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Review Article

High Local Delivery Systems of Antibiotics in the Treatment of Biofilm Related Infections without Serum Toxic Levels

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Abstract

The use of local antibiotic delivery systems is common in the management of biofilm-related infections as they provide high concentrations of local antibiotics while simultaneously avoiding complications from systemic toxicity. Older delivery mechanisms were associated with a high incidence of wound complications (up to 25%) requiring reoperation. The high wound complication rate was thought to be due to impurities from the mined calcium sulfate, hydrophobic behavior, and acidic pH. We are presenting a 100% Pure Synthetic Calcium Sulfate Hemihydrate (PSCSH) powder mixed with 240 mg liquid tobramycin and 500 mg of vancomycin powder per 10 cc of the hemihydrate for use in revision surgeries for Periprosthetic Joint Infections (PJI). The purified carrier demonstrates superior utility to similar vehicles such as Poly-Methyl-Methacrylate (PMMA) due to the bioabsorbablity which takes 2-3 weeks as demonstrated by disappearance of the hydrated crystal on x-ray. This is also preferable to the 4-6 weeks bioabsorbablity seen in the mined crystal calcium sulfate variants. The physiological pH of the PSCSH and the hydrophilicity demonstrated in serum probably account for the low 4% wound complication rate. The elution of vancomycin and tobramycin was greatest on day 1 compared with those concentrations obtained on days 2, 3, 4, and 5 post-operative while serum concentrations were mostly undetectable. Our findings demonstrate that this PSCSH preparation provides therapeutic delivery of vancomycin and tobramycin locally at log 2-3 above the Minimum Inhibitory Concentration (MIC), while avoiding dangerous serum concentrations.

INTRODUCTION

Chronic infection presents a serious complication following the surgical implantation of total joint prosthetics. Once a patient becomes contaminated, bacteria adhere to surfaces of implanted components and start forming colonies of bacteria called biofilm [1-4]. Bacteria entering into this sessile form produce quorum sensing biofilm. Quorum sensing refers to the start of the production of the glycocalyx, exchange of genetic information, and changes in the phenotypic expression of the bacteria. The bacteria proliferate up to a point and stop much like contact inhibition. The lateral exchange of genetic information between various microorganisms is mediated via cell to cell interactions [5,6]. With biofilm development, pathogen genomes are altered through cell-to-cell signaling pathways, becoming phenotypically distinct from planktonic counterparts (singular organisms) [6]. This exchange allows sessile forms to be recalcitrance to antibody mediated immune regulatory mechanisms and relying more on cell mediated immunity. As the biofilm matures, the cell becomes metabolically inactive with the lowest activity seen with pO2 gradients in the central portion in the biofilm and glycocalyx. The cells are called persister cells and because they are not dividing, they are not sensitive to antimicrobial agents [7]. At certain times, the mature biofilm releases active planktonic forms of the pathogen which show all the signs of acute infection. Also, there is concern over the management of the subsequent chronic infection because the cell mediated immunity with histiocytes causing local destruction of bones [5,8-10]. Ideally, parenterally administered antibiotics used in treating biofilm-mediated infections should be capable of disrupting the bacteria's structure [5,8,11-12]. However, this therapy has shown to treat planktonic bacterial infections with more success than suppressing biofilm related infections [5,12]. Osteomyelitis is a bone infection associated with Periprosthetic Joint Infections (PJI) and is multifactorial in etiology [5]. It is caused by some mechanisms including direct inoculation, hematogenous seeding, or airborne contamination, for which the bacteria contacts, adheres, and proliferates on dead bone, tissues, or hardware [5,8].

In response, surgeons employ surgical excision of biofilm related infected tissue, hardware removal, and the use of local antibiotic carriers as an adjunct to one or two-stage revision protocols for PJIs [12-17]. The local delivery systems in the past have included high concentrations of antibiotics in Poly-Methyl-Methacrylate (PMMA) in the two-stage treatment of PJIs [13,18-23]. This treatment causes the local release of antibiotic concentrations between 10-20 times above the MIC the first day and maintains above MIC levels for approximately 2 weeks [24]. This discourages the reformation of biofilm-based infections [21]. The current standard for antibiotic therapy in two-stage revisions of PJI is through the use of antibiotic-impregnated PMMA spacers [5,17,22-26]. However, PMMA spacers are not bioabsorbable so additional surgery becomes necessary for removal followed by revision to the definitive reconstruction [13,17]. The time between the second operation for definitive reconstruction varies amongst institutions from 2 weeks to 6 months [26-28]. Because the spacers used in the first stage are put in loose, it is associated with pain to the patient, loss of functionality, and arthrofibrosis [29-30]. Moreover, once the surface bleaching of the antibiotic impregnated PMMA is below MIC, bacterial adhesion may occur, possibly leading to secondary infection [19,28-33]. Finally, the use of certain types of antibiotic loaded PMMA may be recovered in the serum [17]. This correlates with the observation of sustained antibiotic serum concentrations that may result in allergic reactions or complications secondary to the antibiotics [17, 34].

In this study, we propose the use of a Pure Synthetic Calcium Sulfate Hemihydrate (PSCSH) antibiotic carrier that offers multiple significant advantages over antibiotic loaded PMMA, making it a more favorable option in one-stage procedures. (1) They are bioabsorbable at 2-3 weeks as demonstrated by disappearance of the beads on x-ray. (2) They are good for filling soft tissue dead spaces left after the debridement procedure. (3) The antibiotic loaded beads are hydrophilic and soften when hydrated, therefore they do not scratch the total joints. (4) Mixing with heat sensitive antibiotics remains unproblematic due to minimal heat generation on curing of the antibiotic impregnated PSCSH pellets [35-39].

These advantages make the use of an antibiotic impregnated PSCSH vehicle intriguing for application in several scenarios, including abscess or soft tissue infection treatment, prophylaxis in high risk patients with comorbidities undergoing revision total joints, and for the use with physiologic constructs in one-stage procedures for PJIs as an adjunct to antibiotic loaded PMMA. In this study, the beads were used to treat PJI, however the same carrier mechanism can be extrapolated to guided chemotherapy, radiation, and precision delivery of other pharmaceuticals [19]. Preparation of calcium sulfate beads provides a stable platform for the delivery of antibiotics. In the past, the mined calcium sulfate was associated with a high incidence of wound drainage, requiring surgical intervention as opposed to the PSCSH [40-45].

When combined, vancomycin and tobramycin provide adequate polymicrobial coverage against gram positive and negative organisms, making the drug combination a formidable choice for treating PJIs [46]. However, both drugs cause negative patient side effects when the systemic drug concentration becomes too high [47-49]. Both vancomycin and tobramycin are renally cleared. Therefore, kidney function, determined by creatinine (Cr), is an important consideration when determining the patient's ability to tolerate a given dose [50-52]. The main etiologies contributing to toxicity of either drug include error in dosing and decreased baseline renal function [46-48,53]. Although the mechanism of vancomycin-induced nephrotoxicity is not completely understood, recent data has suggested that vancomycin can oxidize the cells of the proximal renal tubule leading to renal ischemia [54]. Similarly, for tobramycin, current data suggests the toxicity is caused by altered phospholipid metabolism of the renal tubular cells and vasoconstriction of the renal afferent arteriole leading to renal ischemia [49,51,52]. Furthermore, combining multiple nephrotoxic drugs has been shown to increase the risk of nephrotoxicity more than with a single drug administration, with some research finding a 20-30% increased risk of renal injury compared to the use of one nephrotoxic drug alone [54]. Tobramycin also carries a well-published risk of ototoxicity [47,49-53]. Tobramycin is toxic to the ear because it damages the cochlea and presents early with high-frequency sensorineural hearing loss [47,49-53]. There have been case reports of vancomycin-induced ototoxicity, however collective research has not found a significant correlation since the mechanism of action of vancomycin does not impact any processes in the ear [47]. Due to increased awareness of the drug-dependent phenomena, multiple studies have established reliable dosimetric standards for each drug, which has caused a decreased incidence of side effects over-time [47-52]. In recent times, nephrotoxicity and ototoxicity has decreased with dosimetric monitoring of the serum levels of the antibiotics. However, the lower the serum levels the better for the associated complications.

This study examines clinical elution profiles of PSCSH preparation in contrast to other less pure forms of calcium sulfate (Osteoset). Thus, we ask the following: (1) Does PSCSH preparation provide local delivery of antibiotics at concentrations exceeding MIC of common infecting pathogens? (2) Will serum concentrations of antibiotics remain at safe concentrations?

MATERIALS AND METHODS

For the purposes of this study, we chose Stimulan (Biocomposites, Keele Science Park, Staffordshire, United Kingdom) as the purified synthetic antibiotic loaded calcium sulfate hemihydrate. We selected vancomycin and tobramycin to treat gram-positive and gram-negative bacteria, respectively [45]. PSCSH powder is catalyzed by liquid tobramycin and the vancomycin slows down the set time to make the antibiotic beads.

With higher doses of liquid Tobramycin greater than 240 mg and higher doses of Vancomycin greater than 500 mg, the hardening rate of the pellets were prolonged. In order to prepare the antibiotic loaded PSCSH pellets, 6 ml of liquid tobramycin (240 mg) and a 10 cc pack of Stimulan Rapid Cure powder that was mixed with 500 mg of vancomycin powder until it formed a creamy paste (about 2 minutes). The paste was applied to the mold and allowed to harden which took about 10 minutes. 20 cc of pellets were used in each patient regardless of the soft tissue defect caused by the surgical debridement.

In the one stage treatment of PJIs, there is a dirty and clean setup. After the radical debridement and removal of the prior prosthesis and hardware, the wound is irrigated and all gowns, gloves, and drapes are changed. Separate new instrumentation (clean side) is used for placement of the revision prosthesis and implantation instrumentation. The mixing of antibiotic loaded PSCSH powder is performed on the clean instrument side.

Antibiotic impregnated PSCSH pellet preparation and dose were prepared identically for each patient. For surgical placement, the calcium sulfate/antibiotic paste is pressed into a pelletizing mold (supplied with the product) to produce beads of different dimensions. The paste is allowed to set within the mold, and the resulting beads are removed by flexing the mold over a sterile container. The beads remain covered in the container until implantation at the end of the case for management of the resected dead space.

Patients are then fitted with a drain prior to wound closure for collection of the local eluates. In the first five postoperative days, simultaneous serum and drain samples were assayed with Fluorescence Polarization Immunoassay (FPIA) with the Abbott Architect C8000 Chemistry Analyzer to evaluate the eluting characteristics of the Stimulan carrier impregnated with vancomycin and tobramycin at the above-mentioned concentrations. Upon collection and delivery to the lab, protocol provided by the Abbott User Manual was followed [55,56]. The internal standard was sterile water. The upper and lower limits of quantification were 15 and 5 times the concentration of the internal standard, respectively.

The first fifty patients that consented for the procedure were included and patient data included in Table 1. There was no differentiation based on gender or age. All patients' Glomerular Filtration Rates (GFR) was greater than 60 ml/min and had PJIs. Both serum and local drain samples were collected every morning for 5 days at 0600 and taken immediately to the lab for same day analysis. Serum samples were collected in red-top tubes with 3mL aliquots. The local drain samples were collected in sterile glass tubes with 5mL aliquots.

Table 1: Patient demographics and laboratory data (n = 50).

Gender	22 Females 28 Males
Age (years)	Range: 13 – 82 Mean: 61
# of Knee PJI* Cases	33
# of Hip PJI* Cases	15
# of Elbow PJI* Cases	1
# of Shoulder PJI* Cases	1
GFR (mL/min/1.73m^2)	All Patients: >60

*PJI = Periprosthetic Joint Infection

Table 2: Minimum Inhibitory Concentrations (MIC) for tobramycin and vancomycin reported by others [44-47].

Organism (Tobramycin)	MIC Range (μg/mL) (Tobramycin)	Organism (Vancomycin)	MIC Range (μg/mL) (Vancomycin)
E. faecalis	8-32	Enterococci	4.0
E. coli	0.25-1.0	MSSA	<2.0
P. aeruginosa	0.25-1.0	MRSA	<2.0
S. aureus	0.12-1.0	Coagulase-negative Staphylococci	4.0
n/a	n/a	Streptococci other than S. pneumonia	≤1.0

RESULTS

We analyzed 50 patients undergoing revision arthroplasty for infected total joints or major multiple revisions. Cases included 33 knees (1 bilateral), 15 hips, 1 elbow, and 1 shoulder from 22 females and 28 males. Average patient age was 61 years (range:13-82). None of the patients experienced relapse of infection or wound complications secondary to persistent wound drainage. This was compared to a 25% early wound complication rate postoperatively (100 cases) in which Osteoset mined calcium sulfate carrier was used as the carrier of choice to treat PJIs [45]. The Fisher exact statistic was 0.0013 in the comparison with Osteoset ($p<0.01$).

We evaluated local antibiotic concentrations to determine if the concentrations contained in the eluent exceeded the MIC of common infecting pathogens and concentrations in the serum were also evaluated for all subjects [57-60]. Table 2 lists the results of others that were reported in the literature. Vancomycin is primarily effective against gram-positive cocci. *S. aureus* and *S. epidermidis*, both methicillin-susceptible (MSSA & MSSE) or resistant-species (MRSA & MRSE), are typically sensitive to vancomycin with MICs less than 1.5 μg/mL. Most strains of streptococcus are sensitive to vancomycin. Vancomycin is considered bactericidal (MBC/MIC <4 μg/mL) except with enterococci and some tolerant staphylococci (MBC/MIC >32 μg/mL) [58-61].

Mean values obtained from local eluate demonstrated therapeutic concentrations of vancomycin and tobramycin in each of the five postoperative days. Concentrations of both antibiotics peaked on day 1 (Averages: Vancomycin: 297 μg/mL; Tobramycin: 31 μg/mL, & Ranges: Vancomycin: 28.3-736.4; Tobramycin: 6.4-97.2). Table 3 lists the change in mean values of the local eluate from the drains for each of the 5 days for the 50 patients, and Figure 1 and 2 illustrate the trend in mean value reduction over time. For the results of Table 3, assayable values of antibiotics were obtained from local exudate of drain samples. Furthermore, FTIR comparing the Osteoset and PSCSH pellets showed higher degrees of purity with the PSCSH pellets, which is evidenced by the narrower peaks shown in Figure 3.

We evaluated drain and blood serum concentrations of vancomycin and tobramycin on a standard hospital assay for these drugs in the five postoperative days. The assay reported antibiotic concentrations that were detected within specific concentration limits (vancomycin 2μg/mL to 400μg/mL, tobramycin 0.5μg/mL to 20μg/mL). Additional specific maximum

Table 3: Local Antibiotic Concentrations of Vancomycin and Tobramycin from the Eluate in the Drains in our Patients.

	Mean (Range)	Mean (Range)
Postop Day	Vancomycin (μg/mL)	Tobramycin (μg/mL)
1	297 (28.3-736.4)	31 (6.4-97.2)
2	202 (14.2-466.7)	9.4 (2.4-19.6)
3	156 (5.8-394.5)	6.4 (1.6-19.9)
4	121 (19.5-352.5)	5.3 (1.3-18.6)
5	82 (5.8-190.5)	4.6 (2.2-9.8)

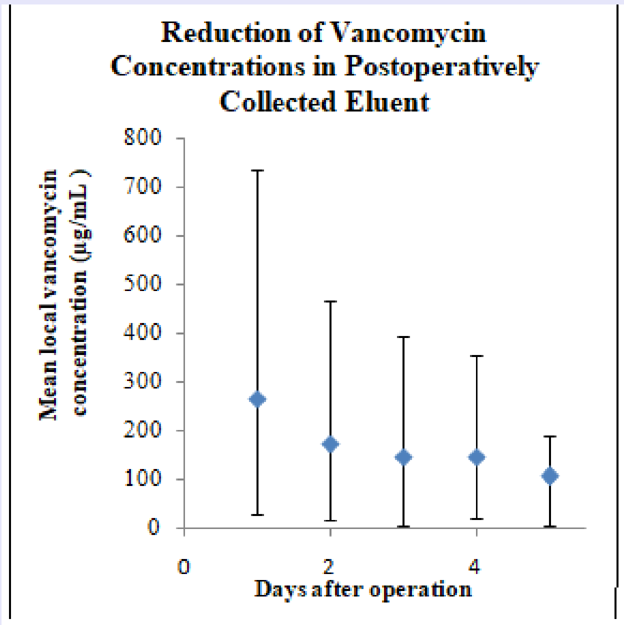

Figure 1 Mean eluent vancomycin concentrations in the five postoperative days. Error bars represent the range of mean local vancomycin concentrations for each day.

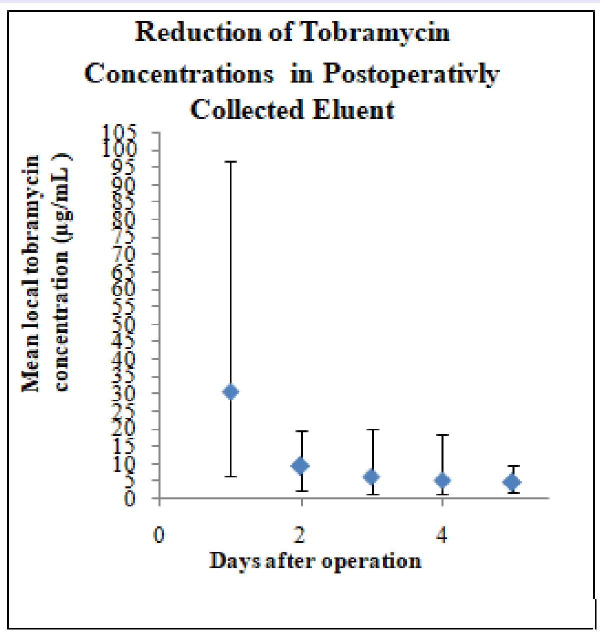

Figure 2 Mean tobramycin concentrations eluent in the five postoperative days. Error bars represent the range of mean local tobramycin concentrations for each day.

assayable values for each antibiotic were recorded for a selection of the results. The majority of patients exhibited antibiotic blood serum concentrations below the lower concentration limits of the standard assay (vancomycin <2µg/mL, tobramycin <0.5µg/mL); However, a few patients exhibited detectable serum concentrations of antibiotics as follows: twelve (of the 50 patients) at day 1, five patients at day 2, and three patients at days 3, and one patient at 4. No patients exhibited detectable serum concentrations on day 5. Table 4 lists the antibiotic serum concentrations for each patient. Note, only patients with detectable serum values were included in Table 4.

DISCUSSION

By controlling the source of infection in PJIs through the disruption of biofilm formation, the surgeon creates an acute wound milieu that helps activate host immune mechanisms for effective wound healing. This control may be accomplished by combining the strict adherence to wound management through radical debridement with the administration of a local antibiotic capable of eluting high concentrations of the antibiotics for eradicating remaining exposed biofilm after the debridement process [61]. Antibiotic-laden PSCSH aid in the management of the dead space after the debridement with high doses of antibiotics and after placement of the definitive prosthesis while avoiding complications of toxicity such as ototoxicity, renal toxicity, and allergic responses associated with parenteral administration of the antibiotics. A mixture of broad-spectrum antibiotics perpetuates eradication of heterogeneous bacterial populations [62]. We prefer vancomycin and tobramycin for this purpose at the concentrations eluded locally to kill biofilm related infections as demonstrated in the center for biofilm engineering drip reactor system [16]. This bead becomes soft after hydration allowing for placement in joints without scratching the articular surfaces and demonstrates complete dissolution within a few weeks [61].

High serum concentrations of vancomycin and tobramycin with these two drugs can result in serious side effects, specifically ototoxicity and nephrotoxicity. The purpose of our study was therefore twofold: To verify that concentrations of vancomycin and tobramycin eluted from calcium sulfate would still be capable at high concentrations of inhibiting bacterial biofilm locally with low serum concentrations avoiding the complications of vancomycin and tobramycin. For reference, previous literature showed peak systemic concentrations of vancomycin after a 20mg/kg dose to average 75.6 mg/L in a patient population with similar kidney function [63].

Limitations of this study include the ceiling placed on assayable values of antibiotic concentrations (as determined by FPIA analysis), the duration of evaluation and the comparison between different volumes placed into wounds. In spite of the truncated measurements, this study still demonstrates expected local and systemic elution characteristics. With regard to the temporal limitations, we would have preferred continued measurement of the antibiotic concentrations. However, our decision to discontinue after five days was based on concern for contamination from prolonged placement of the drains. Some of the patients in which we observed detectable serum concentrations also had concurrent implantation of PMMA cement impregnated with vancomycin and/or tobramycin as part of the reconstructive surgery. This concurrent implantation of an additional antibiotic delivery system may be a contributory factor to the incidences of detectable serum concentrations. Furthermore, controlling for the patient population may have yielded different results. For example, GFR changes with age and gender, therefore medication levels may be different based

Table 4: Serum concentrations of vancomycin and tobramycin in postoperative days 1-5. Detectable values are highlighted in bold.

Detectable serum concentrations of vancomycin and tobramycin in patients on postoperative days 1-5(µg/mL)										
Pt. ID # *	**DAY 1**		**DAY 2**		**DAY 3**		**DAY 4**		**DAY 5**	
	VANC	**TOBRA**	**VANC**	**TOBRA**	**VANC**	**TOBRA**	**VANC**	**TOBRA**	**VANC**	**TOBRA**
04	**2.4**	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
05	<2.0	**0.7**	<2.0	**0.7**	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
06	**2.5**	**0.7**	**2.4**	<0.5	**2.0**	<0.5	<2.0	<0.5	<2.0	<0.5
08	**2.6**	**1.8**	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
16	**3.1**	**1.1**	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
21	**2.2**	**0.9**	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
23	**3.7**	**4.1**	**3.3**	**1.5**	**3.0**	<0.5	**2.5**	<0.5	<2.0	<0.5
26	<2.0	**0.6**	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
28	<2.0	**2.1**	<2.0	**0.8**	<2.0	**0.6**	<2.0	<0.5	<2.0	<0.5
30	<2.0	**0.7**	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
32	<2.0	**1.7**	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5
35	<2.0	**1.7**	<2.0	**0.7**	<2.0	<0.5	<2.0	<0.5	<2.0	<0.5

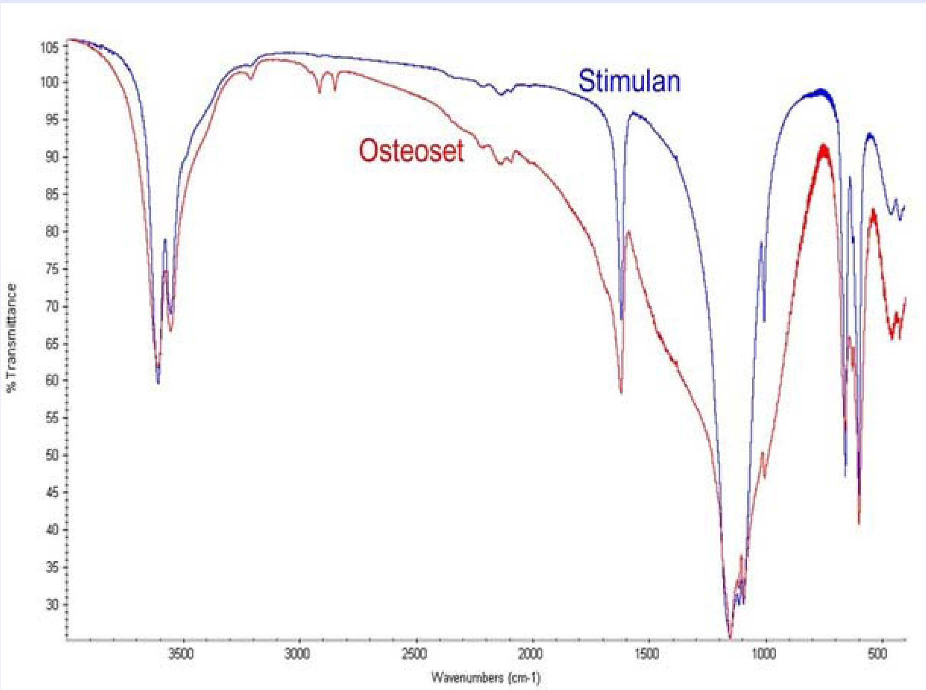

Figure 3 Comparative FTIR analysis of Stimulan&Osteoset pellets. The narrower peaks exhibited by the Stimulan sample indicate higher calcium sulfate purity.

on the specific patient. Also, a comparative group with PMMA or a control was not measured. Inclusion of a comparative group would have improved the specificity of the results and provided more evidence for the superiority of the PSCSH beads. However, there is significant evidence of the inefficacy of the PMMA for antibiotic implantation into bone [16-18]. Compared with mined calcium sulfate variants, the carrier we used was hydrophilic, demonstrated bioabsorbablity (2-3 weeks), had physiological pH in a hydrated crystal, and was synthetically pure as seen by Fourier Transform InfraRed (FTIR) analysis (Figure 3). A commonly encountered problem associated with the less pure forms of calcium sulfate carriers has been persistent postoperative wound drainage and complication rate (25%) [40-45]. We feel this drainage may be due to specific physical properties of mined calcium sulfate preparations, including its hydrophobicity, acidic pH, and impurity due to the presence of trace minerals as seen by FTIR analysis [64].

This study highlighted the efficacy of the PSCSH beads in the setting of treating biofilm related infections, however we do not want to diminish the use of this carrier mechanism outside of antimicrobial management [19]. This carrier mechanism has the ability to deliver other therapies such as chemotherapy and analgesics [65,66]. The overwhelming benefit of high local concentrations and low systemic concentrations provided by the carrier makes local delivery vehicles a promising therapeutic option [65,66]. Nonetheless, it is important to note that to our knowledge the PSCSH beads used have not been studied as a carrier in contexts outside of antibiotic treatment and orthopedics.

The clinical data also possessed limitations due to inaccuracy of antibiotic concentrations in eluent as a result of the standard laboratory assay used. The laboratory agency conducting the FPIA analysis established standard routine reporting of antibiotic concentrations within specific concentration limits (vancomycin 2mg/mL to 400mg/mL, tobramycin 0.5mg/mL to 20mg/mL). In most assays conducted, maximum assayable limits for vancomycin and tobramycin were reported as >400 µg/mL and >20 µg/mL, respectively. As a result, mean values reported are lower than actual values. Additionally, without the drains, higher concentrations of antibiotics would be expected locally for longer periods of time, however drains are standard of care for patients with severe osteomyelitis. The exact values for antibiotic concentrations above the upper limits were not recorded for all patients. Therefore, the data does not give an accurate evaluation of local antibiotic concentrations in these cases. However, the data does indicate that these reported upper limits were present usually for only 1 to 2 days post-implantation. Thus, the use of antibiotic concentrations from eluent to indicate the diminishing local antibiotic concentrations over the five-day period remains possible. In addition, the blood serum concentrations indicate that these high local concentrations post-implantation do not manifest into high systemic antibiotic concentrations. Moreover, additional laboratory data such as hepatic function, coagulation studies and co-morbidities would have been useful in controlling for any other variables that could confound the systemic antibiotic concentration measurements. However, the data was collected at the time of the initial study and retrieval of the other information is not possible due to the deletion of the hospital records given some patient records eclipsed the eight-year maximum storage rule by the hospital system. Another limitation is that this study did not control for variability of the amount of antibiotic based on the volumetric size of the surgical bed. For example, larger surgical beds with the same amount of pellets as smaller surgical beds will have smaller areas of antibiotic diffusion. Additionally, none of the patients underwent audiologic testing before or after administration of the pellets to track the potential for ototoxicity. However, we assumed that since we measured daily serum drug concentration, we would be able to stop the drug concentrations from reaching high enough levels to be ototoxic.

CONCLUSION

Based on our results and clinical experience, the antibiotic loaded pure calcium sulfate hemihydrate demonstrates adequacy as a platform for the local delivery of antibiotics at therapeutic concentrations, as well as a stable vehicle for incorporation of both vancomycin and tobramycin. In each of the 5 postoperative days evaluated, mean local concentrations of antibiotics exceeded values capable of inhibiting common pathogens. We observed no adverse reaction based on the presence of elevated serum concentrations of antibiotics and no occurrence of persistent wound drainage associated with the antibiotic loaded pure calcium sulfate hemihydrate.

REFERENCES

1. Olson ME, Garvin KL, Fey PD, Rupp ME. Adherence of Staphylococcus epidermidis to biomaterials is augmented by PIA. Clin Orthop Relat Res. 2006; 451: 21-24.
2. Barton AJ, Sagers RD, Pitt WG. Measurement of bacterial growth rates on polymers. J Biomed Mater Res. 1996; 32: 271-278.
3. MacKintosh EE, Patel JD, Marchant RE, Anderson JM. Effects of biomaterial surface chemistry on the adhesion and biofilm formation of Staphylococcus epidermidis in vitro. J Biomed Mater Res A. 2006; 78: 836-842.
4. Rohde H, Frankenberger S, Zähringer U, Mack D. Structure, function and contribution of polysaccharide intercellular adhesin (PIA) to Staphylococcus epidermidis biofilm formation and pathogenesis of biomaterial-associated infections. Eur J Cell Biol. 2010; 89: 103-111.
5. Gogia JS, Meehan JP, Di Cesare PE, Jamali AA. Local antibiotic therapy in osteomyelitis. Semin Plast Surg. 2009; 23: 100-107.
6. Costerton JW, Lewandowski Z, Caldwell DE, Korber DR, Lappin-Scott HM. Microbial biofilms. Annu Rev Microbiol. 1995; 49: 711-745.
7. Lewis K. Persister cells. Annual review of microbiology. 2010; 64: 357-372.
8. Fraimow HS. Systemic antimicrobial therapy in osteomyelitis. Semin Plast Surg. 2009; 23: 90-99.
9. Lazar V, Chifiriuc MC. Medical significance and new therapeutical strategies for biofilm associated infections. Roum Arch Microbiol Immunol. 2010; 69: 125-138.
10. Davis SC, Ricotti C, Cazzaniga A, Welsh E, Eaglstein WH, Mertz PM. Microscopic and physiologic evidence for biofilm associated wound colonization in vivo. Wound Rep Reg. 2008; 16: 23-29.
11. Anderl JN, Franklin MJ, Stewart PS. Role of antibiotic penetration limitation in Klebsiella pneumonia biofilm resistance to ampicillin and ciprofloxacin. Antimicrob Agents Chemother. 2000; 44: 1818-1824(Level II).
12. Widgerow AD. Persistence of the chronic wound: implicating biofilm. Wound Healing Southern Africa. 2008; 1: 5-7.
13. Gitelis S, Brebach GT. The treatment of chronic osteomyelitis with a biodegradable antibiotic-impregnated implant. Journal of Orthopaedic Surgery. 2002; 10: 53-60.
14. Le Ray AM, Gautier H, Laty MK, Daculsi G, Merle C, Jacqueline C, et al. In vitro and in vivo bactericidal activities of vancomycin dispersed in porous biodegradable poly(ɛ̀-caprolactone) microparticles. Antimicrob Agents Chemother. 2005; 49: 3025-3027.
15. Kent ME, Rapp RP, Smith KM. Antibiotic beads and osteomyelitis: here today, what's coming tomorrow? Orthopedics. 2006; 29: 599-603.
16. Maale GE. Débridement for Orthopaedic Infection, in: Wellington K. Hsu, MD, Alex C. McLaren, MD, Bryan D. Springer, MD (Editors): Let's Discuss Surgical Site Infections, Chap. 5, Rosemont, IL: American Academy of Orthopaedic Surgeons (AAOS); 2015.
17. Maale GE, Pascoe HR, Piercy EA. A standardized approach for the treatment of infected total joint arthroplasties by the DFW sarcoma group osteomyelitis protocol; staged revisions at 2 weeks using antibiotic-cement-implant composites as spacers. J Arthroplast. 1993; 8: 102.

18. Cierny G III, Mader JT, Pennick JJ. A clinical staging system for adult osteomyelitis. Clin OrthopRelat Res. 2003; 414: 7-24.

19. Kanellakopoulou K, Giamarellos-Bourboulis EJ. Carrier systems for local delivery of antibiotics in bone infections. Drugs. 2000; 59: 1223-1232.

20. Zalavras CG, Patzakis MJ, Holtom P. Local antibiotic therapy in the treatment of open fractures and osteomyelitis. Clin Orthop Relat Res. 2004; 427: 86-93.

21. Van de Belt H, Neut D, Schenck W, van Horn JR, van der Mei HC, Busscher HJ. Infection of orthopedic implants and the use of antibiotic-loaded bone cements. A review, Acta Orthop Scand. 2001; 72: 557-571.

22. Masri BA, Duncan CP, Beauchamp CP. Long-term elution of antibiotics from bone-cement: an in vivo study using the prosthesis of antibiotic-loaded acrylic cement (PROSTALAC) system. J Arthroplasty. 1998; 13: 331-338.

23. Nelson CL. The current status of material used for depot delivery of drugs. Clin Orthop Relat Res. 2004; 427: 72-78.

24. Hsieh PH, Chen LH, Chen CH, Lee MS, Yang WE, Shih CH. Two-stage revision hip arthroplasty for infection with custom-made, antibiotic-loaded, cement prosthesis as an interim spacer. J Trauma. 2004; 56: 1247-1252.

25. Adams K, Couch L, Cierny G, Calhoun J, Mader JT. In vitro and in vivo evaluation of antibiotic diffusion from antibiotic-impregnated polymethylmethacrylate beads. Clinical Orthopaedics and Related Research. 1992; 278: 244-252.

26. Maale GE, Pascoe HR, Piercy EA. A standardized approach for the treatment of infected total joint arthroplasties by the DFW sarcoma group osteomyelitis protocol; Staged revisions at 2 weeks using antibiotic-cement-implant composites as spacers, The Journal of Joint Arthroplasty. 1993; 8: 102.

27. Meek RM, Masri BA, Dunlop D, Garbuz DS, Greidanus NV, McGraw R, et al. Patient satisfaction and functional status after treatment of infection at the site of a total knee arthroplasty with use of the PROSTALAC articulating spacer. J Bone Joint Surg Am. 2003; 85: 1888-1892.

28. Stevens CM, Tetsworth KD, Calhoun JH, Mader JT. An articulated antibiotic spacer used for infected total knee arthroplasty: a comparative in vitro elution study of Simplex and Palacos bone cements. J Orthop Res. 2005; 23: 27-33.

29. Woods J, Boegli WL, Kirker KR, Agostinho AM, Durch AM, Pulcini DE, et al. Development and Application of a Polymicrobial, in Vitro, Wound Biofilm Model. Journal of Applied Microbiology. 2012; 112: 998-1006.

30. El-Husseiny M, Patel S, MacFarlane RJ, Haddad FS. Biodegradable antibiotic delivery systems. J Bone Joint Surg Br. 2011; 93: 151-157.

31. Webb ND, McCanless JD, Courtney HS, Bumgardner JD, Haggard WO. Daptomycin eluted from calcium sulfate appears effective against staphylococcus. Clin Orthop Relat Res. 2008; 466: 1383-1387.

32. Liu SJ, Wen-NengUeng S, Lin SS, Chan EC. In vivo release of vancomycin from biodegradable beads. J Biomed Mater Res. 2002; 63: 807-813.

33. Kinnari TJ, Esteban J, Zamora N, R. Fernandez C. López-Santos F. Yubero, et al. Effect of surface roughness and sterilization on bacterial adherence to ultra-high molecular weight polyethylene. Clin Microbiol Infect. 2010; 16: 1036-1041.

34. Patrick BN, Rivey MP, Allington DR. Acute renal failure associated with vancomycin and tobramycin laden cement in total hip arthroplasty. Ann Pharmacother. 2006; 40: 2037-2042.

35. Calhoun JH, Mader JT. Treatment of osteomyelitis with a biodegradable antibiotic implant. Clin Orthop Relat Res. 1997; 341: 206-214.

36. Kanellakopoulou K, Panagopoulos P, Giannitsioti E, Tsaganos T, Carrer DP, Efstathopoulos N, et al. In vitro elution of daptomycin by a synthetic crystallicsemihydrate form of calcium sulfate, Stimulan. Antimicrobial Agents Chemother. 2009; 53: 3106-3107.

37. Richelsoph KC, Webb ND, Haggard WO. Elution behavior of daptomycin loaded calcium sulfate pellets: a preliminary study. Clin Orthop Relat Res. 2007; 461: 68-73.

38. Kelly CM, Wilkins RM, Gitelis S, Hartjen C, Watson JT, Kim PT, et al. The use of a surgical grade calcium sulfate as a bone graft substitute: results of a multicenter trial. Clin Orthop Relat Res. 2001; 382: 42-50.

39. Grimsrud C, Raymond Raven, A W Fothergill, Hubert T Kim, et al., The In Vitro Elution Characteristics of Antifungal-loaded PMMA Bone Cement and Calcium Sulfate Bone Substitute. Orthopedics. 2011; 34: 378-381.

40. Shirtliff ME, Calhoun JH, Mader JT. Experimental osteomyelitis treatment with antibiotic impregnated hydroxyapatite. Clin Orthop Relat Res. 2002; 401: 239-247(Level II).

41. Sanicola SM, Albert SF. The in vitro elution characteristics of vancomycin and tobramycin from calcium sulfate beads. Journal of Foot and Ankle Surgery. 2005; 44: 121-124 (Level II).

42. Scharer BM, Sanicola SM. The in vitro elution characteristics of vancomycin from calcium phosphate-calcium sulfate beads. Journal of Foot and Ankle Surgery. 2009; 48: 540-542.

43. Cai X, Han k, Cong X, Cai J. The Use of Calcium Sulfate Impregnated with Vancomycin in the Treatment of Open Fractures of Long Bones: A Preliminary Study. Orthopedics. 2010: 152-157.

44. Beuerlein MJ, Mckee MD. Calcium sulfates: what is the evidence? J Orthop Trauma. 2010; 24: S46- S51.

45. Cierny G, DiPasquale D. Comparing OsteoSet and Stimulan as Antibiotic-loaded, Calcium Sulfate Beads in the Management of Musculoskeletal Infection., in 19th Annual Open Scientific Meeting of the Musculoskeletal Infection Society.2009: San Diego, CA, USA.

46. Maale GE, Eager JJ, Srinivasaraghavan A, Mohammadi DK, Kennard N. The evolution from the two stage to the one stage procedure for biofilm based periprosthetic joint infections (PJI). Biofilm. 2020; 100033.

47. Meyerhoff WL, Maale GE, Yellin W, Roland PS. Audiologic threshold monitoring of patients receiving ototoxic drugs. Preliminary report. Ann Otol Rhinol Laryngol. 1989; 98: 950-954.

48. Mei H, Wang J, Che H, Wang R, Cai Y. The clinical efficacy and safety of vancomycin loading dose: A systematic review and meta-analysis. Medicine (Baltimore). 2019; 98: e17639.

49. Rostas SE, Kubiak DW, Calderwood MS. High-dose intravenous vancomycin therapy and the risk of nephrotoxicity. Clin Ther. 2014; 36: 1098-1101.

50. Álvarez O, Plaza-Plaza JC, Ramirez M, Peralta A, Amador CA, Amador R. Pharmacokinetic Assessment of Vancomycin Loading Dose in Critically Ill Patients. Antimicrob Agents Chemother. 2017; 61: e00280-17.

51. LeBras M, Chow I, Mabasa VH, Ensom MH. Systematic Review of Efficacy, Pharmacokinetics, and Administration of Intraventricular Aminoglycosides in Adults. Neurocrit Care. 2016; 25: 492-507.

52. Lim AK, Mathanasenarajah G, Larmour I. Assessment of aminoglycoside dosing and estimated glomerular filtration rate in determining gentamicin and tobramycin area under the curve and clearance. Intern Med J. 2015; 45: 319-329.

53. Smit C, Wasmann RE, Wiezer MJ, van Dongen HPA, Mouton JW, Brüggemann RJM, et al. Tobramycin Clearance Is Best Described by Renal Function Estimates in Obese and Non-obese Individuals:

Results of a Prospective Rich Sampling Pharmacokinetic Study. Pharm Res. 2019; 36: 112.

54. Vora S. Acute renal failure due to vancomycin toxicity in the setting of unmonitored vancomycin infusion. Proceedings (Baylor University. Medical Center). 2016; 29: 412-413.

55. Rice D, Mendez-Vigo L. Daptomycin in bone and joint infections: a review of literature. Arch Orthop Trauma Surg. 2009; 129: 1495-1504.

56. Abbott. Architect c8000 operations manual. Abbott Park: Abbott Core Laboratory. 2005.

57. Dienstag, J and Neu, H. In Vitro Studies of Tobramycin, an Aminoglycoside Antibiotic. Antimicrobial Agents and Chemotherapy. 1972; 1: 41-45.

58. Jumah MTB, Vasoo S, Menon SR, De PP, Neely M, Teng CB. Pharmacokinetic/ Pharmacodynamic Determinants of Vancomycin Efficacy in Enterococcal Bacteremia. Antimicrobial Agents Chemotherapy. 2018; 62: e01602- e01617.

59. Prakash V, Lewis II J, Jorgensen J. Vancomycin MICs for Methicillin-Resistant Staphylococcus aureus Isolates Differ Based Upon the Susceptibility Test Method Used. Antimicroial Agents and Chemotherapy. 2008; 52: 4528.

60. Camara M, Dieng A, Boye CS. Antibiotic susceptibility of streptococcus pyogenes isolated from respiratory tract infections in dakar, senegal. Microbiol Insights. 2013; 6: 71-75.

61. Maale GE, Eager JJ. Local elution profiles of a highly purified calcium sulfate pellet at physiologic pH, loaded with vancomycin and tobramycin, in the treatment of infected total joints. In: the 75th Annual meeting of the Western Orthopaedic Association, Honolulu, HI, USA; 2011.

62. Ehrlich GD, DeMeo P, Palmer M, Sauber TJ, Altman D, Altman G, et al. Culture-Negative Infections in Orthopedic Surgery. Springer Series on Biofilms Culture Negative Orthopedic Biofilm Infections. 2012: 17-27.

63. Zokufa HZ, Rodvold KA, Blum RA. Simulation of vancomycin peak and trough concentrations using five dosing methods in 37 patients. Pharmacotherapy. 1989; 9: 10-16.

64. ThermoNicolet. Introduction to Fourier Transform Infrared Spectrometry. Madison, WI, 53711, USA: ThermoNicolet. 2001.

65. Choi B, Jung H, Yu B, Choi H, Lee J, Kim DH. Sequential MR Image-Guided Local Immune Checkpoint Blockade Cancer Immunotherapy Using Ferumoxytol Capped Ultralarge Pore Mesoporous Silica Carriers after Standard Chemotherapy. Small. 2019; 15: e1904378.

66. de Araújo DR, Ribeiro LNM, de Paula E. Lipid-based carriers for the delivery of local anesthetics. Expert Opin Drug Deliv. 2019; 16: 701-714.

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