Prevention of surgical site sternal infections in cardiac surgery: a two-centre prospective randomized controlled study

Christoph Schimmer1*, Justus Gross2, Elena Ramm1, Björn-Carsten Morfeld1, Grischa Hoffmann1, Bernd Panholzer1, Jürgen Hedderich1, Rainer Leyh1, Jochen Cremer1 and Rainer Petzina1

1 Department of Cardiovascular Surgery, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany
2 Institute of Medical Informatics and Statistics, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany

* Corresponding author. Department of Cardiovascular Surgery, University Hospital Schleswig-Holstein, Campus Kiel, Arnold-Heller Strasse 3, 24105 Kiel, Germany. Tel: +49-431-5977319; fax: +49-431-5972836; e-mail: rainer.petzina@uksh.de (R. Petzina).

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Abstract

OBJECTIVES: Surgical site infection (SSI) of the sternum is a devastating complication in cardiac surgery. The aim of this prospective randomized controlled two-centre clinical study was to compare the use of a gentamicin-collagen sponge (Genta-Coll® resorb) and of a cyanoacrylate-based microbial skin sealant (InteguSeal®) on the SSI rate of the sternum.

METHODS: We analysed data from 996 consecutive patients following isolated coronary artery bypass grafting between 2012 and 2014. The patients were randomized into three groups: standard group (S-group), Genta-Coll group (G-group) and InteguSeal group (I-group). The primary study end-point was to analyse the incidence of superficial and deep sternal SSI. The secondary study end-point was to determine independent risk factors for an increased SSI rate.

RESULTS: Of the 996 patients investigated, 332 patients were in S-group, 336 patients in G-group and 328 patients in I-group. The mean age was 67.7 ± 9.4 years, 18.6% were women and the overall SSI rate was 6.2% with 2.2% deep sternal wound infections. SSI rates were 8.3% (S-group), 5.4% (G-group) and 4.9% (I-group) (P 0.16). Multiple regression analysis demonstrated a preoperative body mass index (BMI) of >30 kg/m² (P 0.047), re-thoracotomy for postoperative bleeding (P < 0.001) and sternum instability (P < 0.001) as independent predictors for an increased SSI rate.

CONCLUSIONS: The application of InteguSeal® or Genta-Coll® resorb had no significant influence on the incidence of the sternal SSI rate in 996 consecutive cardiac surgery patients but demonstrated a trend towards a benefit from using these prophylactic approaches. Multiple regression analysis demonstrated a preoperative BMI of >30 kg/m², re-thoracotomy for bleeding and sternum instability as independent predictors for an increased sternal SSI rate.

Keywords: Cardiac surgery • Surgical site infection • CABG • Mediastinitis

INTRODUCTION

Surgical site infection (SSI) of the sternum is a devastating complication in cardiac surgery after median sternotomy. The incidence of postoperative superficial and deep SSI in cardiac surgery varies from 1.3 to 12.8% [1].

Deep sternal wound infection, also called mediastinitis, is a rare but life-threatening complication after cardiac surgery. Together with postcardiotomy heart failure and stroke, poststernotomy mediastinitis is regarded as one of the three most serious complications following open-heart surgery with median sternotomy. The reported incidence of postoperative mediastinitis varies between 1 and 5% [2–4]. This relatively low incidence is based on modern hygienic standards, the use of perioperative prophylactic antibiotics and improvements in cardiac surgery, cardiac anesthesia and intensive care medicine. The mortality rate of cardiac surgery patients with mediastinitis is >30% higher compared with that of patients without deep sternal wound infection [2, 3, 5]. Furthermore, postoperative mediastinitis is associated with high morbidity, decreased long-term survival, prolonged length of hospital stay and increased costs of health care [6–9]. According to the Centers for Disease Control, SSIs are grouped into superficial and deep SSI [10]. Superficial sternal SSI is limited to the skin and subcutaneous tissue, whereas deep sternal SSI involves muscle, fascia, sternum and organ/spaces.

Coronary artery bypass grafting (CABG) is the most common operative procedure in cardiac surgery. In recent years, complete arterial revascularization using the bilateral internal mammary artery (BIMA) demonstrated improved long-term benefit concerning myocardial revascularization, particularly in patients suffering...
from diabetes mellitus [11, 12]. Otherwise, harvesting the BIMA reduces postoperative sternal perfusion and represents an important risk factor for poststernotomy mediastinitis [13,14].

Different novel approaches are examined to prevent sternal wound infections in cardiac surgery. Local antibiotic eluting products such as a resorbable gentamicin-collagen sponge (Genta-Coll® resorb; Resorba Medical GmbH, Nürnberg, Germany) deliver a high local concentration of gentamicin to limit peri- and postoperative bacterial growth. The Genta-Coll® sponge is placed between and under both sternal halves during osteosynthesis of the sternum at the end of the operation and may reduce the sternal SSI rate [15, 16]. Another prophylactic approach for the reduction of sternal SSI rate is application of a cyanoacrylate-based microbial skin sealant (InteguSeal®, Kimberly-Clark, Roswell, GA, USA) after routine skin disinfection before skin incision in the operating room (OR). This sealant leads to a breathable barrier that prevents migration of skin flora into the incision. The film-forming sealant polymerizes and creates a thin protection film to immobilize remaining skin-borne bacteria [17, 18].

The aim of this clinical study was to analyse the effects of the application of Genta-Coll® or InteguSeal® on the SSI rate of the sternum in patients undergoing CABG and to determine independent risk factors for an increased SSI rate.

MATERIALS AND METHODS

Study design

This study is a prospective randomized controlled two-centre clinical trial of 996 patients following CABG via median sternotomy at the University Hospital Schleswig-Holstein, Campus Kiel, Germany, and the University Hospital Würzburg, Germany, between April 2012 and May 2014. All CABG procedures were performed according to the 2014 ESC/EACTS guidelines on myocardial revascularization [19]. Major inclusion criteria for this study were (i) age ≥18 years, (ii) indication for isolated elective/urgent CABG and (iii) informed consent. Exclusion criteria for this study were, for example, (i) allergy, incompatibility or hypersensitivity to gentamicin, (ii) patients with associated cardiac surgery procedures (e.g. aortic valve replacement) and (iii) emergency cases. The study was approved by the local ethics committees (A 172/11) and was carried out in accordance with the Declaration of Helsinki.

All of the 996 patients were analysed concerning preoperative data [age, sex, body mass index (BMI), left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional classification, renal insufficiency, chronic obstructive pulmonary disease (COPD), diabetes mellitus, peripheral artery occlusive disease (PAOD)], intraoperative data [use of left internal mammary artery (LIMA), right internal mammary artery (RIMA) or BIMA, operation time, time on cardiopulmonary bypass, aortic cross-clamp time, amount of sternal wires], perioperative data (ventilation time, secondary bleeding, re-thoracotomy rate, transfusion of erythrocyte concentrates) and postoperative data (sternum stability, superficial and deep SSI of the sternum). The incidence of superficial and deep sternal wound infections was evaluated during hospital stay and after 3 months postoperatively.

Preoperative preparation of the patients

There was no routine check for Staphylococcus aureus colonization performed on admission to the hospital. We performed a risk-adjusted methicillin-resistant staphylococcus aureus screening for methicillin-resistant Staphylococcus aureus. The preoperative preparation for elective or urgent patients scheduled for CABG followed a standardized protocol. The day before cardiac surgery, hair removal was performed with a clipper. Skin washing was performed the day before surgery with antimicrobial wash lotion (Octениs®). Nasal gel was used for moistening, cleansing and decontaminating by physical cleaning of the nasal vestibule the evening before surgery and the morning of surgery. All patients received perioperative antibiotic prophylaxis with a second-generation cephalosporin (cefoxime). The first dose was given in the OR 30–60 min before skin incision and then continued for 24–48 h. The skin was washed routinely by the resident (sometimes by the consultant) with Octenol® solution with a significant remnant activity within 24 h after surgical hand washing. An additional adhesive plastic barrier on top of the skin was not used.

Infection prophylaxis

The patients were prospectively randomized into one of the three groups: standard group (S-group), Genta-Coll group (G-group) or InteguSeal group (I-group).

Standard group. CABG was performed in a standardized manner without using additional infection prophylaxis devices.

Genta-Coll group. The Genta-Coll® resorb sponge (5 × 20 cm) was inserted between and under the sternal halves during sternum osteosynthesis at the end of the operation (Fig. 1).

InteguSeal group. InteguSeal® was applied to the planned skin incision sternal area after standard skin disinfection at the beginning of the operation (Fig. 2).

Cardiac surgery

All patients underwent isolated elective or urgent CABG. The majority of patients were operated on with the use of cardiopulmonary bypass (CPB), whereas a minority of patients received off-pump coronary artery bypass grafting without CPB. Harvesting of the internal mammary artery (IMA) was performed with the skeletonized and the pedicled technique. Bone wax was not used routinely. Sternotomy and chest closure were performed by the resident, only sometimes by the consultant. After harvesting of the grafts (radial artery, saphenous vein), gloves were changed routinely in both institutions. To ensure appropriate intraoperative glucose management, blood glucose levels were monitored frequently and insulin was administered if necessary to achieve blood glucose levels <200 mg/dl. Postoperatively, we monitored blood glucose levels every hour in the first 24 h on the intensive care unit and did not allow a blood glucose level over 200 mg/dl.

Study end-point

The primary study end-point was to analyse the incidence of superficial and deep SSI in patients following isolated CABG with median sternotomy in the three different groups (S-group, G-group and I-group) during hospital stay and after 3 months postoperatively. The secondary study end-point was to determine independent risk factors for an increased SSI rate of the sternum.
### Statistical analysis

All statistical analyses were carried out by the Institute of Medical Informatics and Statistics, University Hospital Schleswig-Holstein, Campus Kiel, Germany. The analysis is based on the hypothesis of a reduction of the sternal SSI rate from 6 to 2% when using Genta-Coll® resorb sponge or InteguSeal® with a statistical power of 80%. The required sample size was calculated to be at least 296 patients in each group. Prospective randomization of the patients was carried out using block randomization. Continuous variables were expressed as mean ± standard deviation. Categorical variables were summarized as absolute number (percentage). Statistical analysis was performed using the Mann–Whitney test when comparing two groups and the Kruskal–Wallis test when comparing three or more groups. The $\chi^2$ test was used for the comparison of categorical variables. The type of distribution was verified using the Kolmogorov–Smirnov test. A multiple linear regression analysis was performed to identify independent variables for an increased SSI rate of the sternum. $P > 0.05$ was defined as not significant.

### RESULTS

Between April 2012 and May 2014, we included 996 patients in this prospective randomized controlled two-centre clinical study with 501 patients (50.3%) operated on at the University Hospital Schleswig-Holstein in Kiel and with 495 patients (49.7%) operated on at the University Hospital Würzburg. Of the 996 patients investigated, 332 patients (33.3%) were prospectively randomized into the S-group, whereas 336 patients (33.7%) were randomized into the G-group and 328 patients (32.9%) into the I-group (Table 1). Overall, the mean age was 67.7 ± 9.4 years, 18.6% were women, the mean BMI was 28.4 ± 7.4 kg/m² and 94.2% had an LVEF of >30% preoperatively. All preoperative patient characteristics—age, sex, BMI, NYHA classification, diabetes mellitus, LVEF >30%, renal insufficiency, PAOD and COPD—were similarly distributed in all three groups, except for an increased incidence of patients with a BMI of >30 kg/m² (S-group: 28.3%, G-group: 22.9% and I-group: 31.4%; $P$-value 0.046) (Table 2).

CABG procedure with (97.1%) or without (2.9%) CPB, the use of LIMA, RIMA or BIMA, operating time, time on cardiopulmonary bypass, aortic cross-clamp time, ventilation postoperative, bleeding postoperative, number of sternal wires and the occurrence of a symptomatic transitory psychotic syndrome were comparable in all three groups (Table 2). Only the re-thoracotomy rate for bleeding was significantly higher in the S-group (6.9%) compared with that in the G-group (3.3%) and the I-group (3.7%) ($P$-value 0.049) (Table 2).

Postoperative sternal stability was achieved in 98.0% (S-group: 96.7%, G-group: 98.5% and I-group: 98.5%; $P$-value 0.27). Three months after the CABG procedure, 95.9% of the patients had unremarkable conditions of the sternum (S-group: 96.3%, G-group: 96.5% and I-group: 94.8%; $P$-value 0.52). After 3 months, the all-cause mortality was 2.0% (S-group: 2.7%, G-group: 1.8% and I-group: 1.5%; $P$-value 0.52).

The analysis of the primary study end-point demonstrated an overall SSI rate of the sternum of 6.2% with 8.3% in the S-group, 5.4% in the G-group and 4.9% in the I-group ($P$-value 0.16). In detail, the overall rate of superficial and deep SSI was 5.2%/2.2%, with 7.3%/3.1% in the S-group, 3.6%/2.7% in the G-group and 4.6%/0.9% in the I-group ($P$-values 0.08/0.14) (Table 3).

Univariable analysis revealed a preoperative creatinine-level $>1.1$ mg%, BMI $>30$ kg/m², transfusion of $\geq 1$ erythrocyte concentrate, re-thoracotomy for bleeding, sternum instability, increased operating time and prolonged time on CPB as risk factors for a higher sternal SSI rate. Multiple regression analysis identified preoperative BMI $>30$ kg/m² (OR: 1.79; 95% CI: 1.01–3.19; $P$-value 0.047), re-thoracotomy for bleeding (OR: 12.28; 95% CI: 5.03–30.0; $P$-value <0.001) and sternum instability postoperatively (OR: 0.005; 95% CI: 0.002–0.015; $P$-value <0.001) as independent predictors for an increased SSI rate of the sternum.

### Table 1: Randomization of the patients

<table>
<thead>
<tr>
<th>996 patients</th>
<th>University of Kiel</th>
<th>University of Würzburg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard group (332 pat.)</td>
<td>168 pat. (50.6%)</td>
<td>164 pat. (49.4%)</td>
</tr>
<tr>
<td>Genta-Coll group (336 pat.)</td>
<td>167 pat. (49.7%)</td>
<td>169 pat. (50.3%)</td>
</tr>
<tr>
<td>InteguSeal group (328 pat.)</td>
<td>166 pat. (50.6%)</td>
<td>162 pat. (49.4%)</td>
</tr>
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pat.: patients.
DISCUSSION

Mediastinitis is a rare but life-threatening complication after cardiac surgery. It is associated with high morbidity, decreased long-term survival, prolonged length of hospital stay and increased costs of health care [6–9]. The mortality rate of patients with mediastinitis is >3-fold higher compared with that of patients after cardiac surgery without deep sternal wound infection [2, 3, 5]. The relatively low reported incidence of mediastinitis of between 1 and 5% is based on modern hygienic standards, the use of prophylactic antibiotics during and after the operative procedure and improvements in cardiac surgery, cardiac anaesthesia and intensive care medicine [2–4]. At present, we have no reliable data concerning the real incidence of superficial and deep sternal SSI because the existing data are commonly based on single-centre experiences. Therefore, in 2011, the German Society for Thoracic and Cardiovascular Surgery initiated a ‘mediastinitis registry’ as a nationwide project to determine all patients suffering from wound healing disorders after cardiac surgery in Germany [20].

CABG is the most common operative procedure in cardiac surgery. In recent years, complete arterial revascularization using BIMA proved beneficial in the long term for patients undergoing myocardial revascularization, especially in patients suffering from diabetes mellitus [11, 12]. Otherwise, harvesting of BIMA reduces postoperative sternal perfusion and represents an important risk factor for poststernotomy mediastinitis [13, 14]. The major blood supply of the sternum originates from segmental sternal branches of the IMA. After harvesting the IMA, three different types of vessels were identified to supply the sternum with blood: (i) ‘sternal/perforating IMA branches’, (ii) ‘sternal/intercostal IMA branches’ and (iii) posterior intercostal branches [21]. To avoid damaging these collateral branches, harvesting of the IMA should be performed in a skeletonized manner. In another preparation technique, the IMA is harvested with a tissue pedicle, including the internal thoracic vein and a small part of the fascia. This pedicle preparation technique may result in greater damage to the collateral IMA branches with a decreased blood supply of the sternum [22]. In our study, both techniques were performed for harvesting the IMA, the skeletonized and the pedicled technique, according to the surgeon’s preference. Therefore, we did not analyse this fact separately.
The current first-line treatment strategy for postoperative mediastinitis is negative pressure wound therapy (NPWT), also called vacuum therapy [7–9]. NPWT leads to a reduction in the mortality and sternal re-infection rates and to a shorter hospital stay [23].

According to our institutional standardized protocol, the therapy of superficial and deep sternal SSI included frequent wound check, test of sternum stability, check of fever, leucocytes and CRP, swab taking, antibiotic treatment and, if necessary, operative sternal wound revision with NPWT until secondary closure of the chest. In all cases of unsuccessful treatment of superficial sternal SSI and of signs of deep sternal wound infection, a CT scan of the chest was performed.

Different novel prophylactic approaches are examined for the prevention of sternal SSI in cardiac surgery. Local antibiotic eluting products such as the gentamicin-collagen sponge deliver high local antimicrobial concentrations. Raja et al. [15] reported a significant reduction in the sternal SSI rate using the Genta-Coll® sponge in a single-centre propensity score analysis. In 2015, a meta-analysis of 14 studies with 22,135 patients demonstrated a significant risk reduction for sternal SSI using implantable gentamicin-collagen sponges [16]. Otherwise, in a large-scale randomized study of 1,502 cardiac surgical patients at 48 US sites, these findings could not be verified [24]. Another prophylactic method is the application of a cyanoacrylate-based microbial skin sealant after routine skin disinfection. InteguSeal® leads to a protective film to immobilize remaining skin-borne bacteria. Dohmen et al. [17] performed a retrospective study with 500 cardiac surgery patients and demonstrated a significant reduction in SSI by including pretreatment with a microbial skin sealant. A 35.3% relative risk reduction in SSI in the InteguSeal®-treated patients was evaluated in a randomized controlled multicentre trial from von Eckardstein et al. [18]. In contrast, Waldow et al. [25] reported no influence on the incidence of sternal SSI in a single-centre trial of almost 1,000 patients.

The primary aim of our prospective randomized controlled two-centre clinical study of 996 patients was to analyse the effects of the application of Genta-Coll® or InteguSeal® on the sternal SSI rate in patients undergoing CABG. The overall SSI rate of the sternum was 6.2% with 8.3% in the S-group, 5.4% in the G-group and 4.9% in the I-group (P-value 0.16). In detail, the overall rate of superficial and deep SSI was 5.2%/2.2% with 7.3%/3.1% in the S-group, 3.6%/2.7% in the G-group and 4.6%/0.9% in the I-group (P-values 0.08/0.14) (Table 3). These findings were evaluated during hospital stay and after 3 months postoperatively to detect late-onset sternal wound complications. All of the 996 patients investigated were comparable with respect to preoperative morbidities and intraoperative procedures in all three groups (S-group, G-group and I-group) with an all-cause mortality rate of 2.0% after 3 months (S-group: 2.7%, G-group: 1.8% and I-group: 1.5%, P-value 0.52). Sternum stability postoperative was achieved in 98.0% (S-group: 96.7%, G-group: 98.5% and I-group: 98.5%; P-value 0.27). The application of InteguSeal® or Genta-Coll® resorb had no significant influence on the incidence on sternal SSI rate in 996 consecutive cardiac surgery patients but demonstrated a trend towards a benefit. This study was planned and powered for a difference of 6% vs 2% incidence of SSI that could not be demonstrated. However, the actual difference was 8.3% (S-group) versus 4.9% (I-group) and 8.3% (S-group) versus 5.4% (G-group) in the reduction of the overall SSI with a P-value of 0.16 (Table 3). These findings can be interpreted as a positive trend in the reduction of the incidence of sternal SSI for the use of InteguSeal® or Genta-Coll®. The secondary study end-point was to determine independent risk factors for an increased SSI rate of the sternum. Multiple regression analysis demonstrated a preoperative BMI of >30 kg/m² (P-value 0.047), re-thoracotomy for bleeding (P-value <0.001) and sternum instability postoperatively (P-value <0.001) as independent predictors for an increased SSI rate of the sternum. To the best of our knowledge, this is the first prospective, randomized controlled study at two institutions comparing the incidence of sternal wound complications when using Genta-Coll® or InteguSeal®.

Strategies to prevent surgical site sternal infections are major goals in cardiac surgery because superficial and deep sternal wound complications are associated with decreased quality of life for our patients. The ongoing demographic change with more aged patients with increasing comorbidities emphasizes the importance of the prevention of SSI.

LIMITATIONS
This trial examined only cardiac surgery patients receiving isolated CABG. In future, more combined cardiac surgery procedures (CABG with, for example, aortic/mitral valve interventions) must be considered. Additional studies are necessary to evaluate the influence of SSI preventing strategies in that particular patient cohort. One further limitation is the fact that we did not calculate a risk score (e.g. EuroScore) for better comparison of the three groups investigated, but all 996 patients were comparable with respect to preoperative morbidities and intraoperative procedures. The hypothesis of a reduction of the sternal SSI rate from 6 to 2% when using Genta-Coll® or InteguSeal® with a statistical power of 80% is a limiting aspect of this study. But still, this is the first prospective, randomized controlled study at two institutions comparing the incidence of sternal wound complications when using Genta-Coll® or InteguSeal®.

The possible additive effect from using both Genta-Coll® and InteguSeal® on the sternal SSI rate was not examined.

Conflict of interest: none declared.

REFERENCES


