Article focus

- Biomaterials
- Orthobiologics
- Complications

Strengths and limitations

- Large patient case-series with extensive analysis of underlying factors.
- Focuses on one product, difficult to make like-for-like comparisons.

Introduction

The use of calcium sulphate to fill bone defects was first described in 1892 by Dreesmann, in Bonn. He reported the treatment of eight patients with bone voids filled with a mixture of calcium sulphate and phenol.1,2 Peltier further popularised its use in 1959,3 and amongst his conclusions were firstly that the implantation of calcium sulphate into bone or soft tissue does not produce a foreign body reaction; secondly, it stimulates new bone formation when periosteum or bone is also present, and thirdly it is usually absorbed and removed from the site of implantation.3 Today, calcium sulphate beads may be used as an alternative void filler to poly(methyl methacrylate) (PMMA) in the presence of infection, nonunion or bone loss.4,5

Aims

Calcium sulphate has traditionally been used as a filler of dead space arising during surgery. Various complications have been described following the use of Stimulan bio-absorbable calcium sulphate beads. This study is a prospective observational study to assess the safety profile of these beads when used in revision arthroplasty, comparing the complication rates with those reported in the literature.

Methods

A total of 755 patients who underwent 456 revision total knee arthroplasties (TKA) and 299 revision total hip arthroplasties (THA), with a mean follow-up of 35 months (0 to 78) were included in the study.

Results

A total of 32 patients (4.2%) had wound drainage, and this was higher with higher bead volumes and in McPherson grade C patients. There was also a significantly higher bead volume in the 41 patients who developed hypercalcaemia, two of which were symptomatic (p < 0.0001). A total of 13 patients (1.7%) had heterotopic ossification (HO). There was no statistically significant relationship between the development of HO and bead volume (p > 0.05).

Conclusion

The strength of this study lies in the large number of patients and the detailed data collection, making it the most comprehensive report available in the literature on the use of calcium sulphate-based bone substitutes.

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beads require subsequent removal and may develop biofilm on their surface if left in situ for long periods of time. Some authors have shown a relatively short period of antibiotic release with a decrease in local concentrations to 10% of the initial levels within 24 hours. In contrast, as it is absorbed, calcium sulphate releases 100% of its antibiotic load, resulting in superior elution characteristics and higher sustained antibiotic concentrations over a period of several weeks. This results in concentrations of antibiotic locally that can be many times higher than the minimum inhibitory concentration for the relevant pathogen, while also ensuring that systemic levels and associated toxicity remain low. The use of calcium sulphate in orthopaedics has therefore been increasing, both as a bone void filler and as an “off-label” delivery agent for antibiotics in arthroplasty, chronic osteomyelitis, open fractures and combat injuries. As this practice has increased, so has the understanding of the associated benefits and complications, which include transient hypercalcemia, wound drainage and heterotopic ossification (HO). Anecdotally, there has been an increase in complications when higher volumes of beads are used, especially in subcutaneous structures and in patients with comorbidities such as diabetes and long-term steroid use.

This study aims to assess the safety profile of calcium sulphate bio-absorbable beads in revision arthroplasty, comparing complication rates in our patients with those reported in the literature.

**Patients and Methods**

Data were collected prospectively from patients undergoing revision arthroplasty of the knee and hip attending an arthroplasty centre in the United States (Los Angeles Orthopaedic Institute) between September 2010 and June 2016. All procedures were undertaken by a single surgeon (EM). Patients who had a manipulation under anaesthesia or arthroscopic washout and debridement were excluded. Those who underwent conversion of unimpartental knee arthroplasty (UKA) to total knee arthroplasty (TKA) were included.

Demographic data including age and gender, and clinical data including patient staging, indication for revision surgery, procedure-specific information, follow-up, mortality and complications were recorded. Staging was based on the system described by McPherson et al (Tables I and II). The indications were divided into infection, aseptic loosening, instability, periprosthetic fracture, metal allergy, implant failure and clinical need (pain or stiffness). The diagnosis of periprosthetic infection was confirmed using the Musculoskeletal Infection Society criteria (Table III). Procedure-specific data included the type and volume (cc) of Calcium Sulphate (Stimulan, Biocomposites Ltd, Keele, United Kingdom) which were used. Types of procedure included single-stage revision, the first or second stage of a two-stage

**Table I. Staging system for prosthetic joint infection risk (part I)**

| Category | Grading | Description |
|----------|---------|-------------|
| Infection type | 0 | No active infection |
| I | Early postoperative infection (< 3 wks postoperatively) |
| II | Hematogenous infection (< 3 wks' duration) |
| III | Late chronic infection (> 3 wks' duration) |
| Systemic host grade | A | Uncompromised (no compromising factors) |
| (Medical/immune B status) | | |
| C | Significant compromise (> 2 compromising factors) |

**Stage = infection type + systemic host grade + local extremity grade; e.g. I-A-1, III-B-2**

**Table II. Staging system for prosthetic joint infection risk (part II)**

| Systemic host (medical/immune) compromising factors | |
|-----------------------------------------------------|---|
| Age ≥ 80 yrs | |
| Alcoholism | |
| Chronic active dermatitis/ cellulitis | |
| Chronic indwelling catheter | |
| Chronic malnutrition (albumin < 3.0gm/dL) | |
| Current nicotine use (inhalational or oral) | |
| Diabetes (requiring oral agents and/or insulin) | |
| Hepatic insufficiency (cirrhosis) | |
| Immunosuppressive drugs (e.g. methotrexate, prednisone, cyclosporine) | |
| Malignancy (history of, or active) | |
| Renal failure requiring dialysis | |
| Systemic inflammatory disease (e.g., RA, SLE) | |
| Systemic immune compromise from infection or disease e.g., HIV, acquired immunodeficiency | |

**Local extremity (wound) compromising factors**

| Infection of a revision arthroplasty | |
| Recurrent infection after joint debridement with prosthesis retention | |
| Recurrent infection after prosthetic exchange protocol | |
| Recurrent open foot sores (neuropathic or structural) | |
| Multiple incisions (creating skin bridges) | |
| Sinus tract | |
| Vascular insufficiency to extremity: absent extremity pulses, calcific aterial disease, venous insufficiency with skin plaques or intermittent sores | |

SLE, systemic lupus erythematosus; HIV, human immunodeficiency virus; ABG, arterial blood gases

revision, and debridement, antibiotics, exchange of liner and implant retention (DAIR). The latter procedure included the implantation of Stimulan beads and intravenous antibiotics. The first of a two-stage revision
Table III. Musculoskeletal Infection Society definition of peri-prosthetic infection

| Presence of a sinus tract communicating with the prosthesis | OR |  
|-----------------------------------------------------------|----|
| Isolation by culture of a pathogen from ≥ two separate tissue or fluid samples from the affected joint. |    |
| Any four of the following criteria are present: |    |
| Raised ESR and CRP. |    |
| Raised synovial leukocyte count. |    |
| Raised synovial neutrophil percentage. |    |
| Purulence in the affected joint. |    |
| Isolation of a micro-organism in one culture of joint tissue or fluid. |    |

included washout, debridement, removal of the components and the implantation of PMMA spacer and Stimulan beads. The second stage included the removal of the spacer and implantation of revision components and further beads. The diagnosis of metal allergy was made using a lymphocyte transformation test from venous blood (Orthopedic Analysis, Chicago, Illinois).

Routine intravenous antibiotics and 1g tranexamic acid were administered at induction, and approximately 40 minutes prior to closure. An additional dose was given during particularly long procedures. We used commercially pure, synthetic physiological pH calcium sulphate powder - Stimulan (Biocomposites Ltd, Keele, United Kingdom) with the RapidCure kit which includes 10 cc (20 g) of calcium sulphate hemihydrate powder, a pre-mixing solution bulb, pellet mould and spatula. The mould produces three sizes of bead (3, 4.8 and 6 mm in diameter). One gram of vancomycin powder was mixed with each 10 cc of calcium sulphate in the mixing bowl and 240 mg of liquid tobramycin (40 mg/ml) was added. The ingredients were mixed for 30 seconds until “doughy” and the resulting paste was applied to the moulds using the spatula and allowed to set for ten to 15 minutes in a typical theatre temperature of 16°C to 17°C. In patients with fungal infection, 50 mg of amphotericin B was also added. The beads loaded with antibiotics were implanted around the components or the spacer before the wound was closed.

For patients undergoing knee surgery, the beads were placed in the medial and lateral gutters. For those undergoing hip surgery, they were placed deeply, inferior to the acetabulum and around the proximal femur.

PMMA, loaded with vancomycin and/or gentamicin, was used in all cemented procedures and in the first of two-stage procedures requiring the use of spacers. No other cement or absorbable beads were used. Routine postoperative blood tests included a full blood count, CRP, ESR, and bone profile. Routine radiographs were also undertaken prior to discharge from hospital. The patients were reviewed at six weeks, three, six and 12 months postoperatively and bi-annually thereafter. HO around the knee was categorized according to the classification of Harwin et al (Table IV). HO around the hip was categorized according to the classification of Brooker et al (Table V). The levels of calcium in the blood were recorded on the first postoperative day, and at routine review. Hypercalcaemia was defined as a level of ≥ 10.7 mg/dL (equivalent to 2.6 mmol/L).

The complications arising from revision surgery and from the use of the beads were recorded. Any reoperation was classified as a surgical complication and divided into aseptic loosening, fracture, instability and those due to infection. Stimulan-specific complications included wound drainage, HO and hypercalcaemia.

Statistical analysis. Statistical analysis of all Stimulan-related complications was undertaken. Our primary aim was to relate the presence or absence of a complication to the volume of the beads, the grade of the patient and the location using logistic generalised linear model (GLM). The location, the presence of a complication and the relationship between the grade of the patient and type of complication were tested using the chi-squared test. All analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at p < 0.05.

Results

A total of 755 patients with a mean age of 63 years (30 to 94), of whom 456 had revision TKA (RevTKA) and 299 had revision THA (RevTHA) were included in the study. Two patients in the RevTKA group underwent conversion of UKA to TKA. There were 381 women and 374 men. The mean follow-up was 35 months (0 to

Table IV. The classification of heterotopic ossification around the knee according to Harwin et al

| Grade | Radiographic findings |
|-------|----------------------|
| I     | Sessile attached to the peristeum of the anterior femur and limited to the suprapatellar pouch |
| II    | Amorphous or globular pattern limited to the quadriceps expansion |
| IIIa  | Combination of sessile and globular with less than 75% of the height of the soft tissues on lateral radiograph involved. |
| IIIb  | Combination of I and II with greater than 75% of the height of the soft tissues on lateral radiograph involved. |

Table V. The classification of heterotopic ossification around the hip according to Brooker et al

| Grade | Classification |
|-------|----------------|
| Grade I | Ossification islands around the hip |
| Grade II | Bone projection of pelvis or proximal femur at least 1 cm away from the opposite surface |
| Grade III | Bone projection of pelvis or proximal femur reducing space between opposite surface < 1 cm |
| Grade IV | Hip ankylosis |

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Table VI. The demographics of the patients and outcomes (part i)

|                  | Total (n) | Hip (n) | Knee (n) | Total (%) | Hip (%) | Knee (%) | Patient host grade |
|------------------|-----------|---------|----------|-----------|---------|----------|-------------------|
| **Knees**        |           |         |          |           |         |          |                   |
| n = 755          |           |         |          |           |         |          |                   |
| Age (yrs)        |           |         |          |           |         |          |                   |
| 63.87 (29 to 96) | 100       | 34      | 66       | 13%       | 11%     | 14%      |                   |
| Gender           |           |         |          |           |         |          |                   |
| 243 F, 243 M     | 5         | 3       | 2        | 5%        | 5%      | 4%       |                   |
| Avg F/U          |           |         |          |           |         |          |                   |
| 35.08 mths (0 to 78) | 13       | 4       | 9        | 11%       | 9%      | 12%      |                   |
| Stim avg         |           |         |          |           |         |          |                   |
| 21.51 (5 to 80)  | 1         | 0       | 1        | 2%        | 0%      | 4%       |                   |
| **Hips**         |           |         |          |           |         |          |                   |
| n = 299          |           |         |          |           |         |          |                   |
| Age (yrs)        |           |         |          |           |         |          |                   |
| 62.09 (31 to 92) | 34        | 15      | 19       | 5%        | 5%      | 4%       | blank             |
| Gender           |           |         |          |           |         |          |                   |
| 188 F, 160 M     | 32        | 11      | 21       | 4%        | 4%      | 5%       | 3%/5%/5%          |
| Avg F/U          |           |         |          |           |         |          |                   |
| 35.28 mths (0 to 78) | 32       | 15      | 19       | 5%        | 5%      | 4%       | blank             |

Table VII. The demographics of the patients and outcomes (part ii)

|                  | Knees | Hips |
|------------------|-------|------|
| **Single stage** |       |      |
| n = 209          |       |      |
| Age (yrs)        | 62.98 (29 to 96) | 62.78 (32 to 92) |
| Gender           | 127 F, 105 M | 109 F, 91 M |
| Avg F/U          | 34.81 months (0 to 78) | 36.00 mths (0 to 78) |
| Stim avg         | 13.78 | 18.7 |
| Stim range       | 5 to 40 | 5 to 50 |
| Complications    | 33 | 12 |
| Failures         | 14 | 9 |
| Septic           | 4 | 3 |
| Drainage         | 8 | 3 |
| **DAIR**         |       |      |
| n = 49           |       |      |
| Age (yrs)        | 61.29 (43 to 77) | 57.77 (32 to 76) |
| Gender           | 23 F, 30 M | 14 F, 7 M |
| Avg F/U          | 34.13 mths (0 to 77) | 35.18 mths (2 to 57) |
| Stim avg         | 20.75 | 33.00 |
| Stim range       | 5 to 40 | 5 to 60 |
| Complications    | 4 | 2 |
| Failures         | 6 | 1 |
| Septic           | 5 | 1 |
| Drainage         | 2 | 2 |
| **First of 2 stage** | n = 108 | n = 68 |
| Age (yrs)        | 65.24 (28 to 86) | 61.39 (31 to 88) |
| Gender           | 53 F, 59 M | 38 F, 35 M |
| Avg F/U          | 35.57 mths (1 to 75) | 33.22 mths (0 to 73) |
| Stim avg         | 34.15 | 36.58 |
| Stim range       | 10 to 80 | 10 to 60 |
| Complications    | 10 | 13 |
| Failures         | 2 | 4 |
| Septic           | 2 | 4 |
| Drainage         | 2 | 2 |
| **Second of 2 stage** | n = 90 | n = 53 |
| Age (yrs)        | 65.70 (28 to 87) | 62.04 (32 to 88) |
| Gender           | 40 F, 49 M | 27 F, 27 M |
| Avg F/U          | 35.34 mths (3 to 73) | 35.67 mths (1 to 72) |
| Stim avg         | 26.12 | 32.96 |
| Stim range       | 10 to 40 | 10 to 70 |
| Complications    | 19 | 8 |
| Failures         | 12 | 8 |
| Septic           | 9 | 7 |
| Drainage         | 11 | 4 |

DAIR, exchange of liner and implant retention
The indications are shown in Tables VI and VII. Most (387) underwent revision for infection, followed by 118 who underwent revision for instability. All seven patients whose initial indication was implant failure had failure of the acetabular component due to fracture of the ceramic liner. A total of 209 in the RevTKA group had a single-stage revision, 19 using DAIR; 108 had the first of a two-stage revision, and 90 had the second of a two-stage revision. A total of 159 in the RevTHA group had a single-stage revision, 19 using DAIR; 68 had the first of a two-stage revision and 53 had the second of a two-stage revision. A total of 59 (7.8%) were reoperations, 34 were for infection (27 recurrent) and 25 for aseptic causes: loosening (5), instability (13), acetabular failure (2), periprosthetic fracture (1), metal allergy (2) and pain and stiffness (2).

A mean of 23.39 cc (5 to 80) of Stimulan was used per procedure. Stimulan-related complications occurred in 86 operations (11.4%), drainage in 32 (4.2%), hypercalcaemia in 41 (5.4%) and HO in 13 (1.7%) (Table VI).

Drainage occurred in 32 patients (4.2%), 21 knees and 11 hips. If this occurred within five days postoperatively and involved serous or serosanguinous fluid with or without calcium deposits, anti-coagulants were stopped and the wounds re-dressed. If drainage persisted for more than five days postoperatively, or was sanguinous in...
nature, (as in 15 knees and eight hips in our series) a washout under general anaesthesia was undertaken.

Transient hypercalcaemia was detected in 41 patients (5.4%), 22 knees and 19 hips (Table VIII. The mean levels were 11.7 mg/dL (10.8 to 14.9); the levels returned to normal at a maximum of five days postoperatively. Two patients in the RevTHA group developed symptoms and were treated with one IV dose of bisphosphonate and 0.9% saline.

HO occurred in 13 patients (1.7%), five knees and eight hips. Knees (Harwin): Mode – 1; Range – 1-3 Hips (Brooker): Mode – 1; Range – 1-2.

One patient in the RevTKA group with Harwin II HO required manipulation. Two patients in the RevTHA group with HO (Brooker II and III respectively) were treated operatively at time of reimplantation. The remaining four knees and six hips with HO required no treatment. The volume of the beads for the grades of the patients are shown in Table IX.

Stimulan-related complications. Analysis of the factors relating to the presence or absence of a complication and the volume of the beads are shown in Table X. Overall, both bead volume ($p = 0.0014$) and patient grade ($p = 0.0021$) had a significant effect on the presence or absence of a complication. The location had no significant effect ($p = 0.72$; Fig. 1). The volume of the beads was significantly different for types of complication ($p = 0.027$; Fig. 2a). In post hoc comparisons looking at pairwise differences in bead volume between complication type, there was a significant difference between the hypercalcaemia and drain groups (Hypercalcaemia, Hycal – Drain Tukey adjusted $p = 0.045$), while the other pairwise difference were not significantly different (HO – Drain $p = 0.88$; Hycal – HO $P = 0.46$). The volume of the beads was significantly different for body location ($p = 0.0077$; Fig 2c). There was no significant relationship between volume and patient grade ($p = 0.87$; Fig. 2b).

Discussion

Clinical outcomes and patient-reported outcome measures were not the focus of this study and therefore were not reported. However, the demographics of the patients were comparable with those reported in the literature. With a mean age of 63 years, 57% being women, these demographics are similar to the data reported in both the National Joint Registry of England and Wales (NJR) (mean age 69.9, women 51.5%) and the American Joint Replacement Registry (AJRR) (mean age 66.5, women 59.2%) for patients undergoing revision TKA and THA. Infection was the main indication for revision in our series, with 387 patients (51%), 247 RevTKAs and 140 RevTHAs, having proven infection preoperatively. The rate of reoperation was 7.8% at a mean follow-up of 35.2 months, comparable with that of 8.45% reported in the NJR.

Wound drainage. The incidence of wound drainage, of 4.2%, is low, with rates ranging between 3.2% and 51% in the literature. A previous study by the senior author (EM) analysed wound drainage rates following the use of antibiotic impregnated calcium sulphate in a series of 250 revision arthroplasties, reporting a rate of 3.2%. Drainage tended to occur in patients in whom a higher volume of bead had been used, with more subcutaneous placement and in those with a poor host grade, such...
as McPherson grade C.\textsuperscript{9,13} Kelly et al.\textsuperscript{23} reported a rate of drainage of 3.6% in 109 patients treated with calcium sulphate for bone defects using Osteoset (Wright Medical Technology Inc., Arlington, Tennessee). Ferguson et al.\textsuperscript{24} reported a rate of 15.4% when used to treat 195 patients with chronic osteomyelitis. The relative subcutaneous placement of beads and rate of drainage reported in this paper supports a role for location of beads in the development of drainage. Borelli et al.\textsuperscript{25} reported a rate of drainage of 23% (five patients) in the treatment of 26 patients with a nonunion and an osseous defect, using bone graft mixed with calcium sulphate. The highest rate, of 51%, was reported by Ziran et al.\textsuperscript{22} using calcium sulphate combined with demineralized bone matrix in the treatment of nonunions.

We found no significant difference in bead volume between patient drainage groups. There was also no significant difference in the rate of complications (the number of patients with drainage) and location between the RevTKA (22) and RevTHA (19) groups ($p > 0.05$). Therefore, the observation that drainage is increased in large bead volumes remains anecdotal.

Drainage within five days of surgery was managed conservatively but drainage beyond five days was treated surgically with a washout and closure. Therefore, the longer-term implications on infection and clinical outcome are not available for our dataset. However, in a case series reported by Ferguson et al.,\textsuperscript{24} there were no recurrent infections in the drainage group treated non-surgically, all of whom had drainage beyond 14 days postoperatively. This may reflect a high concentration of antibiotic draining from the wound, rather than exudate alone. It is of concern when a carefully undertaken revision joint leaks exudate that is similar to the discharge seen in infection. Wound drainage is a recognized complication after the use of calcium sulphate beads, notably when volumes of $> 20$ cc are used, particularly in subcutaneous bones, as around the knee.\textsuperscript{4,26} As well as physical factors such as volume and anatomical placement, the grade of the patient and the dissolution of calcium sulphate are also thought to play a role.

Calcium sulphate (CaSO$_4$) is inorganic and has three principle forms: anhydrous, known as anhydrite, with the formula CaSO$_4$; hemihydrated with the formula CaSO$_4$$\cdot$0.5H$_2$O and dihydrated with the formula CaSO$_4$$\cdot$2H$_2$O. Once water is added it converts to the dihydrate form, and this is the basis for the setting reaction. Stimulan is the synthetically pure hemihydrated form. It is hypothesized that the placement of calcium sulphate in the operating field alters the osmolality of the wound, leading to the movement of water out of cells with the accumulation of fluid and wound drainage.\textsuperscript{5,11,27,28} Precautions taken by the senior author include reduced volume of Stimulan in subcutaneous tissues and fastidious wound closure (Fig. 3).

**Transient hypercalcaemia.** We found an overall difference in the volume of the beads in the different types of complication, with a larger volume in the group with hypercalcaemia compared to patients without a complication. This corroborates our previous observations\textsuperscript{9,11} about the excessive use of calcium sulphate-based products and the associated risk of hypercalcaemia.

Peltier\textsuperscript{3} initially described transient hypercalcaemia after implantation of calcium sulphate in his experiments in the 1950s. There were raised serum calcium levels after the implantation of calcium sulphate beads in a canine
model, but this elevation was not sustained nor were systemic effects noted. A later study using calcium sulphate to fill osseous defects in five patients did not reproduce this transient hypercalcaemia.29

A previous study reported by the lead author involved 15 patients of whom three developed hypercalcaemia, one with symptoms requiring treatment. This patient had undergone a two-stage revision THA and had received 40 cc of Stimulan with antibiotics implanted around the revision components.

A case report by Carlson et al30 described transient hypercalcaemia in a patient with a peak serum calcium of 14.5 mg/dl on the fifth postoperative day after revision of an infected THA, who was treated with a single subcutaneous dose of calcitonin 200 IU and IV fluids. The calcium level returned to normal four days later. A further case report described a 69-year-old woman who developed convulsions and coma after calcium sulphate beads were implanted during lumbar fusion.31 The authors concluded that these were caused by leakage of calcium sulphate into the cerebrospinal fluid through a dural tear.31 The serum calcium levels remained normal.

There is an active United States Food and Drug Administration adverse reaction report regarding transient hypercalcaemia following the use of vancomycin-infused calcium sulphate beads (Osteoset; Wright Medical Technology Inc.) in a patient undergoing revision THA for infection.32

Precautions should be taken to avoid hypercalcaemia which may cause convulsions, coma and cardiac arrest. All patients should be screened for contraindications and have their calcium levels monitored pre- and postoperatively. In our opinion, the volume of calcium sulphate should be limited to a maximum of 40 cc per operation, increasing to 80 cc if it is placed within the medulla of the bone. FDA guidelines on the use of materials, which include calcium to fill voids in bone, warn of the risks of transient hypercalcaemia, and cautions against their use in the presence of pre-existing disorders of calcium metabolism, as well as warning against “inappropriate material composition which may lead to substantially more rapid resorption of the implant”.33 It is hypothesized that premature breakdown within a short period of time results in the ‘dumping’ of calcium ions in a small area, and rapid absorption by local capillaries. The reasons for this are poorly understood but probably reflect a combination of host factors such as the grade of the patient, and surgical variables, such as excessive saline used to mix the calcium sulphate paste and implantation before complete setting of the beads. It should be noted that adding different antibiotics and combinations of antibiotics has very different effects on setting time.16

Heterotopic ossification (HO). There is little information about HO after revision arthroplasty and less about its incidence after the use of calcium sulphate. The combined rate of HO for revision knees and hips in our series, of 1.7% is low, with rates of up to 56% following revision TKA being reported.34 We found that the volume of the beads had no statistically significant effect on the incidence of HO compared with patients without complication.

To our knowledge, there are no other reports regarding the incidence of HO following the use of calcium sulphate beads in revision surgery apart from those of the senior author. In that series, mild HO (Brooker I – II) occurred in eight of 250 revision TKA and THAs (3.2%) and there was a suggested link between high bead volumes and HO, as well as reduced intra-articular synovial volume, as occurs in osteoarthritic joints and exposed intra-articular bone following periosteal stripping during surgery. HO is the formation of mature lamellar bone in extraskeletal soft tissues.35 Acquired HO is strongly associated with brain injury and other central nervous system conditions including tumours, spinal cord lesions and infection, as well as soft-tissue trauma as occurs in burns, polytrauma and arthroplasty.35,36 Although not fully understood, its aetiology is known to involve the induction of osteoprogenitor differentiation in response to injury, and osteoblast formation with bone deposition.35 Raina et al37 reported that skeletal muscle cells act as an osteoinductive niche for bone formation with the use of a biphasic calcium sulphate/hydroxyapatite biomaterial. Murine skeletal muscle cells were seeded onto hydroxyapatite/calcium sulphate and the phenotype of the cells analyzed after exposure to secretions harvested from rat bone cells to mimic the extracellular matrix proteins and growth factors present in an orthopaedic surgical site. The cells differentiated into osteoblast-like cells, expressing prominent bone markers after seeding on the biomaterial. The media of the cells contained bone morphogenetic protein-2 (BMP-2) (8.4 ng/mg, sd 0.8), and BMP-7 (50.6 ng/mg, sd 2.2). In vitro, this model, similar to that found in the surgical sites of our patients, induced differentiation of skeletal muscle cells towards an osteogenic lineage. In our series, no
intraoperative histological samples were taken and therefore it is not possible to say whether the HO was truly ectopic bone or ectopic calcification of soft tissue following chemical (calcium sulphate) and physical trauma (dystrophic soft-tissue calcification). In either case, it is possible that the deposits represented both a complication of revision surgery and of implanting calcium sulphate, with clustering of beads leading to locally raised concentrations of calcium, increasing the risk of HO. Overall, the effect of HO in our patients was low, and it was brittle and easily removed during second-stage procedures. It did not cause symptoms when left in patients undergoing single-stage procedures. Therefore, it is not felt that HO is a significant issue when using absorbable calcium sulphate beads.

**Patient grade.** We found an overall effect of patient grade on the rate of complications. However, there was no tendency to use a higher volume of beads in grade B and C patients, who subsequently developed complications, suggesting that factors other than volume contribute to the complications.

The study has strengths, including the large number of patients and the detailed data collection, making it the most comprehensive report in the literature, to date, on the use of calcium sulphate-based bone substitutes. The main limitation is the overall design. Although detailed and prospective, the study lacks a control group. Furthermore, although the causes of Stimulan-related complications are likely to be multifactorial, we only assessed the effects of patient grade and bead volume. Also, although bead volume was shown to be a statistically significant factor in the development of hypercalcaemia, we were not able to support anecdotal observations in the literature about drainage and HO, nor did patient grade have a statistically significant effect on the rate of complications.

Overall, these findings contribute to the literature and will help inform surgeons about the risks and benefits of using calcium sulphate. Future studies should focus on multivariate analysis and incorporate control groups to elucidate the risks better.

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R. Kallala: Project concept, study design, data collection, data analysis, manuscript preparation.
W. Edwin Harris: Data analysis, manuscript preparation.
M. Ibrahim: Data analysis, manuscript preparation.
M. Dipane: Data collection, data analysis.
E. McPherson: Project concept, data collection, data analysis, manuscript preparation.

ICMJE COI Statement
None declared

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