Do Antibiotic Impregnated Calcium Sulphate Beads Improve the Healing of Neuropathic Foot Ulcers with Osteomyelitis Undergoing Surgical Debridement?

Abstract

Background: Neuropathic foot ulcers are common and difficult to treat. Calcium sulphate has been used for antibiotic delivery with success in treating osteomyelitis. Recent case series suggest success in treating osteomyelitis of the foot with a mean time to healing of 4 months, however there are few studies with a control group for comparison. This study aimed to determine if antibiotic impregnated CAS beads improved the healing of neuropathic foot ulcers with proven osteomyelitis undergoing surgical debridement.

Methods: A consecutive retrospective cohort study of 50 patients undergoing surgical debridement of neuropathic foot ulcers for osteomyelitis was performed. Exclusion criteria were amputations and microbiology findings inconsistent with osteomyelitis. Patients were analysed comparing one group having sharp surgical debridement (SD) and another having debridement and implantation of calcium sulphate (CAS) impregnated with vancomycin and gentamicin.

Results: 42 eligible patients after exclusions; 29 in the CAS group and 13 in the SD group. In the SD group the mean time to healing was 5.8 months (2 to 9 months), and in the CAS group it was 5.5 months (2 to 13 months). There was no significant difference in ulcer healing (p=0.81), time to healing (p=0.79), re-operation rate (p=0.51), length of stay (p=0.74), or mortality (p=0.13) between the two groups.

Conclusions: Ulcer healing in patients treated with antibiotic impregnated calcium sulphate beads was not significantly improved. Healing rates in both groups were similar to those in the recent literature. Sharp surgical debridement alone may be as effective as supplementation with local antibiotics in a bioabsorbable carrier.

Introduction

The prevalence of diabetes in the United Kingdom is 3.7 million people as of November 2017[1] and diabetic foot ulcers are a common problem with a global prevalence of 6.3%[2]. This is in part due to approximately 50% of diabetic patients being diagnosed with peripheral neuropathy with loss of protective sensation due to micro vascular damage[3]. The lifetime risk of a foot ulcer is estimated at 10% in this population with an estimated 70% 5 year risk of amputation and 50% 5 year risk of death[4]. Foot ulcers are difficult to heal and carry a high recurrence rate[5].

The use of antibiotics within a bioabsorbable carrier has been demonstrated to reduce dead space, improve local antibiotic delivery to tissues delivering higher concentrations to the wound[6] and to eradicate and prevent bacterial biofilms[6,7]. Historically polymethyl methacrylate (PMMA) cement beads have been used, with the disadvantage of the need for a second procedure to remove them[8].

Stimulan® (Biocomposites Ltd, Keele, UK) is a bioabsorbable calcium sulphate (CAS) product, which is prepared at the time of surgery and can be mixed with chosen antibiotics. In vitro studies have demonstrated that antibiotic elution is effective over 40 days[9-11]. A recent study found local concentrations above the minimum inhibitory concentration for *Staphylococci* (4mg/l) 4 weeks after treatment for hip joint infection[8]. Recent studies have reported success treating tibial and femoral osteomyelitis[9-11].

There are few published studies on the outcomes of the use of bioabsorbable antibiotic impregnated CAS beads in the neuropathic foot. Several studies have been performed without any comparative control group treated without augmentation of surgical treatment with CAS beads. One case report of incision and drainage for forefoot osteomyelitis with packing of the wound with vancomycin and gentamicin impregnated CAS beads found the ulcer healed in 4 months[12]. One 12 patient case series concluded CAS beads to be effective in the treatment of calcaneal osteomyelitis when combined with hydroxyapatite with a mean time to healing of 4 months[13]. A large case series of 337 diabetic patients over 5 years concluded success in the treatment of osteomyelitis with 86% ultimately healing however the time to healing was not reported[14]. A 20 patient series of forefoot ulcers treated with gentamicin and vancomycin impregnated CAS beads and closed primarily found a median healing time of 5 weeks[15].

One comparative case series was found which included 60 cases of transmetatarsal ampuation for diabetic forefoot ulcers with failed non operative management. The use of tobramycin impregnated CAS beads resulted no difference in length of stay, time to a dry wound or time to healing when compared to amputation alone[16]. Additionally a 46 patient series found improved average healing time for CAS beads (4 months) when compared to gentamycin impregnated PMMA beads (6 months)[17].

A literature search revealed no study directly comparing the outcomes of the use of CAS in osteomyelitis of the foot in neuropathic ulcers when compared to surgical debridement (excluding amputation), therefore antibiotic impregnated CAS beads have not been proven more effective than surgical debridement. A local audit within our unit demonstrated that patients treated with amputation for foot ulcer all healed within 2 weeks and had amputation through healthy tissue far from the ulcer which grew no organism on microbiological culture. Surgical wounds which are unable to be surgically closed by definition take longer to heal as they must do so by granulation and were the subject of this study.

This study aims to determine if antibiotic impregnated CAS beads improved the healing of neuropathic foot ulcers with proven osteomyelitis undergoing surgical debridement when compared to surgical debridement alone.

Methods

Study design and study population

A retrospective cohort study was performed on a consecutive group of 50 patients undergoing foot ulcer debridement. Inclusion criteria were both medical inpatients and outpatients attending our unit with deep ulcers penetrating to bone. Patients were managed by a multidisciplinary team including an orthopaedic surgeon (foot and ankle consultant), a specialist nurse, an occupational therapist and a consultant physician (consultant in diabetes and endocrinology). A diagnosis of neuropathy was made by the inability to perceive the 10g of force a 5.07 Semmes-Weinstein monofilament. Both diabetic and non-diabetic patients were included. Exclusion criteria were amputations and those where no microbiological culture of organisms occurred from tissue samples taken at the time of the surgical debridement.

Procedure

A consecutive series of 50 patients were identified from operating theatre records. A retrospective analysis of medical and operative records was performed.

Outcome measures

Data was extracted for whether the ulcer ultimately healed or did not heal, whether the ulcer was active at 6 months, if further surgery was performed at any point within the study period, time to healing, length of stay and if the patient was alive at 6 months.

Ulcers were graded using the Sinbad (Site, Ischaemia, Neuropathy, Bacterial infection, Area and Depth) score[18], which is a standardised system recommended by the National Institute of Clinical Excellence (NICE)[4]. The range of scores is 0 to a maximum of 6, with a higher score indicating a more severe foot ulcer. Midfoot and hindfoot ulcers score higher than forefoot ulcers; ischaemia is defined is defined as absence of palpable pedal pulses; neuropathy is defined as loss of protective sensation; ulcer area is divided into greater or less than 1cm^2; depth is divided into ulcers superficial to subcutaneous tissues and those deep reaching muscle, tendon or bone.

Surgical Procedure

Patients were positioned on the operating table without the use of a tourniquet in most cases. The skin was prepared using povidone iodine and extremity draping. In all cases a surgical debridement was performed of all infected and non-viable tissue with multiple bony and soft tissue samples taken using separate sterile instruments to avoid cross contamination. The ulcer was then thoroughly lavaged using 0.9% saline. Those receiving CAS beads received these based on availability and not based on patient or ulcer characteristics. There was no randomisation. In the cases where CAS beads were used, following the surgical debridement, 5cc of CAS was mixed with 1gram of vancomycin and 160mg of gentamicin. 3mm beads were prepared and packed into the clean bed of the ulcer. In all patients the wound was then left open and either dressed with non-adhesive silicone dressings or gauze swabs and bandages. Systemic antibiotics were used following discussion with a consultant microbiologist based on organism growth and antibiotic sensitivities from operative samples and clinical features. Patients who underwent repeat debridement had the same procedure repeated. Any existing CAS beads from a previous procedure were irrigated and debrided from any wounds where sufficient time had not elapsed for them to dissolve.

Ethical approval

This research was registered locally as a service evaluation.

Statistical analysis

Statistical analysis was performed using SPSS version 23[19]. Patients were analysed in two groups; group A had a sharp surgical debridement (SD) alone, group B had a debridement followed by packing of CAS beads into the wound. Categorical outcomes (ulcer healed by the end of the study, active ulcer at 6 months, alive at 6 months, further surgery performed) were compared using a Chi square test. Time to healing was compared using a t-test as the data was normally distributed. Length of stay and duration of antibiotics were compared using the Mann-Whitney U test, as the data was not normally distributed. A correlation analysis was performed to determine if there was a relationship between length of ulcer duration and time to healing.

Results

A 50 patient consecutive series from December 2015 to May 2016 was identified. 8 patients were excluded (5 simple toe amputations and 3 cases of no osteomyelitis found and no growth on culture of specimens). All excluded cased healed within 2 weeks. The remaining eligible patient group numbered 42; 13 in the SD group and 29 in the CAS group (Figure1). Both groups had similar features with no significant differences including age, age of ulcer at presentation and severity of ulcer as assessed by Sinbad score (Table1). 37 of the 42 patients were diabetic (12 of 13 in the SD group and 25 of 29 in the CAS group). Patients who were not diabetic numbered 1 in the SD group and 4 in the CAS group. The cause of their neuropathic foot was renal failure and transplant in one patient and 4 patients suffering from Charcot-Marie-Tooth hereditary sensory and motor neuropathy. The duration of antibiotic treatment was a median 6 weeks in both groups (IQR 6-12 weeks for the CAS group and 2-6 weeks in the SD group), P=0.07. All patients received systemic antibiotics.

There were no significant differences in any of the outcome measures (Table2, Figure2, Figure3). The proportion of patient healed by 12 months was 76.9% in the SD group and 72.4% in the CAS group (p=0.81). The proportion of active ulcers at 6 months was 53.8% in the SD group and 48.3% in the CAS group (p=0.74). The proportion alive at 6 months was 92.3% in the SD group and 100% in the CAS group (p=0.13). Further surgery was performed in 30.8% of the SD group and 58.6% of the SD group (p=0.51). Time to healing was mean 5.8 months in the SD group and 5.5 months in the CAS group (p=0.79). Length of stay was median 16 days in the SD group and 10 days in the CAS group (p=0.74).

The most common organisms grown were Gram stain positive bacteria, usually *Staphylococcus aureus*. Similar organisms were grown from both patient groups (Figure4).

A subgroup analysis revealed no differences in outcome measures comparing surgeon grade (consultant versus registrar), use of pulsed lavage versus washout using syringe and intravenous giving set and whether the organisms were sensitive to vancomycin or not. Duration of ulcer at presentation did not correlate with time to healing (P=0.980, R=-0.005).

There was one death in the SD group, which was unrelated to the foot ulcer and was not due to sepsis. There were no cases of malignant transformation.

Discussion

This study aimed to determine if antibiotic impregnated CAS beads improved the healing of neuropathic foot ulcers with proven osteomyelitis undergoing surgical debridement when compared to surgical debridement alone.

We found a mean time to healing of 5.7 months overall with no significant difference between the two groups (CAS group mean 5.5 months, range 2-13, SD2.9; SD group mean 5.8 months, range 2-9, SD2.4). This is comparable to the literature with other authors reporting healing in approximately 4 months[13,16,17]. Our population group differed from those in the literature as we included patients with vascular deficiency and sepsis and excluded simple forefoot amputations with wounds suitable for primary closure. Wounds were left open to granulate and CAS beads were used to pack the dead space within the soft tissue as well as the bony defects. This may explain the observed slightly longer healing time. The inclusion of patients with vascular insufficiency is significant as in our group 31% patients did not have palpable peripheral pulses, reflecting the high incidence of this comorbidity that adversely effects outcomes.

Patients received antibiotic treatment individually guided by bacterial growth and antibiotic sensitivity from tissue samples taken at the time of debridement. There was no difference in the duration of antibiotics between groups. There was no difference in the number of patients who had growth of an organism from biopsy samples taken following debridement and irrigation in each group.

Although other authors have concluded treatment with antibiotic impregnated CAS to be effective in treating infection in the diabetic foot as well as elsewhere in the body, this study represents the first comparative study of the outcomes of treatment of infected diabetic foot ulcers that included all regions of the foot. The only other study comparing outcomes found on literature search was a single 60 patient case series of transmetatarsal ampuations for diabetic forefoot ulcers with failed non operative management. The authors compared tobramycin impregnated CAS beads to amputation without CAS beads and found no difference in length of stay, time to a dry wound or time to healing[16].

Other studies did not have a comparison group. One 12 patient case series treating calcaneal osteomyelitis combined CAS with hydroxyapatite using a novel technique with a mean time to healing of 16 weeks[13]. A large case series of 337 diabetic patients over 5 years concluded success in the treatment of osteomyelitis with 86% ultimately healing however the time to healing was not reported [14]. This study excluded patients suffering from peripheral vascular disease, Charcot arthropathy, sepsis and inability to offload. Another 20 patient series of forefoot ulcers treated with gentamicin and vancomycin impregnated CAS beads found a median healing time of 5 weeks only. However, this study included only forefoot ulcers with wounds that all underwent primary closure[15].

Within our unit we used CAS with vancomycin and gentamicin supplementation for over 2 years with perceived success. Our results suggest that surgical debridement was as effective. Interestingly the only other study comparing a group treated with CAS and without also found similar outcomes[16].

The cost implication of the use of CAS beads is not insignificant. In our hospital, 5cc of CAS cost £260 ($336), 1 gram of vancomycin cost £1.97 ($2.55) and 160mg of gentamicin cost £1.06 ($1.37). The total price for treatment in materials alone was therefore £263.03 ($340) in addition to the theatre time required to prepare the beads.

Limitations

This study has some limitations being a small series of retrospectively analysed patients. In our unit gentamicin and vancomycin impregnated CAS beads were being introduced and therefore were often used as an adjunct in the treatment of diabetic foot ulcers following surgical debridement when available. There was no randomisation and therefore there is a possibility of selection bias. The use of a consecutive series reduced this bias however resulted in unequal groups with more patients in the CAS group. As we used SINBAD scoring for vascular assessment we used palpation of pedal pulses which may have been inaccurate and prone to bias.

Conclusions

In conclusion, the use of antibiotic impregnated CAS beads in conjunction with surgical debridement of neuropathic foot ulcers with osteomyelitis did not result in significantly faster healing, reduced length of stay or need for further debridement undergoing surgical debridement. Further prospective investigation with randomised controlled trial is warranted to provide higher level evidence.

Tables and Figures

Table1. Demographics of patients in each group; sharp surgical debridement alone (SD) and those treated with debridement followed by antibiotic impregnated calcium sulphate beads (CAS).

	SD (n=13)	CAS (n=29)
Age (SD)	64.6 (10.2)	62.8 (15.5)
Age range	51 to 84	36 to 89
Sex	12 M, 1 F	21 M, 8 F
Deaths	1 (8%)	0 (0%)
Malignant change	0 (0%)	0 (0%)
Age of ulcer at presentation (SD)	9.0 (7.2)	7.3 (7.4)
Wagner (SD)	2.8 (0.9)	3.5 (1.4)
Sinbad (SD)	4 (1)	3.4 (1.4)
Presence of pus	4 (31%)	8 (28%)
Diabetic (type1, type2)	12 (2, 10)	25 (4, 21)
Location: Forefoot or midfoot	3 (23%)	18 (62%)
Location: Hindfoot	10 (77%)	11 (38%)
Charcot	2 (16%)	5 (18%)
Insulin	3 (23%)	10 (35%)
CKD	2 (16%)	7 (24%)
Vascular insufficiency	4 (31%)	9 (31%)
Smoker	0 (0%)	3 (10%)
Transplant	0 (0%)	1 (4%)
Care home	0 (0%)	2 (7%)
Surgeon: Registrar	4 (31%)	11 (38%)
Surgeon: Consultant	9 (69%)	18 (62%)
Pulsed lavage	6 (46%)	20 (69%)
Revision case	3 (23%)	6 (21%)
Joint involved	1 (8%)	9 (31%)
Weeks of antibiotics weeks (SD)	5.1 (3.1)	7.5 (3.0)
Sensitive to vancomycin	7 (54%)	26 (100%)

Table2. Key outcome measures of patients in each group; sharp surgical debridement alone (SD) and those treated with debridement followed by antibiotic impregnated calcium sulphate beads (CAS).

	SD (n=13)	CAS (n=29)	Test	Significance
Healed by 12 months	10 (76.9%)	21 (72.4%)	Chi square	p=0.81
Active ulcer at 6 months	7 (53.8%)	14 (48.3%)	Chi square	p=0.74
Alive at 6 months	12 (92.3%)	29 (100%)	Chi square	p=0.13
Further surgery performed	4 (30.8%)	17 (58.6%)	Chi square	p=0.51
Time to healing (months) (SD)	5.8 (2.4)	5.5 (2.9)	T-test	p=0.79
Length of Stay (days) (IQR)	16 (6)	10 (7)	Mann-Whitney U	p=0.74

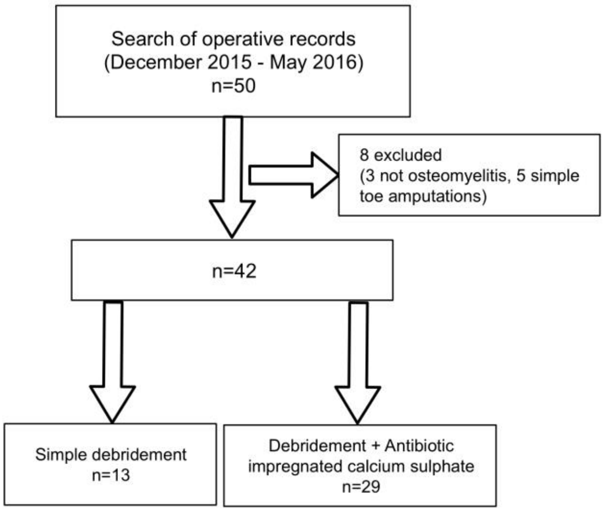

Figure1. Patient flowchart

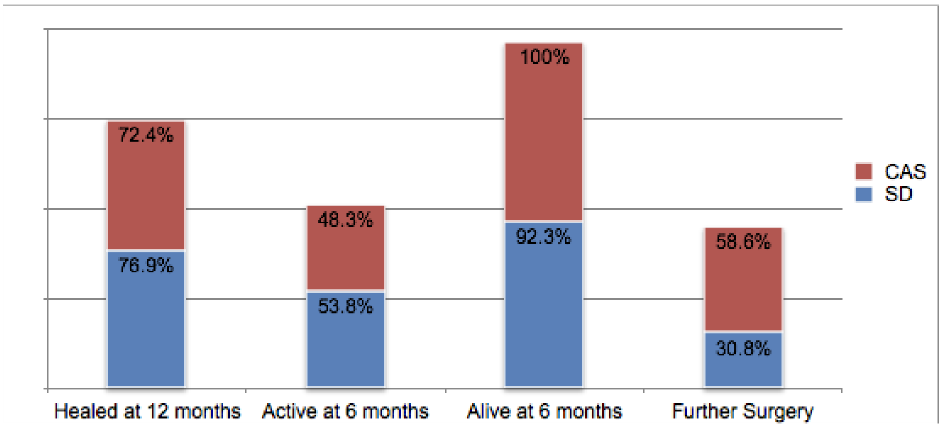

Figure 2. Bar chart of outcomes for patients treated with sharp surgical debridement alone (SD) and those treated with debridement followed by antibiotic impregnated calcium sulphate beads (CAS).

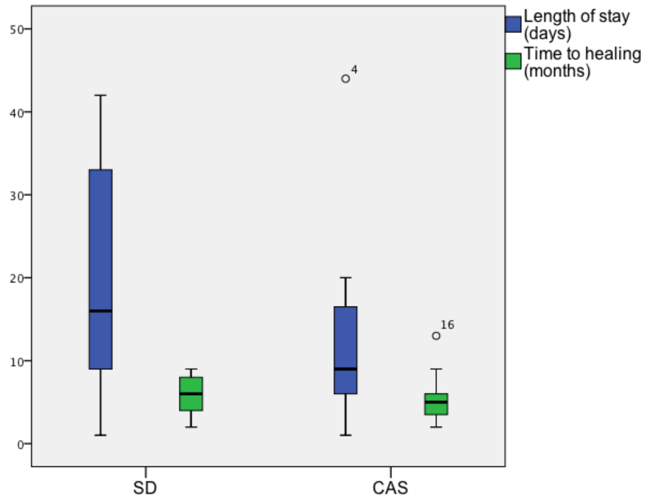

Figure 3. Box and whisker plot of length of stay (days) and time to healing (months) for patients treated with sharp surgical debridement alone (SD) and those treated with debridement followed by antibiotic impregnated calcium sulphate beads (CAS).

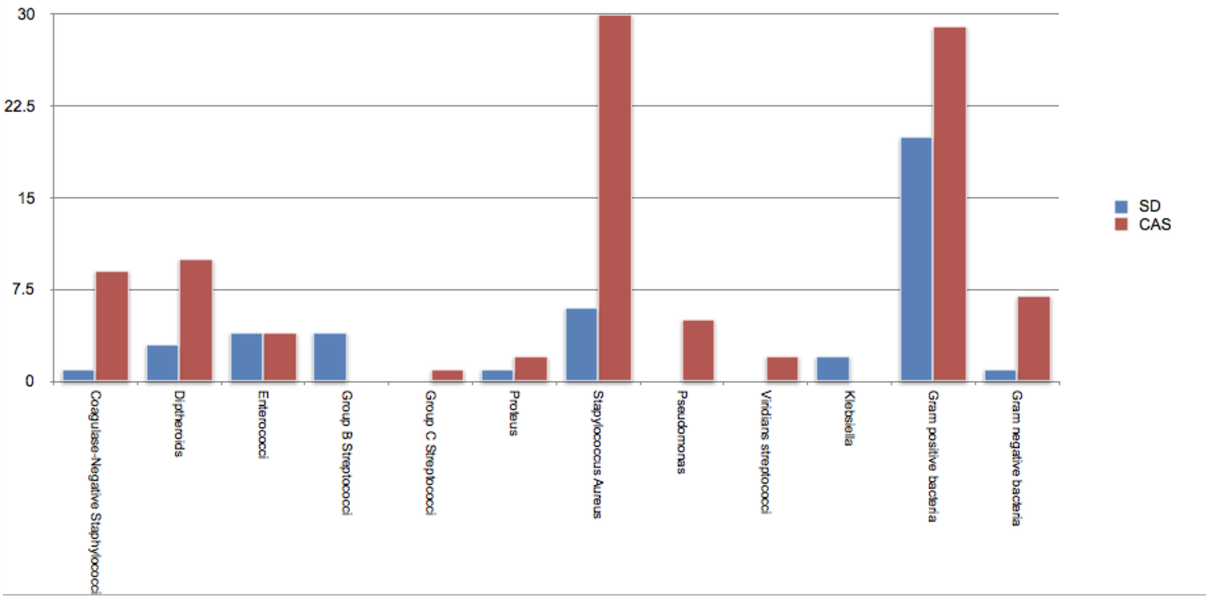

Figure 4. Bar chart of organisms grown for patients treated with sharp surgical debridement alone (SD) and those treated with debridement followed by antibiotic impregnated calcium sulphate beads (CAS).

References

1. UK D. Diabetes Prevalence 2017 (November 2017). https://www.diabetes.org.uk/professionals/position-statements-reports/statistics/diabetes-prevalence-2017. Accessed 7.9.2018, 2018
2. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis (dagger). Annals of medicine. 2017;49(2):106-116
3. Dyck PJ, Kratz KM, Karnes JL, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. Neurology. 1993;43(4):817-824
4. Diabetic foot problems: prevention and management. *National Institute for Health and Care Excellence*2015
5. Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. The New England journal of medicine. 2017;376(24):2367-2375
6. Aiken SS, Cooper JJ, Florance H, Robinson MT, Michell S. Local release of antibiotics for surgical site infection management using high-purity calcium sulfate: an in vitro elution study. Surgical infections. 2015;16(1):54-61
7. Howlin RP, Brayford MJ, Webb JS, Cooper JJ, Aiken SS, Stoodley P. Antibiotic-loaded synthetic calcium sulfate beads for prevention of bacterial colonization and biofilm formation in periprosthetic infections. Antimicrobial agents and chemotherapy. 2015;59(1):111-120
8. Wahl P, Guidi M, Benninger E, et al. The levels of vancomycin in the blood and the wound after the local treatment of bone and soft-tissue infection with antibiotic-loaded calcium sulphate as carrier material. Bone Joint J. 2017;99-b(11):1537-1544
9. Gramlich Y, Walter G, Gils J, Hoffmann R. [Early Results of Adjuvant Topical Treatment of Recurrent Osteomyelitis with Absorbable Antibiotic Carriers]. Zeitschrift fur Orthopadie und Unfallchirurgie. 2017;155(1):35-44
10. Luo S, Jiang T, Yang Y, Yang X, Zhao J. Combination therapy with vancomycin-loaded calcium sulfate and vancomycin-loaded PMMA in the treatment of chronic osteomyelitis. BMC Musculoskelet Disord. 2016;17(1):502
11. Steven G, Gregory TB. 2002
12. Morley R, Lopez F, Webb F. Calcium sulphate as a drug delivery system in a deep diabetic foot infection. Foot (Edinburgh, Scotland). 2016;27:36-40
13. Drampalos E, Mohammad HR, Kosmidis C, Balal M, Wong J, Pillai A. Single stage treatment of diabetic calcaneal osteomyelitis with an absorbable gentamicin-loaded calcium sulphate/hydroxyapatite biocomposite: The Silo technique. Foot (Edinburgh, Scotland). 2017;34:40-44
14. Gauland C. Managing lower-extremity osteomyelitis locally with surgical debridement and synthetic calcium sulfate antibiotic tablets. Advances in skin & wound care. 2011;24(11):515-523
15. Jogia RM, Modha DE, Nisal K, Berrington R, Kong MF. Use of highly purified synthetic calcium sulfate impregnated with antibiotics for the management of diabetic foot ulcers complicated by osteomyelitis. Diabetes care. 2015;38(5):e79-80
16. Krause FG, deVries G, Meakin C, Kalla TP, Younger AS. Outcome of transmetatarsal amputations in diabetics using antibiotic beads. Foot Ankle Int. 2009;30(6):486-493
17. Raglan M, Scammell B. Diabetic foot ulcers. Bone and Joint 360. 2016;3(5):2-6
18. Ince P, Abbas ZG, Lutale JK, et al. Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. Diabetes care. 2008;31(5):964-967
19. *IBM SPSS Statistics for Mac* [computer program]. Version Version 23.0: IBM Corp., Armonk, N.Y., USA;

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