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Original Research

Comparison and Use of Allograft Bone Morphogenetic Protein Versus Other Materials in Ankle and Hindfoot Fusions

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ABSTRACT

Bone grafting is a common procedure in foot and ankle surgery. Because autogenous graft use results in comorbidity to the patient, the search has been ongoing for the ideal substitute. A novel processing technique for allograft using bone marrow, which retains many of the growth factors, has shown promise in the spinal data and early reports of foot and ankle surgery. We performed a retrospective, comparative study of patients undergoing hindfoot and ankle arthrodesis, with a total of 68 patients included. Of the 68 patients, 29 (42.65%) received a bone morphogenetic protein allograft and 39 (57.35%) did not. The patient demographics and social and medical history were similar between the 2 groups and both groups had a similar time to union ($p = .581$). Of the 29 patients in the bone morphogenetic protein allograft group, 3 (10.3%) experienced nonunion and 4 (13.8%) developed a complication. Of the 39 patients undergoing other treatment, 7 (17.9%) experienced nonunion and 14 (35.9%) developed a complication. The difference for nonunion was not statistically significant ($p = .5$). However, the difference in the overall complication rate was statistically significant ($p = .04$). We found that this novel bone graft substitute is safe and can be used for foot and ankle arthrodesis.

Bone grafting in foot and ankle surgery for fractures, osteotomy, and arthrodesis is a common practice (1). Many options exist for the surgeon to choose from, and all will have varying bone graft properties, including osteogenesis, osteoinduction, and osteoconduction. The selection of the exact bone graft to be used for the procedure should be determined by the properties needed for the procedure and the patient. A survey of foot and ankle surgeons found that a variety of clinical and radiographic factors can influence surgeons to use a bone graft (2). Historically, an autogenous bone graft harvested at surgery has been used. However, concerns have been raised regarding the limited amount of bone available and donor site morbidity (3,4). Modern autograft substitutes have challenged the need for an autogenous bone graft.

In foot and ankle surgery, a few autograft alternatives have been suggested as alternatives for high-risk procedures, including recombinant human bone morphogenetic protein (BMP), allograft viable mesenchymal stem cells (MSCs), and recombinant human platelet-derived growth factor (PDGF). BMPs are powerful osteoinductive graft materials and have demonstrated clinical effectiveness in the treatment of nonunion, segmental defects, and long bone fractures (5–8). Evaluation of its application (off-label) in foot and ankle surgery has generally reported favorable outcomes (9–13). MSCs have also demonstrated effectiveness in surgery (14). Commercially available MSCs approved for use in foot and ankle arthrodesis provide osteogenic, osteoconductive, and osteoinductive properties and have been recommended for various applications (15–17). PDGF has shown clinical efficacy in promoting bone healing owing to its effects on mesenchymal cells and preangiogenic properties (18,19). Recently, it has had excellent findings in foot and ankle surgery, even compared with autograft (20,21).

The allogeneic morphogenetic protein (AMP; OSTEOAMP®; Bioventus LLC, Durham, NC) used in the present study has been previously evaluated in studies of the spine. A study of 321 patients undergoing various spinal fusion operations was undertaken to compare AMP and BMP. The 226 patients in the AMP arm compared very well to the 95 patients in the BMP arm in terms of the fusion rate, time to fusion, and complications (22). In addition, the investigators previously reported an initial case series that also indicated its effectiveness in foot and ankle surgery (23).

The present study was undertaken to compare the outcomes in which AMP was used with those in which was not used in a group of hindfoot and ankle arthrodesis procedures. Our hypothesis was that AMP would be at least as effective and safe as other bone graft options

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in a comparative, larger, and more homogenous group of patients than has been previously studied in foot and ankle surgery.

Patients and Methods

The institutional review board approved the present study (approval no. 16-47E). We performed a retrospective medical record and radiographic review for patients who had undergone ankle, subtalar, or talonavicular arthrodesis, or any combination or revision of these. The study period included patients who had undergone surgery from July 1, 2014 until December 31, 2015. The patients were identified through the billing department using Current Procedural Terminology codes 27870, 27871, 28715, 28705, 28725, 28730, 28735, 28737, 28740, 28320, 28322, 29899, and 29907. We then performed a manual review of the medical records to ensure the procedures included only those of interest to the present study. Initially, 168 patients were identified; however, only 71 had undergone the procedures of interest. The primary endpoints were the fusion rate and complications. The time to arthrodesis was a secondary endpoint. The inclusion criterion was primary or revision arthrodesis of the ankle, subtalar, or talonavicular joints or a combination of these, which included triple (subtalar, talonavicular, calcaneocuboid), double (talonavicular, subtalar), tibiotalocalcaneal, and pantalar arthrodeses. Additional inclusion criteria were age >18 years and ≥7 months of follow-up data available. The use of other concomitant procedures was not an exclusion criterion, but these were not evaluated for arthrodesis or graft use. The exclusion criteria were arthrodesis only of a joint not included in the present study (e.g., isolated tarsometatarsal joint arthrodesis) and inadequate follow-up data because of loss to follow-up, death, or inadequate records. The patients were pooled during data collection but divided into groups according to who had received AMP (AMP group) and who had not (other group) for data analysis.

The surgical approach and fixation was procedure dependent but consistent principles were applied. In all cases, the proposed fusion site was exposed, and any remaining articular surface was removed past the subchondral bone. For nonunion revision, this included debridement of fibrotic material to raw, bleeding bone. The area was then fenestrated with a small drill or pin. Once the surface was prepared, it was packed with orthobiologic substances as deemed necessary by the surgeon. Both of us used AMP at approximately the same rate when it was thought to be indicated. This lack of a clear indication is a noted limitation of the present study and has been discussed further in the present report. Although fixation was procedure dependent and by surgeon preference, in all cases, fixation was meant to provide compression and stability. The patients were kept non-weightbearing in a splint and then a cast for 6 to 8 weeks. At that point, the patients were allowed to start weightbearing in a controlled ankle motion boot until clinical and radiographic evidence of adequate healing was seen. The patients were then allowed to progress to an ankle brace and then shoes, with physical therapy.

A review of the medical records was undertaken to record the patient demographics (age, sex, side of surgery) and medical and social history. The medical history specifically entailed recording the presence of hypertension, hyperlipidemia, coronary artery disease, hypothyroidism, multiple sclerosis, osteopenia/osteoporosis, chronic kidney disease, osteoarthritis, diabetes mellitus, obstructive sleep apnea, complex regional pain syndrome, and atrial fibrillation. No analysis of the treatment or level of control of each of the conditions was undertaken. The social history included smoking status, alcohol use, and illegal drug use. Tobacco use included current, former, and never smoked, and alcohol use was further stratified by alcohol users and abusers, which in the present study was defined as ≥10 alcoholic drinks weekly. The clinical outcomes, including time to weightbearing and any complications, were also recorded from the medical records. Complications included any events that were considered unexpected and required further intervention, whether operative or not. Delayed union was considered present if clinical and radiographic signs of nonunion (i.e., pain, swelling, radiographic lucency) were seen at 6 weeks but had resolved by 12 weeks postoperatively. Nonunion was considered present if those clinical signs persisted after 12 weeks or required surgical intervention. The specific procedure was also recorded. The use of any bone graft materials was recorded and was later used to compare patients between the AMP group and the other group. The initial selection of the specific graft materials was surgeon dependent. Although an attempt was made to augment the arthrodesis with AMP in the "high-risk" population, this determination was subjective because no specific criteria had yet been established. A radiographic review of plain film radiographs was performed to assess the time to bony union. Union was defined as radiographic evidence of bridging bone across ≥3 cortices on ≥2 image projections, with a lack of motion or hardware complications due to motion. The radiographs were reviewed by both of us, with each surgeon reviewing the other surgeon's radiographs to minimize bias. In addition, we were unaware of the use of any biologic agents, including AMP. Computed tomography was not routinely used but was evaluated when available. The use of computed tomography was case dependent and at the surgeons' discretion. The ultimate nonunion rate was determined by a combination of clinical and radiographic findings. This was a limitation of our study and has been discussed in more detail.

Statistical analysis was performed by an independent statistician. All the category variables are reported as frequencies and percentages across the 2 groups (AMP and other). For the comparison of the distribution of the category variables across the grouping variable, as appropriate, the χ^2 or Fisher exact test was used. For continuous variables, a 2-tailed t test for independent samples was used. For all statistical tests, an α level of 0.05 was used, and all statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

A total of 68 patients met the inclusion and exclusion criteria, with 2 patients lost to follow-up and 1 patient who had died of unrelated issues. Of the 68 patients, 29 were in the AMP group (42.6%) and 39 were in the other group (57.4%). The average follow-up time was 388 ± 121 (range 201 to 634) days in the AMP group and 413.1 ± 163.2 (range 201 to 641) days. The average age of the AMP group was 56.2 ± 12.6 (range 27 to 80) years, with 12 male (41.6%) and 28 white (96.6%) patients. The average age in the other group was 56.9 ± 13.1 (range 34 to 81), with 16 male (41.0%) and 36 white (92.3%) patients. The difference was not statistically significant between the 2 groups ($p = .47$ for age, and $p = .98$ for sex). The AMP group had 4 current smokers (13.8%) and 3 alcohol abusers (10.3%). The other group had 10 current smokers (25.6%) and 5 alcohol abusers (12.8%). The differences between the 2 groups was not statistically significant ($p = .36$ for smokers and $p = .75$ for alcohol abusers). The medical history also showed no statistically significant differences between the 2 groups (Table 1).

A variety of procedures and ancillary procedures were recorded. In the AMP group, 10 patients (34.5%) underwent double arthrodesis, 6 (20.7%) underwent tibiotalocalcaneal arthrodesis, 6 (20.7%) underwent subtalar arthrodesis, 6 (20.7%) underwent ankle arthrodesis, and 1 (3.4%) underwent triple arthrodesis. Only 4 patients (13.8%) underwent only 1 of the study procedures, and the rest received a variety of ancillary procedures. In the other group, 18 patients (46.2%) underwent double arthrodesis, 4 (10.3%) underwent tibiotalocalcaneal arthrodesis, 5 (12.8%) underwent subtalar arthrodesis, 7 (17.9%) underwent ankle arthrodesis, 3 (7.7%) underwent triple arthrodesis, and 2 (5.1%) underwent talonavicular arthrodesis, both in conjunction with total ankle replacement. Again, only 4 patients (10.3%) underwent only 1 study procedure (Table 2). The difference between the 2 groups was not statistically significant for either the primary procedure ($p = .34$

Table 1
Patient characteristics

Variable	AMP (n = 29)	Other (n = 39)	p Value
Age (y)	56.2 ± 12.6	56.9 ± 13.1	.47
Male sex	12 (41.4)	16 (41.0)	.98
Follow-up (days)	388 ± 121	413.1 ± 163.2	.14
White race	28 (96.6)	36 (92.3)	.63
Smoking status			
Current	4 (13.8)	10 (25.6)	.36
Former	13 (44.8)	14 (35.9)	.46
Alcohol status			
Users	14 (48.3)	21 (53.8)	.65
Abusers*	3 (10.4)	5 (12.8)	.75
Medical history			
HTN	16 (55.2)	16 (41.0)	.24
Hyperlipidemia	15 (51.7)	12 (30.8)	.08
CAD	2 (6.9)	3 (7.7)	> .99
Hypothyroidism	2 (6.9)	2 (5.1)	> .99
MS	0 (0.0)	1 (2.6)	> .99
Osteopenia/osteoporosis	4 (13.8)	5 (12.8)	> .99
CKD	2 (6.9)	3 (7.7)	> .99
OA	6 (20.7)	4 (10.3)	.31
DM	3 (10.3)	4 (10.3)	> .99
Sleep apnea	4 (13.8)	2 (5.1)	.39
CRPS	1 (3.4)	1 (2.6)	> .99
Atrial fibrillation	1 (3.4)	2 (5.1)	> .99

Data presented as mean ± standard deviation or n (%).
Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; CRPS, complex regional pain syndrome; DM, diabetes mellitus; HTN, hypertension; MS, multiple sclerosis; OA, osteoarthritis.
* More than 10 drinks weekly.