Effectiveness and safety of biodegradable calcium sulfate antibiotic beads as adjuvant therapy in vascular graft infections

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Abbreviations:

AKI: acute kidney injury; CI: confidence interval; MRSA: methicillin resistant Staphylococcus aureus;
NNT: needed to treat; PMMA: polymethyl methacrylate; RR: relative risk; VGI: vascular graft infection
Abstract: This is a retrospective cohort study evaluating the safety and effectiveness of biodegradable calcium sulfate antibiotic beads in vascular graft infections compared to 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 to 14 patients that had recurrence in the 45 patient non-bead cohort with a NNT of 4.0.

Keywords: Vascular graft infections; Local antibiotic therapy; Prosthesis-related infections; Acute Kidney injury; Calcium sulfate
Introduction:

Vascular grafts reduce morbidity and mortality of patients with severe arterial disease. However vascular graft infections (VGI) 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 to standard of care therapy.

Methods:

This retrospective cohort study (approved by 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, (3) had follow up longer than 6 weeks. Patients were excluded if they (1) didn’t have VGI (2) had beads implanted but were later removed (3) had hemodialysis vascular graft infections.
(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. 1 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 VGI’s to these antibiotics. Only 10 ml or 20 ml of calcium sulfate were 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 were used for the duration of the patients follow up. Determination for the need to implant beads was decided by vascular surgeons in consultation with infectious diseases physicians.

    Data was collected on patient demographics, comorbidities, microbial pathogens, intracavitary or extracavitary and retention of grafts (Table 1). Intracavitary referred to vascular grafts in body cavity while extracavitary referred to grafts outside of body cavity. Partial removal of infected grafts were categorized as retention of grafts. Primary outcome was VGI recurrence which was determined by infection in the surgical tissues and/or graft that required further surgical intervention during the follow up period. VGI recurrence was also stratified by intracavitary versus extracavitary location of graft, and retained versus removal of infected graft. All-cause mortality was a secondary outcome. Safety was evaluated by comparing rates of acute kidney injury (AKI), hypercalcemia and heterotopic ossification. AKI was defined as a 1.5 fold increase in the serum creatinine compared to baseline. Hypercalcemia was determined by serum calcium over 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 bead versus no bead cohorts. Continuous and categorical variables were analyzed using Mann-Whitney U test and Fischer Exact test, respectively. P-value <0.05 was considered statistically significant. Risk ratios (RR) with 95% confidence intervals (CI) and absolute risk difference with number needed to treat
(NNT) and 95% CI were used to compare cohorts. For any RR analysis with zero cell present, one was added to each cell. Analyses were done with SAS version 9.4 (SAS Institute, Cary, NC) and Medcalc (https://www.medcalc.org/calc/relative_risk.php).

Results:

There were 195 patients identified with vascular infections of which, 137 patients 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 patients who had beads implanted but had them removed several days later (N=2) because assistant surgeons erroneously thought they were non-biodegradable beads. Out of the remaining 58 patients, 13 had implantation of beads and were included in 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 to non-bead cohort (14 vs. 6 months). The non-bead cohort had greater percentage of extracavitary VGI compared to 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 non-bead cohort had infection recurrence (0.21 95% CI 0.03 – 1.45) with 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=0.02) and retained grafts had trend towards recurrence (28% vs 23%, p=0.66). When stratified by location of graft, RR for extracavitary was 0.29 (95% CI 0.04 to 1.9) and intracavitary was 0.7 (95% CI 0.08 - 5.9) Similarly, when stratified by retained graft versus graft removal, 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 to 7 patients in the non-bead cohort (RR 0.91, 95% CI 0.75 – 1.1). Acute kidney injury occurred equally in both cohorts with RR 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 VGI. Given the novelty and off-label use, the bead cohort was very small (n=13) thereby limiting the ability to achieve statistical significance. However, no recurrence occurred in the bead cohort compared to 14 patients in the non-bead cohort. This resulted in a 79% decrease in VGI recurrence risk in patients who received beads versus standard care alone. Four patients would need to receive these beads to avoid one infection recurrence in VGI. There were also no safety concerns with respect to AKI, hypercalcemia or heterotrophic 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 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% [4,21,22]. Therefore, innovative strategies are needed to reduce infection recurrence.

The use of antibiotic beads hold promise given their slow release of antibiotics over a prolonged period of time [6,7]. Use of polymethyl methacrylate (PMMA) antibiotic beads in VGI have shown potential but these are not biodegradable and require surgical removal [23-25]. Unlike PMMA beads, the use of biodegradable beads is an attractive adjuvant therapy to sterilize deep soft tissues and surgical dead spaces while circumventing need for surgical removal [25]. However limited studies have evaluated the safety and potential effectiveness of these beads in VGI [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. A 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 of 7 months) and longer follow up in bead cohort ensured that recurrent infections were being captured. In addition, 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 to extracavitary grafts but this needs further investigation. In the bead cohort only one death occurred which was a consequence of critical limb ischemia. While mortality was 15% in the non-bead 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 mortality reduction with the use of this intervention.

We assessed safety of this adjuvant therapy by comparing rates of AKI between the two 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 (over 40 ml of calcium sulfate) were used [8]. The amount of antibiotics placed into each 10 ml of beads is small (1 gram of vancomycin and 240 mg of gentamicin or tobramycin) and the amount of elemental calcium in each 10 ml of beads is roughly 5.7 g which are eluted over 4-8 weeks [6,7,26]. 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 FDA [8, 27]. In this study, no hypercalcemia was observed and we observed no increased risk of AKI with these beads compared to 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, 28]. 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 non-randomized 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 contribute to this 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 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 non-bead 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, 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 zero recurrence 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 VGI especially when limited volumes are used. These beads may also have a potential benefit in reducing infection recurrence in VGs. However randomized, prospective studies are needed to fully validate the efficacy of this adjuvant therapy in VGs.
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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.
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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) | Non-bead group (N=45) | p-value |
|--------------------------------|--------------|-------------------|-----------------------|---------|
| Age, years (median, IQR)       | 66 (66-74)   | 65.5 (61-69)      | 66 (61-74)            | 0.49    |
| Female (%)                     | 32 (55)      | 5 (39)            | 27 (60)               | 0.21    |
| **Comorbidities**              |              |                   |                       |         |
| CV disease (%)                 | 45 (78)      | 12 (92)           | 33 (73)               | 0.26    |
| Renal Disease (%)              | 6 (10)       | 2 (15)            | 4 (9)                 | 0.61    |
| Diabetes Mellitus (%)          | 17 (29)      | 5 (38)            | 12 (27)               | 0.72    |
| Immunocompromised\(^1\) (%)    | 6 (10)       | 3 (23)            | 3 (7)                 | 0.12    |
| **Graft characteristics**      |              |                   |                       |         |
| Extracavitary graft infection (%)\(^2\) | 34 (59)   | 6 (46)            | 28 (62)               | 0.35    |
| Retention of infected graft (%)| 18 (31)      | 4 (31)            | 14 (31)               | 1.00    |
| **Pathogens**                  |              |                   |                       |         |
| 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)               | 0.75    |
| Culture negative (%)           | 5 (9)        | 1 (8)             | 2 (4)                 | 1.00    |
| Follow up\(^3\), months (median, IQR) | 7 (4-12) | 14 (8-18) | 6 (4-9) | 0.01 |

\(^1\) HIV, malignancy and transplant; \(^2\) Remaining were considered intracavitary, \(^3\) To time of recurrence or last documentation in chart; CV cardiovascular disease MRSA methicillin resistant S. aureus
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 (%) | Non-Bead group N=45 (%) | Risk ratio (95% CI) |
|------------------|---------------------|-------------------------|---------------------|
| **Effectiveness**|                     |                         |                     |
| Recurrence of infection | 0 (0)              | 14 (31)                 | 0.21 (0.03 – 1.45)  |
| Extracavitary \(^1\) | 0 (0)              | 12 (43)                 | 0.29 (0.04 - 1.9)   |
| Retained graft \(^1\) | 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)           | --                      | --                  |

\(^1\) Stratified analysis