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*Foot Ankle Int* published online 5 March 2013  
DOI: 10.1177/1071100713481459

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# A Prospective Pilot Study of B2A-Coated Ceramic Granules (Amplex) Compared to Autograft for Ankle and Hindfoot Arthrodesis

Foot & Ankle International  
XX(X) 1–9  
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DOI: 10.1177/1071100713481459  
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## Abstract

**Background:** To reduce fusion nonunion, autogenous bone graft is often incorporated into foot and ankle fusion procedures. B2A peptide-coated ceramic granules, with encouraging results in pilot studies of transforaminal lumbar interbody fusion, were here reformulated into Amplex with a coating concentration of 225  $\mu\text{g}$  B2A/ $\text{cm}^3$  ceramic granules (B2A-granule) with the goal of eliminating autogenous bone graft in foot and ankle arthrodesis. The purpose of this study was to perform a multicenter prospective randomized pilot clinical trial designed to compare the safety and effectiveness of B2A-granule to autogenous bone graft in patients undergoing foot and ankle arthrodesis surgery.

**Methods:** This study was a multicenter, prospective, randomized, pilot clinical trial designed to compare safety and effectiveness of B2A-granule to autogenous bone graft in patients undergoing foot and ankle arthrodesis surgery. Twenty-four patients were enrolled and randomized (1:1) into 2 groups: autogenous bone graft control and B2A-granule. Primary outcome measures at 6 months (with follow-up at 9 and 12 months) included radiographic fusion assessed by computerized tomography and Ankle Osteoarthritis Scale scores for pain and disability.

**Results:** Radiographic fusion success rates were similar in both groups (100% in the B2A-granule group, 92% autograft). Both the B2A-granule group and the autograft group had improvements in the pain and disability scores over the course of the study. Graft harvest-site pain affected only autograft-treated patients. There were no adverse events attributed to the graft material in either the B2A-granule or autograft group.

**Conclusion:** The results of this pilot study are supportive of a larger clinical trial to assess the safety and efficacy of B2A-granule as a bone graft substitute in foot and ankle fusions.

**Level of Evidence:** Level II.

**Keywords:** clinical trial, B2A, bone graft, ankle fusion, arthrodesis, synthetic peptide

End-stage ankle arthritis (ESAA) causes severe compromise in patient's health-related quality of life.<sup>14</sup> Currently, the most accepted and common operative treatment for ESAA is ankle arthrodesis. Haddad et al<sup>16</sup> reviewed the literature on intermediate and long-term outcomes of ankle arthrodesis, including 39 papers for treatment of ESAA that ranged from Level I to Level IV evidence. The results of that systematic review provide support for the surgical treatment of ESAA with arthrodesis, citing improvements in health-related quality of life, improvements in joint-specific clinical outcome scores, and acceptable complication rates.

The most common surgical technique for arthrodesis of the ankle and other hindfoot joints is an open operative technique with rigid internal fixation.<sup>15,20,21</sup> This technique involves operative exposure of the joint to be fused, removal

of remaining cartilage and subchondral bone from the arthritic joint surfaces, interposition of bone graft in gaps between the prepared joint surfaces, and anatomic reduction with compression of the joint surfaces using rigid internal fixation devices. Supplemental autogenous bone graft, placed between the joint surfaces to be fused, is commonly employed to decrease nonunion rates.<sup>12</sup>

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The most common cause of failure of ankle arthrodesis has been nonunion, with rates ranging from 10 to 41%.<sup>13,19</sup> In addition, there are problems associated with the use of autogenous bone graft including donor site morbidity (eg, infection, healing problems, pain, and nerve damage),<sup>2,4,8</sup> variability in the quality and quantity of graft available from certain donor sites or patient populations,<sup>3</sup> and additional operating time including operating room resources associated with harvesting the autogenous bone.<sup>1</sup> As a result, in the past 5 years, new bone graft substitutes for enhancing arthrodesis of the ankle and foot joints have been explored (C. W. DiGiovanni et al, unpublished data, 2011).<sup>7</sup>

Recently, B2A-coated ceramic granules (formulated as Prefix) were described as a new bone graft extender that augmented spinal fusion in experimental animals.<sup>6,27</sup> B2A is not a recombinant growth factor or hormone. B2A is a synthetic peptide designed to augment osteodifferentiation.<sup>18</sup> B2A appears to augment the cellular action of endogenous BMP-2 by modulating receptors on preosteoblasts present locally in the arthrodesis site, thereby enhancing osteoblastic differentiation.<sup>25</sup> Thus, no exogenous BMP or exogenous stem cells are required. Previous animal studies,<sup>6,27</sup> albeit in spinal fusion models, have revealed that B2A-coated granules have a higher fusion rate than the (osteoconductive) granules only, indicating that B2A is contributing to fusion outcomes in these models.

When used as a bone graft extender for spinal fusions in pilot clinical trials, B2A-coated ceramic granules gave indications of safety and effectiveness.<sup>25</sup> If B2A-coated ceramic granules can similarly be proven to be safe and efficacious for use in ankle and hindfoot fusion procedures, it could potentially improve fusion rates and, most important, decrease morbidity associated with traditional autogenous bone graft harvest.

The purpose of this study was to perform a multicenter prospective randomized pilot clinical trial to compare the safety and effectiveness of B2A-granules to autogenous bone graft in patients undergoing foot and ankle arthrodesis surgery.

## Methods

### Study Design

A prospective multicenter clinical trial was performed in patients undergoing midfoot, hindfoot, or ankle fusions. The study was approved by the Institutional ethics review boards of all the centers involved and conducted under Health Canada Investigational Testing Authorization (ITA#) 174045 with informed consent obtained from all patients. The study was registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) under Study ID NCT01224119. The device status was Investigational; Amplex is an investigational device not approved by the US

**Table 1.** Key Inclusion and Exclusion Criteria.

#### Key Inclusion Criteria

- Indicated for foot and ankle surgery described as either single, double, or triple arthrodesis of the ankle-, subtalar-, calcaneocuboid-, or talonavicular joints
- 18-75 years of age
- Have not been sufficiently responsive to an adequate trial of nonoperative treatment
- Women of childbearing potential had to have a negative pregnancy test prior to surgery and agree to use contraception for the first 6 months after surgery

#### Key Exclusion Criteria

- Have a large bone deficit requiring a structural graft
- Charcot joints from neuropathic destruction
- Previous fusion or osteotomy of the proposed site; required osteotomy of the midfoot joints
- BMI greater than 45 kg/m<sup>2</sup>
- Osteoporosis
- Known complications of diabetes; HgbA1C level greater than 7
- Has a history of systemic malignancy or currently untreated malignant neoplasm(s)

FDA nor Health Canada and was also not available for sale or use except under investigational protocols.

Patients were enrolled at 3 institutions following approval by the local Research Ethics Board at each institution. All subjects met study inclusion and exclusion criteria (Table 1). The study randomized 24 subjects, in a 1:1 ratio, to receive either autograft or B2A-coated ceramic granules. The granules were coated at 225 µg of B2A per cm<sup>3</sup> of granules (5 cm<sup>3</sup> total granule volume). Two sets of randomization codes were developed for each site, stratifying for smokers and nonsmokers. Smokers were enrolled into the study; however, randomization was designed to ensure an even distribution of smokers across the study and across sites. Each randomization set was developed using random blocks of 2 and 4 subjects to prevent investigators from inferring the next assignment. The randomization assignment was not disclosed to the subject until after surgery to prevent bias due to subjects dropping out due to noncompliance with the randomization (eg, does not want to be in the control group). Postoperatively, subjects were able to infer their group assignment because of the presence (or absence) of an incision for graft harvest.

Twenty-four subjects were enrolled over a 10-week period. Table 2 provides a description of the demographics, graft materials, and aspects of the surgery. There were 12 subjects in each group with 1 smoker in the B2A-granule group and 2 smokers in the autograft group. One subject in the autograft group was enrolled as a nonsmoker but later disclosed that he or she was, in fact, a smoker. There were a higher proportion of females in the autograft group

**Table 2.** Subject Demographics and Descriptions of the Surgery and Graft Materials.

	Amplex	Autograft
<b>Demographics</b>		
Number of subjects	12	12
Age (years)	54.5 ± 14.3	57.9 ± 14.0
Weight (kg)	87.3 ± 20.2	89.2 ± 14.3
BMI	30.8 ± 5.5	30.3 ± 4.7
Gender	5M, 7F	10M, 2F*
Smoker, n (%)	1 (8.3)	2 (16.6)
<b>Graft volume implanted</b>		
<b>Autograft</b>		
Proximal tibia (n = 5)	—	5.6 ± 2.2 cm <sup>3</sup>
Distal tibia (n = 7)	—	4.6 ± 0.8 cm <sup>3</sup>
Amplex	4.2 ± 0.9	—
<b>Surgery</b>		
Ankle	6	8
Subtalar	5	4
Talonavicular	1	0
Blood loss estimate (ml)	35 ± 58	58 ± 78
Surgery time (minutes)	95 ± 24	105 ± 31

Data are presented as the average ± SD. Amplex was used as a bone graft substitute and did not contain autograft. BMI = body mass index; F = female; M = male.

\*Statistically significant,  $P = .035$ .

compared to the B2A-granule group. All subjects enrolled in the study underwent single joint arthrodesis surgery. In the B2A-granule group, the operative joints included 5 subtalar-, 6 ankle-, and 1 talonavicular joint(s). In the autograft group, the operative joints included 4 subtalar- and 8 ankle joints. All subtalar joints received 2 compression screws. The ankle joints in the B2A-granule group averaged 2.3 screws, and the autograft group averaged 2.4 screws per joint. The talonavicular joint in the B2A-granule group received 2 screws.

The operative procedure included debriding the joint surfaces to bleeding bone and placing graft material into the joint. Subjects were evaluated before surgery to set a baseline, and then followed up at 6 weeks and 3, 6, 9, and 12 months for radiographic outcomes and clinical improvement. Computerized tomography (CT) was conducted at 6 and 9 months with subsequent quantitative fusion analysis.

### Operative Procedure and Postoperative Care

All surgeries were performed by orthopedic surgeons fellowship trained in foot and ankle reconstruction. Perioperative prophylactic antibiotics were administered before surgery. Standard surgical technique was employed to gain access to each fusion site and to ensure rigid fixation of the fusion site. The entire joint was exposed and denuded to subchondral bone, and the subchondral plate

was perforated to augment the subsequent fusion. While the protocol was permissive for at least 1 but no more 3 compression screws, the investigators elected to use 2 or 3 compression screws across the joint.

Amplex was provided to the clinical sites in a kit format (BioSurface Engineering Technologies, Rockville, MD, USA). Each kit contained 1 vial each of lyophilized B2A peptide and porous granules (80% tricalcium phosphate/20% hydroxyapatite). Each subject randomized to the B2A-granule arm of the study received material from 1 B2A-granule kit. B2A, used at a coating concentration of 225 µg/cm<sup>3</sup> granules, formulated 5 cm<sup>3</sup> of graft material.

In subjects randomized to receive autograft, the investigators chose to obtain autograft bone from the distal- or proximal tibia. Both proximal tibia and distal tibia are used clinically as autograft harvest sites for foot and ankle arthrodesis, and reportedly with a low complication rate.<sup>12,26,30</sup> The autograft was harvested and morselized using standard procedures. The maximum volume of graft material that could be used per patient under the protocol was 5 cm<sup>3</sup>, the actual volume used per joint was, however, less than that and depended in large part on joint anatomy. Regardless of the type of graft material used (autograft group or B2A-granule), the amount of graft material placed in the joint was estimated by subtracting from the total pre-operative volume of graft material, the unused, residual volume after packing the joint (Table 2).

Subjects were discharged when they were comfortable on oral pain medications and could adequately care for themselves. Subjects were instructed to avoid oral, systemic, and local injections of nonsteroidal anti-inflammatory drugs or corticosteroid injections into the foot for the first 6 months following surgery. Electromagnetic, ultrasound, or osteobiologic treatments intended to stimulate bone growth were not allowed. After surgery, the operative extremity was immobilized (splint, walker boot, or cast) for 6 weeks of non-weight bearing followed by progressive weight bearing over the next 4 weeks in a protective orthosis. Patients were made aware of the importance of compliance with immobilization and weight bearing.

### Clinical Follow-Up

Subjects were evaluated before surgery to set a baseline and then followed up at 6 weeks and 3, 6, 9, and 12 months for radiographic outcomes and clinical improvement. In this study, the primary outcome measure was CT-defined fusion at 6 months, although radiographic outcomes included CT scans at 6 and 9 months. Plain-film radiographs were obtained at 6 weeks and 3, 6, 9, and 12 months. Clinical improvement was tracked at each follow-up time interval using the Ankle Osteoarthritis Scale (AOS).<sup>10</sup>

Laboratory assessment (red blood cell count, white blood cell count, hemoglobin, sodium, chloride, potassium,

calcium, inorganic phosphate, carbon dioxide, magnesium, albumin, total protein, alkaline phosphatase, gamma-glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase) was performed preoperatively and again at 6 weeks and 3 months after surgery. Serum samples were collected preoperatively and at 6 weeks and 3 months postoperatively and were used to evaluate the presence or absence of antibodies reactive with the B2A peptide.

### Radiographic Analysis

The radiographic assessments (X-ray and CT) were performed by eImage, Inc (Blue Bell, PA), a qualified, core imaging laboratory. All radiographic data were interpreted by an independent, blinded radiologist. The radiologist was board certified and fellowship trained. The collection and evaluation of radiographic information and its assessment were governed by an Imaging Protocol/Manual and included quantitative assessment of bone healing at the fusion site and qualitative assessments of screw loosening, migration, and new fractures. The Imaging Protocol/Manual was used to help standardize radiographic image collection, to minimize variations associated with CT slice analysis, and to ensure similar imaging and evaluation parameters were used at the 6- and 9-month intervals. The primary outcome measure in this study was bone healing at the fusion site at 6 months, as assessed by an independent radiology reviewer using CT scans.

The technique for CT acquisition at all sites was guided by an Imaging Protocol/Manual that emphasized symmetry between the 2 extremities, wherein the plantar aspects of the feet were pressed against the flat surface with a mild amount of pressure simulating weight bearing. The patients were supine, with hips and knees flexed sufficiently to allow full insertion of the hindfoot in the scanner aperture. The transverse (axial) plane images were done at a 90-degree angle to the end of the table extension. For coronal plane images, the patient was supine, with the feet placed in extension with a 20-degree incline plane. The gantry was tilted 20 degrees to compensate for the incline plane of 20 degrees and was maintained in perpendicular alignment with the plantar aspect of the foot.

For analysis of CT fusion success, each joint was assigned a preferential plane to make the CT measurements (ankle joint measured in coronal plane; subtalar and talonavicular joints measured in sagittal plane). The actual CT slice thicknesses ranged from 0.6 mm to 2.0 mm and number of slices representing a joint was dependent on how many slices it took to span the joint surface. For each slice, the length of the articulating surface (excluding regions obscured by the screws) and the length of bridging bone were measured. With these data, the percentage bone formation across the fusion for each slice was determined. The percentage fusion across the entire joint surface was also determined. Note that this

was not a simple average of individual slices, but the sum of the bridging lengths divided by the sum of the articular lengths (from each slice) and multiplied by 100. This appropriately weighted the slices with longer sections of the joint visible in the plane. Radiographic fusion success was defined as a percentage joint fusion greater than 50%. The 50% threshold was based on other foot and ankle arthrodesis studies where CT has been used.<sup>5,9</sup>

The investigator's clinical assessment of fusion was also recorded and was a qualitative assessment based on plain film radiographs, the overall condition of the subject, and clinical assessments. The investigator rated the subjects as "fused," "progressing toward fusion," or "not fused." While radiographs and manual assessment may have been misleading, these were the most common tools available in the clinical practice. The desire was to compare these assessments to those of the blinded radiologist's interpretation of the CT scans.

### Ankle Osteoarthritis Scale

The AOS questionnaire<sup>10</sup> was used to track clinical improvement at each visit. The AOS is a patient self-assessment questionnaire designed for use with patients with ankle arthritis, and has been used in a number of foot and ankle fusion studies.<sup>23,24</sup> The questionnaire has 2 sections, pain and disability, with each section containing 9 questions, and responses recorded on a 10 cm visual analog scale. Due to postoperative restrictions, not all questions could be answered at every time point, most notably at the 6-week visit. Specifically, for the pain subscale, these restrictions related to (1) walking wearing shoe inserts or braces and (2) standing wearing shoe inserts or braces. For the disability subscale these included items related to (1) walking 4 blocks or more, (2) standing on tiptoes, and (3) walking fast or running. In light of those postoperative restrictions, a subject had to answer at least 5 of 9 questions in each of the pain or function subcomponent to affect a recordable AOS score.

## Results

### Radiographic Outcomes

Fusion assessments for the B2A-granule and autograft groups are provided in Tables 3 and 4, and for individual patients in Figure 1. Examples of CT slices from 2 patients treated with B2A-granules are provided in Figure 2.

In both B2A-granule and autograft groups, the maximum % fusion in any single slice was similar, averaging  $99.7\% \pm 0.05$  and  $98.0\% \pm 3.5$ , respectively. Using all CT slices to quantitate the percentage fusion across the joint, the B2A-granule group at 6 months (Table 3) had a higher average % fusion ( $83.7 \pm 12.2\%$  vs  $75.2 \pm 22.0\%$ ). The



**Table 3.** Fusion Assessments for the Amplex and Autograft Groups at 6 Months.

6 Months	Amplex Arm	Autograft Arm
Radiographic assessment		
Fusion success (≥ 50%), n (%)	12/12 (100)	11/12 (92)
Complete union (≥ 66%), n (%)	11/12 (92)	8/12 (67)
Average % fusion across joint	83.7 ± 12.2	75.2 ± 22.0
Clinical assessment		
Fused, n (%)	11/12 (92)	9/12 (75)
Progressing toward fusion, n (%)	1/12 (8)	3/12 (25)
Not fused, n (%)	0/12 (0)	0/12 (0)

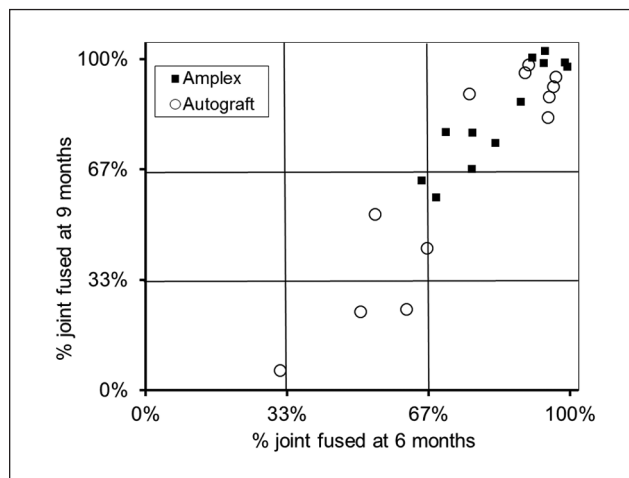
Radiographic assessments (independent radiologist) were based on CT scans. Fusion success was defined as bridging bone over at least 50% of the joint. Complete union<sup>10</sup> was defined as > 66% bridging bone in the joint. Percentage fusion is presented as the average percentage fusion ± SD. Clinical assessments (clinical physicians) were based on plain film radiographic images and clinical examination.

**Table 4.** Fusion Assessments for the Amplex and Autograft Groups at 9 Months.

9 Months	Amplex Arm	Autograft Arm
Radiographic assessment		
Fusion success (≥ 50%), n (%)	12/12 (100)	8/12 (67)
Complete union (≥ 66%), n (%)	10/12 (83)	7/12 (58)
Average % fusion across joint	83.4 ± 15.9	65.9 ± 33.8
Clinical assessment		
Fused, n (%)	11/12 (92)	9/12 (75)
Progressing toward fusion, n (%)	1/12 (8)	2/12 (17)
Not fused, n (%)	0/12 (0)	1/12 (8)

Radiographic assessments (independent radiologist) were based on CT scans. Fusion success was defined as bridging bone over at least 50% of the joint. Complete union<sup>10</sup> was defined as greater than 66% bridging bone in the joint. Percentage fusion is presented as the average percentage fusion ± SD. Clinical assessments (clinical physicians) were based on plain film radiographic images and clinical examination.

radiographic fusion success rate, defined as evidence of bridging bone over at least 50% of the joint, was similar in both groups: 12/12 (100%) in the B2A-granule group and 11/12 (92%). Also, the B2A-granule group had a higher rate of complete union (defined post hoc as being greater than 67% bridging bone in the joint) compared to the autograft group, 11/12 (92%) and 8/12 (75%), respectively, suggesting a more robust fusion. The outcomes for individual patients (Figure 1) were suggestive of a higher, sustained quality of union.



**Figure 1.** Fusion quality for individual patients over time (6 and 9 months) with 6-month data on the x ordinate and 9-month data on the y ordinate. Fusion quality was assessed as in Jones et al,<sup>17</sup> with nonunion = 0 to 33%, partial union ≥ 33 to 66.7%, and complete union ≥ 66.7%

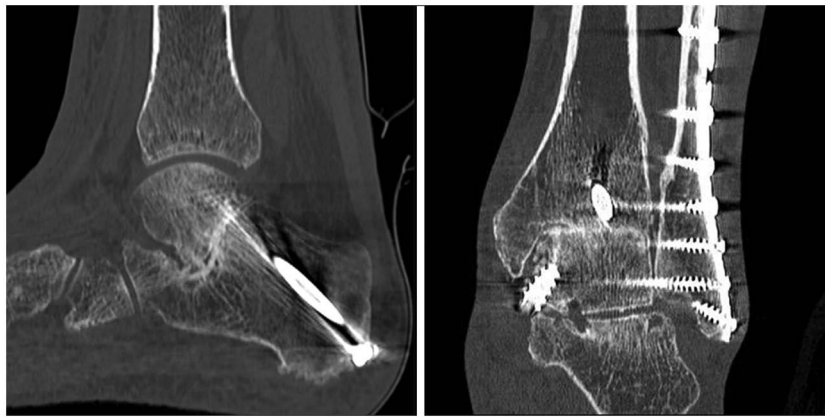
The clinical investigator assessments at 6 months indicated a similar trend to improved fusion in the B2A-granule group (11/12 fused) as compared to the autograft group (9/12). Clinical Investigator assessments indicated no patient with clinically established nonunion.

Table 4 provides a similar analysis for the 9-month time point. Overall, there appeared to be radiographic stability in the B2A-granule group, whereas in the autograft group, there may have been deterioration in radiographic outcome. The fusion outcomes from individual patients were consistent with this observation (Figure 1). The cases that were fused at 6 months but not at 9 months all had less than 67% fusion at 6 months, whereas no patients with fusion greater than 67% later fell below the 50% threshold. A post hoc definition of “complete fusion” was therefore created at threshold of 67% fused. At both 6 and 9 months, clinical assessment of fusion by the investigators was consistent with the independent radiologist assessment of fusion.

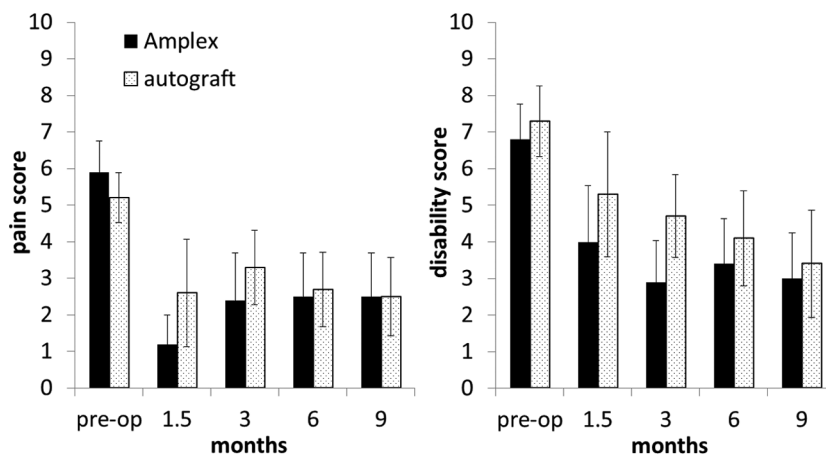
In the B2A-granule group at 6 months, the radiologist noted that 1 subject had subchondral cysts with anterior lucency. No subject evidenced screw loosening, or graft migration. In the autograft group, 4/12 subjects were noted to have areas of limited or nonunion at 9 months (< 50% joint fusion), and 1 was noted to have a postfracture.

**Clinical Outcomes**

The AOS outcome scores for pain and disability are provided in Figure 3. Both the B2A-granule group and the autograft group had improvements in the pain and disability scores over the course of the study. Pain scores were lowest at 6 weeks, improved and plateaued thereafter toward the



**Figure 2.** Sagittal slice of hindfoot fusion (left) and coronal slice of ankle fusion (right) at 6 months following arthrodesis surgery using Amplex. CT scans from patients with % joint fusion closest to the average % joint fusion for Amplex group.



**Figure 3.** Ankle Osteoarthritis Scale (AOS) scores for pain (left panel) and disability (right panel) over time. Data are presented as the score average  $\pm$  CI.

end of the study (12 months). At 6 months, 7/12 subjects in both groups had a decrease in pain scores of at least 30%. On the other hand, 1/12 subjects in both groups had an increased pain score. As with pain scores, the disability scores in both groups also decreased over the course of the study. At 6 months, 9/12 subjects in both groups had a decrease in disability scores of at least 30%, and in both groups, 1/12 subjects had an increased disability score. Follow-up evaluation at 12 months indicated that both the B2A-granule and autograft groups continued to improve in both the pain and disability components. With the numbers available, increases in AOS score did not appear to relate to low percentage of joint fusion.

### Graft Harvest-Site Pain in Autograft-Treated Patients

B2A-granule patients did not have graft harvest and therefore did not have graft harvest-site pain. Graft harvest-site pain affected only autograft-treated patients. In this group, graft site pain was reported at 6 weeks (1/11 patients), 3 months (2/12 patients), and 6 months (2/12 patients). The maximum graft site pain in any subject (5 on a 0 to 10 scale) was found in the 1 patient reporting pain at 6 weeks. At the 6-month time interval, the maximum graft site pain intensity was 3 (0 to 10 scale), and 1 subject complained of the graft site interfering with his or her life "several times

**Table 5.** Postoperative Adverse Events.

	Amplex	Autograft
Hemorrhoids	1	
Superficial wound infection	1	
Transient liver enzyme increase	2	2
Possible wound infection	1	
Wound breakdown	1	
Lateral ankle pain	1	
Above knee DVT operation		1
Detached retina		1

DVT = deep vein thrombosis.

per month” (similarly at 3 months). Nine patients (9/12) at the 6-month interval reported that graft site pain did not cause a significant problem, and there were no reoperations at the graft site.

### Safety

A listing of the adverse events is provided in Table 5. There were no adverse events attributed to the graft material in either the B2A-granule or autograft group, and there were no serious adverse events. In the B2A-granule group, 1 subject had wound breakdown of moderate severity. The onset of this adverse event was 98 days postoperative, and it was recognized as having resolved 253 days postoperative. All other adverse events were mild and included 1 patient with a superficial infection that resolved and another with a possible wound infection. In the autograft group, there were 2 adverse events of moderate severity including a case of an above-the-knee deep vein thrombosis (DVT) and a case of a detached retina. The onset date of the DVT was registered as 119 days postoperative and was unresolved at the 12-month visit. The detached retina had an onset date at 145 days postoperative, and was resolved the next day with a medical procedure.

Hematology and clinical laboratory assessment of patients in each group revealed similarity in outcomes and were generally unremarkable, although there were occasional mild excursions in both groups. Both groups included 2 patients who demonstrated transient elevations in liver enzymes after surgery, which resolved without intervention. There was no evidence of drug-induced liver damage. No B2A-granule or autograft subjects developed antibodies to B2A.

### Discussion

This study was designed to serve as a pilot study to establish the potential for a larger, well-designed, randomized controlled trial that mirrors the current study to determine whether Amplex with B2A, a synthetic peptide designed to

augment osteodifferentiation, has an equivalent safety and efficacy profile compared to autograft. During foot and ankle arthrodesis, B2A is hypothesized to impact mesenchymal stem cells and preosteoblasts from surgically generated bleeding bone and local synovial membranes, periosteum, and muscle, and to augment the normal BMP-2 signaling associated with bone fractures and bone healing.<sup>22,29</sup>

Along a similar line, pilot studies by Daniels et al<sup>7</sup> and DiGiovanni et al<sup>9</sup> using recombinant growth factor rhPDGF-BB and a  $\beta$ -tricalcium phosphate matrix (Augment) to enhance ankle and hindfoot fusion have led to a larger randomized controlled trial to support a marketing application in the United States. The results suggest that Augment as a bone graft substitute was noninferior to autograft without donor site morbidity.

This current pilot study on B2A was conducted with well-designed and robust methodologies that include safety, clinical, and radiographic outcome measures similar to the best studies (C. W. DiGiovanni et al, unpublished data, 2011)<sup>7</sup> in the literature. The results, by the nature of the pilot study, are statistically underpowered but do show comparable safety and efficacy between B2A-granule and autograft for enhancing arthrodesis of ankle and hindfoot fusions. In the current study, efficacy was assessed primarily using CT scans to assess successful fusion at 6 months. Similar techniques have been used by other investigators in foot and ankle arthrodesis studies.<sup>9,11,17,28</sup>

When compared to autograft, the B2A-granule group had a trend for a higher radiographic fusion rate (100% vs 92%) at 6-month follow-up as defined by evidence of bridging bone over at least 50% of the joint. The fusion rates for B2A-granules in the current study were higher than those observed in the pilot study of Daniels et al<sup>7</sup> using rhPDGF-BB, which showed a fusion rate of 75% (44/59) at 36 weeks. It is possible that these rates differ based on sample size or on the definition of successful fusion, which was defined differently by the Daniels study as osseous bridging and/or disappearance of the joint space subchondral bone.

The fusion rates of the current pilot study are also higher for bone graft substitute and autograft (100% vs 92%, respectively) compared to the fusion rates (77% vs 78%) of a level 1 randomized controlled trial by DiGiovanni et al (C. W. DiGiovanni et al, unpublished data, 2011). It is also noteworthy that the B2A-granule group in the current pilot study had a higher rate of complete union at 9 months<sup>17</sup> (greater than 67% bridging bone in the joint) compared to the autograft group (92% vs 75%), and compared to those rates cited in other studies (C. W. DiGiovanni et al, unpublished data, 2011).<sup>7</sup> This study showed a trend for autograft fusions to have less fusion mass compared to the B2A group, notably when the percentage fusion at 6 months was less than 67%. All of these observations suggest a more



robust fusion with B2A-granule group, accepting that this study is underpowered to confirm this observation. If there was actual deterioration in the autograft group but not in the Amplex group, this would need further clarification; it is thought that a larger, prospective, randomized study would be needed to confirm and fully understand the observed decrease in radiographic fusion from 6 to 9 months in the autograft group.

Secondary outcome measures for clinical success were assessed by clinical outcomes scores that included the AOS joint-specific clinical outcome score for ankle pain and disability, which improved over the course of the study. Similar findings were noted in the other studies (C. W. DiGiovanni et al, unpublished data, 2011)<sup>7</sup> using the American Orthopaedic Foot and Ankle Society joint-specific clinical outcome score for ankle pain and disability.

One of the most obvious benefits of bone graft substitutes is the lack of graft harvest-site pain and other complications. In the current study, B2A-granule patients did not receive any autograft and, as such, did not have graft harvest-site pain. Graft harvest-site pain was reported over the course of the study in the autograft group, with 1 subject complaining of the graft site interfering with his or her life "several times per month." In other similar studies (C. W. DiGiovanni et al, unpublished data, 2011),<sup>7</sup> graft harvest-site pain was reported in the autograft groups.

Last, and likely most important, it is essential to report on the safety of bone graft substitutes. In the current study, there were no serious adverse events attributed to the graft material in either the B2A-granule or autograft group. These results were similar to other, larger, studies where the majority of events that were reported were considered to be standard and expected complications in foot and ankle surgery. There were no unexpected trends or complications related to the investigational device.

Overall the results of the present pilot study are encouraging. However, larger, appropriately powered pivotal clinical studies would be needed to address subgroup variables such as fixation instrumentation and specific arthrodesis site. Similarly, additional studies would be needed to evaluate if Amplex could be useful in patients with factors predisposing to nonunion (bone deficits, diabetes, and osteoporosis among others).

## Conclusion

In conclusion, this pilot study demonstrated comparability in safety and efficacy between B2A-granule and autograft when used in foot and ankle fusions with the small population examined. The results of this pilot study, while not statistically definitive, are supportive of a larger, statistically powered, randomized controlled trial that mirrors the current study to determine whether B2A-granule has an equivalent safety and efficacy profile compared to autograft.

## Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Glazebrook was paid for consulting work by BioSurface Engineering Technologies.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded, in part, by BioSurface Engineering Technologies. Thanks are due to research assistant Patricia Francis. Thanks are also due to Drs Murray Penner and Kevin Wing, fellowship-trained orthopedic surgeons who contributed patients with end-stage ankle arthritis to the study population.

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