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IMAGE-GUIDED INJECTION OF ANTERIOR CRUCIATE LIGAMENT TEARS WITH AUTOLOGOUS BONE MARROW CONCENTRATE AND PLATELETS: MIDTERM ANALYSIS FROM A RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: There has been a recent emergence in the use of orthobiologics, including platelet-rich plasma (PRP) and bone marrow concentrate (BMC), in the treatment of various musculoskeletal conditions. The goal of this study was to determine if injection of BMC and platelet products into partial and full-thickness anterior cruciate ligament (ACL) tears can facilitate primary ligament healing in patients failing conservative care, resulting in improved outcomes compared to exercise therapy.

Methods: Patients were randomized to either exercise therapy or percutaneous injection of autologous BMC with PRP and platelet lysate into the ACL under fluoroscopic guidance. Pain and function were assessed at baseline and at 1, 3, 6, 12, and 24 months. Baseline and 6-month post-treatment magnetic resonance imaging (MRI) were obtained to evaluate interval healing. Laxity was assessed using the Telos device.

Results: There was significant improvement in functional outcomes in the BMC group, compared to baseline for LEFS at time points 3 up to 24 months s = 0.000000005), and significant improvement in pain in the BMC group at 6 ($p = 0.00054$), 12 ($p = 0.00127$), and 24 months ($p = 0.002$). There was no significant improvement in pain or function at any time point in the exercise therapy group. There was significant improvement in ACL MRI ImageJ quantitative assessment in the BMC group ($p = 0.001$) and no difference in the exercise group ($p > 0.05$). No serious adverse events were reported.

Conclusion: Autologous BMC and platelet product injection into ACL tears improved patient function compared to exercise, observed through 24 months. Patients treated with BMC demonstrated quantitative improvements in post-treatment MRI scans suggestive of interval ligament healing.

Keywords: *anterior cruciate ligament*, *ACL tear*, *bone marrow concentrate (BMC)*, *platelets*, *regenerative medicine*

INTRODUCTION

The anterior cruciate ligament (ACL) is a key ligamentous stabilizer of the knee that prevents anterior translation of the tibia and serves to restrain tibial rotation. It is the most commonly injured ligament in the body and occurs at an estimated incidence of 200,000 cases each year in the United States, resulting in approximately 150,000 ACL reconstructive surgeries performed yearly.[1,2]

The current standard of care for complete ACL ruptures is surgical ACL reconstruction (ACLR), although there are several limitations and risks including graft failure/re-tear, persistent instability, infection, and loss of range of motion.[3,4] A common complication after ACL injury, treated both nonoperatively and operatively, is the subsequent development of osteoarthritis (OA).[5] Ajuied et al. found that 20.3% of ACL-injured knees progressed to either moderate or severe osteoarthritis within 10 years, compared to 4.9% incidence of osteoarthritis in the uninjured contralateral knee.[6] Barenius et al. demonstrated a three fold increased prevalence of OA in ACL reconstructed knees versus the contralateral nonoperative knee.[7] ACL graft failure is another less common but potentially devastating complication following ACLR. Wright et al. evaluated graft failure rates in a systematic review comparing studies with 5+ year follow-up and found that ipsilateral failure rate ranged from 1.8 to 10.4%, and similarly a review by Crawford et al. determined that one in nine patients undergoing ACLR will have re-rupture or clinical failure, as determined by new or persistent clinical laxity at long-term (greater than 10 years) follow-up.[8,9] Given the risks and unique challenges in surgical ACLR, it is important to continue exploring less invasive and potentially alternative treatment options for ACL injuries.

There has been a recent emergence in the use of orthobiologics, including platelet-rich plasma (PRP) and bone marrow concentrate (BMC), in the treatment of various musculoskeletal conditions.[10] BMC is a source of mesenchymal stem cells (MSC) which have been shown to be an integral part of skeletal tissue healing and repair.[11–14] Theoretically, the healing of a native ACL would have the advantage of maintaining its natural orientation and thus preserving knee kinematics, while potentially keeping the ACL's proprioceptive properties intact.[15] Several animal models have demonstrated promise in the use of bone marrow MSCs for ACL injury when incorporated into a scaffold or matrix.[16–18] Data on the use of BMC in the treatment of ACL injuries in humans are limited; however, several case series have shown clinical evidence of improvements in ACL integrity and increased function in patients treated with percutaneous BMC and platelet injection to the ACL.[19–21] These studies propose the use of blood products to augment surgical repair in complete ACL tears; however, to the authors' knowledge, no randomized study to date has evaluated orthobiologic injection as a primary treatment of ACL tears.

The aim of this present study was to present a midterm analysis for a randomized controlled crossover trial evaluating percutaneous, image-guided injection using a specific protocol of autologous BMC and platelets into partial or full thickness, nonretracted ACL tears.

METHODS

This ongoing randomized, controlled, crossover study for symptomatic patients with partial or full-thickness, nonretracted ACL tears was approved by the International Cellular Medicine Society Institutional Review Board (OHRP Registration #IRB00002637).

The sample comprised 50 patients, with 25 patients in the exercise therapy group and 25 in the treatment group. This distribution was determined to have 70% power to detect a 11.5 point difference in mean change from baseline to 3-month International Knee Documentation Committee (IKDC) scores between treatment groups at $\alpha = 0.05$. This estimation was based on IKDC outcomes reported by Irrgang et al.[22] for the treatment of ACL injury with surgical intervention and Mihelic et al.[23] for the nonoperative treatment of ACL injury. Study randomization was 1:1 between the exercise therapy and BMC groups. A computer-based randomization program was used, and the allocation of the study

group was revealed by opening sequentially numbered envelopes with the study group enclosed.

Patients, aged 18–65 years, presenting to an interventional pain practice with persistent knee pain and/or instability despite at least 3 months of conservative treatment, with magnetic resonance imaging (MRI) evidence of a partial or complete, nonretracted ACL tear, and documented clinical laxity, were eligible to enroll in the study. An informed consent was obtained from all participants. Those who enrolled were then randomized to receive either an exercise therapy program focusing on isometric and isotonic quadriceps and hamstring strengthening, or percutaneous injection of autologous BMC and platelets into the ACL under fluoroscopic guidance. Those randomized to the exercise therapy group had the option to cross over to the BMC treatment group after 3 months.[24,25] ACL tear was defined by patient history of instability following a specific injury event, asymmetric clinical laxity based on provider assessment (Lachman or anterior drawer), and abnormal ACL morphology on MRI consistent with ACL tear.

ACL laxity was determined by both physical exam with positive Lachman and objective measured stress radiography with Telos SD 900 stress device (Austin & Associates, Inc., Millersville, MD, USA), a common measurement device in clinical practice.[26,27] Ipsilateral Telos measurements were obtained at baseline, and between 3 and 6 months post procedure to assess for changes in knee stability following both BMC treatment and exercise therapy.

Patients were excluded if they had undergone previous reconstructive surgery to the affected ACL, prior injection-based therapy (PRP, corticosteroid, etc.) to the affected knee within 3 months of enrollment, concomitant ipsilateral knee osteoarthritis (Kellgren–Lawrence grade II or greater), posterior cruciate ligament tear, collateral ligament tear, or meniscus tear/cartilage injury that was considered an active pain generator by the treating physician.

Treatment protocol

Harvest and bone marrow concentration

On the day of BMC treatment, a bone marrow harvest was performed followed by isolation of the nucleated cell portion of the aspirated sample in preparation for reinjection. Prior to procedure, patients were instructed to refrain from taking corticosteroids and nonsteroidal anti-inflammatory drugs for at least 2 weeks, so as not to hinder the potential for soft tissue healing.[28–31] Whole bone marrow was harvested from patients' iliac crests under ultrasound or fluoroscopic guidance. Approximately 10–15 mL of bone marrow aspirate was drawn from six sites into heparinized syringes. There were 1000 units of heparin (NDC 25021-403-01 and 25021-404-01) per 1 mL of volume collected in the syringe. Bone marrow aspirate was then processed by hand in a sterile ISO-7-class clean room and in ISO-5-class laminar flow cabinets to isolate the buffy coat after centrifugation. Please see our prior publication for a detailed description of the bone marrow aspiration and concentration protocol.[20,45] This isolation produced 2–5 mL of BMC, which was sterilely transported from the clinic-based laboratory to the clinic procedural suite. A total nucleated cell (TNC) count of the injectate was performed and recorded by lab staff with a cell counter (TC10; Bio-Rad Laboratories, Hercules, CA, USA). In addition, approximately 60 mL of heparinized venous blood was drawn to be used to isolate PRP and platelet lysate (PL). To prepare the PRP, blood was centrifuged at 200 × g to separate the plasma and buffy coat layers from the red blood cells. The resultant liquid plasma layer lying above the buffy coat (supernatant) was red cell/white cell poor. The preparation method for PL followed identical technique previously described[32] in which PRP was drawn off, pelleted via centrifugation, and stored at −80°C until frozen. The purpose of freezing was to initiate lysis of the platelets. The pellet was then warmed with the addition of platelet-poor plasma. No commercial automated systems were used. All samples were processed in a current good manufacturing practice air-handling lab by a dedicated laboratory staff.

Injection of the BMC

Each patient was brought to a procedure room and placed in a supine position, with bolster under the treatment knee placing it at approximately 45 degrees of flexion. An intercondylar notch view

was obtained with C-arm fluoroscopy (OEC 9900 C-Arm, GE Healthcare, Chicago, IL, USA). A 25 gauge 3.5 inch Quinke needle (#405170; BD Biosciences, Franklin Lakes, NJ, USA) was inserted through the skin just beneath the patella and was directed through the patellar tendon, into the joint space, with care taken to maintain a midline position at the level of the tibial spine. A lateral radiograph was then used to determine appropriate needle depth with needle placement at the expected ACL attachment on the tibial spine. Iodixanol (Visipaque™ NDC 0407-2223-06; GE Healthcare, Chicago, IL, USA) radiographic contrast was injected to confirm contrast flow pattern in both bundles of the ACL traveling between the radiographic origin and insertion landmarks, in both views (Figure 1). If the contrast spread pattern failed to achieve insertion to origin flow in both of the AM and PL bundles, the needle was moved to either a second insertion site or to the femoral origin site and the process was repeated until full coverage was achieved. This was followed by injection of 2–3 mL of equal parts BMC, PRP, and PL. Following ACL injection, the needle was withdrawn from the ligament and, while still in the joint, approximately 2–3 mL of the same injectate was injected into the joint space. Hence, both the cruciate ligament and the intra-articular knee joint space were injected.

Post-procedure, all patients were encouraged to follow a standard rehabilitation protocol. No bracing was required. Patients were directed to refrain from activities that caused more than a 2/10 pain for their rehabilitation duration. For weeks 1–4, patients were instructed to maintain maximum protection, and perform a range of motion exercises, light strength training, and gentle balance training. Weeks 5–12, patients were encouraged to begin resistance training: light squats, leg press, core, hip abductor, and hamstring strengthening; strengthening balance using balance board; jogging straight at 6 weeks if not painful; progress to combo strength and balance exercises; single leg exercises. Weeks 13–20, patients were encouraged to participate in guided sport-specific training and noncutting sports. Months 4.5–12, patients were encouraged to follow Santa Monica Sports Medicine Prevent Injury and Enhance Performance program for return to sport. Return to full sport only with physician clearance.

Outcome measures

Patient outcomes were tracked prospectively via an electronic database system using ClinCapture software (Clinovo Clinical Data Solutions,

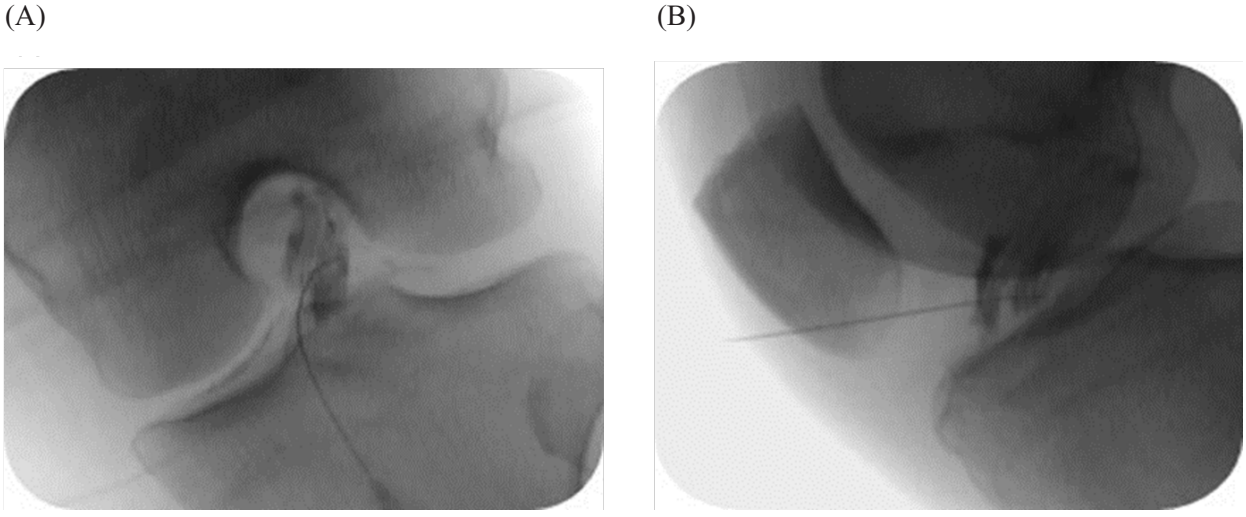

Figure 1. Anteroposterior (AP) fluoroscopic image of needle placement into the ACL with contrast confirmation demonstrating spread into both anteromedial and posterolateral bundles (A). Lateral fluoroscopic image of needle placement into the posterolateral bundle of the ACL with contrast spread throughout both bundles (B).

Sunnyvale, CA, USA). The program includes an automated emailing system to send patients clinical outcome questionnaires to complete. Outcomes were Numeric Pain Scale (NPS) as well as patient reported functional outcomes including the IKDC subjective score,[33] Lower Extremity Functional Scale (LEFS), and a modified Single Assessment Numeric Evaluation (SANE), which allowed responses from −100 to +100 to reflect 100% worse to 100% improved.[34,35] Outcome measures were recorded preoperatively and postoperatively at 1 month, 3 months, 6 months, 12 months, and 24 months. Minimal clinically important difference (MCID) as defined as improvement of 9 points and 11.5 points on LEFS and IKDC, respectively, was also measured to compare patient-reported outcomes.[36,37]

Tear classifications

To classify the ACL tears, two blinded graders scored the tears using the following tear/morphology grading system from the best sagittal image(s) from the pre-treatment MRI for all patients that received treatment:

- Partial tear (PT)-grade 2 ligament tear-high signal less than 50% of ligament width
- Complete nonretracted tear type 2 (CNR2)-ligament has normal morphology with high signal in >50% ligament width;high signal spans less than 5 mm longitudinally
- Complete nonretracted type 1 (CNR1)-ligament has "blown out" morphology with high signal in >50% ligament width
- Complete retracted tear (CR)-no visible ligament fibers that connect between O/I, retracted more than 5 mm

Imaging assessment

Patients had pre- and post-treatment MRIs (approximately 3–6 months) done. To quantify and reduce the variability in the interpretation of the changes in the MRI appearance of the ACL ligaments, we used ImageJ software to assess changes in signal intensity. ImageJ is a public Java image processing and analysis program developed at the National Institutes of Health (http://rsbweb.nih.gov/ij/). The use of this imaging analysis as a proxy for ACL integrity has been previously described in detail and validated.[21] ImageJ objectively measures the metrics of mean gray value, modal gray value, median, skewness, and raw integrated density throughout a region of interest (ROI) to assess the appearance of the ACL. Lower signal measurements reflected a more intact ACL. The image selected for the ligament integrity assessment was either sagittal T2 weighted sequence, proton density (PD)-weighted ACL sequence, PD sequence, PD fast spin-echo sequence, or PD fat saturation sequence—whichever image visualized the greatest cross-sectional area of the ACL. When possible, MRI with ACL sagittal oblique sequences were utilized. For all pre- and post-procedure MRI evaluations, the same MRI sequence type with the closest matching sagittal slice that best visualized the complete course of ACL fibers was selected for comparison. Using ImageJ software, the examiner manually outlined the ACL to create a ROI. The examiner was instructed to only outline where they believed the ACL to be on the image, and that the posterior extent of the ROI should not be more posterior than the posterior margin of the femoral condyle (Figure 2).[20]

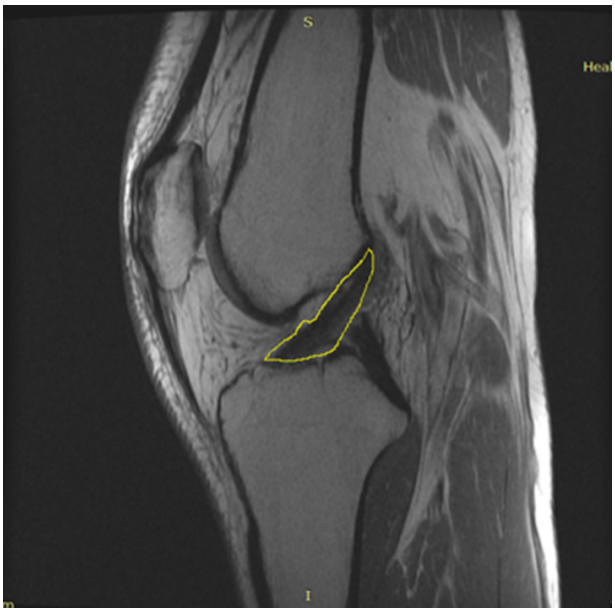

Figure 2. ACL ROI tracing using ImageJ analysis program.

Return to sport

Patients' level of return to sport was gauged from responses to items #7 and #8 on the IKDC. Question 7 asks, "What is the highest level of activity you can perform without significant giving way in your knee?" Question 8 asks, "What is the highest level of activity you can participate in on a regular basis?" Response 4 reports very strenuous activities like jumping or pivoting as in basketball or soccer and response 3 reports strenuous activities like heavy physical work, skiing, or tennis. Response 2 reports moderate activities like running or jogging, while response 1 reports only light activities.

Statistical analysis

Patient-reported outcome scores after 1 and 3 months of exercise therapy were compared to baseline scores via paired Wilcoxon signed-rank tests. These scores were also compared to scores reported after 1 and 3 months of BMC treatment via Wilcoxon signed-rank tests, and Cohen's effect size was calculated. Scores reported from 1 to 24 months after BMC treatment were assessed using linear mixed-effects models. If the models showed scores that changed significantly between time points, post-hoc Tukey was applied. Mixed-effects models were used to assess whether injury chronicity affected response to BMC treatment. Percentages of outcome scores that met the MCID for various metrics were calculated for each time point. Pre- and post-exercise, as well as pre- and post-BMC treatment ACL ROIs on MRI were compared via paired *t*-tests, both before and after normalization to a region of the gastrocnemius muscle, a protocol previously described.[21] Inter-rater reliability for tear classification was calculated using Cohen's kappa for two raters.

RESULTS

Patient demographics

Of the 30 enrolled patients from August 2013 to July 2017, 17 were male (56.7%) and 13 were female (43.3%), aged 39 ± 10.5 years (Mean ± SD). A summary of the demographic data for patients that received treatment are shown in Table 1. Sixteen patients were randomly assigned to receive treatment with BMC and platelet injection into the injured ACL, and 14 patients were randomized to exercise therapy (Figure 3). Three patients randomized to the exercise therapy group voluntarily withdrew from the study upon randomization. All 11 patients who moved forward with exercise therapy elected to cross over to receive BMC treatment after 3 months. Their outcomes were included in the treatment group analysis. Table 2 shows the classifications of tears (IRR = 0.956; $p < 0.001$). Study power at this midterm analysis is 49.8%.

Table 1. Demographic Data for Patients that received Treatment

	BMC Treatment			Exercise		
Variable	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Age (years)	16	38.1	11.4	11	39.1	10.1
BMI (lbs/in^2)	15	24.4	3.3	9	24.9	4.7
TNCC (millions)	16	670	350	11	756	324
	N		%	N		%
Gender	16			11		
Male	10		63	6		55
Female	6		37	5		45
Age Breakdowns						
18–25	2		12.5	0		0
26–35	4		25	4		36.4
36–45	7		43.75	4		36.4
46–55	2		12.5	2		18.2
56–65	1		6.25	1		9

BMC: Bone marrow concentrate; BMI: Body mass index; N: Number; SD: Standard deviation; TNC: Total nucleated cells.

Patient-reported outcomes

At 3 months, there was significant improvement in both LEFS ($p = 0.00000667$, 11.0 ± 9.3) and IKDC ($p = 0.0000058$, 17.2 ± 11.9) in the BMC group compared to baseline, and this improvement was sustained at all time points from 3 to 24 months (24 months IKDC, $p = 0.000000012$) (Table 3, Figure 4). There was also significant improvement in NPS in the BMC group at 6 months ($p = 0.00054$, −1.8 ± 2.3) compared to baseline, which was sustained at all follow-up time points up to 24 months ($p = 0.00502$). There was no significant improvement

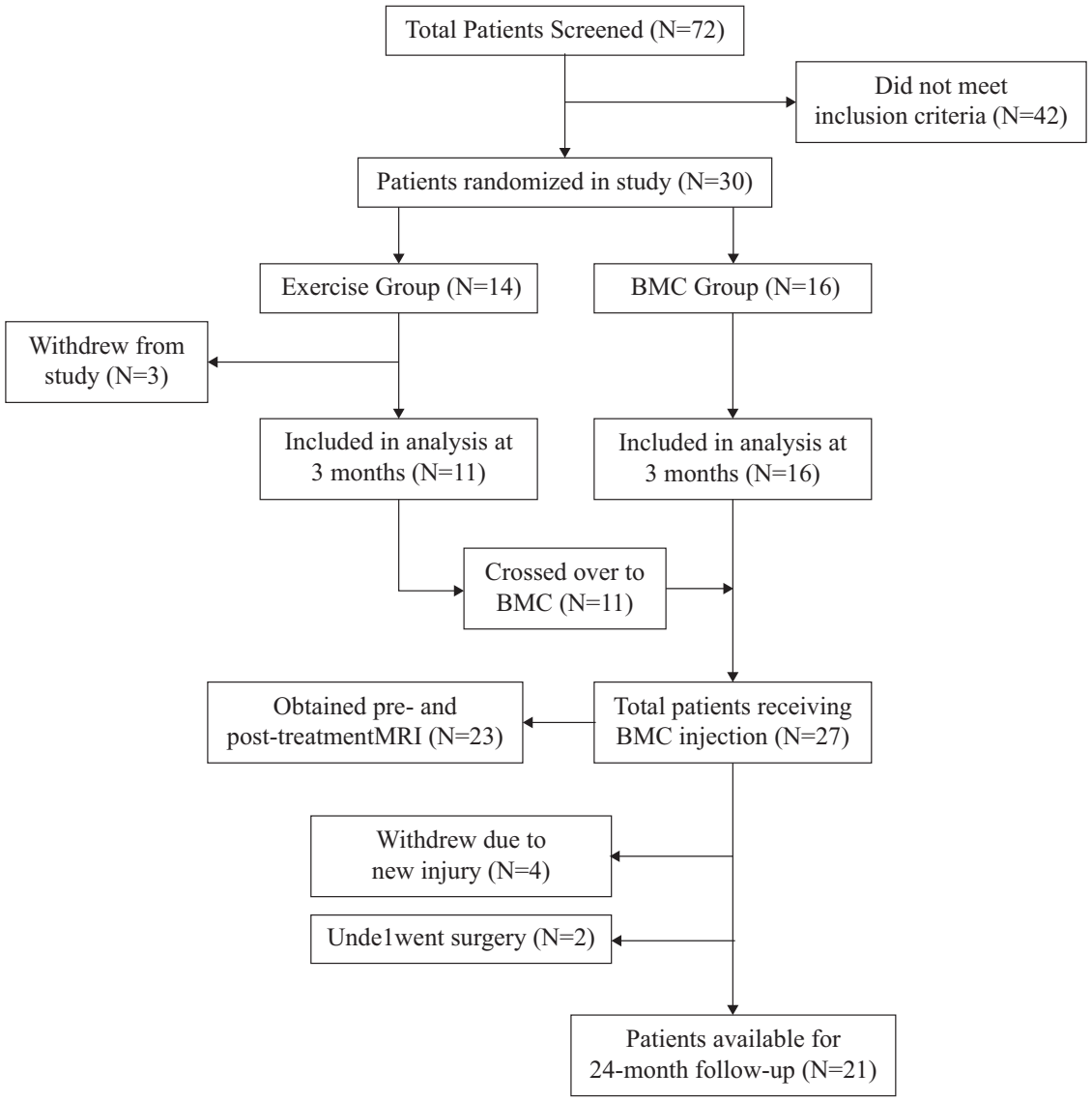

Figure 3. Flow diagram of the study.

Table 2. Classification of ACL Tears

Tear Type	N	%
PT	1	4%
CNR2	8	30%
CNR1	16	59%
CR	2	7%

PT: Partial Tear; CNR2: Complete nonretracted tear type 2; CNR1: Complete nonretracted tear type 1; CR: Complete retracted tear.

in pain or function at any time point for the exercise therapy group when compared to baseline (NPS 3M: $p=0.45$, 0.25 ± 1.9; LEFS 3M: $p=0.34$, 3.1 ± 9.8; IKDC 3M: $p=0.18$, 7.4 ± 16.2). There were significant differences between the exercise group and the BMC treatment group in SANE (treatment effect size of 1.1, $p<0.01$) and LEFS (treatment effect size of 0.82, $p=0.02$) at 3 months. At 3 months, 20% of the exercise group met MCID in LEFS (defined as improvement of nine points or greater) versus 58% in the BMC group, and similarly 30% met MCID for IKDC (defined as improvement of 11.5 points

Table 3. BMC Treatment Outcome Change Scores from Baseline

Metric	Time point	N	Mean	SD	P value	Confidence interval
NPS	1 month	25	−0.8	2.7	0.15	[−1.9, 0.3]
	3 months	24	−1.0	2.6	0.07	[−2.1, 0.1]
	6 months	25	−1.8	2.3	0.0005	[−2.8, −0.9]
	12 months	23	−1.9	2.3	0.001	[−2.8, −0.8]
	24 months	21	−1.7	2.5	0.005	[−2.8, −0.6]
LEFS	1 month	25	3.5	10.3	0.10	[−0.7, 7.8]
	3 months	24	11.0	9.3	0.000007	[7.0, 14.9]
	6 months	25	16.0	11.4	0.0000003	[11.3, 20.7]
	12 months	24	19.2	11.0	0.00000001	[14.6, 23.9]
	24 months	20	19.7	10.1	0.00000005	[14.9, 24.4]
IKDC	1 month	21	5.9	15.3	0.10	[−1.1, 12.8]
	3 months	19	17.2	11.9	0.000006	[11.5, 23.0]
	6 months	20	25.0	15.4	0.0000007	[17.8, 32.2]
	12 months	19	26.3	10.9	0.000000004	[21.0, 31.5]
	24 months	15	32.2	10.6	0.00000001	[26.3, 38.0]

NPS: Numeric pain scale; LEFS: Lower extremity function scale; IKDC subjective: International Knee Documentation Committee subjective questionnaire.

or greater) versus 68% in the BMC group. In the exercise group, 36% met MCID for NPS versus only 25% for BMC at 3 months (Figure 5). For those who received BMC, including those who elected to cross over, cellular analysis of the injectate demonstrated a mean TNC count of 705 million ± 336 million and mean bone marrow aspirate volume of 67 mL.

A subgroup post-hoc analysis demonstrated that those treated within 12 months of initial injury reported significantly improved functional outcomes at all time points from 3 months to 24 months when compared with those treated after 12 months (SANE: $p = 0.005$ and IKDC: $p = 0.01$).

Patients' level of return to sport was gauged from responses to IKDC subjective questions #7 and #8 at the 2-year follow-up. For question #7, 84% of patients answered 3 or 4 for participating in strenuous or very strenuous activities without giving way of the knee, while 12% answered 2 (moderate) and 4% answered 1 (light). For question #8, 76% of patients answered 3 or 4, while 24% answered 2 for moderate activities being the highest level they could participate in on a regular basis.

MRI outcomes

Pre- and post-treatment MRIs were obtained for 11 patients in the exercise group and for 16 in the BMC group. A total of 27 patients had both pre- and post BMC treatment MRIs. Three patients did not have the same MRI sequence for comparison and thus were not included in the analysis. ImageJ pixel quantitative assessment demonstrated significant differences between pre- and post BMC treatment MRI ROIs for mean ($p = 0.001$), mode = 0.0004), and median gray values ($p = 0.0007$) as well as raw integrated density ($p = 0.009$); however, no significant differences were found between mean, median, and mode gray values, or integrated density between pre- versus post exercise MRI ROIs ($p > 0.05$). There was no significant difference in objective laxity measurement with Telos at baseline compared to 6 months post BMC injection ($p = 0.55$, 0.25 cm ± 1.3 cm).

Adverse events

There were two reported adverse events (AEs) following treatment including a case of transient paresthesia corresponding to the use of knee brace

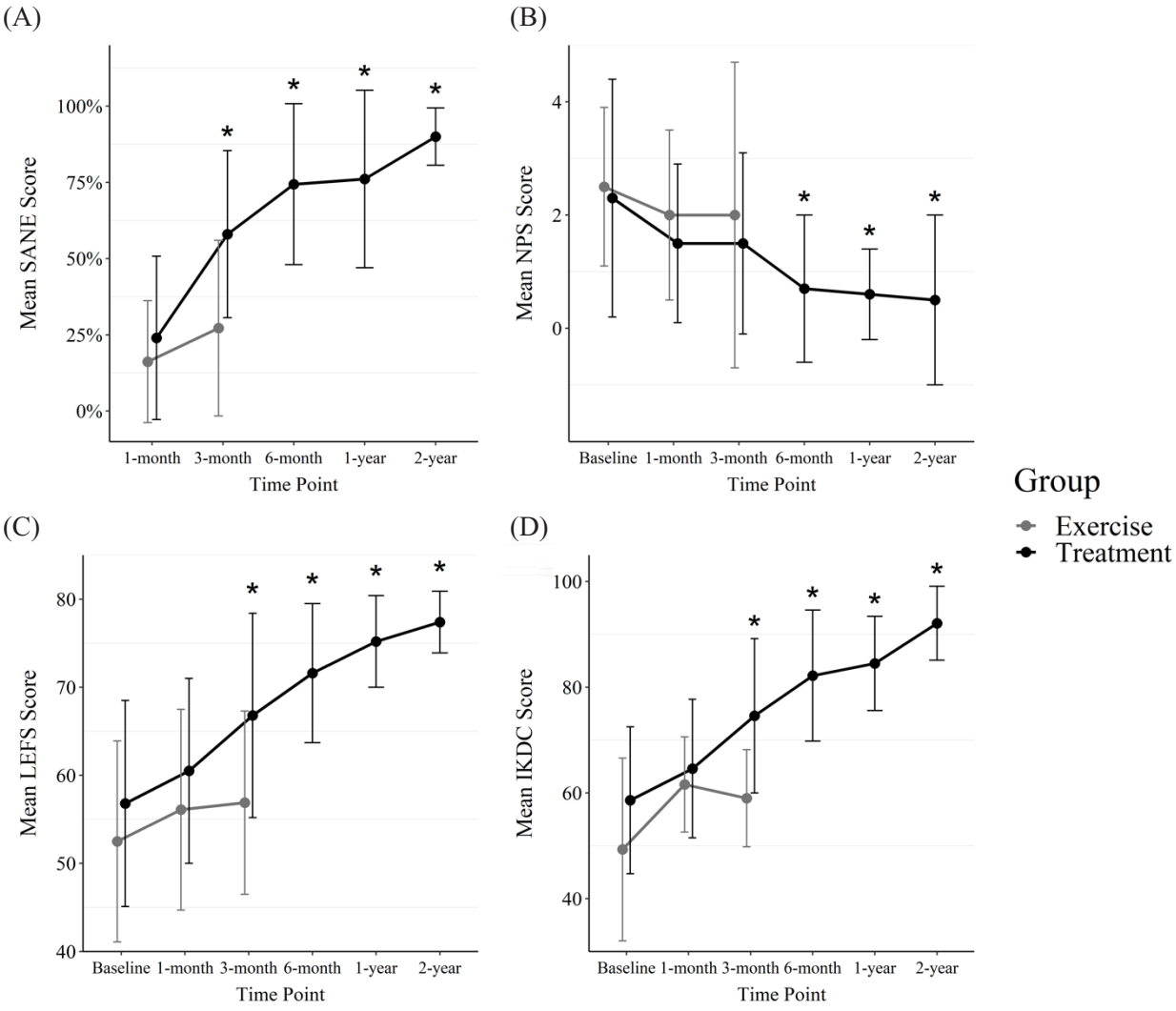

Figure 4. Clinical outcome scores with standard deviation bars for all patients receiving BMC treatment compared to exercise. Significant differences from baseline *$p < 0.01$ for (A) modified SANE; (B) NPS; (C) LEFS; (D) IKDC.

after treatment and one case of knee effusion following treatment requiring aspiration. There were no serious AEs. No patients were lost to follow-up throughout the duration of the study. Five patients did not complete the study; two received ACLR 1 year following BMC injection, one suffered a new meniscus tear in the treatment knee shortly after the procedure, one sustained LCL injury (ACL stayed intact), and one experienced ACL re-rupture with premature return to competitive sport at 6 months.

DISCUSSION

In a randomized controlled trial comparing autologous BMC injection versus exercise therapy for patients with pain and functional disability following nonretracted ACL tear, there was lasting improvement in pain and function of up to 2 years following injection of ACL with BMC. The BMC treatment improved patient knee function at 3 months compared to the exercise group, with double the number of patients in the BMC group meeting the MCID compared to exercise. In addition, MRI

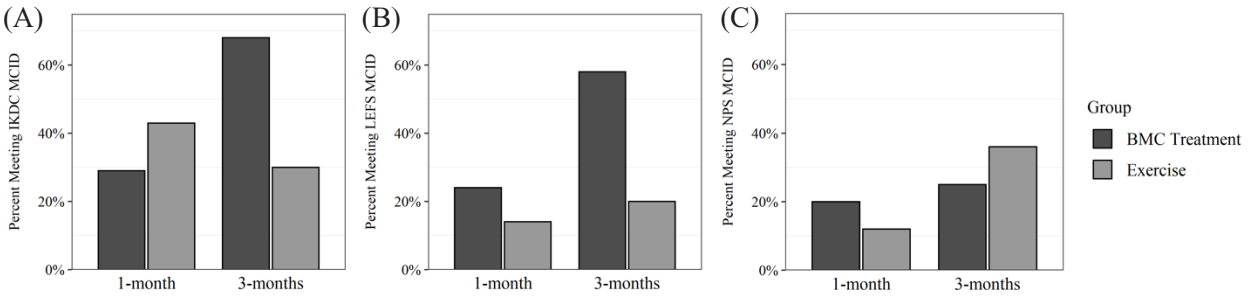

Figure 5. BMC and exercise group clinical outcome comparisons. IKDC, LEFS, and NPS at 1 and 3 months follow up expressed as percent of patients reaching MCID.

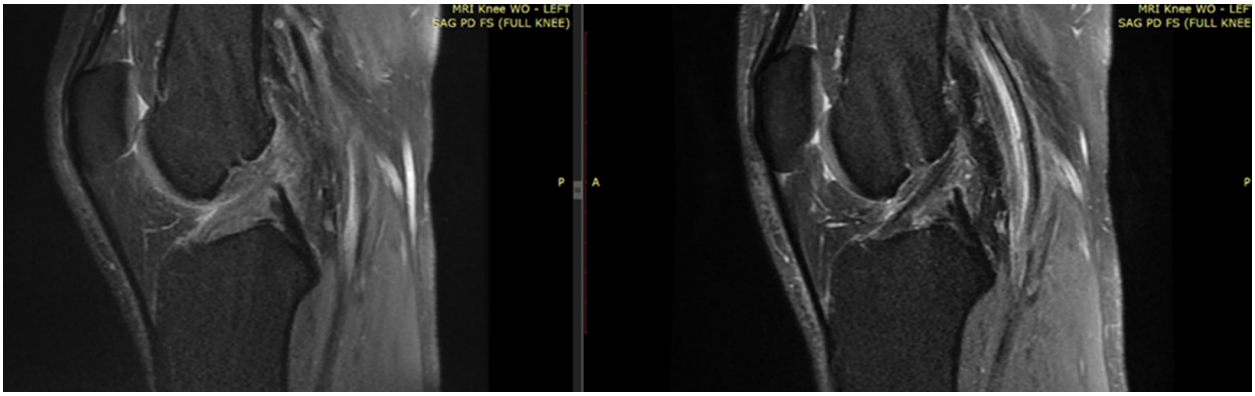

Figure 6. Comparable sequence sagittal MRI comparison of pre-treatment ACL (left) with wavy morphology and proximal ligamentous disruption and 6 months post-treatment ACL (right) demonstrating interval ligamentous healing improved ligament architecture.

evaluation at 6 months post procedure demonstrated lower mean gray values consistent with imaging evidence of ACL healing suggestive of interval ACL collagen deposition and fiber maturation in the presence of autologous BMC (Figure 6). Although this midterm outcomes data does not include a robust sample size, to the authors' knowledge this is the first randomized trial investigating the treatment of partial or complete, nonretracted ACL tears with percutaneous injection of BMC into the remaining ligament. This study builds on previous registry-based data that demostrated functional improvements and morphological changes on MRI with the use of BMC for ACL tears.[21]

A relative strength of the current study is the use of ample patient-reported outcome measures (NPS, LEFS, IKDC, and SANE) while including several different objective measurements of ligament integrity via both ImageJ and Telos. Both the LEFS and IKDC functional outcome measures, as well as the pain scale showed significant improvement from baseline from 6 months up to 24 months following the procedure.

Despite improvements of ACL integrity on MRI, there was no significant difference in Telos laxity measurements from baseline versus 6 months post procedure. Thus, the changes on MRI do not necessarily equate to improvements in anterior tibial translation as assessed via stress radiographs over this time period. The importance of this finding is not fully understood. Interestingly, through retrospective chart review, in many instances, the treating physician noted clinically improved laxity post procedure based on Lachman, and patients' subjective reports showed an improved sense of stability. The results of this study are similar to several outcome

studies in the surgical ACLR literature which found no correlation between the extent of anterior tibial laxity postoperatively and patient-reported improvement following surgical ACLR.[38,39] In fact, it has been more recently thought that tibial rotation, not anterior tibial translation, may be a better predictor of functional stability and patient outcomes following surgical reconstruction.[40] In this study, one could hypothesize that percutaneous BMC injection into the subset of patients with partial thickness disruption in theory preserves both bundles, and may be responsible for preserved rotational kinematics, thus explaining the findings of improved functional outcomes despite no difference in anterior tibial translation.

Another limitation to this study was the early crossover study design. Because patients in the exercise therapy group experienced ongoing pain and/or functional limitations and all elected to cross over to the treatment group at 3 months, it was not possible to compare between-group outcome measures for the complete duration of the study. However, an early cross-over was allowed due to the possible increased risk associated with prolonged nonoperative treatment.[43,44] In addition, injury chronicity was uncontrolled in this study. Patients with chronic (>3 month) ACL tears were included in the study with several patients being >2 years post injury. A subgroup analysis demonstrated that those treated within 12 months of injury reported significantly improved functional outcomes versus those treated after 12 months. One hypothesis is that chronicity of injury may play a considerable role in treatment outcome from both physiologic and biomechanical standpoints. Several patients with chronic injury demonstrated MRI findings of mucoid infiltration in the remnant ACL which may hinder healing potential by creating a barrier to organized collagen deposition and remodeling. The importance of adequate blood supply and angiogenesis is well established in ligament healing models and several authors have demonstrated a blunted healing response of the ACL when compared with MCL.[41,42] Perhaps, biologic augmentation in the early phases of healing response within several weeks after initial injury, corresponding to the proliferation and remodeling phases, would be beneficial in improving clinical outcomes.

Future studies should focus on earlier intervention (acute and subacute injuries), incorporating a blinded study design and the inclusion of a sham treatment to rule out potential for placebo effect.

CONCLUSION

The results of this midterm analysis suggest that autologous BMC injection under fluoroscopic guidance into partial or full-thickness, nonretracted ACL tears resulted in improved patient function at 3 months when compared to exercise alone, and this treatment effect was sustained through 24 months across multiple functional outcome measures. MRI analysis was suggestive of interval ligament healing and maturation at 6 months. Further studies focusing on earlier intervention with BMC injection, including acute, sub-acute, and chronic tears, are warranted to further identify an optimal group of responders within this population.

DECLARATIONS

Ethics approval and consent to participate.

Patients provided verbal and written consent. The International Cellular Medicine Society provided IRB oversight and approval (OHRP Registration #IRB00002637). Trial registration number: NCT01850758.

AUTHORS' CONTRIBUTIONS

CC was involved in study design, data acquisition, interpretation, and manuscript editing. ML was concerned with manuscript writing and editing, data acquisition, and interpretation. IS was responsible for manuscript writing and editing, data analysis, and preparation of figures and tables. ED focused on patient recruitment, data acquisition and interpretation, manuscript editing, and table and figure editing. All authors read and approved the final manuscript.

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COMPETING INTERESTS

CC is a shareholder and CMO of Regenexx, LLC and president and owner of the Centeno-Schultz Clinic. ML, IS, and ED have declared no competing interests.

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