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Full title: The Use of Antibiotic Beads to Salvage the Infected Breast Implant

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Abstract

Purpose:

When an implant becomes infected, implant salvage is often performed where the implant is removed, capsulectomy is performed, and a new implant is inserted. The patient is discharged with a PICC line and 6-8 weeks of IV antibiotics. This method has variable success and subjects the patient to long-term systemic antibiotics. In the 1960s, the use of antibiotic-impregnated beads for the treatment of chronic osteomyelitis was described. These beads deliver antibiotic directly to the site of the infection, thereby eliminating the complications of systemic IV antibiotics. The goal of this study is to present a case series illustrating the use of STIMULAN calcium sulfate beads loaded with vancomycin and tobramycin to increase the rate of salvage of the infected implant and forgo IV antibiotics.

Methods:

A retrospective analysis was performed of patients who were treated at Mount Sinai Hospital for implant infection with salvage and antibiotic beads.

Results:

Twelve patients were identified, ten of whom had breast cancer. Comorbidities included hypertension, smoking, and immunocompromised status. Infections were noted anywhere from 5 days to 8 years post-operatively. Salvage was successful in nine out of the twelve infected implants through the use of antibiotic bead therapy without home IV antibiotics.

Conclusions:

The use of antibiotic beads is promising for salvaging infected breast implants without IV antibiotics. 75% of the implants were successfully salvaged. Of the three patients who had unsalvageable implants, one was infected with antibiotic resistant rhodococcus that was refractory to bead therapy and one was noncompliant with post-operative instructions.

Introduction

Although many different options for breast reconstruction exist, implant based reconstruction remains the most common method in the literature. In 2015, this accounted for 81% of all breast reconstructions.[1] Generally implant based reconstruction is a well tolerated procedure with few complications. Implant infection is among the complications of such reconstruction, and can affect between 1-35% of patients according to the literature.[2] A 2008 study estimated the burden of cost to be over $4000 per patient.[3] Such patients are generally treated aggressively with broad-spectrum intravenous antibiotics and frequently return to the operating room for drainage and washout of the infected pocket. Those patients who do not respond to initial treatment are often treated with implant removal. This does not prohibit the patient from future attempts at reconstruction, although secondary and tertiary surgeries are generally significantly more difficult leading to suboptimal results.[4] Additionally, implant loss can lead to psychological distress.[5]

When faced with implant infection, the surgeon has the option of oral or intravenous antibiotic therapy, removal of the implant, or pocket exploration with implant salvage. In 1965, Perras described salvaging infected implants in primary implant augmentation by using antibiotic lavage.[6] Over the next 40 years, a number of variations of implant salvage have been described, ultimately arriving at a new trend including systemic antibiotics, implant removal, and exchange with a new device. The patient is often placed on postoperative intravenous antibiotics for several weeks to clear the infection. While imperfect, this technique has been shown to result in a decrease in morbidity and an increase in in the salvage of the breast reconstruction with success rates ranging from 37% to 76% in a number of studies.[4,7]

Although promising, this protocol for implant salvage has variable success rates and morbidity through the use of intravenous antibiotics. Antibiotic treatment for implant infection frequently involves the use of intravenous broad-spectrum antibiotics for several weeks, which come with their own host of complications. Parenteral administration of antibiotics, depending on the selection of medications, can cause nephrotoxicity, ototoxicity, and allergic complications. Additionally, high doses are required to attain therapeutic levels in infection sites, which increase the likelihood of such complications.[8] On top of everything, the peripherally inserted central catheter (PICC) line through which the antibiotics are administered can cause bleeding, infection, blood clots, and significant discomfort. One study in patients undergoing long-term antibiotic therapy for osteomyelitis through PICC lines showed a 20% complication rate for the lines all resulting in removal.[9] All of these reasons have led to the search for an alternative to this aspect of treatment.

In 1970, Buchholz et al described a technique using antibiotic-impregnated polymethylmethacrylate (PMMA) bone cement for infected arthroplasties.[10] With that, a new era of antibiotic-impregnated materials for direct administration of antibiotics began. While PMMA has been the most commonly used delivery vehicle for antibiotics, there has been a recent emergence of biodegradable materials such as calcium sulfate, which can be loaded with antibiotics and placed into a surgical site prior to closure. Over time, these beads break down, releasing controlled doses of antibiotics slowly that fight infection. Both PMMA and calcium sulfate beads have

been used mainly by orthopedic surgeons for the treatment of hardware infection and refractory osteomyelitis.

In the present study, the authors present a single center case series of patients with breast implant infections who were treated with implant removal, debridement, partial capsulectomy, and immediate implant exchange. Prior to closure, STIMULAN (Biocomposites, USA) Calcium Sulfate antibiotic beads reconstituted with 1gm vancomycin and 1.2gm tobramycin, were placed into the implant pocket. The goal of the study is to demonstrate that the use of antibiotic beads during implant salvage leads to an increase in the rate of implant salvage as well as bypassing the need for postoperative long term intravenous antibiotics, thus decreasing morbidity.

Patients and Methods

Study Design

A single-center, retrospective analysis of all patients who underwent implant-based breast reconstruction at Mount Sinai Hospital was performed. All patients who developed an implant infection and then received treatment with antibiotic-impregnated beads for implant salvage were included in the study. Patient demographics, medical history, operative complications, and surgical outcomes were reviewed. Patients were evaluated for type of implant infection and efficacy of treatment with antibiotic beads. The Icahn School of Medicine at Mount Sinai Institutional Review Board, in accordance with the Mount Sinai Hospital's Federal Wide Assurances to the Department of Health and Human Services, approved this study.

Implant Salvage Technique

Patients with an implant pocket were brought to the operating room (OR) for implant removal, partial capsulectomy, and debridement of the nonviable tissue. The pocket was pulse lavaged with bacitracin irrigation. STIMULAN antibiotic beads impregnated with 1g Vancomycin and 1.2g Tobramycin were placed in the implant pocket and a new implant or tissue expander was placed. Patients were kept for observation with IV antibiotics until clinical signs of infection abated and discharged home on oral antibiotics.

Results

Between May 2013 and August 2016, 12 patients underwent implant salvage using antibiotic bead therapy at Mount Sinai under the care of two attending surgeons. The average age of the subjects was 51.3 years. Ten had a history of cancer in the affected breast. Five patients received radiation therapy in the affected breast. Two subjects had hypertension, none had diabetes, and three were active smokers. One subject was immunocompromised with a diagnosis of HIV. Other comorbidities included coronary artery disease, hypothyroidism, and obesity.

There were twelve instances of implant pocket infection. Of the six cultures that came back positive, infectious agents included staphylococcus epidermitis, staphylococcus aureus, enterobacter, yeast, and rhodococcus. Infections were noted

anywhere from 5 days to 8 years post initial implant surgery. Four of the patients were direct to implant, seven were implant following tissue expander, and one patient had a tissue expander in place. The surgical team was able to successfully salvage nine out of the twelve infected implants through the use of antibiotic bead therapy without the continued use of IV antibiotics **(See Figure 1A-D)**. The follow up time ranged from 3 months to 19 months with an average of 10.6 months. No implant ruptures were noted. **(See Table 1)**

Discussion

When Dr. Buchholz first illustrated his antibiotic-laden bone cement in infected arthroplasties, he fundamentally changed the treatment of complex osteomyelitis. He would place polymethylmethacrylate (PMMA) bone cement impregnated with gentamicin into the bone cavity and was met with great success in eradicating the infection. His technique, however, did have several drawbacks; the use of the bone cement prevents drainage of the affected area and makes future debridement challenging, as the cement became difficult to remove once hardened.

In the mid-1970s, Dr. Klaus Klemm improved on Buchholz's technique by creating a series of PMMA beads soaked with gentamicin and stringing them on a surgical wire, allowing for easy removal and debridement.[11] Dr. Klemm demonstrated how gentamycin impregnated beads achieved supratherapeutic levels at the infection site while simultaneously resulting in low serum and urine concentrations, thus decreasing the risk of nephro and ototoxicity, two of the most feared complications of systemic antibiotic use. In one of his many studies on chronic osteomyelitis, Dr. Klemm reported a 90% success rate in a series of 405 patients using his beads technique.[12]

The use of PMMA impregnated with gentamicin was rapidly expanded beyond acute and chronic osteomyelitis. In 1983, Barton et al described the use of gentamicin-PMMA beads as soft-tissue infection prophylaxis in head and neck surgery followed by Aubry et al who published a similar study in 1986 for abdominal surgery.[13,14] Over time, the benefit of such methods over systemic administration of broad-spectrum antibiotics became more apparent.

Even with the advent of beads strung on surgical wire, PMMA still poses a number of challenges to the reconstructive surgeon, as it is a permanent material that often eventually necessitates removal.[15] In Europe and Canada, the use of biodegradable alternatives for local antibiotic delivery has been under investigation and in use since the early 90s. In 1997, Drs. Jason Calhoun and Jon Mader published a rabbit trial of biodegradable antibiotic implants made from polylactic acid combined with poly(DL-lactide) and loaded with Vancomycin for staphylococcal osteomyelitis. They found that the implants lasted long enough to deliver therapeutic levels of antibiotic to the infection site and did not require a secondary procedure as they were biodegradable.[16] This was followed by McKee et al in 2002 who published the results of a prospective trial using tobramycin-impregnated calcium sulfate pellets (the same delivery vehicle used in this study) in 25 patients with osteomyelitis. They found that their model was effective in 23 out of 25 patients.[17]

Interest in calcium sulfate and other similar biodegradable substrates finally made its way to America in 2005, when Darryl Thomas published a study of tobramycin-impregnated calcium sulfate for the treatment of osteomyelitis in a sheep model with considerable success.[15] Similar studies and clinical trials followed leading to the more widespread use of calcium sulfate as a bone graft substitute and antibiotic delivery vehicle in the US. Calcium sulfate scaffolds have also been used to treat diabetic foot ulcers and prosthetic vascular graft infections.[18,19]

Reconstructive surgeons treating implant pocket infections following breast reconstruction or augmentation have been faced with many of the same issues seen by those treating osteomyelitis or orthopedic hardware infections. Namely, the implant pocket requires sufficiently high doses of antibiotic in order to clear the infection, and such treatment usually requires long term, high dose medications. Thus, utilizing a local antibiotic delivery system would be an ideal situation. There is a precedent for such a technique: Steven Albright et al illustrated the only attempt at such treatment with the use of antibiotic-impregnated PMMA plates in conjunction with tissue expanders for one-step salvage of the infected implant. Their technique resulted in the successful sterilization of the implant pocket in all 14 of their patients. The PMMA was explanted along with the tissue expander down the road and exchanged for an implant.[20]

This study is the first to describe the use of calcium sulfate beads as a method for immediate salvage of the infected breast implant. As enumerated above, calcium sulfate acts as a far superior vector for antibiotic delivery directly to the site of infection as it is an FDA approved, biodegradable material that delivers therapeutic doses and does not require removal upon completion of treatment. One-step immediate salvage was successful in 9 out of the 12 patients in this study, a success rate of 75%, higher than most other conventional attempts at implant salvage. Additionally, the three that were unsalvageable were all exceptionally complicated situations. One patient traveled outside the country immediately following the surgery and was lost to follow up for some time. The second failure required implant removal due to inadequate soft tissue coverage secondary to radiation treatment and went on to have SGAP flap reconstruction. The third and final failure was due to a highly atypical infection with antibiotic-resistant rhodococcus. All other patients are doing well at an average of 10.6 months follow up.

One limitation of this study is that the STIMULAN beads are loaded with a specific amount of antibiotic that is not altered to meet the needs of various patients. In a similar vein, the antibiotics used were standard for all patients and were not specifically chosen based on the cultures received. Future use of the bead therapy could benefit from tailoring the antibiotic to the patient. A final limitation is the low size of the study population. The study team will continue to use this practice in the Mount Sinai Hospital and update the literature as our sample size increases.

Conclusions

This study lays out the successful usage of vancomycin and tobramycin impregnated STIMULAN calcium sulfate beads for the one-step salvage of the infected breast

implant. While the protocol requires adjustment for different patients, it is an option in the management of these complicated cases. Further trials are required to elucidate exactly how to use these beads in individual patients, but this represents the foundations of a new option for treatment that may result in significantly reduced morbidity and improved results for the patient.

Figure 1 Legend: A: Preoperative photograph prior to mastectomy and implant-based reconstruction of the right breast. **B:** Post-operative day 2–Cellulitis of breast skin and incision site. **C.** Return to OR–Dermal flap creation and placement of beads and new tissue expander. **D.** One year after permanent implant placement.

Table 1 Legend: Patient characteristics and results.

Conflict of Interest, Funding, and Ethical Approval

This study did not require any funding and does not have any source of funding. There are no conflicts of interest that are relevant to this study. Dr. Marco Harmaty has been a paid consultant for Gore Medical in the past. This study was approved by the Institutional Review Board at the Icahn School of Medicine at Mount Sinai.

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Conflicts of Interest: None declared
Ethical Approval: Approved by Mount Sinai IRB

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Patient	Age	Cancer (Y/N)	Radiation (Y/N)	Comorbidities	Time of Infection Post Op	Culture	Salvage (Y/N)	Follow Up Time
1	50	Y	N	Smoker, HIV+	5 Days	Staph Epidermitis	Y	8 Months
2	31	N	N	Smoker	5 Days	Negative	Y	14 Months
3	69	Y	N	CAD, COPD, HTN	12 Days	Negative	Y	8 Months
4	50	Y	N	——	3 Months	Rhodococcus	N	19 Months
5	47	Y	Y	Smoker	3 Weeks	Staph Epidermitis	Y	12 Months
6	32	N	N	——	2 Months	Enterobacter	Y	13 Months
7	65	Y	Y	——	2 Years	Yeast	N	15 Months
8	46	Y	N	Smoker	1 Week	Negative	Y	4 Months
9	49	Y	N	——	2-3 Weeks	Staph Aureus	N	Lost to F/u
10	48	Y	Y	——	1 Month	Negative	Y	18 Months
11	73	Y	Y	HTN	6 Years	Negative	Y	3 Months
12	56	Y	Y	——	8 Years	Negative	Y	3 Months

Table 1: Patient characteristics and results.