Prospective Randomized Trial of Biologic Augmentation With Bone Marrow Aspirate Concentrate in Patients Undergoing Arthroscopic Rotator Cuff Repair

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Background: Although initial studies have demonstrated that concentrated bone marrow aspirate (cBMA) injections promote rotator cuff repair (RCR) healing, there are no randomized prospective studies investigating clinical efficacy.

Hypothesis/Purpose: To compare outcomes after arthroscopic RCR (aRCR) with and without cBMA augmentation. It was hypothesized that cBMA augmentation would result in statistically significant improvements in clinical outcomes and rotator cuff structural integrity.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: Patients indicated for aRCR of isolated 1- to 3-cm supraspinatus tendon tears were randomized to receive adjunctive cBMA injection or sham incision. Bone marrow was aspirated from the iliac crest, concentrated using a commercially available system, and injected at the aRCR site after repair. Patients were assessed preoperatively and serially until 2 years postoperatively via the following functional indices: American Shoulder and Elbow Surgeons (ASES), Single Assessment Numeric Evaluation (SANE), Simple Shoulder Test, 12-Item Short Form Health Survey, and Veterans RAND 12-Item Health Survey. Magnetic resonance imaging (MRI) was performed at 1 year to assess rotator cuff structural integrity according to Sugaya classification. Treatment failure was defined as decreased 1- or 2-year ASES or SANE scores as compared with preoperative baseline, the need for revision RCR, or conversion to total shoulder arthroplasty.

Results: An overall 91 patients were enrolled (control, n = 45; cBMA, n = 46): 82 (90%) completed 2-year clinical follow-up and 75 (82%) completed 1-year MRI. Functional indices significantly improved in both groups by 6 months and were sustained at 1 and 2 years (all $P < .05$). The control group showed significantly greater evidence of rotator cuff retear according to Sugaya classification on 1-year MRI (57% vs 18%; $P < .001$). Treatment failed for 7 patients in each group (control, 16%; cBMA, 15%).

Conclusion: cBMA-augmented aRCR of isolated supraspinatus tendon tears may result in a structurally superior repair but largely fails to significantly improve treatment failure rates and patient-reported clinical outcomes when compared with aRCR alone. Additional study is warranted to investigate the long-term benefits of improved repair quality on clinical outcomes and repair failure rates.

Registration: NCT02484950 (ClinicalTrials.gov identifier).

Keywords: rotator cuff; bone marrow aspirate; clinical trial

Rotator cuff tears are a common cause of shoulder pain and loss of function, often requiring surgical repair.[31] Depending on the fixation method, reattachment of the torn supraspinatus tendon to the footprint of the greater tuberosity may be susceptible to incomplete healing or retear at the tendon-bone interface.[12,31] This can result in persistent pain, functional or strength deficits, limited range of motion (ROM), and stiffness, and in the case of retears, it may necessitate revision surgical repair.[17,24,25]

Connective tissue progenitor products have the potential to differentiate into a variety of mature cell lines and provide a source of growth factors for tissue regeneration. Minimally manipulated connective tissue progenitor

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products are currently utilized to augment several orthopaedic surgical procedures, most commonly in the form of concentrated bone marrow aspirate (cBMA). These procedures include rotator cuff repair (RCR), osteochondral allograft transplantation, and Achilles tendon repair.[7,13,14,18,24] Tendon repair augmented with cBMA products may promote a more favorable healing environment, thereby producing a more structurally robust and native tendon-bone interface.[2,32] Regarding RCR, animal studies have demonstrated that adjunctive cBMA cuff repair can improve tendon integrity, which is theorized to decrease the likelihood of reinjury or repair failure.[10,23,35] Ideally, the use of cBMA may facilitate optimal healing at the bone-tendon interface, thereby improving the overall function of the repaired rotator cuff. Potential challenges include product quality, delivery, and maintenance within the healing environment, particularly in the setting of arthroscopic surgery.

To our knowledge, this is the first prospective randomized clinical trial investigating the effect of cBMA augmentation in patients undergoing arthroscopic RCR (aRCR). The primary aim of the study was to compare clinical outcomes after aRCR with and without adjunctive cBMA injection. The secondary aim was to compare the incidence of persistent structural defects in the repaired tendon on 1-year postoperative magnetic resonance imaging (MRI).[33] It was hypothesized that patients who underwent aRCR with cBMA augmentation would demonstrate statistically superior clinical outcomes by 2 years after surgery and rotator cuff structural integrity on 1-year MRI when compared with patients treated with aRCR alone.

METHODS

Patient Selection

This prospective, single-blinded, randomized clinical trial was conducted from December 2015 until May 2022 under the approval and guidance of the local institutional review board (ORA15042707) and in concordance with the CONSORT (Consolidated Standards of Reporting Trials) checklist. Consecutive patients were identified who were between 18 and 70 years of age and undergoing primary aRCR for a 1- to 3-cm full-thickness tear of the supraspinatus tendon, as indicated by preoperative MRI; patients provided informed consent and were prospectively enrolled by study staff. Tears were remeasured intraoperatively with use of an arthroscopic probe to confirm appropriate tear size.

Exclusion criteria included the following: tears measuring >3 cm on preoperative MRI, previous RCR, irreparable tear, involvement of multiple rotator cuff tendons, pregnant or breastfeeding status, current drug and alcohol abuse, HIV or hepatitis B or C infection, history of platelet-rich plasma injection, other platelet-based product or biologic injection in the past 12 months in the ipsilateral shoulder, lack of decisional capacity, or any other clinically significant finding that would place the patient at health risk or affect the study or its completion. Chronic rotator cuff tears were defined as tears with identifiable injury and/or onset of symptoms >3 months before aRCR.

Patient Randomization and Intervention

At the time of consent, patients were randomized via a random number generator to the treatment or placebo group. Only patients were blinded to treatment. Randomization was performed by study staff and occurred in a 1:1 ratio between groups. For patients assigned to the treatment group, 60 mL of BMA was drawn from the iliac crest before shoulder arthroscopy and concentrated into a cBMA injection using commercially available light absorption sensor technology (Angel System; Arthrex) set to 7% hematocrit concentration. The control group received a 0.5-cm incision on the hip to maintain blinding. After completion of the aRCR, half the volume of cBMA was injected into the tendon at the junction of the bone, with the other half injected at the site of the footprint, while saving minimal amounts of BMA and cBMA for fluorescence activated cell sorting (FACS) analysis.

FACS was performed on BMA and cBMA to determine mesenchymal stem cell (MSC) concentration based on

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criteria set forth by the International Society for Cellular Therapy.[6] BMA and cBMA samples were stained in 12 × 77–mm tubes according to the BD Stemflow hMSC Analysis Kit (BD Biosciences) per the manufacturer's instruction. After antibody staining, cells were treated with lysing buffer (BD Pharm Lyse; BD Biosciences), washed with FACS buffer, and resuspended to a final volume of 0.5 mL in 1% paraformaldehyde. For flow cytometry, cells (0.5 mL) were transferred into BD Trucount Tubes and acquired on a BDFortessa flow cytometer using FACSDiva software (Version 6.1.3 or 8.0.2). Fluorescence parameter photomultiplier tubes were normalized with Rainbow Calibration Particles, Peak 7 (Spherptech). Scatter voltages were normalized using BD Trucount beads.

The samples were then analyzed with FlowJo software (Version 9.9.6; TreeStar Inc) to identify the number of Trucount bead events and the number of events within the multipotent MSC phenotype, defined at a minimum as cell-surface coexpression of the antigens CD105, CD73, and CD90 (≥95% positive) and the absence of hematopoietic lineage markers CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR (≤2% positive). Absolute MSC count was determined by dividing the number of BD Trucount beads acquired by the known total number of beads in the tube lot.

Surgical Technique and Rehabilitation

Depending on the size of the tear, all patients underwent repair with 1 of 4 techniques—transosseous equivalent, double row, single row, or combination—, with additional side-to-side or luggage tag repair utilized as necessary. The optimal repair technique was evaluated on a case-by-case basis and dictated by tear size, morphology, and location. Subacromial decompression was performed in all patients. If biceps pathology was identified during diagnostic arthroscopy, open or arthroscopic biceps tenodesis was concurrently performed.

Postoperatively, all patients completed an institutionally standardized aRCR rehabilitation protocol. In the immediate postoperative period, patients were restricted to the use of a sling for 4 to 6 weeks with gentle hand, wrist, elbow, and pendulum exercises. At 4 weeks, patients began passive ROM under the care of a physical therapist. By 8 weeks, patients progressed to active-assisted ROM, including wall slides and isometric exercises. Finally, at 10 to 12 weeks after surgery, patients were allowed to begin strengthening and active ROM as tolerated.

Outcome Measurements

Physical examination and patient-reported outcome measurements (PROMs) were performed preoperatively and at specified postoperative time points. The physical examination consisted of strength measurements with a portable dynamometer and active ROM. Physical examination was to be assessed at 6 months, 1 year, and 2 years. However, serial in-person follow-up was largely abandoned owing to safety precautions related to the COVID-19 pandemic.

TABLE 1
Sugaya Classification[a]

Sugaya Type	Description
1	Homogeneous tendon with sufficient thickness; low signal intensity on T2-weighted MRI
2	Partial high-intensity signal from within the tendon, with sufficient thickness
3	Insufficient tendon thickness; no tendon discontinuity
4[b]	Minor discontinuity on >1 MRI slice suggestive of small full-thickness tendon tear
5[b]	Major discontinuity on >1 MRI slice suggestive of a moderate or large full-thickness tendon tear

[a]MRI, magnetic resonance imaging.
[b]Sugaya classification type 4 or 5 is suggestive of full-thickness tendon tear.

PROMs were obtained from a series of validated patient-reported outcome questionnaires—specifically, the American Shoulder and Elbow Surgeons (ASES), Single Assessment Numeric Evaluation (SANE), Simple Shoulder Test, 12-Item Short Form Health Survey (SF-12), and Veterans RAND 12-Item Health Survey (VR-12). The PROMs were collected using proprietary software (OBERD; PatientIQ) either on-site with a Health Insurance Portability and Accountability Act–compliant device or remotely on the patient's own device. All investigative-related evaluations were scheduled to be performed preoperatively and at 6 months, 1 year, and 2 years postoperatively. All patients also underwent repeat MRI at 1 year to evaluate rotator cuff healing and structural integrity. One of 2 board-certified and fellowship-trained musculoskeletal radiologists (G.M.W. and M.L.R.), both blinded to the treatment group, graded each MRI scan according to the Sugaya classification system (Table 1).[33] Treatment failure was defined as (1) decreased 1- or 2-year postoperative ASES or SANE scores as compared with preoperative baseline, (2) the need for revision RCR, or (3) the need for conversion to total shoulder arthroplasty.

Statistical Analysis

All statistical analyses were performed with RStudio Version 4.1.1 (R Foundation for Statistical Computing). A power analysis was conducted on the basis of previously published data by MacDonald et al[26] and Cvetanovich et al.[5] MacDonald et al reported ASES scores at 2-year follow-up in patients undergoing aRCR with acromioplasty (mean ± SD, 90.5 ± 13.4) and without (85.6 ± 19.1), while Cvetanovich et al established the minimal clinically important difference (MCID) in ASES scores to be 11.1 after aRCR. These standard deviations and MCID values resulted in an effect size of 0.673 (Cohen *d*). It was then estimated that a cohort size of 36 patients each would be powered at 80.4% to detect a difference in ASES scores. Chi-square or Fisher exact testing was utilized to compare

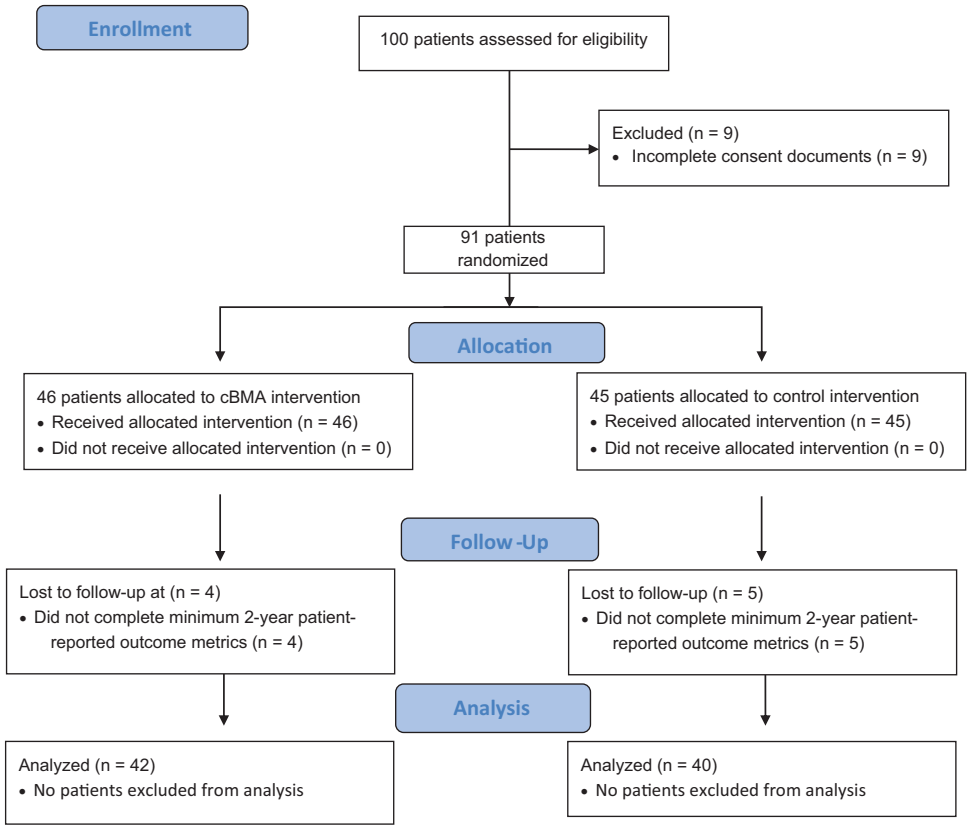

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram shows patient inclusion and follow-up. cBMA, concentrated bone marrow aspirate.

categorical pre- or intraoperative variables. Shapiro-Wilk testing determined normality of the data, and Mann-Whitney *U*, Wilcoxon signed-rank, and unpaired or paired *t* tests were used accordingly for comparing pre- and postoperative PROMs. Univariate logistic regression was performed to assess whether the use or amount of cBMA augmentation was predictive of clinical improvements relative to the MCID, Patient Acceptable Symptom State, and substantial clinical benefit thresholds established for aRCR by Cvetanovich et al.

RESULTS

Patient Demographics

A total of 100 patients were assessed for study eligibility. After 9 patients were excluded for incomplete consent documentation, 91 patients undergoing aRCR for full- or partial-thickness tears converted to full-thickness tears of the supraspinatus tendon were prospectively enrolled and randomized in a 1:1 ratio (Figure 1). Of the total, 45 patients were enrolled in the control group and 46 in the cBMA injection group. Patient demographics and preoperative functional characteristics are summarized in Table 2. The groups were balanced with respect to preoperative characteristics, with the exception that the control group had a higher proportion of men.

Intraoperative Details

The average rotator cuff tear size was 2.33 ± 1.25 cm for the control group and 1.85 ± 0.93 cm for the cBMA group, a difference that was not statistically significant ($P = .100$). There were no significant differences in repair technique utilized or number of concomitant procedures performed. Repair technique and concomitant procedure details are summarized in Table 3.

In the cBMA group, a mean 63 ± 15.5 mL of bone marrow was aspirated from the ipsilateral anterior superior iliac crest. Based on flow analysis, a mean 3.03 ± 1.92 mL of cBMA was injected into the repair site, resulting in an average delivery of 44,114 ± 55,096 MSCs/mL (range, 4045-272,971). Flow analysis demonstrated the successful concentration of MSCs per milliliter in cBMA versus BMA with a ratio of 3.44 ± 3.70 ($P < .05$).

Postoperative Follow-up

Of the 91 enrolled patients, 82 (90%) completed the minimum 2-year clinical follow-up, while 90 (99%) completed

TABLE 2
Preoperative Patient Variables[a]

Variable	cBMA (n = 46)	Control (n = 45)
Demographics and comorbidities		
Age, y	56.1 ± 10.1	55.3 ± 9.6
Female sex	21 (46)	13 (29)
Body mass index	28.9 ± 5.6	30.4 ± 5.5
Smoking status	13 (28)	15 (33)
Diabetes mellitus	3 (6.5)	3 (6.7)
Workers' compensation	4 (8.7)	4 (8.9)
Shoulder laterality, right	24 (52)	28 (62)
Chronic tear >3 mo	36 (78)	35 (78)
Follow-up, y	3.28 ± 1.42	3.20 ± 1.41
Range of motion, deg		
Forward flexion	155 ± 31	144 ± 49
IR in 90° of abduction	44 ± 30	43 ± 33
ER in 90° of abduction	71 ± 24	62 ± 34
ER from arm at side	54 ± 28	53 ± 24
Abduction from arm at side	142 ± 39	134 ± 50
Strength, kg		
Forward elevation	8 ± 8	8 ± 8
External rotation	7.8 ± 6.1	9.2 ± 5.6
Curl	16.0 ± 10.9	11.9 ± 4.7

[a]Data are presented as No. (%) and mean ± SD per cohort. cBMA, concentrated bone marrow aspirate; ER, external rotation; IR, internal rotation.

TABLE 3
Intraoperative Variables[a]

Variable	cBMA (n = 46)	Control (n = 45)	*P* Value
Tear size, cm, mean ± SD	1.85 ± 0.93	2.33 ± 1.25	.100[b]
Complications	0 (0)	1 (2.2)	.495[c]
Repair technique			
Transosseous equivalent	37 (80)	31 (69)	.205[d]
Double row	4 (8.7)	3 (6.7)	>.999[c]
Single row	3 (6.5)	7 (16)	.197[c]
Multiple	2 (4.3)	4 (8.9)	.434[c]
Concomitant procedures			
Distal clavicle excision	2 (4.3)	8 (16)	.050[c]
Labral repair	0 (0)	1 (2.0)	.495[c]
Labral debridement	13 (28)	6 (12)	.080[d]
Biceps tenodesis	30 (64)	31 (62)	.710[d]
Biceps tenotomy	2 (4.3)	4 (8.0)	.434[c]
Total	47	50	.491[d]

[a]Data are presented as No. (%) per cohort, unless otherwise indicated. cBMA, concentrated bone marrow aspirate.
[b]Mann-Whitney *U* test.
[c]Fisher exact test.
[d]Pearson chi-square test.

≥1 year of clinical follow-up. The average final follow-up for all enrolled patients was 3.24 ± 1.40 years (range, 0.24-5.35). When stratified by treatment, 40 of 45 (89%) patients in the control group and 42 of 46 (91%) in the injection group completed the minimum 2-year follow-up. The average final follow-up was 3.20 ± 1.41 and 3.28 ± 1.42 years in the control and cBMA groups, respectively.

At preoperative baseline, there were no significant differences between groups in the patient-reported pain and function metrics (all $P > .142$). By 6-month follow-up, the ASES, SANE, SF-12 physical health, Simple Shoulder Test, and VR-12 physical health metrics were significantly improved in both groups ($P < .003$). These improvements were sustained at 1 and 2 years (all $P < .001$). There were no statistically significant improvements at any postoperative time point in the SF-12 mental health and VR-12 mental health metrics. Furthermore, there were no significant differences in PROM scores between the control and cBMA groups at any postoperative time point (Table 4).

Postoperative ASES and SANE scores for both groups were analyzed for significant differences in clinical outcomes. Mean 2-year index scores for both groups were compared with the MCID, Patient Acceptable Symptom State, and substantial clinical benefit values previously established for aRCR by Cvetanovich et al.[5] The percentage of patients who achieved a clinically significant outcome did not differ between groups for any of the 3 indices at any postoperative time point. Univariate logistic regression demonstrated that, with the exception of achieving the MCID in SANE scores at 1 year, the presence, absence, or amount of injected cBMA was not associated with achieving clinically significant outcomes.

Functional strength and ROM examination was performed at 6 months and 1 year. Collection of 2-year strength and ROM metrics was abandoned secondary to the COVID-19 pandemic; follow-up at 1 year was also partially affected. An overall 55 (60%) and 44 (48%) patients completed strength and ROM physical examination at 6 months and 1 year, respectively. In the control group, there was no improvement in strength or ROM at any postoperative time point relative to baseline metrics. In the cBMA group, there was significant improvement in internal rotation in 90° of abduction ($P = .010$) and external rotation with the arm at the side ($P = .049$) at 6 months when compared with baseline. At 1 year, internal rotation in 90° of abduction ($P < .001$) and external rotation with the arm at the side ($P = .003$) maintained improvement, while abduction from the arm at the side ($P = .006$) and forward elevation strength ($P = .036$) also demonstrated improvement relative to baseline. Internal rotation in 90° of abduction was significantly improved as compared with the control group, although this was the only significant improvement in postoperative strength or ROM relative to the control group at either time point.

After 2 patients were excluded from each group who required revision aRCR within 1 year of aRCR, 87 patients were eligible for 1-year MRI to assess rotator cuff tendon structural integrity. Of the 87 patients, 75 (86%) completed the postoperative scan: 37 of 41 (90%) in the control group and 38 of 44 (86%) in the cBMA group. Each MRI scan was graded according to the Sugaya classification system of rotator cuff tendon integrity (Table 1).[33] The average Sugaya score was significantly higher among controls (3.43 ± 1.04) than for patients treated with cBMA augmentation (2.63 ± 0.91) ($P < .001$). In total, 21 (57%) MRI scans from the control group were graded Sugaya 4 or 5—classifications reserved for magnetic resonance evidence of

TABLE 4
Patient-Reported Outcome Measures[a]

Variable	cBMA (n = 46)	cBMA vs Baseline[b]	Control (n = 45)	Control vs Baseline[b]	cBMA vs Control[c]
Baseline					
ASES	48.8 (21.0)		45.3 (17.4)		.427
SANE	34 (21)		37 (23)		.486
SF-12 mental	54 (11)		55 (9)		.576
SF-12 physical	38 (8)		35 (7)		.059
SST	47 (27)		41 (26)		.397
VR-12 mental	58 (11)		57 (9)		.725
VR-12 physical	40 (8)		38 (7)		.142
6 mo					
ASES	74 (21)	<.0001	81 (16)	<.0001	.160
SANE	74 (19)	<.0001	68 (27)	<.0001	.274
SF-12 mental	58 (6)	.4338	55 (8)	.8558	.107
SF-12 physical	44 (8)	.003601	45 (9)	<.0001	.802
SST	70 (26)	.0001863	75 (17)	<.0001	.397
VR-12 mental	61 (6)	.3714	58 (10)	.4591	.074
VR-12 physical	47 (7)	.000314	46 (9)	<.0001	.563
1 y					
ASES	89 (13)	<.0001	87 (16)	<.0001	.623
SANE	85 (18)	<.0001	75 (26)	<.0001	.081
SF-12 mental	56 (8)	.9639	55 (7)	.9519	.636
SF-12 physical	48 (8)	<.0001	47 (9)	<.0001	.721
SST	86 (16)	<.0001	82 (25)	<.0001	.403
VR-12 mental	59 (9)	.788	58 (9)	.311	.462
VR-12 physical	50 (7)	<.0001	48 (9)	<.0001	.407
2 y					
ASES	89 (15)	<.0001	91 (14)	<.0001	.699
SANE	83 (18)	<.0001	88 (20)	<.0001	.351
SF-12 mental	57 (8)	.9045	56 (6)	.7252	.638
SF-12 physical	49 (10)	.00004	49 (9)	<.0001	.934
SST	84 (20)	<.0001	89 (21)	<.0001	.293
VR-12 mental	60 (8)	.1959	56 (12)	.6289	.092
VR-12 physical	51 (9)	<.0001	50 (10)	<.0001	.638

[a]Data are presented as mean (interquartile range). ASES, American Shoulder and Elbow Surgeons; cBMA, concentrated bone marrow aspirate; SANE, Single Assessment Numeric Evaluation; SF-12, 12-Item Short Form Health Survey; SST, Simple Shoulder Test; VR-12, Veterans RAND 12-Item Health Survey.
[b]*P* value according to paired sample *t* test.
[c]*P* value according to Welch 2-sample *t* test.

rotator cuff tear—as opposed to 7 (18%) scans from the cBMA group ($P < .001$). Further statistical analysis demonstrated a strong association between cBMA augmentation and Sugaya score ≤ 3 ($P < .001$) (Table 5).

Overall failure rates between the control and cBMA groups did not differ significantly ($P = .964$). Seven patients in the control group (16%) and 7 in the cBMA group (15%) met criteria for treatment failure by final follow-up (Table 5). In the control group, treatment for 2 patients failed within 1 year of aRCR, and they underwent revision RCR. A third patient from the control group had MRI-documented evidence of a symptomatic rotator cuff retear at 2.77 years after aRCR and was treated nonoperatively. Four additional controls met criteria for clinical failure. Three patients had SANE scores at 1 year that were below preoperative levels, and 1 patient had a postoperative ASES score below the preoperative level. One additional patient in the control group developed postoperative arthrofibrosis, which was successfully managed with arthroscopic capsular release, lysis of adhesions, and manipulation under anesthesia. The patient did not meet criteria for treatment failure, as there was no evidence of rotator cuff retear on MRI or during diagnostic arthroscopy and the ASES and SANE scores remained improved at and >1 year versus baseline reporting. In the cBMA group, there were 2 surgical and 5 clinical failures. Surgically, 2 patients from the cBMA group required revision RCR within the 1-year follow-up period. Clinically, when compared with baseline indices, 1 patient had a lower 1-year ASES score, 2 patients had lower 2-year ASES scores,

TABLE 5
Association of cBMA Factors With Sugaya Scores and Treatment Failure[a]

	Overall Frequency			Use of cBMA			Amount of cBMA Injected, mL		
Variable	cBMA	Control	*P* Value[b]	OR	95% CI	*P* Value[c]	OR	95% CI	*P* Value[c]
Structural integrity									
Sugaya ≥4	7/38 (18)	21/37 (57)	**<.001**	0.17	0.06-0.47	**<.001**	0.81	0.57-1.08	.199
Failure[d]									
Overall	7/46 (15)	7/45 (16)	.964	0.97	0.31-3.10	.964	0.92	0.60-1.25	.644
Surgical: arthroplasty	2/46 (4.3)	3/45 (6.7)	.677	0.64	0.08-4.02	.630	1.01	0.56-1.45	.971
1-y PROM									
ASES	1/46 (2.2)	1/45 (2.2)	>.999	0.98	0.04-25.2	.987	0.97	0.30-1.61	.931
SANE	0/46 (0)	3/45 (6.7)	.117	0.00		.995	0.00		.996
2-y PROM									
ASES	2/46 (4.3)	0/45 (0)	.495	105,584,915	0.00-NA	.997	1.26	0.49-2.08	.432
SANE	2/46 (4.3)	0/45 (0)	.495	105,584,915	0.00-NA	.997	0.89	0.08-1.79	.850

[a]Data are presented as No. / per cohort (%). Bold indicates $P < .05$. ASES, American Shoulder and Elbow Surgeons; cBMA, concentrated bone marrow aspirate; NA, not applicable; OR, odds ratio; PROM, patient-reported outcome measure; SANE, Single Assessment Numeric Evaluation.

[b]Pearson chi-square test or Fisher exact test.

[c]Univariate logistic regression.

[d]Failure is defined as revision surgery (revision rotator cuff repair or arthroplasty) or inferior patient-reported outcome scores at 1- or 2-year time point.

and 2 patients had lower 2-year SANE scores. There were no other documented complications or instances of treatment failure.

DISCUSSION

The results of this prospective randomized controlled trial demonstrate that cBMA augmentation of aRCR results in significant improvements from baseline in ROM and functional outcomes by as early as 6 months, as well as superior tendon structural integrity and healing at 1 year when compared with nonaugmented controls. However, cBMA augmentation largely fails to significantly improve treatment failure rates and patient-reported clinical and functional outcomes as compared with aRCR alone.

Biological augmentation, specifically cBMA, has become an area of increasingly active investigation in the realm of RCR and other common orthopaedic procedures.[3,9,22,34] Proof-of-concept and translational research has demonstrated that autologous cBMA adjuncts can improve the intrinsic healing capabilities of rotator cuff tendons after repair.[10,20,23] Gulotta et al[10] utilized a rat model to show that at 4 weeks after surgery, RCRs augmented with cBMA developed less fibrocartilage, had a higher load and stress to failure, and were less stiff than isolated RCRs. Liu et al[23] reported similar findings in their RCR model with rabbits, including higher load to failure and improved collagen fiber continuity and orientation after cBMA-augmented repair as compared with repair alone. The results of this study support the data in these preclinical investigations. Based on the Sugaya classification, adjunct cBMA delivery resulted in improved tendon healing and a structurally superior repair when compared with controls.

Although generally promising, the existing body of clinical investigation into the efficacy of cBMA injection augmentation of RCR is limited and of low evidence level.[4,7,13,14,28] Havlas et al[13] completed a 10-patient case series of cBMA augmentation of aRCR, which showed improved clinical function by 6 weeks and a fully healed repair site in all patients on 6-month MRI. Hernigou et al[14] published a more robust case-control comparison of 45 patients treated with cBMA augmentation of a single-row aRCR with concomitant subacromial decompression, as opposed to 30 patients treated with isolated aRCR using the same technique. When compared with the control group, patients treated with cBMA augmentation demonstrated improved tendon integrity and healing on 6-month ultrasound and MRI; in addition, there were significantly lower rotator cuff retear rates by 10-year follow-up. The results of this investigation support that patients treated with cBMA at the time of RCR had significant improvements in multiple PROM indices; however, no statistically or clinically significant difference in outcomes was observed when compared with controls treated with RCR alone.

In our study, the differences in tendon integrity were indirectly observed through the superior Sugaya classification in the cBMA-augmented repair group. On 1-year MRI, evidence of rotator cuff retear was identified in just 18% of patients in the cBMA group versus 57% in the control group. This finding coincides with existing reports of improved rotator cuff tendon structural integrity after cBMA augmentation of RCR.[7,13,14] However, the clinical implications of improved structural integrity after RCR remains to be elucidated. As noted in previous studies, tendon integrity after RCR does not strongly correlate with patient-reported clinical outcomes. This information should be considered when evaluating patients who may

be candidates for cBMA augmentation, particularly given the substantial out-of-pocket costs of the adjunct treatment.

Several studies report that patients who have a persistent tear at the time of follow-up have diminished strength and poorer satisfaction when compared with their counterparts without a tear.[8,12,19,36] Haque and Pal Singh[11] performed a meta-analysis of functional outcomes after RCR and concluded that patients with intact rotator cuffs were more likely to achieve the MCID for ASES scores than patients with evidence of rotator cuff retear. Yoshida et al[36] also reported that Sugaya classification of rotator cuff structural integrity demonstrated significant correlation with arm abduction strength. However, Russell et al[30] performed a meta-analysis of similar literature that partially contests these positive findings: while superior rotator cuff structural integrity correlated with significant improvement in Constant-Murley and University of California, Los Angeles, shoulder scores as well as strength in forward elevation (all $P < .001$), there was no clinically significant improvement in these metrics or in multiple other validated indices or functional outcomes. Nonetheless, the findings of the present investigation suggest that cBMA augmentation may improve autologous healing capacity at the bone-tendon junction, which has potentially far-reaching implications for the standard of care in aRCR.

We attempted to optimize the BMA-harvesting technique and method of cBMA preparation to create the most effective environment for healing and regeneration.[13,15] BMA harvest from the posterior iliac crest has been shown to result in significantly greater cellular yield with higher proliferative potential than BMA harvested from appendicular locations.[1,16,29] A linear relationship has been also highlighted between the number of progenitor cells in BMA and cBMA and its effect on healing, potentially contributing to a wide range of clinical outcomes dependent on cBMA quality.[15] In the present study, BMA harvest from the posterior iliac crest produced a similar yield of BMA and cBMA but a wide range of MSC concentrations on a per-patient basis, which may have affected clinical results. Nonetheless, regression determined that cBMA augmentation was associated with Sugaya scores ≤ 3.

This study is not without limitations. It enrolled patients indicated for primary aRCR for the treatment of 1- to 3-cm tears of the supraspinatus tendon and thus may not be generalizable to larger injuries or injuries involving multiple rotator cuff tendons. The relatively short minimum follow-up of 2 years is another study limitation, and additional long-term prospective evaluation of cBMA augmentation of aRCR is warranted. Furthermore, 5 surgeons performed the surgical procedures, and there was variability in the repair technique utilized secondary to tear size, morphology, location, and surgeon discretion. Although there was no significant difference in the total number of concomitant procedures performed or type of concomitant procedure performed, the overall high prevalence of concomitant surgery could have influenced the clinical and radiologic outcomes. No analysis was performed to assess the influence of concomitant procedures on outcomes. The surgeons were also responsible for BMA harvesting and thus not blinded to treatment. No analysis was performed to assess for differences among providers with respect to MSC count or treatment outcomes.

Even though the overall rate of clinical follow-up was a relative strength of the study (n = 82/91) and adequately powered to assess postoperative ASES scores, our study may have been underpowered to comment on other PROM indices and Sugaya score differences identified on MRI. Postoperative MRI was collected only at 1 time point and analyzed by 1 of 2 radiologists. Both are board-certified, fellowship-trained, diagnostic musculoskeletal radiologists who were blinded to treatment intervention, but there was no inter- or intraclass correlation analysis performed on Sugaya scoring of rotator cuff structural integrity to assess for consistency. Nonetheless, other similar investigations have reported substantial agreement between inter- and intrarater reliability and reproducibility.[21,27] Last, the COVID-19 pandemic was an inherent limitation on the collection of in-person strength and ROM evaluation from a large faction of the study population, particularly at the 1- and 2-year time points.

CONCLUSION

cBMA injected into the shoulder after aRCR of small to medium tears was associated with improved ROM and structural integrity on postoperative MRI. However, there were no statistical or clinical differences in functional outcome scores or clinical failures. These findings suggest that adjunctive cBMA treatment at the time of aRCR may possess the ability to enhance the structural integrity and bone-tendon healing of the repaired rotator cuff but may not result in short-term clinical improvements.

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