ORIGINAL RESEARCH

Effectiveness of an Antibiotic-impregnated Bioabsorbable Carrier for the Treatment of Chronic Intramedullary and Diffuse Osteomyelitis

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Abstract

Aim: The surgical management of chronic intramedullary osteomyelitis involves debridement of affected non-viable tissue and the use of antibiotics. Where surgery leaves a cavity, dead-space management is often through antibiotic-impregnated bone cement. These depots of local antibiotics are variable in elution properties and need removal. We review our unit's experience using a bioabsorbable synthetic calcium sulphate to deliver gentamicin as an adjunct in the treatment of osteomyelitis involving the medullary canal.

Materials and methods: We retrospectively reviewed 34 patients with chronic osteomyelitis who were treated using this method in our institute. Variables recorded included aetiology, previous interventions, diagnostic criteria, radiological features, serology, and microbiology. The Cierny–Mader system was used to classify. Follow-up involved a survival analysis to time to recurrence, clinical and functional assessment (AOFAS-Ankle/IOWA knee/Oxford Hip/DASH scores) and a general health outcome questionnaire (SF36). The primary outcome measure was clinical recurrence of infection.

Results: There were 24 male and 10 female patients. The mean age at presentation was 47 years (20–67). Clinical, laboratory, radiological, and patient reported outcomes were obtained at a median follow-up of 2.5 years (1.4–6.6 years). The bones involved were the femur (14, 41%), tibia (16, 47%), radius (1, 3%), and humerus (3, 9%). There were 13 cases classified as Cierny–Mader stage IV (diffuse with intramedullary osteomyelitis) and 21 cases as Cierny-Mader stage I. The median Oxford Hip score was 38 (11 patients, range 9–48). The median AOFAS score was 78 (14 patients, range 23–100). The median IOWA knee score was 71 (25 patients, range 22–95). The median DASH score was 33 (2 patients, range 1.7–64.2). There were two recurrences. The treatment success to date is 94%.

Conclusion: In our series of patients, bioabsorbable carriers of antibiotics appear to be effective adjuncts to surgical treatment of osteomyelitis and were associated with high clinical success rates.

Keywords: Antibiotics-loaded calcium sulphate, Bioabsorbable, Calcium sulphate, Chronic osteomyelitis, Cierny and Mader classification, Cohort Study, Osteomyelitis.

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Introduction

Chronic intramedullary osteomyelitis in long bones presents a significant treatment challenge and remains a major cause of morbidity.[1] It has considerable health–economic implications in terms of the use of antimicrobials, hospital stay, and cost of surgery.[2–5] Chronic osteomyelitis can be classified by the Cierny–Mader staging system (Table 1), which is clinically relevant and easily understood. It is based upon the anatomical location of the infection but importantly also accounts for the immunocompetence of the host, which may impact physiological response to infection and surgical intervention.[6] In stages I–III, overall integrity of the bone is retained, whilst stage IV (diffuse osteomyelitis) there is circumferential involvement with loss of stability, as in an infected non-union. The host is defined as either type A, B, or C. The A hosts are patients without systemic or local compromising factors. Type B hosts are affected by one or more compromising factors whereas C hosts are patients so severely compromised that the radical treatment necessary would have an unacceptable risk-benefit ratio.[7,8]

The principles of surgery for the eradication of infection include surgical debridement of non-viable bone and soft tissue

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Table 1: Cierny–Mader staging system

Anatomic type	Stage I	Medullary osteomyelitis
	Stage II	Superficial osteomyelitis
	Stage III	Localised osteomyelitis
	Stage IV	Diffuse osteomyelitis
Physiologic class	A Host	Normal host
	B Host	Systemic compromise (Bs)
		Local compromise (Bl)
		Systemic and local compromise (Bsl)
	C Host	Treatment worse than the disease

Bs, Malnutrition, renal or hepatic failure, diabetes mellitus, chronic hypoxia, immune disease, extremes of age, malignancy, immunosuppression or immune deficiency; Bl, Chronic lymphedema, venous stasis, major vessel compromise, arteritis, extensive scarring, radiation fibrosis, small-vessel disease, neuropathy

and delivery of high concentration antibiotics, usually given systemically and often supplemented by local delivery through antibiotic-impregnated carriers.[8] Six weeks of systemic therapy is most often used.[9] When surgical debridement of necrotic and infected tissue is performed, a cavity is produced, this is no different following debridement of intramedullary osteomyelitis. Common practice for the management of this intramedullary dead-space is through placement of antibiotic-impregnated cement within the canal. However, these depots of local antibiotics vary in their elution properties and require removal. The presence of cement does not encourage bone regrowth. For medually infection, 'cement nails' are often used. However, these do not provide sufficient stability in the majority of situations with diffuse osteomyelitis and may fracture, complicating removal.

An alternative to deliver local antibiotics is antibiotic-impregnated calcium sulphate (Stimulan®, Biocomposites Ltd, Keele, England), a synthetic high purity calcium sulphate biocompatible bone graft material that is resorbable. It has some osteoconductive properties that are favourable to subsequent bone formation and has been shown, in some circumstances, to stimulate new bone formation comparable with autogenous bone.[10–12] It can be mixed safely with antibiotics and has favourable elution properties.[13,14] It has the advantage of being easier to instil than cement, but most importantly, does not require removal due to its eventual resorption. The use of antibiotic-impregnated carriers delivers high levels of antibiotics and obliterates the dead-space that occurs after bone debridement.[15–18] Although numerous successful experimental studies have been performed in animal models using bioabsorbable carriers to treat infection. There are few human clinical studies in the literature.[19]

In our institution, it has become standard practice to use a bioabsorbable synthetic carrier to deliver local antibiotics in the treatment of intramedullary osteomyelitis following debridement. The objective of this retrospective study was to evaluate the effectiveness of this approach in patients with chronic osteomyelitis classified as either intramedullary or diffuse with intramedullary extension (Cierny–Mader stage I or IV).

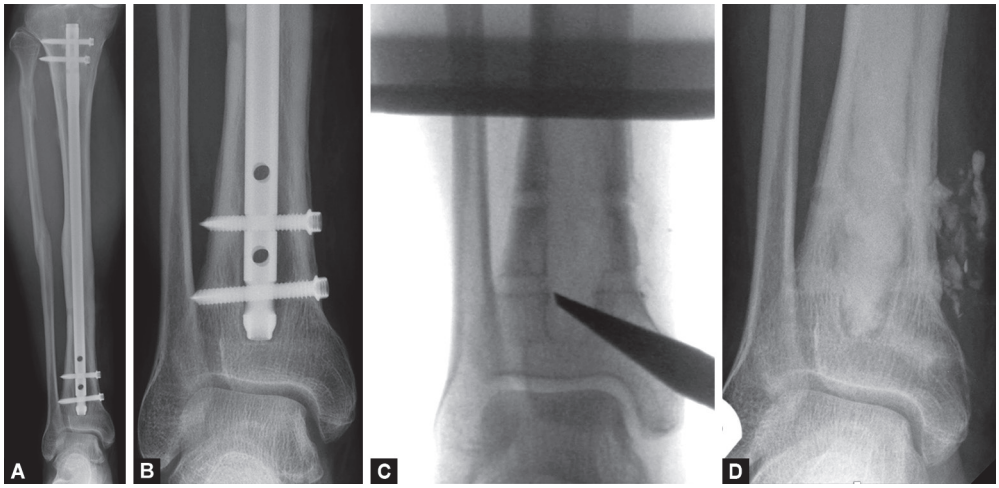
Materials and Methods

The local institution review board approved data collection for this review. Consecutive cases of chronic osteomyelitis involving the medullary canal, treated using antibiotic-impregnated calcium sulphate (Stimulan®, Biocomposites Ltd, Keele, England) as an adjunct in management from 2006 were identified. Data were collected from patient records including patient demographics, aetiology of osteomyelitis, details of primary or prior interventions (if any), smoking status, medical co-morbidities, and estimated duration of osteomyelitis. Clinical symptoms and signs were documented at consultation and used to aid in the assessment of the limb to determine the likelihood of infection. In all patients presenting to the outpatients, preoperative serological investigations (white cell count, C-reactive protein, and erythrocyte sedimentation rate) were performed. Further assessments included radiological investigations of plain radiography in two orthogonal planes, computed tomography (CT) and magnetic resonance imaging (MRI). Specific features that were suggestive of infection on radiological studies were recorded. Patients with Cierny–Mader stage I (intramedullary) or stage IV (diffuse) but with evidence intramedullary spread were included. We did not identify any patients with stage III disease (cortical sequestration and cavitation). We have noted that in our practice, this is an unusual form of presentation of chronic osteomyelitis. Host immunocompetence was recorded.

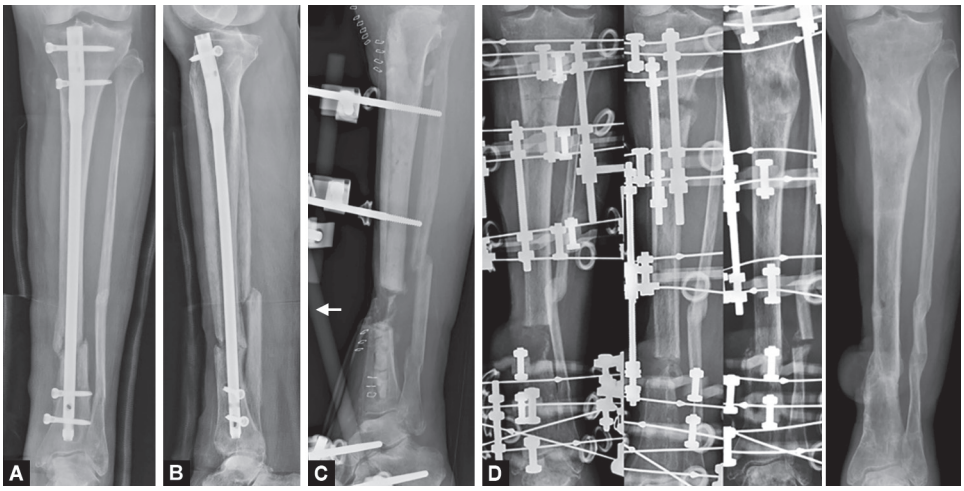
Surgical treatment was in accordance with an established protocol for the unit and involved the removal of orthopaedic hardware, resection of necrotic or infected bone and soft tissue and intramedullary debridement using reamers followed by copious saline lavage of the residual dead-space. Of note in the technique of debridement is the establishment of a distal portal in communication with the medullary canal (Fig. 1). This allowed retrograde reaming and lavage of the intramedullary canal in addition to the standard antegrade procedures. At least five samples of bone and tissue were taken for microbiological analysis as well as samples for histology. Following debridement and lavage, the entire surgical team is re-attired with clean gowns and gloves and there is a complete change of the surgical instruments. The limb is re-prepped and re-draped before insertion of the calcium sulphate carrier with antibiotic. Stimulan® is available in pellet form or as an injectable paste which is easy to apply via a syringe or pressurised gun (Fig. 1). It is mouldable and sets rapidly and tends to be resorbed over 6–8 weeks. All patients had the aminoglycoside antibiotic gentamicin impregnated into the Stimulan® using a mix of 160 mg gentamicin with every 10 cc. All cases were treated with systemic antibiotic therapy for 6 weeks as guided by microbiology results and following discussions with specialist microbiologists. Residual bone defects, when present, were treated either by bone grafting or through bone transport when clinical evidence of sepsis was not evident and often after 6–8 weeks of the primary surgery (Fig. 2).

The primary outcome measure was clinical recurrence of infection by most recent clinical follow-up. The diagnosis of recurrence of infection was based on several parameters and not a single entity or result of investigation. To be deemed free of infection, there had to be the absence of any local symptoms or signs, such as pain, swelling, erythema, discharge or systemic signs of malaise, sweats, fever in the entire follow-up period.

Conflict of interest: Dr. Badri Narayan is associated as the Specialty Section Editor (Trauma) of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of this editorial board member and his research group.



Figs 1A to D: Tell-tale signs of an intramedullary infection and the technique of debridement. (A) A healed fracture but with signs and symptoms of ongoing sepsis; (B) A close look at the distal tibia reveals cavitation (the sump abscess) around the tip of the nail (and no evidence of nail loosening) as well as periosteal new bone formation around the ends of the interlocking screws; (C) The nail is extracted and before intramedullary reaming and lavage commences, an exit portal that communicates with the base of the sump abscess is created. The portal can be large enough for retrograde reaming and lavage; (D) The management of dead space using antibiotic-laden calcium sulphate. Note the filler extends into the distal portal created earlier



Figs 2A to D: Reconstructing the bone defect created after intramedullary debridement and segmental resection of an infected tibial fracture with a draining sinus. (A and B) The infected intramedullary nail with evidence distally of a sump abscess the cavitation around the tip of the nail; (C) Following the extraction of the nail, intramedullary debridement, segmental resection and lavage, the canal was filled with antibiotic-laden calcium sulphate (Stimulan) and the limb stabilised with an external fixator; (D) The definitive reconstruction of the bony defect was undertaken by bone transport

Radiographs taken after treatment and at latest follow-up had to show no evidence of new bone lysis at the site of original infection or elsewhere. Serological investigations did not serve a useful monitor owing to the procedures that had to be undertaken for treating residual bone defects (bone transport, bone grafting, etc.) which would have caused an elevation of inflammatory markers in the interim periods. Likewise, periosteal new bone formation in relation to the procedures above for bone union in the reconstruction of the residual bone defect were excluded. Recorded secondary outcome measures included clinical and functional assessment of the joints above and below the diaphyseal bone involved (AOFAS-Ankle, IOWA knee, Oxford Hip, and DASH scores) and a general health outcome questionnaire (SF36). Data were analysed descriptively by using proportions and frequencies for categorical variables. Means, standard deviations, and ranges were used for continuous variables as appropriate.

Results

Thirty-four patients were identified with chronic intramedullary or diffuse osteomyelitis with medullary extension. There were 24 male and 10 female patients. The mean age at presentation was 46.8 years (20–67). There were 14 cases involving the femur (41%), 16 involving the tibia (47%), and 4 in the upper limb (12%, 1 radial and 3 humeral). Twenty-eight cases (82%) were postoperative infections (20 closed and 6 open fractures) and six (18%) were of

haematogenous, non-surgical, origin. There were 13 cases classified as stage IV and 21 classified as stage I, according to Cierny and Mader. All but 4 patients were classified as type A hosts, the rest being type B. Only 2 patients had no prior operations on their limb (four cases of infection from haematogenous sources had previous debridement). For the 32 cases who had undergone previous surgeries, the mean number of operations prior to the index surgery with the use of antibiotic-impregnated calcium sulphate was 1.8 (range 0–5, standard deviation 1.2). In 21 cases there were previous interventions for documented osteomyelitis. In 13, there was no previous osteomyelitis documented. The estimated duration of osteomyelitis prior to presentation and subsequent treatment had a median of 1.5 years (range 3 weeks–50 years). Of the 28 cases treated surgically the initial fixation performed was intramedullary nailing in 23 (82%), plating in 2 (7%) and external fixation in 3 (11%).

Radiological Investigations

Thirty-two of the 34 cases had retrievable radiographs. The presence of cortical thickening (new bone laid down in response to deep infection) was evident along the medullary canal in 25/32 (78%) cases. Cross-sectional imaging (CT or MRI) was available in 20 cases. In established cases of infection, erosion of the distal end of the bone around the tip of the nail was evident as well as new bone formation arising around the distal interlocking screws. This cavitation around the tip of the nail was referred to as a 'sump abscess' by Charles Lautenbach of South Africa. Additionally, we found, in 19 cases, diffuse cortical thickening on the CT and MRI images. Increased intramedullary signal on T2-weighted image was found on all those who had MRI scan (16/16). Increased intramedullary signal on T1-weighted image was only evident on 56% (9/16).

Serological Investigations

Preoperative inflammatory serological investigations were reviewed. Ten cases did not have an ESR recorded. The remaining 24 values ranged from 5 to 156, with a median of 26.5. In three patients, no CRP value was found. Two were normal at <5 mg/L and in the remaining 29, these ranged from 7 to 434 mg/L, with a median of 26 mg/L.

Microbiological Findings

Following surgical debridement, infected bone tissue was sent for laboratory analysis with final results as follows: four cases failed to deliver a causal organism despite the clinical presence of infection (12%) and positive histology for infection; 18 cases had *Staphylococcus aureus* species (52%) identified. The remaining cases had a wide spread of variety in causal organisms: 1 had Methicillin-resistant *Staphylococcus aureus* (MRSA, 3%); 1 with coliforms (3%); 1 with enterococci (3%); 1 grew *Clostridia* species (3%); 1 with *Pseudomonas* (3%); 1 with *Streptococcus* species (3%) and 6 with coagulase-negative *Staphylococcus aureus* (18%). There were 10 cases which grew more than a single bacteria (29%).

Surgical Treatment of the Residual Bone Defect

Three cases had primary bone grafting for treatment of the residual bone defect after an interval treatment period with systemic and local antibiotics (usually after 6–8 weeks). Twelve cases were treated with bone transport to achieve union following initial debridement (Fig. 2). One case had a compression–distraction technique performed to achieve union. Eighteen cases had no significant bone defect thus did not require any grafting or bone transport. Two patients required plastic surgery as part of their surgical treatment. One patient required a medial gastrocnemius flap and split-thickness skin graft and the second patient a local perforator-based fasciocutaneous flap.

Recurrence

The median follow-up for the cohort was 2.5 years (1.4–6.6 years). Based on the defined criteria, recurrence occurred in two cases (6%). One case was a Cierny–Mader stage I disease in the proximal resulting from an open tibial fracture and the second was a Cierny–Mader stage IV distal femoral osteomyelitis. Both patients had repeat treatment using the same treatment strategy of debridement, targeted systemic antibiotic therapy and local antibiotic delivery. One is now infection-free whereas the second continues to live with an intermittent draining sinus and has considered but not opted for an amputation. The remaining 94% had uneventful completion of treatment and final follow-up.

Functional Assessment and General Health Status

The joints adjacent to the affected bone segment were examined and scored using the Oxford Hip Score, the American Orthopaedic Foot and Ankle Score (AOFAS), the disabilities of the arm, shoulder and hand (DASH) score and the IOWA knee score. The median Oxford Hip score was 38 (11 patients, range 9–48). The median AOFAS score was 78 (14 patients, range 23–100). The median IOWA knee score was 71 (25 patients, range 22–95). The median DASH score was 33 (two patients, range 1.7–64.2).

The SF36 data were used to compare the health of the cohort with that of the UK population norms matched for gender. The eight categories of the SF36 are: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH) (Fig. 3). The eight scales can be summed to represent two categories of health, the physical component summary (PCS) and mental component summary (MCS) (Fig. 4). When compared with UK population norms, it is clear that chronic bone infection has a strong impact on the physical component of health despite successful treatment. The chronicity of the condition prior to treatment may influence the ability to recover full physical fitness, and this cohort had a mean of 7.2 years of the chronic infection before the index treatment. All scales that measured physical health scored below the UK population norm and the subsequent impact on SF can be seen. The contrast between those who remained infection-free and those who had a recurrence is clear. However, the scales that reflected MH were better and this was seen in the MCS measure that was near normal.

Discussion

The treatment of chronic osteomyelitis remains challenging despite advances in diagnosis, techniques to reconstruct defects created by debridement, and antibiotics. The most important steps in the management of this condition are surgical debridement, dead-space management, and the targeted use of antibiotics. Antibiotics delivered locally have advantages over the parenteral route; much higher concentrations are achieved without producing systemic toxicity. Several studies have looked at the different means local antibiotic delivery with the commonly used carriers being bone cement (Polymethylmethacrylate—PMMA), bone graft substitute (calcium sulphate), synthetic polymer, and metal (titanium).[20]

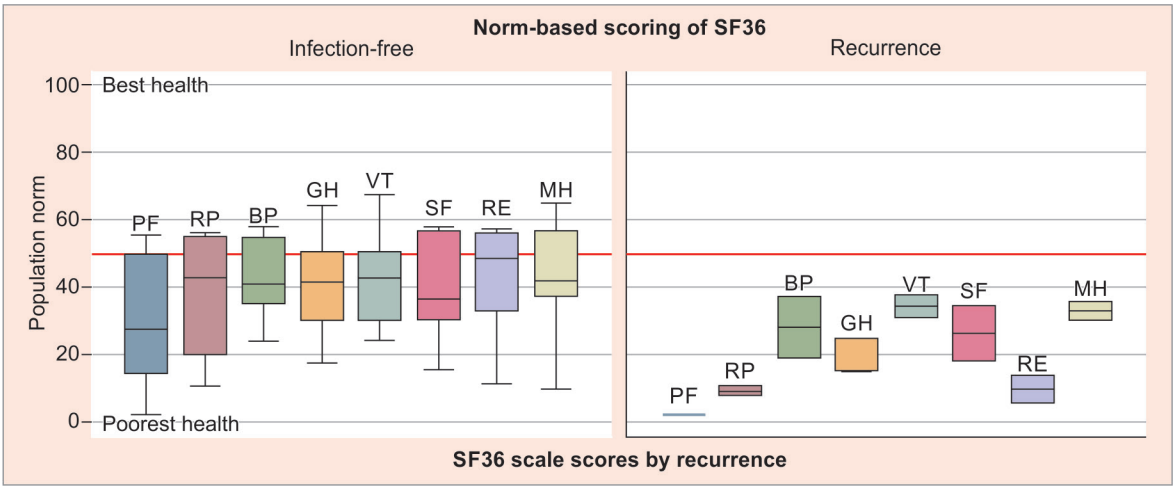


Fig. 3: Norm-based scoring of the SF36 scales of those who remained infection-free and those who had recurrence. Physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH)

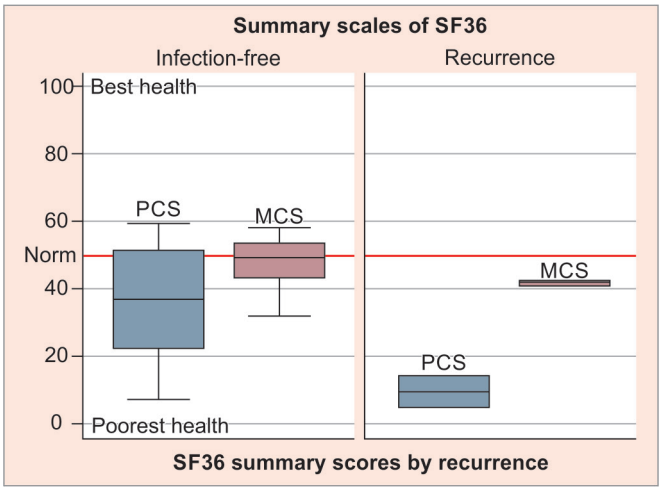


Fig. 4: Summary measures of the SF36 by recurrence of infection PCS (physical component summary) MCS (mental component summary)

Gentamicin belongs to the protein synthesis inhibitor family of antibiotics, binding to the bacterial ribosomal 30S subunit to achieve a bacteriostatic effect through transcription errors during cell division. It also has bactericidal properties by disrupting the bacterial cell membranes.[21] This antibiotic is broad spectrum in action, and with high local concentrations, can be effective against gram-negative organisms and some gram-positive organisms such as *Staphylococcus*.[22]

In 1970, Buchholz and Engelbrecht[23] reported that bone cement mixed with antibiotics was effective in the treatment and prophylaxis of infection in total hip arthroplasty. A literature review reveals good results with PMMA mixed with different antibiotics.[24–26] It is widely used and represents a standard as an antibiotic delivery vehicle in orthopaedic surgery.[25] However, the elution of antibiotics from PMMA is variable and can drop to below MIC (mean inhibitory concentration) levels after 2 weeks. Furthermore, non-biodegradable carriers such as PMMA can attract glycocalyx-producing bacteria despite the presence of antibiotics. The resulting biofilm can act as a foreign body and a surface for bacterial colonization which could lead to a secondary infection.[27] A further procedure is needed for its removal. Furthermore, PMMA has no osteoconductive or osteoinductive potential and defect management, after extraction of the PMMA, will be required either through bone grafting or other techniques. The biodegradable carriers have advantages: additional surgery for their removal is not needed; the elution of antibiotics extends beyond 2 weeks owing to the continual breakdown of the carrier and release of more antibiotics.[7,28,29] Calcium sulphate releases its entire antibiotic load on resorption and has been shown to deliver adequate concentration locally for up to 4 weeks with safe serum levels.[30,31] It is safe, well tolerated and has a low systemic exposure in patients.[32] Studies have also shown that the level of serum calcium does not rise in human as calcium is absorbed.[27,33]

Several different biodegradable carriers have been studied in animal models and in humans including calcium hydroxyapatite, plaster of Paris and chitosan.[19,29,34–36] Calcium sulphate has a rapid resorption profile and carries some osteoconductive properties.[25,29] In some instances, this can avoid a further bone grafting procedure although this was not the experience from this cohort.[33] The cohort in this study represented patients with intramedullary or diffuse (with intramedullary extension) chronic osteomyelitis and the resultant bone defects after debridement made additional bone grafting or bone reconstruction procedures necessary.

McKee et al.[33] showed that tobramycin-impregnated calcium sulphate eradicated osteomyelitis in 92% (2 recurrences) of cases after a mean follow-up of 28 months. The success rate in treating chronic osteomyelitis using gentamicin with calcium sulphate in our study was very similar. Humm et al.,[37] in their retrospective study, showed that when OSTEOSET®-T (calcium sulphate pellets preloaded with 4% tobramycin) was used as adjuvant therapy, this eradicated chronic osteomyelitis of the tibia in 95% of patients in their sample. It is not clear whether these patients had diffuse intramedullary osteomyelitis or localised osteomyelitis.

Some authors have advocated the addition of demineralised bone matrix to calcium sulphate to achieve osteoconductive and osteoinductive properties. Beardmore et al.[38] showed that tobramycin-impregnated calcium sulphate pellets and demineralised bone matrix were effective in preventing intramedullary *Staphylococcus aureus* infection in contaminated goat fracture model. All patients in our study cohort had been

prepared for two stages in treatment for chronic osteomyelitis, and as such, no attempts were made to add demineralised bone matrix or bone graft at the index operation.

These results from the use of gentamicin-loaded calcium sulphate are promising. This is especially when the chronicity of the osteomyelitis (mean 7.2 years) and the anatomical extent (intramedullary or diffuse with intramedullary extension) are considered. The authors maintain that the key steps in surgical treatment of chronic bone infection involve a meticulous debridement (of at least marginal or wide boundaries), dead-space management and targeted antibiotics. Of special mention is the attention to detail when debridement is performed in intramedullary osteomyelitis: in addition to sequential reaming and lavage, the most distal end of the medullary cavity needs to be accessed in order to ensure this too is cleaned out at surgery. The availability of biodegradable antibiotic carriers has provided an improved elution profile of high concentration local antibiotics to the arsenal.

The extend of disease involvement was determined using a combination of clinical examination and imaging which included plain radiographs, CT scans, and MRI scans. All four components as well as consideration of patient's past surgical history had an influence on surgical strategy. Out with the study period, the use of PET-CT scan to determine the extent of bone involvement has become used more frequently, results are currently being evaluated in a separate study.

Chronic osteomyelitis affecting the long bones of either the upper or lower extremity impacts greatly on physical function, despite successful treatment. The data on patient outcomes in this work highlight this clearly. The joint function measures (Oxford hip, IOWA knee, AOFAS, DASH) show residual limitations which are reflected in the physical function scales and PCS of the SF36. These data may caution against over-optimism when counselling patients on likely outcomes after treatment. However, treatment does improve the emotional and MH well-being of patients and most had scored close to the population norm.

There are several limitations to the work presented. The short follow-up (mean 2.5 years) in some patients is a relative weakness of this study. Both the recurrences that occurred in our study were 3 years post-initial treatment for chronic osteomyelitis. Additionally, there is a relatively small number of patients and no control group. Both these will affect the extrapolation of the conclusions obtained herewith.

In patients with intramedullary osteomyelitis, debridement of non-viable tissue, dead-space management with antibiotic-impregnated calcium sulphate in addition to systemic antibiotics was effective in eradicating bone infection in 32 out of 34 patients. This study supports the continued use of bioabsorbable carriers of antibiotics as efficacious adjuncts to surgical treatment of intramedullary osteomyelitis.

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