Systematic Review and Meta-Analysis

Medicine

OPEN

Calcium sulfate in the management of osteomyelitis

A systematic review and meta-analysis of comparative studies

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Abstract

Background: Calcium sulfate (CS) is used extensively as an antibiotic carrier in the treatment of chronic osteomyelitis, largely due to its biodegradable nature. The aim of this systematic review and meta-analysis is to analyze the comprehensive performance of CS in the literature when compared to other biomaterials or treatments for osteomyelitis. We assess the ability of CS to eradicate infection and achieve other key clinical outcomes.

Methods: All studies comparing the use of CS to any other surgical technique for the surgical management of osteomyelitis were eligible for analysis. The indication for surgery in each case was chronic osteomyelitis. The minimum dataset required included details regarding infection eradication rates, union rates (in cases of nonunion), all-cause revision surgery and wound leakage. The primary outcome variables of concern were infection eradication and all-cause revision surgery. Secondary outcome variables included union and wound leakage. A random effects meta-analysis was performed.

Results: Five studies were deemed eligible for inclusion. The CS group had a significantly higher rate of infection eradication ($P = .013$) and a significantly lower rate of revision for all causes ($P < .001$) when compared to the comparative group. In total, the CS group had 30 cases of wound leakage compared to 8 in the comparative group ($P = .064$).

Conclusion: CS demonstrates superior rates of infection eradication and all-cause revision when compared with alternative treatment methods for chronic osteomyelitis. While the current study reports on differing but nonsignificant rates of wound leakage between CS and other treatments, future studies are required to accurately investigate this clinically important complication.

Abbreviations: BMP = bone morphogenic protein, CI = confidence interval, CS = calcium sulfate, EU = European Union, PMMA = polymethylmethacrylate, RR = relative risk.

Keywords: calcium sulfate, calcium sulphate, nonunion, osteomyelitis, posttraumatic infection

1. Introduction

Calcium sulfate (CS) has been utilized as a bioabsorbable bone substitute for over 100 years.[1] In modern orthopedic practice, it is used in many settings including as an antibiotic carrier in the prevention and treatment of chronic osteomyelitis, largely due to its biodegradable nature.[2,3] Complete dissolution of CS over the course of 3 to 6 weeks in soft tissue, or 6 to 12 weeks in bone, allows for delivery of high concentrations of antibiotic locally at the site of infection.[4,5] Moreover, no substrate remains in vivo that may facilitate bacterial colonization or biofilm formation, nor is any additional procedure required for removal since the inserted biomaterial dissolves completely. Despite the numerous advantages associated with CS, concerns of persistent postoperative wound drainage, with rates ranging from 4% to 51% of cases, remain.[6,7]

While there are a wide variety of treatment methods currently used in the management of chronic osteomyelitis, infection eradication remains challenging both for patients and physicians. This is largely due to the multitude of microorganisms that may be involved, the complexity of the clinical context (i.e., posttraumatic open injuries), its refractory course, the role of biofilm, the host immune status, and the challenging nature of its diagnosis and treatment.[2] The development and use of biodegradable antibiotic-loaded devices; however, has shown promising results, with a recent systematic review of 15 studies demonstrating 80% to 100% infection eradication rates with these biodegradable materials.[8]

The aim of this systematic review and meta-analysis is to analyze the comprehensive performance of CS in the literature when compared to other biomaterials or treatments for osteomyelitis. We assess the ability of CS to eradicate infection and achieve other key clinical outcomes.

2. Materials and methods

2.1. Eligibility criteria

All studies comparing the use of CS to any other surgical technique for the surgical management of osteomyelitis were eligible for analysis. The indication for surgery in each case was chronic

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Sheridan GA, Falk DP, Fragomen AT, Rozbruch SR. Calcium sulfate in the management of osteomyelitis: A systematic review and meta-analysis of comparative studies. Medicine 2022;101:45(e31364).

Received: 14 July 2022 / Received in final form: 22 September 2022 / Accepted: 27 September 2022

http://dx.doi.org/10.1097/MD.0000000000031364

osteomyelitis. Studies analyzing the use of CS for the management of acute fractures with bone loss were not eligible for inclusion. The minimum dataset required included details regarding infection eradication rates, union rates (in cases of nonunion), all-cause revision surgery and wound leakage. The PRISMA guidelines were adhered to throughout this study.[9] Given the nature of the study, Institutional Review Board approval was not required.

2.2. Search strategy

On November 5, 2020, a collection of clinical trial registries and electronic bibliographic databases were searched using the following MeSH terms: "calcium sulfate," "calcium sulphate," "osteomyelitis," "nonunion," and " bone infection." These were searched for in a number of combinations to return the highest number of articles possible that may have been eligible for review. Locations searched included PubMed, ClinicalTrials.gov, the Cochrane Library, the EU clinical trials register, and the International Clinical Trials Registry Platform (World Health Organization). Returned abstracts were reviewed by 2 authors and excluded or included for full article review based on the above-mentioned criteria. Any contention on final study review was resolved through consensus with all authors. Study selection was unblinded.

2.3. Data extraction

An electronic data collection form was used to collect the following variables: *author, year of publication, study design, journal, nationality, outcomes measured (infection eradication, union, time to union, revision surgery, wound leakage, other complications), number of limbs, comparative techniques used, minimum follow-up, age, gender, Cierny-Mader classification, mean defect size, microorganism detected, antibiotic protocol used*.

2.4. Statistical analysis

Demographic data was analyzed using descriptive statistics. The primary outcome variables of concern were infection eradication and all-cause revision surgery. Secondary outcome variables included union and wound leakage. A random effects meta-analysis was performed. The relative risk (RR) for each outcome measure was calculated with 95% confidence intervals (CIs), and a percentage weight was attributed. The results were illustrated on a forest plot graph where the horizontal line width for each study represented the 95% CI, with the central square area proportional to the weight of each individual study. Studies with a line traversing the midline were deemed inconclusive. The accumulated 95% CI for all studies was represented by the width of the diamond which represented all studies overall. A P value of <.05 was taken to be statistically significant when analyzing RRs. The contribution of potential inter-study heterogeneity was analyzed using the chi-squared test and the I^2 statistic. Variation in RR because of heterogeneity was expressed as a percentage, and a P value of <.05 inferred that heterogeneity had no significant impact on the results described.

2.5. Bias

To eliminate the effect of publication bias, the effects of small studies were analyzed visually using a funnel plot. To assess the funnel plot for statistically significant asymmetry, the Egger test for small-study effects was used and a P value of <.05 was taken to indicate significant asymmetry.

3. Results

3.1. Study results

The PRISMA flow diagram demonstrates our search strategy and study selection process (Fig. 1). On review of all databases, there were 686 titles for review. Based on these titles, only 24 were deemed appropriate for abstract review. Two authors reviewed 24 abstracts and 17 were deemed ineligible for inclusion based on this review. The complete texts of 7 studies were reviewed and based on the complete dataset required for inclusion in the meta-analysis, a final 5 studies were deemed eligible for inclusion (Table 1).[2,10–13]

On review of our funnel plot, there was no evidence of publication bias noted. Egger's test for small study effects demonstrated no statistically significant asymmetry in the funnel plot (P = .229) and so we can conclude that study size had no impact on the validity of our findings (Fig. 2).

3.2. Infection eradication

The eradication of infection was defined as complete resolution of infection without any further indication for surgery or antimicrobial therapy. In the CS group, there was a 93.3% rate of infection eradication (126/135). The comparative group had a significantly lower rate of eradication at 66.1% (80/121). Luo et al reported that one additional operation was required to achieve total eradication for one patient in the CS group and 2 patients in the comparative group.[2]

Using random effects meta-analysis, it was demonstrated that the CS group had a significantly higher rate of infection eradication when compared to the comparative group (P = .013) (Fig. 3). Using the I^2 statistic, it was shown that the variation in results due to heterogeneity was 52.8% and these was statistically insignificant (P = .076). The cumulative RR of persistent infection in the comparative group was significantly higher (RR = 1.15, 95% CI 1.03–1.29) than the CS group as illustrated in the forest plot in Figure 3.

3.3. All-cause revision and complications

In the CS group, a total of 13 patients (9.6%) required further surgery (single or multiple procedures) for any cause compared to 31 patients (25.6%) in the comparative group. When analyzing both groups using random effects meta-analysis, the CS group had significantly lower rates of revision for all causes (P < .001) (Fig. 4). Using the I^2 statistic, it was shown that the variation in results due to heterogeneity was high at 82% and this was statistically significant (P < .001). The cumulative RR of all-cause revision in the comparative group was significantly higher (RR = 1.37, 95% CI 1.17–1.60) than the CS group as illustrated in the forest plot in Figure 4.

Many patients underwent multiple procedures for various indications, usually associated with persistence or recurrence of infection. Table 2 demonstrates the complications requiring revision procedures in both groups.

3.4. Wound leakage

All 5 studies included reported on the incidence of wound leakage in both groups. In total, the CS group had 30 cases of wound leakage compared to 8 in the comparative group (P = .064). Using the I^2 statistic, it was shown that the variation in results due to heterogeneity was high at 74.8% and this was statistically significant (P = .003). The comparative group RR for developing this complication when compared to the CS group was 0.90 (95% CI 0.81–1.01) (Fig. 5).

3.5. Nonunion

Only 2 studies included in this study commented on union rates in both groups.[2,10] McKee et al reported high nonunion rates of 8/15 patients in both the CS group and the comparative group. Luo et al reported nonunion rates of 10/26 in the CS group and 10/25 in the comparative group. Due to the low rate of

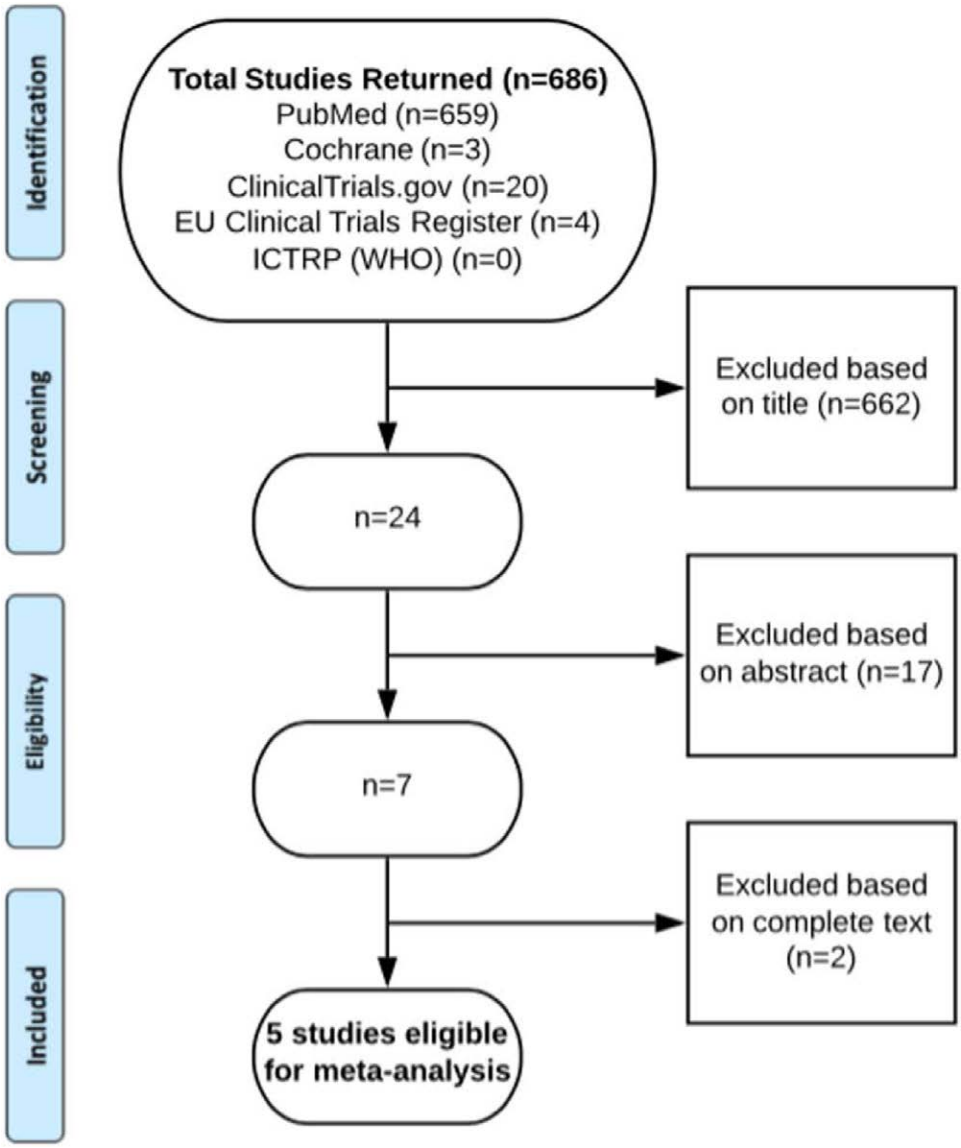

Figure 1. PRISMA flow diagram.

reporting of this specific complication, we did not perform a meta-analysis based on this outcome measure.

Mean time to union was only reported by McKee et al as 9 months in the CS group and 14 months in the comparative group. Qin et al did report on the external fixation index (d/cm) as 41.8 in the CS group and 53.6 in the comparative group.[10]

4. Discussion

This systematic review and meta-analysis was performed to compare CS with other forms of treatment used in the surgical management of chronic osteomyelitis. Results demonstrate significantly higher rates of infection eradication and significantly lower rates of all-cause revision with CS compared to other materials in the surgical treatment of chronic osteomyelitis. Infection eradication rates with CS ranged from 86% to 98%, in line with eradication rates reported in the literature. Among the other techniques used in the comparative studies included in this analysis, infection eradication rates demonstrated greater variability. Infection eradication rates were reported at 70% for suction and irrigation, 72% to 86% for polymethylmethacrylate (PMMA) antibiotic-loaded cement, 86.3% for tricalcium phosphate demineralized bone matrix and 91.7% to 92.6% for bioactive glass bioactive glass S53P4. Interestingly, in the study by Qin et al, 4 out of 6 patients who developed re-infection following their initial surgery with bone resection and suction irrigation were actually revised to be treated with CS, with a 100% success rate.[11] Based on these findings, CS appears to be the treatment of choice for successful infection eradication.

There were also significantly fewer cases requiring revision surgery in the CS group (13/135 vs 31/121, $P < .001$). The most common indication for revision surgery among the included studies was persistent or recurrent infection. The highest rate of revision for this complication was observed by Luo et al, where 9/25 (36%) patients treated with PMMA antibiotic-loaded cement alone underwent additional procedures. By contrast, in the same study only 2/26 (7.69%) of patients treated with combination therapy of CS pellets with PMMA antibiotic-loaded cement required additional procedures for persistent or recurrent infection.[2] The combination of CS and PMMA antibiotic-loaded cement in this particular study allows one to infer that when the only variable differing between treatment methods is the presence or absence of CS, the presence of CS delivers superior results. This stark difference further illustrates the morbidity

Table 1

Details of all studies included in final analysis.

Author	Year	Journal	Design	Nationality	Indication	Calcium sulfate group	Comparison group	CS total limbs	Other total limbs	Follow-up (mo)
McKee et al	2010	*Journal of Orthopaedic Trauma*	pRCT*	Canada	1. Chronic nonhematogenous osteomyelitis 2. Infected nonunion	Tobramycin-impregnated calcium sulfate Osteoset T (Wright Medical, Arlington, TN)	Tobramycin-impregnated PMMA† beads (Simplex P Cement) (Stryker, Hamilton, Canada)	15	15	24 (minimum)
Luo et al	2016	*BMC musculoskeletal disorders*	Retrospective cohort study	China	1. Chronic nonhematogenous posttraumatic osteomyelitis 2. Postoperative osteomyelitis of the lower extremity	Combination vancomycin-loaded calcium sulfate pellets + vancomycin/gentamicin loaded PMMA spacer (Stimulan; Biocomposites Ltd, UK) (Heraeus Medical GmbH, Germany)	Vancomycin/gentamicin-loaded PMMA spacers only PALACOS R + G (Heraeus Medical GmbH, Germany)	26	25	24 (mean)
Qin et al	2018	*Injury*	Retrospective cohort study	China	1. Lower limb chronic osteomyelitis of the femur or tibia treated with segmental bone resection followed by bone transport	Calcium sulfate	Irrigation-suction (with antibiotic infused normal saline)	54	20	7.25 minimum in CS‡ group 14.75 minimum in comparative group
Romano et al	2014	*The Bone & Joint Journal*	Retrospective cohort study (3 groups)	Italy	1. Patients with chronic osteomyelitis of long bones requiring surgical debridement and bone void filling	(Group B) Antibiotic-loaded hydroxyapatite and calcium sulphate (PerOssal, aap Biomaterials GmbH, Dieburg, Germany)	(Group A) Bioactive Glass (BAG) S53P4 (BonAlive, BonAlive Biomaterials Ltd, Biolinja, Finland) (Group C) Combination tricalcium phosphate (Calcibon granules, Biomet Deutschland GmbH, Berlin Germany) and teicoplanin-loaded demineralized bone matrix (Targobone, Ossacur AG, Oberstenfeld, Germany)	27	Group A (n = 27) Group C (n = 22)	12 (minimum)
Ferrando et al	2017	*Journal of Bone and Joint Infection*	Retrospective cohort study	Spain	1. Patients with cavitary bone defects and chronic osteomyelitis	Calcium sulfate mixed with vancomycin/gentamicin (Stimulan, Biocomposites Ltd, Staffordshire, England)	Bioactive Glass (BAG) S53P4 (BonAlive, BonAlive Biomaterials Ltd, Turku, Finland)	13	12	12 (minimum)
Total								135	121	

*Prospective randomized controlled trial.
†Polymethylmethacrylate.
‡Calcium sulfate.

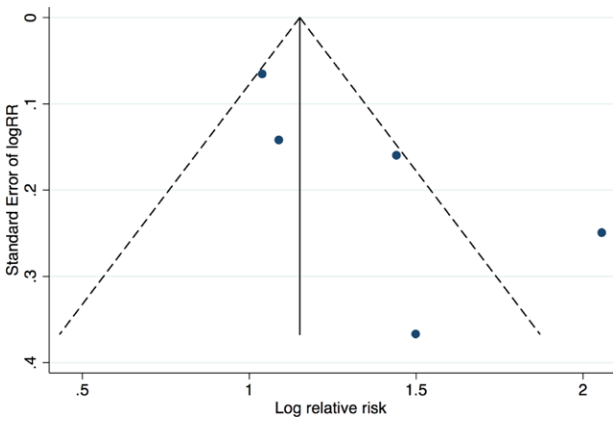

Figure 2. Funnel plot with pseudo 95% confidence intervals.

that can be associated with chronic osteomyelitis, as failing to eradicate infection can often culminate in additional surgery for over one third of patients. Given that the current study suggests that CS is more successful at eradicating infection, it is intuitive that fewer additional surgeries to treat persistent or chronic infection were observed in the CS group, although these 2 important clinical outcomes are not mutually exclusive.

Another common cause of revision surgery identified in the current analysis was docking site obstruction, observed by Qin et al[11] In their review of 74 patients treated with bone resection, CS implantation or wound suction-irrigation, followed by bone transport, the authors found that CS was associated with a significantly lower incidence of docking site obstruction requiring additional surgery (7.41% vs 30%, $P < .001$).[11] CS has typically fully resorbed by the time the transport segment has reached the docking site, thereby allowing unobstructed movement of the bone segments. Another possible explanation for this is the osteoconductive properties of calcium that may promote healing of the transported bone to the docking target.

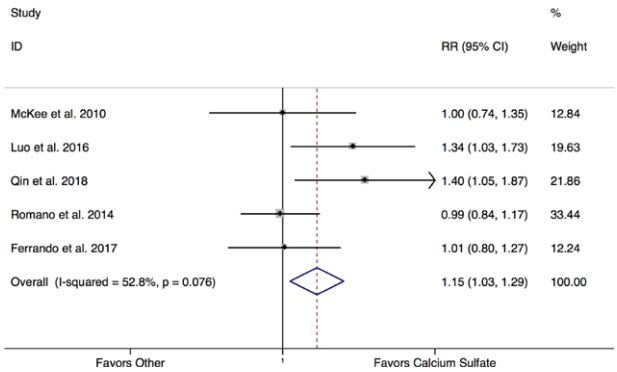

Figure 3. Infection eradication.

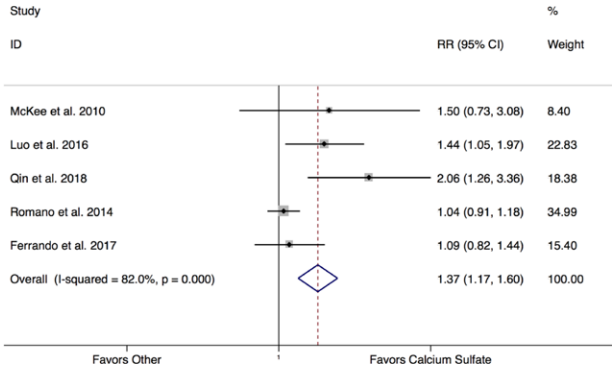

Figure 4. All-cause revision.

Table 2

Complications requiring further surgery in both groups.

Author	Year	CS group	Comparative group
McKee et al	2010	4 revision fixation 2 incision and drainage for wound infection 1 knee flexion contracture release	6 removal of PMMA beads with autogenous iliac crest bone grafting 3 revision of fixation 2 removal of hardware 2 ORIF after refracture 2 amputations (1 for persistent infection and one for refracture)
Luo et al	2016	4 recurrent infection after 1st stage	12 persistent infection after 1st stage 14 recurrent infection after 1st stage (recurrence defined as more than 3 months post-op)
Qin et al	2018	4 docking site consolidation procedures	6 docking site consolidation procedures 4 calcium sulfate implantations 1 irrigation and debridement
Romano et al	2014	1 soft tissue reconstruction (plastic surgery)	1 local muscular flap (8 months after surgery for skin necrosis and bone exposure) 1 ex-fixator for spontaneous fracture at the site of infection
Ferrando et al	2017	1 chronic expanding hematoma of the muscle flap donor site (requiring surgical drainage)	1 delayed wound closure (reoperated on by plastics and covered with a lateral thigh free flap)

CS = calcium sulfate, PMMA = polymethylmethacrylate, ORIF = open reduction internal fixation.

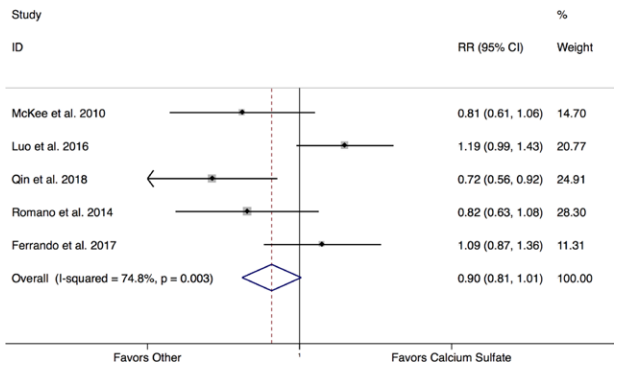

Figure 5. Wound leakage.

CS is an inorganic compound that does not inherently contain osteoinductive substances, but it may react with surrounding tissues in the local environment to promote osteoconduction and osteogenesis.[11] It has been shown to increase local levels of bone growth factors such as bone morphogenetic protein bone morphogenic protein (BMP)-2, BMP-7, transforming growth factor-β, and platelet-derived growth factor, though the exact mechanism remains unknown.[14] While docking site obstruction is a complication specific to bone transport, the lower incidence of this complication observed with CS illustrates another potential advantage favoring its utilization.

In the comparative group, a common indication for re-operation was implant removal. PMMA is not biodegradable nor does it promote new bone growth. Consequently an additional surgical procedure is usually required to remove PMMA beads. CS, as previously discussed, is biodegradable and may promote bone formation without the need for removal. It is therefore associated with less morbidity as its use does not inherently necessitate an additional surgical procedure.

Wound leakage is commonly cited as a considerable complication associated with CS, the current results suggest no significant difference in the rate of wound leakage with CS when compared to other treatment methods. These results were statistically insignificant (30/135 vs 8/121, $P = .064$) but may be clinically important and further larger scale meta-analyses should be performed in the future when more extensive evidence is available to gain an accurate insight into the impact of this commonly cited complication. The rate of wound leakage observed in this study is similar to that observed in other studies. In a case series of 195 patients treated with CS antibiotic loaded beads for chronic osteomyelitis, Ferguson et al[15] observed wound leakage in 36/195 cases (18.5%). Moreover, they found that wound leakage was not predictive of recurrent infection. Similarly, others have shown that wound leakage alone does not indicate treatment failure and stress the importance of evaluating the quality of the discharge in the context of other clinical signs/symptoms.[16] Just as in these other studies, our findings emphasize the importance of informing patients about the very real possibility of wound leakage, and also illustrate that the potential downside of wound leakage should not outweigh the significantly higher rates of infection eradication and the lower rates of all-cause revision observed with CS use when compared to other treatment methods.

4.1. Limitations

The nature of the variable etiology of osteomyelitis and the various treatments available makes it difficult to attain homogenous groups for comparison. We report on the success of CS in relation to multiple treatment methods and so by definition the comparison group is heterogeneous. It may be the case that differing surgical techniques and varying anatomical surgical sites may impact on the outcomes measured reported here. We only claim that independent of all of these potential confounders, CS appears to provide preferable results in relation to infection eradication when compared to the same techniques that do not use CS. Ideally, follow-up times would all be in excess of 48 months minimum. For this reason, future study should continue into this area. Missing data were accounted for using a random-effects meta-analysis model. The risk of bias due to heterogeneity was assessed using the I^2 statistic and in each meta-analysis performed, it was found that there was no evidence to suggest that heterogeneity has had any effect on the findings of the current study.

5. Conclusion

CS demonstrates superior rates of infection eradication and all-cause revision when compared with alternative treatment methods for chronic osteomyelitis. While the current study reports on similar rates of wound leakage between CS and other treatments, future studies are required to accurately investigate this clinically important complication.

Author contributions

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Writing – review & editing: Gerard A. Sheridan, Austin T. Fragomen.

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