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Bone marrow aspirate concentrate with cancellous allograft versus iliac crest bone graft in the treatment of long bone nonunions

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Abstract

Objectives: The purpose of this study was to compare bone marrow aspirate concentrate (BMAC) with cancellous allograft to iliac crest bone graft (ICBG) in the treatment of long bone nonunions.

Design: Retrospective cohort study.

Setting: A single level I trauma center.

Patients: 26 patients with long bone diaphyseal or metaphyseal nonunions with defects >2 mm and treated with open repair and BMAC, compared to 25 patients with long bone diaphyseal or metaphyseal nonunions with defects >2 mm and treated with open repair and ICBG.

Intervention: Open repair of long bone nonunion using either autologous ICBG or BMAC with cancellous allograft.

Main outcome measure: Nonunion healing, radiographically measured by the modified Radiographic Union Score for Tibia (mRUST) score. Secondary outcomes included risk factors associated with failed repair.

Results: The union rates for the BMAC and ICBG cohorts were 75% and 78%, respectively ($P = .8$). Infection was the only risk factor of statistical significance for failure.

Conclusion: In this study, we found no significant difference in union rate for long bone nonunions treated with ICBG or BMAC with allograft. BMAC and allograft led to 75% successful healing in this series. Given the heterogeneity of the control group and loss to follow-up, further prospective investigation should be conducted to more rigorously compare BMAC to ICBG for nonunion treatment.

Level of evidence: III, retrospective cohort.

Keywords: allograft, autograft, bone marrow aspirate, nonunion

1. Introduction

Approximately 5% to 10% of fractures result in delayed union or nonunion, although some studies have reported rates as high as 25% for the tibia and femur.[1,2] For nonunions that require surgical treatment, osteogenic augmentation is often a necessary component of a successful treatment plan.[3–5] Many options for grafting exist, although little comparative data exist regarding efficacy between different biological adjuncts.[3,4,6]

Autologous ICBG is currently the gold standard for biologic augmentation of nonunion repair.[2,7] ICBG is efficacious in facilitating bone healing for nonunion repair and arthrodesis.[2,4,7–10] However, it provides a limited source of graft material, requires a second surgical incision, and is associated with potential complications (donor site pain, infection, hematoma, and peripheral nerve injury).[4,7,11–13]

BMAC has gained popularity recently as an alternative to ICBG for nonunion treatment. This technique utilizes the osteogenic mesenchymal stem cells in bone marrow while minimizing donor site morbidity with a minimally invasive approach.[3,11,14–16] BMAC can be surgically applied either percutaneously for small defects or as an open approach with structural augmentation for larger defects. In a recent systematic review of animal long bone fracture models, BMAC demonstrated increased bone formation compared to controls, earlier bone healing, and higher final torsional strength.[14] While human

studies demonstrate the safety and potential efficacy of BMAC, they are limited to small case series in which percutaneous BMAC was used to treat fracture gaps <1 cm.[11,15–18] There are no studies comparing outcomes of BMAC combined with cancellous allograft for open nonunion repair compared to other techniques.

The purpose of this study was to compare the results of open treatment of long bone nonunions with BMAC plus cancellous allograft versus ICBG. The primary outcome was bony union.

2. Methods

The institutional review board approved this retrospective cohort comparative study at a level I tertiary care center. Adults (≥18 years old) who received open surgical repair for nonunions of the tibia, femur, or humerus between October 2008 and December 2015 were included. Patients were compiled from a list of all nonunions treated by the Orthopaedic Trauma Service. Nonunion was defined according to the United States Food and Drug Administration (FDA) as a fracture that had not completely healed within 9 months of injury or showed no signs of healing for 3 consecutive months on serial radiographs.[5] Patients treated with open nonunion debridement with BMAC grafting for a ≥2 mm defect were included in the study. This defect size threshold was selected in order to capture all nonunions with true cortical gaps that would require open surgical management and possibly being an indication for some type of structural graft. A control cohort of patients treated with ICBG from the same time period was compiled using the same inclusion criteria as above. The use of BMAC or ICBG was used based upon the preference of the attending surgeon. In our institution, one author preferred using BMAC over ICBG, while 2 other authors tended to use ICBG, but all surgeons used both techniques. Because the purpose of the study was to compare graft choice and technique, comparison of patients treated by multiple surgeons was felt to improve the generalizability of the patient population. In the ICBG group, any ancillary treatment, including cancellous allograft, bone morphogenic protein (BMP), and structural allografts were used at the surgeons' discretion (Table 1). All surgeons used Infuse (Medtronic, Minneapolis, MN), a recombinant human (BMP-2), a recombinant human bone morphogenetic protein-2 (rhBMP-2). In the BMAC group, all patients received BMAC mixed with cancellous allograft.

Patient demographics, index injury, and clinical outcome data were obtained from the medical records. Index injury data included whether injuries were open, required fasciotomy or flap coverage, or the presence of vascular injury. Preoperative nonunion defect size was measured in millimeters on the immediate preoperative radiographs from the cortical discontinuity on 4 cortices, and the largest measurement was considered the defect size. Patients with multiple nonunion repair surgeries for the same fracture were grouped according to the graft received (BMAC or ICBG) during the initial nonunion repair. All prior and subsequent nonunion surgeries were recorded, as well as the final implant used. Hypertrophic nonunions were defined as abundant callus on radiographs with a visible radiolucent line. Oligotrophic and atrophic nonunions were defined as little or no callus formation on radiographs with a visible gap at the fracture site. Patients were determined to have hypovitaminosis D if 25-hydroxyvitamin D levels were drawn and found to be ≤20 ng/mL.

The primary outcome was radiographic union, without further nonunion surgery. Radiographic healing was defined by the modified Radiographic Union Score for Tibia (mRUST) score as having bridging callus on ≥3 cortices, or a mRUST score of 9.[19] Postoperative radiographs were independently reviewed by 2 authors (KML and JTV). Any disagreements were adjudicated by a third author (CDP). The earliest follow-up visit when a patient fulfilled both clinical and radiographic healing was considered the date of union. Patients were considered to have failed treatment if they met FDA criteria for nonunion following their repair, or required repeat nonunion surgery. Any patient who was recommended to undergo repeat repair was also considered to have failed treatment regardless of whether the repeat surgery was performed. If a patient refused revision, failure was recorded from the last date of clinical follow-up. Patients who were scheduled for additional follow-up, but never returned to clinic within 9 months following surgical repair were considered lost to follow-up. Secondary outcomes included infection, defined as either return to the operating room for debridement with positive cultures or with positive cultures at the nonunion repair. Complications were only recorded if they were present sometime at or after the diagnosis of nonunion.

Subanalysis was performed to separately assess the treatment success of patients with tibial, femoral, and humeral nonunions. We also investigated the success of revision repairs among treatment failures and the effect of initial injury characteristics, cortical defect size, infection, implant failure, final implant type, and the use of additional cancellous allograft, structural allograft, or BMP on the treatment failure.

2.1. Surgical technique

Nonunion site preparation by each of the 3 surgeons was generally based on the same principles. After exposure, curettes and rongeurs were used to remove nonviable interposed fibrous tissue. Necrotic and sclerotic bone ends were debrided until healthy appearing, bleeding bone was identified. Sclerotic caps at the nonunion site were perforated with a drill to penetrate the intramedullary space.

ICBG or BMAC was harvested from the ipsilateral iliac crest unless previously harvested for other procedures. For ICBG harvest, graft was obtained using a standard surgical approach to the iliac crest. A cortical window was made to obtain cancellous autograft or a small diameter reamer (typically 42–48 mm in diameter) was used against the inner table to obtain cortico-cancellous autograft. The treating surgeon decided this based on surgical preference and the graft volume needed.

BMAC was obtained by a standard method using the Harvest system (Plymouth, MA). A small incision was made 5 to 6 cm

Table 1

Cohort surgical data.

	BMAC (n=26) n (%)	ICBG (n=25) n (%)	P value
Largest defect size, cm[†]	1.1 (0.51–4.7)	0.88 (0.39–7.3)	.2
ASA[‡]			
1	4 (15)	4 (16)	1.0
2	14 (54)	10 (40)	.3
3	8 (31)	10 (40)	.5
Unknown	0 (0)	1 (4)	.5
Hypertrophic nonunion	16 (62)	8 (32)	.04[*]
Final implant			.7
Plate	19 (73)	17 (68)	
Nail	7 (27)	8 (32)	
Ancillary graft treatment			
BMP	1 (3.8)	6 (24)	<.001[*]
Cancellous allograft	26 (100)	7 (28)	.05[*]
Strut	0 (0)	4 (16)	.051

[*] Statistical significance.
[†] Largest defect size results in median (range) centimetres.
[‡] ASA, American Society of Anesthesiologists.

posterior to the anterior superior iliac spine along the gluteus medius tubercle, and a stylet and trocar were inserted between the inner and outer tables approximately 5 cm deep. A total of 120 cc of bone marrow was aspirated, with frequent turning and depth repositioning of the needle (with every 5–10 cc aspirated) to aspirate marrow from different locations; aspirated marrow was passed off the field and centrifuged. The resulting concentrate (typically 14–20 cc) was then mixed with crushed cancellous allograft in a ratio of 30 cc cancellous allograft per 20 cc BMAC.

2.2. Statistical analysis

The student's *t*-test was used for normal, continuous variables, and the Mann–Whitney *U* test for non-normal continuous variables. The Chi-square and Fisher's exact tests were used for categorical variables. All tests were performed using a 2-sided *P*-value at alpha = 0.05. The outcomes were calculated as binary ("success" or "failure"), excluding those who were lost to follow-up. In addition, an unadjusted time-to-event analysis of the treatment success was assessed using the cumulative incidence function, with treatment failure as a competing risk. We also performed this analysis for the treatment failure, using treatment success as a competing risk. All patients were included in this analysis (including those lost to follow-up). We also adjusted for the largest defect size by calculating a proportional hazard model using the method of Fine and Gray.[20] Statistical tests were performed using a standard software package (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY). The time-to-event analysis was done using R software (version 3.3.0, Vienna, Austria).[21] The STROBE (Strengthening the Reporting and Observational Studies in Epidemiology) statement was used as a guide for reporting in this study.[22] A post-hoc power analysis was done using the primary outcome to estimate the needed sample size for a noninferiority/superiority prospective study.

3. Results

Fifty-one patients were included in this study (BMAC = 26 and ICBG = 25). Both cohorts were predominantly middle-aged white males. There was no statistically significant difference among demographic data or index injury data (Table 2). The fractures were diaphyseal in 46% and 40% of BMAC and ICBG groups, respectively (*P* = .559). The remaining fractures were metaphyseal. Table 1 shows no statistical difference amongst final implants. The ICBG group received BMP statistically more frequently compared to the BMAC group. The median (range) of

Table 2

Patient demographic and index injury data.

	BMAC (n = 26) n (%)	ICBG (n = 25) n (%)	P value
Age, years, (SD)	52 (16)	46 (15)	.2
Gender (male)	18 (69)	18 (72)	.8
Race (white)	22 (85)	21 (84)	1.0
Tobacco user	15 (58)	16 (64)	.6
DM	8 (31)	3 (12)	.1
Diaphyseal fracture	12 (46)	10 (40)	.6
Open fracture	9 (35)	12 (48)	.3
Fasciotomy	2 (8)	1 (4)	1.0
Flap coverage	3 (12)	4 (16)	.7
Vascular injury	1 (4)	4 (16)	.2

DM = diabetes mellitus, SD = standard deviation.

Table 3

Nonunion repair outcome.

	BMAC (n = 26) n (%)	ICBG (n = 25) n (%)	P value
All			.8
Success	15 (75)	18 (78)	
Failure	5 (25)	5 (22)	
Tibia			.3
Success	5 (56)	6 (86)	
Failure	4 (44)	1 (14)	
Femur			.3
Success	7 (100)	9 (75)	
Failure	0 (0)	3 (25)	
Humerus			1
Success	3 (75)	3 (75)	
Failure	1 (25)	1 (25)	

follow-up was 5.2 (1.8–39) months for BMAC and 6.8 (1.8–62) for ICBG (*P* = .036). The mean defect size in the BMAC group was 1.1 (0.5–4.7) cm, versus 0.9 (0.4–7.3) cm in the ICBG group (*P* = .22). There were significantly more hypertrophic nonunions in the BMAC group (62% vs 32%) compared to the ICBG group. Four patients received prior nonunion repair before receiving a graft (2 in each group).

Nonunion healing occurred in 75% and 78% of BMAC and ICBG cases, respectively (*P* = .8) (Table 3). Among the BMAC treatment failures (n = 5), 3 received revision surgery, 1 refused revision surgery, and 1 failed based on FDA criteria. Among the ICBG treatment failures (n = 5), all received revision surgery. There were 6 lost to follow-up in the BMAC group and 2 in the ICBG group.

There was no statistically significant difference between groups for either infection or implant failure (Table 4). Subanalysis by anatomic region showed treatment success was greatest in the femur, without any statistical significance (*P* > .3) (Table 3). All humeral nonunions, 74% of femurs, and 50% of tibias had a plate as a final implant, and the remaining nonunions received a nail. There was no statistically significant difference between the ICBG and BMAC groups for femur/tibia cases treated with a plate vs. nail (*P* = .839). For potential causes of nonunion, 7 had hypovitaminosis D: 3 (12%) in the BMAC group and 4 (16%) in the ICBG group (*P* = .6). While small numbers precluded formal analysis by nonunion type, 75% (12/16) of hypertrophic nonunions in the BMAC group healed, and 88% (7/8) of hypertrophic nonunions in the ICBG group healed.

Patients with associated infections, either prior to or following repair, were statistically significantly higher in the failure group versus the success group (Table 5). Eight patients (BMAC = 3 and ICBG = 5) went on to receive repeat nonunion repairs. Following revision surgery, 2 patients in the BMAC and 4 patients in the ICBG group achieved bony union.

Table 4

Complications data relative to initial nonunion graft repair.

	BMAC (n = 26) n (%)	ICBG (n = 25) n (%)	P value
Prior to nonunion repair*:			
Implant failure	4 (15)	3 (12)	.7
Infection	6 (23)	2 (8)	.2
Postnonunion repair:			
Implant failure	5 (19)	5 (20)	.9
Infection	1 (4)	2 (8)	.6

* Complication was at least a partial cause for the nonunion.

Table 5

Index injury and postnonunion repair complication's effect on failure.

	Success (n = 33) n (%)	Failure (n = 10) n (%)	P value
Largest cortical defect, cm	1.0 (—)	0.81 (—)	.8
Open fracture	12 (36)	5 (50)	.4
Fasciotomy	1 (3)	1 (10)	.4
Flap coverage	3 (9)	2 (20)	.6
Vascular Injury	4 (12)	1 (10)	1.0
Infected nonunion repair	4 (12)	4 (40)	.05*
Infection post-repair	0 (0)	3 (30)	.01*
Implant failure post-repair	3 (9)	7 (70)	<.001*
Final implant (plate)†	24 (73)	6 (60)	.4
Cancellous allograft	20 (61)	6 (60)	1.0
BMP	5 (15)	2 (20)	.7
Strut	3 (9)	1 (10)	1.0

* Statistical significance.
† Dichotomous outcome between either plate or nail for final implant.

A post-hoc noninferiority power analysis was performed to estimate the number of patients that would be needed to complete a prospective study. The union rates of 75% for BMAC and 78% for ICBG and a margin for statistical/clinical importance of 10% were used. Planned equal sample sizes, power of 80%, and alpha of 0.05 were assumed. This yielded a sample size of 132 for each cohort. Presuming a loss to follow-up rate of 20%, the number needed for a prospective study would be 160 in each cohort.

4. Discussion

Current evidence supports ICBG as the gold standard for autograft despite the potential disadvantages of donor site morbidity and limited harvest volume.[4,6–9] However, BMAC has been increasingly utilized despite lack of high level evidence comparing its efficacy to ICBG. BMAC is an attractive alternative due to its minimally invasive approach, ability to combine the aspirate with various forms of allograft (increasing the amount of graft available for use), and providing osteogenesis, osteoinduction, and osteoconduction to a nonunion site.[5,7,10–12] In this study, treatment success in nonunion repair was also compared between ICBG and BMAC. These 2 modalities resulted in similar overall rates of union.

Major and minor complications following ICBG harvest range as high as 25% and 39%, respectively,[23,24] although some studies have also reported lower rates.[25] Pain at the donor site is the most frequent complaint, and can last up to 2 years postoperatively.[26] Multiple options other than ICBG exist, including other cancellous sources, reamer/irrigator/aspirator bone graft, demineralized bone matrix, recombinant human bone morphogenetic protein-2 (rhBMP2), and BMAC.[27,28] Flierl et al[6] retrospectively compared the time to union and rate of revision following nonunion repair with autograft, allograft, a combination of autograft/allograft, and rhBMP2. They observed that surgical revision was lower in the autograft group (17.1%) than in the allograft group (47.4%).[6] Furthermore, the autograft group had a statistically significant shorter time to union than the allograft group.[6] However, the autograft group consisted of patients receiving ICBG, RIA, and other forms of graft.[6]

While autograft is preferred over allograft in the treatment of nonunions, some studies compared the union rates between the gold standard (ICBG) and other graft options. A recent retrospective study compared rhBMP2 to ICBG and found no statistical difference in the rates of healing between the 2 groups

(68.4% vs 85.1%).[29] Dawson et al[30] compared ICBG to RIA and found similar union rates at 86% and 82% respectively. They also noted that RIA had lower donor site pain scores than ICBG. Our study has comparable union rates to these previous studies. Additionally, multiple patients who were showing signs of clinical and radiographic union in as little as 2 months did not return after the second appointment and were lost to follow-up.

BMAC injected percutaneously has been described as an option for tibial nonunions and delayed unions.[15] In a retrospective series, Desai et al[31] analyzed the efficacy of using percutaneous BMAC with an osteoinductive agent, DBM, or rhBPM-2. They found an overall healing rate of 79.6% in 4.7 months. However, the rate of healing for the DBM compared to rhBMP-2 was 86.4% and 70.8%, respectively (P=.036).[31] To our knowledge union rates with a BMAC and allograft mixture for larger defects have not been published. Our study showed comparable union rates between ICBG and BMAC overall, which is encouraging for further study of the use of BMAC in the treatment of nonunion repair. There was no significance when comparing the 3 separate long bones, though these subgroups were small. A difference of 25% and 30% between the 2 cohorts for the femur and tibia, respectively, in a larger series would likely be statistically significant. However, we had comparable results to other techniques using BMAC and 2 different osteoinductive agents. This is supported by the statistically significant shorter time to union in the BMAC group when only treatment successes were included. The only factor that influenced the primary outcome of union was infection, both prior to repair or following repair. This suggested that reducing postoperative complications was more influential to successful treatment than the characteristics of the initial injury.

The limitations in this study include the retrospective design, which potentiates selection bias. Also, the combined analysis of multiple long bone nonunions (femur, tibia, and humerus) made subanalysis and more granular outcomes more difficult. However, nonunions represent a relatively rare event, and combining long bone nonunions enhances the ability to detect differences in union rates between ICBG and BMAC cohorts. Most nonunion literature is comprised of heterogeneity due to this reason. Similarly, the overall nonunion population is very heterogenous in terms of defect size and shape (e.g., circumferential defect versus near contact on 1 or more planes) and in this retrospective study with relatively small sample size, stratified analysis by strict groupings based on size or shape of defect are unfeasible and our study population is thus heterogenous. In addition, there was a larger proportion of hypertrophic nonunions in the BMAC group, which may have acted as a confounder for success given that hypertrophic nonunions generally have biologically viable bone ends compared to atrophic or oligotrophic nonunions. However, all of these nonunions had a gap, given the inclusion criteria, and no literature clearly indicates that hypertrophic nonunions heal more predictably than oligotrophic or atrophic nonunions. There was also a difference amongst ancillary treatment (BMP, cancellous allograft, and strut) used between the 2-cohorts. This limitation was due to the retrospective nature of the study, as these treatments were used at the discretion of each attending surgeon, but this allows comparison of the BMAC/allograft group to a real-life cohort in which nonunion treatment is highly individualized. An ideal study would have robust subgroup analysis or matched cohorts based on various patient factors (diabetes, smoking status, other medical comorbidities), anatomic factors (bone involved, metaphysis versus diaphysis, subgroup-

ings of defect size, or nonunion type), as well as surgical technique factors (compression plating versus exchange nailing, etc.). Further prospective studies should consider using a more standardized protocol to minimize these potential confounders. Though our study is limited to a single center, limiting generalizability, 3 different fellowship-trained orthopaedic traumatologists contributed to the patient cohort, adding heterogeneity to treatment management. While the study was limited to a small sample size, the results are encouraging and provide support for conducting a prospective multicenter study to look at patient outcomes, cost, donor site morbidity, and surgical time/efficiency between various types of autograft.

In conclusion, the use of BMAC or ICBG for nonunion repair in long bones did not demonstrate statistically different rates of treatment success. BMAC mixed with allograft led to healing in 75% of nonunions. In the present cohorts, infection was related to a higher rate of treatment failure. Given other considerations such as operative time and patient factors, BMAC mixed with allograft may be a preferable alternative in the management of nonunions with cortical gaps.

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