

OSTEOSET® T

Medicated Bone Graft Substitute

TECHNICAL MONOGRAPH



WRIGHT.

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Proper surgical procedures and techniques are the responsibility of the medical professional. The following guidelines are furnished for information purposes only. Each surgeon must evaluate the appropriateness of the procedures based on his or her personal medical training and experience. Prior to use of the system, the surgeon should refer to the product package insert for complete warnings, precautions, indications, contraindications and adverse effects. Package inserts are also available by contacting Wright Medical Technology, Inc.

Introduction

OSTEOSET® T is a unique medical grade calcium sulfate bone graft substitute which is enhanced for use in infected sites by incorporating 4% tobramycin sulfate. This product is a resorbable bone graft substitute which acts as a scaffold for new bone formation, **Figures 1-4**, while releasing tobramycin at a predictable rate. The tobramycin is released locally, allowing therapeutic antibiotic levels at the graft site, while maintaining low systemic antibiotic levels. This local treatment of infection allows new bone formation in the defect site, while decreasing potential systemic effects.



Figure 1
Radiograph taken immediately after implantation of OSTEASET® T with 4% tobramycin sulfate in a surgically-created canine humeral defect.



Figure 2
Radiograph taken at 2 weeks, showing pellet resorption with a corresponding increase in bone density along original bone defect edge.



Figure 3
Radiograph taken at 6 weeks, showing complete pellet resorption and the formation of new bone within the original defect. High local levels of tobramycin have had little or no effect on bone formation.

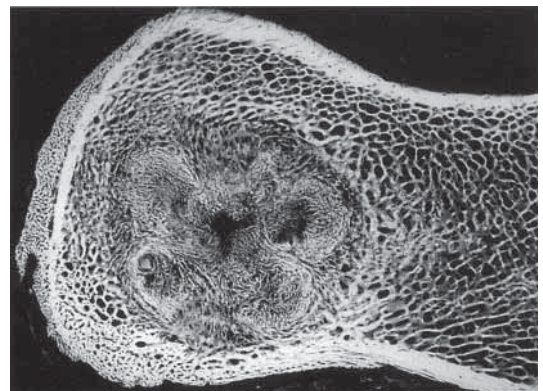


Figure 4
Contact radiograph of canine humerus that had been implanted with OSTEASET® T pellets shows concentric lamellae (ringlets) of new bone formed at the site.

Overview of OSTEOSSET®

Many reports in the literature describe the use of calcium sulfate as a bone graft substitute. As early as 1892, Dreesmann¹ reported on the results of filling osseous defects with calcium sulfate. Peltier² conducted a thorough literature review of studies which described the successful filling of bone void defects with calcium sulfate materials. Calcium sulfate was found in these studies to be generally well tolerated by tissues and resorbed. These encouraging but sometimes inconsistent results sparked additional investigation on the use of calcium sulfate as a bone graft substitute containing antibiotics to treat infected bone.

Over the past 15 years, scientists and clinicians associated with United States Gypsum Company have extensively studied and characterized calcium sulfate. They discovered that by controlling the shape and size of the compound's hemihydrate crystals, the resorption rate of the final product could be controlled.³ OSTEOSSET® is the product of that research.

OSTEOSSET® pellets offer a framework into which a patient's bone can grow. ***The pellets are resorbed at a rate consistent with the new bone growth*** (an average of 4-8 weeks). OSTEOSSET® pellets were cleared by the Food and Drug Administration in June 1996 and received CE mark late the same year. Since those clearances, OSTEOSSET® has been used in thousands of cases and proven to be safe, predictable, and effective.

The effectiveness of OSTEOSSET® pellets can be illustrated by the following case of a 73 year-old male who underwent revision total knee arthroplasty. Bone had been lost from lysis about the tibial stem and from removal of the implant. Pellets were placed into the defect and around the revision tibial stem. **Figure 5A** X-ray at nine months demonstrated dissolution of the OSTEOSSET® pellets with early restoration of trabecular bone. **Figure 5B**



Figure 5A



Figure 5B

Medical Grade Calcium Sulfate

The crystalline form of the base material OSTEASET® can be described as an alpha-hemihydrate. The alpha-hemihydrate is process in the following manner:



The medical grade alpha-hemihydrate calcium sulfate is critical for the consistent bone response in OSTEASET® pellets. The crystalline structure, composition, and particle size distribution resulting from the use of the alpha-hemihydrate are the functional attributes contributing to the controlled resorption and uniform bone response. However, the complete mechanism of bone formation with OSTEASET® is currently being investigated. **Figures 6 and 7** show the differences in the crystal structure and shape of the OSTEASET® alpha-hemihydrate raw material and other available calcium sulfate materials.

The OSTEASET® manufacturing process creates a uniform crystalline structure of specific size and shape resulting in a controlled resorption rate consistent with the rate of the new bone formation. This crystalline structure is found consistently only in OSTEASET®.

Other non-medical grade calcium sulfates may resorb too rapidly, preventing creeping substitution of newly woven bone. Conversely, slow resorption of non-medical grade calcium sulfate may inhibit new bone growth. Accordingly, the use of common forms of calcium sulfate have historically resulted in sporadically successful outcomes.^{1,2}

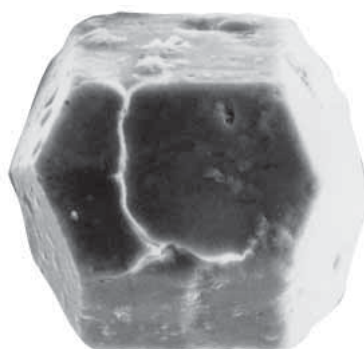


Figure 6
OSTEASET® medical grade calcium sulfate

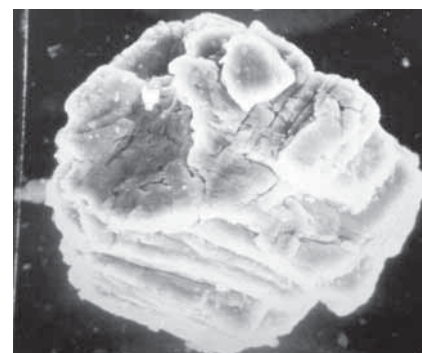


Figure 7
OSTEASET® non-medical grade calcium sulfate

Antibiotic Impregnated Bone Graft Substitute

Several clinical studies exist reporting the use of antibiotic-impregnated calcium sulfate materials. Sulo, *et al.*⁴ used gentamicin-impregnated plaster-of-Paris (POP) beads as a bone void filler in 409 cases with chronic osteomyelitis. The author's summary of the results states: "The technique was associated with large surgical excisions of the septic area, stabilization of the infected site and coverage using flaps. About 95% of patients were cured after a 37-month average follow-up." It was concluded that, "This technique allowing an immediate filling of the bone loss using a resorbable material and leading to high antibiotic concentrations is reliable." However, complete filling of the bone loss was obtained in only 42% of the cases with results somewhat age dependent, as younger patients completely filled the defect with bone more frequently than did older patients.

Kovacevic⁵ (reviewed by Mackey) reported on three patients who had osteomyelitis of the tibia and whole defects were treated with cylinders of POP containing additives of penicillin and sulfonamide powder. Healing and reconstitution of the diaphysis occurred in each patient.

Aminoglycosides

The aminoglycosides family is a group of antibiotics which includes tobramycin, gentamicin, netilmicin, kanamycin, and amikacin.⁶ The name aminoglycoside comes from the fact that these substances contain amino sugars linked to an aminocyclitol ring by glycosidic bonds. These agents are primarily used to treat infections caused by gram-negative bacteria. The aminoglycosides are bactericidal and function by interfering with microbial protein syntheses. They enter bacteria by diffusing through the aqueous channels in the outer cell membrane. Once inside the cell, the aminoglycosides bind to polysomes and interfere with protein synthesis, producing aberrant proteins. These aberrant proteins are inserted into the cell membrane, altering permeability and increasing aminoglycoside transport. Cell leakage then begins with small ions, larger molecules, and proteins leaving the cell, disrupting the cell envelope and resulting in cell death. The bactericidal effect takes place rapidly and the effect is concentration dependent. Residual bactericidal activity is present after the serum concentration has fallen below the minimum inhibitory concentration.⁷

Aminoglycosides are highly polar and are very poorly absorbed by the gastrointestinal tract, requiring intravenous or intramuscular administration to achieve the desired bactericidal effect. Since these substances are polar, they are excluded from most cells, leading to low concentrations in secretions and tissues. The only areas of potentially high concentration are the renal cortex and the endolymph and perilymph of the inner ear, which can lead to the two most common toxic effects of aminoglycoside treatment, nephrotoxicity and ototoxicity, respectively.

Osteomyelitis is most commonly caused by *Staphylococcus aureus* (*S. aureus*). Klemm, *et al*⁸ reported that *S. aureus* is responsible for approximately 65% of all osteomyelitis cases. The literature reports on the usage of many types of antibiotics to treat this type of infection. Frequently, treatments utilize beta-lactam or cephalosporin antibiotics. If a gram-negative pathogen is present, the use of aminoglycosides, is recommended.¹⁰ Some of the aminoglycosides, including tobramycin and gentamicin, are also effective against gram-positive *S. aureus*.⁷

There are, however, toxicity issues associated with systemic delivery of aminoglycoside antibiotics. According to Whelton, comparisons of gentamicin and tobramycin have shown that tobramycin is less nephrotoxic and potentially less ototoxic.¹² Additionally, Chambers and Sande⁷ report that animal studies suggest that tobramycin may be less toxic to hair cells in the cochlear and vestibular end organs and cause less renal tubular damage than does gentamicin.

In summary, tobramycin was chosen as the antibiotic to incorporate into OSTEASET[®] because of its activity against causative agents of osteomyelitis and, compared with gentamicin, fewer toxicity issues.



In vitro Elution Profiles

The release profile of tobramycin from OSTEASET® T pellets has been determined from *in vitro* experiments in phosphate buffered saline (PBS). A representative profile is shown in **Figure 8**. For the results shown here, 8 pellets were placed in 20ml of PBS. The PBS was replaced on a daily basis. A maximum amount of tobramycin was released on the first day, approximately 122 μ g/ml, followed by a decline in release to a second day concentration of approximately 10 μ g/ml. Subsequent release from day 3 to day 22 showed a gradual decline in concentration from approximately 15 μ g/ml to 3 μ g/ml, respectively. The concentrations from days 3 to 22 are above minimum inhibitory concentrations (MIC) for many osteomyelitis causative agents. The Physician's Desk Reference reports a MIC range of 0.12 to 1.0 μ g/ml for *S. aureus*.¹³

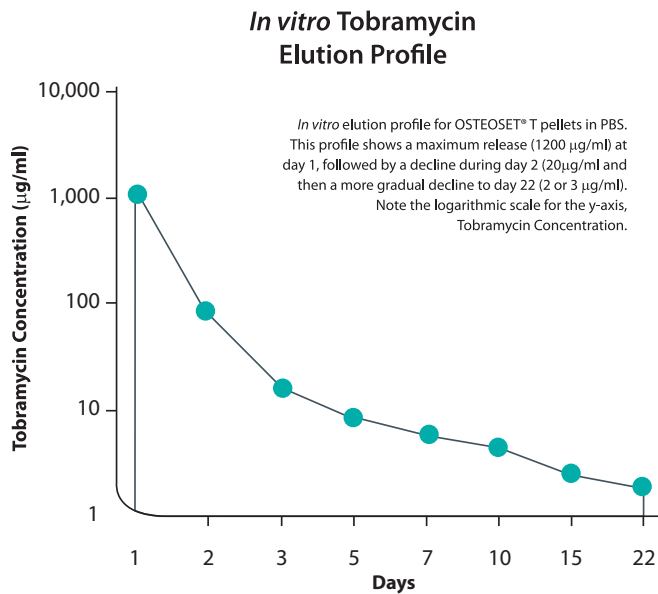


Figure 8

In vivo Elution Profiles

A canine animal model was used to determine systemic and local tobramycin levels after the implantation of OSTEOSET® T pellets in surgically-created humeral bone defects.¹⁴ In the study reported here, each animal weighed approximately 31kg and was implanted with 50 pellets containing a total of 200mg of tobramycin sulfate, which, based on stoichiometry, corresponds to 130mg of tobramycin, or approximately 4.1mg of tobramycin per kg of body weight. Serum and surgical site samples were collected at various time periods and later analyzed to determine systemic and local tobramycin levels. The canine serum and local tobramycin levels are shown in **Figure 9**. The systemic and local tobramycin elution profiles exhibited similar characteristics as those shown for *in vitro* experiments. As was the case for the *in vitro* profiles, **Figure 8**, systemic and local profiles showed maximum tobramycin elution within the first day, followed by a decline during the second day with a more gradual decline for the remaining time period.

An important difference between the systemic and local levels was the amount of tobramycin present. Systemic levels reached a maximum of only 3.3µg/ml at 1 hour, a level of 0.28µg/ml at day 1 and undetectable levels (<0.2µg/ml) for all remaining time periods. Given the dosage level in the canine study, the blood serum levels remained below 12µg/ml, the reported nephrotoxic and ototoxic serum level for humans with normal renal function.¹³

In contrast to the low systemic tobramycin levels, the local tobramycin levels were much greater, with levels of approximately 2100µg/ml at 1 hour and 125µg/ml at day 1. In addition, levels greater than minimum inhibitory concentrations (MIC) were maintained for the time periods between 14 and 28 days. Again, for *S. aureus*, the MIC range is 0.12-1.0µg/ml.¹³ It should be noted that the maintenance of MIC locally is in contrast to the non-detectable serum levels for the same time period.

These results show that implantation of OSTEOSET® T pellets has the desired effect of concentrating tobramycin levels locally while simultaneously maintaining low to no-detectable serum levels, thus minimizing possible systemic toxic effects.

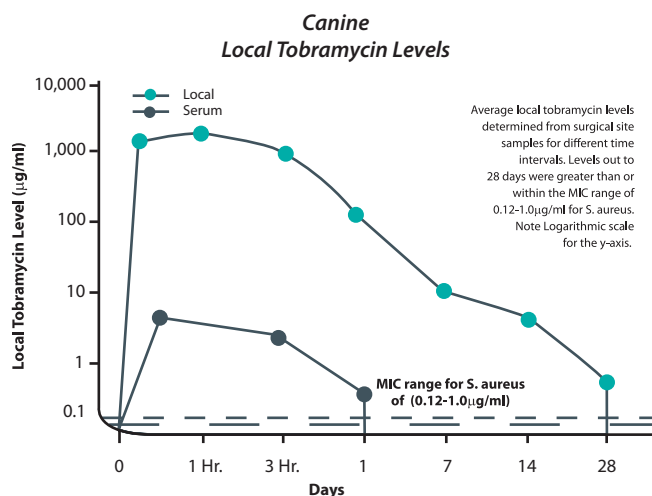


Figure 9

Preclinical Results

Osteomyelitis Treatment

Experimentally-induced osteomyelitis with *S. aureus* (ATCC 42923) in an established rabbit model was used to evaluate the treatment of efficacy of OSTEASET® T.¹⁵ A segment of the radius was removed and injected with *S. aureus* and replaced. After four weeks with no adjuvant therapy, the rabbits underwent surgical debridement and were randomized to four weeks of treatment with either OSTEASET® T pellets containing 10% tobramycin sulfate, placebo unmedicated calcium sulfate pellets or debridement only.



Figure 10A
Pre-debridement



Figure 10B
Pre-debridement with OSTEASET® T pellets in place.



Figure 10C
4 weeks post-debridement and treatment with OSTEASET® T demonstrates abatement of infection and bone repair.

Figure 10A shows radiographically the infected site before surgical debridement. **Figure 10B** shows the same infected site after debridement and implantation of OSTEASET® T pellets with a temporary passive catheter to measure local tobramycin levels in the exudate. **Figure 10C** shows the same site at four weeks and radiographically illustrates that the pellets have been resorbed and replaced by bone.

The rabbits treated with OSTEASET® T pellets showed significantly higher treatment efficacy rates ($p=0.049$ Fisher Exact test) than rabbits in other treatment groups. **Figure 11** High local levels of tobramycin (greater than 100 times MIC) were produced while maintaining low systemic levels. The OSTEASET® T treatment group demonstrated abatement of the infection, and in some animals, repair of the critical-size bone defect.

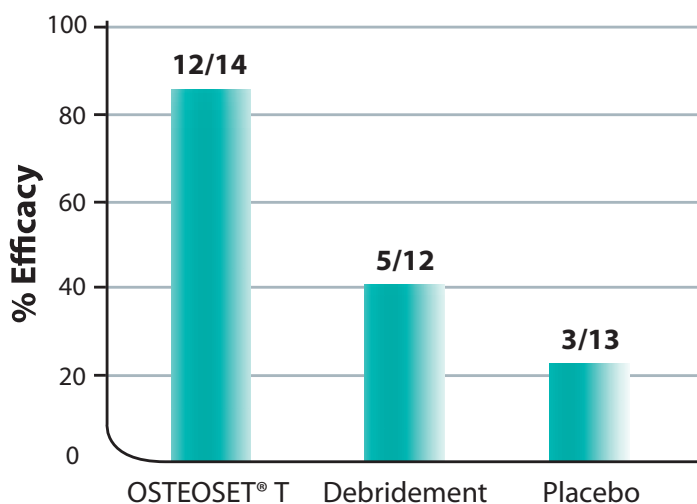
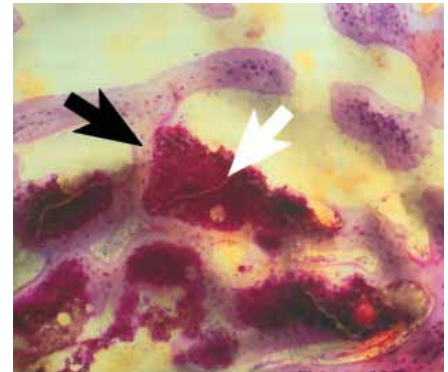
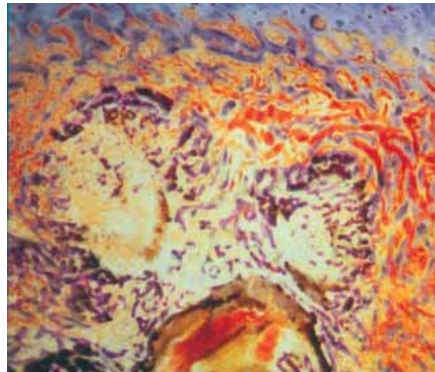


Figure 11

Histology results for OSTEOSSET® T (4% tobramycin sulfate, larger pellet) implanted for 6 weeks in the canine animal model demonstrated bone repair in the site of a surgically-created defect.¹⁴ After 6 weeks, some residual OSTEOSSET® T material remained. **Figure 12** shows bone forming on the surface of a residual OSTEOSSET® T pellet in a series of concentric lamellar structures. Thin trabeculae of bone have also developed independently in the drilled cavity by creeping substitution as the pellets resorb. **Figure 13** shows newly-formed woven bone with prominent osteoblastic rimming surrounding residual calcium sulfate. Residual OSTEOSSET® T material was totally incorporated by new bone formation with no evidence of foreign body reaction, granulomas, abnormal giant cells or inflammatory cells.



Biocompatibility

OSTEOSSET® T passes all biocompatibility guidelines established by ISO, USP and ASTM.¹⁶⁻¹⁸ These results are shown in **Table 1**.

Cytotoxicity	→	Pass
Sensitization	→	Pass
Genotoxicity	→	Pass
Implantation	→	Pass
Systemic Toxicity	→	Pass
Intracutaneous Reactivity	→	Pass

Table 1
Biocompatibility test results.

Dimensions and Composition

The OSTEOSSET® T pellets are made of medical grade calcium sulfate containing 4% tobramycin sulfate. The typical dimensions are depicted in **Figure 14**. In the canine pre-clinical study, tobramycin was eluted over a period of 28 days, and a direct comparison of the resulting local and serum tobramycin concentration profiles is illustrated in Figure 9. During the first day, the serum concentration peaked at 3.3µg/ml on average and was not detectable at day 3. During the same time period, the local concentration of tobramycin was 500 times higher than the serum concentration.

In the ongoing human clinical study, the trend on serum levels of tobramycin validates those observed in the animal studies. Specifically, serum tobramycin approaches undetectable levels between day one and day three. The maximum volume of OSTEOSSET® T pellet to be implanted per unit of body weight is given in **Table 2**, as well as the corresponding amount of tobramycin. Should the volume of the defect require more than the recommended usage of OSTEOSSET® T pellets, the remainder of the defect can be filled with unmedicated OSTEOSSET® pellets.

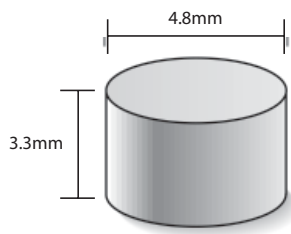


Figure 14
Typical dimensions of an OSTEOSSET® T pellet.

For Patients Weighing:		Maximum Volume of Pellets (cc)	Amount of Tobramycin (mg)
In Kilograms	In Pounds		
40	88	16	416
50	110	20	520
60	132	24	624
70	154	28	728
80	176	32	832
90	198	36	936
100	220	40	1040

Table 2
Usage chart.

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The Use of OSTEOSET® T Medicated Bone Graft Substitute to Treat an Infected Tibial Non-Union

Patient Profile

A 20 year-old male was involved in a motor vehicle accident and sustained a grade IIIB open left tibia fracture.

Initial treatment consisted of wound debridement, stabilization and external fixation. Post-operatively, this patient drifted into extension and varus with a draining wound. Numerous wound debridements were performed and cultured positive for Enterococcus. **Figure 15A**

Surgical Method

The patient was brought to the operating room and underwent wound debridement with application of OSTEOSET® T (medicated with tobramycin) into the bony defect. **Figure 15B**

Discussion

Three months post-operatively, the radiographs demonstrate early distal tibial union in appropriate alignment with no complications and no wound drainage. **Figure 15C**



Figure 15A



Figure 15B

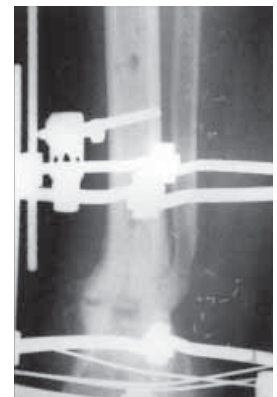


Figure 15C

OSTEOSET® T is a bone graft substitute made from medical grade calcium sulfate with the incorporation of tobramycin. *In vitro* and *in vivo* elution tests have shown sustained release of therapeutic levels of tobramycin locally, with low to undetectable systemic levels. The results of the pre-clinical canine studies and clinical case presentations reported here demonstrate excellent bone healing response and biocompatibility of OSTEOSET® T pellets. Thus, OSTEOSET® T pellets have been shown to be effective in treating bone voids and provide therapeutic local levels of tobramycin for extended periods.

Refer to the OSTEOSET® T package insert for additional information related to WARNINGS, PRECAUTIONS, CONTRAINDICATIONS AND ADVERSE REACTIONS.



This device is not yet cleared by the FDA for distribution in the United States.

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