Platelets-rich-plasma in management of non operative post cruciate ligament injury

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Abstract

Posterior cruciate ligament (PCL) injury is a rare ligamentous knee injury which most commonly occurs due to direct trauma; it represents only 0.65% of knee injuries. On the basis of magnetic resonance imaging (MRI), PCL injury is divided into surgical and non-surgical. In the last few years we have witnessed an increasing interest in regenerative medicine. The use of innovative techniques allow the reduction of rehabilitation times in sports injuries. Platelet-Rich-Plasma (PRP) is a plasma-derived which stimulate the tissue repair. The objective of our work is to compare the rehabilitation times in PCL non-operative injuries treated with standard conservative treatment and PCL injuries treated with autologous PRP followed by rehabilitation program. We divided patients into two different groups: Group A formed by patients who underwent a standard conservative rehabilitation program and Group B which included patients treated by ultrasound guided PRP injection and following physiotherapy program. Both groups of patients resumed sports activities; however the rehabilitation times for patients which had undergone treatment with autologous PRP injection were reduced compared to patients who underwent a standard conservative treatment.

Key Words: platelets-rich-plasma; management; non operative; cruciate ligament injury.

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Posterior cruciate ligament injury is a rare ligamentous knee injury which most commonly occurs due to a direct trauma. Majewski et al. have shown that Posterior Cruciate Ligament (PCL) injury accounts for 0.65% of knee injuries.[1] PCL injury is divided into surgical and non-surgical lesions according to the grade of ligament injury (1st- 2nd- 3rd grade) and the posterior translation of the tibia on the femur (> 8mm) [2] MRI is considered the gold standard for the diagnosis of PCL lesion. On the basis of MRI examination PCL injury is also classified into partial or complete lesion. Surgical treatment is reserved exclusively for complete lesion which causes knee instability. Non-surgical treatment can be supported by mini-invasive procedures with Platelet-Rich-Plasma (PRP) which are performed to stimulate ligament repair processes. The ultrasound examination, and the presence of an expert sonographer, allow us the identification of PCL and to inject the PRP inside the ligament structure. PRP is an autologous plasma- derivative in which platelet concentration is higher than baseline. The platelets release growth factors and cytokines through the α-granules. The growth factors which are present in PRP are mainly: TGF-β (Transforming Growth Factors β) which regularizes cell migration and proliferation and stimulates the production of collagen. Others growth factors are : VEGF, PDGF, IGF, FGF, HGF TNF, IL-10. The α-granules contains also a pool of molecules and proteins which stimulate neoangiogenesis and tissue repair actions. These molecules are: serotonin, histamine, dopamine, adenosine, ADP, ATP, calcium, catecholamines.[3] The high concentration of platelets, which are an important reserve of growth factors and other bioactive molecules stimulates cell migration, modulates inflammation and generates anabolic stimuli. In our work we used Pure Platelet Rich Plasma (P-PRP).[4-6]

The growing interest in mini-invasive techniques has led to testing new protocols for non-surgical treatment of PCL lesion.[7-9] This study analyzes the rehabilitation program in patients with non-surgical PCL injury. In particular the main objective is to compare patients

treated with a standard conservative program with patients undergoing a combined physiotherapy treatment with PRP injection.

Materials and Methods

Between December 2014 and March 2018, 7 patients (4 males and 3 females), aged between 15 and 33, amateur sportsmen (4 football, 2 basketball and 1 rugby players) with clinical and instrumental diagnosis, via MRI, of non-surgical lesion of the PCL within 10 days of the injury were evaluated.

All procedures performed in studies involving human participants were in accordance with the ethical standards of Helsinki Declaration. Institutional review board (IRB) approval and informed consent from the patients included in the cases report was obtained.

All treated patients had a BMI between 18.9 and 24.9. Patients with previous knee surgery or ligament injuries were excluded. Patients were divided into two groups based on the treatment performed.

Group A which included 2 males and 1 female were treated with a conservative "standard" protocol. After the injury a 4 points rigid knee brace to immobilize the knee at no more than 60° flexion was used. The brace was removed 20 days from the injury after which the patients started the rehabilitation program.

Group B: which included 4 patients (2 males and 2 females) were treated with ultrasound-guided infiltrative treatment with autologous PRP. Subsequently the infiltration a 4 point brace to immobilize the knee at no more than 60° flexion was applied. The brace was removed on the 6th day and the rehabilitation program started 7 days after PRP injection.

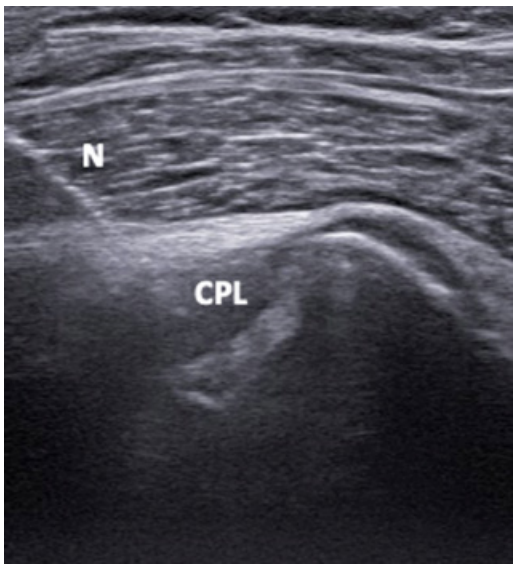

Fig 1. *The image shows the needle insert by an in-plane via into the CPL. N= needle; PCL= posterior cruciate ligament.*

The PRP, used for the procedure, was obtained from a venous blood sample of the patient; the blood was subsequently centrifuged to obtain a split of the plasma component which is characterized by an high platelets concentration. The PRP was isolated and then infiltrated into the ligament lesion by ultrasound-guided procedure (Figure 1).

The patients were placed in prone position; sterilization using povidone-iodine and chlorhexidine were performed. Subsequently the PCL an ultrasound examination using a linear ultrasound probe (7-12 Mhz) was performed to guide the PRP injection into the tendon structure using 20 G needle.

Standard rehabilitation program following isolated LCP Injury

Following a clinical and functional evaluation performed by a physiatrist a rehabilitation program, divided into three different phases, was prescribed.[10,11]

1st Phase

The first phase lasts until the end of the immobilization period. The clinical examination allows us to evaluate the presence of rubor, calor, dolor, tumor. The main objectives of this phase are the flogosis and pain reduction. Criotherapy for 10-15 minutes 3 times a day was performed to reduce knee swelling. Nd-YAG laser-therapy with an antinflammatory program was used (fluence 810-1170 mJ/cm^2 - frequency 10-30Mhz - energy 2000-3000 J).[12]

2nd Phase

The second phase started with a myo-articular examination. The physiatrist and the physiotherapist evaluate the tone, strength, muscular recruitment and joint excursion which were reduced. The second rehabilitation phase objectives were: the recovery of tone and strength, the recovery of passive and active Range of Motion (ROM, the early proprioceptive readaptation, the recovery of correct gait pattern. Isometric exercises, several times a day with a maximum of 30 isometric contractions per exercise, were performed to maintain and recover the muscle tone and strength.[13]

Continuous Passive Motion (CPM) to recover ROM without exceeding excessive joint excursions during early stage of rehabilitation was used. Flexion-extension movement of the knee with limited ROM in order to elasticize the joint capsule, proprioception exercises using proprioceptive tablets which increase the neuro-sensory stimuli were performed. In this second phase the patient still wears the brace which is modulated in flexion-extension until it was completely removed.

Hydrokinesitherapy for gait training was introduced. In rehabilitation swimming pool the absence of gravity force is important to recover a correct walking pattern and muscular strange not overloading the joint.[14] Muscle and joint stretching exercises on all muscle groups of both the lower limbs and the trunk were introduced. During immobilization period motor patterns altered; these exercises are fundamental for recovery of neuromotor coordination. In this phase is important not

to perform opened kinetic chain exercises involving knee flexors. The second phase ends between the 9th and the 12th week from the injury (the variability depends on individual response to treatment) when the patient recovered complete passive ROM and the correct gait pattern.

3rd Phase

The third phase of the rehabilitation program was performed in a physio-gym: the objective was to recover the correct running pattern, increase strength and muscle tone, and then resume the sport gesture. In this phase closed kinetic chain exercises were introduced; advanced proprioceptive exercises in a stabilometric platform, which improves balance reactions, strengthening exercises with leg press and leg extension and isokinetic exercises were introduced. This phase ends between the 13th and 16th week from the injury, when the patient resumed sporting activities.

Rehabilitation program post ultrasound-guided PRP injection

The ultrasound-guided autologous PRP injection was performed within a week from the injury.[15] The patient wearied a semi-locked brace no more than 60° of knee flexion, and the rehabilitation program started 7 days after autologous PRP injection. This immobilization period is necessary to ensure the tissue repair effects of platelet-rich-plasma. The rehabilitation program wass divided into three phases.

1st Phase

The first phase started on the 7th day after PRP injection. During this rehabilitation phase the sessions were daily. The main objectives were weaning from the brace, prevention of capsular and/or tendon retraction and recovery or joint ROM. Isometric contraction exercises, passive mobilization and active stretching exercises were introduced. The Continuous Passive Mobilization (CPM) to recover passive ROM with a progressive and controlled increase of joint excursion was used; in this phase the range of motion was from 60° to 100° of knee flexion. Proprioceptive and neurocognitive exercise to recover the correct motor pattern activating superior cortical functions were performed. At the end of rehabilitation session cryotherapy was applied to prevent the inflammatory reaction due to the overloading of the joint.

2nd Phase

The second phase lasted from the 15th to the 28th day from the procedure. In this phase the rehabilitation sessions are daily. The objectives are: the recovery of the complete passive and active ROM; the improvement of muscular strength to stabilize the knee: in particular strength exercises for vastus medialis which represents the antagonist of posterior tibial translation were performed; and the recovery of proprioception.[16]

The rehabilitation sessions included passive and active functional reeducation exercises in flexion-extension for 15 minutes per session with the patient placed both in supine and prone decubitus. Neurocognitive exercise to recover the complete active ROM and also to increase the muscle strength, tone and recruitment were performed.[17] Other exercises for muscle strengthening included electrostimulation and biofeedback exercises for the quadriceps, isometric and half-squat (0-45°), exercises with elastic bands for hip abductor and adductor muscles. Stretching exercises for hamstrings, quadriceps and triceps surae to avoid overload and maintain joint were performed for 10 minutes per session. The rehabilitation session continued with monopodalic and bipodalic proprioception exercises on a tablet for about 7 minutes. In this phase hydrokinesitherapy to improve muscle strength and to recover neuromotor gait pattern not overloading the joint was used.[14] The second rehabilitation phase ends when the patient recovers the complete active and passive ROM and the corrected gait pattern. Aerobic exercises using bike, for 10 to 15 minutes, with the saddle higher than normal to minimize the activity of Hamstring and with the foot not locked on the pedal to allow the dorsal and plantar flexion of ankle in order to avoid overloading the knee joint were performed.

3rd Phase

The third phase lasted from the 29th to the 45th day from the procedure. The main objectives are: the improvement of muscle strength, the recovery of corrected running pattern and sporting activities. Opened kinetic chain exercises with leg-extension and isokinetic, and plyometrics exercises were introduced. Propaedeutic exercises to recover the corrected running pattern were also performed. In this phase the aerobic work on the bike is integrated with running on the treadmill. Stabilometric platform with a visual biofeedback which allow to perform advanced proprioceptive exercises was used. These exercises were performed in monopodalic and bipodalic stance and lasted about 10 minutes per session. All data were analyzed with GraphPad Prism software (GraphPad Software, Inc., La Jolla, CA, USA, Version 9.4.1). In relation to the size of the sample two non-parametric tests were used: to analyze the distribution of the values within each group in the three different analysis times the Wilcoxon Test was used, while to compare the distribution in the two groups the Mann-Whitney. Test was used. Statistical significance was set for all testing at $p < 0.05$.

Results

Isometric strength tests to evaluate the strength recovery of knee extensor and flexor muscles and the Numerical Rating Scale (NRS) to evaluate the pain were administered. The tests were performed at T0, T1 and T2 (respectively 15-60-90 days after the injury). We analyzed the asymmetric strength between the healthy and injured limb. The data show a faster recovery of strength which is statistically significant ($p < 0.05$) in patients of group B (% asymmetry of T1 extensor strength group A 26 ± 3.6 % VS group B 9 ± 1.2 - % T1 flexor asymmetry group A 28 ± 2.3 % VS group B 9.5 ±

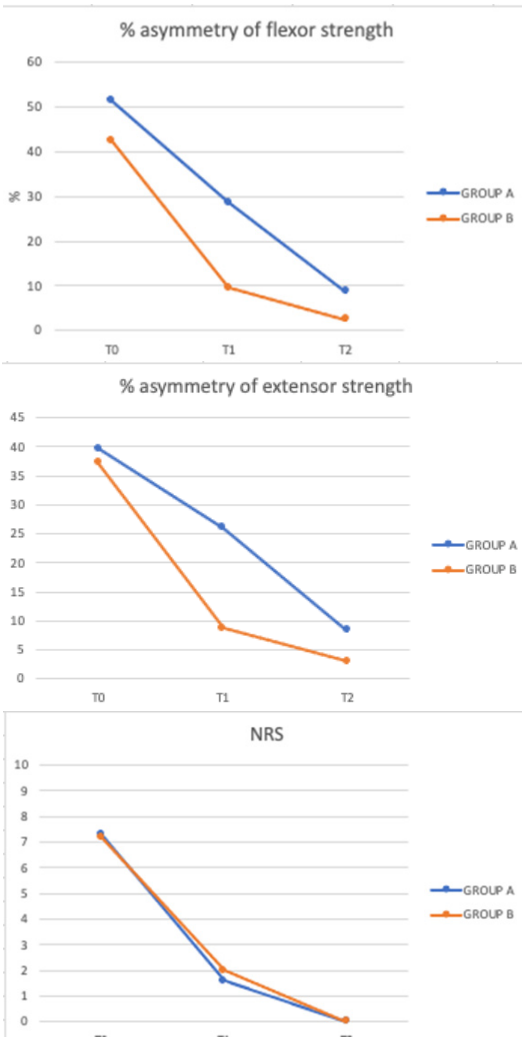

Fig 2. *The graph shows the trend of strength recovery in isometric tests for the knee flexors (Top) and extensors (Medium). The graph shows which group B patients improve muscle strength parameters earlier than group B. Bottob figure shows that pain improvement is comparable in the two groups.*

1.9) (Figure 2a-b). The results between the two groups, however, do not show a statistically significant difference of regression of painful symptoms (NRS T0 group A 7.3 ± 0.5 VS group B 7.25 ± 0.9 - NRS T1 group A 1.7 ± 0.7 group B 2 ± 0.8) (Figure 2c). This data underlines the regression of painful symptoms is comparable in the two groups.

Data analysis showed also a significant difference in complete joint ROM, gait pattern and sporting activities recovery time.

Group A (standard rehabilitation) recovered the complete ROM and muscle tone between the 45th and 60th day

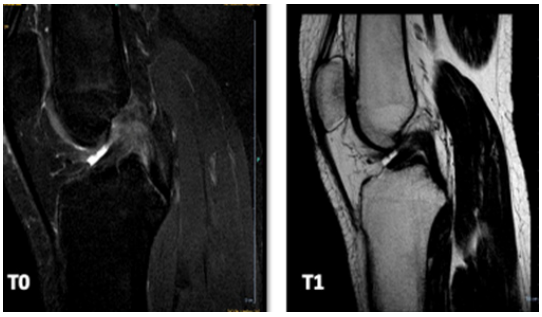

Fig 3. *The figures refer to a patient treated with ultrasound-guided PRP injection. MRI at T0 shows the PCL injury; 45 from the procedure (T1) there is the absence of the previous PCL lesion*

from injury. Correct gait pattern is obtained approximately on the 85th day from injury and resumption of sports activities between the 90th and 120th day.

Group B underwent ultrasound-guided autologous PRP injection and following the rehabilitation program, recovered complete joint ROM and muscle tone between the 15th and 30th day from injury. At the same time basic proprioception was recovered. Correct gait pattern and advanced proprioception was restored between the 40th and 45th day. Resumption of sports activities was obtained from the 60th day from injury.

Discussion

The data analysis highlighted a significant difference between the results of the two groups. The patients who were treated with ultrasound-guided autologous PRP injection, recovered joint ROM, muscle strength, correct gait patter and resumed sports activities earlier than patients who were treated with a standard conservative protocol without PRP injection. Comparing the conservative treatment to autologous PRP injection we highlighted further advantages of PRP treatment, which allows us a resumption of sports activities earlier than the standard conservative treatment. Furthermore PRP is also used for prevention of osteoarthrosis, which is more common in patients affected by sports injury.

Ultrasound-guided autologous PRP injection is a safe treatment. An expert sonographer and a correct ultrasound examination of PCL allow us to inject autologous PRP into the tendon lesion. The patients who have undergone autologous PRP injection could start the rehabilitation program, after medical evaluation, on the 7th day from the procedure, compared to the 25th day of the standard conservative treatment and to the 10th day of the patient undergoing surgical reconstruction of the posterior cruciate ligament. In addition, the first phase of rehabilitation lasts about 7 days for patients treated with autologous PRP, versus 20 days for patients treated with standard protocol. The ROM, correct gait pattern and

advanced proprioception were obtained in about 45 days from the injury with autologous PRP injection while with the standard treatment were obtained no earlier than 85th day. The resumption of sports activities for patients of Group B was reached at about 60 days from injury, instead for patients of Group A it was reached at 120 days from injury. The advantages for rehabilitation after PRP injection is represented by the possibility of starting the physiotherapy program earlier than standard times. This is possible thanks to the intrinsic features of autologous PRP: i) to stimulate tissue repair; ii) to reduce inflammatory response and iii) to obtain a quicker pain reduction.

MRI follow-up showed also an earlier recovery of normal intensity of PCL in patients treated with PRP than standard conservative treatment. (Figure 3)

The early rehabilitation for patients of Group B was referred also to the possibility to insert exercises for the recovery of the ROM in flexion, and to improve trophism and muscle tone. Furthermore the use of PRP the reduction of the immobilization period and to remove the brace earlier; it also anabled to limit the reduction of strength and muscle tone, and to recover the complete ROM earlier. The early rehabilitation allowed resumption of sports activities about 60 days after injury.

PRP could be considered also a viable alternative to surgical treatment. This is possible for the injuries which are not characterized by a posterior translation of the tibia on the femur > 8mm. Several elements suggest better response to ultrasound-guided PRP injection than surgical and non-surgical treatment, including:i) surgical and anesthetic risk reduction: ii) absence of fibrous adhesions phenomena on the skin and intra-articular scar (which would entail limitation of the joint ROM); iii) reduction of health expenditure; iv) possibility of starting within 15 days specific rehabilitation exercises and reducing associated risks as thrombo-embolic phenomena and lymphatic stasis; v) lack of intake to anti thromboembolic, anti-inflammatory and analgesic drugs. The advantages of rehabilitation treatment with PRP injection is summarized in: precocity, intensity and short duration of rehabilitation treatment, aimed at the possibility of a rapid resumption of sports activities. All these factors also allow a major patient compliance.

In relation to the intrinsic features of platelet-rich-plasma, the possibility of reducing rehabilitation times, limits and complications of the standard non-surgical and surgical approaches, the ultrasound-guided percutaneous treatment represents secure and valid treatment for recovery from PCL injury. The treatment with autologous PRP and the following specific rehabilitation program, represent an innovative and effective method of treatment of isolated lesions of the posterior cruciate ligament, especially when the patients affected by these lesions are young and athletes.

On the other hand, the mean limitation of hthis study is represented by the small sample size.Therefore further studies on this matter with larger sample of patients could confirm or not the validity of the proposed treatment.

List of acronyms

CPM - continuous passive motion
IRB - institutional review board
MRI - magnetic resonance imaging
PCL - posterior cruciate ligament
PRP - platelet-rich-plasma
ROM - range of motion

Contributions of Authors

Conceptualization: GM, PC; data curation: MT; formal analysis: CM: investigation: EMI; methodology: AI; supervision: AI, PC; writing – original draft: FM; writing – review and editing: FM, GM.

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Conflict of Interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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