Clinical Research on Foot & Ankle

ISSN: 2329-910X

Research Article Open Access

A Retrospective Comparison of Clinical and Patient-Reported Outcomes in Foot and Ankle Arthrodesis Procedures Using Two Cellular Bone Allografts

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Abstract

Objective: The purpose of this retrospective study was to compare clinical and patient-reported outcomes following foot and ankle arthrodesis (FAA) procedures using two cellular bone allografts containing viable lineage-committed bone forming cells (V-CBA) versus mesenchymal stem cells (T-CBA), each within an osteoconductive matrix mixed with demineralized bone.

Methods: A total of 47 consecutive patients underwent foot and ankle arthrodesis procedures: 31 patients received V-CBA and 16 patients received T-CBA. Baseline characteristics were summarized. Clinical (rates of ankle and subtalar [when applicable] fusion at 6 months and rates of complications) and patient-reported outcomes (satisfaction, and pre- and postsurgical visual analog scale [VAS] for pain) were compared between the two grafts.

Results: The use of V-CBA led to significantly higher rates of ankle fusion at 6 months (100% *vs*. 50.00%; $P<0.0001$), equitable subtalar fusion rates (89.29% *vs* 71.43%, ns), and significantly fewer complications (6.45% *vs* 62.50%; $P<0.0001$), in spite of patient comorbidities and lifestyle characteristics that would be expected to negatively affect such outcomes. Additionally, all of the patients who received V-CBA were satisfied with their postsurgical outcomes (versus a significantly lower 68.75% in the T-CBA group; $P=0.0028$), and they reported a significantly lower average postsurgical VAS of 1.40 points (a reduction of 7.52 points from presurgical), compared with 3.15 points in the T-CBA group (4.84-point reduction; $P=0.0099$).

Conclusion: Clinical and patient-reported outcomes were significantly improved following the use of V-CBA versus T-CBA, except for subtalar fusion rates, which were equitable. The results of this study support preclinical findings suggesting that viable lineage-committed bone cells may be a more suitable choice for enhancing bone fusion compared to MSCs, and suggest that V-CBA in FAA procedures can result in early fusion with minimal complications, less influence from relevant comorbidities and lifestyle risks, and more successful clinical and patient-reported outcomes.

Keywords: Cellular bone allograft; CBA; Foot and ankle arthrodesis; FAA; Mesenchymal stem cells; MSC; Outcomes; Trinity; ViviGen

Introduction

Since the 1990s, the use of foot and ankle arthrodesis (FAA) procedures has risen rapidly in the US for the correction of debilitating arthritis, instability, poor alignment, and pain [1,2]. Several FAA procedures have been described in the literature [3-10], and it remains the consistently preferred treatment in many cases, particularly in patients with extensive preoperative comorbidities [11]. The most common complication following FAA is nonunion, with reported rates varying from 2% to 40% [12,13]. Nonunions often lead to revision surgeries, which are typically more invasive procedures. These revision surgeries frequently require a longer time to achieve fusion compared to primary arthrodesis and are subject to additional complexity, including removal of previous hardware, permanent bracing, or gait aides [13]. Delayed union following primary or revision FAA extend the patient's non weight-bearing immobilization time and increase the likelihood of excessive motion at the fusion site, with subsequent erosion, bone loss, and sclerosis. In such cases, the additional surgery to treat the delayed union is associated with less predictable outcomes [7]. Taken together, complications from non- and delayed unions translate to increased medical care costs, both direct (eg, additional procedure and product costs, extended operating and anesthésia time) and indirect (eg, loss of income and benefits, decreased social and family time, reduced quality of life). Therefore, enhancing fusion speed and quality are especially important for improving FAA clinical outcomes.

Generally, successful bone fusion requires three critical factors: Osteoconductivity, osteoinductivity, and osteogenicity, such as found in healthy autograft [14]. Although autograft bone has been the historically preferred graft source, its supply is inherently limited and the procedure increases operative time, blood loss, risk of infection, and post-operative pain [15]. Cellular bone allografts (CBAs) have emerged as an alternative grafting material that is capable of providing all three critical factors, but without the inherent drawbacks of autografts [16]. The most widely available CBAs are purported to contain adult mesenchymal stem cells (MSCs) with osteogenic potential and osteoconductive and osteoinductive bone allograft material (such as Trinity Evolution®

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Received August 21, 2020; **Accepted** September 14, 2020; **Published** September 28, 2020

Citation: Roukis TS, Wetzell B, McLean JB, Dorsch K, Moore MA (2020) A Retrospective Comparison of Clinical and Patient-Reported Outcomes in Foot and Ankle Arthrodesis Procedures Using Two Cellular Bone Allografts. Clin Res Foot Ankle 8: 300.

and Trinity Elite®; T-CBA; MTF Biologics, Edison NJ). However, while MSCs may differentiate into bone-forming osteoblasts given enough time and a precise microenvironment, they may also differentiate into other, unwanted cell types (eg, adipocytes, myocytes, neurons), potentially impeding the speed and quality of fusion.

To address this uncertainty, a more advanced CBA (ViviGen® and ViviGen Formable®; V-CBA; LifeNet Health®, Virginia Beach VA) was uniquely developed to contain viable lineage-committed bone-forming cells within a cortico-cancellous bone matrix (ie, osteoconductive and osteogenic components), as well as demineralized bone matrix (DBM; ie, osteoinductive component) [7,10]. Preclinical comparisons suggest that bone cells outperform MSCs, both in speed and quality of bone deposition [17,18]. Although examples of the successful use of V-CBA in FAA procedures have been described in the literature previously [7,10], there have been no direct comparisons to date between the more conventional MSC based CBAs and V-CBA. Thus, the purpose of this retrospective study was to compare clinical and patient reported outcomes following the use of V-CBA versus T-CBA in FAA procedures with and without subtalar arthrodesis.

Methods

This was a retrospective study of de-identified data from consecutive cases involving FAA procedures with and without subtalar arthrodesis, performed by the first author (TSR) at a hospital-based practice from February 2011 to December 2019. Data were manually isolated into two groups: Cases using V-CBA versus cases using T-CBA. Cases in which neither CBA was used were excluded. The protocol for this study was submitted to, and approved by, the first author's institutional review board.

Baseline patient and procedure characteristics that were assessed included age; sex; race; incidences of obesity (defined as body mass index ≥ 30 kg/m^2), tobacco use, concomitant medication use relevant to bone fusion (eg: NSAIDs, corticosteroids, proton pump inhibitors), and Charlson comorbidities; and primary indications for surgery. Charlson comorbidity index (CCI) scores were calculated for each patient and summarized for each group (ie, V-CBA or T-CBA) [19]. Continuous variables were summarized as means and standard deviations (SDs) and categorical variables were summarized as numbers and percentages of patients within each group.

Clinical outcomes that were assessed included incidences of ankle fusion at 6 months (defined as osseous union on multiple weight-bearing ankle and hindfoot radiographs), subtalar joint fusion at 6 months (when applicable), and post-surgical complications (i.e., hardware failure, nonunion, deep infection, and subsequent below-knee amputation). Patient reported outcomes that were assessed included overall satisfaction (verbally indicated by the patient as "satisfied" upon query during follow up), and pre- and postsurgical pain ratings using the Visual Analog Scale (VAS) [20]. Incidences of fusion, complications, and satisfaction were presented as numbers and percentages of patients within each group and comparisons between groups were conducted using Fisher's exact test. Pre-and postsurgical VAS ratings were presented as means and standard error of the mean (SEM) and compared between groups using two-sided T-tests.

Statistical analyses were performed using Prism (Version 8.3.0; GraphPad Software; San Diego CA; www.graphpad.com), and statistical significance was assessed at the 0.05 alpha level.

Results

The data-selection flow-chart for this study is presented in Figure 1. A total of 94 consecutive patients were assessed for inclusion, of whom 46 patients did not receive V-CBA or T-CBA and were subsequently excluded from analysis. Outcome data were not available for 1 patient receiving V-CBA, who was also excluded. The final analysis included 47 patients: 31 patients received V-CBA and 16 patients received T-CBA. Among V-CBA patients, 30 patients received ViviGen, 1 patient received ViviGen Formable, and adjunct use of ConformFlex® DBM (MTF Biologics, Edison NJ) was reported for 4 patients. Among T-CBA patients, 5 patients received Trinity Evolution, 11 patients received Trinity Elite, and adjunct use of Vitoss BB Trauma® synthetic bone graft (Stryker, Kalamazoo MI) was reported for 2 patients.

The distributions of baseline patient and procedure characteristics are presented in Table 1. Although statistical comparisons were not conducted, the mean ages and distributions of sex and race appeared, at face value, to be similar between the groups, as did the incidence of obesity and relevant concomitant medications. The T-CBA group had a higher percentage of tobacco users compared to the V-CBA group (25.00% *vs*. 16.13%, respectively). Mean CCIs were similar between the groups (V-CBA=1.87, T-CBA=1.81); however, the V-CBA group had a higher incidence of chronic obstructive pulmonary disorder (29.03% *vs*. 18.75%). Further, while the T-CBA group had a higher incidence of diabetes with chronic complications (31.25% *vs*. 16.13%), the V-CBA group had a higher incidence of diabetes without chronic complications (12.90% *vs*. 6.25%). Finally, regarding primary indications for surgery, more T-CBA patients were seen for primary degenerative joint disease (25.00% *vs*. 16.13%) and failed agility total ankle replacement (18.75% *vs*. 6.45%), whereas more V-CBA patients were seen for lateral ankle instability degenerative joint disease (35.48% *vs*. 6.25%).

The clinical outcomes for this study are presented in Figure 2. At 6 months postoperative, ankle fusion was achieved in significantly more V-CBA patients than T-CBA patients (100% *vs*. 50.00%, respectively; $P<0.0001$). Among patients undergoing procedures involving subtalar fusions (V-CBA n=28, T-CBA n=14), the rate of fusion at 6 months was roughly equivalent (V-CBA=89.29%, T-CBA=71.43%; not significant [ns]). Complication rates for the V-CBA group (6.45%) were significantly lower than those observed in the T-CBA group (62.50%; $P<0.0001$). The complications reported in the V-CBA group were hardware failure (n=2), while the complications reported in the T-CBA group were hardware failure (n=2), nonunion unstable (n=2), nonunion fibrous stable (n=5), nonunion ankle (n=7), nonunion subtalar (n=3), deep infection (n=1), and below-knee amputation (n=1) In the T-CBA group, multiple complications were reported for some patients. Additionally, in the T-CBA group, there was no evidence of correlation between the adjunct use of synthetic bone graft in 2 patients and the rates of fusion or complications. Successful ankle fusion at 6 months was reported for only 1 of these 2 patients, subtalar joint fusion was reported for neither, and complications were reported for the patient whose ankle did not fuse (data not shown).

Of the 5 patients in the T-CBA group for whom comorbid diabetes with complications was reported, ankle fusion at 6 months was observed in 3 patients (60.00%), subtalar joint fusion was observed in 4 of 5 applicable patients (80.00%), and complications were reported for 4 patients (80.00%; data not shown). Yet, ankle fusion was observed in all 5 such diabetic patients in the V-CBA group, subtalar joint fusion in 3 of 4 applicable patients (75.00%), and no complications were reported. For the only patient in the T-CBA group with comorbid diabetes without complications, ankle fusion at 6 months was not successful, subtalar joint fusion was observed, and postsurgical complications were reported (data not shown). However, ankle fusion was observed in all 4 such patients in the V-CBA group, subtalar joint fusion was

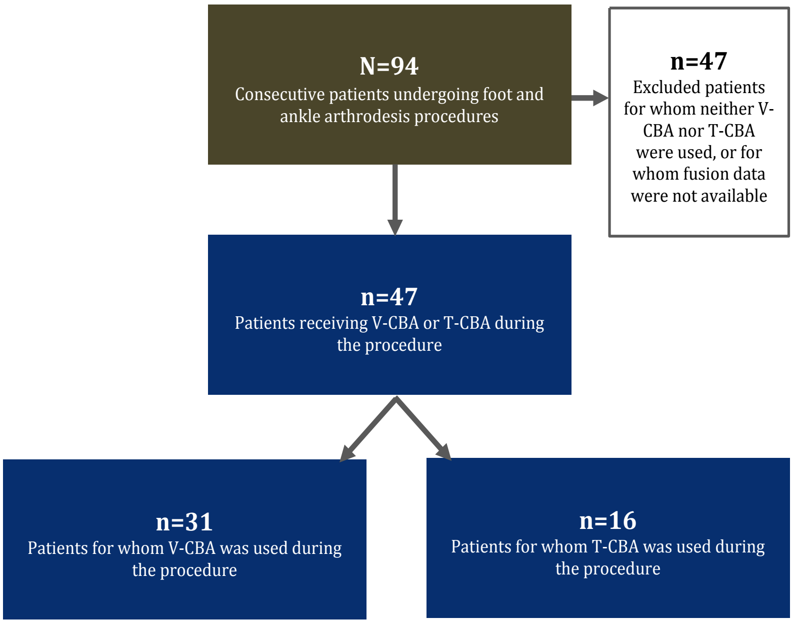

Figure 1: Data-selection flow chart for patients undergoing FAA procedures with and without subtalar arthrodesis using V-CBA or T-CBA from February 2011 to December 2019.

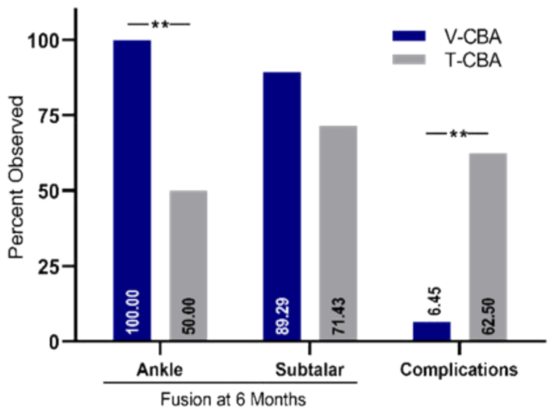

Figure 2: Clinical outcomes. V-CBA n=31, T-CBA n=16. Subtalar joint fusions were applicable to V-CBA n=28 and T-CBA n=14. **P<0.0001, Fisher's exact test.

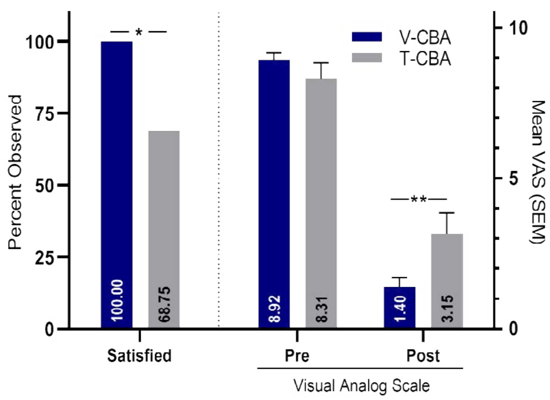

Figure 3: Patient-reported outcomes. V-CBA n=31, T-CBA n=16. Pre-and postoperative VAS were reported by V-CBA n=25 and T-CBA n=13. *P=0.0028, Fisher's exact test. **P=0.0099, two-sided T-test.

Characteristic, unit	Group	
	VCBA (n = 31)	**TCBA (n = 16)**
Age in years, mean (Std. Dev.)	60.48 (10.86)	62.75 (10.38)
Sex, n (%)		
Male	21 (67.74)	13 (81.25)
Female	10 (32.26)	3 (18.75)
Race, n (%)		
White	30 (96.77)	16 (100.0)
Black	1 (3.23)	0 (0.00)
Obesity, n (%)	18 (58.06)	8 (50.00)
Tobacco use, n (%)	5 (16.13)	4 (25.00)
Relevant concomitant medications, n (%)	2 (6.45)	0 (0.00)
Charlson comorbidities, n (%)		
Any malignancy	0 (0.00)	0 (0.00)
Cerebrovascular disease	1 (3.23)	0 (0.00)
Congestive heart failure	1 (3.23)	1 (6.25)
Chronic obstructive pulmonary disorder	9 (29.03)	3 (18.75)
Dementia	1 (3.23)	2 (12.50)
Diabetes with chronic complications	5 (16.13)	5 (31.25)
Diabetes without chronic complications	4 (12.90)	1 (6.25)
Hemiplegia or paraplegia	3 (9.68)	3 (13.04)
HIV/AIDS	0 (0.00)	0 (0.00)
Metastatic solid tumor	0 (0.00)	0 (0.00)
Myocardial infarction	3 (9.68)	2 (12.50)
Mild liver disease	1 (3.23)	0 (0.00)
Moderate or severe liver disease	0 (0.00)	0 (0.00)
Peptic ulcer disease	7 (22.58)	3 (18.75)
Peripheral vascular disease	3 (9.68)	1 (6.25)
Renal disease	6 (19.35)	3 (18.75)
Rheumatic disease	0 (0.00)	0 (0.00)
Charlson comorbidity index, mean (Std. Dev.)	1.87 (1.84)	1.81 (1.72)
Primary indication for surgery, n (%)		
Primary degenerative joint disease	5 (16.13)	4 (25.00)
Posttraumatic degenerative joint disease	1 (3.23)	1 (6.25)
Lateral ankle instability degenerative joint disease	11 (35.48)	1 (6.25)
Charcot FA for Chopart Amputation	2 (6.45)	0 (0.00)
Neuromuscular deformity/dropfoot	5 (16.13)	3 (18.75)
Talar avascular necrosis	2 (6.45)	2 (12.50)
Tibial avascular necrosis	1 (3.23)	0 (0.00)
Failed agility total ankle replacement	2 (6.45)	3 (18.75)
Revision ankle arthrodesis	1 (3.23)	1 (6.25)
Ankle fracture complication/infection	1 (3.23)	1 (6.25)

Table 1: Baseline patient and procedure characteristics.

successful in 3 of 4 applicable patients (75.00%), and no complications were reported. Among tobacco users, 2 of 4 patients (50.00%) receiving T-CBA had ankle fusion at 6 months; however, successful ankle fusion was reported for all 5 such patients receiving V-CBA (data not shown).

The patient-reported outcomes for this study are presented in Figure 3. A significantly higher proportion of V-CBA patients (100.00%) reported satisfaction with the outcomes of their surgeries than T-CBA patients (68.75%; P=0.0028). Among patients for whom VAS were reported (V-CBA n=25, T-CBA n=13), although there was no significant difference in mean VAS between the groups prior to surgery (V-CBA=8.92, T-CBA=8.31; ns), the postsurgical mean VAS in V-CBA patients (1.40, mean decrease of 7.52) was significantly lower than in T-CBA patients (3.15 [P=0.0099], mean decrease of 5.15).

Discussion

The purpose of this study was to retrospectively compare clinical and patient-reported outcomes following the use of V-CBA versus the MSC-based T-CBA in FAA procedures with and without subtalar arthrodesis. This was the first known study to directly compare outcomes following the use of these two CBA options in such procedures. Successful fusion can be challenging to achieve in FAA procedures, which are known to have high rates of non- and delayed union, as well as numerous complications. Therefore, graft options that can demonstrably achieve early fusion with minimal complications are important for reducing cost and enhancing clinical and patient-reported outcomes.

The present results suggest that the use of V-CBA in FAA procedures is more effective than T-CBA, leading to significantly higher ankle fusion rates at 6 months (100.00% *vs* 50.00%), equitable subtalar fusion rates (89.29% *vs*. 71.43%), and significantly fewer complications (6.45% *vs* 62.50%), in spite of patient comorbidities and lifestyle characteristics that would be expected to negatively affect such outcomes. Additionally, 100.00% of patients who received V-CBA were satisfied with their postsurgical outcomes (versus a significantly lower proportion of 68.75% in the T-CBA group), and they reported a significantly lower average postsurgical VAS of 1.40 (a 7.52-reduction from presurgical), compared with 3.15 in the T-CBA group (a 4.84 point reduction).

There are few reports of fusion rates in FAA procedures using V-CBA; however, for T-CBA and other widely available MSC-based CBAs, the present results are similar to those reported in the literature. In a prospective study by Jones et al, FAA procedures using T-CBA in 92 patients resulted in a fusion rate of 68.5% at 6 months postoperative, and 71.1% in 76 patients at 12 months [21]. It was further reported that when comorbidities were considered, there was no significant difference between high-risk patients and lower risk patients, except for smokers, who had a statistically significant risk of nonunion. Tobacco use is cited as one of the greatest lifestyle risks for delayed and nonunion [22,23], and only 2 of 4 tobacco-users (50.0%) receiving T-CBA in the present study had ankle fusion at 6 months. However, successful ankle fusion was reported for all 5 tobacco using patients receiving V-CBA.

Further, a retrospective study by Loveland and colleagues reported a higher fusion rate of 93.3% at 12 months in 70 patients following FAA procedures using T-CBA [24]. However, in another study by Dekker et al. the authors found that 23 patients, 74.0% of whom had a least one high risk factor, had a fusion rate of 82.6% at a mean follow up of 15 months with another MSC-based CBA (MAP3®, RTI Biologics, Marquette, MI) [25]. Interestingly, the authors in that study reported fusion in only 25.0% of patients with diabetes. A subsequent study by the same authors using the same CBA found an 83.0% fusion rate in 36 high-risk patients at a mean follow-up of 13 months, with only 33.0% of diabetic patients achieving fusion [26].

In the present study, of the 5 patients with comorbid diabetes with complications in the T-CBA group, ankle fusion at 6 months was observed in 60.0% of patients and complications were reported in 80.0%. In contrast, ankle fusion was observed in all 5 such diabetic patients in the V-CBA group and no complications were reported. For the only patient with comorbid diabetes without complications in the T-CBA group, ankle fusion at 6 months was not successful and complications were reported. However, ankle fusion was observed in all 4 such diabetic patients in the V-CBA group and no complications were reported. Thus, while the present results are in line with most other reports of T-CBA and other MSC-based CBAs used in FAA procedures, the use of V-CBA in the present study consistently resulted in notably higher fusion rates with fewer complications, despite the presence of relevant comorbidities and lifestyle risks.

Finally, the complications reported for the V-CBA group in this study were restricted to hardware-related failures and were thus presumably unrelated to the choice of graft. In contrast, the complications reported for the T-CBA group represented a wider breadth of nonunion, a deep infection, and a below-knee amputation. While it is not possible to infer that these complications are a direct result of graft choice, their absence in the greater number of cases involving V-CBA is notable.

Limitations of this study include the relatively small sample size per group, which likely contributed to the perfect fusion rate in the V-CBA group. While this specific result should not be assumed to generalize, other clinical reports likewise support a high rate of fusion with V-CBA [7,10,27,28]. Nonetheless, more work is needed to establish a true average fusion rate for V-CBA. Next, this study reflects the work of only one surgeon at a single center, and fusion status in this study was determined by the surgeon. However, given its retrospective nature, these assessments were made as part of the surgeon's regular practice prior to study planning and are thus less subject to bias. Further, fusion in this study was assessed by radiograph alone, rather than by computed tomography (CT) scan. The surgeon's standard practice is to assess cases of non-obvious union via sagittal plane stress weight-bearing radiographs in maximum dorsiflexion/plantar flexion to identify any motion between the tibia and talus, or talus and calcaneus, thus obviating the need for regular, more expensive, CT scans in all patients. Other limitations include that a variety of retrograde intramedullary nails were used during this study, which may have influenced some outcomes in individual cases. However, the selection of the most appropriate form of fixation for each case was independent of graft choice and based solely on the patient's anatomy and structural needs. Thus, any potential effects of this variation should distribute across the V-CBA and T-CBA groups and exert minimal influence on comparisons between them. Lastly, the procedures in this study were conducted over a nearly 9-year span, during which time some fixation systems became unavailable and were replaced with newer systems. Application of any new technology would be expected to result in a learning curve, which could contribute to individual hardware failures and nonunion. Yet, no temporal trends in the rate of nonunion were observed in this study (data not shown), suggesting that application of newer fixation systems over time did not influence the present results. In spite of these limitations, the present study makes an important contribution to our knowledge of clinical and patient-reported outcomes with more conventional MSC-based CBAs versus V-CBA, and provide clinical support for preclinical findings that bone-forming cells are more ideal than MSCs for promoting successful fusion.

Conclusion

In this retrospective comparison of V-CBA versus T-CBA in 47 patients undergoing FAA procedures with and without subtalar arthrodesis, V-CBA resulted in significantly higher fusion rates and lower rates of complications, which appeared unaffected by relevant comorbidities and lifestyle risks. In addition, patients receiving V-CBA were significantly more likely to report satisfaction with their surgical outcomes, with a greater reduction in postsurgical VAS versus T-CBA. The results of this study support preclinical findings that viable lineage-committed bone cells may be a more suitable choice for enhancing bone fusion compared to MSCs, and suggest that V-CBA in FAA procedures can result in early fusion with minimal complications, less influence from relevant comorbidities and lifestyle risks, and more successful clinical and patient-reported outcomes.

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