

Original research

Do Antibiotic-Loaded Calcium Sulfate Beads Improve Outcomes After Debridement, Antibiotics, and Implant Retention? A Matched Cohort Study

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ABSTRACT

Background: Dissolvable antibiotic-loaded calcium sulfate beads are used as an intraoperative adjunct during debridement with antibiotics and implant retention (DAIR) for periprosthetic joint infections (PJI) to reduce the historically higher failure rates than one- or two-stage exchange. This study evaluated clinical outcomes after DAIRs performed with and without these antibiotic beads. The primary outcome was post-DAIR failure secondary to recurrent PJI at 2 years. The secondary outcome was early failure secondary to recurrent PJI within 90 days.

Material and methods: DAIRs performed for acute or acute hematogenous PJI at a single institution were retrospectively identified between 2013 and 2018. All DAIRs with adjunctive antibiotic beads (cases) were then exactly matched to a cohort of DAIRs without beads (controls) based on Charlson Comorbidity Index. The McNemar's test and Wilcoxon signed-rank test were used to evaluate differences in outcomes and patient characteristics.

Results: Twenty DAIR cases (with antibiotic beads) were matched with 20 DAIR controls. There was no difference in age, sex, body mass index, joint, erythrocyte sedimentation rate, C-reactive protein, microbiology profile, antibiotic-resistance profile, or intraoperative lavage adjuncts between groups. There were no statistically significant differences between cases and controls for either overall infection-related failure at 2 years ($P = .21$) or early infection-related failure at 90 days ($P = 1.00$).

Conclusion: Adjunctive dissolvable antibiotic-loaded calcium sulfate beads did not reduce the incidence of recurrent PJIs at 2 years or 90 days postoperatively after DAIR. Given the added cost of these antibiotic dissolvable beads without clinical benefits, we cannot recommend their use as an adjunct treatment during DAIRs.

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Introduction

In total hip (THA) and total knee arthroplasty (TKA), periprosthetic joint infection (PJI) significantly increases morbidity and carries a 5-year mortality rate higher than that of many cancers [1,2]. PJI after THA and TKA continues to be a leading cause of revision worldwide [3]. Current treatment options for PJI after THA

and TKA include one-stage revision, two-stage revision, and debridement with antibiotics and implant retention (DAIR) [4]. Of these, DAIR represents the least invasive option for surgical PJI management, with previous studies reporting shorter hospital stays and lower cost in addition to functional outcomes that are comparable to primary total joint arthroplasty [5–7]. Unfortunately, the efficacy of DAIR for PJI treatment remains unclear, with reported failure rates of DAIR procedures in the literature varying from 0% to as much as 84% [8–11].

One of the reasons for increased failure compared with one-stage or two-stage exchange and the variable outcomes reported after DAIR is retained biofilm formation on orthopedic implants

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[12]. Unfortunately, pulsatile lavage with or without antibiotics is ineffective at eradicating bacterial and/or fungal biofilms [13], suggesting that minimally invasive or arthroscopy-based procedures are ineffective in achieving pathogen control. Therefore, current consensus recommendations describing DAIR call for a wide, excisional debridement of surrounding tissues and vigorous scrubbing of all implant surfaces. Unfortunately, this alone does not guarantee total biofilm removal.

Additional intraoperative measures have been introduced to improve DAIR outcomes, which include chemical lavage with adjunctive microbicidal solutions such as povidone-iodine, chlorhexidine, and peroxide, as well as topical antibiotic powder (usually vancomycin) to improve biofilm eradication. The combination of vancomycin powder and povidone-iodine lavage was demonstrated to reduce DAIR failure from 37% to 16.7% at approximately 2-year follow-up [14]. Intraosseous antibiotics have also been proposed as an adjuvant technique to increase local antibiotic concentration. A very recent study with minimum 1-year follow-up found that intraosseous vancomycin was efficacious for DAIR survivorship when used to treat acute PJIs, resulting in an eradication rate of 93.1%, but not chronic PJIs, resulting in an eradication rate of just 44.4% [15]. However, compared to these options, antibiotic-impregnated, bioabsorbable calcium sulfate beads placed into infected joints provide much greater long-term antibiotic control, while still offering comparable ease of use. An *in vitro* antibiotic elution study individually studying vancomycin-, gentamicin-, tobramycin-, and rifampicin-loaded beads found that the eluted concentrations of each surpassed the reported minimum inhibitory concentration for common PJI pathogens during the entire 42-day study period [16]. In the context of these findings, the use of dissolvable antibiotic-loaded calcium sulfate beads has received strong interest as an adjunct treatment to improve PJI treatment outcomes, particularly DAIR procedures [17]. However, to our knowledge, there are no comparative existing studies that have evaluated the efficacy of these beads in DAIRs against a control group in the acute or acute hematogenous PJI setting.

The objective of this study was to address this literature gap through a matched retrospective cohort study. We sought to determine if there was a difference in infection-related failures at 2

years and 90 days postoperatively after DAIR for acute and acute hematogenous PJIs between patients who received adjunctive dissolvable antibiotic-loaded calcium sulfate beads and those who did not.

Material and methods

After obtaining institutional review board approval, we performed a retrospective review of all DAIR procedures for THA or TKA PJI performed at our institution in which antibiotic-loaded calcium sulfate beads were used as an adjunctive treatment (cases) over a 6-year period (2013–2018). These were compared to a matched cohort of patients who were treated with DAIR but without the use of antibiotic-loaded calcium sulfate beads (controls; Fig. 1).

Patients were identified using our institutional database according to the International Classification of Diseases-10 code for PJI (T84.50XA) and included in this study only if they met the 2018 Musculoskeletal Infection Society criteria for diagnosis of PJI [18]. All PJI infections in this study were either acute (occurring within 6 weeks of the index procedure) or acute hematogenous (defined as infections presenting with no more than 6 weeks of symptoms in a previously well-functioning prosthesis) as per the 2018 International Consensus Meeting on Periprosthetic Joint Infection [19,20]. Patients with chronic PJI were excluded.

Our institutional protocol for DAIR involves arthrotomy and open debridement of the joint, complete synovectomy, and copious pulsatile lavage with antibiotic saline. Exchange of all modular components (head/liner in THA; polyethylene liner in TKA) is performed whenever possible. However, this decision is tailored to each patient and may not be feasible in scenarios in which the risks of doing so outweigh the potential benefits. On a case-by-case basis as per individual surgeon preference, patients were also treated with further adjuncts such as a 3-minute intra-articular dilute povidone-iodine, 10% povidone-iodine, and/or hydrogen peroxide wash before closure. Intraoperative lavage was classified as either general bactericidal, consisting of just antibiotic saline solution, or adjunctive, if povidone-iodine and/or peroxide solutions were also used. Postoperatively, each patient was treated with pathogen-specific

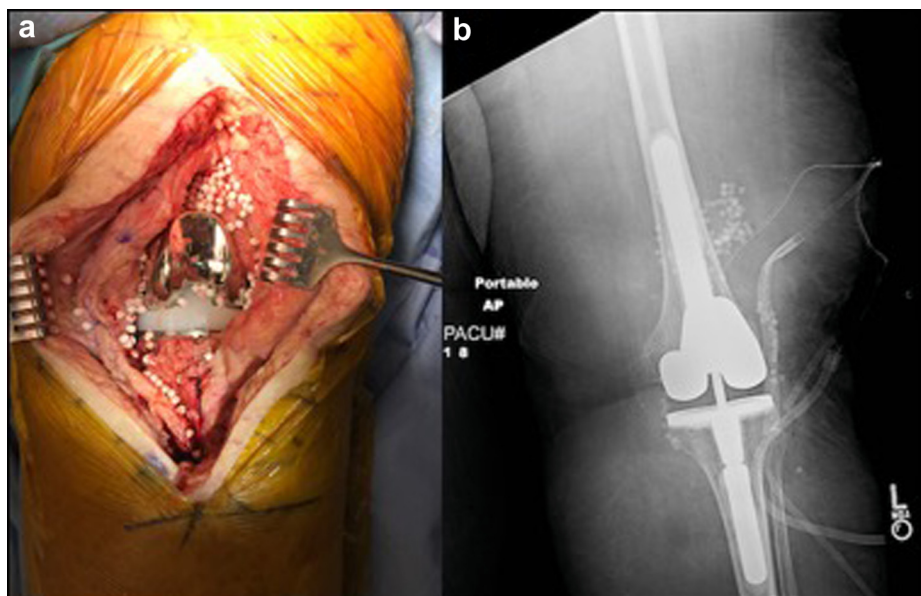


Figure 1. Dissolvable antibiotic-loaded calcium sulfate beads implanted during a DAIR for PJI in a TKA. (a) Clinical intraoperative photograph with beads in the suprapatella pouch, lateral and medial gutters. (b) Postoperative radiograph demonstrating bead location in the suprapatella pouch, lateral, and medial gutters.

Table 1
Demographic characteristics.

Demographic	Cases (n = 20)		Matched controls (n = 20)		P value
	Mean	Std. dev.	Mean	Std. dev.	
Sex					.7491
Male (%)	60		55		
Female (%)	40		45		
Joint					.17
Total hip replacement (%)	40		20		
Total knee replacement (%)	60		80		
Age (y)	72.1	11.8	71.1	8.2	.97
BMI (kg/m ²)	34.0	7.5	32.0	7.3	.42
ESR (mm/h)	58.7	29.4	72.1	31.0	.36
CRP (mg/L)	15.0	9.9	11.4	11.4	.22

intravenous antibiotics via a peripherally inserted central catheter for a minimum period of 6 weeks under the supervision of a board-certified infectious disease specialist. Patients were hospitalized until wounds were dry, and they were able to be safely discharged home or to a rehabilitation facility. All patients were monitored in multidisciplinary outpatient clinics every 2 weeks.

For this study, patient demographics including age and body mass index (BMI), preoperative erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and Charlson Comorbidity Index (CCI) were recorded. In addition, case details for the index DAIR procedure, including the joint operated on, intraoperative lavage volume, use of an intra-articular antiseptic solution, use and dosage of calcium sulfate beads, and intraoperative culture results, as well as any infection-related revisions at 90 days or 2 years post-operatively, were collected.

Statistical analysis

Patients were exactly matched on CCI. Our primary outcome was infection-related revision within 2 years of the index DAIR procedure. Our secondary outcome was early infection-related revision occurring within 90 days of the index DAIR. McNemar's test was used to evaluate for differences between groups for our primary and secondary outcomes. The Wilcoxon signed-rank test was used to evaluate for differences in baseline patient characteristics and treatments, including age, sex, BMI, ESR, CRP, microbiology, and intraoperative lavage type. All analyses were performed

Table 2
Distribution of microbiology results for each group.

Culture result	Cases (n = 20)		Matched control (n = 20)	
	Frequency	Percent	Frequency	Percent
Methicillin-sensitive <i>Staphylococcus aureus</i>	7	35	3	15
Methicillin-sensitive <i>Staphylococcus epidermidis</i>	1	5	1	5
Methicillin-resistant <i>S. aureus</i>	4	20	3	15
Methicillin-resistant <i>S. epidermidis</i>	1	5	5	25
<i>Escherichia coli</i>	1	5	0	0
<i>Enterobacter cloacae</i>	1	5	0	0
<i>Enterococcus faecalis</i>	0	0	1	5
Group A <i>Streptococcus</i>	1	5	0	0
Group B <i>Streptococcus</i>	1	5	1	5
<i>Acinetobacter baumannii</i>	1	5	0	0
<i>Morganella morganii</i>	0	0	1	5
<i>Proteus mirabilis</i>	0	0	1	5
<i>Pseudomonas aeruginos</i>	0	0	1	5
Culture negative	2	10	3	15

There was no difference in overall microbial spectra (P = .38) or antibiotic-resistant organisms (P = .54) between groups.

with SAS version 9.3 (SAS Institute, Inc., Cary, NC); a P value less than .05 was considered statistically significant.

Results

During the study period, a consecutive series of 20 patients who underwent DAIR procedures for acute or acute hematogenous PJI with dissolvable antibiotic-loaded calcium sulfate beads (cases) as an adjunct treatment were compared to 20 CCI-matched patient controls. There were no significant differences in demographic characteristics, including age, BMI, and sex, between the 2 groups (Table 1). For the total cohort, the mean age of patients was 71.6 ± 10.0 years, mean BMI was 33.0 ± 5.8 kg/m², and 57.5% were male. There was no difference between hip and knee PJIs among the groups (P = .17). The mean CRP for cases was 15.0 ± 9.9 mg/dL (normal range 0.0-1.0 mg/dL), compared with 11.4 ± 11.4 mg/dL for controls (P = .22). The mean ESR was 58.7 ± 29.4 mm/h for cases (normal range 0.0-20.0 mm/h), compared with 72.1 ± 31.0 mm/h for controls (P = .36).

Intraoperative tissue culture results are presented in Table 2. Five patients (2 cases and 3 controls) were found to have negative intraoperative cultures. There was no difference in overall microbiology distribution (P = .38) or antibiotic-resistant organisms (P = .54) between groups.

Intraoperative lavage use for the 2 groups is presented in Table 3. There was no difference in the use of general bactericidal or adjunctive lavage solutions between the groups (P = .31).

In total, 16 patients (40%) did not receive a modular component exchange during their DAIR based on intraoperative considerations as discussed previously. This was evenly distributed among the groups, with 8 of these patients found in both the cases and controls (P = 1.00).

Within the case group, the dose of antibiotics used in calcium sulfate beads was available for 18 patients (90%) and varied according to the size of the patient and/or surgeon preference: Fifty percent of the cases used a 10 cc pack (1.2 g of tobramycin + 1 g of vancomycin), 28% used 20 cc (2.4 g of tobramycin + 2 g of vancomycin), and the remaining 22% used 30 cc (3.6 g of tobramycin + 3 g of vancomycin).

Outcomes

In total, 14 patients (35%) required a revision surgery at 2-year follow-up because of recurrence of PJI. There was no statistically

Table 3
Intraoperative DAIR irrigation volume, irrigation type, and adjunct treatments for each group.

Intraoperative irrigation	Cases (n = 20)		Matched control (n = 20)		P value
	Mean/Frequency	Percent	Mean/Frequency	Percent	
Irrigation amount	9.9 L		8.3 L		
Antibiotic saline (general bactericidal)	8	40	5	25	.31
Antibiotic saline + povidone-iodine and/or peroxide (adjunctive)	12	60	15	75	

There was no difference in irrigation solution type (general bactericidal or adjunctive) between groups ($P = .31$).

significant difference between cases ($n = 9$, 45%) and controls ($n = 5$, 25%) for this outcome ($P = .21$).

In addition, we examined infection-related early failure (occurring within the first 90 days postoperatively). Two patients (5%) from the entire cohort underwent a revision procedure within 90 days of their index DAIR procedure. There was no statistically significant difference between cases ($n = 1$, 5%) and controls ($n = 1$, 5%) for this outcome ($P = 1.00$). These outcome breakdowns are summarized in Table 4.

Discussion

This matched cohort of 20 patients is the first comparative study assessing the efficacy of antibiotic-loaded calcium sulfate beads as an adjunct for DAIR in the setting of acute or acute hematogenous PJI. In our cohort, there was no difference in overall reinfection rate at 2-year follow-up or early infections within 90 days between the DAIR group that received adjunctive antibiotic beads and the control group that did not.

Several studies have been conducted to evaluate the efficacy of antibiotic-loaded calcium sulfate beads in other procedures. Outside of the scope of arthroplasty, a prospective randomized controlled trial (RCT) of the treatment of chronic osteomyelitis and infected nonunion reported an 86% infection eradication rate for the group who received antibiotic-loaded calcium sulfate beads to fill the bony defect after surgical debridement [21]. The authors concluded that for this procedure, antibiotic-loaded calcium sulfate beads demonstrated potential to improve upon the current surgical standard of care. These calcium sulfate beads were also reported to be safe and effective as an adjunct to one-stage and two-stage PJI revisions, with no reported recurrence of PJI at 5-month postoperative follow-up visits and minimal bead-associated complications [22].

In contrast, no significant improvement in the success of DAIR with antibiotic-loaded calcium sulfate beads has been reported in the acute or acute hematogenous PJI setting [23,24]. The only other comparative study reporting on calcium sulfate beads in the literature included 56 total DAIRs of chronic PJIs only. Although the authors found that the cohort receiving adjunctive antibiotic beads had a significantly lower reinfection rate of 34.8% than the 81.8% in the control group that did not receive beads at 3-year follow-up, this study was notably limited by significant differences in bacterial spectra between groups [25]. In addition, the known shortcomings of DAIRs in the chronic PJI setting limit the applicability of these results. Of the remaining studies that have been published on

the use of calcium sulfate beads for DAIR, none include a control group for comparison, and their reported failure rates vary considerably. Kallala and Haddad reported a 10.3% failure rate for their combined prospective case series of TKA and THA patients who received a DAIR with antibiotic-loaded calcium sulfate beads [26]. In contrast, Flierl et al. published a retrospective study concluding that 48% of PJI patients treated with DAIR and antibiotic-loaded calcium sulfate beads ultimately failed within 3 months of the DAIR procedure [24]. The results from our study produce a similar message to the findings of Flierl et al., with a high 45% ($n = 9/20$) failure rate for infection at 2 years in our DAIR cases with calcium sulfate beads. In addition, there were no differences in either this overall infection-related outcome or our early infection-related failure outcome compared with our control group.

An essential part of achieving treatment success with DAIR is the identification of pathogen rather than specific adjuncts. *Staphylococcus* species overall, as well as methicillin-resistant *Staphylococcus* species specifically, have been demonstrated to significantly decrease the likelihood of successful implant retention [27]. Thus, the highly varying success rates of DAIR in the literature may be attributable to differences in infectious organisms among different studies, as well as variations in other known predictors of DAIR failure, such as PJI chronicity, patient comorbidities, and varying preoperative levels of inflammatory markers [5,27–30].

After accounting for these and other factors that influence DAIR success in this study, we cannot recommend the routine use of calcium sulfate antibiotic beads. This is particularly true when considering the cost of approximately \$1200 for 10 cc and \$2000 for 20 cc of calcium sulfate antibiotic beads, which raises significant concern regarding the use and cost-effectiveness of antibiotic-loaded calcium sulfate beads to improve DAIR surgical outcomes. Furthermore, although some studies have concluded that calcium sulfate beads can be used safely, as stated previously, it has also been reported that the use of these beads in PJI revisions may contribute to increased rates of hypercalcemia in addition to other complications [26]. Of particularly important long-term clinical relevance is the potential for increased polyethylene wear (via a third body mechanism) that may also result from the use of antibiotic-impregnated calcium sulfate beads in DAIR procedures. Polyethylene components displayed 39%–89% greater wear in the presence of calcium sulfate beads than controls during in vivo testing in one study, [31] raising concern for accelerating polyethylene wear. However, our study did not evaluate for the presence of polyethylene wear in those patients in whom calcium sulfate beads were used and who subsequently went on to require a revision surgery.

Table 4
Outcomes after DAIR for both groups.

Postoperative outcome	Cases (n = 20)		Matched control (n = 20)		P value
	Frequency	Percent	Frequency	Percent	
Failure for recurrent infection at 2 y	9	45	5	25	.21
Failure for early infection within 90 d	1	5	1	5	1.00

There was no statistically significant difference for infection-related failure at either 2 years or 90 days postoperatively.

There are several important limitations to consider in our study. First, this is a retrospective review with a matched cohort comparison; an ideal study design would have been a blinded RCT, but an RCT may not be feasible. Second, modular implant exchange was not performed for each DAIR case because of patient-specific intraoperative considerations. We recognize that this contravenes current consensus recommendations and has been shown to be a key negative prognosticator for DAIR success [32]. However, these instances were equally distributed between the case and control groups, mitigating the effect that modular implant retention may have had on differences in failure rates. Furthermore, this study reflects the pragmatic intraoperative decision-making made in real time. Finally, the sample size of this study was limited. However, this is attributable to strict inclusion criteria, as all patients met the most recent 2018 Musculoskeletal Infection Society PJI criteria and qualified as having acute or acute hematogenous PJIs during their index DAIR according to the definitions outlined in the 2018 International Consensus Meeting. In addition, virtually all potential confounding variables were accounted for, including an exact CCI-match for patient comorbidities and statistically equivalent distributions of patient demographics, preoperative inflammatory markers, microbiology and antibiotic-resistance profiles, and intraoperative lavage adjuncts. Thus, we believe we were able to reliably isolate the effect of antibiotic calcium sulfate beads on DAIR outcomes in this study design.

Conclusion

In this case-control study of acute or acute hematogenous PJIs treated with DAIR with and without adjunct dissolvable antibiotic beads, we found no clinically meaningful improvements in DAIR outcomes when beads were used. This finding, combined with the significant cost and the potential for hypercalcemia and increased polyethylene wear, necessitates further investigation into the efficacy, cost-effectiveness, and safety of antibiotic-loaded synthetic calcium sulfate bead use during DAIR procedures for the treatment of PJI. Based on current data, we believe there is little justification to use antibiotic-loaded calcium sulfate beads during DAIR in the treatment of PJI.

Conflicts of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: A. Carli is a paid consultant for Heraeus Medical. C. W. Jones gave a paid presentation at the Revision Knee Masters Symposium DePuy Synthes, Sydney, March 2019, and received institutional research funding from Zimmer Biomet. P. K. Sculco is in the speakers' bureau of or gave paid presentations for DePuy Synthes, Intellijoint Surgical, and EOS imaging; is a paid consultant for DePuy Synthes, Intellijoint Surgical, Lima Corporate, and EOS imaging; and receives research support from Intellijoint Surgical. All other authors have no conflicts to disclose.

For full disclosure statements refer to <https://doi.org/10.1016/j.artd.2022.01.023>.

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