Gentamicin collagen sponges for the prevention of sternal wound infection: A meta-analysis of randomized controlled trials

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Objective: The study objective was to determine whether the application of gentamicin collagen sponges reduces sternal wound infections in patients undergoing cardiac surgery.

Methods: A meta-analysis of randomized controlled trials was performed.

Results: Four randomized controlled trials were eligible for inclusion. By pooling data from 4 randomized controlled trials (4672 per-protocol patients), gentamicin collagen sponges reduced deep sternal wound infections (risk ratio, 0.62; 95% confidence interval, 0.39-0.97) and any sternal wound infections (risk ratio, 0.61; confidence interval, 0.39-0.98). In contrast, no benefit was demonstrated regarding superficial sternal wound infections (4 randomized controlled trials [4672 patients]; risk ratio, 0.65; 95% confidence interval, 0.34-1.25) and all-cause mortality (3 randomized controlled trials [3994 patients]; risk ratio, 0.90; 95% confidence interval, 0.57-1.42). On the basis of data from 2 randomized controlled trials (3410 patients), gentamicin collagen sponges also seemed to reduce surgically treated sternal wound infections (risk ratio, 0.59; 95% confidence interval, 0.41-0.86). The most commonly isolated pathogens were coagulase-negative *Staphylococcus* spp (43%) and *Staphylococcus aureus* (28%).

Conclusions: Gentamicin collagen sponges seem to reduce the sternal wound infection rate in patients undergoing cardiac surgery. The statistical heterogeneity among the existing trials underlines the need for additional large, high-quality randomized controlled trials. (J Thorac Cardiovasc Surg 2012;144:1235-40)

Sternal wound infections (SWIs) after open cardiac surgery are relatively common and potentially grave complications, with significant associated costs.¹⁻³ Risk factors include diabetes, obesity, smoking, hemodynamic instability, transfusions, reoperation, prolonged operative time, prolonged ventilation, type of operation, and others.^{2,4-6} Although antimicrobial prophylaxis is routinely administered, SWIs remain a major threat, leading surgeons to seek additional preventive measures. Gentamicin collagen sponges (GCSs) were developed to provide high local antibiotic concentrations in the wound, with low serum values, thus preventing systemic adverse events (mainly nephrotoxicity). GCSs have been widely used for the prevention and treatment of surgical site infections since 1985; however, no consensus regarding their use in patients undergoing cardiac surgery has been reached.

The first 2 randomized controlled trials (RCTs) evaluating the effectiveness of GCSs in patients undergoing cardiac surgery were published in 2005. The study by Friberg and colleagues⁷ (2000 patients, Sweden) reported significantly lower SWI rates in the arm receiving GCSs, whereas the study by Eklund and colleagues⁸ (542 patients, Finland) failed to do so; this was attributed to inadequate sample size. In 2010, a multicenter RCT from 48 US centers (1502 patients) reported no difference in SWI rates between the 2 patient arms⁹; this finding became the subject of heated debate.¹⁰⁻¹² An additional RCT from Germany (800 patients) recently was performed (the first one to use placebo collagen sponges in the control arm), again claiming that GCSs significantly reduced SWI.¹³ The contradictory findings of the existing trials preclude safe conclusions regarding the effectiveness of GCSs in patients undergoing cardiac surgery. In this context, we sought to systematically review the available published evidence and synthesize the relevant data using the methodology of meta-analysis.

MATERIALS AND METHODS

Literature Search

A systematic search of the literature was performed on PubMed, Scopus, and clinicaltrials.gov databases in September 2011. The applied search pattern was (gentamicin OR aminoglycoside) and (carrier OR material OR sponge OR implant or collagen) and (cardiac OR sternal). The references of the relevant articles, including review studies, were also hand-searched in an attempt to identify additional potentially eligible trials. No limitation on the year of publication was set.

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Abbreviations and Acronyms

CDC = Centers for Disease Control
 CI = confidence interval
 GCS = gentamicin collagen sponge
 RCT = randomized controlled trial
 RR = risk ratio
 SWI = sternal wound infection

Study Selection

Literature search and study selection were independently performed by 2 investigators (M.N.M., P.K.M.). To be eligible, a study should be an RCT, evaluate GCS use in patients undergoing cardiac surgery, and assess the effectiveness of GCS. Both blinded and open-label trials were considered eligible. There were no language restrictions. Unpublished studies reported as abstracts in conferences were searched but not included in this review.¹⁴

Data Extraction

Data extraction was independently performed by 2 investigators (M.N.M., P.K.M.); any disagreement was resolved by consensus in meetings with all investigators. Data were extracted regarding the study design (methodology, exclusion criteria, follow-up), patient population and characteristics, preoperative and perioperative variables (antibiotic prophylaxis, operation performed), and reported outcomes of each trial (any SWI, deep SWI, superficial SWI, surgically treated SWI, mortality). A quality assessment of the reviewed trials was also performed using the modified Jadad criteria; studies with a score of 3 or more were considered of high quality.¹⁵

Analyzed Outcomes: Definitions

The primary outcomes for this review were deep SWI and any SWI (defined as the total of deep and superficial SWI). Superficial SWI, surgically treated SWI, and mortality comprised secondary outcomes. All analyses

were performed on the per-protocol populations (patients who met all inclusion and exclusion criteria, received the intervention, and had complete follow-up data).

SWI was defined according to the Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network criteria¹⁶; briefly, it refers to a sternal infection occurring within 1 month and related to the operation, which may involve only the skin and subcutaneous tissue of the incision (superficial SWI) or extend to the fascia and muscle layers (deep SWI). Infections involving organ space (ie, mediastinitis) were considered deep SWI.

Statistical Methods

The statistical analyses were performed with Review Manager (RevMan), version 5.1 (Copenhagen: the Nordic Cochrane Centre, the Cochrane Collaboration, 2011). Statistical heterogeneity between studies was assessed by using a chi-square test and I^2 ; a P value less than .10 for the chi-square test or I^2 greater than 50% indicated significant heterogeneity. Publication bias was not assessed because of the small number of included trials.¹⁷ Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous variables (ie, SWI) using the DerSimonian-Laird random effects model.¹⁸ Statistical significance was set at $P < .05$.

RESULTS

The search process generated 188 studies, of which 17 were considered potentially eligible. After detailed evaluation, 4 RCTs (enrolling 4844 patients undergoing cardiac surgery) were included in the meta-analysis (Figure 1). The methodology and patient characteristics of the reviewed trials are shown in Table 1.

Trial Design and Quality Assessment

Two trials were single-center (in Finland and Germany),^{8,13} 1 trial was 2-center (in Sweden),⁷ and 1 trial was multicenter (48 centers in the United States).⁹ Two trials had a double-blind design,^{7,13} and 2 trials had

FIGURE 1. Flow diagram of reviewed studies. No additional articles were identified through hand searching. RCT, Randomized controlled trial.

TABLE 1. Methodology and patient characteristics of the reviewed trials

Trial	Trial quality*	Trial population†	Intervention (per-protocol population)‡	Antibiotic prophylaxis	Trial exclusion criteria‡	Within-trial differences among compared arms
Friberg and colleagues ⁷ Sweden	DC DB RCT [4]	2000 patients Elective and emergency cardiac and ascending aorta surgery FU: 2 mo	2× GCS (not premoistened) containing 260 mg gentamicin vs no sponge [983 vs 987]	Oxacillin Cloxacillin Mouthwash (in 1 center) No nasal antibiotics	Aminoglycosides within 2 wk	Intervention: more likely to have received aspirin preoperatively and to undergo CABG Control: more likely to have received oral steroids preoperatively
Eklund and colleagues ⁸ Finland	SC RCT [3] Surgeon-blinded	542 patients Elective CABG FU: 3 mo	GCS (premoistening NR) containing 130 mg gentamicin vs no sponge [269 vs 269]	Cefuroxime (85%) Cefuroxime + vancomycin (15%)	Severe renal insufficiency (uremia or need for dialysis) or previous kidney transplant/redone procedure	The compared arms were balanced.
Bennett-Guerrero and colleagues ⁹ USA	MC RCT [3] Patient-blinded	1502 patients Elective CABG and valvuloplasty FU: 3 mo	2× GCS (premoistened) containing 260 mg gentamicin vs no sponge [727 vs 733]	Cefazolin (53%) Cefuroxime (24%) Vancomycin (30%) Ciprofloxacin (2%) Nasal mupirocin (48%) Chlorhexidine shower (89%) Mouthwash (30%)	Only adult patients at high risk for infection (obese or diabetic) were enrolled. Concomitant surgery/preoperative cardiac mechanical assistance device/systemic infection/aminoglycosides within 2 wk/renal insufficiency (serum creatinine > 3 mg/dL or need for dialysis)/major organ transplantation, malignancy, or immuno-suppression/significant drug or alcohol abuse/life expectancy < 3 mo	The compared arms were balanced.
Schimmer and colleagues ¹³ Germany	SC DB RCT [4]	800 patients Elective and emergency CABG and valvuloplasty FU: 1 mo	GCS (not premoistened) containing 130 mg gentamicin vs placebo sponge [353 vs 367]	Cefuroxime	Preexisting osteitis/immunosuppression	Control: more likely to be female, to have LVEF < 30% and higher preoperative serum creatinine, and to undergo a reoperation

DC, Dual-center; DB, double-blind; RCT, randomized controlled trial; FU, follow-up; GCS, gentamicin collagen sponge; CABG, coronary artery bypass grafting; SC, single-center; NR, not reported; MC, multicenter LVEF, left ventricular ejection fraction. *Trial quality assessment was performed following the modified Jadad criteria for RCTs. The score is reported in brackets.¹⁵ †Trial population refers to the number of patients enrolled in each trial. The compared per-protocol patient arms are reported in brackets in the "Intervention" column. ‡Exclusion criteria not reported in the table but pertaining to all reviewed trials comprised hypersensitivity to gentamicin, inability to communicate or obtain informed consent, or participation in another ongoing trial and pregnancy/lactation (apart from the trial of Eklund and colleagues⁸).

a single-blind design (1 was surgeon-blind⁸ and 1 was patient-blind⁹). Proper allocation concealment through a placebo collagen sponge was performed in only 1 trial¹³; all other trials used no sponge in the control arm. All RCTs were considered of high quality (range, 3-4, according to the Jadad criteria). All 4 trials reported sponsoring by the GCS manufacturers.

Two trials enrolled patients undergoing CABG or valvuloplasty,^{9,13} 1 trial enrolled only patients undergoing CABG,⁸ and 1 trial enrolled patients undergoing a variety of cardiac or ascending aorta operations⁷; 2 trials included both elective and emergency operations,^{7,13}

whereas the remaining 2 excluded patients undergoing emergency operations.^{8,9} The mean follow-up of the trials was 2.25 months (range, 1-3 months). Two trials used GCSs containing 130 mg of gentamicin in the intervention arm,^{8,13} whereas the other 2 trials used 2 sponges in each patient (260 mg gentamicin).^{7,9} The GCS was reported to be premoistened in normal saline in 1 trial.⁹ In all trials, intravenous prophylactic antibiotics were administered preoperatively (<60 minutes from surgery) and discontinued within 48 hours; diagnosis of SWI was established using the CDC criteria in all trials.

FIGURE 2. Forest plots depicting the RRs of SWI for GCS versus control (vertical line = “no difference” point between the 2 regimens; squares = risk ratios; diamonds = pooled RRs for all RCTs; horizontal lines = 95% CI). GCS, Gentamicin collagen sponge; M-H, Mantel-Heinzel; CI, confidence interval; SWI, sternal wound infection; df , degrees of freedom.

Primary and Secondary Outcomes

All trials reported on the deep SWI rate. By pooling data from the 4 trials (4672 patients), GCS use seemed to significantly reduce deep SWI rate (RR, 0.62; 95% CI, 0.39-0.97; $P = .04$) (Figure 2). The same pattern was evident when any SWI was considered; by pooling data from the 4 trials (4672 patients), the RR was 0.61 (95% CI, 0.39-0.98; $P = .04$) (Figure 2).

With regard to superficial SWI rate, GCS use demonstrated no benefit (4 trials, 4672 patients; RR, 0.65; 95% CI, 0.34-1.25; $P = .20$) (Figure 2). Although only 2 trials (3410 patients) provided data on surgically treated SWI, GCS use seemed beneficial (RR, 0.59; 95% CI, 0.41-0.86; $P = .005$). In regard to all-cause mortality, when data from 3 trials (3994 patients) were pooled, no difference was demonstrated between the 2 arms (RR, 0.90; 95% CI, 0.57-1.42; $P = .66$).

The extracted data on the primary and secondary outcomes of the reviewed trials are presented in Table 2. The most commonly isolated pathogens among patients with a SWI were gram-positive cocci; specifically, coagulase-negative *Staphylococcus* spp and *Staphylococcus aureus* grew in 43% (83/193) and 28% (54/193) of all positive

cultures, respectively. Gram-negative bacteria were responsible for 23% (44/193) of positive cultures (Table 2).

DISCUSSION

The main finding of this meta-analysis, pooling data provided by 4 published RCTs with a total of 4672 per-protocol patients, is that the incidence of deep SWI after cardiac surgery among patients treated with implantable GCSs was significantly lower compared with controls. Specifically, the probability for deep SWI to occur in the control arm was 1.6 times higher than the corresponding probability in the GCS arm. It should be noted that this difference was significant at a level of 4% using a random effects model. No difference was noted for superficial wound infections, but the overall wound infection rate was significantly lower in the GCS arm. Our findings suggest that the application of GCSs perioperatively may be beneficial in preventing postoperative SWIs in patients undergoing cardiac surgery.

We used the random effects model in all analyses because of the observed statistical heterogeneity. SWI rates in the control arms of all trials were comparable (deep SWI, 2.5%-3.5%; any SWI, 5.9%-9%; superficial SWI, 3%-6.1%). At large, the observed statistical heterogeneity

TABLE 2. Reported outcomes in the reviewed trials (gentamicin collagen sponge vs control, as assessed in the per-protocol population)

Trial	Any SWI	Deep SWI	Superficial SWI	SWI treated surgically	Mortality (end of follow-up)	Isolated pathogens (no., %)
Friberg and colleagues ⁷ Sweden	4.3% vs 9% (<i>P</i> < .001)	2.3% vs 3.3% (<i>P</i> = .2)	1.9% vs 5.7% (<i>P</i> < .001)	2.1% vs 3.9% (<i>P</i> = .02)	1.9% vs 1.8% (<i>P</i> = .8)	CoNS 44/102 (43%), <i>S aureus</i> 28 (27%), gram-negative 5 (5%), other (or multimicrobial) 25 (25%)
Eklund and colleagues ⁸ Finland	4% vs 5.9% (<i>P</i> = .2)	1.9%* vs 3.3%* (<i>P</i> = .4)	2.2% vs 3% (<i>P</i> = .6)	NR	1.1% vs 0.4% (<i>P</i> = .6)	CoNS 13/17 (76%), <i>S aureus</i> 3 (18%), <i>E faecalis</i> 2 (12%).
Bennett-Guerrero and colleagues ⁹ USA	8.4% vs 8.6% (<i>P</i> = .9)	1.8% vs 2.5% (<i>P</i> = .4)	6.6% vs 6.1% (<i>P</i> = .7)	3.2% vs 4.9% (<i>P</i> = .09)	2.6% vs 3.6% (<i>P</i> = .2)	CoNS 13/59 (22%), <i>S aureus</i> 22 (37%, including 6 MRSA isolates (10%), <i>E faecalis</i> 2 (3%), gram-negative 37 (63%), other 8 (14%)
Schimmer and colleagues ¹³ Germany	2.5% vs 6.5% (<i>P</i> = .1)	0.6% vs 3.5% (<i>P</i> = .01)	2% vs 3% (<i>P</i> = .5)	NR	2.5%	CoNS 13/15 (87%), <i>S aureus</i> 1 (7%), <i>P acnes</i> 2 (13%), gram-negative 2 (13%)†

SWI, Sternal wound infection; CoNS, coagulase-negative Staphylococcus spp; NR, not reported; MRSA, methicillin-resistant Staphylococcus aureus. *Patients in whom mediastinitis or osteitis developed were in the deep SWI group. †Refers to the patients in whom deep SWI developed.

is mostly attributed to the unexpectedly high rate of superficial SWI in the GCS arm of the US trial (6.6%), raising an issue of superficial SWI misdiagnosis.⁹ However, trial investigators reported an apparently proper infection diagnosis protocol, using 3 blinded infectious disease specialists in a clinical event committee and standardized criteria, including those from the CDC¹⁶ and the ASEPSIS scoring system (a scoring system based on need for Additional treatment, the presence of Serious discharge, Erythema, Purulent exudate, and Separation of the deep tissues, the Isolation of bacteria, and the duration of inpatient Stay).¹⁹

Some have argued that the US trial's negative results may be associated with the practice of premoistening the GCS by dipping it in normal saline before implantation¹¹; none of the other trials have reported such practice. However, this explanation seems unlikely taking into account that the patients' serum gentamicin levels in the US trial were similar to those in the Swedish trial. Patients enrolled in the US trial were all considered at risk for SWI (obese, diabetic patients), in contrast with the other 3 trials; this is also unlikely to have contributed to the nonappearance of benefit in the GCS arm, especially because relevant data from the Swedish trial underline the benefit of GCSs in this group of patients.⁷

It has also been highlighted that gram-negative pathogens were implicated in a significant proportion of SWI in the US trial (63% vs 0%-13% in the other trials). By taking into account that skin flora mostly consist of gram-positive cocci, especially of the *Staphylococcus* spp, this may raise concerns that patients' SWI was not acquired perioperatively, but postoperatively.¹² In addition, the unique pharmacokinetic/pharmacodynamic properties of aminoglycosides may account for a difference in the efficacy of gentamicin against gram-positive versus gram-negative

pathogens²⁰ in the setting of local administration via a collagen sponge. In general, gentamicin is active against various gram-positive and gram-negative bacteria, such as *Staphylococcus* spp (including methicillin-resistant *S aureus*), *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp, *Pseudomonas aeruginosa*, and *Acinetobacter* spp; however, resistant strains have developed and disseminated.^{20,21}

A common finding among all reviewed trials was the relatively high incidence of postoperative SWI (2.5%-9%). Although numerous modalities (preoperative topical antiseptics, eradication of *S aureus* carriage, intravenous prophylaxis, topical application of antibiotics, and others) have been tried, the SWI rate has not decreased significantly.² In regard to antibiotic prophylaxis, there are reports underlining that surgeons' self-reported practice does not conform to the existing guidelines: In an international survey, 26% of cardiac surgeons did not administer the prophylaxis within 60 minutes of the incision, and 14% continued the administration even after postoperative day 4.²² In addition, it has been claimed that the standard antimicrobials used may need to be reconsidered in this era of advancing antimicrobial resistance.^{21,23} Furthermore, differences in the antimicrobial formulations used (ie, generic vs original cefuroxime) may have an impact on the development of SWI.²⁴ Other strategies that may aid in reducing SWI rates include strict glucose management, nasopharyngeal decontamination with mupirocin, skin decontamination with chlorhexidine showers, and topical application of antibiotics (ie, bacitracin or vancomycin) postoperatively.^{25,26}

Study Limitations

The results of this study should be considered in view of several limitations. First, only 4 trials were identified and

pooled; however, all trials had a large sample size, resulting in a pooled sample size of 4672 per-protocol patients, and were of high quality. Second, there was considerable statistical heterogeneity among the trials (2 reported a significant benefit with GCS use, and 2 reported no difference) and, to a lesser degree, clinical heterogeneity: Two trials used 1 sponge (Table 1, 130 mg gentamicin), and 2 trials used 2 sponges (260 mg gentamicin); it should be noted that only 1 study using 130 mg and 1 study using 260 mg of gentamicin have managed to demonstrate a significant reduction of SWI. This is a relatively new intervention, and dosing and application technique need to be standardized. Last, patients enrolled in each trial received different antibiotic prophylaxis regimens (Table 1).

CONCLUSIONS

Despite the limitations of this meta-analysis, it provides evidence to support the use of GCSs for the prevention of postoperative SWIs in patients undergoing cardiac surgery. Synthesis of the available evidence, provided by 4 published RCTs with a total of 4672 patients who had rather conflicting results, showed that the incidence of postoperative deep SWI among patients undergoing cardiac surgery treated with GCSs was significantly lower compared with controls. However, additional large, high-quality RCTs are warranted to further elucidate this field.

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