EC ORTHOPAEDICS
Research Article

Allograft Bone as an Alternative to Autograft in Foot and Ankle Arthrodesis and Nonunion Repair

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Received: February 27, 2019; **Published:** March 27, 2019

Abstract

Bone graft augmentation for arthrodesis and nonunion repair is common in foot and ankle surgery. Autograft serves as the gold standard for bone graft material because it has osteoconductive, osteoinductive, and osteogenic properties, ideal for increasing healing potential. However, autograft harvesting can be associated with significant donor-site morbidity and other related complications. Therefore, the present retrospective study evaluated the efficacy of an allogenic cancellous/cortical/periosteal cellular bone matrix with mesenchymal stem cells and angiogenic growth factors. The population consisted of 34 patients and 35 procedures with varied comorbidities that historically have increased risk of delayed union or nonunion. Age, body mass index, diabetes, and nicotine use were evaluated as potential risk factors. In addition, many of the included patients were injured while at work which has been shown as a risk factor leading to suboptimal outcomes and delayed healing times in prior studies. Radiographic consolidation at the fracture or fusion site was reviewed at regular intervals until healing was confirmed. The retrospective study indicated that allograft bone, particularly an allograft with mesenchymal stem cells, has the potential to produce successful consolidation and high union rates when applied to foot and ankle arthrodesis and nonunion repair. Overall 34/35 (97.1%) procedures successfully progressed to full osseous consolidation at the fracture or arthrodesis site. The use of allograft is an effective way to achieve high union rates and can be used as an alternative to autograft.

Level of Evidence: IV.

Keywords: *Bone Healing; Fusion; Bone Graft Augmentation; Workers Compensation*

Introduction

Bone graft augmentation for arthrodesis and nonunion repair is a common treatment modality reported in the literature for foot and ankle surgery. In a systematic review evaluating union rates with the use of different graft materials in foot and ankle surgery, the nonunion rate when no graft material was utilized was 10% [1]. The gold standard for bone graft material is autograft, which has osteoconductive, osteoinductive, and osteogenic properties, ideal for increasing healing potential [1]. However, autograft harvesting can be associated with significant donor-site morbidity, limited graft volume availability, and other related complications.

Given the known potential complications of autograft; allografts have emerged as a reproducible tool to achieve a high union rate. Advancements in research and processing methods have significantly improved the quality of allograft alternatives. Today many allograft products are used in foot and ankle surgery to fill bone voids and facilitate high union rates [2,3]. Recombinant human bone morphogenetic protein (BMP), allograft viable mesenchymal stem cells (MSCs) and other growth factors have become added elements to many allograft compositions. BMPs provide allograft with osteoinductive potential which has been shown to be effective in the treatment of nonunion repair, segmental defects, and long bone fractures [2,3]. MSCs provide osteoconductive, osteoinductive, and osteogenic properties to an allograft, which allows for improved results [4]. Rush., *et al.* reported on 23 patients that underwent mesenchymal allograft implantation for revisional foot and ankle surgeries and showed a union rate of 91.3% lending credence to the use of mesenchymal stem cell allografts in foot and ankle surgery [4].

The present study evaluates the efficacy of an allograft bone matrix composed of periosteal, cancellous, and cortical bone chips (Bio4, Stryker, Kalamazoo, MI). This allograft contains vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), endogenous bone supportive growth factors (including BMPs), and mesenchymal stem cell markers CD105 and CD166. These markers ensure that there are significant numbers of viable MSCs. PDGF has preangiogenic properties and can mobilize MSCs to promote early phases of bone healing and blood vessel formation [5]. Retaining the periosteum maintains a higher concentration of VEGF, which promotes angiogenesis by vascular ingrowth and therefore aids in bone healing [6]. Street., *et al.* showed fracture healing was improved with exogenous VEGF application [7].

This retrospective study reports on the results from 35 surgical procedures, including 34 patients that underwent foot and ankle arthrodesis or revision nonunion repair and the procedure was augmented with allograft containing viable cellular bone matrix. The clinical and radiographic results, as well as potential complicating factors and co-morbidities were evaluated. The purpose of the study was to present the union rate when allograft bone was used as an adjunct to bone healing.

Patients and Methods

A retrospective review of medical records and digital radiographs was undertaken for patients that underwent consecutive midfoot/hindfoot/ankle joint arthrodesis surgery or revision nonunion repair procedures with the use of the allograft material between August, 2015 and March, 2018. Approval for the study was granted by the Jersey Shore University Medical Center institutional review board. All surgeries were performed by a single board certified surgeon (SH). The pertinent patient data included: age, gender, number of days from surgical procedure to radiographic union, body mass index (BMI), tobacco use (active, former, or never), diagnosis of diabetes mellitus (DM), and work-related injury (workmen's compensation insurance (WCI)). Inclusion criteria included use of the allograft in arthrodesis of the ankle joint, subtalar joint, calcaneocuboid joint, talonavicular joint, naviculocuneiform joints, tarsometatarsal joints, and non-union sites. All 34 patients that met the inclusion criteria were consecutive in nature. The patients included in the study must have completed follow up from the time of surgery to radiographic union and into pre-operative shoe gear. Successful fusion or union on radiographic inspection was defined using criteria preciously described by Rush., *et al.* [3]: bony trebeculation across the joint, total obliteration of the joint line, no notable joint lucency or marginal joint sclerosis, and no failure of internal fixation or external fixation. Consolidation across the fusion site on plain radiographs was confirmed in three different views and across four cortices. Radiographs were obtained post-operatively at the first post-operative visit, 4 weeks, 6 weeks, 8 weeks, 12 weeks, and at regular intervals beyond 12 weeks, until full union or nonunion was confirmed. Failed union was defined as widening, lucency, or lack of trabecular bridging across the arthrodesis, and/or failed hardware. In one patient a computed tomography (CT) scan was obtained to further assess for union, as the radiographs were equivocal. The radiographs were independently and retrospectively reviewed by the authors to determine bony consolidation. Exclusion criteria included a lack of sufficient follow-up and Charcot neuroarthropathy. Delayed union was defined as lack of bony consolidation at 3 months, nonunion was defined as no radiographic progression of healing from 3 to 6 months post-operatively. After application of the inclusion and exclusion criteria, we reviewed a total of 34 patients and 35 lower extremity procedures; including one patient who required a revision surgery in the setting of a nonunion, this patient successfully went onto fusion.

Surgical technique

A single board-certified reconstructive foot and ankle surgeon (SH) performed all procedures in the study. A bone allograft material, as previously described, was utilized in every patient enrolled in the study. For all procedures, an incision was made and careful dissection was performed down to the joint or nonunion site. When performing a joint arthrodesis, the surgical technique for preparation of the joint included denuding the cartilaginous surfaces with a combination of a powered osteotome, curettes, and a sagittal saw. The subchondral plate was drilled and fenestrated until bleeding bone was seen. The consistent allograft preparation technique involved placing the sterile container in warm sterile saline for 10 minutes until the contents were sufficiently thawed. The allograft, a moldable cancellous chip consistency with attached periosteum, was placed into the joint or nonunion site. Careful attention was taken to not over pack the site. The joint or nonunion was reduced and fixated once the graft was carefully packed and tamped into the site. Subsequent internal fixation was used; the type of hardware (screws, plates, and intramedullary rods) varied by type of arthrodesis. Figures 1 and 2 demonstrate examples of the internal fixation that was utilized.

Figure 1: *Pre-operative lateral radiograph showing degenerative changes and equinus deformity to the ankle and subtalar joint after open subtalar and closed ankle dislocation. Post-operative lateral radiograph showing successful arthrodesis across the ankle and subtalar joint.*

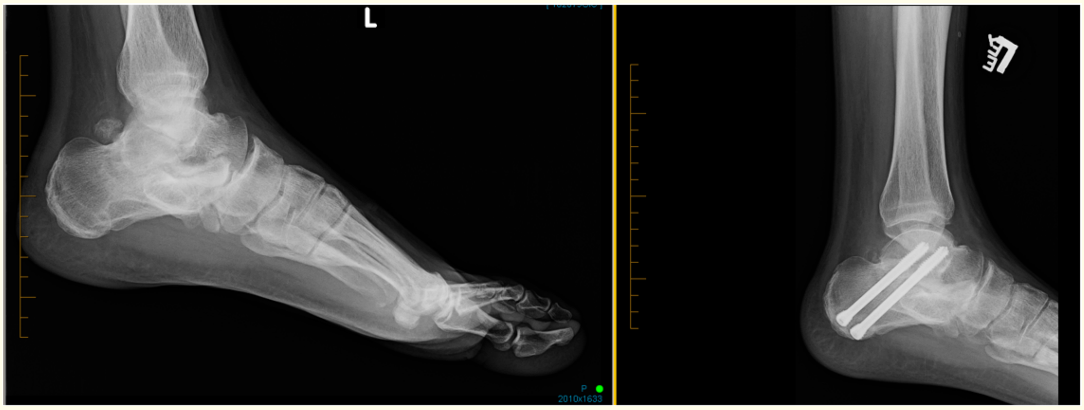

Figure 2: *Pre-operative lateral radiograph showing arthritic changes at subtalar joint following nonoperative treatment of calcaneal fracture. Post-operative lateral radiograph showing successful arthrodesis across the subtalar joint.*

Results

The data was collected and statistical evaluation was performed utilizing the Wilcoxon Rank Sum test, the Fisher Exact test, and the Kruskal-Wallis test. Statistical significance was defined at the 5% ($P \leq 0.05$) level. The demographic data of the patient cohort is depicted in table 1. There were 34 patients in the cohort (n = 34) and 35 procedures (s = 35) were performed. Nineteen patients and 19 surgeries were performed on patients with WCI, the rest of the cohort were patients with standard commercial insurance. The average age of the full patient cohort was 47.9 years old. The minimum age was 27 and the oldest was 70 years old. Comparing the patients with and without

WCI, the difference in age was approaching statistical significance (p=0.06). The average age of patients in the study with WCI was 43.5 years. The average age of patients without WCI was 51.3 years. The full patient cohort was comprised of 22 (64.7%) males and 12 (35.3%) females. Other patient variables that were evaluated were BMI, tobacco use, and DM. The overall average BMI was 29.9 ± 6.5. The average BMI among patients with WCI was 28.9 ± 3.8. The average BMI among patients without WCI was 30.1 ± 8.1, this was not statistically different (p = 0.65). There were 10 (29.4%) current smokers at the time of surgery in the overall group, 4 (11.8%) were former smokers, and 20 (58.8%) had never smoked. There was no statistical difference among patients with and without WCI in regards to tobacco use (p = 0.39). Overall, 6 (17.6%) patients had DM and 28 (82.4%) did not. There was no statistical difference among the insurance groups in regards to DM history (p = 1.0).

	Full Patient Cohort (n = 34; s = 35)	Standard Commercial Insurance (n = 19, s = 19)	Workmen's Compensation Insurance (n = 15, s = 16)	
Age at Time of Surgery (Years)	n = 34	n = 19	n = 15	Wilcoxon Rank Sum Test: p = 0.06
Min	27	29	27	Not Significantly Different
Max	70	70	66	Approaching Statistical Significance
Mean ± SD	47.9 ± 11.7	51.3 ± 10.7	43.5 ± 11.8	
Median [Q1, Q3]	47.5 [38.5, 57.8]	57.0 [42.5, 59.0]	41.0 [35.0, 53.0]	
Gender	n = 34	n = 19	n = 15	
Male	22 (64.7%)	10 (52.6%)	12 (80%)	
Female	12 (35.3%)	9 (47.4%)	3 (20%)	
BMI at Time of Surgery	n = 34	n = 19	n = 15	Wilcoxon Rank Sum Test: p = 0.65
Min	20.5	20.5	21.1	Not Significantly Different
Max	54.6	54.6	33.7	
Mean ± SD	29.9 ± 6.5	30.1 ± 8.1	28.9 ± 3.8	
Median [Q1, Q3]	28.6 [26.7, 31.8]	28.3 [25.7, 31.5]	29.1 [27.4, 31.8]	
Smoking Status	n = 34	n = 19	n = 15	Wilcoxon Rank Sum Test: p = 0.39
Never Smoked	20 (58.8%)	10 (52.6%)	10 (66.7%)	Not Significantly Different
Prior Smoker	4 (11.8%)	2 (10.5%)	2 (13.3%)	
Current Smoker	10 (29.4%)	7 (36.9%)	3 (20.0%)	
Diabetes Status	n = 34	n = 19	n = 15	Fisher Exact Test: p = 1.0
No	28 (82.4%)	16 (84.2%)	12 (80.0%)	Not Significantly Different
Yes	6 (17.6%)	3 (15.8%)	3 (20.0%)	

Table 1: *Patient demographics.*

All 34 patients were followed until union at the arthrodesis or nonunion site was obtained. The overall average time to union was 70.4 ± 25.5 days. Among patients with WCI, the average time to union was 65.1 ± 24.5 days. The average time to union was 74.6 ± 26.2 days in patients with nonwork related issues. All patients were followed until they returned to regular shoe gear. The overall average return to shoe gear was 84.2 ± 22.0 days; patients with WCI returned to regular shoe gear was 80.5 ± 17.1 days, those without WCI returned to shoe gear at an average of 87.2 ± 25.3 days. This was not statistically significant (p = 0.46). Overall 34/35 (97.1%) procedures successfully progressed to full osseous consolidation at the arthrodesis or nonunion site. One patient developed a nonunion of an ankle arthrodesis site. It was revised 7 months after the index procedure; the same type of allograft bone was used and after strict compliance without postoperative protocols, the patient went on to complete union at 72 days after the second procedure. Other complications include: a tibial stress fracture while reaming for a tibiotalocalcaneal arthrodesis resolved with immobilization and conservative care, one deep vein thrombosis treated with standard anticoagulation, and two cases of wound dehiscence with subsequent superficial infection that resolved with short courses of oral antibiotics. A brief description of the types of procedures performed is depicted in table 2. The average days to union was 81.5 ± 28.8 in patients with DM and 68.0 ± 24.7 in patients without DM. This was not statistically significant (p = 0.28). The average days to union among current, former, and never smokers were 72.9 ± 29.7, 58.8 ± 16.5, and 71.5 ± 25.2 respectively. This was not statistically significant (p = 0.68). The results for days to fusion and return to shoe gear/walking in patients with successful fusion are summarized in table 3.

	Full Patient Cohort (n = 34; s = 35)	**Standard Commercial Insurance (n = 19, s = 19)**	**Workmen's Compensation Insurance (n = 15, s = 16)**
	s = 35	**s = 19**	**s = 16**
Ankle Arthrodesis	3 (8.6%)	1 (5.3%)	2 (12.5%)
Tibiotalocalcaneal Arthrodesis	3 (8.6%)	1 (5.3%)	2 (12.5%)
Subtalar and Talonavicular Arthrodesis	1 (2.9%)	1 (5.3%)	0 (0.0%)
Calcaneal-Cuboid Distraction and Talonavicular Joint Arthrodesis	1 (2.9%)	1 (5.3%)	0 (0.0%)
Subtalar Joint Arthrodesis	16 (45.7%)	9 (47.4%)	7 (43.8%)
Talonavicular Arthrodesis	3 (8.6%)	3 (15.8%)	0 (0.0%)
Calcaneal-Cuboid Joint Arthrodesis	1 (2.9%)	1 (5.3%)	0 (0.0%)
1st, 2nd, 3rd Tarsometatarsal Joint Arthrodesis	2 (5.7%)	0 (0.0%)	2 (12.5%)
Ankle Arthrodesis Nonunion Revision	1 (2.9%)	0 (0.0%)	1 (6.2%)
Fibular Fracture Nonunion Revision	3 (8.6%)	2 (10.5%)	1 (6.2%)
Medial Cuneiform Nonunion Revision	1 (2.9%)	0 (0.0%)	1 (6.2%)

Table 2: *Surgical procedures*

Days to Fusion	**Full Patient Cohort (s = 35)**	**Standard Commercial Insurance (s = 19)**	**Workmen's Compensation Insurance (s = 16)**	**Wilcoxon Rank Sum Test: p = 0.37**
Min	29	29	30	Not Significantly Different
Max	128	128	112	
Mean ± SD	70.4 ± 25.5	74.6 ± 26.2	65.1 ± 24.5	
Median [Q1, Q3]	70.0 [50.5, 90.0]	72.0 [51.5, 91.5]	58.0 [51.0, 76.0]	
No Fusion	1 (2.9%)	0 (0.0%)	1 (6.2%)	
Days to Return to Shoe Gear/Walking	**Full Patient Cohort (s = 35)**	**Standard Commercial Insurance (s = 19)**	**Workmen's Compensation Insurance (s = 16)**	Wilcoxon Rank Sum Test: p=0.46
Min	45	45	50	Not Significantly Different
Max	162	162	112	
Mean ± SD	84.2 ± 22.0	87.2 ± 25.3	80.5 ± 17.1	
Median [Q1, Q3]	83.5 [71.3, 95.5]	90.0 [71.5, 96.5]	80.0 [71.5, 91.0]	
No Fusion	1 (2.9%)	0 (0.0%)	1 (6.2%)	
Days to Fusion	**Non-DM (s = 29)**	**DM (s = 6)**	Wilcoxon Rank Sum Test: p=0.28	
Min	29	47	Not Significantly Different	
Max	128	112		
Mean ± SD	68.0 ± 24.7	81.5 ± 28.8		
Median [Q1, Q3]	66.5 [51.5, 84.8]	84.5 [56.5, 106.5]		
No Fusion	1 (3.4%)	0 (0.0%)		
Days to Fusion	**Never Smoker (s = 20)**	**Former Smoker (s = 5)**	**Current Smoker (s = 10)**	Kruskal-Wallis Test: p = 0.68
Min	33	38	29	Not Significantly Different
Max	128	72	111	
Mean ± SD	71.5 ± 25.2	58.8 ± 16.5	72.9 ± 29.7	
Median [Q1, Q3]	65.5 [51.5, 85.5]	62.5 [49.3, 72.0]	83.0 [49.8, 90.0]	
No Fusion	0 (0.0%)	1 (20.0%)	0 (0.0%)	

Table 3: *Days to fusion and return to shoe gear/walking in patients with successful fusion.*

Discussion

Historically, autograft has been the gold standard for bone graft material in foot and ankle surgery. Autograft has all the ideal properties for healing: osteoconductive, osteogenic, and osteoinductive. For the lower extremity, the most commonly utilized sites for autograft harvest are the iliac crest, tibia, and calcaneus. Neurologic compromise, infection, pain, and iatrogenic fractures can occur at any of these harvest sites. In 2011, Dimitriou., *et al.* conducted a systematic review on complications related to iliac crest autograft harvest. They included 92 articles and reported a complication rate of 19.37% after iliac crest harvest [8]. Baumhauer., *et al.* found lower extremity autograft harvest site pain was present in 12% of patients at 24 weeks after surgery, and 8.5% at 52 weeks [9]. Other concerns regarding autograft include low graft volume availability, variable biologic quality, and the additional operating time that subjects the patient to a longer period of anesthesia [10].

Given the known potential complications and burdensome harvesting requirements of autograft; allografts have emerged as a reproducible tool to achieve high union rates, especially in high-risk patients. When considering a patient population with significant comorbidities and risk factors, like many included patients in the current study, the nonunion rate can reach as high as 28% [11]. The additional time and expense of reoperation to correct a nonunion lends credence to the primary use of allograft material in foot and ankle surgery. In a review by Lareau., *et al.* the use of cancellous allograft decreased the nonunion risk by approximately half [1]. In the present retrospective review of surgical patients undergoing foot and ankle arthrodesis or nonunion repair, augmented by allograft with viable cellular bone matrix, there was a union rate of 97.4% among the entire patient cohort.

The allograft used in this study has reproducible results and standardized processing methods to ensure a minimum of 70% viable MSCs and 600,000 viable cells per cc. MSCs provide the three components of bone healing (osteogenesis, osteoinduction, and osteoconduction) and have been shown to promote healing in patients with nonunions following fracture repair [12]. In addition to the lower extremity literature, MSC use in spine procedures has been well documented. In a literature review of lumbar spinal fusions, MSCs through commercially available products, harvested from autogenous iliac crest bone marrow, had a high fusion rate of 90.2% to 92.3% [13]. BMPs similarly can increase the union rate. Specifically, BMP2 allows a synthetic graft to have comparable results to autograft [14-16]. The addition of periosteum to the graft composition provides angiogenic growth factors (VEGF, PDGF), which have been shown to play a role in the healing cascade [6]. Therefore the present study utilized an allograft with osteogenic, osteoconductive, osteoinductive, and angiogenic potential.

The union rates of patients were evaluated; many patients had multiple risk factors including, but not limited to, diabetes mellitus, tobacco use, and high BMI. Our results show no statistically significant differences in days to fusion with these potential risk factors. In addition, we have evaluated and compared consolidation rates of patients with WCI to those with standard commercial coverage policies. Work related injuries have been shown to be a deterrent to a timely recovery and the ability to return to work at the preinjury level. In an article by Thornes., *et al.* patients that suffered calcaneal fractures and underwent open reduction and internal fixation had significantly worse outcome scores when the injury occurred at work compared to similar, nonwork related, calcaneal fractures [17]. The days to union among patients with WCI in the present study was 65.1 ± 24.5. This was not statistically different from the patients in the study with standard commercial coverage policies. The average days to union among the patients with standard insurance plans was 70.4 ± 25.5. The explanation for this unusual finding may be because the WCI patients were younger at the time of surgery than the SCI patients (average of 43.5 ± 11.8 and 51.3 ± 10.7 years respectively, this difference was approaching statistical significance) and would likely have better healing potential.

This study has many strengths. All of the surgeries were performed by the senior author (SH) in a consecutive manner. The radiographic and clinical signs of healing were evaluated independently by the other authors. The same allograft material was used in all patients. There are several weaknesses of the study, firstly the intraobserver reliability of fusion across a joint or bone healing at fracture site. Plain radiographs and clinical evaluations are fraught with potential for bias. Computed tomography (CT) imaging is the gold standard to assess for delayed/nonunion and was performed in one patient with continued pain and equivocal plain radiograph results. In the other patients, CT imaging would have been considered an overutilization of resources with additional, unnecessary exposure to radiation. CT scans would have been performed if a patient was not progressively improving radiographically and clinically and if they were unable to return to preinjury activity. Secondly, no validated clinical scoring system was used to evaluate subjective or objective patient outcomes. Thirdly, no control was used for this study. A study that directly compared the use of allograft to no graft would be better suited to determine the benefit of allograft material. Finally, this was also a single center/one surgeon, retrospective study with short term follow-up. Despite these issues, we believe this study has merit in highlighting the high union rate with readily available bone allografts, such as the one used in this study. The studied allograft proved to be effective in assisting bone healing and avoids all complications associated with autograft.

Conclusion

Bone graft is a frequently used adjunct to assist in foot and ankle arthrodesis procedures and nonunion revision surgery. As an alternative to autograft, the present study reviewed the use of an allogenic cancellous/cortical/periosteal bone graft. The population consisted of 34 patients and 35 procedures with varied comorbidities that historically have increased risk of delayed union or nonunion. In addition, many of the patients evaluated were injured workers, which has been shown as a risk factor leading to suboptimal outcomes and delayed healing times in prior studies. Based on the results of this study, allograft bone containing viable cellular bone matrix may serve as an excellent alternative to autograft and an effective adjunct in surgery, especially in high-risk patients. The use of allograft is an effective way to achieve high union rates in patients undergoing foot and ankle arthrodesis or nonunion repair.

Acknowledgments

The authors acknowledge Patricia Greenberg, Biostatistician at the Office of Research Administrations at Jersey Shore University Medical Center, for her assistance with statistical analysis.

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