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Original Research Paper

Orthopaedics

THE USE OF ANTIBIOTIC LOADED, HIGH-PURITY CALCIUM SULPHATE IN THE SURGICAL MANAGEMENT OF INFECTION IN TRAUMA REVISION.

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ABSTRACT

Aims: Surgical site infections can have a profound effect on patient quality of life, often associated with considerable morbidity.

Patients And Methods: This review identified 60 patients with infected surgical sites, subsequently implanted with beads of calcium sulphate combined with antibiotics as part of surgical infection management .

Antibiotics were chosen according to the identified pathogen. If the pathogens were not identified, a broad spectrum combination was used.

Calcium sulphate beads combined with antibiotics were implanted in and adjacent to bone, and in soft tissue to fill dead space following the debridement procedure.

Results: Reoccurrence of infection was observed in one patient at 2 months post surgery. The patient underwent subsequent procedure to remove the external fixator with extensive debridement and repeat placement of calcium sulphate beads combined with antibiotics. At 5 month post reoperation, bone union was evident with no sign of infection.

Conclusions: The use of calcium sulphate in an infection management strategy for trauma revision shows promise in supporting new bone growth, managing dead space and enabling the release of high levels of tailored antibiotics to the surgical site to minimise the risk of infection re-occurrence. The efficacy of this treatment warrants further investigation in a larger trial.

KEYWORDS : Infected Wounds, Antibiotic Calcium Sulphate Beads, Antibiotics in orthopaedics, Stimulan

INTRODUCTION:

Surgical site infections are a distressing and unwelcome occurrence for patients and clinicians alike. When they occur, they can have a profound effect on quality of life for the patient, and are often associated with an extended hospital stay and considerable morbidity. The associated financial burden to healthcare providers or patients can be considerable(1, 2). In patients undergoing fixation of open fractures, infection rates may be in excess of 30%(3). This is understandable considering the potential for deep contamination of the surgical site as a result of the injury, and the risk of bacterial colonisation on the surface of the implanted fixation device in the form of a biofilm(4, 5).

Once a biofilm-associated infection is established, it is difficult to eradicate due to a reduced susceptibility to antimicrobial drugs and host defence cells. When comparing the planktonic minimum bactericidal concentrations (MBCs) with those of the pathogen in biofilm form, literature has shown that in all cases where planktonic bacteria were initially sensitive, biofilms were >100 times more resistant(6, 7) and in some cases >7,000(6).

Extensive surgical debridement plays a major factor in reducing bacterial load(8, 9), in addition to the administration of systemic antibiotic therapy. In cases where an implant-related infection is present or suspected, the presence of a biofilm can result in a persistent infection. The use of aggressive and intensive antibiotic treatment may reduce the biofilms, but is not able to eradicate the biofilm infections, as the MBC of mature biofilm is difficult to safely reach in vivo(10, 11). In the majority of cases the removal of the infected implant is required(11).

Despite a surgeon's best efforts, it is difficult to completely eradicate residual biofilm from an infected surgical site, increasing the risk of persistent infection. Therefore use of local antibiotics as part of an infection management strategy has been widely employed in an attempt to reduce re-infection rates. The use of polymethylmethacrylate (PMMA) cement in this function has been long established(12-14) providing a means of dead space management following hard and soft tissue debridement and elevated local antibiotic levels. An alternative material to PMMA for this application is calcium sulphate(15-18). This offers the advantage that it releases high levels of antibiotics locally, and is resorbed in-vivo and therefore does not require subsequent surgical removal.

Herein we report our experience with a high purity calcium sulphate (Stimulan, Biocomposites Ltd, UK) in combination with antibiotics as part of our infection management strategy in sixty infected revision trauma patients.

PATIENTS AND METHODS:

This review identified 60 patients (44 male, 16 Females) presenting with infected surgical sites involving osteomyelitis following trauma surgery between May 2018 and August 2020, all of whom had been treated with calcium sulphate combined with antibiotics, in the form of beads, as part of surgical infection management protocols. Full patient notes, radiographs and laboratory results were reviewed for each patient. At presentation, the average patient age was 40.3 (range 14 to 68). 42 of the cases were lower-limb infection and 18 were upper-limb.

Each of the patients underwent surgery by the author to revise previous surgery. All sixty patients presented with multiple signs of infection following the previous surgical treatment, associated with either internal or external fixation devices. Figure 1: three different bead sizes (3, 4.8 and 6mm diameter)For each patient, surgery consisted of removal of the infected devices and thorough open surgical debridement of necrotic bone and soft tissue. This was followed by lavage with normal saline/betadine /hydrogen peroxide solution. Beads of calcium sulphate (Stimulan, Biocomposites Ltd, UK) combined with antibiotics were then prepared intraoperatively, and implanted in and adjacent to bone, and in the soft tissue as required in order to fill dead space following the debridement procedure. Each surgical site was then closed as appropriate. Post-operatively , each patient received I.V.

antibiotics (3 to 10 days) and oral antibiotics (5 to 14 days). (Table 1)

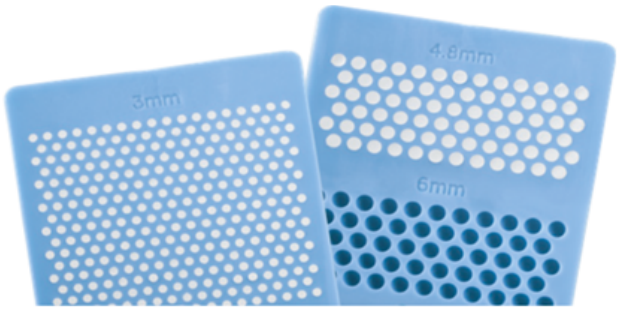


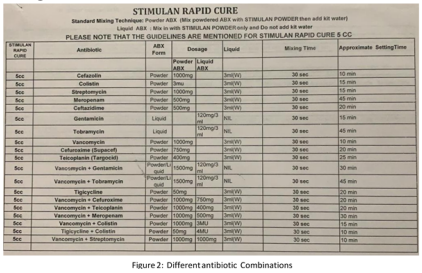
Figure 1: three different bead sizes (3, 4.8 and 6mm diameter)

Table 1: Age of Patients versus Microbe, Gender and Limb

Limb/Gender /Age Group/ Microbe	Upper Limb								Lower Limb								Total
	Male				Female				Male				Female				
	S. Aureus	Poly-microbial	E. Coli	No Growth	S. Aureus	Poly-microbial	E. Coli	No Growth	S. Aureus	Poly-microbial	E. Coli	No Growth	S. Aureus	Poly-microbial	E. Coli	No Growth	
10-20	1	0	0	1	1	0	0	0	1	1	0	1	1	0	0	1	8
21-30	1	1	0	1	0	0	0	0	1	2	0	2	1	0	0	0	9
31-40	1	0	0	1	0	0	1	0	1	2	0	4	1	0	0	1	12
41-50	1	0	0	2	0	0	0	1	2	1	0	3	0	0	1	2	13
51-60	0	1	0	0	0	0	0	1	0	3	0	2	0	2	0	1	10
61-70	0	1	0	2	0	0	0	0	0	1	0	3	0	0	0	1	8
Microbe Total	4	3	0	7	1	0	1	2	5	10	0	15	3	2	1	6	60
Gender Total	14				4				30				12				60
Limb Total	18								42								60

The intra-operative preparation of the calcium sulphate beads was carried out in the sterile field. The calcium sulphate is provided as a powder and liquid that are combined to form a smooth paste that can be transferred to a bead mat. The paste then sets in the bead mat. The bead mat is designed to enable the preparation of three different bead sizes (3, 4.8 and 6mm diameter) (Figure 1).

The calcium sulphate is not provided pre-loaded with antibiotics. Antibiotics were chosen for each patient dependent upon the identified pathogen if known. If the pathogens were not identified, a broad spectrum combination was used (Figure 2).


STIMULAN RAPID CURE

Standard Mixing Technique: Powder ABX (Mix powdered ABX with STIMULAN POWDER then add kit water)
Liquid ABX - Mix in with STIMULAN POWDER only and Do not add kit water

PLEASE NOTE THAT THE GUIDELINES ARE MENTIONED FOR STIMULAN RAPID CURE 5 CC

STIMULAN RAPID CURE	Antibiotic	ABX Form	Dosage Powder ABX	Dosage Liquid ABX	Liquid	Mixing Time	Approximate SettingTime
5cc	Cefazolin	Powder	1000mg		3ml(W)	30 sec	10 min
5cc	Colistin	Powder	3mu		3ml(W)	30 sec	15 min
5cc	Streptomycin	Powder	1000mg		3ml(W)	30 sec	15 min
5cc	Meropenam	Powder	500mg		3ml(W)	30 sec	45 min
5cc	Ceftazidime	Powder	500mg		3ml(W)	30 sec	20 min
5cc	Gentamicin	Liquid		120mg/3 ml	NIL	30 sec	15 min
5cc	Tobramycin	Liquid		120mg/3 ml	NIL	30 sec	45 min
5cc	Vancomycin	Powder	1000mg		3ml(W)	30 sec	10 min
5cc	Cefuroxime (Supacef)	Powder	750mg		3ml(W)	30 sec	20 min
5cc	Teicoplanin (Targocid)	Powder	400mg		3ml(W)	30 sec	25 min
5cc	Vancomycin + Gentamicin	Powder + Liquid	1000mg	120mg/3 ml	NIL	30 sec	30 min
5cc	Vancomycin + Tobramycin	Powder + Liquid	1000mg	120mg/3 ml	NIL	30 sec	45 min
5cc	Tigicycline	Powder	50mg		3ml(W)	30 sec	20 min
5cc	Vancomycin + Cefuroxime	Powder	1000mg	750mg	3ml(W)	30 sec	20 min
5cc	Vancomycin + Teicoplanin	Powder	1000mg	400mg	3ml(W)	30 sec	20 min
5cc	Vancomycin + Meropenam	Powder	1000mg	500mg	3ml(W)	30 sec	30 min
5cc	Vancomycin + Colistin	Powder	1000mg	3MU	3ml(W)	30 sec	15 min
5cc	Tigicycline + Colistin	Powder	50mg	4MU	3ml(W)	30 sec	10 min
5cc	Vancomycin + Streptomycin	Powder	1000mg	1000mg	3ml(W)	30 sec	10 min

Figure 2: Different antibiotic Combinations

Antibiotics were supplied by pharmacy and were combined with the calcium sulphate powder. The liquid provided with the calcium sulphate was discarded and replaced with antibiotic solution. In each case, the beads were prepared at the start of the procedure to ensure they had set hard, and remained in the sterile field until required, at which point the beads were removed from the bead mat and implanted at the surgical site (Figure 3).

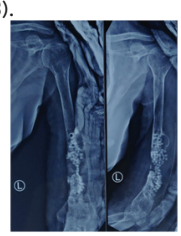


Figure 3: Antibiotic Calcium Sulphate Beads used in a case of Infected Shaft humerus Plate

RESULTS

Although all patients presented with signs of an active infection, it was only possible to identify the pathogens in thirty of the cases (13 Patients - S. aureus, 15 Patients - polymicrobial and 2 Patients - E. Coli), with the cultures from all other cases indicating no bacterial growth. It is not however uncommon to observe negative cultures in cases in which overt signs of infection are present(19). Therefore the use of broad spectrum antibiotics in combination with the calcium sulphate (vancomycin, gentamicin, cefuroxime) was prudent to obtain antimicrobial coverage of potential gram negative and gram positive pathogens.

The average follow-up was 8 months (range 3 to 16 months).

Reoccurrence of infection was observed in 2 patient at 2 months post surgery. The patient underwent subsequent removal of the external fixator and re-operation. This consisted of extensive debridement and the placement of 10cc of calcium sulphate beads combined with gentamicin and colistin/polymyxin. Serous discharge from the surgical site was observed post operatively that gradually decreased and stopped within 72 hours. At 5 month post reoperation, callus formation and bone union was evident, with no sign of infection.

In the other patients in the series, all fifty eight progressed to satisfactory healing of the bone defect, with radiological signs of union confirmed.

DISCUSSION

Surgical management of infection involving both bone and soft tissue must encompass effective debridement of necrotic tissues(9, 20). If the procedure fails to remove all necrotic tissues, these will act as a nidus for re-infection. Therefore aggressive debridement is key; in the case of osteomyelitis, the excision of bone to leave only healthy bleeding bone (the "paprika sign").

The removal of implants such as plates, pins and wires is essential. Biofilm infections on implants are frequently

observed, and pose a number of clinical challenges due to their resistance to immune defence mechanisms and antimicrobials. Microbial infections resulting from bacterial adhesion to biomaterial surfaces have been observed on most medical devices(21).

However, an infected surgical site cannot be sterilized by debridement alone. Debridement and removal of infected implants can remove a significant amount of bioburden but even thorough cleaning cannot prevent residual small bacterial colonies being displaced to new areas of the debrided site(20).

Following radical debridement, management of dead space is a cornerstone of clinical practice in septic surgery(22). This can be achieved through the use of muscle flaps to minimize soft tissue dead space(23-25), but residual dead space can fill with hematoma, an ideal environment for bacterial growth and potential source of infection re-occurrence. The use of local tissue flaps is not always possible following extensive debridement.

Antibiotic impregnated PMMA beads have been used in infected cases for over 30 years(26). This is traditionally in the form of beads on a wire or in a pouch to provide dead space management and enable the release of high local levels of antibiotic in the surgical site(27). Although effective in both these functions, PMMA has some disadvantages. It requires surgical removal once it has performed its function. If it is not removed, after initial high levels of antibiotic released at the site of implantation, it will continue to release sub-inhibitory levels of antibiotic, which may contribute to antibiotic resistance and may become a nidus for future infection(28-30). The use of alternative materials to PMMA has been reported, a number of which have the potential to provide osteoconductive support to bone growth at the site of implantation(31, 32). One material that offers some unique advantages as a material for dead space management in complex trauma revision cases is calcium sulphate. Firstly, as an osteoconductive material it can support new bone regeneration when implanted in debrided bone tissue(33, 34). Secondly, as it is only osteoconductive, it can be used to manage dead space in soft tissue, without the risk of inducing heterotopic ossification, and is fully resorbed in soft tissue within weeks(35, 36). Thirdly, it is possible to combine calcium sulphate with a wide range of antibiotics, including antibiotics that cannot normally be mixed with PMMA (antibiotic solutions, and thermosensitive antibiotics due to the high temperatures generated during PMMA curing)(37).

The potential for calcium sulphate to release high concentrationss of antibiotic at supra-MIC levels has been demonstrated in-vitro and in the clinical setting(37, 38), and there is evidence for its ability to prevent biofilm formation(6).

The calcium sulphate used in this series of six patients is not provided pre-loaded with antibiotic, and therefore has the advantage that it is possible to combine with a tailored antibiotic combination to target specific pathogens, or combine with two or more broad spectrum antibiotics in order to provide a broad spectrum coverage of both gram negative and gram positive bacteria. In cases of infected trauma where it is not always to possible to identify the infecting pathogens, this approach has obvious benefits. This broad spectrum approach to local antibiotic release has been successfully applied to the management of dead space with calcium sulphate in revision of infected total joints(18, 39).

In this series of patients presenting with challenging infections, we believe that the application of antibiotic loaded calcium sulphate was an ideal complement to the treatment modality of debridement, implant removal and I.V./oral antibiotic therapy. Re-occurrence of infection was observed in one patient. However, the subsequent re-operation, consisting of extensive debridement, removal of metalwork and the placement of calcium sulphate beads combined with an alternative antibiotic combination (gentamicin and colistin/polymyxin) demonstrates the versatility of calcium sulphate in surgical site infection.

CONCLUSIONS

The use of calcium sulphate as a tool in an infection management strategy for trauma revision shows promise in supporting new bone growth, managing dead space and enabling the release of high levels of tailored antibiotics to the surgical site to minimise the risk of infection re-occurrence. The efficacy of this treatment warrants further investigation in a larger trial.

Conflict Of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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