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Reduction in surgical site infection in patients treated with microbial sealant prior to coronary artery bypass graft surgery: a case–control study

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Cardiac surgery;
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Summary Surgical site infection (SSI) is a serious complication after cardiac surgery. This case–control study investigated the effect of a cyanoacrylate-based microbial skin sealant (IntegeuSeal®) applied preoperatively on the SSI rate in patients undergoing coronary artery bypass graft (CABG) surgery. Of 676 patients who underwent CABG surgery with or without concomitant procedure(s) between March and November 2007, 545 received standard preoperative care and 131 also received pretreatment with the microbial sealant. Of these, 90 cases pretreated with microbial sealant and 90 controls were matched using established preoperative and intraoperative risk factors for SSI. Preoperative risk scores for SSI were 9.9 ± 4.3 and 9.7 ± 4.0 ($P = 0.747$) for the microbial sealant and the control group, respectively, and combined preoperative–intraoperative risk scores were 9.7 ± 4.1 and 8.7 ± 3.5 ($P = 0.080$), respectively. Carotid artery disease ($P = 0.019$), congestive heart failure ($P = 0.019$), acute myocardial infarction ($P = 0.001$) and emergency surgery ($P = 0.026$) were significantly more common in the microbial sealant group. Follow-up was 100% for both groups. Superficial or deep sternal infection 30 days post surgery developed in seven patients (7.8%) in the control group compared with one patient (1.1%) in the microbial sealant group (odds ratio 7.5). In summary, the inclusion of microbial sealant in preoperative patient preparation seems to reduce the incidence of SSI following CABG surgery; further larger studies are needed before firm conclusions can be drawn.
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Introduction

Postoperative surgical site infection (SSI) is a potentially serious complication in patients undergoing cardiac surgery. Sternal wound infection can range from superficial, where only skin and subcutaneous tissues are affected, to deep, with sternal osteomyelitis and, in the worst cases, septicaemia. The incidence of sternal wound infection reported by different studies ranges from 0.9% to 20.0%, with numerous factors related to the patient, the surgical procedure and the clinical environment contributing to the overall risk of infection.[1–4] Reported rates also depend on the definition of infection, as well as the duration and method of follow-up.

Patients with infected sternal wounds may require extensive therapy and prolonged hospitalisation. Despite this, mortality in patients who develop sternal wound infection following cardiac surgery is high, with reported mortality rates of up to 39%.[5] A large proportion of SSI — almost 50% of sternal wound infections and 80% of donor site infections — are diagnosed after patients have left the hospital following cardiac surgery, necessitating effective post-discharge surveillance and rapid readmission of patients who develop SSI.[6] Postoperative SSI in patients undergoing coronary artery bypass graft (CABG) surgery thus has important consequences in terms of morbidity, mortality, quality of life and healthcare costs.[7,8]

Efforts to reduce the rate of SSI in cardiac surgery have sought to address modifiable risk factors with preventive procedures focused on reducing bacterial contamination of the surgical site, administering appropriate antibiotic prophylaxis, minimising local injury through surgery, and optimising host defences.[9] Scrubbing of the operative site with an antiseptic solution prior to surgery is recognised as standard procedure but, while this substantially reduces the skin flora, ~20% remain buried deep in hair follicles and sweat glands and persist after scrubbing.[10] Thus, complete sterilisation of the skin is not possible.

The incorporation of a microbial sealant treatment into the preparation of a patient for surgery is a recent technological development with potential to reduce rates of SSI. On application to the skin, the sealant polymerises to form a continuous but breathable barrier that prevents migration of skin flora into the incision. Importantly, and in contrast to conventional skin preparations, the sealant also seals microabrasions on the skin, so preventing recolonisation of such spaces with residual potential pathogens following skin sterilisation. This paper reports the effect of pretreatment with *n*-butyl cyanoacrylate-based microbial skin sealant (IntéguSeal®, Kimberly-Clark Health Care, Roswell, GA, USA) on the incidence of SSI in a series of patients and case-matched controls undergoing CABG.

Methods

Patients

This study included patients undergoing CABG surgery at the Department of Cardiovascular Surgery, Charité Hospital, Berlin, Germany. A database was created to prospectively register all patients aged ≥18 years who underwent CABG surgery between March and November 2007. Of the 676 patients registered, 545 received standard preoperative care by one of five academic staff surgeons and 131 received pretreatment with microbial sealant in addition to standard preoperative care by a single academic staff surgeon (P.M.D.).

Data were de-identified and grouped according to demographics including patient characteristics, operative data, postoperative data and postoperative complications.

This retrospective study included all patients operated upon during this period with exclusion of patients who met the following criteria: (1) patients ($N = 5$) with skin hypersensitivity to iodine (all patients received standard preoperative care), or (2) patients ($N = 113$) with associated procedure(s) other than valve replacement (72 of these patients received standard preoperative care, and 41 patients received pretreatment with microbial sealant in addition to standard preoperative care).

Of the remaining 558 patients, 90 patients were identified as having received pretreatment with microbial sealant in addition to standard preoperative care. For each of these cases, one control was chosen from the patients who received only standard preoperative care. Controls were matched for preoperative and intraoperative risk factors as described by Fowler *et al.*[3] In this scoring system, a higher score predicts a higher risk of developing SSI. Preoperative risk factors were age, gender, obesity, diabetes mellitus, arterial hypertension, hyperlipidaemia, chronic obstructive pulmonary disease, chronic renal failure, peripheral vessel disease, carotid artery disease, cerebral vascular accident, ejection fraction, congestive heart failure, acute myocardial infarct within one

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month, and previous bypass or valve surgery. The intraoperative risk factors were number of anastomoses, use of internal mammary arteries, use of bilateral internal mammary arteries, duration of perfusion, surgical status (emergency, urgent or elective), concomitant procedures and insertion of an intra-aortic balloon pump.

All healthcare-associated infections were registered, and all complications during follow-up recorded in the German Nosocomial Infection Surveillance System (Krankenhaus Infektions Surveillance System, KISS). Participation in the surveillance system is approved by the Institutional Board on the Ethics of Clinical Studies. The method of surveillance remained unchanged throughout the study period and, as all investigations represented routine diagnostic procedures, informed consent was considered unnecessary.

Standard preoperative preparation

For patients scheduled for elective or urgent surgery, hair removal was performed by depilatory cream (stable patients) or a clipper (unstable patients) in the afternoon of the day before surgery. Patients then washed by shower using only soap and showered again on the morning of surgery. For patients undergoing emergency surgery (defined as surgery with no delay following admission), hair was removed by clipper immediately prior to surgery and patients did not shower. Following hair removal, the skin was disinfected using povidone-iodine. Care was taken to allow the disinfecting solution to dry completely before application of microbial sealant (case patients) and iodine-impregnated drapes (all patients).

Microbial sealant pretreatment

For patients who received microbial sealant pretreatment, the sealant was applied to the skin after preoperative skin preparation had been completed and 5—10 min before surgery commenced. The IntéguSeal IS100 applicator was used to apply a single, even layer of microbial sealant over an area of $\sim 50 \times 25$ cm around the sternal incision mark, which was allowed to dry completely before iodine-impregnated drapes were positioned. Microbial sealant was not used on saphenous donor sites.

Intraoperative care

All patients underwent normothermic cardiopulmonary bypass and care was taken to maintain optimal temperature during surgery. Blood glucose levels were monitored regularly. If required, insulin was administered to counter transient hyperglycaemia. Oxygenation was also kept optimal throughout the operative period.

Microbiological methods

Bacterial isolates obtained from wound and other samples of patients with SSI were identified using routine microbiological diagnostic procedures.

Study endpoint

The primary study endpoint was the occurrence of superficial or deep SSI within 30 days of follow-up. Superficial or deep SSIs were defined according to the guidelines of the Centers for Disease Control and Prevention.[11] Diagnosis of deep sternal wound infection required at least one of the following criteria: (1) an organism isolated from culture of mediastinal tissue or fluid; (2) evidence of mediastinitis seen during operation; or (3) chest pain, sternal instability, or fever ($>38\,^{\circ}$C) present, and either purulent discharge from the mediastinum or an organism isolated from blood culture or culture of drainage of the mediastinal area. Diagnosis of superficial sternal wound infection (involving only skin and subcutaneous tissue) required at least one of the following criteria: (1) purulent drainage from the superficial incision; (2) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision; (3) at least one of the following signs or symptoms of infection: pain or tenderness, localised swelling, redness, or heat, and superficial incision deliberately opened by surgeon and is culture positive or not cultured; (4) diagnosis of superficial incisional SSI by the surgeon or attending physician. Deep SSIs were treated with vacuum-assisted closure (VAC) before discharge and/or readmission within 30 days of surgery; superficial SSIs were treated with or without VAC therapy with closed sternum before discharge and/or readmission within 30 days of surgery.

Statistical analysis

The study design was a retrospective matched case—control study, the case:control ratio being 1:1. Categorical variables were analysed using χ^2-test and Fisher's exact test. Continuous variables were analysed with Student's *t*-test. $P < 0.05$ was considered to be significant on two-tailed testing. A conditional logistic regression was used to assess the effect of pretreatment with *n*-butyl cyanoacrylate-based microbial skin sealant on the incidence of SSI in the two matched groups. Data

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were analysed using SPSS software (version 13.0; SPSS, Inc., Chicago, IL, USA).

Results

Patients

Characteristics of patients receiving microbial sealant pretreatment ($N = 90$) and controls ($N = 90$) are shown in Table I. Patients had a mean (SD) age of 67.0 (7.6) years and 69.1 (7.1) years, respectively, and in both patient groups most patients (73.3% and 70.0%, respectively) were male. Approximately three-quarters of patients were hyperlipidaemic and almost all were hypertensive. The prevalence rates of diabetes mellitus, peripheral artery disease and other comorbidities were as expected for this surgical population. Mean (SD) ejection fraction values were 47.3% (13.3%) in the microbial sealant pretreatment group and 49.7% (8.6%) in the control group ($P = 0.152$). Congestive heart failure (22.2% vs 10.0%, $P = 0.026$), carotid artery disease (24.4% vs 11.1%, $P = 0.019$) and myocardial infarction (54.4% vs 23.3%, $P = 0.001$) were significantly more common among patients receiving microbial sealant pretreatment than in controls (Table I).

Table I Patient characteristics

	Microbial sealant treatment ($N = 90$)	Control ($N = 90$)
Age (years), mean (SD)	67.0 (7.6)	69.1 (7.1)
Gender		
Male	66 (73.3)	63 (70.0)
Female	24 (26.7)	27 (30.0)
Hyperlipidaemia	70 (77.8)	61 (67.8)
Arterial hypertension	89 (98.9)	89 (98.9)
COPD	10 (11.1)	16 (17.8)
Diabetes mellitus	33 (36.7)	32 (35.6)
Peripheral artery disease	19 (21.1)	13 (14.4)
Carotid artery disease	22 (24.4)*	10 (11.1)
Cerebrovascular accident	11 (12.2)	6 (6.7)
Renal failure	11 (12.2)	10 (11.1)
Ejection fraction, mean (SD)	47.3 (13.3)	49.7 (8.6)
Congestive heart failure	20 (22.2)*	9 (10.0)
Acute myocardial infarction	40 (54.4)**	21 (23.3)
Previous CABG	7 (7.8)	4 (4.4)
Previous valve replacement	2 (2.2)	1 (1.1)

CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease.
Data are *N* (%) unless otherwise indicated.
*$P < 0.05$ and **$P < 0.01$ for intergroup comparison.

CABG surgery: microbial sealant vs controls

In both groups, the majority of patients, 70% of the microbial sealant pretreatment group and 83% of the control group, underwent elective surgery. Few cases were urgent (one vs two patients, respectively), but significantly more patients in the microbial sealant pretreatment group than in the control group underwent emergency CABG surgery (29% vs 14%, $P = 0.019$). Other characteristics of the surgical procedure were similar in the two patient groups (Table II).

SSI risk scores and occurrence during follow-up

Preoperative risk scores for SSI were 9.9 ± 4.3 for the microbial sealant group and 9.7 ± 4.0 for the control group ($P = 0.747$) and risk scores for SSI according to combined preoperative–intraoperative factors were 9.7 ± 4.1 and 8.7 ± 3.5 ($P = 0.080$), respectively. The rates of SSI predicted by these risk scores were 3.1% (preoperative) and 3.0% (combined) with microbial sealant and 3.0% (preoperative) and 2.7% (combined) for controls. At 30 days after surgery, the clinical endpoint of the study, SSI was recorded for 1.1% ($N = 1$) of patients in the microbial sealant pretreatment group compared with 7.8% ($N = 7$) in the control group [odds ratio: 7.5; 95% confidence interval: 0.904–62.317; $P = 0.062$ (Wald test)] (Figure 1). Follow-up for both patient groups was 100%.

Table II Operative characteristics of patients undergoing coronary artery bypass graft surgery

	Microbial sealant treatment ($N = 90$)	Control ($N = 90$)
Distal anastomoses, mean (SD)	2.7 (0.8)	2.7 (0.9)
LIMA	85 (94.4)	80 (88.9)
BIMA	9 (10.0)	3 (3.3)
Perfusion time (min)		
<100	72 (80.0)	67 (74.4)
100–200	17 (18.9)	22 (24.4)
>200	1 (1.1)	0
Concomitant procedures	22 (24.4)	24 (26.7)

BIMA, bilateral internal mammary artery graft; LIMA, left internal mammary artery graft.
Data are *N* (%) unless otherwise indicated.

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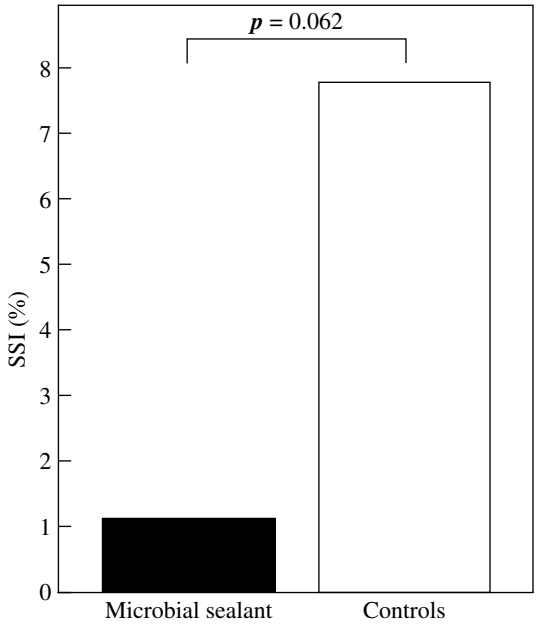

Figure 1 Incidence of surgical site infection (SSI) in patients undergoing coronary artery bypass graft surgery who were treated with microbial sealant (cases) and matched untreated patients (controls).

In the single case of SSI in the microbial sealant pretreatment group, meticillin-resistant *Staphylococcus aureus* (MRSA) was cultured from blood samples. Although initial microbiological sampling of the surgical wound proved negative, MRSA was isolated from the sternal wound some three weeks after surgery. Vancomycin-resistant enterococci and extended spectrum β-lactamase-producing Enterobacteriaceae were also isolated from this patient, who recovered after treatment with an appropriate antibiotic regimen and supportive measures.

In the control group, sternal site samples at wound closure yielded positive cultures in seven patients, including meticillin-sensitive *S. aureus* (MSSA) ($N = 2$), *S. epidermidis* ($N = 2$), MSSA and *S. epidermidis* ($N = 1$), *Klebsiella pneumoniae* ($N = 1$), and *Pseudomonas aeruginosa* ($N = 1$) (Table III). Four patients in the control group died due to deep SSI.

Discussion

Coronary revascularisation by CABG is one of the most common major surgical procedures, but although generally considered to be a routine procedure, it carries an age-dependent mortality risk of 2.5%–10% at 30 days.[12] Infection of surgical sites, particularly sternal wound infection, following CABG surgery is an infrequent yet potentially disastrous event, leading to prolonged hospitalisation, repeated surgical procedures, high associated morbidity and mortality, and increased healthcare costs.

The results of this study suggest that the use of a microbial sealant prior to surgery could help to reduce the rate of SSI among patients undergoing CABG compared with matched controls who were undergoing the same surgical procedure in the same surgical unit. Both case and control groups had a high prevalence of preoperative characteristics known to increase the risk for SSI. Although statistical significance was not reached, patients without pretreatment with microbial sealant had a seven-fold increased risk of developing infection compared with the matched patients pretreated with microbial sealant. Notably, pretreatment with microbial sealant had a beneficial effect on the occurrence of SSI despite the statistically significant higher prevalence of several risk factors – congestive heart failure, carotid artery disease, myocardial infarction or emergency surgery – in the group of patients who received pretreatment compared with the controls. CABG surgery involving bilateral internal mammary arteries, an intraoperative risk factor for sternal infection, was also carried out in more patients in the sealant treatment group than in the control group, although the difference was not significant.[13] Despite these differences, careful and systematic matching of patients in the two groups using established preoperative and combined preoperative–intraoperative risk scores provides an objective basis for the observed positive treatment effect.[3]

The risk of developing SSI after surgery depends in part on the number of bacteria that colonise the surgical wound. While the operative wound following CABG surgery is considered to be 'clean' the surgical site may be contaminated by airborne bacteria-carrying particles in the operating room and ICU, by bacteria from endogenous sources such as the patient's mucous membranes that are spread on the hands of theatre personnel, or by direct contamination by the patient's normal skin microflora.[14] Bacteria from these three sources have been isolated from surgical wound infections following CABG procedures, but the majority of such infections are caused by staphylococci and other species of the patient's own microflora.[15,16]

Sternal infection with *S. aureus* is associated with high morbidity and mortality and carries a worse prognosis than that of other aetiologies.[17] Overall, wound infections caused by *S. aureus* in cardiac surgery patients vary between 12% and 36.4% of wound infections.[18] Coagulase-negative staphylococci are also major pathogens in sternal

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Table III Microbiology of patients in the control group who developed surgical site infection (SSI)

Patient	Concomitant procedure	Deep or superficial SSI	Microbial sp./spp. isolated from infected sternal wound	Microbial sp./spp. isolated from blood
1[a]	—	Deep	*Klebsiella pneumoniae*	*Enterococcus faecium* *Candida glabrata*
2	AVR	Superficial	MSSA	*Staphylococcus epidermidis*
3	—	Deep	MSSA	*S. epidermidis*
4[a]	AVR	Deep	*Pseudomonas aeruginosa* Meticillin-susceptible *S. epidermidis* *E. faecium*	—
5	—	Deep	MSSA Meticillin-resistant *S. epidermidis*, meticillin-susceptible *S. epidermidis*	MSSA Meticillin-resistant *S. epidermidis*
6[a]	MVR	Deep	*S. epidermidis*	*S. warneri*
7[a]	AVR	Deep	*S. epidermidis*	—

AVR, aortic valve replacement; MSSA, meticillin-sensitive *S. aureus*; MVR, mitral valve replacement.
[a] Patient subsequently died.

infections, particularly when implanted material, such as stainless steel wires for sternotomy closure, is introduced.[17] The endogenous route of SSI after cardiac surgery has been demonstrated for *S. aureus* and, to a lesser extent, coagulase-negative staphylococci.[15,18]

SSI and systemic infection with MRSA have a significant morbidity in cardiac surgery patients. In this study, a quarter of those in the microbial sealant pretreatment group received emergency surgery, circumstances in which the medical need outweighs the need for the results of microbiological tests to determine the presence of MRSA or to achieve decolonisation of carriers before surgery.

In addition to *S. aureus* and coagulase-negative staphylococci, *Escherichia coli*, *Klebsiella* spp., *Propionibacterium acnes*, streptococci, enterococci, and other less common pathogens have also been isolated from infected sternal wounds.[2,7,16–21] This emphasises the need for broad as well as targeted measures to prevent SSI.

Intravenous antibiotic prophylaxis is established practice in cardiac surgery and achieves an approximate five-fold reduction in surgical wound infection rate.[22] However, the use of broad-spectrum antibiotics for surgical prophylaxis adds to the selective pressure driving the development of resistant pathogens.[23] Patients infected with antibiotic-resistant bacteria experience higher mortality, prolonged hospitalisation, and increased healthcare costs compared with those infected with non-resistant organisms.[24] As noted earlier, the skin microbial flora has a predominant role in SSI. Inhibiting the migration of endogenous potential pathogens appears to be a rational approach to reduce surgical wound contamination. Importantly, this approach to immobilising all skin-borne micro-organisms in situ is effective for all pathogens and does not promote the common mechanisms of bacterial resistance.

Previous in-vitro and in-vivo studies have shown that the microbial sealant preparation is highly efficient in reducing the recovery of pathogens from incision sites and is more effective than antimicrobial surgical drapes (Kimberly-Clark Health Care, unpublished data). Treatment with microbial sealant also significantly improves the effect of povidone-iodine while still allowing normal skin transpiration (Kimberly-Clark Health Care, unpublished data). This eliminates the 'greenhouse effect' that occurs under plain or antimicrobial-impregnated adherent plastic drapes where bacteria can proliferate in a warm moist environment close to the incision during surgery.[25]

In a separate study, we found a significant beneficial effect of the microbial sealant on the incidence of SSI in patients undergoing routine cardiac surgery (valve replacement with or without CABG and miscellaneous procedures such as atrial septal defect closure) and we have reported positive preliminary results for this preoperative intervention in CABG surgery patients elsewhere.[26] These data and the results of the present study add to the limited published reports of the effect of the microbial sealant in SSI prevention.[27] Further clinical studies are needed, and a randomised, multicentre clinical trial of microbial sealant pretreatment in CABG patients has been started.

This investigation has some limitations. First, the study was carried out at a single, large university hospital, and the results may not reflect

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the impact of pretreatment with microbial sealant on SSI in CABG patients in other settings. Second, although cases and controls were carefully matched by risk factors, case patients were operated on by one surgeon whereas one of five other surgeons operated on control patients; this and incomplete or inexact matching of other characteristics of case—control pairs may have introduced bias. Third, we compared superficial or deep SSI within 30 days of follow-up, but it is possible that the use of a longer follow-up period may have yielded different results. Finally, the low overall number of expected and observed SSIs may have weakened the accuracy of the probability calculated for the case—control comparison. All these limitations could have contributed to the absence of a statistically significant result. Despite this, we consider the reduction in SSI in this vulnerable group of patients to be a valid interpretation of the data and, more importantly, clinically significant.

In conclusion, this study shows that the use of a microbial skin sealant prior to surgery could reduce the rate of SSI among patients undergoing CABG. There were no cases of skin sensitivity or other reaction following application of the microbial sealant, which can be used with a variety of skin preparation solutions and with most wound closure techniques. The pretreatment is straightforward and has been easily integrated with existing routine preoperative procedures at this surgical centre. Microbial sealant may thus be a useful addition to the multimodal approach to minimise bacterial contamination of surgical incisions, key in SSI prevention.

Conflict of interest statement
None declared.

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