **Materials and method:** A RCT was done among athletes with partial ACL injury who visited Department of Sports Medicine, RIMS, Imphal. Patients with MRI diagnosed partial ACL injury (N=48) randomized into PRP injection plus rehabilitation, (n=24) and dextrose prolotherapy plus rehabilitation (n=24) groups. The outcomes were compared using International Knee Documentation Committee (IKDC) score and VAS at baseline, 1st month, 4th month, 8th month and 12th month respectively. **Results:** All the outcome measures improved significantly in both groups in all follow-ups ($p < 0.05$). There were statistically significant difference in mean changes of VAS and IKDC score between the two groups from baseline to 1st ($p = 0.007$); ($p = 0.003$), 4th ($p = 0.003$); ($p = 0.001$) and 8th months follow-ups ($p = 0.049$); ($p = 0.020$) respectively with PRP group having more improvement. However, there was no statistically significant difference in mean changes of VAS and IKDC score between groups from baseline to 12th month follow up ($p = 0.05$). **Conclusion:** USG guided PRP injection along with standard rehabilitation program might be a treatment choice for partial ACL tear with sooner return to play through faster progression of rehabilitation.

KEYWORDS

ACL, PRP, Prolotherapy, IKDC score, VAS.

INTRODUCTION:

ACL injuries are one of the most common knee injuries.¹ ACL is an intra-articular and extra-synovial structure with two separate bundles, anteromedial and posterolateral bundles which maintain different tensions according to different degrees of knee flexion angle.² ACL plays an important role in knee stability and normal biomechanics.³ It prevent excessive forward motion of the tibia relative to the femur during flexion and extension. The ACL additionally provides rotational stability to the knee with varus or valgus stress.⁴ Trauma to the ACL can occur during contact and high-impact sports, but is most commonly sustained in non-contact situations, as when an athlete decelerates, pivots/turns quickly, or lands hard from a jump.⁵ Injuries at this site, mainly developed in sports participation, have been associated with instability, decreased physical activity, low quality of life overall and are considered to be some of the most devastating knee injuries.⁶ 78% of these injuries occur during soccer, baseball, basketball, and skiing training.⁷

Females are particularly vulnerable to ACL injuries due to anatomical, biomechanical, neuromuscular and hormonal differences.⁸ Partial tears of ACL account for 10% to 30% of all ACL tears.⁹ If the knee is injured, it increases the risk of tissue damage to cartilage, degenerative meniscus, and functional instability.¹⁰ In Long-term, patients with ACL

lesions have the risk of developing degenerative changes in the knee, meniscal tears or chondral lesions.¹¹

There is still considerable controversy regarding the diagnosis, natural history and treatment of this type of lesion. Diverse criteria are often used to define a partial ACL tear. Magnetic resonance imaging (MRI) features include the estimation of the percentage of torn fibers, specific affected bundle (anteromedial or posterolateral) and location of the tear (proximal, middle third or distal). A partial ACL tear combines a positive Lachman's test with a firm endpoint.¹² The physical examination is decisive in this type of lesion. Finally, arthroscopy remains the gold standard for the diagnosis of macroscopic integrity of the intact bundle.⁹

Partial ACL ruptures are a challenging condition for orthopaedic surgeons.¹¹ Therapeutic options for treatment of partial ACL tears historically range from conservative treatment up to partial reconstruction in terms of bundle augmentation/ complete ACL reconstruction according to injured bundles.¹³ Conservative therapy of partial ACL tears is associated with a high failure rate and often consecutive complete ACL rupture, followed by ACL reconstruction. Initial ACL reconstruction is reported to be potentially associated with diminished proprioception, postoperative muscular weakness, not fully

restoration of normal kinematics, donor site morbidity, and possible premature osteoarthritis. Thus, ACL preserving techniques have to be favoured.¹³ Conservative and surgical treatments do not differ markedly in the long-term follow-up of the progression of knee osteoarthritis. Nevertheless, surgical treatment has a long rehabilitation period before returning to competition, and, in some cases, depending on the athletes' social background, they choose conservative treatment.¹⁴

Early return to play is the goal of both amateur and professional athletes. Multiple emerging therapies and modalities are being explored to hasten the healing process. These include modalities such as platelet-rich plasma injection, prolotherapy, stem cells, porcine small intestine scaffolding, gene therapy, and growth factors.¹³

Platelet-rich plasma (PRP) shows promising results for minimally invasive treatment of knee lesions through enhanced healing potential of damaged cartilage, tendons, and ligaments.¹⁶ PRP is an autologous blood product containing various growth factors.¹¹ The mechanism of action relies on releasing cytokines and growth factors from alpha granules such as interleukin 1 β , interleukin 8, TNF- α , PDGF, PDEGF, TGF- β 1, IGF-1, FGF-2, HGF and VEGF-A. These enhance healing by stimulating cell proliferation, migration and differentiation, alongside interaction with the immune system, inflammation, and angiogenesis.¹⁶ This healing process starts with platelet aggregation and clot formation and forms a scaffold, which acts as a temporary matrix for cell growth and differentiation.¹⁷ Studies have shown that PRP treatment can be an alternative to surgery and improve patient performance and disability.¹⁸

Prolotherapy is an increasingly popular regenerative injection-based therapy and using for damaged or degenerated connective tissue healing, such as ligaments, tendons and cartilage.¹⁸ Mechanism of dextrose works by dehydrating cells at the injection site, causing inflammation, which will attract granulocytes and macrophages and enhance the healing process.³ The general concept is that injectates initiate a local inflammatory response that ultimately triggers a healing cascade. Release of cytokines and growth factors promote proliferation of fibroblasts and deposition of collagen deposition, strengthening the ligaments, tendon and joint stabilizing structures and reducing pain.²⁰

PRP or prolotherapy can be precisely applied to the ACL torn region under ultrasound guidance. With the assistance of sonography, the architecture, quality, insertion, and origin of the soft tissue can be evaluated. Moreover, we gain more confidence of identifying ACL torn region.²¹

This study was conducted taking into consideration that use of platelet-rich plasma (PRP) or prolotherapy can expedite the physiological repair of the ligament. It can have pain reduction effect that may assist in faster rehabilitation progress, shorter return to play and less detraining which is crucial to professional athletes. There are very less studies determining the effectiveness of these two regenerative therapies i.e., PRP injection and prolotherapy in the treatment of ACL injury. Therefore, we conducted this study to determine the effectiveness of ultrasound guided platelet rich plasma injection and prolotherapy on improving pain and function among the athletes with partial ACL injury of knee.

MATERIALS AND METHOD:

A randomized controlled trial was done among athletes with partial ACL injury who visited department of Sports Medicine, RIMS, Imphal during June 2020-December 2021. Patients with knee pain following injury were clinically examined and sent for MRI. Patients with MRI diagnosed partial ACL injury (n=48) randomized into PRP injection plus rehabilitation, (n=24) and rehabilitation alone, (n=24) groups.

Inclusion criteria:

Patient of age between 18 to 40 years, with history of knee pain following injury within 3 months duration and MRI diagnosed partial ACL tear, platelet count more than 1.8 lakh/microliter were included in the study.

Exclusion criteria:

MRI proven associated PCL injury, grade 3 meniscal tear and grade 3 collateral ligament tear, patients who received corticosteroid injection within last 12 weeks, history of platelet dysfunction syndromes,

malignancy, systemic illnesses were excluded from the study.

A sample size of 48 was calculated using formula

$$N = (Z\alpha + Z\beta)^2 (s_1^2 + s_2^2) / (m_1 - m_2)^2$$

According to a study conducted by Kumar et al considering 90% power, and 5% level of significance and 10% for drop outs to counter attrition bias.²²

Outcome measures:

Pain and functional activities measured by IKDC and Visual analogue scale for pain.

Patient who met inclusion and exclusion criteria and gave consent for participation in the study were randomized (n=48) into PRP injection plus rehabilitation, (n=24) and prolotherapy with rehabilitation, (n=24) groups by block randomization technique. After taking informed consent, all subjects were evaluated for IKDC score and VAS at baseline before starting any intervention. And after starting the interventions, at the end of 1st month, 4th month, 8th month and 12th month, patients were evaluated with IKDC score and VAS.

PRP injection plus rehabilitation group:

PRP was prepared using Double spin method. 25ml whole blood was drawn under proper aseptic and antiseptic precautions, and put in 3 vials containing acid citrate dextrose anticoagulant. The three vials were centrifuged at 2400 revolutions per minute for 10 minutes. The clear supernatant fluid was taken out using a 20-gauge spinal needle and put in plain vials and centrifuged again at 3600 rpm for 15 minutes. The lower 1/3rd was PRP and upper 2/3rd was platelet-poor plasma (PPP). 4 ml of PRP was procured by removing the PPP.

The patient lied in the supine position with knee flexion at 90°. The 5-12 MHz linear probe was placed parallel to patellar tendon with the proximal end of transducer pivoting to the lateral side of the knee joint to clarify the insertion of both anteromedial and posterolateral bundles over tibial plateau. The needle tip reached tear region of ACL under out-of-plane approach. 4 ml of PRP was given under USG guidance.

After the injections, patients were asked to withdraw from using any non-steroidal anti-inflammatory drugs (NSAID). Patients were instructed to rest the involved knee for next 2 days. Acetaminophen and cold therapy were allowed for pain control.

Prolotherapy injection plus rehabilitation group:

Dextrose prolotherapy injection solution was prepared by a combination of 6ml of 25% dextrose, 2ml of normal saline and 2ml of 0.5% lignocaine. The patient lied in the supine position with knee flexion at 90°. The 5-12 MHz linear probe was placed parallel to patellar tendon with the proximal end of transducer pivoting to the lateral side of the knee joint to clarify the insertion of both anteromedial and posterolateral bundles over tibial plateau. The needle tip reached tear region of ACL under out-of-plane approach. 4ml of dextrose prolotherapy solution was given inside the ACL and 6ml was given around the ACL intra-articularly.

Both the group followed a functional rehabilitation program including ROM exercises, progressive strengthening exercises of muscles, neuromuscular proprioceptive balance training.

Informed Consent and Ethics Approval:

All the participants were informed about the nature of the study and those who agreed to participate were asked to sign the informed consent form. Participants were assured that they could withdraw from the study at any time. The study was approved by Institutional Ethics Committee.

Statistical Analysis:

Data were entered and analyzed by using SPSS version 21. The baseline characteristics between the PRP plus rehabilitation group and corticosteroid injection plus rehabilitation group were studied by chi-square test for categorical variables, and independent t-test was used for continuous variables. For descriptive statistics, mean and standard deviation were used. For outcome measures, the mean changes from baseline to 1st month, 4th month, 8th month and 12th month follow-up for each group were compared by repeated measure ANOVA test followed by post hoc analysis (Bonferroni). For comparison between the groups, independent t-test was used. p-value < 0.05 was taken as significant.

RESULT:

The baseline characteristics of the patients in control and intervention group were not statistically significant (Table 1). ACL injury was more commonly seen in female athletes in both the groups (56.3%; n=27), 45.8% (n=22) of them play soccer, 60.4% (n=29) are due to non-contact types of injury. Outcome measures at baseline were not statistically significant (Table 2). At the end of 1st month, there was statistically significant improvement in both mean changes of IKDC score (p=0.003) and VAS (p=0.007) from baseline.

At the end of 4th month, there is statistically significant improvement in both mean changes of IKDC score (p=0.001) and VAS (p=0.003) from baseline. At the end of 8th, there is statistically significant improvement in both mean changes of IKDC score (p=0.020) and VAS (p=0.049) from baseline. At the end of 12th month, there is improvement in mean changes of IKDC score (p=0.336) and VAS (p=0.679) from baseline, were observed however not statistically significant (Table 3).

Table 1: Comparison of baseline characteristics between the groups, (N=48)

Variables	PRP + Rehabilitation (n=24) No.(%)	Prolotherapy+Rehabilitation (n=24) No.(%)	P-value*
Age			0.773
18-25	12(50.0%)	11(45.8%)	
26-40	12(50.0%)	13(54.2%)	
Gender			0.771
Male	10(41.7%)	11(45.8%)	
Female	14(58.3%)	13(54.2%)	
BMI (kg/m ²)			0.765
18.5-20.5	7(29.2%)	6(25.0%)	
20.5-22.5	8(33.3%)	8(33.3%)	
22.5-24.5	9(37.5%)	10(41.7%)	
Type of Sports			0.991
Soccer	11(45.8%)	11(45.8%)	
Basketball	6(25.0%)	7(29.2%)	
Wushu	3(12.5%)	2(8.3%)	
Badminton	2(8.3%)	2(8.3%)	
Judo	2(8.3%)	2(8.3%)	
Side of affection			0.773
Right	12(50.0%)	11(45.8%)	
Left	12(50.0%)	13(54.2%)	
Type of Injury			0.768
Contact Injury	9(37.5%)	10(41.7%)	
Non-Contact Injury	15(62.5%)	14(58.3%)	
Duration			0.768
1-2 months	14(58.3%)	15(62.5%)	
2-3 months	10(41.7%)	9(37.5%)	

*chi-square test #independent t-test p value <0.05 was taken as significant

Table 2: Comparison of baseline outcome measures.

Outcome measures	PRP + Rehabilitation (n=24) (Mean±SD)	Prolotherapy + Rehabilitation (n=24) (Mean±SD)	p-value*
IKDC	34.58 ± 2.35	35.58 ± 3.18	0.223
VAS	8.513 ± 0.72	8.650 ± 0.66	0.500

*Independent t-test p value <0.05 was taken as significant

Table 3: Comparison of mean changes of IKDC score and VAS scores between the two groups from baseline to 1st month, 4th month, 8th month and 12th month follow up, (N=48).

	Mean changes from base line		
Mean differences	PRP + Rehabilitation (n=24) (Mean ± SD)	Prolotherapy + Rehabilitation (n=24) (Mean ± SD)	p-value*
IKDC score			
1st month	18.35 ± 5.89	14.00 ± 5.89	0.003
4th month	29.08 ± 4.75	21.87 ± 6.08	0.001
8th month	40.37 ± 3.93	37.83 ± 3.35	0.020
12th months	49.29 ± 4.73	47.87 ± 5.35	0.336
Mean differences	PRP + Rehabilitation (n=24) (Mean ± SD)	Rehabilitation (n=24) (Mean ± SD)	P-value*
VAS score			
1st month	-1.96 ± 0.83083	-1.18 ± 1.04	0.007

4th month	-3.79 ± 1.35	-2.69 ± 1.02	0.003
8th month	-5.09 ± 0.806	-4.60 ± 0.86	0.049
12th months	-6.26 ± 1.29	-6.10 ± 1.26	0.679

*Independent t-test

p value <0.05 was taken as significant

DISCUSSION:

In our study, we gave PRP injection and dextrose prolotherapy inside the torn ligament under ultrasound guidance in both control and study group respectively which was followed by functional rehabilitation program. There was significant improvement in pain, symptoms perception, function and ability to participate in sports in the subsequent follow up in both the groups. And, there was significant improvement in the PRP plus rehabilitation group in 1st, 4th and 8th month follow up in comparing with dextrose prolotherapy plus rehabilitation group. At 12th months follow up, there was improvement in PRP plus rehabilitation group in comparing with dextrose prolotherapy plus rehabilitation group, however not statistically significant.

PRP injection reduces the pain intensity in short term therefore rehabilitation program can be accelerated to its later stages in a shorter time with sooner returning to sport activities, which is a major issue in athletes. Our study showed that PRP injection causes a significant improvement of perception of symptoms, knee function in the 1st, 4th and 8th month follow up which allows faster progression of rehabilitation, and sooner return to sport activities, though prolotherapy group have that same level of improvement in pain, perception of symptoms and function later, in the 12th month follow up.

Zicaro JP et al found that all the patients returned to sports at a mean of 3.8 months in PRP plus rehabilitation group and 4.2 months in rehabilitation alone group.¹² Hada S et al reported two cases of anterior cruciate ligament injuries treated conservatively with platelet-rich plasma. They returned to the same preinjury level as early as 4 and 3.5 months.¹⁴ Elasmis S et al compared ACL repair by arthroscopy and another treated by PRP injection in ACL tear. They have found that patients in both groups had significantly decreased pain severity after 14 months after treatments. In addition, they had significantly improved OKS score and ROM. However, patients in the surgical reconstruction group had significantly lower pain and higher ROM compared to PRP group.¹⁸ Steadman et al developed the healing response technique to promote ACL tissue healing. Based on their purpose to preserve healthy ACL tissue and regarding the increasing knowledge about stimulation of endogenous regenerative potential by the use of biologic agents, such as growth factors and stem cells.²³ Centeno et al concluded that a minimally invasive, percutaneous injection of bone marrow concentrate and platelet products into the ACL under fluoroscopic guidance may be a viable alternative to surgical ACL reconstruction for the treatment of grade 1, 2 and non-retracted grade 3 tears of the ACL.²⁴ Reeves KD et al concluded that in patients with symptomatic anterior cruciate ligament laxity, intermittent dextrose injection resulted in clinically and statistically significant improvement in ACL laxity, pain, swelling, and knee range of motion.²⁵

Christensen T et al concluded that prolotherapy does not appear effective in the short term (6 months), but may be effective in reducing pain and increasing function compared with baseline long term (1–3 years).²⁶ Grote W et al document the non-surgical repair of a high-grade partial or complete ACL tear using prolotherapy and at-home exercise. By 15 weeks, the patient had no instability climbing and descending stairs, the anterior drawer test was negative and MRI showed an intact ACL with fibrosis. Subsequently, she returned to full sport activity.²⁷ Patients who underwent nonsurgical ACL treatment produced limb symmetry index, with the side-to-side torque difference expressed as a percentage, and values at or above 90% for all 4 single-leg hop tests and strength tests similar to ACL-r patients.²⁸

Partial ACL tears must be treated early enough to prevent a large number of secondary instability-derived events, particularly meniscal damage, accelerated cartilage degenerative changes and functional disability. Preserving native ACL remnant fibers, when partially torn, may provide several theoretical advantages over reconstruction, including preservation of the natural anatomy, physiology, proprioception, and intrinsic cell populations, as well as some of the complex biomechanical properties of the knee.¹¹ These alternatives to the current surgical reconstruction techniques have the potential to

preserve the native insertion site of the remaining fibers and therefore its proprioceptive function, which may in turn lead to biomechanics that are more natural.¹¹

Limitation of the study:

The study could have been more reproducible if done with bigger sample size and longer follow ups.

CONCLUSION:

Partial ACL tears which are often managed conservatively may be more satisfactorily treated with the addition of PRP or dextrose prolotherapy to stimulate repairs. Enhanced healing effect and short term pain reduction effect of PRP is definitely beneficial for the elite athletes who needs faster recovery and sooner return to the play through faster progression of rehabilitation so it can be recommended to use PRP injection in athletes with partial ACL tear. Moreover, we can avoid the deleterious effect of surgical reconstruction of ACL tear. Under ultrasound guidance, PRP or prolotherapy could be precisely injected to the torn region of ACL. It can thus be concluded that both interventions were effective in relieving pain and function during all follow ups. However, at short term follow-up, the improvement in pain and function in PRP group was more than that in dextrose prolotherapy. Therefore, in view of the better results, it is suggested that ultrasound-guided Platelet-Rich Plasma injection may be used as the preferred method of treatment in the management of partial tear anterior cruciate ligament. Further studies are warranted with bigger sample size and longer follow to define the role of these approaches in the treatment of the partial tears of ACL and to assess the long-term outcomes.

Acknowledgement:

I would like to express my gratitude to all my teachers for providing support and guidance. Without them, I would not have been able to complete my work.

Declaration:

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee.

REFERENCES:

1. Yu B, Garrett WE. Mechanisms of non-contact ACL injuries. *Br J Sports Med.* 2007;41(1):i47-51.
2. You CK, Chou CL, Wu WT, Hsu YC. Nonoperative choice of anterior cruciate ligament partial tear: Ultrasound-guided platelet-rich plasma injection. *J Med Ultrasound.* 2019;27:148-50.
3. Rhatomy S, Margaretha E, Rahmadian R. Dextrose Prolotherapy for Muscle, Tendon and Ligament Injury or Pathology: A Systematic Review. *ARRB [Internet].* 17Oct.2020 [cited 22Oct.2022];35(10):43-62. Available from: <https://journalarrrb.com/index.php/ARRB/article/view/30288>
4. Evans J, Nielson JJ. Anterior Cruciate Ligament Knee Injuries. [Updated 2022 May 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK499848/>
5. Griffen L, Agel J, Albohm MJ, Arendt EA, Dick RW, Garrett WE, et al. Noncontact ACL injuries: risk factors and prevention strategies. *J Am Acad Orthop Surg.* 2000;8:141-150.
6. Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care practice. *Prim Care.* 2010 Mar;37(1):65-80.
7. Fernandez L, Seijas R, Pérez-Bellmunt A, Ragazzi P, Peillon O, et al. Anterior Cruciate Ligament Reconstruction with Platelet Rich Plasma: Systematic Review. *Int J Sports Exerc Med.* 2019 Sep;5(9):1-4.
8. Shuterback S. The incidence of ACL tears in men and women collegiate soccer players. *Ortho Trans.* 1996;20:259.
9. Herdea A, Struta A, Derihaci RP, Ulici A, Costache A, Furtunescu F, Toma A, Charkauoi A. Efficiency of platelet-rich plasma therapy for healing sports injuries in young athletes. *Exp Ther Med.* 2022 Mar;23(3):215.
10. Smith MA, Smith WT, Kosko P. Anterior cruciate ligament tears: reconstruction and rehabilitation. *Orthop Nurs.* 2014 Jan;33(1):14-24.
11. Dallo I, Chahla J, Mitchell JJ, Pascual-Garrido C, Feagin JA, LaPrade RF. Biologic Approaches for the Treatment of Partial Tears of the Anterior Cruciate Ligament: A Current Concepts Review. *Orthop J Sports Med.* 2017;5(1):1-9.
12. Zicaro ZP, Mansilla IG, Zuain A, Yacuzzi C, Paz MC. Has platelet-rich plasma any role in partial tears of the anterior cruciate ligament? Prospective comparative study. *World J Orthop.* 2021;12(6):423-32.
13. Koch M, Mayr F, Achenbach L, Krutsch W, Lang S, Hilber F et al. *BioMed Res. Int.* 2018;2018(1):1-9.
14. Hada S, Ishijima M, Omiya H, Tomita Y, Hada M. Two cases of contact athletes with anterior cruciate ligament injuries who returned to competition early after conservative treatment with PRP therapy. *Int J of Surg.* 2022 Jun;95(1):1-4.
15. Duffy PS, Miyamoto RG. Management of medial collateral ligament injuries in the knee: an update and review. *Phys Sportsmed.* 2010 Jun;38(2):48-54.
16. Trams E, Kulinski K, Kaminska KK, Pomianowski S, Kaminski R. The clinical use of platelet-rich plasma in knee disorder and surgery- a systemic review and meta-analysis. *Life.* 2020 Jun 25;10(94):1-41.
17. Sharaki F, Esfahani MP, Sajjadi MM, Salehi S, Abedi AH, Hassabi M. Determination of effect of platelet rich plasma injection on improving pain and function in young healthy

- athletes with isolated grade 2 or 3 knee medial collateral ligament sprains. *Novelty in Biomedicine.* 2019 Apr 16;7(3):147-57.
18. Eslami S, Fattah S, Taher SA, Rezasoltani Z. Platelet-rich plasma therapy or arthroscopic surgery on repair of anterior cruciate ligament rupture. *Eur J Transl Myol.* 2022 Aug 1;32(3):10538.
19. Solmaz, I, Orsceklik, A. Features and Clinical Effectiveness of the Regenerative Injection Treatments: Prolotherapy and Platelet-Rich Plasma for Musculoskeletal Pain Management. In: Cascella, M., editor. *From Conventional to Innovative Approaches for Pain Treatment [Internet].* London: IntechOpen; 2019 [cited 2022 Oct 22].
20. Zhao AT, Caballero CJ, Nguyen LT, Vienne HC, Lee C, Kaye AD. A Comprehensive Update of Prolotherapy in the Management of Osteoarthritis of the Knee. *Orthop Rev (Pavia).* 2022 May 31;14(4):33921.
21. Lundblad M, Hagglund M, Thomee C, Senorski EH, Ekstrand J, Karlson J, et al. Medial collateral ligament of the knee in male professional football players: a prospective three-season study of 130 cases from the UEFA Elite Club Injury Study. *Knee Surg Sports Traumatol Arthrosc.* 2019 Apr 4;27(11):3692-8.
22. Kumar S, Singh K, Chadha G. Comparative study of anterior cruciate ligament reconstruction versus conservative treatment among non-athletes: A 10-years follow-up. *J Orthop Trauma Surg Rel Res.* 2018;13(1):46-50.
23. Steadman JR, Rodkey WG. Role of primary anterior cruciate ligament repair with or without augmentation. *Clin Sports Med.* 1993;12(1):685-95.
24. Centeno C, Markle J, Dodson E. Symptomatic anterior cruciate ligament tears treated with percutaneous injection of autologous bone marrow concentrate and platelet products: a non-controlled registry study. *J Transl Med.* 2018;16(246):1-13.
25. Reeves KD, Hassanein KM. Long-term effects of dextrose prolotherapy for anterior cruciate ligament laxity. *Altern Ther Health Med.* 2003 May-Jun;9(3):58-62.
26. Christensen, Trent & Slattengren, Andrew. (2014). Is prolotherapy an effective nonsurgical treatment option for a partial ACL tear?. *Evidence-Based Practice.* 17. 10.1097/01.EBP.0000540712.82932.dd.
27. Grote W, Delucia R, Waxman R, Zgierska A, Wilson J, Rabago D. Repair of a complete anterior cruciate tear using prolotherapy: a case report. *Int Musculoskelet Med.* 2009 Dec 1;31(4):159-165.
28. Hunt ER, Parise CN, and Butterfield TA. Alterations in Quadriceps Neurologic Complexity After Anterior Cruciate Ligament Reconstruction. *JSR.* 2021; 29(7):103237.