The role of bioceramics in the management of osteomyelitic voids

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Abstract

Background

Bioceramics are gaining popularity as dead space management in chronic osteomyelitis. They are bioabsorbable, have good antimicrobial activity, promote bone healing, and have a low complication profile. Several bioceramics are available in South Africa. This study investigates our experience of bioceramics in terms of outcomes and complications in managing osteomyelitic dead space.

Methods

A retrospective review was conducted on bioceramics in the management of chronic osteomyelitis of the appendicular skeleton between January 2016 and November 2022. The bioceramics used as dead space management strategies are: bioactive glass (S53P4 - BonAlive Biomaterials), and antibiotic-impregnated bone substitutes, i.e. Cerament G/V (Bonesupport) or Osteoset with added gentamycin (Wright Medical Group).

Results

The final cohort comprised 90 patients with a mean age of 34 years. The mean follow-up was 12 months (12.7 ± 8.6). Most patients were classified as Cierny and Mader (C&M) type 3 (61%), followed by C&M type 4 (37%). A total recurrence rate of 3% was noted. The recurrence rate per bioceramic used was 0% for Osteoset, 2% for bioactive glass, and 5% for Cerament.

Conclusion

Bioceramics are a popular alternative to PMMA in the management of osteomyelitic voids, especially in the setting of single-stage surgery. Several bioceramics are currently available in South Africa. Outcomes of bioceramics in the management of chronic osteomyelitis are encouraging and in keeping with international literature.

Level of evidence: Level 2

Keywords: bioceramic, osteomyelitis, fracture-related infection, dead space

Introduction

Fracture-related infection and chronic osteomyelitis are common problems following musculoskeletal trauma, orthopaedic surgery, and the sequelae of acute haematogenous osteomyelitis.[1,2] Following surgical debridement, bone and soft tissue defects or dead space need to be managed to prevent recurrence of infection.[1,3,4] Multiple dead space management strategies are available; however, choosing the appropriate strategy is controversial.[5]

The materials used for dead space management can be divided into biodegradable and non-biodegradable (polymethylmethacrylate [PMMA]).[6,7] Biodegradable materials include proteins (collagens), bone graft substitutes (bioactive glass and calcium sulphate), and synthetic polymers (polylactide). Investigations into materials that are reliable and effective are ongoing.[7]

Biodegradable alternative materials to PMMA as a delivery vehicle for depot antibiotics in musculoskeletal infections are gaining popularity.[7] This is because PMMA is not resorbable and needs to be removed with a second surgery. It has also been criticised for the theoretical risk of antibiotic resistance due to its prolonged low-level release of antibiotics.[7] In the past, morselised bone grafts, aqueous solutions, allografts, gels and collagens have all been used as biodegradable alternatives; however, they have proven to be inefficient as their release of antibiotics has been rapid and uncontrolled.[8]

Bioceramics are becoming increasingly popular as effective void fillers in managing chronic osteomyelitis.[6,9] They do not require secondary surgeries for removal, have local antimicrobial activity, promote bone healing and have a low side-effect profile.[4,9] These properties make them an attractive dead space management strategy, especially for single-stage surgery.[4] Several bioceramics are available today, each with its respective shortcomings and advantages.[4,10,11] This study investigates our experience of bioceramics in terms of outcomes and complications in managing osteomyelitic dead space.

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Materials and methods

All patients presenting with chronic osteomyelitis of the appendicular skeleton requiring dead space management between January 2016 and November 2022 were included in the study. Patients not managed with a bioceramic or follow-up of less than six months were excluded from the study. Data regarding patient demographics, aetiology and site of infection, type of bioceramic, causative organism, follow-up period and outcome in terms of resolution of infection were collected.

Chronic osteomyelitis was defined as an infection involving bone with a duration of at least ten days, where the causative organisms were thought to have persisted either intracellularly or in interactive biofilm-based colonies.[12] All patients were classified anatomically according to the Cierny and Mader classification system (C&M) and physiologically into A, B, or C types according to the modified C&M classification proposed by Marais et al.[13,14] Dead space management strategies included bioactive glass (S53P4, BonAlive Biomaterials), and antibiotic-impregnated bone substitutes, i.e. Cerament G/V (Bonesupport) or Osteoset (Wright Medical Group). Osteoset is mixed with antibiotics in theatre. In our unit we add 240 mg of gentamycin and 1 g of vancomycin to 25 ml of Osteoset. The dead space was managed following judicious debridement according to point-of-care testing and microbiological culture of the infected tissue. Skeletal stabilisation and soft tissue reconstruction were implemented as required. Intravenous broad-spectrum empiric antibiotics were given postoperatively and changed to six weeks of directed oral or intravenous antibiotics based on antibiogram results.

Resolution of infection was defined as the absence of clinical signs at a minimum of six months following surgery. Treatment failure was defined as failure to achieve remission, including ongoing clinical signs of infection, unplanned reoperation or amputation.

Results

All patients treated with bioceramics as a form of dead space management in the treatment of chronic osteomyelitis between January 2016 and November 2022 were included in the study. The final cohort comprised 90 patients with a mean age of 34 years (33.7 ± 15.0). Of the patients, 82% (n = 64) were male and 37% (n = 33) were smokers. The mean follow-up was 12 months (12.7 ± 8.6) (*Table I*). Most infections involved the tibia (50%), followed by the femur (16%) and the forearm (13%) (*Figure 1*). Most patients were classified as C&M type 3 (61%), followed by C&M type 4

Table I: Demographics of included patients

	Osteoset	Cerament G/V	BonAlive	Total
Number	11	38	41	90
% Male (n)	82 (9)	71 (27)	68 (28)	71 (64)
Age (years, mean ± SD)	34.5 ± 12.2	36.8 ± 14.2	30.5 ± 16.0	33.7 ± 15.0
% Smoker (n)	27 (3)	47 (18)	29 (12)	37 (33)
% Diabetes mellitus (n)	0 (0)	5 (2)	0 (0)	2 (2)
% HIV positive (n)	10 (1)	8 (3)	5 (2)	7 (6)
Anatomy (%, n)				
Humerus	0 (0)	8 (3)	15 (6)	10 (9)
Humerus + ulna	0 (0)	2 (1)	0 (0)	1 (1)
Radius/ulna	0 (0)	16 (6)	15 (6)	13 (12)
Femur	18 (2)	13 (5)	22 (9)	18 (16)
Femur + tibia	9 (1)	0 (0)	0 (0)	1 (1)
Tibia	73 (8)	45 (17)	49 (20)	50 (45)
Tibia + talus	0 (0)	8 (3)	0 (0)	3 (3)
Calcaneus	0 (0)	8 (3)	0 (0)	3 (3)
Anatomical type (%, n)				
C&M stage 1	18 (2)	0 (0)	0 (0)	2 (2)
C&M stage 2	0 (0)	0 (0)	0 (0)	0 (0)
C&M stage 3	0 (0)	45 (17)	93 (38)	61 (55)
C&M stage 4	82 (9)	55 (21)	7 (3)	37 (33)
Host status (%, n)				
C&M Class A	36 (4)	24 (9)	63 (26)	43 (39)
C&M Class B_S	36 (4)	29 (11)	5 (2)	19 (17)
C&M Class B_L	18 (2)	24 (9)	22 (9)	22 (20)
C&M Class $B_{L/S}$	9 (1)	24 (9)	10 (4)	16 (14)
Soft tissue cover (%, n)				
Direct closure	55 (6)	60 (23)	85 (35)	71 (64)
Skin graft	0 (0)	5 (2)	0 (0)	2 (2)
Deformity-assisted closure	18 (2)	13 (5)	0 (0)	8 (7)
Fasciocutaneous flap	18 (2)	11 (4)	3 (1)	8 (7)
Muscle flap	9 (1)	11 (4)	12 (5)	11 (10)
Bacteriology (%, n)				
No growth	9 (1)	21 (8)	22 (9)	20 (18)
Pure culture	64 (7)	66 (25)	71 (29)	68 (61)
Polymicrobial organisms	27 (3)	13 (5)	7 (3)	12 (11)
% Recurrence (n)	0 (0)	5 (2)	2 (1)	3 (3)
Follow-up (months, mean ± SD)	9.0 ± 3.1	8.2 ± 2.8	18.0 ± 10.1	12.7 ± 8.6

B_S: B-host, compromised systemically; B_L: B-host, compromised locally; B_{LS}: B-host, compromised locally and systemically

Table II: Organisms isolated from intraoperative samples (n = 73)

	Osteoset (n = 13)	Cerament G/V (n = 35)	BonAlive (n = 35)	Total (n = 73)
Staphylococci				
Methicillin-susceptible *S. aureus*	5	12	20	37
Methicillin-resistant *S. aureus*			4	4
Coagulase-negative staphylococci	3			3
Streptococci				
Group B *Streptococcus*		4		4
Streptococcus constellatus			1	1
Enterococci				
Enterococcus faecalis		1		1
Enterobacterales				
Proteus mirabilis			3	3
Proteus hauseri		1		1
Enterobacter cloacae	1	5	1	7
Klebsiella pneumoniae	2	2	1	5
Serratia marcescens		1		1
Providencia stuartii		1		1
Escherichia coli		2	1	3
Morganella morganii		1	1	2
Citrobacter freundii/ braakii		2		2
Non-fermenting Gram-negative bacilli				
Pseudomonas aeruginosa	1	1	1	3
Miscellaneous Gram-negative bacilli				
Aeromonas hydrophila/ caviae	1			1
Anaerobes				
Finegoldia magna		1		1
Bacillus cereus		1		1
Bifidobacterium species			1	1
	13	**35**	**35**	**73**

(37%). The C&M subtype, host status, and type of soft tissue cover required are illustrated in *Table I* and categorised according to each bioceramic used. A breakdown of the organisms cultured is depicted in *Table II*.

A total recurrence rate of 3% was noted. The recurrence rate per bioceramic used was 0% for Osteoset, 2% for bioactive glass, and 5% for Cerament. The bacteriology consisted of pure growth in 68% of cases, 20% no growth and 12% polymicrobial growth.

Discussion

Until recently, PMMA beads or spacers were considered the gold standard for treating osteomyelitis voids following surgical debridement in a two-stage strategy. With the development of biodegradable antibiotic-loaded bone graft substitutes, single-stage treatment has become possible.[15,16] These void fillers have become increasingly popular as effective alternatives to PMMA for managing dead space following chronic osteomyelitis debridement.[6,9] Commercially available bioceramics include

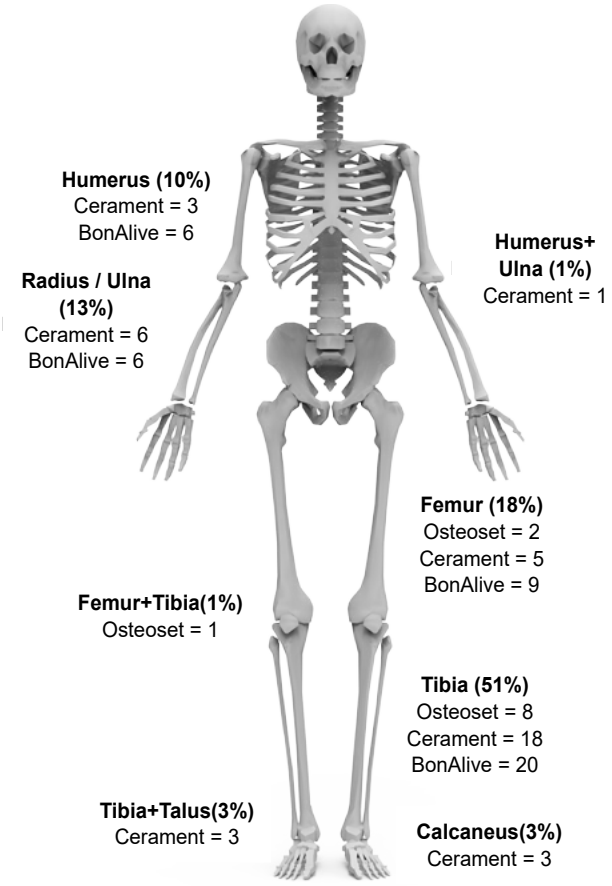

Figure 1. Anatomical location of infection and distribution of bioceramic utilised

BonAlive, Cerament G/V, Osteset T, Prodense, Herofill G, Stimulan and Perrosal.[9] Osteoset, Prodense, Cerament G/V and bioactive glass are available in South Africa. We present our experience with bioactive glass, Cerament G/V, and Osteoset as commercially available bioceramics in South Africa.

Osteoset and Prodense are bone graft substitutes from Wright Medical Group. Prodense is an injectable regenerative bone graft substitute that combines calcium sulphate and phosphate, whereas Osteoset consists of α-hemihydrate calcium sulphate only.[17] Neither preparation is currently available in South Africa with preloaded antibiotics. Preloaded antibiotic preparations (Osteoset-T) function through the resorption of calcium sulphate, which leads to the release of high concentrations of tobramycin.[18,19] Tobramycin interferes with protein synthesis and disrupts bacterial cell membranes. It has good Gram-positive and Gram-negative cover and high elution of antibiotics remains for up to 22 days.[18,19] The calcium sulphate is osteoconductive and acts as a scaffold for new bone formation. Several studies have reported effective remission rates between 86% and 92%.[17,20,21] A notable concern with Osteoset-T is slow bony ingrowth which may predispose to fracture and is thought to be due to the rapid dissolution of the calcium sulphate.[17,21] Our experience using Osteoset consists of 11 patients and involved mixing gentamycin and Osteoset in theatre. We are not certain what effect this has on product properties and the concentration of antibiotic delivered; however, our remission rate of 0% is encouraging. We concede that our limited patient numbers are problematic, and we believe further local and international comparative studies are needed.

Cerament G and Cerament V are calcium sulphate-hydroxyapatite cement containing either gentamycin or vancomycin. Cerament G/V have been considered as a single entity because their mechanical properties are identical. The difference between the two is their

antimicrobial properties. We carefully consider which mixture is more appropriate based on previous bacterial isolates, and patient history. Cerament G and Cerament V can also be added together to provide a broader antimicrobial profile. Cerament has been demonstrated to be highly effective as dead space management in managing chronic osteomyelitis.[4] It is injected as a thick liquid that can coat the surface of bone which then hardens to a similar compressive strength of cancellous bone.[6] The use of high-dose antibiotics in Cerament has shown no clinically significant adverse effect on renal function, and systemic levels eluted from this carrier are very low.[22] Results from the Oxford bone infection unit report remission rates of 97% at one year and 94% at six years in a series of more than 100 patients.[15] The incidence of secondary fracture after definitive management is thought to be low due to the direct bone formation on the biomaterial.[3,15] Our experience with Cerament G/V is encouraging. The current series showed a remission rate of 95% with a mean follow-up of 8.2 ± 2.8 months. We have found Cerament to be versatile and effective. It can be used as a liquid to fill small screw holes or hard-to-reach voids; alternatively, it can be moulded into beads which increase the surface area and can be used to fill intramedullary cavities or large voids. Using either gentamycin, vancomycin or both is helpful in directing local antibiotic therapy to the known or suspected pathogen. Our experience using Cerament is positive, and our remission rates are in keeping with international literature.[15]

Bioactive glass is a class of bioceramics that has been proven useful in managing bony voids. Its properties are entirely different to the biomaterials mentioned above. One particular variation, S53P4, consisting of 53% silicone dioxide (SiO_2), 23% sodium oxide (Na_2O), 20% calcium oxide (CaO) and 4% phosphorus pentoxide (P_2O_5), is specifically useful as it is the only bioactive glass that exhibits bacterial growth-inhibiting properties.[11] Bioactive glass has a wide range of antimicrobial properties against Gram-positive and -negative bacteria. When implanted in the body, the glass granules undergo rapid surface and chemical changes. Cation exchange leads to a high local pH and increased local osmolar pressure, which leads to bacterial cell wall failure.[11,16] It also stimulates angiogenesis via an increase in vascular endothelial growth factor (VEGF) and has osteoconductive, osteoinductive and osteostimulative properties.[11,23] Bioactive glass incorporates well into bone through the precipitation of calcium and phosphorus salts onto a gel substrate that eventually mineralises, forming a hydroxyapatite-like substrate.[23] Several studies have shown promising results in managing chronic osteomyelitis, with remission rates of up to 92%.[24-31] In our experience, bioactive glass is easy to handle and effective. Our experience with bioactive glass is encouraging, with a series of 41 patients and a remission rate of 98%.

It is worth noting that most patients in the current series treated with bioceramics were classified as C&M 3 (61%) and C&M 4 (37%) type osteomyelitis. That said, bioceramics do not possess the structural properties required to treat voids following extensive segmental resections. In our experience, two-stage surgery with PMMA is still the dead space strategy of choice for type 4 chronic osteomyelitis requiring segmental resections larger than 20 mm. We caution users that all the bioceramics may lead to prolonged postoperative wound drainage, but this often resolves with time. To our knowledge, this is the largest published series in South Africa investigating the outcomes of bioceramics in the management of chronic osteomyelitis.

This study is limited by its retrospective nature and relatively small sample size. Further multicentre randomised controlled trials would be beneficial to identify the ideal void filler for each clinical scenario.

Conclusion

Bioceramics are becoming a popular alternative to PMMA in the management of osteomyelitic voids. They are a versatile, effective and reliable dead space management strategy in treating chronic osteomyelitis, and their biodegradability is especially attractive in single-stage surgery. Several bioceramics are available in South Africa, and our outcomes are encouraging and in keeping with international literature.

Ethics statement

The authors declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010.

Prior to commencement of the study, ethical approval was obtained from the Stellenbosch University Ethics Committee, HREC reference number: N22/01/007. This study was a retrospective review of patient records only. Informed consent was waivered. The Ethics committee was in agreement with the waiver of informed consent.

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Declaration

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

Author contributions

NF: conceptualisation and design of the study, acquisition of data, analysis and interpretation of data; drafting the article, revising it critically for important intellectual content, final approval of the version to be submitted; sound scientific research practice

GZE: conceptualisation and design of the study, acquisition of data, analysis and interpretation of data; drafting the article, revising it critically for important intellectual content, final approval of the version to be submitted; sound scientific research practice

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