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REGENERATION OF PARTIAL ANTERIOR CRUCIATE LIGAMENT TEARS USING THE TECHNIQUE OF BIOLOGIC AUGMENTATION WITH BONE MARROW CONCENTRATE AND PLATELET-RICH PLASMA UNDER ARTHROSCOPIC VISUALIZATION: A PROSPECTIVE STUDY AT 2-YEAR FOLLOW-UP

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Abstract

To present clinical outcomes in a preliminary patient cohort using a biologic augmentation technique consisting of intra-ligamentous and intra-articular infiltration of bone marrow aspirate concentrate (BMAC) and platelet-rich plasma (PRP) under arthroscopic visualization for treatment of isolated and acute partial anterior cruciate ligament (ACL) tears. Athletes with an acute symptomatic partial ACL injury with clinical examination findings of increased anterior tibial translation without rotational instability were treated with the biologic augmentation technique. Patients were followed for 2 years postoperatively. The Lysholm Knee Questionnaire, IKDC Objective score, physical examination findings, MRI, and the KT-1000 arthrometer were used to assess clinical outcomes. Five patients were included in the analysis with a median age of 22. All patients were determined to have a healed ACL on MRI 8 months postoperatively. The median Lysholm Score at the final follow-up of 99 was significantly increased from the median pre-operative score ($p = 0.042$). In addition, the objective IKDC score improved in all patients postoperatively, and no clinical examination findings of knee instability were identified at the final follow-up. The median side-to-side difference in KT-1000 arthrometer testing was 3 mm pre-operatively and 0 mm at the last follow-up ($p = 0.038$). The treatment of appropriately indicated partial ACL injuries in this study has demonstrated that restoration of ligamentous structure and function may be achieved by a biologic augmentation technique using intra-ligamentous and intra-articular infiltration of BMAC and PRP. This technique is performed with minimal technical difficulty, leading to excellent 2-year clinical outcomes in this preliminary series of patients.

Keywords: *ACL primary repair*; *ACL biologic repair*; *ACL tear*; *biologic augmentation*; *BMAC*; *knee arthroscopy*; *platelet-rich plasma*

INTRODUCTION

The anterior cruciate ligament (ACL) is composed of two distinct ligamentous bundles termed the anteromedial and posterolateral bundle, which may suffer partial rupture under specific mechanisms of injury.[1] Since the initial descriptions of ACL injury patterns, there persists a lack of consensus regarding the natural history of these injuries classified as partial tears and disagreement on the

most appropriate treatment methods.[2] The healing processes of the injured ACL are complex. There is a cellular deficiency of ligamentous fibroblasts, hypovascularization, and a scarcity of locally available trophic factors. Spontaneous repair and remodeling capabilities of injured ACL tissue are poor. In many cases, surgical reconstruction or augmentation to restore knee stability is currently the preferred treatment due to the limited intrinsic healing potential.[3] ACL reconstruction procedures have several disadvantages, including limited restoration of proprioception, postoperative muscle weakness and deconditioning, the inability to re-establish normal joint kinematics, and possibly increased risk of developing osteoarthritis.[4,5]

Due to evolution in the knowledge of regenerative medicine and improvements in tissue engineering techniques, there has been increasing attention given to the development of new biological augmentation techniques to address partial lesions of the ACL. The use of biologic approaches, including the application of different growth factors, PRP, stem cells, biological scaffolds, and augmented primary ACL repairs, are expanding to regenerate injured tissue and improve healing of the native ACL and other anatomic structures.[6,7–10]

Alternative biologic approaches to the current standard surgical reconstruction techniques can potentially preserve the anatomic footprint of healthy ligamentous fibers, which may lead to greater retention of proprioceptive function and natural biomechanics. Therefore, a biologic approach to treating ACL injury is presented in this study as a possible future treatment for a specific subset of partial ligamentous lesions.

This study aims to present clinical outcomes in an initial patient cohort using a biologic augmentation technique consisting of intra-ligamentous and intra-articular infiltration of BMAC and PRP under arthroscopic visualization for treatment of isolated and acute partial ACL tears.

METHODS

Over the study period from January 2015 to June 2015, 21 patients with ACL lesions were evaluated. Five patients met the inclusion criteria and were prospectively followed for 2 years after undergoing biologic augmentation treatment of partial ACL injury. Inclusion criteria were patients aged between 15 and 30 years who played competitive soccer and suffered an isolated partial ACL lesion within the previous 2 months. The average time from injury to treatment was 25 days (1560 days). Documented medical history of a traumatic antecedent sporting incident, physical examination findings of a positive grade 2 Lachman test with a negative pivot shift test, and MRI findings are consistent with partial ACL tear were used as criteria to determine appropriateness for treatment by the biologic augmentation method. In addition, diagnostic arthroscopy was used to determine the final classification of the degree of ACL injury before undertaking treatment of partial ACL tear with the biologic augmentation method using the intra-ligamentous and intra-articular application of BMAC and PRP.

Statistical analysis was performed using SPSS software (Version 20.0. Armonk, NY: IBM Corp.). The Lysholm Knee Questionnaire was used for the subjective evaluation of clinical outcomes. The IKDC objective score, Lachman testing, and pivot shift testing were used to objectively assess clinical outcomes.[2,11–14] The Wilcoxon Signed-Rank test was used to examine the differences between pre-and post-treatment scores and examination findings. The level of statistical significance was considered to be $p < 0.05$.

OPERATIVE TECHNIQUE

Preparation of PRP Isolate

The Argentine Association of Hemotherapy, Immunohematology, and Cellular Therapy (AAHI) standards were adhered to for PRP preparation. A 150 cc volume of autologous venous whole blood was extracted from the antecubital fossa under sterile conditions. Extracted blood was combined with 30 cc of sodium citrate (CSL Plasma Inc. 155 Medical Sciences Dr. Union, SC 29379 USA), then underwent a two-step centrifugation process. The first centrifugation was performed at 1600 g for 10 minutes. The plasma was then transferred via a closed circuit into a second sterile containment bag, centrifuged at 3000 g for 10 minutes

(Thermo Scientific™ Sorvall™ Waltham, MA USA). This process results in a leukocyte-poor PRP isolate with a four-fold increase in the concentration of platelets from the baseline value free of red blood cells. A 1 cc volume from each prepared PRP isolate was examined in a hemoanalyzer (HORIBA Yumizen H1500, USA) to confirm platelet, and red and white blood cell concentrations.

Preparation of BMAC

The patient was positioned prone, and a sterile field was prepared about the posterosuperior iliac crest. Bone marrow was aspirated from the posterosuperior iliac crest using a 16 G Jamshidi needle (Carefusion TJC6008 – USA) (Figure 1A). A 10 mL syringe containing an anticoagulating solution of 50 IU/ml sodium heparin (Fisher Scientific - Thermo Scientific™ Waltham, MA USA) was used to extract a total volume of 60 cc of bone marrow aspirate (BMA). The total volume was obtained in 10 cc increments, using sequential needle repositioning to maximize the concentration of the desired marrow constituents, which were then cleared of bony debris through a 200-micron filter (GVS S.p.A. Via Roma 50 40069, Bologna Italy). The BMA was then fractioned into 15 cc separate volumes within four sterile tubes under a laminar flow hood (BIOBASE BBS_V 1300 9, Jinan, Shandong, China (Figure 1B). Centrifugation was performed at 2000 g for 5 minutes. A 2.5 cc volume of the buffy coat was then removed from each tube, which was combined, resulting in a final BMAC volume of 10 cc. A 1 cc sample of BMA and 1 cc of BMAC was examined in a hemoanalyzer (HORIBA Yumizen H1500, USA) to quantify the concentration of platelets and red and white blood cells.

Intraoperative Application of PRP and BMAC

The patient was placed into the supine position, positioned for standard knee arthroscopy within a sterile field. An anterolateral portal was created for diagnostic arthroscopy, followed by an anteromedial portal under direct visualization. An arthroscopic diagnostic assessment was performed to examine for associated lesions and confirm an ACL injury appropriate for treatment by biologic augmentation. Intra-articular fluid was then drained from the knee in preparation for dry arthroscopy. A 21 gauge normal needle was used to infiltrate the ACL along the entirety of injured and non-injured tissue using multiple needle insertion sites with 2 cc of BMAC, followed by 2 cc of PRP (Figure 2). Following intra-ligamentous infiltration, 3 cc of BMAC and 3 cc of PRP were injected into the intra-articular space.

Postoperative Rehabilitation Protocol

All patients followed the same postoperative protocol. A knee immobilizer was used to position

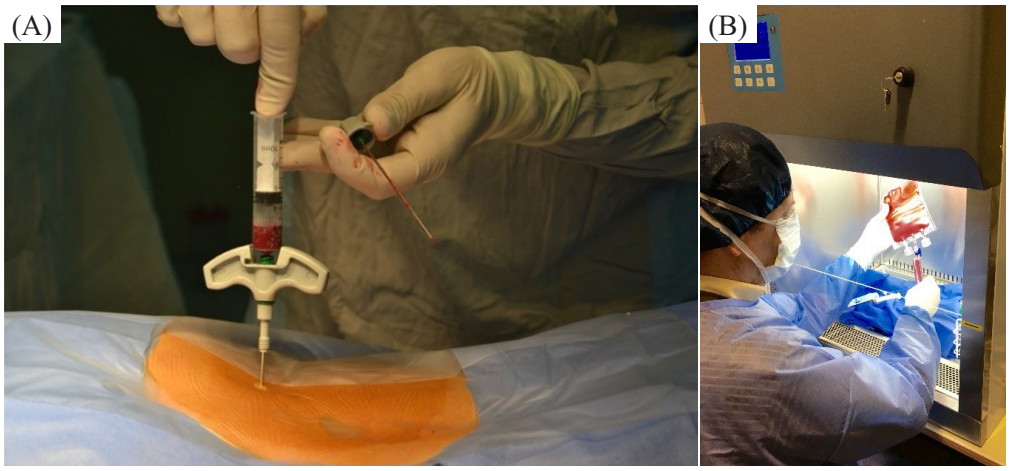

Figure 1. (A) Bone marrow aspiration is performed from the posterosuperior iliac crest with a 16 gauge Jamshidi needle, patient positioned pronely. (B) Bone marrow fractionation under a laminar flow hood.

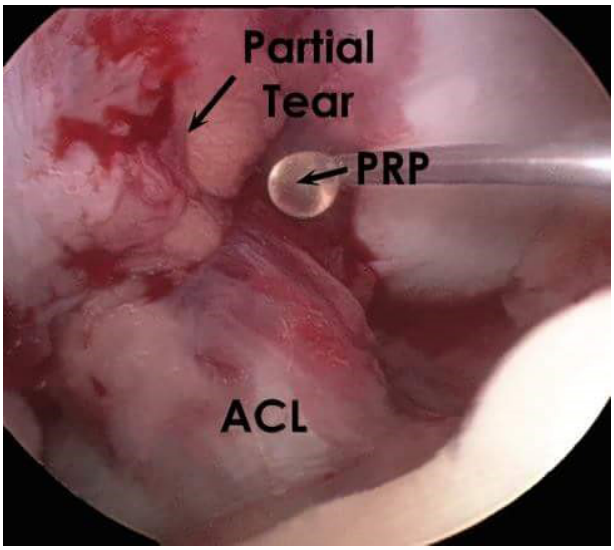

Figure 2. Arthroscopic view from the anterolateral portal depicting the technique of intra-ligamentous infiltration of Bone Marrow Aspirate Concentrate and Platelet-rich Plasma (BMAC-PRP) into the anterior cruciate ligament (ACL).

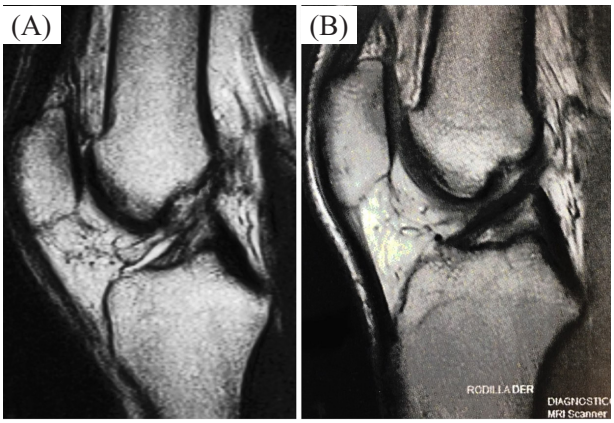

Figure 3. (A) Preoperative Knee MRI sagittal view showing the heterogeneous hyperintense signal suggestive of partial ACL injury (B) Knee, MRI sagittal view at 8 months, follow up where the hypointense and homogeneous continuous signal of ACL is seen, suggestive of ACL healing.

the knee in extension for 15 days, with the patient allowed to remove the immobilizer to perform passive and active mobilization and isometric quadriceps exercises 5 times per day. Patients were weight-bearing as tolerated. Restoration of the full range of motion is expected by 30 days postoperatively. Until 3 months postoperatively, rehabilitation progress followed the same protocol as for standard ACL reconstruction, with closed chain exercises up to 2 months, followed by open chain exercises emphasizing proprioception, balance, flexibility, and strengthening. After 3 months, straight-line running was permitted. At 6 months, isokinetic testing was performed to evaluate comparative muscle strength with the contralateral extremity for consideration of a return to play.

RESULTS

All 5 patients who met the inclusion criteria were evaluated 6, 12, and 24 months after the procedure and included in the analysis. The median patient age at the treatment time was 22 years (range 16–30 years). All patients were determined to have a healed ACL on MRI performed 8 months postoperatively (Figure 3). The median Lysholm score was significantly increased in patients at the final follow-up compared to pre-operative scores ($p = 0.042$), with a median postoperative score of 99 achieved at the last follow-up. Pre-operatively, the objective IKDC score was categorized as B (almost normal), with a positive grade 2 Lachman test and negative pivot shift test identified in all patients. Postoperatively, all patients were categorized as A (normal) according to the objective IKDC score and had negative Lachman and pivot shift tests at the final 2-year assessment. The median side-to-side difference in KT-1000 arthrometer testing was 3 mm pre-operatively and measured postoperatively as 0 mm at the 2-year assessment in all patients ($p = 0.038$). All patients' pre- and post-treatment scores are detailed in Table 1 and Table 2, respectively. In all cases, isokinetic testing determined restoration of strength, allowing for a return to sport at 6 months postoperatively. The average time for a patient return to sport was 8 months postoperatively. There were no complications related to the procedure and no ACL re-ruptures.

Table 1. Pre-Treatment Score Epidemiological data

Pte N:	Sex	Age	Type	Lysholm	IKDC	Lachman	Pivot Shift	KT1000
1	M	30	1	88	B	++	_	3 mm
2	M	22	1	90	B	++	_	3 mm
3	M	20	2	92	B	++	_	2 mm
4	M	16	1	91	B	++	_	2 mm
5	M	25	3	87	B	++	_	3 mm

Table 2. Post-treatment Scores at 6, 12 and 24 months

N:	Lysholm	IKDC	Lachman	Pivot Shift	KT1000
1	99	A	_	_	0
2	99	A	_	_	0
3	100	A	_	_	0
4	100	A	_	_	0
5	99	A	_	_	0

DISCUSSION

Noyes defined partial lesions according to the percentage of remaining healthy ligamentous tissue at the time of arthroscopy and reported that direct visualization of total rupture remains the only means available to accurately determine the quality of residual ACL tissue.[12] DeFranco and Bach categorized partial lesions based on a combination of knee laxity on physical examination and appearance under arthroscopic visualization.[15] There continues to be debate regarding the most valuable classifications of partial ACL injury and disagreement on the most effective treatment options. We consider partial ACL lesions to be characterized by a positive Lachman test with a firm end-point, a side-to-side KT-1000 arthrometer difference of <5 mm, the hyperintense signal within the ACL fibers on MRI, and arthroscopic findings of partial rupture.

Some reports in the literature document spontaneous healing of partial ACL ruptures.[16,17] Recent clinical and animal studies suggest the possibility of ACL healing after primary ligament suture and biologic augmentation using growth factors and bone marrow-derived mesenchymal stem cells. Supplementation of repaired ACL tissue with biologic factors is likely clinically significant, given that these growth factors and bioactive proteins contained within plasma and bone marrow have the potential to regulate critical processes in tissue repair, including cell proliferation, chemotaxis, migration, cell differentiation, and extracellular matrix synthesis.[18]

Platelet-rich plasma (PRP) contains numerous growth factors and has been a focus of attention concerning many non-invasive therapies. The array of bioactive agents within PRP may mediate the healing processes of various tissues following injury through effects during phases of repair, such as inflammation and remodeling.[19] Platelets are involved in homeostasis, aggregation, and clot formation and can ultimately impact the rate of tissue healing and the quality of repair tissue.[20] These processes are mediated by the release from alpha granules of such factors as platelet-derived growth factor (PDGF), transforming growth factor-beta 1 (TGF-β1), vascular endothelial growth factor, basic fibroblast growth factor (bFGF), and epidermal growth factor. Among these growth factors, PDGF and TGF-β1 have been reported to be particularly critical in the modulation of healing processes by contributing to the increased proliferation of fibroblasts and the production of collagen.[21]

Seijas et al. reported a high rate of return to sports in 19 professional soccer players with partial ACL rupture treated with intra-ligamentous infiltration of

PDGFs into the intact bundle. In addition,[22] PDGFs were applied using the technique described by Anitua (PRGF-Endoret).[23] Postoperative MRI was performed in all patients to examine the properties of the ACL, with the good anatomic restoration of ligamentous fibers, described one year after surgery.

Gobbi et al. evaluated the clinical results of ACL suture repair combined with microfracture of the intercondylar notch and augmentation with PRP injection in 50 athletes for 5 years.[24] Of the treated patients, 78% returned to pre-injury sporting activities. Furthermore, there was a significant improvement in the side-to-side difference of anterior tibial translation, which decreased from a mean of 4.1 mm pre-operatively to 1.4 mm postoperatively at the final follow-up evaluation.

Cellular therapies have been extensively studied in pre-clinical in vitro studies. For example, in a rat model with partial ACL rupture, Kanaya et al. reported that intra-articular injection of mesenchymal stem cells sourced from bone marrow improved the healing of ligaments with a superior histological score and a better resistance to failure load compared to non-treated controls.[25] In a study by Oe et al., intra-articular injection of BMAC was performed one week after ACL transection in a rat model.[16] It was demonstrated that there were more mature spindle cells with higher levels of TGF-β in the group treated with BMAC than those without.

In a case series involving human subjects, Centeno et al. reported on ten patients with ACL ruptures treated with an intra-ligamentous injection of BMAC using fluoroscopic guidance.[26] This study examined patients who suffered partial or complete ACL tears with less than 1 cm of retraction. ACL ruptures were evaluated by pre-and post-injection magnetic resonance imaging. Seven of ten patients showed improvement in most measurements used to objectively assess the quality of ACL tissue on MRI. While the improvement in subjective patient visual analog scale was not significant, there was a significant improvement in the lower extremity functional scale.

More recently Centeno et al.[27] in a midterm analysis from a randomized controlled trial using an image-guided injection of ACL tears with autologous bone marrow concentrate and platelets comparing with a group of patients treated with physical therapy alone. They showed significant improvement in ACL MRI ImageJ quantitative assessment in the BMC group ($p = 0.001$) and no difference in the exercise group ($p > 0.05$).

In the current study, all patients with an ACL injury who met the inclusion criteria and were treated with the technique of biologic augmentation repair had demonstrably stable knees 2 years postoperatively and had returned to full activities without limitation or functional deficit. There are several essential aspects of this treatment method that should be highlighted. First, this therapeutic approach was restricted to those who met stringent criteria that determined there was partial ACL injury resulting in symptomatic instability. While this type of injury is a particular subset of ACL lesions, these successful clinical outcomes should provide encouragement in the pursuit of biologic treatments of such injuries, given that many of these cases would likely have otherwise undergone a standard ACL reconstructive technique that would sacrifice native ligamentous anatomy and much of the associated proprioceptive and biomechanical functions.

Our study has some limitations that warrant discussion. First, the cohort is composed of a small sample. Second, short-term follow-up. Third, our research has no control group to compare patient-reported outcomes and clinical definitions of treatment failure (e.g., MCID, PASS) to protect the results against bias, and lastly, the treating physician scoring all metrics.

Advances in tissue engineering and regenerative medicine have led to renewed interest in alternative treatments of partial ACL ruptures, including techniques that utilize a variety of biologic therapies. While the current study's findings are encouraging, longer-term studies with larger cohorts of patients will be necessary to clarify the expected clinical results of this therapeutic approach.[28]

CONCLUSIONS

The treatment of appropriately indicated partial ACL injuries in this study has demonstrated that restoration of ligamentous structure and function may

be achieved by a biologic augmentation technique using intra-ligamentous and intra-articular infiltration of bone marrow aspirate concentrate and PRP. This technique is safe, reproducible, performed with minimal technical difficulty, and has led to excellent 2 year clinical outcomes in this preliminary series of patients.

DISCLOSURE

The authors declare no conflicts of interest or funding sources related to this study.

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