



Open Access

Review Article

A Novel Bone Void Filler for Use in Prosthetic Joint Infections

David C Evans¹, Ashok C Khandkar², Bruce G Evans^{3*}

¹Mass General Brigham, Harvard Medical School, Boston, MA 02114, USA

²Elute Inc., Salt Lake City, UT 84108, USA

³Steward Medical Group Orthopaedic and Sports Medicine, Jordan Valley Medical Center, 3584 W. 9000 S. West Jordan, UT 84088, USA

***Corresponding Author:** Bruce G Evans, Steward Medical Group Orthopaedic and Sports Medicine, Jordan Valley Medical Center, 3584 W. 9000 S. West Jordan, UT 84088, USA; Email: bgevansmd@gmail.com

Received Date: 26-02-2022; **Accepted Date:** 22-03-2022; **Published Date:** 30-03-2022

Copyright © 2022 by Evans BG, et al. All rights reserved. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Abstract

Bone grafts and Bone Void Fillers (BVF) have multiple applications in total joint reconstruction surgeries. However, despite their widespread use, they are contraindicated in Prosthetic Joint Infections (PJI). A BVF device is needed that will provide sustained antimicrobial protection to prevent biofilm formation and, ultimately, will resorb and be replaced by host bone. Currently, BVF are only used in noninfected cases in which powder antibiotics are added in hopes of preventing future infections. These BVF do not provide a sustained antibiotic level and, therefore, are not recommended for infected cases. A novel BVF, EP Granules with Tobramycin, was designed to fulfill the need for successful bone growth when infection is present. To create this unique and original BVF, an osteoconductive biomaterial was combined with clinically used degradable polymers, resulting in a composite ceramic polymer. Initial *in-vitro* elution studies followed by successful and animal *in-vivo* testing have demonstrated its effectiveness.

Keywords

Prosthetic Joint Infections; Bone Graft; Total Joint Arthroplasty; Tobramycin

Evans DC | Volume 3; Issue 1 (2022) | JOSR-3(1)-026 | Review Article

Citation: Evans BG, et al. A Novel Bone Void Filler for Use in Prosthetic Joint Infections. J Ortho Sci Res. 2022;3(1):1-14.

DOI: <http://dx.doi.org/10.46889/JOSR.2022.3102>

Introduction

Bone grafts are commonly used in orthopaedic surgery and have evolved throughout the years. Historically, autografts were the first recommended graft source, given their osteoinductive and osteoconductive properties. However, autografts have many limitations due to donor-site morbidity and limited supply. Allografts, another type of bone graft, have greater availability and are used in larger bone defects. Alternatives to allografts were designed when transmission of disease and cost became known factors. Synthetic Bone Graft Substitutes (BGS) were created to fill the need for a larger volume of bone graft requirement and to reduce the risk of disease transmission to patients. The primary composition of BGS is cells, factors, ceramics and polymers [1]. Another common classification for synthetic bone is Bone Void Fillers (BVF).

Bone grafts have multiple applications in orthopaedic trauma, tumor and joint reconstruction. Despite their widespread use, they are contraindicated in all orthopaedic infections. Allograft bone grafts impregnated with antibiotics have been described for treatment in single-stage revisions for prosthetic knee joint infections [2]. However, these bone grafts have not changed the current standard of care, which recommends avoiding any bone graft material in an orthopaedic application until infection is eradicated.

In joint replacement surgery, Prosthetic Joint Infection (PJI) following primary implantation occurs in approximately 1.3% of patients [3]. The infection rate for second-time surgery is as high as 19% [4]. One of the common features of prosthetic infection is osteolysis or bone loss, resulting from either the infection alone or removal of the implant. Currently, the bone void created in surgery is filled with Antibiotic-Loaded Bone Cement (ALBC), which serves two purposes: it fills the void and it delivers antibiotic to the surrounding infected bone and soft tissues. The most common use of ALBC is in the treatment of 2-stage revisions for PJI where removal of implant and placement of antibiotic spacers is completed [5].

While revision utilizing ALBC is a common PJI treatment, the approach has notable shortcomings. The ALBC antibiotic elution exhibits rapid, large bolus release for just a few days, followed by extended sub therapeutic elution for weeks [6]. Subtherapeutic antibiotic concentrations, which can be identified as early as 4 weeks post-application, create opportunities for antibiotic resistant PJI development. These infections are difficult to eradicate and can lead to multiple surgeries with significant patient morbidity. Associated difficulties arise from adherent bacteria forming protective biofilms, which impede antibiotic penetration and produce persistent colonies with delayed virulence beyond the temporal antimicrobial window provided by ALBC [7]. In addition, ALBCs that are intended for filling bone defects and providing fixation of cemented prostheses to bone are nonresorbing, rigid, hydrophobic, dense, glassy materials. They represent a permanent foreign body in the revision implant site, hence a continuing location for the foreign body response, which results in compromised immune competence as long as the implant is present. Furthermore, many reports indicate that

Evans DC | Volume 3; Issue 1 (2022) | JOSR-3(1)-026 | Review Article

Citation: Evans BG, et al. A Novel Bone Void Filler for Use in Prosthetic Joint Infections. J Ortho Sci Res. 2022;3(1):1-14.

DOI: <http://dx.doi.org/10.46889/JOSR.2022.3102>

less than 50% of ALBC is bioavailable. Moreover, the bioavailable portion is released in an uncontrolled, suboptimal fashion, which does not adequately address infection [8,9]. This finding could be one reason why revision implant infection rates are higher than primary implant infection rates [3,4].

Significant loss of bone stock is another problem in the surgical treatment of PJI. Standard of care involves a 2-stage total joint arthroplasty revision. In the first stage, the primary implant is removed after debridement of the soft tissues and thorough irrigation of the bone with a solution containing an active antimicrobial. The patient is then treated with systemic antibiotics. After device removal, ALBC spacers are placed in the bone canal before closing the patient. This surgery is followed by another course of systemic antibiotics. Typically, 6-8 weeks of IV antibiotics are required to clear the infection. The patient is surgically treated in the second stage by removing the spacers, filling the voids with an antibiotic-containing bone cement and/or metal augments and affixing the revision implant.

Despite significant bone loss, no BVFs are currently indicated for use during the first stage of PJI revision as they increase the risk of infection and inhibit bone growth. Accordingly, the bone voids are filled with either permanent ALBC or metal augments or both. An improved and reliable method to grow new bone in sites of previously infected bone is needed. A bone graft that survives an infection has the potential to significantly increase available bone stock, which is known to improve longevity of the revision implant and overall patient satisfaction [5]. In addition, if future surgery is required, a larger amount of host bone would be available for the revision.

There is a clinical need for a BVF that provides the initial requirement of bone void filler that will resorb and ultimately be replaced by new host bone. In addition, since any implant increases host tissue susceptibility to infection, the BVF device should simultaneously provide sufficient antimicrobial protection to prevent biofilm formation on the device. The BVF will act as a temporary foreign body until the active infection is completely cleared or the implanted device has resorbed, restoring a normal tissue healing environment.

A novel BVF that will survive in an infected environment has been designed. It combines well-known osteoconductive biomaterial bound together with clinically used degradable polymers containing solid tobramycin, resulting in a composite ceramic-polymer (Fig. 1). This product is known as EP Granules with Tobramycin and was created in collaboration with orthopaedic surgeons and bioengineers. These granules are primarily composed of osteoconductive, resorbable solid Calcium (Ca)-salt matrix that elutes tobramycin. In contrast to ALBCs, EP Granules with Tobramycin are 100% resorbable, releasing 100% of the tobramycin sulfate load to the local implant site over an extended period during its presence as a resorbing foreign body in bone. *In-vitro* elution studies demonstrated that this BVF continuously released tobramycin as it resorbed, providing a sustained release above the Minimum Bactericidal Concentration (MBC) of *Staphylococcus aureus* for 4-5 weeks followed by release above the Minimum

Inhibitory Concentration (MIC) until 8 weeks (Fig. 2). This process allowed restoration of tissue site homeostasis and immune competence was then reinstated [10]. Thus, the device does not present a permanent foreign body onto which bacteria more readily colonize.

The Ca-salt resorbable BVF acts as a carrier for the antibiotic and as a scaffold for bone growth. The product is intended to provide an osteoconductive scaffold for new bone growth when placed in a bone void or defect that is not intrinsic to the stability of the bone. The product is resorbable, such that the BVF scaffold is entirely replaced with ingrown new bone and tissue (Fig. 3). The addition of the tobramycin sulfate to the BVF is designed to allow new bone growth into the BVF scaffold, even in the presence of infection. Local tobramycin is used to prevent bacterial contamination and colonization of the BVF and to facilitate host bone infiltration. Specifically, the product is intended for use in the first stage of an infected Total Joint Arthroplasty (TJA) revision. Importantly, use of EP Granules with Tobramycin is not intended to eradicate the active infection but can be used while any such infection is being treated with standard of care methods, namely systemic antibiotics.

Tobramycin was selected due to its wide gram-positive and gram-negative microbacterial coverage and its universal use in all infected PJI cases. An infectious organism is often unknown at the time of intervention and tobramycin is used as a first line additive to control the infection. Vancomycin combined with EP granules has also been tested with predicted sustained release in elution studies and can be used for resistant bacteria to tobramycin.



Figure 1: Polymers containing solid tobramycin, resulting in a composite ceramic-polymer.

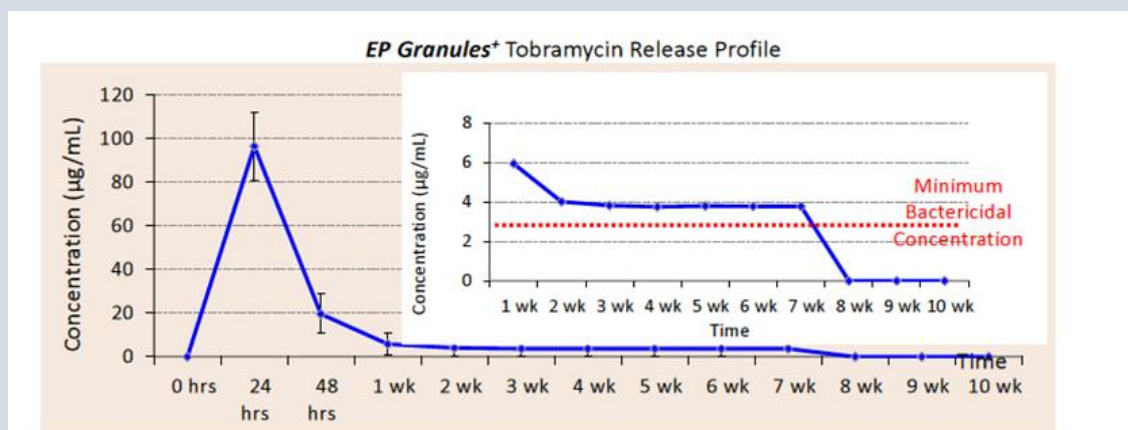


Figure 2: Antibiotic elution kinetics for tobramycin from proposed BVF device. Minimum bactericidal concentration for the *S. aureus* strain as determined experimentally is shown in red. Sustained antimicrobial release to 8 weeks is shown.

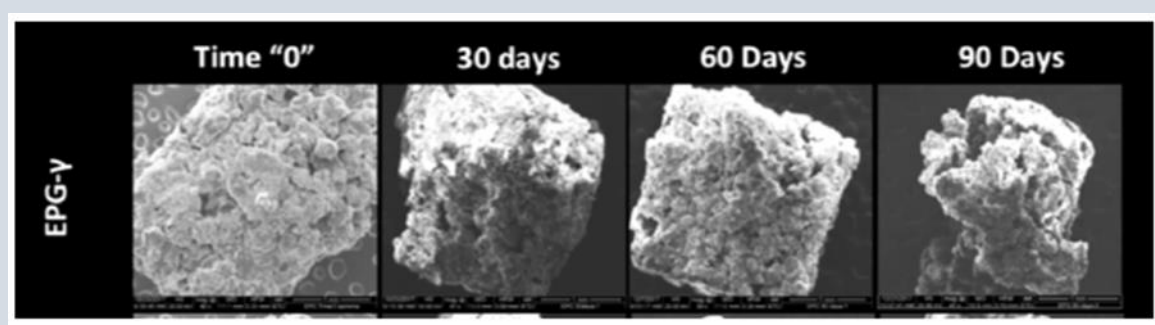


Figure 3: SEM micrographs of the surface of EP Granules with Tobramycin showing erosion of the surface with time.

Materials Composition of EP Granules with Tobramycin

EP Granules with Tobramycin are comprised of calcium Hydroxyapatite (HA), Calcium Carbonate (CaCO_3) and Calcium Chloride (CaCl_2) particles bound together with a degradable polymer-based binding matrix of Poly Caprolactone (PCL), Poly Lactide-Co-Glycolide (PLGA) and a water-soluble Poly Ethylene Glycol (PEG) with a broad spectrum antibiotic, tobramycin sulfate. This device is homogeneously distributed as a fine powder into the polymer matrix that binds the granules. The HA, CaCO_3 and CaCl_2 particles are dispersed uniformly throughout the volume of the compound. The process of manufacturing EP Granules with Tobramycin exploits the use of solid tobramycin sulfate particles blended directly into the molten polymer + osteoconductive HA and CaCO_3 particle matrix mixture, followed by solidification to form the granulated BVF product. Particulate tobramycin sulfate is thereby

dispersed homogeneously throughout the BVF granules, bound together and surrounded by the device's polymer blended matrix and other solid, soluble porogens that facilitate matrix resorption and osteoconduction. The tobramycin sulfate is encapsulated in blended hydrophobic polymers, PCL and PLGA, hindering tobramycin sulfate dissolution and release, except when directly exposed to aqueous milieu on the device surface (the initial burst fraction). The principal role of PLGA in EP Granules with Tobramycin is to provide a degradable hydrophobic matrix binder that degrades concomitant with the water ingress and PEG dissolution, but does so more rapidly than PCL degradation. This process further exposes the osteoconductive CaCO_3 and HA particles to the patient's own bone-forming cells, which then can attach and proliferate to form new bone. The purpose of PCL is to slow hydrophobic polymer degradation. This function maintains the binding of PCL to ceramic constituents over a longer period of time, providing stability for the structure as bone growth continues and matures. While undergoing controlled resorption, all three polymer binders promote bone growth through time-controlled exposure of the device's Ca-salt components (HA and CaCO_3) to absorbing patient proteins, physiological aqueous milieu and invading bone-producing cells. The three polymer components imbue the matrix with time-controlled drug release properties that allow different phases of tobramycin release based on varied polymer degradation.

***In-vivo* Studies to Investigate Ep Granules with Tobramycin**

New Zealand Rabbit Study

EP Granules with Tobramycin have been studied in small and large animal models. A summary of the studies is provided in Table 1. The first study involved New Zealand white rabbits and focused on the early version of EP Granules, with and without tobramycin [11]. The tobramycin was made with an HA- CaCO_3 composite, PCL and PEG. The HA- CaCO_3 composite was a commercial bone graft substitute biomaterial (ProOsteon 500R, Zimmer-Biomet). The overall study objective was to assess the effect of extended and controlled release of tobramycin in both infected and noninfected distal radius bone defects in New Zealand white rabbits.

This pilot study had seven cohorts:

1. ProOsteon control no infection
2. ProOsteon inoculated with 10⁵ Colony Forming Units (CFU) of *S. aureus*
3. EP Granules without tobramycin no infection
4. EP Granules without tobramycin inoculated with 10⁵ CFUs of *S. aureus*
5. ProOsteon with 10% antibiotic soak inoculated with 10⁵ CFUs of *S. aureus*

Evans DC | Volume 3; Issue 1 (2022) | JOSR-3(1)-026 | Review Article

Citation: Evans BG, et al. A Novel Bone Void Filler for Use in Prosthetic Joint Infections. J Ortho Sci Res. 2022;3(1):1-14.

DOI: <http://dx.doi.org/10.46889/JOSR.2022.3102>

6. EP Granules with tobramycin no infection

7. EP Granules with tobramycin inoculated with 10^5 CFUs of *S. aureus*

Test Outline and Objective	# Animals / Groups	Time Points	Assessments	Key Outcomes
Rabbit study to assess ability of EP Granules with Tobramycin to grow bone in infected and noninfected defects.	7 rabbits per group; 7 groups: 1, 2. ProOsteon BVF with and without infection 3, 4. EP Granules with PCL, PEG polymers without antibiotic, with and without infection 5. ProOsteon soaked in 10% antibiotic with infection 6, 7. ProOsteon with PCL, PEG polymers and tobramycin, with and without infection	8 weeks	Electron microscopy, μ CT, histomorphometry and light microscopy analyses	In contrast to the bone filler only controls, which provided no antibiotic protection and required euthanasia 3 weeks post-operatively. Tobramycin releasing BVF animals showed no signs of infection (clinical, microbiological or radiographic) when euthanized at the 8-week study endpoint.
Sheep study to assess ability of EP Granules with Tobramycin to grow bone in infected and noninfected defects using ProOsteon 500R as control BVF.	7 sheep per group; 4 groups: 1. ProOsteon without infection 2. EP Granules with tobramycin without infection 3. ProOsteon with infection 4. EP Granules with tobramycin with infection	12 weeks	Electron microscopy, μ CT, histomorphometry and light microscopy analyses	The experimental group inoculated with <i>S. aureus</i> showed no detectable bacteria at the study's 12-week endpoint, while infection controls required euthanasia 6-11 days post-inoculation due to infection. All groups, except the infection control, exhibited bone formation comparable to commercial filler ProOsteon® 500R.

Table 1: Summary of *in-vivo* Studies for EP Granules with Tobramycin.

Results of New Zealand Rabbit Study

Necropsy was completed at 8 weeks, at which time the radius was dissected and x-ray images of the defect site were obtained. Subsequently, the bone tissue was embedded in Polymethyl Methacrylate (PMMA) for quantitative microscopic histomorphometric analysis with staining for light microscopy. Preoperative, postoperative and weekly radiographic images were taken at the 8-week necropsy time point to assess inflammation, bone necrosis, widening of the bone

Evans DC | Volume 3; Issue 1 (2022) | JOSR-3(1)-026 | Review Article

Citation: Evans BG, et al. A Novel Bone Void Filler for Use in Prosthetic Joint Infections. J Ortho Sci Res. 2022;3(1):1-14.

DOI: <http://dx.doi.org/10.46889/JOSR.2022.3102>

shaft, new bone formation and adjacent soft tissue reactions (Fig. 4). The EP Granules with Tobramycin combination device demonstrated extended bactericidal activity with eradication of the infection challenge over the 8-week implantation, even in the presence of a rigorous, persistent, local *S. aureus* infection challenge. By comparison, rabbits implanted with a control device without antibiotics had to be euthanized in 2-4 weeks due to excessive local infection. Notably, in this study, none of the defects treated with EP Granules with Tobramycin were found to be colony-positive in either bone or soft tissue, indicating that local tobramycin release effectively rendered the infected bone void site sterile. In contrast, the ProOsteon 500R control devices provided no antibiotic protection and required animals to be euthanized between 2-4 weeks postoperatively. Rabbits with tobramycin-releasing EP Granule devices showed no signs of infection (clinical, microbiological or radiographic) and exhibited no observable signs of soft tissue inflammation when euthanized at the 8-week study endpoint. Osteointegration was only peripherally evaluated in this pilot study since the 8-week endpoint was likely insufficient to allow host bone integration. However, histology indicated that the defect sites exhibited fibrous encapsulation with some minimal osteointegration, which was observed for both the EP Granules with Tobramycin and the control device cohorts. This outcome was attributed to the early device formulation not being optimized for degradability and matrix porosity for effective osteointegration. Overall, the rabbit study showed that this version of EP Granules with Tobramycin BVF was effective for controlled and extended release of tobramycin in contaminated bone voids. Successful demonstration of this feature of EP Granules with Tobramycin led to further optimization of the device porosity by adding a porogen, CaCl_2 and PLGA to the polymer blend, which created a resorbable polymer to control matrix degradation kinetics and enhance osteointegration, thus providing a clinically meaningful benefit.

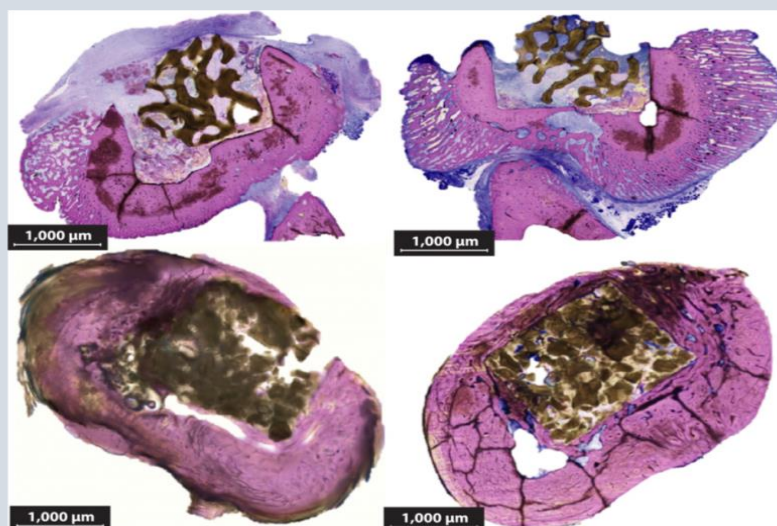


Figure 4: Sanderson's Rapid Bone Stain of showing Ca-salt resorbable BVF devices in rabbit radial defects inoculated with *S. aureus*: Top row (BVF + tobramycin without

polymers), Bottom row (BVF + tobramycin encapsulated in polymers). Note presence of fibrous capsule (blue), immune cells and infection in top row and integration with host bone (purple) in bottom row, indicating benefits of polymer controlled extended release for better host bone - device response.

Sheep Study

Based on the pilot New Zealand rabbit study, a second statistically powered study in sheep (distal femur defect model) was completed [12]. This model evaluated bone growth in distal femur defects loaded with 105 CFUs *S. aureus* and noninfected defects. The sheep study used an Institutional Animal Care and Use Committee (IACUC) approved animal protocol. The hypothesis stated that the EP Granules with Tobramycin device will grow new bone in a distal femoral defect, even in the presence of active infection. Two groups of sheep were utilized in this *in-vivo* study: the control group used ProOsteon 500R granules and the challenge group used EP Granules with Tobramycin device. The EP Granules with Tobramycin device was made into 2 x 2 x 6 mm sized granules, which were sterilized and surgically implanted in a rectangular defect in the medial face of the femoral condyle of each sheep. The bone-device interface was evaluated after animal sacrifice at 12 weeks postimplantation, using backscatter electron microscopy, as well as standard histology and histomorphometry methods. Microbiologic analysis was completed with cultures on all specimens during the study period.

The sheep implant treatment study included 4 groups with n=7 in each group:

1. ProOsteon 500R in a noninfected, surgically created distal condylar cancellous defect
2. EP Granules with Tobramycin in a noninfected, surgically created distal condylar cancellous defect
3. ProOsteon 500R in an infected, surgically created distal condylar cancellous defect with 105 CFUs of *S. aureus* (ATTC 49230)
4. EP Granules with Tobramycin in an infected, surgically created distal condylar cancellous defect with 105 CFUs of *S. aureus* (ATTC 49230)

Results of Sheep Study

The analysis of study data specifically aimed to quantify and compare the percentage of new bone and the percentage of residual ceramic remaining for all treatment groups at 12 weeks (Table 1). When no infection was introduced, both EP Granules with Tobramycin and ProOsteon 500R were found to be osteoconductive, with normal bone remodeling. No statistically significant difference was noted between the EP Granules with Tobramycin and the control ProOsteon 500R device in terms of new bone generated, residual ceramic remaining and bone mineral apposition. Actively remodeling bone was observed in infected voids filled

with EP Granules with Tobramycin and in noninfected voids filled with either ProOsteon 500R or EP Granules with Tobramycin, evidenced by fluorescing Calcein signals in bone. Importantly, all sections exhibited accelerated mineral apposition rates (mean $\sim 1.4 \mu\text{m/day}$), roughly doubling normal bone remodeling rates in sheep ($0.71 \pm 0.21 \mu\text{m/day}$). This finding supports the hypothesis that new bone formation is not adversely affected by local controlled tobramycin release or by resorption of the bone void fillers.

Bone formation observed in groups 1, 2 and 4 was not statistically different ($p > 0.05$) for either perimeter or center of defect mineral apposition rates. Analysis of histological samples using Sanderson's rapid bone stain on sections ground for light microscopy corroborated findings from the back scattered electron microscopy and mineral apposition rate analyses (Fig. 5). Bone formation and integration of the bone void filler granules were observed in the infected group that was filled with EP Granules with Tobramycin and in the noninfected groups filled with either ProOsteon 500R or EP Granules with Tobramycin. Active bone formation, characterized by osteoclastic resorption coupled with osteoid deposition, was observed throughout cohort bone void sites.

However, animals treated with ProOsteon 500R in infected voids, group 3, exhibited signs of infection (limping) and survived only 6-11 days. After euthanization, microbiological examinations showed severe inflammatory responses consistent with osteomyelitis. Numerous inflammatory cells, including neutrophils and lymphocytes, characterized this signal, as well as numerous osteoclasts and extensive osteoclastic resorption. The EP Granules with Tobramycin group inoculated with *S. aureus* showed no detectable bacteria in bone or adjacent soft tissues at the study's 12-week endpoint. Conversely, infection control animals treated with ProOsteon 500R (without any antibiotic) had to be euthanized 6-11 days postinoculation due to systemic infection and obvious signs of pain. This sheep study validated that EP Granules with Tobramycin were able to withstand the bacterial insult, growing new bone and degrading equivalently to the control group. Overall, the sheep study showed that EP Granules with Tobramycin were safe and effective as a BVF to grow new bone in infected bone voids [12].

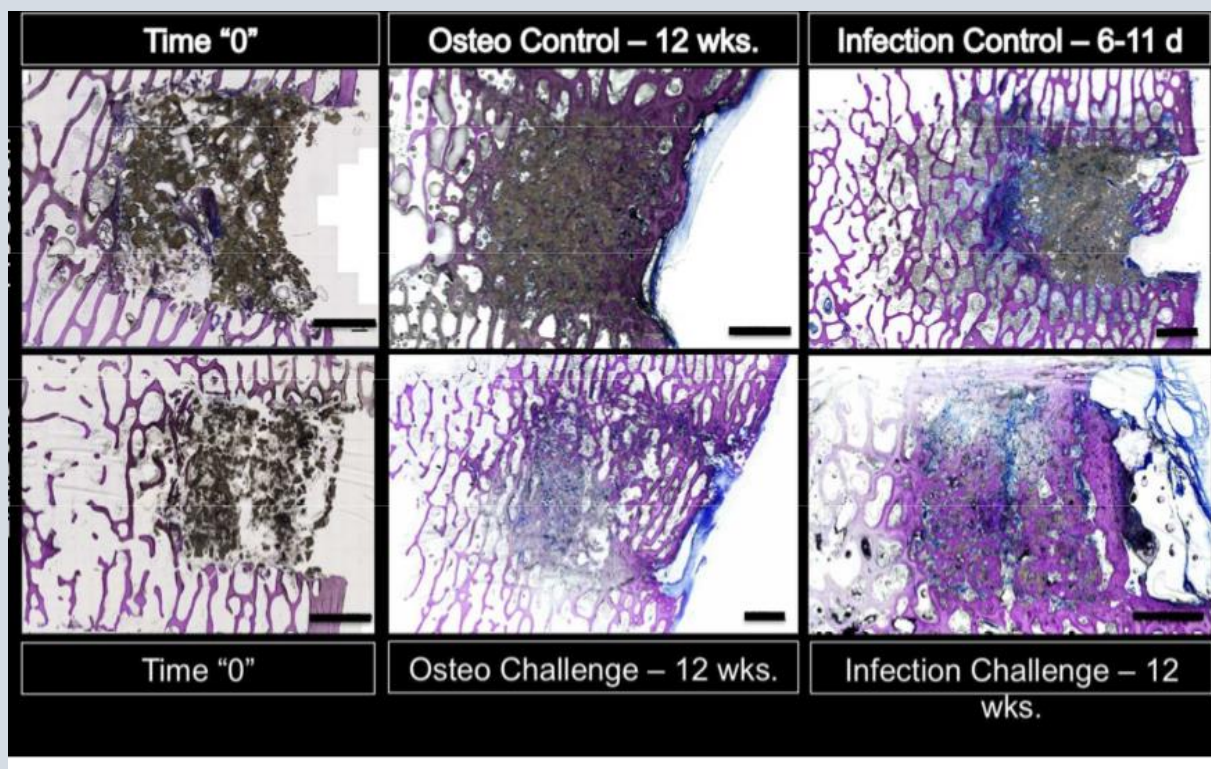


Figure 5: Sanderson's Rapid Bone Stained Images of BVF implants in distal femur defects with and without *S. aureus* inoculation: Top row: standard Ca-salt resorbable BVF, Bottom row: Ca-salt resorbable BVF with polymer encapsulated tobramycin: extensive new bone formation evident in both the non-infected (bottom row, middle) and infected defects (bottom row, right). By contrast, standard Ca-salt resorbable BVFs show fibrous encapsulation after ~ 6 -11 days of implantation (top row, right), Black line marker = 2000 μm .

Discussion

All orthopaedic implants are known sources for implant-centered infections. To date, bone grafting has been contraindicated in orthopaedic infections and is performed only when all signs of infection have ceased. Untreated infection in bone and tissue, which colonizes the BVF when no antimicrobial is present, is correlated with the absence of new bone deposition/formation. Attempts to simply add antibiotics to BVFs by soaking or mixing topically have not been successful and are not widely used. There is no consistent delivery of antibiotics to the surrounding tissue and only an initial short-term release of local antibiotic. Introduction of a BVF that provides long-term antibiotic elution to bone and surrounding soft tissues will provide a much-needed addition to the current armamentarium required to treat orthopaedic infections. Not only will bone volume increase, but also chronic infection and osteomyelitis avoidance of chronic infection or osteomyelitis will be possible can be avoided

with this BVF. Additionally, a BVF that controls local infection may act as a bone graft extender for autogenous bone grafting.

The design of EP Granules with Tobramycin at this study phase, in the animal model, has demonstrated that this BVF remains colonization free during an active local infection when initial bone remodelling is critical to the device's supportive function in bone regeneration. With this novel design, neither clinical signs nor pathogenic CFUs culturable from the implant site have been found. In addition, substantial new bone deposition was observed. Testing of EP Granules with Tobramycin devices validated performance via determination of both *in-vitro* characteristics and antimicrobial properties and *in-vivo* animal models (small animals, rabbits and large animals, sheep) [10-12]. In contrast to nonantibiotic containing BVFs, animals (rabbit model) treated with EP Granules with Tobramycin BVFs showed no signs of infection (clinical, microbiological or radiographic). This outcome demonstrated that locally controlled and sustained antibiotic release from these devices in infected bone sites prevented device colonization by bacteria in this 8-week *in-vivo* study. Finally, a pivotal preclinical sheep study showed in a statistically significant manner that tobramycin eluting bone void filler prevents device colonization and grows new bone in 100% of animals with infected defects. However, 100% of the animals with infected defects treated with conventional (non-antibiotic containing) bone void fillers had to be euthanized within 11 days due to infection.

The cumulative results of the *in-vitro* and *in-vivo* test data show that EP Granules with Tobramycin are safe and effective in growing new bone in bone voids that have been contaminated with *S. aureus*. The presence of new bone formed by progressive resorption and replacement of the granules has been verified by both radiological and histomorphometric evaluations. Resorption rate and bone formation were found to be similar to that of control devices without tobramycin. This finding suggests that EP Granules with Tobramycin will provide bone stability for future implants. In a study by Oakes, et al., impaction grafting with a cemented prosthesis had favorable outcomes for 1 year and beyond. They verified that bone growth progressed in and around the impaction grafted BVF voids [13]. The sheep study demonstrated additional support for continued bone growth, evidenced by radiographs and μ CT scans, as well as histological and histomorphometric evaluations. The infection data also verified that a balance is achieved between the site-specific antibiotic release to mitigate known implant infection risks and the ability to grow new bone without threats of compromised bone growth function.

Sheep study results have led to FDA approval for a human multicenter clinical trial for infected total knee replacements. The potential advantages of EP Granules with Tobramycin in human clinical trials would be preservation of bone mass with new bone formation and possible reduced reinfections. While the limitations of this BVF include inability to support implants alone, as well as a small percentage of graft resorption that was observed at final healing in the sheep study, overall bone volume was increased and the future graft will be supported with augmentation and cement at the time of implantation. Based on future positive clinical results

of new bone formation, the FDA has allowed for product approval through a De Novo 510(k) submission.

Summary

This novel BVF design, EP Granules with Tobramycin, uses an osteoconductive biomaterial, as well as antibiotic binding degradable polymers, which results in a composite ceramic-polymer that has the potential for treatment in orthopaedic infections. The initial design is for application in stage-1 surgery for PJI where BVF is currently contraindicated. This product has the potential to provide greater bone growth and may result in fewer infected revisions. Overall, the battery of preclinical *in-vitro* and *in-vivo* studies demonstrates that the EP Granules with Tobramycin BVF combination product has met the efficacy criteria and has fulfilled the requirements for an FDA- approved clinical multicenter trial.

Conflict of Interest

The authors declared no conflicts of interest with respect to the research, authorship and/or publication of this article.

References

1. Laurencin C, Khan Y, El-Amin SF. Bone graft substitutes. *Exp Rev Med Devices*. 2006;3(1):49-57.
2. Winkler H, Kaudela K, Stoiber A, Menschik F. Bone grafts impregnated with antibiotics as a tool for treating infected implants in orthopedic surgery-one stage revision results. *Cell Tiss Banking*. 2006;7(4):319-23.
3. Bohm ER, Dunbar MJ, Frood JJ, Johnson TM, Morris KA. Rehospitalizations, early revisions, infections, and hospital resource use in the first year after hip and knee arthroplasties. *J Arthroplasty*. 2012;27(2):232-7.
4. Corona PS, Vicente M, Carrera L, Rodríguez-Pardo D, Corró S. Current actual success rate of the two-stage exchange arthroplasty strategy in chronic hip and knee periprosthetic joint infection: insights into non-completed second-stage cases. *Bone Joint J*. 2020;102(12):1682-8.
5. Petis SM, Perry KI, Mabry TM, Hanssen AD, Berry DJ, Abdel MP. Two-stage exchange protocol for periprosthetic joint infection following total knee arthroplasty in 245 knees without prior treatment for infection. *JBJS*. 2019;101(3):239-49.
6. Fletcher M, Spencer R, Langkamer VG, Lovering A. Gentamicin concentrations in diagnostic aspirates from 25 patients with hip and knee arthroplasties. *Acta Orthop Scand*. 2004;75(2):173-6.
7. Belt HV, Neut D, Schenk W, Horn JR, Mei HC, Busscher HJ. Gentamicin release from polymethylmethacrylate bone cements and *Staphylococcus aureus* biofilm formation. *Acta Orthop Scand*. 2000;71(6):625-9.
8. Sorensen TS. Rapid release of gentamicin from collagen sponge: *in-vitro* comparison with plastic beads. *Acta Orthop Scand*. 1990;61:353-6.
9. Campana V, Milano GI, Pagano E, Barba M, Cicione C, Salonna G, et al. Bone substitutes in orthopaedic surgery: from basic science to clinical practice. *J Mat Sci: Mater Med*. 2014;25(10):2445-61.

Evans DC | Volume 3; Issue 1 (2022) | JOSR-3(1)-026 | Review Article

Citation: Evans BG, et al. A Novel Bone Void Filler for Use in Prosthetic Joint Infections. *J Ortho Sci Res*. 2022;3(1):1-14.

DOI: <http://dx.doi.org/10.46889/JOSR.2022.3102>

10. Brooks AE, Brooks BD, Davidoff SN, Hoglebe PC, Fisher MA, Grainger DW. Drug Delivery Transl Res. 2013;3:518-30.
11. Brooks BD, Sinclair KD, Grainger DW, Brooks AE. A resorbable antibiotic-eluting polymer composite bone void filler for perioperative infection prevention in a rabbit radial defect model. PloS One. 2015;10(3):e0118696.
12. Ferrell Z, Grainger DW, Sinclair KD. Antibiotic-eluting resorbable bone-void filler evaluated in a large animal infection prevention model. Eur Cell Mater. 2019;37:265-76.
13. Oakes DA, Cabanela ME. Impaction bone grafting for revision hip arthroplasty: biology and clinical applications. J Am Acad Orthop Surg. 2006;14(11):620-8.