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Case report

Calcium sulphate as a drug delivery system in a deep diabetic foot infection

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HIGHLIGHTS

- Calcium sulphate as a drug delivery system is an effective adjunct in deep diabetic foot infection.
- Local application produces high antimicrobial concentration at the site of infection.
- When given in isolation local application reduces potential toxicity compared to other routes.
- This method of administration can reduce costs and reduce reliance on patient adherence.

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ABSTRACT

Treating diabetic foot infection is costly, time consuming and challenging for the patient and clinician alike. It requires a multidisciplinary approach to provide a favourable outcome but all too often results in amputation.

We present a patient with Type 2 diabetes who attended clinic with a limb threatening foot infection complicated by osteomyelitis and requiring emergency surgery and antibiotic administration.

Our patient underwent surgery by means of an incision and drainage procedure with local antibiotic administration to augment systemic antibiotics. The wound was packed with calcium sulphate (Stimulan® Biocomposites Ltd.) impregnated with gentamicin and vancomycin to enable high antibiotic concentrations at the site of infection. The patient made a full recovery at four months requiring only minimal bone excision to maintain a functional foot.

This case demonstrates an alternative route for antibiotic administration to overcome some of the limitations of systemic administration including penetration at the site of infection, systemic toxicity, prolonged hospital admission and cost. This route of administration is being increasingly used as an alternative to systemic antibiotics at our centre.

1. Introduction

Osteomyelitis is an infective process in bone accompanied by bone destruction [1] and characterised by substantial morbidity [2]. It presents significant therapeutic difficulties [3] usually requiring a multidisciplinary approach [4] with the goal of treatment to eradicate infection, promote repair of skeletal defects, heal offending wounds and restore function [3,5,6]. Treatment usually requires combined surgical debridement and appropriate antimicrobial therapy [3,7].

Systemic antibiotics however are often ineffective [8] even after prolonged intravenous treatment and recurrence of infection is not uncommon [6]. Efficacy of systemic antibiotics may be limited by impaired blood flow of infected bone [7] and bacterial strains forming biofilms leading to actual or apparent resistance [5,6]. Long term duration and high doses of antibiotics whether parenteral or oral are also associated with severe adverse effects [5,6,9] including systemic toxicity with liver and renal impairment [10]. Furthermore increased costs and lack of patient adherence are further disadvantages to long term antimicrobial therapy [6]. Surgical debridement meanwhile of non-viable infected bone and soft tissue can leave large defects resulting in dead space [7] with loss of function.

Local administration of antibiotics have been used as an adjunctive therapy to oral and parenteral antibiotics [4] and in some cases as a viable alternative [5,6]. Drug delivery systems in the form of bone void fillers have been shown to produce prolonged high concentrations at the site of infection, minimise systemic levels [5,7], eliminate concerns with regards to antibiotic penetration [6] and fill dead space [7].

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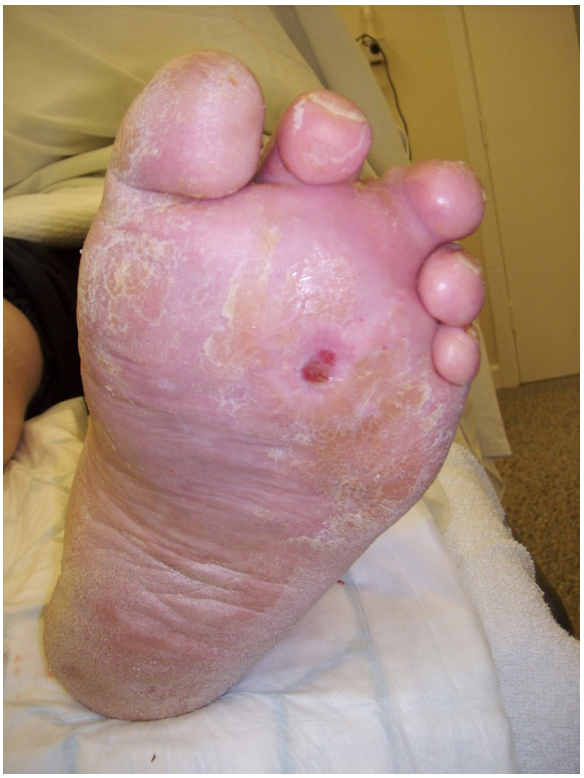

Fig. 1. Plantar ulcer and source of infection.

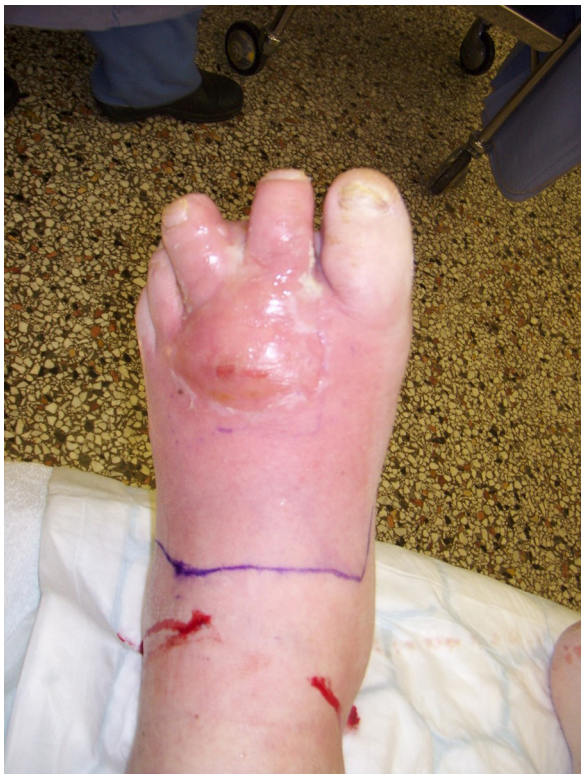

Fig. 2. Formation of abscess on dorsal surface of the foot.

In this case study we demonstrated the use of a synthetic, biodegradable and biocompatible form of calcium sulphate (CS) as a drug delivery system to treat a deep diabetic foot infection complicated by osteomyelitis.

2. Case report

A 52 year old male patient with Type 2 diabetes of 19 years duration with controlled hypertension and hypercholesterolaemia was referred from the diabetes specialist podiatrist for immediate assessment due to a limb threatening foot infection. The diabetologist had counselled the patient with regards to the likelihood of amputation.

The patient presented with an eight month history of recurrent plantar ulceration to left foot (Fig. 1) measuring 8 mm × 6 mm and probing to the third metatarsophalangeal joint. The lesion had deteriorated significantly in the last few days with abscess formation evident both clinically (Fig. 2) and sonographically (Fig. 3). Plain radiographs demonstrated osteomyelitis of the third metatarsal head and base of the proximal phalanx (Fig. 4).

The patient felt generally well, there was no pyrexia. However, further observations demonstrated tachycardia with an elevated pulse of 106 (60–100) along with elevated random blood glucose levels of 11 mmols/L. Vascular status revealed bounding biphasic posterior tibial and dorsalis pedis pulses while neurological testing demonstrated profound peripheral neuropathy with no ability to appreciate a 10 g monofilament or vibration sensation within the foot.

Drug history revealed ramipril, doxasosin, simvastatin and exenatide to control comorbidities. The patient was further prescribed oral ciprofloxacin 750 mg twice daily and clindamycin 600 mg three times daily for the infection based on previous microbiology results which identified a polymicrobial infection including *Staphylococcus aureus*, *group B Streptococcus*, *Enterococcus faecalis* and *Pasteurella multocida*.

Based on clinical and radiographic examination a decision was made to operate immediately under local anaesthesia via ankle blockade. This would involve an incision and drainage, thorough suction irrigation and packing with CS beads impregnated with vancomycin and gentamicin.

A longitudinal incision over the second intermetatarsal space of the left foot was performed to drain the large abscess of copious pus (Fig. 5). This was followed by sharp and blunt dissection to the third metatarsal and proximal phalanx. This revealed soft brown bone consistent with devitalised tissue. The base of the proximal phalanx and 3 cm of the distal aspect of the third metatarsal were excised back to healthy looking tissue. Soft tissues were examined in the operative area and excised as necessary and sent to microbiology for culture and sensitivity testing. The plantar ulcer was curetted and a sinus was removed which extended dorsally to the abscess.

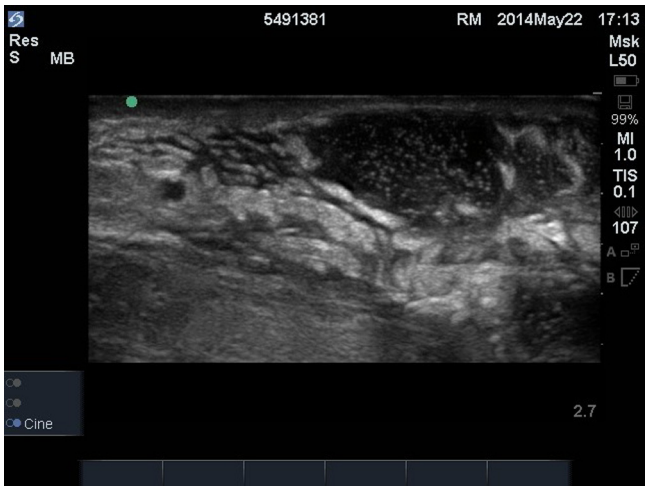

Fig. 3. Ultrasound demonstrating large collection of pus.

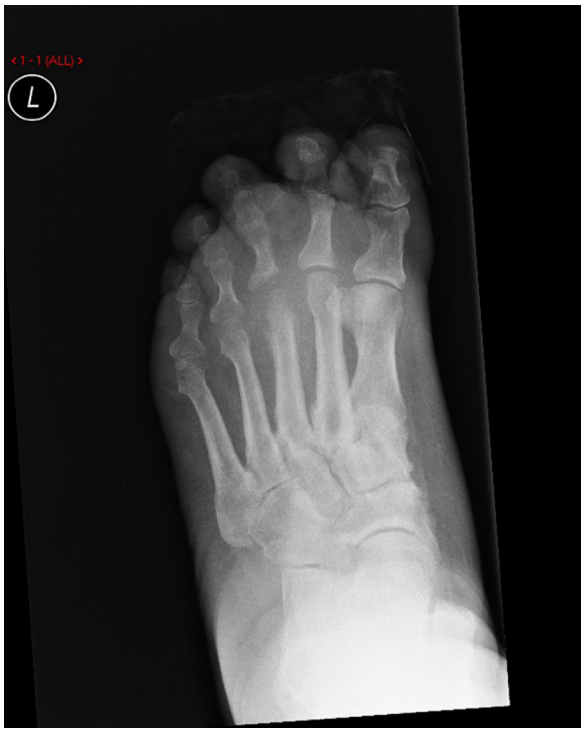

Fig. 4. Plain film demonstrating osteomyelitis of the third metatarsophalangeal joint.

Thorough suction irrigation using 50/50 betadine and saline mix ensued.

Preparation of the CS bone substitute involved mixing gentamicin in liquid form (3 mL/120 mg) to vancomycin (1 g) in powder form and 5 ccs of CS hemihydrate. This is subsequently placed in a mould to produce multiple beads. These crystallise and set with the liberation of little heat (up to 37 °C) to form CS dihydrate [4,11–13] or gypsum. Setting time is determined by the time taken for conversion of hemihydrate to dihydrate [4] which using these doses and volume of CS is generally 5 min. The final result is a synthetic biocompatible material acting as a drug delivery system.

The beads were packed into the wound and around the remaining bone to ensure thorough coverage within the foot (Fig. 6). The skin edges were apposed with single non absorbable interrupted sutures and dressed appropriately. The patient was placed on crutches and advised to be non weight-bearing. The patient was reviewed after 24 h following the surgical intervention (Fig. 7).

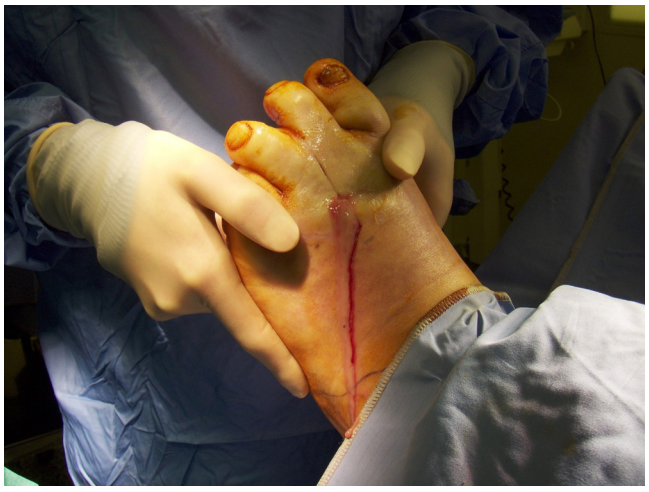

Fig. 5. Intraoperative photograph showing the 'milking' of pus.

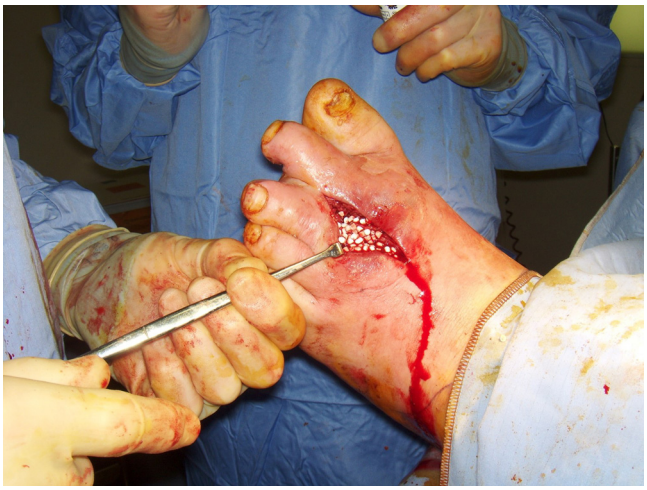

Fig. 6. Antibiotic beads packed within the second intermetatarsal space.

Twenty-four hours following surgery the wound was clean with a degree of erythema reduction.

An MRI had been arranged in-order to determine the extent of osteomyelitis to aid preoperative planning. However, due to the urgency of the surgery this was not performed until 24 h post-surgical intervention. The result demonstrated bone oedema in the remaining portion of the third metatarsal which was reported by radiology as possible osteomyelitis. This was felt to be more likely a consequence of the surgical trauma. However, due to the uncertainty the multidisciplinary team consisting of the diabetologist, microbiologist and podiatric surgeon recommended a commencement of four weeks of oral linezolid 600 mg twice daily and eight weeks of oral ciprofloxacin 750 mg twice daily. This was based on

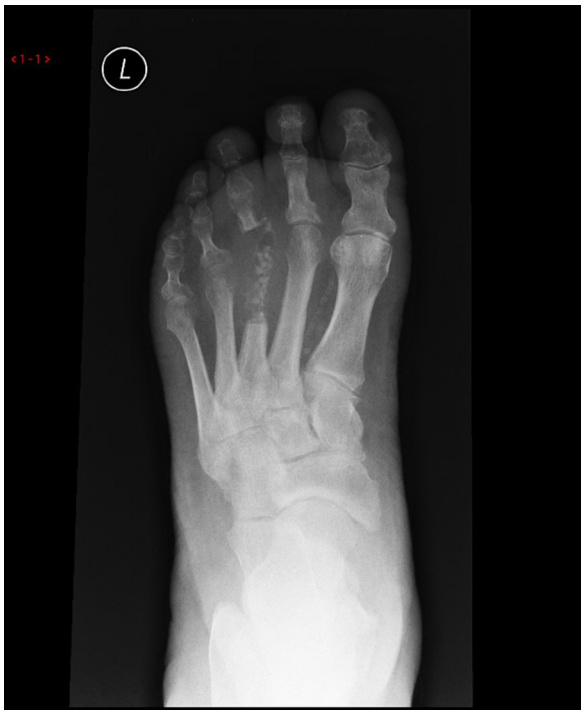

Fig. 7. A plain film four weeks post-operatively demonstrating residual CS beads in situ.

Enterococcus faecalis and *Cornyebacterium striatum* cultures derived from the pus and bone samples. The oral route of administration also enable discharge from hospital.

The patient continued to be reviewed twice weekly. Both the plantar ulcer and dorsal surgical wound healed at just over one month and three months respectively and a full recovery was noted at four months. Bespoke footwear was subsequently arranged to accommodate the altered foot pressures. Eleven months following the surgery the patient remains healed to date.

3. Discussion

The external use of calcium sulphate or plaster of Paris has been used since the seventeenth century [14] to splint fractured bones and more latterly by Dreesmann in 1892 who first used it as an internal bone defect filler [15]. Medical grade CS belongs to a synthetic ceramic group of bone graft substitutes [14] which came about in the latter half of the twentieth century following extensive work by Peltier [7]. It was introduced as a biocompatible, biodegradable bone graft material [1,5] which has been found to be a safe, effective and economically viable [14] which may help preserve function along with reduction of dead space [1,6,13]. It has the longest proven clinical history as a bone graft substitute and widely used in non-loading bone injuries such as radial fractures [11] to support mechanical stability. It overcomes many of the limitations of autograft as a gold standard such as limited supply, additional surgery, increased tourniquet times and donor site morbidity [14].

CS has also been shown to provide osteoconductive properties [6,11,13] allowing neovascularisation and ingrowth of new bone formation [14] further enabling fibrovascular tissue to take its place once fully resorbed over which bone can consolidate [14]. Iannuccelli et al. [8] studied 15 cases of bone grafting using CS for various bone defects 13 of which showed new bone incorporation with no incidence of hypercalcaemia or soft tissue calcification. Aseptic serous discharge was found to be the most common complication lasting three to four weeks. We have found that good soft tissue coverage, primary closure and appropriate dressings can help minimise this complication.

More recently bone defect fillers have been used as antibiotic drug delivery systems. These include non-biodegradable materials such as acrylic bone cement in the form of polymethyl methacrylate (PMMA) beads or biodegradable materials such as CS [1,3].

Non-biodegradable PMMA beads impregnated with antibiotics have been used since the early 1970s [10] and are widely accepted as a major non-biodegradable carrier system to deliver antibiotics locally [6]. However, they may require further invasive surgery for their removal on completion of drug release [3,5,13] and incomplete and very slow release has been demonstrated [10,11]. Furthermore cement polymerisation is an exothermic reaction limiting choice to heat stable antibiotics. During hydration of CS hemihydrate however there is no thermal damage to the drug due to lower curing temperatures. This enables the use of a wider range of antibiotics including vancomycin, teicoplanin, tobramycin, cefazolin and fucidin [4].

CS as a drug delivery system was first demonstrated in 1928 by Petrova who successfully inserted the antiseptic Rivanol into the long bones of canines [16]. More recently CS has been shown to be successful as a controlled drug delivery system in surgical prophylaxis as well as in the treatment of acute and chronic soft tissue and bone infections including the diabetic foot [6,10] and in the prevention of biofilms [17]. Furthermore the biodegradable properties negate the need for further surgical intervention, which could otherwise induce further infection and jeopardise bone healing [1,4,7,9,11].

In terms of disadvantages, calcium sulphate does not provide structural support [14] and there is potential for antibiotic losses through wound discharge [10]. In addition, transient cytotoxic effects leading to inflammatory reactions have been observed suspected to be calcium rich fluid formed during resorption [13,18]. This can present as erythema and oedema in the peri-incisional area accompanied by the release of copious serous discharge from the wound [19]. However, in 36 cases performed at our centre we have not experienced any cytotoxic inflammatory reactions following implantation.

The purity of medical grade CS ensures predictable dissolution [10] with the beads showing in vivo resorption in three to four weeks [4]. This also ensures predictable antibiotic release with in vitro elution shown to last 28 days and antibiotic levels surpassing 200 times the minimum inhibitory concentration for an organism over 14 days [6]. Kanellakopoulou et al. [12] meanwhile demonstrated sustained release of moxifloxacin from CS for 35 days with greatest release on day seven with complete eradication of MRSA in animal models with osteomyelitis.

Deciding which antibiotic to mix with CS depends on multiple factors including likely microorganisms, sensitivities, allergies and setting times. Various extracts and antibiotics have been used previously to help eradicate infection locally including plant derived antiseptics [20] moxifloxacin, fucidic acid [3], vancomycin [3,9,11], tobramycin [5,7,10], gentamicin [2,5,17] and daptomycin [4]. Aminoglycosides and glycopeptides predominate due to their broad spectrum, thermostability, kinetic release and efficient adhesion to the carrier [7,8] ensuring rapid setting times. Aminoglycosides also demonstrate low hypersensitivity and low tissue toxicity and operate through concentration dependant killing so high local concentrations are favourable [10].

It was decided in this case that gentamicin and vancomycin would be used due to the aforementioned characteristics of these drugs and on culture and sensitivity results. In addition, these have been used in combination on previous occasions with favourable results. Rausschmann et al. [13] demonstrated a tenfold minimum inhibitory concentration of in vitro gentamicin and vancomycin susceptible bacteria within the first 3 and 4 days respectively. Gauland [6] meanwhile found this combination demonstrated a high rate of success despite microbiological sensitivities and numerous choices for implantation. Three hundred and twenty-three patients with osteomyelitis of the lower extremity underwent surgical debridement and antibiotic implantation of which 70% did not require systemic antibiotics.

One of the most important advantages of local antibiotic administration are the low systemic levels reducing potential toxic reactions and has been demonstrated in numerous studies [5,12]. At our centre we have previously successfully used antibiotic impregnated CS as an alternative to systemic antibiotic administration where patients have previously developed *Clostridium difficile* following prolonged courses of antibiotics. Bypassing the digestive system in these patients is clearly advantageous in reducing the potential for further episodes.

The prospect of systemic toxicity however following local implantation should not be overlooked especially in biodegradable materials where all of the antibiotics are likely to be eluted [10]. This is particularly pertinent for drugs such as aminoglycosides including gentamicin which are known to be exclusively excreted unchanged by glomerular filtration [10] and hence require adequate renal function not always evident in the elderly and in patients with diabetic nephropathy. Wahl et al. [10] recommended aminoglycosides be used with caution in patients with low to very low creatinine clearance after examining the pharmacokinetic effects of 4% tobramycin using CS as a carrier material although no specific values were given. Additionally, serum levels were based on predictions and the authors openly admit the

uncertainty of aminoglycoside toxicity and pharmacokinetic variability. Prior to implantation our patient had recently undergone bloodwork demonstrating normal creatinine clearance with an estimated glomerular filtration rate of greater than 60 mL/min (>60).

4. Conclusion

Overall this case demonstrates calcium sulphate as a drug delivery system to be an effective adjunct in deep diabetic foot infection. Local application produces high antimicrobial concentration at the site of infection reducing the reliance on vascular permeability required in conventional routes of administration. Moreover, when this route is given in isolation the low antibiotic serum concentration reduces potential toxicity when compared to systemic antibiotics. Additionally, the avoidance of multiple dosing over prolonged periods to inevitably reduce cost and less reliance placed on patient adherence are favourable advantages.

We acknowledge however that there is limited evidence with regard to adverse effects, elution rates over time and overall efficacy and further research is required in the form of a randomised controlled trial comparing this method of treatment with standard management protocols.

Conflicts of interests

The authors declare that there are no conflicts of interests involved in this paper. No funding was provided and no benefits in kind of any description have been received. There have also been no indirect benefits as a result of producing this case study.

References

[1] Nandi SK, Mukherjee P, Roy S, Kundu B, De DK. Local antibiotic delivery systems for the treatment of osteomyelitis – a review. Mater Sci Eng C 2009;29:2478–85.
[2] Thein E, Tafin UF, Betrisey B, Trampuz A, Borens O. In vitro activity of gentamicin-loaded bioabsorbable beads against different microorganisms. Materials 2013;6:3284–93.
[3] Panagopoulos P, Tsaganos T, Plachouras D, Carrer D-P, Papadopoulos A, Giamarellou H, Kanellakopoulou K. In vitro elution of moxifloxacin and fucidic acid by a synthetic crystallic semihydrate form of calcium sulphate (Stimulan). Int J Antimicrob Agents 2008;32:485–7.
[4] Agarwal S, Healey B. The use of antibiotic impregnated absorbable calcium sulphate beads in management of infected joint replacement prostheses. J Arthrosc Joint Surg 2014;1(2):72–5.
[5] Fleiter N, Walter G, Bösebeck H, Vogt S, Büchner H, Hirschberger W, Hoffmann R. Clinical use and safety of a novel gentamicin-releasing resorbable bone graft substitute in the treatment of osteomyelitis/osteitis. Bone Joint Res 2014;3(7):223–9.
[6] Gauland C. Managing lower-extremity osteomyelitis locally with surgical debridement and synthetic calcium sulphate antibiotic tablets. Adv Skin Wound Care 2011;24(11):515–23.
[7] Papegelopoulos PJ, Mavrogenis AF, Tsiodras S, Vlastou C, Giamarellou H, Soucacos PN. Calcium sulphate delivery system with tobramycin for the treatment of chronic calcaneal osteomyelitis. J Int Med Res 2006;34:704–12.
[8] Iannuccelli V, Coppi G, Bondi M, Pinelli M, Mingione A, Cameroni R. Biodegradable intraoperative system for bone infection treatment II. In vivo evaluation. Int J Pharm 1996;143:187–94.
[9] Wang Y, Wang X, Li H, Xue D, Shi Z, Qi Y, Ma Q, Pan Z. Assessing the character of the rhBMP-2- and vancomycin-loaded calcium sulphate composites in vitro and in vivo. Arch Orthop Trauma Surg 2011;131:991–1001.
[10] Wahl P, Livio F, Jacobi M, Gautier E, Buclin T. Systemic exposure to tobramycin after local antibiotic treatment with calcium sulphate as carrier material. Arch Orthop Trauma Surg 2011;131:657–62.
[11] Tsai Y-F, Wu C-C, Fan F-Y, Cheng H-S, Liaw Y-C, Huang Y-K, Hsu L-H, Yand K-C. Effects of the addition of vancomycin on the physical and handling properties of calcium sulfate bone cement. Process Biochem 2014;49:2285–91.
[12] Kanellakopoulou K, Galanopoulos I, Soranoglou V, Tsaganos T, Tziortzioti V, Maris I, Papalois A, Giamarellou H, Giamarellos-Bourboulis J. Treatment of experimental osteomyelitis causes by methicillin-resistant *Staphylococcus aureus* with a synthetic carrier of calcium sulphate (Stimulan) releasing moxifloxacin. Int J Antimicrobiol Agents 2009;33:354–9.
[13] Rausschmann MA, Wichelhaus TA, Stirnal V, Dingeldein E, Zichner L, Schnettler R, Alt V. Nanocrystalline hydroxyapatite and calcium sulphate as biodegradable composite carrier material for local delivery of antibiotics in bone infections. Biomaterials 2005;26:2677–84.
[14] Kumar YC, Nalini KB, Menon J, Patro DK, Banerji BH. Calcium sulfate as bone graft substitute in the treatment of osseous bone defects, a prospective study. J Clin Diagn Res 2013;7(12):2926–8.
[15] Beardmore AA, Brooks DE, Wenke JC, Thomas DB. Effectiveness of local antibiotic delivery with an osteoinductive and osteoconductive bone-graft substitute. J Bone Joint Surg Am 2005;87:107–12.
[16] Petrova A. Gipsfulung von Knochenhohlen bei Osteomyelitis. Zentral Ges Chir 1928;43:885.
[17] Hui T, Yongping X, Tiane Z, Gang L, Yonggang Y, Mutao J, Jun L, Jing D. Treatment of osteomyelitis by liposomal gentamicin-impregnated calcium sulfate. Act Orthop Trauma Surg 2009;129:1301–8.
[18] Robinson D, Alk D, Sandbank J, Farber R, Halperin N. Inflammatory reactions associated with a calcium sulfate bone substitute. Ann Transplant 1999;4:91–7.
[19] Lee GH, Khoury JG, Bell J-E, Buckwalter JA. Adverse reactions to osteoset bone graft substitute: the incidence in a consecutive series. Iowa Orthopaedic J 2002;22:35–8.
[20] Sherry E, Boeck H, Warnke PH. Percutaneous treatment of chronic MRSA osteomyelitis with a novel plant-derived antiseptic. BMC Surg 2001;1(1), http://dx.doi.org/10.1186/1471-2482-1-1.