Original Article

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

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Abstract

Background: Knee medial collateral ligament (MCL) sprain is common in athletes, which keeps them away from trainings. Platelet-rich plasma (PRP) injection is used as an adjunct for treatment of musculoskeletal injuries. This study was supposed to define effect of PRP injection on high-grade MCL sprain healing, in comparison to rehabilitation alone.

Materials and Methods: This study was performed on 46 healthy athletes with high-grade MCL sprains who came to sports medicine clinic of Taleghani Hospital, Tehran over a one-year period (2017-2018). In first visit injury grade, its location, baseline pain, Lysholm score and joint stability was determined. Participants randomly allocated to 2 groups (n=23), "group A" had 12-week functional rehabilitation and "group B" had the same rehabilitation plus a single PRP injection. At 4-week intervals valgus stress testing, pain and Lysholm scores was reassessed. The scores of 4th, 8th and 12th weeks was compared to the baseline scores.

Results: Mean baseline pain score in control and intervention group was 5.09±0.949 and 5.26±0.810 respectively that in the fourth week of study reduced to 1.30±0.765 and 2.43±0.507 ($p<0.001$). In intervention group, fourth week pain was significantly reduced while stability and Lysholm scores of the groups had no significant difference.

Conclusion: PRP injection had a short-term statistically significant pain reduction effect that may assist in faster rehabilitation progress, shorter return to play and less detraining which is crucial to professional athletes.

Keywords: Knee medial collateral ligament, Platelet rich plasma, Sprain, Joint instability, Analog pain scale, Lysholm knee scale

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Introduction

Platelet-rich plasma **(**PRP) was originally used in clinical practice as an adjunct to surgery to assist in the healing of various tissues. It is used in open-heart surgery, prosthetic surgery to promote tissue healing, implant integration, and to control blood loss. Application of activated PRP has an effect on pain and analgesic use following open subacromial decompression surgery. Injectable PRP is used for the

management of common muscle, tendon and cartilage injuries. Platelets' α granules contain more than 30 bioactive proteins, many of which play a role in hemostasis or tissue healing. They contain, synthesize and release large amounts of biologically active proteins that promote tissue regeneration[1].

PRP injection in knee osteoarthritis (OA) has been shown to have anti-inflammatory effects through growth factors such as TGF-β and IGF1, stimulatory effects on mesenchymal stem cells and fibroblasts. Multiple studies have indicated that PRP is superior to hyaluronic acid (HA) and corticosteroids in improving patient-reported pain and function[2]. In a case of lateral ankle sprain with complete tear of ATFL, PRP injection caused complete healing and early ankle stabilization therefore it can prevent chronic ankle instability[3]. Three cases who sustained high-grade ulnar collateral ligament (UCL) injury underwent two PRPs and cleared to full return to play at a mean 36-day post injury. Follow-up examination demonstrated full range of motion, without tenderness over the UCL, stability also improved, although not symmetric to the contralateral side. All continued to play at the same level as preinjury without any complaints, none had recurrence injury[4]. PRP aims to mediate inflammatory and catabolic factors through the secretion of anti-inflammatory factors and chemotaxis effects. A growing number of studies have demonstrated the clinical benefit of PRP for OA management[5]. Evidence for PRP injection in knee OA showed inhibition long-term pain and improving its function[6]. Intra-articular knee PRP injection may be an effective alternative treatment for mild OA. PRP may reduce pain of lateral epicondylitis and rotator cuff injuries[7]. A single PRP injection was better in knee OA compared to HA or NSAID therapy, but had no effect on cartilage progression[8]. In a retrospective study assessing PRP injections for chronic tendinopathy, a moderate improvement in pain was observed in most cases particularly in patellar and lateral epicondylar tendinopathy, female patients, upper extremity tendinopathy and older patients[9]. Evidence suggest that PRP may provide some benefit in patients with knee OA or lateral epicondylitis but appears to be inconsistent or shows a minimal benefit in rotator cuff repair, patellar and Achilles tendinopathies, hamstring injuries, ACL repair and medial epicondylitis[10]. PRP injections in 25 patients with partial elbow medial ulnar collateral ligament (MUCL) tears plus rehab, 22 patients (96%) could return to play and demonstrated reconstitution of the MUCL on MRI, this treatment was less effective in patients with previous surgery for MUCL[11].

Medial collateral ligament (MCL) sprains are among the most common knee injuries in young athletes, more common in men, in any sport, especially those involving contact or pivoting (e.g. soccer, rugby, basketball, skiing)[12]. MCL originates on the medial femoral condyle and inserts 5 cm distal to the joint line on the tibia, is about 11 cm long, 1.5 cm wide. Medial knee has three layers, composed of a superficial and deep band that is the primary medial knee stabilizer. Superficial MCL converges with the posterior oblique ligament, forming the posteromedial joint capsule that plays an important stability role. Deep MCL forms a thickening in the middle portion of medial joint capsule and attaches to the medial meniscus. MCL is static medial stabilizer, resisting valgus and external rotation stresses. Superficial MCL is the primary restraint to valgus stress in slight flexion. Most injuries occur with a direct blow to the lateral of slightly bent knee. The most common injury mechanism is forced valgus to a planted foot (isolated MCL), also external rotation in an open kinetic chain along with valgus force (MCL sprain may be associated with posterior oblique ligament and posteromedial components' injury). It has three grades (I – III). Grade I injury is partial tearing without laxity. Grade II consist of partial tearing with joint opening up to 5 mm. Grade III leads to joint instability (>10° of joint opening)[13]. MCL is exrtrasynovial therefore responds well to conservative treatment and almost none needs surgery. Mean rehabilitation time to return to sport depends on the severity of injury, about 8 weeks in 2nd degree injuries and 12 weeks in 3rd degree injuries[14]. The aim of our study was to answer this question, Can PRP injection help to injured ligament to heal sooner?

Methods

This study was a randomized clinical trial and done over one-year period (2017-2018). Participants were healthy young athletes, 15-35 years old, who had come for a visit to orthopedic clinic for their medial knee

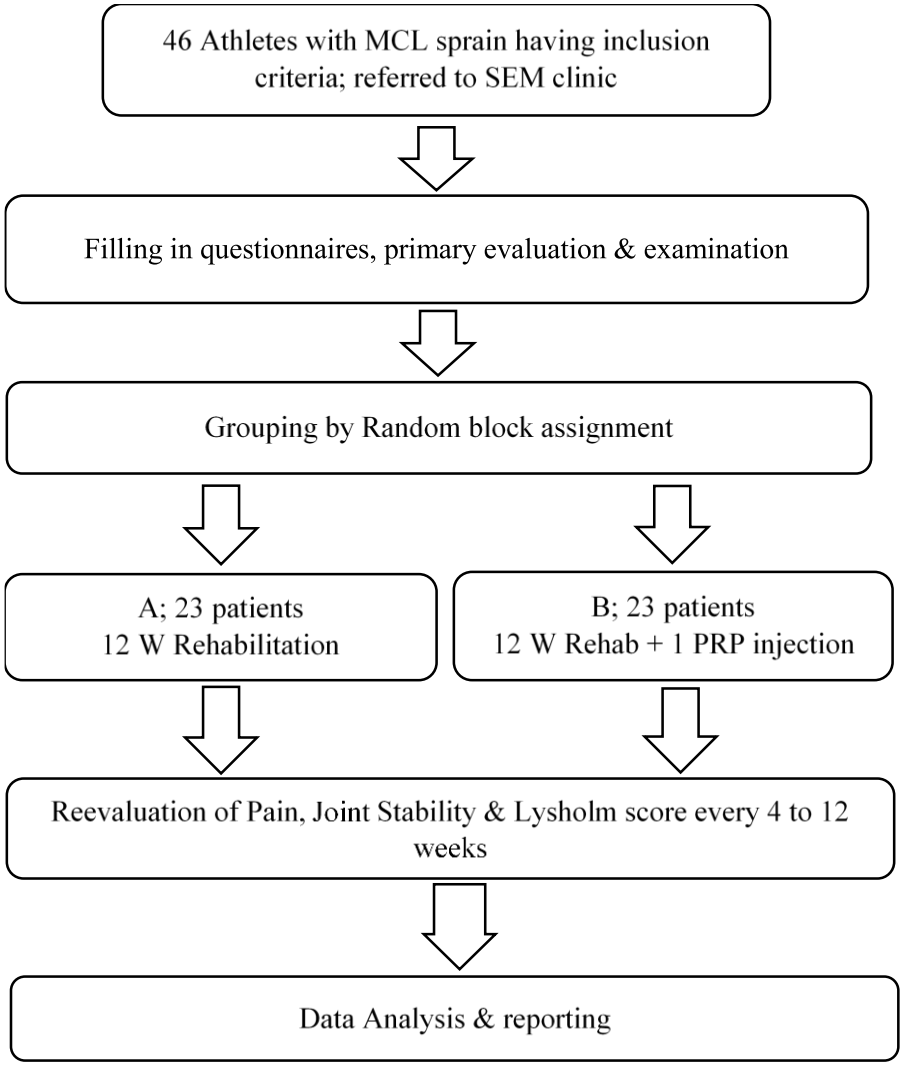

Figure 1. Flowchart of the study.

pain and referred to sports medicine clinic. Inclusion criteria were 1) 15-35 years old, 2) Having injured their MCL during a sport activity, 3) Grade 2 or 3 MCL sprain, 4) Not having surgery indications (e.g. Associated ACL, PCL, POL, PMC, meniscal injury, avulsion of the MCL and tibia side complete MCL rupture). Exclusion criteria were 1) Having an indication for MCL repair/reconstruction, 2) Having absolute/ relative Contraindications for PRP (e.g. Platelet disorders, Severe thrombocytopenia, local infection around the knee, Hemodynamic instability / hematological or bone malignancies, recent use of corticosteroid, NSAID's, cigarette smoking, addiction, 3) uncontrolled diabetes mellitus, 4) pregnancy, Nursing mother, 5) not willing to have the injection 6) Not willing to comply with the rehabilitation program or participate in the follow up sessions. Accordingly, in the first visit, each patient had to fill in questionnaires (personal information, age, weight, height, sport, discipline, chief complaint, date and mechanism of injury, past medical history, drug/ habit/ allergy history) then was examined and our orthopedic

Table 1: Age distribution of the participants.

Participants' Age					
	Mean	SD	Min	Max	P value
Control	26.09	4.78	18	34	0.039
PRP	27.48	4.99	17	35	

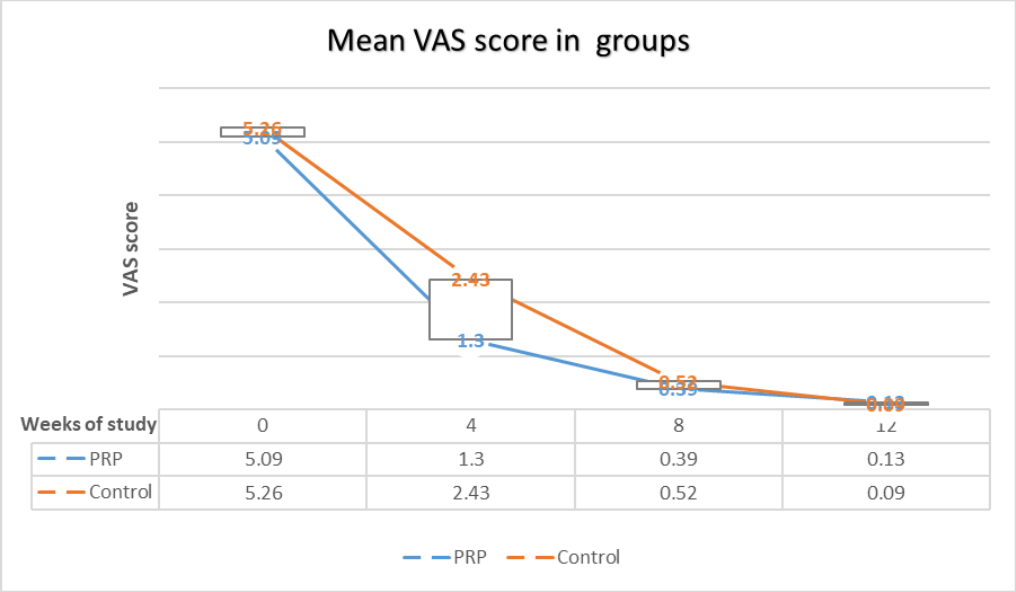

Figure 2. Mean VAS score of the groups of the study.

surgeon graded his injury, radiographs being requested. If inclusion criteria were met, patient was referred to sport medicine clinic. The process of treatment was explained and discussed in details, due to ethical considerations each patient had to read and sign the informed consent forms. In the sport medicine clinic, each patient was reevaluated for precise location of injury. VAS pain score assessed their pain; their knee stability was assessed by valgus stress testing examination and Lysholm knee score was calculated and recorded for later comparison. Regardless of gender, age or sport the patients were divided randomly by "random block assignment" into 2 groups, 23 people in each group. Group A or control group was supposed to be rehabilitated by physical therapists according to a phased functional rehabilitation program including modalities for pain and inflammation reduction, restoring range of motion (ROM) of the joint, manual soft tissue therapeutic modalities, gradual progressive strengthening of muscles, neuromuscular proprioceptive balance training and in the last phase sport specific agility trainings, depending on the grade of injury, patients' symptoms and signs. Group B or intervention group received a single PRP injection at the site of injury and 7 days post injection started the same functional rehabilitation program. Each patient attends first two sessions of rehabilitation phase in the clinic, needed modalities explained and exercises taught in order to performed them correct and effectively. At 4 weeks, intervals each patient was reassessed for pain, Lysholm score and joint stability. The scores of each period were recorded to allow comparison to the initial scores. The pain of participants was quantified by visual analogue scale (VAS) (the least pain was 0 and the most pain was 10), by looking at the VAS scale ruler[15]. Lysholm knee score as a functional score was used to quantify athletes' abilities that is valid as patient-administered scores. It has acceptable test-retest reliability (intraclass correlation coefficient = 0.9)[16]. It is a functional score that is calculated by summing the points of a questionnaire, which covers 8 individual activity related items pain, giving way sensation, locking sensation, squatting, climbing stairs, swelling after activity, using cane or crutches and limping. Total Lysholm score in a normal person is 100 and in

Table 2: Sex distribution of the participants.

		Control	PRP	
No.(%)	Male	13(56.5)	15(65.2)	P value
No.(%)	Female	10(43.5)	8(34.8)	0.546

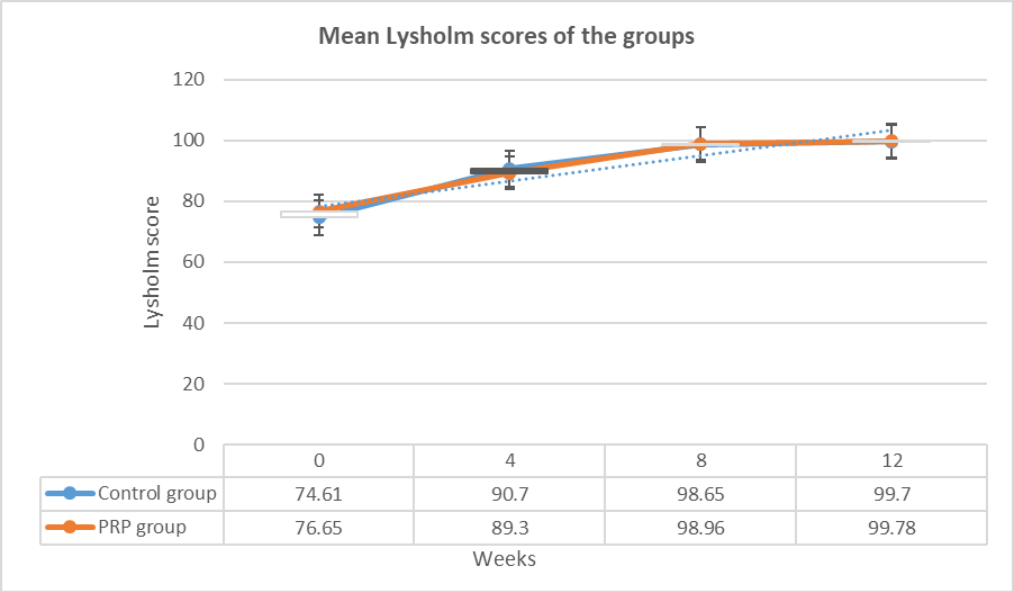

Figure 3. Mean Lysholm scores of the groups of the study.

Table 3: Sport distribution of participants.

Sport discipline	Number(%)
Soccer	15(32.6%)
Basketball	5(10.9%)
Wushu	4(8.7%)
Wrestler	4(8.7%)
Skiers	4(8.7%)
Marshal art	3(6.5%)
Taekwondo	3(6.5%)
Karate	2(4.3%)
Judo	2(4.3%)
Handball	1(2.2%)
Badminton	1(2.2%)
Roller skater	1(2.2%)
Kick boxer.	1(2.2%)

Table 4: Participants sport type; No (%).

Sports	Control	Intervention	P value
Contact	10(43.5%)	9(39.1%)	0.951
Semi-contact	10(43.5%)	11(47.8%)	
Non-contact	3(13%)	& 3(13%)	

exhausted person, the score is lowered (Lysholm questionnaire showed in the appendix page). Knee stability was assessed by Valgus stress testing in two positions: 0 and 30 degrees' flexion, which identify the integrity of MCL, Posteromedial corner (PMC) elements and can differentiate isolated MCL sprains from associated MCL and posteromedial components' injuries[17]. Grading is based on the joint gap on Valgus stress testing in flexion and presence or absence of endpoint. Other tests like anterior drawer testing, Lachman's, joint line tenderness are also used for other knee structure examination. Intervention group had a platelet count prior to venipuncture, also the final PRP was checked for platelet count. Most of the previous clinical trials used one injection[11, 18-21] and some two injections and in a case report, they used 3 PRP injections[22,23], in this study we used one injection. Special PRP kits was used "Standard Kit®" that is specifically produced for PRP production by a local

Table 5: Description & comparison of participants' Weight, Height, BMI.

	Control		PRP		P value
	Max-Min	**Mean±SD**	**Max-Min**	**Mean±SD**	
Weight	102.5-46.8	72.88±13.36	114-56.5	80.16±13.69	0.075
Height	185-145	169.3±9.31	204-158	173±10.71	0.218
BMI	33.86-20.31	25.27±3.26	30.92-22.48	26.64±2.57	0.120

Table 6: Participants injury severity.

	All cases No (%)	**Control no.**	**Intervention no.**
Grade 2	30(65.2%)	16	14
Grade 3	16(34.8%).	7	9

Table 7: Sex distribution & injury severity.

	Male	Female
Grade 2	15 (53.6%)	15 (83.3%)
Grade 3	13(46.4%)	3(16.7%)

Table 8: Injury grades by sport type.

	Contact Sports	**Semi-contact**	**Non-contact**
Grade 2	10	14	6
Grade 3	9	7	0

company, which is a colleague of "Iranian Blood Donation Organization", which needs 25-30 ml of peripheral blood and uses 2 phases of centrifugation before PRP extraction and provides 4 ml of PRP. PRP injected was done under US guidance. We did not have any sample loss. Data analysis done by SPSS 16.0 and significant level of statistical tests were considered 0.05. As other interventions (dry needling, saline injection) had therapeutic effects, we couldn't do patient blinding, our statistical analyst was unaware of intervention type. Figure1 shows stages of the study.

The study subject was approved by the Ethics Committee of the School of Medicine of SBMU with the Code of Ethics IR.SBMU.MSP.REC.1396.74.

Results

Forty-six athletes with isolated grade 2 and 3 knee MCL sprains participated in the study. There was no statistically significant difference regarding age, sex, weight, height, body mass index (BMI) and injury grades between the participants of the groups of study. Grade 3 injury was 77% lower in females; injury severity was significantly lower in females than males ($p \leq 0.047$). Compared to first visit joint stability was improved statistically significant in the 8 weeks of study in both groups ($P<0.001$), regarding joint stability there was no statistically significant difference between the groups.

Comparing first visit VAS scores of the groups showed no statistically significant difference between the two groups ($p=0.507$), by the 4 weeks of the study VAS score in the intervention group was statistically significant lower than control group ($p<0.001$). There was no statistically significant difference in VAS score between the groups in the 8 and 12 weeks of the study ($p=0.458$ and 0.639). Bonferroni correction showed that VAS score of the groups lowered statistically significant ($p<0.001$) from first visit to 4, 8 and 12 weeks. Analysis of variances of repetitive measures revealed that cross effect of time and group was statistically significant ($p<0.001$) therefore the changes of VAS score during the study was significantly

Table 9: Description & comparison of Injury severity by Age, weight, height & BMI.

	Grade 2		Grade 3			
	Mean	**SD**	**Mean**	**SD**	**Chance ratio (95%CI)**	**P value**
Age	26.43	4.69	27.44	5.32	1.05 (0.919-1.19)	0.503
Weight	73.51	14.35	82.16	11.30	1.05 (0.999-1.11)	0.055
Height	169.6	10.83	174.1	8.09	1.05 (0.981-1.12)	0.164
BMI	25.39	3.26	27.02	2.05	1.22 (0.973-1.52)	0.086

Table 10: Joint stability changes in control group by 8th week.

			8th week		Total
			Stable	+1 laxity	
1stvisit	+1 laxity	No.	16	0	16
		%	69.6%	0.0%	69.6%
	+2 laxity	No.	4	3	7
		%	17.4%	13.0%	30.4%
Total		No.	20	20	23
		%	87.0%	13.0%	100.0%

Table 11: Joint stability changes in intervention group by 8th week.

			8th week		Total
			Stable	+1 laxity	
1stvisit	+1 laxity	No.	15	0	15
		%	65.2%	0.0%	65.2%
	+2 laxity	No.	6	2	8
		%	26.1%	8.7%	34.8%
Total		No.	21	2	23
		%	91.3%	8.7%	100.0%

different in the groups ($p<0.001$) and pain was statistically significant reduced in both groups. Group effect was meaningful ($p<0.008$).

Table 12: Describes pain VAS score of groups.

	Control		PRP		
Time	Mean	SD	Mean	SD	P value*
1st visit	5.09	0.949	5.26	0.810	0.507
	<0.001		<0.001		P value**
4th week	1.30	0.765	2.43	0.507	<0.001
	<0.001		<0.001		P value**
8th week	0.390	0.499	0.520	0.593	0.458
	<0.001				P value**
12th week	0.130	0.344	0.090	0.288	0.639
	<0.001		<0.001		P value**

* according to independent T test & Mann-Whitney u test, ** according to Wilcoxon test compared to primary scores

Lysholm scores of the groups in the first visit, 4, 8 and 12 weeks' visits had no statistically significant difference (p=0.363). Regardless of the group, Lysholm score had a statistically significant steady rise from first to 12 weeks (p<0.001). Mean Lysholm scores of the groups in the first visit (p=0.375) also in 4 (p=0.375), 8 (p=0.571) and 12 weeks (p=0.613) had no statistically significant difference. Bonferroni correction also showed that mean Lysholm scores in 4, 8 and 12 weeks compared to the first visit had statistically significant improved (p<0.001). Mean Lysholm scores of the groups had no meaningful differences, group effect not detected (p=0770).

Discussion

Healing process starts with platelet aggregation and clot formation and forms a scaffold, which acts as a

Table 13: Lysholm knee score of groups.

	Control		PRP		
Time	Mean	SD	Mean	SD	P value*
1st visit	74.61	8.53	76.65	7.40	0.390
	<0.001		<0.001		P value**
4th week	90.70	5.67	89.30	4.83	0.375
	<0.001		<0.001		P value**
8th week	98.65	1.95	98.96	1.67	0.571
	<0.001				P value**
12th week	99.70	0.635	99.78	0.518	0.613
	<0.001		<0.001		P value**

*according to independent T test, **according to paired P test compared to primary scores

temporary matrix for cell growth and differentiation. Platelets actively secrete pre-synthesized growth factors (GF) and synthesize more GFs for several days during their life span[24]. MCL is exrtrasynovial and have the potential chance of healing. PRP injection in short term (4 weeks) reduces pain more 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. Completion of functional rehab provides the same result but in a longer duration. Our study showed that PRP injection causes a significant pain reduction in the first month, which allows faster progression of rehab, and sooner return to sport activity, though control group have that same level of pain reduction later, within 12 weeks, and there is no difference in Lysholm score or joint stability. Short-term pain reduction effect of PRP is definitely beneficial for sooner return to play. Short-term pain reduction allows faster rehabilitation and sooner return to the play, which is beneficial in those who need faster recovery including elite athletes so it can be recommended to use PRP injection in professional athletes with MCL sprains.

Conclusion

Based on this study use of injectable PRP in MCL sprain cases has a significant short-term pain reduction effect while completion of functional rehabilitation program is the mainstay of treatment. Use of PRP injection can be suggested for professional athletes in order to shorten the returning time to play and sport.

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LYSHOLM KNEE SCORING SCALE

This questionnaire is designed to give your Physical Therapist information as to how your knee problems have affected your ability to manage in everyday life Please answer every section and mark only the ONE box which best applies to you at this moment.

Name: _____ **Date:** _____

SECTION 1 - LIMP
- ☐ I have no limp when I walk. (5)
- ☐ I have a slight or periodical limp when I walk. (3)
- ☐ I have a severe and constant limp when I walk. (0)

SECTION 2 - Using cane or crutches
- ☐ I do not use a cane or crutches. (5)
- ☐ I use a cane or crutches with some weight-bearing. (2)
- ☐ Putting weight on my hurt leg is impossible. (0)

SECTION 3 - Locking sensation in the knee
- ☐ I have no locking and no catching sensation in my knee. (15)
- ☐ I have catching sensation but no locking sensation in my knee. (10)
- ☐ My knee locks occasionally. (6)
- ☐ My knee locks frequently. (2)
- ☐ My knee feels locked at this moment.. (0)

SECTION 4 - Giving way sensation from the knee
- ☐ My knee gives way. (25)
- ☐ My knee rarely gives way, only during athletics or vigorous activity. (20)
- ☐ My knee frequently gives way during athletics or other vigorous activities. In turn I am unable to participate in these activities. (15)
- ☐ My knee frequently gives way during daily activities. (10)
- ☐ My knee often gives way during daily activities. (5)
- ☐ My knee gives way every step I take. (0)

SECTION 5 – PAIN
- ☐ I have no pain in my knee. (25)
- ☐ I have intermittent or slight pain in my knee during vigorous activities. (20)
- ☐ I have marked pain in my knee during vigorous activities. (15)
- ☐ I have marked pain in my knee during or after walking more than 1 mile. (10)
- ☐ I have marked pain in my knee during or after walking less than 1 mile. (5)
- ☐ I have constant pain in my knee. (0)

SECTION 6 – SWELLING
- ☐ I have swelling in my knee. (10)
- ☐ I have swelling in my knee on1y after vigorous activities. (6)
- ☐ I have swelling in my knee after ordinary activities. (2)
- ☐ I have swelling constantly in my knee. (0)

SECTION 7 – CLIMBING STAIRS
- ☐ I have no problems climbing stairs. (l0)
- ☐ I have slight problems climbing stairs. (6)
- ☐ I can climb stairs only one at a time. (2)
- ☐ Climbing stairs is impossible for me. (0)

SECTION 8 – SQUATTING
- ☐ I have no problems squatting. (5)
- ☐ I have slight problems squatting. (4)
- ☐ I cannot squat beyond a 90deg. Bend in my knee. (1)
- ☐ Squatting is impossible because of my knee. (0)

Total: _____/100

Instructions: Please place a mark on the line to indicate the amount of pain you have had in your knee(s) in the past 24 hours.

RIGHT KNEE
No pain at all _____ **Worst pain possible**

LEFT KNEE
No pain at all _____ **Worst pain possible**