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BRIEF REPORT

Effectiveness and Safety of Biodegradable Calcium Sulfate Antibiotic Beads as Adjuvant Therapy in Vascular Graft Infections

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This is a retrospective cohort study evaluating the safety and effectiveness of biodegradable calcium sulfate antibiotic beads in vascular graft infections compared with standard of care. No differences in acute kidney injury or hypercalcemia were observed between the cohorts. Recurrence of infection did not occur in the 13-patient bead cohort compared with 14 patients who had recurrence in the 45-patient nonbead cohort with a number needed to treat of 4.0.

Keywords. acute kidney injury; calcium sulfate; local antibiotic therapy; prosthesis-related infections; vascular graft infections.

Vascular grafts reduce morbidity and mortality in patients with severe arterial disease. However, vascular graft infections (VGIs) complicate outcomes, with mortality approaching 20% [1–4]. VGIs occur secondary to surgical contamination, hematogenous seeding, or contiguous spread from overlying wounds [4]. The wounds overlying vascular grafts are difficult to treat secondary to poor wound healing, impaired blood flow, and complex surgical dead space management. Use of negative pressure wound therapy, muscle flaps, systemic antibiotics, and local wound care have varying rates of success [3–5]. Therefore, better adjuvant therapies are needed.

Stimulan is a biodegradable, delayed-release antibiotic vehicle comprised of calcium sulfate. Antibiotics can be mixed with calcium sulfate to make beads that can be implanted into tissues, thereby releasing high local concentrations of antibiotics over 4–8 weeks [6, 7]. These beads have been studied in orthopedic surgery, but only small studies have shown potential benefits outside of orthopedic surgery [8–15]. The benefit is theorized to be secondary to sterilization of surgical dead spaces and deep soft tissues [11–15]. However, there is a paucity of data evaluating calcium sulfate antibiotic beads in VGIs [16, 17]. The objectives of this study were to assess the effectiveness and safety of adjuvant calcium sulfate antibiotic beads in VGI compared with standard-of-care therapy.

METHODS

This retrospective cohort study (approved by the University of Maryland Internal Review Board HP-00091934) targeted patients with VGIs between 5/01/2016 and 4/30/2020 at the University of Maryland Medical Center. Patients were identified using the antimicrobial stewardship antibiotic database. Patients included if they (1) were over 18 years old, (2) underwent VGI surgical intervention, and (3) had follow-up longer than 6 weeks. Patients were excluded if they (1) did not have VGI, (2) had beads implanted but later removed, (3) had hemodialysis vascular graft infections, or (4) were active intravenous drug users. Patients with beads implanted were included in the intervention cohort, and patients without bead insertion were included in the control cohort. One gram of vancomycin and either 240 mg of tobramycin or 240 mg of gentamycin were placed into 10 mL of calcium sulfate and formed into beads to be implanted. These antibiotics were chosen because of their broad spectrum of activity and limited resistance at our institution to bacteria implicated in VGIs to these antibiotics. Only 10 mL or 20 mL of calcium sulfate was used per patient. All patients were treated with standard-of-care intravenous antibiotic therapy for 6 weeks directed to pathogens isolated. For VGIs with retention of grafts, oral suppression antibiotic therapy was used for the duration of follow-up. Determination of the need to implant beads was decided by vascular surgeons in consultation with infectious diseases physicians.

Data were collected on patient demographics, comorbidities, microbial pathogens, intracavitary or extracavitary, and retention of grafts (Table 1). Intracavitary referred to vascular grafts in body cavities, while extracavitary referred to grafts outside of body cavities. Partial removal of infected grafts was categorized as retention of grafts. The primary outcome was VGI recurrence, which was determined by infection in the surgical tissues and/or a graft that required further surgical intervention during the follow-up period. VGI recurrence was also stratified by intracavitary vs extracavitary location of grafts and retention vs removal of infected grafts. All-cause mortality was a secondary outcome. Safety was evaluated by comparing rates

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Table 1. Baseline Characteristics of Patients Hospitalized Between 5/01/2016 and 4/30/2020 for Vascular Graft by Antibiotic Bead Exposure (n = 58)

	Total (n = 58)	Bead Group (n = 13)	Nonbead Group (n = 45)	*P* Value
Age, median (IQR), y	66 (66–74)	65.5 (61–69)	66 (61–74)	.49
Female, No. (%)	32 (55)	5 (39)	27 (60)	.21
Comorbidities, No. (%)				
CV disease	45 (78)	12 (92)	33 (73)	.26
Renal disease	6 (10)	2 (15)	4 (9)	.61
Diabetes mellitus	17 (29)	5 (38)	12 (27)	.72
Immunocompromised[a]	6 (10)	3 (23)	3 (7)	.12
Graft characteristics, No. (%)				
Extracavitary graft infection[b]	34 (59)	6 (46)	28 (62)	0.35
Retention of infected graft	18 (31)	4 (31)	14 (31)	1.00
Pathogens, No. (%)				
MRSA	6 (10)	1 (8)	6 (13)	1.00
Pseudomonas	7 (12)	1 (8)	6 (13)	1.00
Polymicrobial	22 (38)	4 (31)	18 (40)	.75
Culture negative	5 (9)	1 (8)	2 (4)	1.00
Follow-up,[c] median (IQR), mo	7 (4–12)	14 (8–18)	6 (4–9)	.01

Abbreviations: CV, cardiovascular disease; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a]HIV, malignancy, and transplant.

[b]The remaining were considered intracavitary.

[c]To time of recurrence or last documentation in chart.

of acute kidney injury (AKI), hypercalcemia, and heterotopic ossification. AKI was defined as a 1.5-fold increase in the serum creatinine compared with baseline. Hypercalcemia was determined by serum calcium >10.5 mg/dL. Heterotopic ossification was evaluated on repeat computed tomography (CT) imaging.

Descriptive statistics were used to analyze overall study patients and compare the bead vs nonbead cohorts. Continuous and categorical variables were analyzed using the Mann-Whitney *U* test and Fisher exact test, respectively. A *P* value <.05 was considered statistically significant. Risk ratios (RRs) with 95% CIs and absolute risk differences with number needed to treat (NNT) and 95% CIs were used to compare cohorts. For any RR analysis with 0 cells present, 1 was added to each cell. Analyses were done with SAS, version 9.4 (SAS Institute, Cary, NC, USA), and Medcalc (https://www.medcalc.org/calc/relative_risk.php).

RESULTS

There were 195 patients identified with vascular infections, of whom 137 were excluded for not having infections (n = 36), infections of dialysis grafts (n = 48), infections of the vascular system without grafts (such as mycotic aneurysms; n = 45), active intravenous drug use (n = 6), and having beads implanted and then subsequently removed several days later (n = 2) because assistant surgeons erroneously thought they were nonbiodegradable beads. Out of the remaining 58 patients, 13 had implantation of beads and were included in the intervention cohort. The remaining 45 vascular graft infection patients were included in the control cohort. All bacteria isolated from the index infections were sensitive to vancomycin or aminoglycosides.

Table 1 displays baseline characteristics. Follow-up was significantly longer for the bead cohort compared with the nonbead cohort (14 vs 6 months). The nonbead cohort had a greater percentage of extracavitary VGI compared with the bead cohort (62% vs 46%). Table 2 displays VGI recurrence, all-cause mortality, and safety outcomes. Recurrent VGI did not occur in any patient in the bead cohort, while 14 patients in the nonbead cohort had infection recurrence (0.21; 95% CI, 0.03–1.45), with an NNT of 4.0 (95% CI, 2.0–166). It was also observed that extracavitary grafts were more likely than intracavitary grafts to have recurrence (35% vs 8%; *P* = .02) and retained grafts had a trend toward recurrence (28% vs 23%; *P* = .66). When stratified by location of graft, the the RR was 0.29 for extracavitary (95% CI, 0.04–1.9) and 0.7 for intracavitary (95% CI, 0.08–5.9) Similarly, when stratified by retained graft vs graft removal, the RR was 0.44 (95% CI, 0.07–3.0) and 0.3 (95% CI, 0.04–2.0), respectively. Death from all causes occurred in 1 patient in the bead cohort compared with 7 patients in the nonbead cohort (RR, 0.91; 95% CI, 0.75–1.1). Acute kidney injury occurred equally in both cohorts, with an RR of 1.0 (95% CI, 0.66–1.5). No hypercalcemia or heterotopic ossification was observed.

DISCUSSION

To our knowledge, this is the first study to assess the safety and show a potential benefit of using these beads to prevent infection recurrence in VGIs. Given the novelty and off-label use, the bead cohort was very small (n = 13), limiting the ability to achieve statistical significance. However, no recurrence

Table 2. Effectiveness and Safety Outcomes of Patients Hospitalized Between 5/01/2016 and 4/30/2020 for Vascular Graft by Antibiotic Bead Exposure (n = 58)

	Bead Group (n = 13), No. (%)	Nonbead Group (n = 45), No. (%)	Risk Ratio (95% CI)
Effectiveness			
Recurrence of infection	0 (0)	14 (31)	0.21 (0.03–1.45)
Extracavitary[a]	0 (0)	12 (43)	0.29 (0.04–1.9)
Retained graft[a]	0 (0)	5 (36)	0.44 (0.07–3.0)
All-cause mortality	1 (8)	7 (15)	0.91 (0.75–1.1)
Safety			
Acute kidney injury	4 (31)	14 (31)	1.0 (0.66–1.5)
Hypercalcemia	0 (0)	0 (0)	—
Heterotopic ossification	0 (0)	—	—

[a]Stratified analysis.

occurred in the bead cohort, compared with 14 patients in the nonbead cohort. This resulted in a 79% decrease in VGI recurrence risk in patients who received beads vs standard care alone. Four patients would need to receive these beads to avoid 1 infection recurrence in VGI. There were also no safety concerns with respect to AKI, hypercalcemia, or heterotophic ossification.

Treatment recommendations for VGI lack standardized guidelines, but Samson classifications have structured treatment protocols for extracavitary VGI [4, 18–20]. Traditional surgical management is complete resection of the infected graft followed by 6 weeks of intravenous antibiotic therapy [4, 18–20]. For patients not able to tolerate en bloc resection, debridement with retention of the infected graft can be associated with graft preservation, but patients are usually committed to indefinite oral antimicrobial suppression therapy [4]. Even with these interventions, recurrence can occur, with rates ranging widely from 5% to 30% [3, 4, 21]. Therefore, innovative strategies are needed to reduce infection recurrence.

The use of antibiotic beads holds promise given their slow release of antibiotics over a prolonged period of time [6, 7]. Use of polymethyl methacrylate (PMMA) antibiotic beads in VGIs has shown potential, but these are not biodegradable and require surgical removal [22–24]. Unlike PMMA beads, the use of biodegradable beads is an attractive adjuvant therapy to sterilize deep soft tissues and surgical dead spaces while circumventing the need for surgical removal [24]. However, few studies have evaluated the safety and potential effectiveness of these beads in VGIs [16, 17].

The benefit of these beads likely occurs from sterilization of surgical dead space as a consequence of prolonged release of antibiotics. Bacteria are therefore unable to proliferate in these surgical dead spaces that systemic antibiotics have difficulty treating. The remarkably low NNT seen in this small sample is reassuring, but large-scale prospective studies are needed to validate this intervention. The prolonged follow-up time (median, 7 months) and longer follow-up in the bead cohort ensured that recurrent infections were being captured. In addition, an attempt at stratification by retained graft and location of graft was done to discern these factors from bead effect on recurrence. It appears that the impact of the bead may be diminished in intracavitary grafts (RR, 0.7), perhaps from the larger surgical dead space that is present compared with extracavitary grafts, but this needs further investigation. In the bead cohort, only 1 death occurred; it was a consequence of critical limb ischemia. While mortality was 15% in the nonbead cohort, the difference was not statistically significant. Many factors contribute to all-cause mortality in VGI patients, and without well-powered prospective studies, it will be difficult to demonstrate a mortality reduction with the use of this intervention.

We assessed the safety of this adjuvant therapy by comparing rates of AKI between the 2 cohorts and identifying hypercalcemia and heterotopic ossification in the bead cohort. These side effects have been reported in orthopedic literature, especially when higher bead volumes (>40 mL of calcium sulfate) were used [8]. The amount of antibiotics placed into each 10 mL of beads was small (1 g of vancomycin and 240 mg of gentamicin or tobramycin), and the amount of elemental calcium in each 10 mL of beads was roughly 5.7 g, eluted over 4–8 weeks [6, 7, 25]. However when higher volumes of these beads are used, there is an increased risk for significant systemic absorption of both antibiotics and calcium, as warned by the Food and Drug Administration [8, 26]. In this study, no hypercalcemia was observed, and we observed no increased risk of AKI with these beads compared with the control cohort. Heterotopic ossification has been shown to occur with low incidence (1%–3%) in the orthopedic literature, but no heterotopic ossification was seen on serial CT scans in this study [8, 27]. Given the retrospective nature and the use of vacuum-assisted closure therapies, sterile wound drainage could not be assessed, which is another rare side effect [8]. While encouraging that no adverse side effects occurred, prospective studies are needed to further evaluate the safety of these beads in vascular graft infections, especially if higher volumes of calcium sulfate beads are to be used.

There are several limitations of this study. First, the retrospective design has the potential for information and reviewer

bias. As a nonrandomized observational study, selection bias or confounding by indication can bias the estimate away from the null. Location and retention of graft, as well as immunocompromised status, were variables that were unequally distributed that may have contributed to confounding. Nonetheless, the higher proportion of immunocompromised patients in the bead group suggests that perhaps beads were placed in higher-risk patients who were less able to tolerate recurrent surgeries and therefore be at increased risk for infection recurrence, thereby bringing the true estimate further away from the null. On the other hand, extracavitary was more likely to be associated with recurrence. Stratification was done to attempt to account for this difference, though the sample size diminished further; however, we demonstrated a smaller impact of the beads on recurrence in the intracavitary stratum, which needs further evaluation. Second, the VGI recurrence rate in the nonbead cohort is on the higher range of what is reported in the literature (30%), which may bias the risk estimate away from the null; however, a 30% recurrence rate is likely appropriate in a tertiary academic medical center treating high-risk patients. Finally, the small sample size may not be powered sufficiently to detect a statistically significant difference, demonstrated by the 0 recurrences in the bead group and wide confidence intervals. Even with these limitations, the significant reduction in infection recurrence warrants prospective evaluation of this adjuvant therapy in VGIs.

In conclusion, this study suggests that biodegradable calcium sulfate antibiotic beads may be safe to use in VGIs, especially when limited volumes are used. These beads may also have a potential benefit in reducing infection recurrence in VGIs. However, randomized prospective studies are needed to fully validate the efficacy of this adjuvant therapy in VGIs.

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Patient consent. Each patient provided written informed consent to undergo the surgical procedures and medical treatments discussed. The retrospective study was approved by the University of Maryland Internal Review Board (HP-00091934).

Author contributions. J.D., J.B., E.H., K.S., S.T.: study concept, interpretation of data, and drafting the manuscript; J.D., M.B., J.K., S.T.: collection of data; J.D., S.T., J.K.: carried out the clinical experimental treatment.

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