The Heart Surgery Forum #2012-1032
15 (5), 2012 [Epub October 2012]
doi: 10.1532/HSF98.20121032

Online address: http://cardenjennings.metapress.com

Impact of Gentamicin-Collagen Sponge (Collatamp) on the Incidence of Sternal Wound Infection in High-Risk Cardiac Surgery Patients: A Propensity Score Analysis

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ABSTRACT

Objective: Local delivery of prophylactic antibiotic to the wound site with an implanted, reabsorbable, gentamicin-containing collagen sponge (Collatamp) is a strategy that has been claimed to prevent sternal wound infection after cardiac surgery. The purpose of this study was to review our experience with Collatamp in cardiac surgery patients deemed at high risk for sternal wound infection.

Methods: From January 2007 to December 2010, Collatamp was used in 107 patients deemed at high risk for sternal wound infection. Applying the propensity score, we matched 97 patients with Collatamp (group I) with 97 patients who did not receive Collatamp (group II). All individuals received routine intravenous antimicrobial prophylaxis. Postoperative wound-infection rates as well as routine outcomes were compared. Information for the study was obtained from the cardiac surgical Patients Analysis and Tracking System (PATS) database and from hospital records.

Results: The superficial sternal wound infection rate was 2.1% (2/97) in group I and 6.2% (6/97) in group II (P = .01). The rates of deep sternal wound infection rate were similar (2.1% versus 3.1%, P = .87). There was no mediastinitis in the study population. In addition, more patients in group II received an intra-aortic balloon pump (5.2% versus 2.1%, P = .04) and underwent hemofiltration (7.2% versus 3.1%, P = .02). No side effects were noted.

Conclusion: Gentamicin-containing collagen sponge (Collatamp) is a useful adjunct to meticulous surgical technique and postoperative wound care in reducing the incidence of sternal wound infection in high-risk cardiac surgery patients. An adequately powered study is needed, however, to validate the safety and efficacy of this strategy.

Presented at the 21st Congress of the World Society of Cardio-Thoracic Surgeons, June 12-15, 2011, Berlin, Germany.

Received March 6, 2012; received in revised form June 24, 2012; accepted June 26, 2012.

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INTRODUCTION

Sternal wound infections are a major cause of morbidity and mortality in patients undergoing cardiac surgery. They occur in 1% to 3% of patients who undergo open heart surgery and carry a mortality rate of 20% to 40% [Beckmann 2011]. Sternal infections can range from minor, superficial infections to open mediastinitis with invasion of the sternum, heart, and great vessels. The risk of a patient developing sternal wound infection is related to comorbidities, type of procedure, and other factors, such as length of surgery and the use of prosthetic implants [Borger 1998; Cayci 2008; Ariyaratnam 2010]. Currently, only a few of these risk factors can be characterized as modifiable [Fynn-Thompson 2004], and the mainstay of preventing sternal wound infection, in addition to strict aseptic surgical technique, is the use of antibiotic prophylaxis administered systemically, both pre- and postoperatively. There is evidence, however, to suggest that prophylaxis with topical antibiotics could have an additive effect on the incidence of sternal wound infections when combined with routine systemic prophylaxis [Vander Salm 1998; Friberg 2005; Lazar 2011].

The emergence of such technologies as resorbable gentamicin-containing collagen sponge (Collatamp®), which delivers high local concentrations of gentamicin with correspondingly low serum levels, offers a means of reducing rates of sternal wound infection following cardiac surgery, lowering the risk of antibiotic resistance by reducing the need for long-term administration of systemic antibiotics, avoiding the toxicity associated with systemic antibiotics, and avoiding the need for reoperation because the implant is fully resorbable. The use of collagen as a carrier also has positive effects on wound healing [de Bruin 2010].

This study reviews our experience of using gentamicin-collagen sponge (Collatamp; EUSA Pharma [Europe], Oxford, UK) in cardiac surgery patients deemed at high risk for sternal wound infection.

METHODS

Study Sample

This study consisted of a retrospective analysis of a prospectively collected cardiac surgery database (Patients

Analysis and Tracking System [PATS]; Dendrite Clinical Systems, Ltd, Oxford, UK). Informed consent was waived for this study. The PATS database captures detailed information on a wide range of preoperative, intraoperative, and hospital postoperative variables (including complications and mortality) for all patients undergoing cardiac surgery in our institution. The database was collected and reported in accordance with the database criteria of the Society for Cardiothoracic Surgery in Great Britain and Ireland. In addition, the medical notes and charts of all the study patients were reviewed. From January 2007 to December 2010, Collatamp was used in 107 patients deemed at high risk for sternal wound infection (Table 1). The use of Collatamp was influenced by the surgeon's preference. During the same period, 743 patients considered at high risk for sternal wound infection underwent cardiac surgery without the use of Collatamp. Applying the propensity score, we matched 97 patients with gentamicin-collagen sponge (group I) with 97 patients who did not receive gentamicin-collagen sponge (group II).

Table 1. Characteristics of 107 Patients Receiving Collatamp Sponge*

Characteristic	Patients, n (%)
Overweight (BMI >30 kg/m^2) diabetics needing BITA	39 (36.4)
Diabetic patients needing BITA	32 (29.9)
Diabetic patients with renal failure needing BITA	11 (10.3)
Patients on long-term steroid therapy	10 (9.3)
Patients requiring reoperative surgery	8 (7.5)
Procedures with a CPB time >2 h	7 (6.6)

*Mean logistic EuroSCORE, 7.3 ± 5.2. BMI indicates body mass index; BITA, bilateral internal thoracic arteries; CPB, cardiopulmonary bypass.

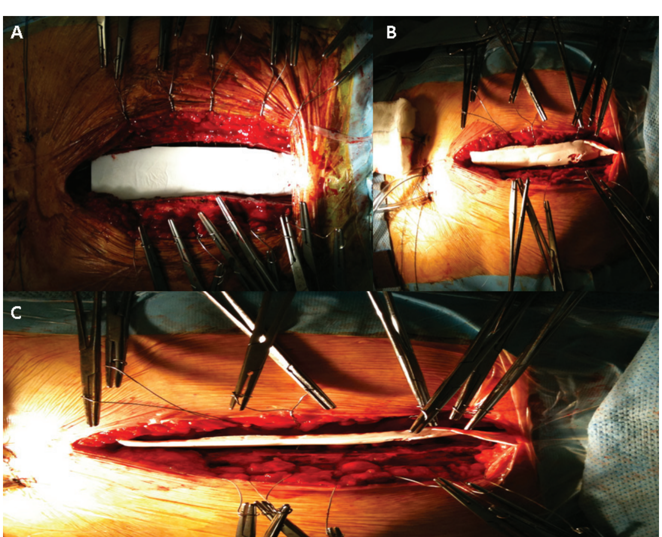

Figure 1. Technique of sponge placement.

Table 2. Perioperative Outcomes of 194 Propensity-Matched Patients*

Outcome	Group I (n = 97)	Group II (n = 97)	*P*
In-hospital mortality, n (%)	2 (2.1)	3 (3.1)	.87
Perioperative MI, n (%)	6 (6.2)	8 (8.2)	.68
Stroke/TIA, n (%)	2 (2.1)	3 (3.1)	.87
Ventilation >24 h, n (%)	10 (10.3)	11 (11.3)	.81
Atrial fibrillation, n (%)	24 (24.7)	27 (27.8)	.73
Superficial sternal infection, n (%)	2 (2.1)	6 (6.2)	.01
Deep sternal infection, n (%)	2 (2.1)	3 (3.1)	.87
Blood product use, n (%)	53 (54.6)	55 (56.7)	.76
Return to OR for bleeding, n (%)	5 (5.2)	6 (6.2)	.79
Inotrope use, n (%)	95 (97.9)	93 (95.9)	.84
Hemofiltration, n (%)	3 (3.1)	7 (7.2)	.02
Postoperative IABP, n (%)	2 (2.1)	5 (5.2)	.04
Chest infection, n (%)	36 (37.1)	40 (41.1)	.61
Median ITU stay, d (IQR)	5 (7–31)	5 (7–42)	.85
Median hospital stay, d (IQR)	12 (9–56)	12 (10–61)	.82

*MI indicates myocardial infarction; TIA, transient ischemic attack; OR, operating room; IABP, intra-aortic balloon pump; ITU, intensive therapy unit; IQR, interquartile range.

Sponge Use Technique

Prior to closure of the sternum and after placement of the sternal wires, a single Collatamp sponge (20×5×0.5 cm; 1 cm^2 containing both 2.8 mg native collagen fibrils of equine origin and 2 mg gentamicin sulfate equivalent to 1.10-1.43 mg gentamicin) was implanted retrosternally without premoistening (Figure 1). Sternal wires were then tightened. The closure technique used was with trans-/peristernal double wires (Figure 1). The wound was then closed in layers by sutures and covered with a sterile dressing. Each patient routinely received guideline-compliant perioperative prophylaxis with intravenous cefuroxime (1.5 g twice daily), starting 30 minutes before the operation and continuing for up to 48 hours postoperatively. The pre-, intra-, and postoperative protocol for preventing wound infections was not changed during the study period.

Variables and Data Collection

Preoperative variables of interest included age, sex, chronic obstructive pulmonary disease, diabetes, hypercholesterolemia, renal insufficiency (preoperative serum creatinine 200 μmol/L), hypertension, peripheral vascular disease, cerebrovascular disease, left ventricular ejection fraction, body mass index >30 kg/m^2, urgency (operation performed <24 hours versus >24 hours from the time of referral), and steroid therapy. Intraoperative variables of interest included the use of bilateral internal thoracic arteries and a cardiopulmonary bypass time >2 hours. Postoperative variables of interest included the following: in-hospital mortality; intraoperative or postoperative use of an intra-aortic balloon pump; postoperative myocardial infarction, stroke, or transient ischemic attack; prolonged ventilation (>24 hours); atrial fibrillation; superficial sternal wound infection; deep sternal infection; blood product use; use of inotropes of patients leaving the operating room; chest infection; length of stay in the intensive therapy unit; and length of hospital stay. Information about sternal wound infection was collected up to 6 weeks after the index surgery.

Statistical Analysis

Patients who received Collatamp (n = 107) were compared with those who did not (n = 743) by means of the Student t and Kruskal-Wallis tests for continuous variables and with the 2 test for categorical variables. A propensity analysis was performed for modeling the probability of receiving Collatamp. In brief, a nonparsimonious multivariate logistic regression model that used clinically relevant variables was generated to compute a propensity score for each patient (Table 2). All clinically relevant variables were included in the model. The propensity score (or the probability of receiving Collatamp) was then used to obtain a one-to-one match of all Collatamp cases with non-Collatamp controls via a "greedy matching" technique [Parsons 2001]. In-hospital outcomes were compared for these matched groups.

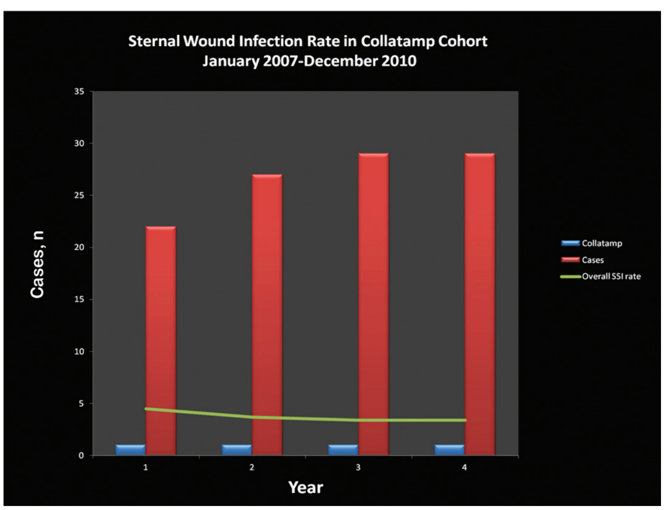

Figure 2. Rate of sternal wound infection in Collatamp cohort. SSI indicates sternal surgical site infection.

RESULTS

Of the 107 patients who received Collatamp, 97 were included in the final analysis. Ten patients were excluded because they either had the Collatamp removed within 24 hours of placement and not replaced (n = 9) or died in the immediate postoperative period (n = 1). Nine patients who had the Collatamp removed underwent revision surgery for bleeding (n = 4), tamponade (n = 4), and regrafting (n = 1). Hospital mortality was 2.1% for the Collatamp group and 3.1% for the control group (P = .87). The propensity score model included 21 patient variables, which are listed in the Appendix along with their confidence intervals. The value of the c statistic for this model was 0.82 (Hosmer-Lemeshow goodness-of-fit, P = .3059). We were able to match 97 Collatamp cases with 97 control patients. The 2 groups were well matched for all the patient variables.

The median length of hospitalization was 12 days in both groups, with an interquartile range of 9 to 56 days for group 1 and 10 to 61 days for group 2 (P = .98). The 2 groups did not differ significantly with respect to major morbidity (Table 2); however, significantly more patients in the control group required hemofiltration (7.2% versus 3.1%, P = .02), received a postoperative intra-aortic balloon pump (5.2% versus 2.1%, P = .04), and had superficial sternal wound infection (6.2% versus 2.1%, P = .01), compared with the matched Collatamp patients. The overall rate of annual sternal wound infection for the Collatamp cohort was well below the annual infection rate for the entire cardiac surgical cohort during the study period (Figure 2).

DISCUSSION

Infective sternal wound complications occur in 1% to 3% of patients undergoing cardiac surgery [Beckmann 2011]. They remain a significant source of mortality, and treatment entails extended hospitalization(s), long-term antibiotic use, multiple operative procedures, and high cost [Douville 2004]. Meticulous attention to sternal closure and prophylactic use of antibiotics are recognized strategies to prevent or minimize sternal wound infections after median sternotomy [Fynn-Thompson 2004]. In recent years, prophylaxis with topical antibiotics in addition to systemic antibiotics has emerged as a safe and effective intervention to reduce the incidence of sternal wound infection [Vander Salm 1998; Eklund 2005; Friberg 2005; Lazar 2011; Schimmer 2012]. Topical application of gentamicin-impregnated collagen sponge (Collatamp) is one such intervention that has proved useful [Eklund 2005; Friberg 2005; Schimmer 2012]. The present study confirms the safety and efficacy of Collatamp in reducing the overall rate of sternal wound infection in high-risk patients and supports the findings of 3 previously published large randomized controlled trials on the subject [Eklund 2005; Friberg 2005; Schimmer 2012].

Unlike the randomized studies [Eklund 2005; Friberg 2005; Bennett-Guerrero 2010; Schimmer 2012], the present study retrospectively compared 2 groups of patients deemed at extremely high risk for sternal wound complications. We have attempted to make meaningful comparisons between the Collatamp group and a contemporaneous group of non-Collatamp control patients. To do this, we have used propensity modeling, a technique that has been strongly advocated in several recent publications [Austin 2007] as a better way to evaluate treatment comparisons from nonrandomized clinical experiences. The propensity score is the probability of a patient receiving a given intervention (in this case Collatamp) in a nonparsimonious model derived from preoperative patient variables. The propensity model thus reduces many variables to a single balancing score, thus facilitating meaningful intergroup comparisons.

Gentamicin-collagen sponge seems to limit the risk of surgical site infection in several ways. Collagen causes faster coagulation to stop bleeding [Stemberger 1997; de Bruin

2010] and reduces the risk of seroma and hematoma formation that can accelerate bacterial proliferation [Bendavid 1997]. The breakdown of the gentamicin-collagen sponge by macrophage collagenases increases the number of collagen fibers released, which attracts fibroblasts and stimulates the fibroblasts to proliferate and lay down new collagen during the healing process [Stemberger 1997].

Immune responses against collagen implants are uncommon [Stemberger 1997; de Bruin 2010], and collagen implants act as effective drug carriers [Kinel 1984]. Drugs are released from the collagen matrix via a combination of diffusion and natural enzymatic breakdown of the collagen matrix, thereby providing rapid (diffusion) and prolonged (breakdown of the matrix) drug release [Kinel 1984; de Bruin 2010].

The antimicrobial profile of gentamicin seems to be appropriate for use with collagen sponge. The use of gentamicin allows sterilization of the sponge by gamma rays and does not seem to affect collagen's clotting features, as discussed above [Chvapil 1977; de Bruin 2010]. The local use of gentamicin delivers a bactericidal concentration that is much higher than that allowed by systemic injection. Consequently, antibiotic blood concentrations remain low, reducing the chance of adverse effects (eg, nephrotoxicity), whereas local drug concentrations are kept high for at least 48 hours [Moore 1987; de Bruin 2010]. In this way, resistance to antibiotics caused by low drug dosage is avoided [Blaser 1987], and gentamicin behaves like a broad-spectrum antibiotic [Blaser 1987; Moore 1987].

In this study, we used a single (20×5×0.5 cm) sponge and placed it between the 2 halves of the sternum after placing the sternal wires. Thus, part of the sponge projects both above and below the sternum in addition to being compressed between the 2 halves of the sternum upon tightening of the sternal wires. Placement of the sponge in this manner may have produced equally higher retrosternal and presternal gentamicin levels, leading to low rates of both superficial and deep sternal wound infections in the treatment group.

To date, only the trial from the United States [Bennett-Guerrero 2010] has shown gentamicin-collagen sponge to be ineffective in preventing sternal wound infections in the context of cardiac surgery. In addition to the several limitations of that trial, however, it is important to highlight that the investigators of the trial were instructed to dip the sponge in normal saline solution for 1 to 2 seconds prior to implantation. That practice is not in line with instructions given in the European national product information (which generally state that the product should be used dry) and may have led to degradation of the product's gentamicin-release characteristics, given that gentamicin sulfate is highly soluble in aqueous solutions [Corn 2010]. Such degradation may explain in part the results of that study, which are, as the authors stated, contrary to expectations based on a number of European studies with positive results [Eklund 2005; Friberg 2005; Schimmer 2012].

The primary limitation of the study is its retrospective nature. Propensity score adjustment is no substitute for a properly designed randomized controlled trial. The retrospective nature of the study cannot account for the unknown variables affecting the outcome that are not correlated strongly with measured variables. Retrospective comparisons with propensity score adjustment are more versatile, however, and offer a useful way of interpreting large amounts of audit data and of seeking answers to questions that may present insuperable difficulties in the design of randomized controlled trials. The small sample size compared with the sample sizes of previously published studies is another obvious limitation.

CONCLUSION

Gentamicin-containing collagen sponge (Collatamp) is a useful adjunct to meticulous surgical technique and postoperative wound care in reducing the incidence of sternal wound infection in high-risk cardiac surgery patients. An adequately powered study is needed, however, to validate the safety and efficacy of this strategy.

APPENDIX

Logistic Regression Model to Generate Propensity Scores for Treatment Group (n = 107) versus Control Group (n = 743)*

Effect	Point Estimate	95% Wald Confidence Limits: Lower	Upper	*P*
Age				
<60 y	0.791	0.689	1.123	.23
60–74 y	0.774	0.675	1.035	.19
>75 y	0.789	0.596	1.119	.21
Sex	0.745	0.598	1.054	.20
Diabetes	0.786	0.611	1.087	.17
Hypertension	1.114	0.976	1.657	.49
Hypercholesterolemia	1.546	1.231	2.105	.56
PVD	0.799	0.658	1.114	.23
Previous stroke/TIA	1.113	0.832	1.987	.64
COPD	0.986	0.732	1.347	.41
Ceratinine 200 μmol/L	0.943	0.755	1.121	.24
Previous surgery	1.746	1.431	2.321	.59
BMI > 30 kg/m^2	0.884	0.601	1.287	.22
Steroid therapy	0.788	0.621	1.123	.26
LVEF < 30%	1.446	1.331	1.921	.43
Surgery necessity				
Elective	0.724	0.665	1.033	.21
Urgent	0.674	0.475	1.011	.22
Emergency	1.614	1.896	2.157	.47
BITA use	0.988	0.738	1.312	.42
CPB time > 2h	0.967	0.654	1.110	.46
Logistic EuroSCORE	0.946	0.731	1.129	.28

*PVD indicates peripheral vascular disease; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; BMI, body mass index; LVEF, left ventricular ejection fraction; BITA, bilateral internal thoracic arteries; CPB, cardiopulmonary bypass.

ACKNOWLEDGMENTS

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written. We thank Dimple Chudasama, audit and clinical-effectiveness analyst, and Siobhan Daley, clinical-outcomes officer, for assistance with data collection.

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