Prevention of Nosocomial Infection in Cardiac Surgery by Decontamination of the Nasopharynx and Oropharynx With Chlorhexidine Gluconate

A Randomized Controlled Trial

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Context Nosocomial infections are an important cause of morbidity and mortality after cardiac surgery. Decolonization of endogenous potential pathogenic microorganisms is important in the prevention of nosocomial infections.

Objective To determine the efficacy of perioperative decontamination of the nasopharynx and oropharynx with 0.12% chlorhexidine gluconate for reduction of nosocomial infection after cardiac surgery.

Design, Setting, and Participants A prospective, randomized, double-blind, placebo-controlled clinical trial conducted at the Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands, between August 1, 2003, and September 1, 2005. Of 991 patients older than 18 years undergoing elective cardiothoracic surgery during the study interval, 954 were eligible for analysis.

Intervention Oropharyngeal rinse and nasal ointment containing either chlorhexidine gluconate or placebo.

Main Outcome Measures Incidence of nosocomial infection, in addition to the rate of *Staphylococcus aureus* nasal carriage and duration of hospital stay.

Results The incidence of nosocomial infection in the chlorhexidine gluconate group and placebo group was 19.8% and 26.2%, respectively (absolute risk reduction [ARR], 6.4%; 95% confidence interval [CI], 1.1%-11.7%; $P=.002$). In particular, lower respiratory tract infections and deep surgical site infections were less common in the chlorhexidine gluconate group than in the placebo group (ARR, 6.5%; 95% CI, 2.3%-10.7%; $P=.002$; and 3.2%; 95% CI, 0.9%-5.5%; $P=.002$, respectively). For the prevention of 1 nosocomial infection, 16 patients needed to be treated with chlorhexidine gluconate. A significant reduction of 57.5% in *S aureus* nasal carriage was found in the chlorhexidine gluconate group compared with a reduction of 18.1% in the placebo group ($P<.001$). Total hospital stay for patients treated with chlorhexidine gluconate was 9.5 days compared with 10.3 days in the placebo group (ARR, 0.8 days; 95% CI, 0.24-1.88; $P=.04$).

Conclusion Decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate appears to be an effective method to reduce nosocomial infection after cardiac surgery.

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NOSOCOMIAL INFECTIONS AFter open heart surgery are recognized as an important cause of mortality, morbidity, prolonged hospital stay, increased need for antimicrobial therapy, and higher concomitant costs. Nosocomial infections also decrease patients' quality of life.[1-9] Incidence rates of more than 20% are reported for nosocomial infection after cardiac surgery.[1,4,6-9] Because surgical procedures are increasingly performed in older patients with more comorbidities, it is expected that the incidence of nosocomial infections will increase, unless prevention is improved.[1,10]

Colonization of the host by potentially pathogenic microorganisms is a prerequisite for the development of nosocomial infections. Although potentially pathogenic microorganisms can be transmitted to patients from the hands of health care workers and contaminated equipment,[11,12] the patient's own flora is the primary source.[13,14]

Considerable efforts have been made to reduce the occurrence of nosocomial infections. One strategy involves use of selective decontamination of the digestive tract,[15-17] which is designed to prevent nosocomial infection, especially lower respiratory tract infection (LRTI), through antimicrobial therapy to eradicate potentially pathogenic microorganisms from the oropharynx, stomach, and gut. Decontamination of the oropharynx, in particular, seems important, because there is direct evidence of an association between pulmonary infection and oral health.[14,18-22]

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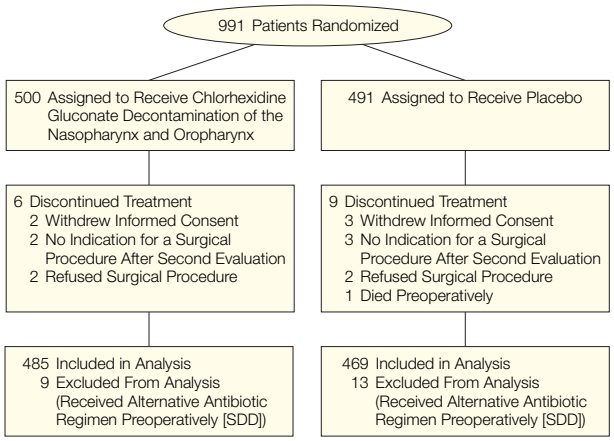
Another important strategy involves the eradication of *Staphylococcus aureus,* the most important pathogen responsible for surgical site infections (SSIs). The most common reservoir of *S aureus* is the anterior nares, and eradication can be achieved by the application of topical antimicrobials.[13] One such agent, mupirocin, is a cornerstone of treatment of methicillin-resistant *S aureus* colonization. In the Netherlands, hospitals are required to participate in a national search-and-destroy policy for patients colonized with methicillin-resistant *S aureus*. Therefore, widespread use of mupirocin for other purposes is not desirable because of the concern of rising resistance rates.[23]

Although promising results have been reported for both selective decontamination of the digestive tract and *S aureus* decolonization, they are not widely used as routine prevention methods for several reasons, including inconclusive study results, variability of trial design, concern about antimicrobial resistance, and increased costs.[23-26] Further research is essential to evaluate antimicrobial agents, different protocols, and cost-effectiveness.

Figure 1. Flow of Patients



SDD indicates selective decontamination of the digestive tract.

METHODS

Trial Design

A prospective, randomized, double-blind, placebo-controlled clinical trial was conducted at the Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands. In this 480-bed community hospital, 1200 cardiac surgical procedures are performed annually. The trial protocol was approved by the institutional medical ethics committee. Written informed consent was obtained from all participants.

The local pharmacy dispensed either active or placebo trial medications after computer-generated randomization to ensure allocation concealment. Blinding was ensured by identical packaging of trial medication, labeled only with the randomization number, and was continued until data collection was completed. Treatment remained blinded throughout the follow-up period for the patients, entire surgical and intensive care unit staff, and investigators. Blinding was to be overruled only in the case of severe allergic reactions or adverse effects.

Eligibility

Between August 1, 2003, and September 1, 2005, all patients older than 18 years who were scheduled to undergo sternotomy for cardiothoracic surgery were eligible for the trial. Exclusion criteria included emergency procedures; preoperative infection, preoperative use of antimicrobials, or both; hypersensitivity to chlorhexidine gluconate; absence of written informed consent; or treatment with an alternative prophylactic regimen like selective decontamination of the digestive tract. In our hospital, patients receive selective decontamination of the digestive tract whenever a prolonged intensive care stay (>5 days) or prolonged mechanical ventilation (>48 hours) is expected after surgery. Patients who were hospitalized less than 1 day before their surgery were not included in the study.

Study Medication

A 0.12% chlorhexidine gluconate solution was used as an oral rinse and as a gel for nasal application. The chosen concentration has previously been shown to be safe and effective.[18,19,27,28] The experimental drug and the placebo were of comparable color, taste, and smell and were delivered in identical packaging to the patient care areas, labeled only with the randomization number.

Trial Protocol

After allocation and directly after hospitalization, patients were administered an oropharyngeal rinse and a nasal ointment containing either chlorhexidine gluconate or placebo. The oropharyngeal solution (10 mL) was used as a mouth rinse and applied to buccal, pharyngeal, gingival, and tooth surfaces for 30 seconds 4 times daily. The nose ointment was applied 4 times a day in both nostrils. The protocol was continued until the nasogastric tube was removed, usually the day after surgery. If the patient was unable to follow the protocol independently, the nurse performed the procedures with the aid of a sponge. To identify *S aureus* nasal carriage, cultures of the nares were taken in a standardized manner before randomization and at time of surgery. For a subgroup of patients selected at random (n=300), nares cultures were also taken at discharge. Screening for other pathogens was not performed.

All patients were treated according to the local open heart surgery protocol. On admission, preoperative preparations consisted of 2 showers using antiseptic chlorhexidine gluconate soap (40 mg/mL) on the day before surgery and excessive hair removal in the operating department with an electric clipper device. Cefuroxime (1.5-g intravenously) was

administered prophylactically 30 minutes before incision and another dose was added to the priming fluid of the extracorporeal circulation. If surgical procedures exceeded 4 hours, an additional dose was administered.[11] Cefuroxime was continued for 24 hours postoperatively. The skin was disinfected with a chlorhexidine-alcohol solution (0.5%/70%). Surgical procedures were performed by all surgeons independently of the trial protocol.

Follow-up, End Points, and Definitions

Follow-up was completed by contacting and visiting the referring cardiology departments. Medical records of all patients were reviewed. Culture results were provided by the departments of medical microbiology in our hospital and in referring hospitals.

The primary outcome measure was the overall incidence of nosocomial infection. Secondary outcomes included the incidence of LRTI and SSI, *S aureus* nasal carriage, nonprophylactic antimicrobial use, duration of hospital stay, in-hospital mortality, and trial medication adverse effects. Whether the duration of trial medication before the procedure influenced the incidence of nosocomial infection was also a point of interest. We also calculated the EuroSCORE (European System for Cardiac Operative Risk Evaluation), an established scoring system in cardiac surgery, as a relevant predictor of patient outcome.[29] This score allocates incremental risk points up to 17 risk factors to give a score that is reflective of operative mortality.[30]

The diagnosis of nosocomial infection was made according to the criteria developed by the Centers for Disease Control and Prevention.[11,31] All records were screened by the investigators to ensure that criteria for infection were met. Because most SSIs occur within 30 days of an operative procedure and since this follow-up period is used in other research,[7,8,26] we used this modified period. Any LRTI occurring during hospital stay or within 48 hours after discharge was considered an infection related to the surgical procedure. A deep SSI was defined as a wound defect in which infection is present beneath the subcutaneous layers; for example, in the mediastinal region with or without sternal involvement.

Table 1. Demographic and Patient Characteristics

Characteristics	No. (%) of Patients	
	Chlorhexidine Gluconate (n = 485)	Placebo (n = 469)
Age, mean (SD), y	65.3 (10.4)	66.4 (9.9)
Men	362 (74.6)	336 (71.6)
BMI, mean (SD)	27.3 (11.0)	26.8 (3.8)
EuroSCORE, mean (SD)*	4.2 (2.7)	4.4 (2.8)
Surgical procedure		
Coronary artery bypass grafting	270 (55.7)	237 (50.5)
Off-pump coronary artery bypass	43 (8.9)	62 (13.2)
Left internal mammarian artery	300 (83.4)	303 (87.7)
Both internal mammarian arteries	17 (4.8)	13 (3.8)
Valve	96 (19.8)	104 (22.2)
Combined	65 (13.4)	57 (12.2)
Aortic	9 (1.9)	9 (1.9)
Other†	2 (0.4)	0
Procedure/CPB time, mean (SD), min	215/91 (54.5/35.6)	216/91 (52.2/36.8)
Previous cardiac interventions	22 (4.5)	10 (2.1)
Diabetes mellitus	92 (19.0)	93 (19.8)
COPD	61 (12.6)	62 (13.2)
Active smoking	90 (18.6)	86 (18.3)
Left ventricular dysfunction	135 (27.8)	134 (28.6)
NYHA class III or IV‡	273 (56.3)	260 (55.4)
Recent myocardial infarction	66 (13.6)	43 (9.2)
Renal clearance, <60 mL/min§	79 (16.3)	89 (20.0)
Extracardiac arteriopathy	35 (7.2)	49 (10.5)
Immunosuppressive disease	10 (2.1)	6 (1.3)
Postoperative characteristics		
Reoperation	43 (8.9)	39 (8.3)
Perioperative myocardial infarction‖	11 (2.3)	10 (2.1)
Prolonged inotropic support, >24 h	15 (3.1)	15 (3.2)
Mechanical ventilation, mean (SD), h	12.3 (13.1)	13.5 (18.8)
Renal failure	24 (5.0)	28 (6.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; EuroSCORE, European System for Cardiac Operative Risk Evaluation; NYHA, New York Heart Association.
*If a risk factor is present in a patient, a weight or number is assigned (range, 0 to approximately 44); the higher the score, the higher the risk.
†Maze surgery.
‡Class III indicates marked limitation of physical activity (comfortable at rest but less than ordinary activity causes fatigue, palpitation, or dyspnea); class IV indicates unable to perform any physical activity without discomfort (symptoms of cardiac insufficiency at rest and if any physical activity is undertaken, discomfort is increased).
§Calculated by the Cockroft-Gault formula.
‖New Q waves on postoperative electrocardiogram or creatine kinase MB/total creatine kinase of more than 10%.

Statistical Analysis

To detect a clinically relevant reduction in nosocomial infection rate of 25%, with a confidence level of 5% and a power of 80%, a minimum of 936 patients were required. Anticipating a dropout rate of approximately 5%, we planned to include 990 patients. A 1-tailed analysis was planned for nosocomial infection. The rationale for testing a 1-sided hypothesis was that there was no theoretical or empirical rationale for chlorhexidine gluconate to be harmful. Based on previous research on nasal and oropharyngeal decontamination, chlorhexidine gluconate was considered likely to have only a positive effect on the incidence of nosocomial infection.[14,16,18-22] Other end points were tested by a 2-tailed analysis.

Differences between the 2 trial groups were analyzed by means of a χ^2 or *t* test. Possible independent factors influencing the occurrence of nosocomial infection were analyzed by univariable and multivariable logistic regression analysis. For the analysis of nasal cultures within patients in time, a general linear model (repeated measures) was used. Because of the repeated measures model, $P<.01$ was considered significant. Analyses were performed on a modified intention-to-treat basis, calculating absolute risk reductions (ARR), 95% confidence intervals (CIs), and numbers needed-to-treat (NNT) to prevent 1 infection. Statistical analysis was performed using SPSS version 12.0.1 (SPSS Inc, Chicago, Ill).

RESULTS

Patient Characteristics

The flow of participants is shown in FIGURE 1. Between August 1, 2003, and September 1, 2005, 991 patients were randomly assigned to the 2 treatment groups. Of these, 15 patients discontinued treatment and 22 were excluded from analysis because they received preoperative selective decontamination of the digestive tract after inclusion in this trial. Thus, a total of 954 patients were enrolled in the trial analysis. Demographic and clinical characteristics are shown in TABLE 1. Follow-up was complete in all patients and identical in both groups.

Nosocomial Infection

A total of 96 patients (19.8%) in the chlorhexidine gluconate group were diagnosed with 116 nosocomial infections compared with 123 patients (26.2%) with 164 nosocomial infections in the placebo group (ARR, 6.4%; 95% CI, 1.1%-11.7%; $P=.002$). The incidence of LRTI in the chlorhexidine gluconate and placebo groups was 9.3% and 15.8%, respectively, resulting in an ARR of 6.5% (95% CI, 2.3%-10.7%; $P=.002$), with an NNT of 15 patients. Incidence of overall SSI was 9.9% in the chlorhexidine gluconate group and 10.9% in the placebo group, which did not differ significantly. However, in the chlorhexidine gluconate group, a deep SSI was observed in 9 patients (1.9%). In the placebo group, deep SSIs were observed in 24 patients (5.1%), which represents an ARR of 3.2% (95% CI, 0.9%-5.5%; $P=.002$; with an NNT of 31 patients). Superficial SSIs in the chlorhexidine gluconate and placebo groups were observed in 8% and 6%, respectively. Patients in the placebo group tended to receive more nonprophylactic antimicrobials (ARR, 7.9%; 95% CI, 7%-10%; $P=.02$), as judged necessary by the treating physician.

Primary and secondary end points are described in TABLE 2 and TABLE 3.

Pathogens causing LRTIs and SSIs are shown in TABLE 4 and TABLE 5. No resistant pathogens were identified in either group. The prevalence of *S aureus* was isolated more often in deep SSIs than in superficial SSIs, but the difference was not statistically significant (73% vs 57%, respectively; $P=.08$).

Nasal *S aureus* Carriage

On enrollment into the study, 321 patients (33.7%) carried methicillin-susceptible *S aureus* in their nares. Methicillin-resistant *S aureus* was found in 2 patients (0.2%). There was no difference in methicillin-susceptible *S aureus* colonization in the chlorhexidine gluconate and placebo groups (36.5% and 30.7%, respectively). At the time of the operative procedure, positive *S aureus* cultures were reduced by 57.5% (from 36.5% [n=177] to 15.5% [n=75])

Table 2. Primary Outcomes

	No. (%) of Patients		
	Chlorhexidine Gluconate (n = 485)	Placebo (n = 469)	*P* Value*
No. of nosocomial infections (cumulative)	116	164	.002
Lower respiratory tract infection	45 (9.3)	74 (15.8)	.002
Urinary tract infection	14 (2.9)	21 (4.8)	.09
Bacteremia	9 (1.9)	17 (3.6)	.001
Primary	4 (0.8)	4 (0.9)	.96
Endocarditis	1 (0.2)	2 (0.9)	.54
No. of surgical site infections (cumulative)	48	52	.61
Deep	9 (1.9)	24 (5.1)	.002
Sternal	25 (5.2)	29 (6.4)	.49
Deep and sternal	5 (1.0)	14 (3.0)	.001
Donor site	20 (4.1)	22 (4.7)	.67
Other	3 (0.6)	2 (0.9)	.97

*One-tailed.

Table 3. Secondary Outcomes

	No. (%) of Patients		
	Chlorhexidine Gluconate (n = 485)	Placebo (n = 469)	*P* Value*
Nonprophylactic antimicrobial agents	66 (13.6)	101 (21.5)	.02
Duration of hospital stay, mean (SD), d			
Preoperative	1.6 (1.2)	1.9 (1.9)	.22
Intensive care	1.2 (1.1)	1.3 (1.3)	.30
Total	9.5 (7.0)	10.3 (9.5)	.04
Nosocomial infection (intensive care stay)	1.4 (1.4)	2.6 (5.3)	.05
Nosocomial infection (total stay)	13.2 (10.8)	16.8 (16.1)	.05
Surgical site infection (total stay)	14.4 (13.8)	22.1 (21.0)	.03
Readmission	19 (3.9)	23 (4.9)	.46
Death	8 (1.7)	6 (1.3)	.64
Preoperative duration of trial medication, mean (SD), d	1.9 (1.2)	1.9 (1.2)	.48
Trial medication adverse effects	1 (0.2)	0	.32

*Two-tailed.

Table 4. Results of Respiratory Cultures From Patients With Lower Respiratory Tract Infection*

	No. of Cultures	
	Chlorhexidine Gluconate (n = 45)	Placebo (n = 74)
Haemophilus species	18	24
Staphylococcus aureus	1	6
Staphylococcus species	1	2
Methicillin-resistant *S aureus*	0	0
Moraxella species	4	9
Pseudomonas species	5	5
Klebsiella species	8	2
Enterobacter species	3	4
Escherichia coli	0	6
Fungi	1	6
Serratia species	3	2
Streptococcus species	1	4
Culture negative	6	8
Other†	2	11

*Multiple pathogens were identified in some patients; therefore, total pathogens identified do not add up to the total number of patients.
†Species only found once or twice.

Table 5. Results of Surgical Wound Cultures From Patients With Surgical Site Infections*

	No. of Surgical Wound Cultures	
	Chlorhexidine Gluconate (n = 48)	Placebo (n = 52)
Staphylococcus aureus	23	29
Other *Staphylococcus* species	3	6
Methicillin-resistant *S aureus*	0	0
Streptococcus species	8	5
Anaerobes	4	5
Enterobacter species	4	3
Pseudomonas species	5	2
Proteus mirabilis	1	3
Culture negative	1	5
Other†	5	6

*Multiple pathogens were identified in some patients; therefore, total pathogens identified do not add up to the total number of patients.
†Species only found once or twice.

in the chlorhexidine gluconate group ($P<.001$), resulting in an ARR of 37.5% (95% CI, 27.7%-47.3%). No significant differences were found between cultures taken at admission (30.7% [n=144]) and those taken at surgery (24.5% [n=115]) in the placebo group (reduction of 18.1%). The 2 patients with positive cultures for methicillin-resistant *S aureus* remained positive at the time of surgery.

In a subgroup (n=300), 292 patients (152 patients in the chlorhexidine gluconate group and 140 patients in the placebo group) were eligible for analysis of nasal cultures taken on discharge (mean day 10 after admission). Eight patients were excluded for missing cultures. In the chlorhexidine gluconate group, there was an increase in cultures positive for *S aureus* from 15.5% at the time of surgery to 21.2% (n=32) at discharge (FIGURE 2). In the placebo group, the prevalence of positive cultures at discharge remained similar to the prevalence at the time of admission (30.0% vs 30.7%; n=42).

Trial Medication

Patients started the chlorhexidine gluconate or placebo treatment a mean 1.9 days (SD, 1.2 days) before surgery. Analysis of the duration of treatment before the procedure showed a similar incidence of nosocomial infections for patients decontaminated for 1 day compared with those treated for a longer period.

An adverse effect from chlorhexidine gluconate was observed in 1 patient (0.2%) who experienced temporary minor discoloration of the teeth.

Hospital Stay

The duration of hospitalization in patients with a nosocomial infection was prolonged compared with those without a nosocomial infection (15.2 days vs 8.3 days; ARR, 6.9 days; 95% CI, 12.3-17.5; $P<.001$). The mean intensive care unit stay for patients treated for a nosocomial infection was 1.6 days compared with 1.2 days in the noninfected group (ARR, 0.4 days; 95% CI, 0.26-0.61; $P<.001$). Total mean hospital stay for patients treated with chlorhexidine gluconate was 9.5 days compared with 10.3 days in the placebo group (ARR, 0.8 days; 95% CI, 0.24-1.88; $P=.04$).

Mortality

Total in-hospital mortality was 1.5%. No significant differences were found between groups. Mortality resulting from nosocomial infection occurred in 2 cases. In the placebo group, 1 patient (0.2%) died from sepsis caused by an SSI. In the chlorhexidine gluconate group, 1 patient (0.2%) died from respiratory failure after an LRTI and exacerbation of chronic obstructive pulmonary disease. The remaining 12 patients (1.3%) died because of heart failure (n=4) or other nonsurgical causes (cardiac tamponade [n=2], respiratory failure [n=3], myocardial infarction [n=1], ventricular fibrillation [n=1], and neurological [n=1]).

COMMENT

Despite advances in antisepsis, asepsis, antibiotic prophylaxis, and in (minimally invasive) surgical techniques, nosocomial infections continue to complicate the postoperative course in many patients. Advances in perioperative management are allowing older patients with more complex medical conditions to be treated. Without additional infection control measures, an increased rate of nosocomial infection can be expected in these patients.[1] Therefore, prevention of nosocomial infections remains of the utmost importance. Our trial found that decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate resulted in a clinically important reduction in nosocomial infection, LRTI, deep SSI, and nonprophylactic antimicrobial use. In addition, as the prevention of nosocomial infection improved with chlorhexidine gluconate, a shorter mean hospital stay was observed.

Suppressing the patients' own pathogens appears to be a promising and logical method of infection prevention. In addition to the key role of nasal *S aureus* carriage in the development of SSI,[13,32] it has been shown that the oral cavity is a potential reservoir for respiratory pathogens.[14] Lower mortality and potentially pathogenic microorganism colonization rates have been reported after selective decontamination of the digestive tract.[15] However, this method is used only in a high-risk population. It is prescribed for patients who are expected to experience a prolonged intensive care unit stay or prolonged period of mechanical ventilation. Another objection to selective decontamination of the digestive tract is that the antimicrobial agents used might select resistant pathogens.[24,25] In general hospital populations, resistant pathogens have been found in more than 40% of all cultures.[5] Also, the selective decontamination of the digestive tract

method targets not only the oropharynx, but also the entire digestive tract. Nevertheless, it has been reported that decontamination of the oropharynx solely results in important reductions in nosocomial infection.[14,18-21]

Intranasal application of mupirocin to eradicate *S aureus* has been used in various studies with the goal to decrease SSI after cardiac surgery.[13,26,33,34] Although the results were promising, these studies used historical placebo groups or had inconclusive test results for SSI. Furthermore, mupirocin is a cornerstone drug for eradication of methicillin-resistant *S aureus* carriage. Widespread use of mupirocin is therefore not desirable because of the potential increase in mupirocin-resistant strains of *S aureus*.

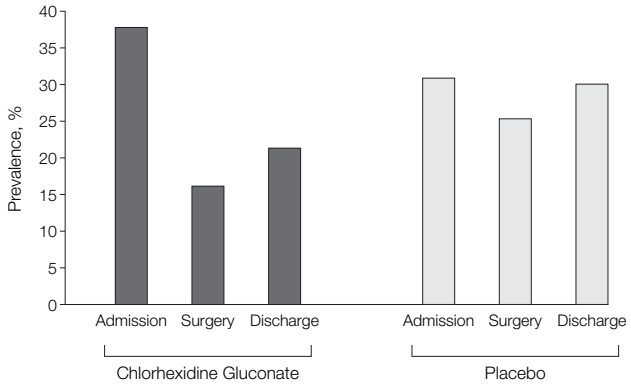
For our study, we developed a preventive regimen that would focus on the most prevalent and devastating nosocomial infections after cardiac surgery, LRTIs and SSIs, and chose a potent disinfectant with a strong antibacterial activity. Our solution, chlorhexidine gluconate, was an inexpensive and effective solution. Chlorhexidine gluconate has a high level of antibacterial activity and a strong affinity for the skin and mucous membranes. It binds electrostatically to surfaces, where it continues to exert both bactericidal and bacteriostatic effects for up to 12 hours. Adequate susceptibility of gram-positive or gram-negative bacterial strains, including *S aureus*, viruses, and fungi to chlorhexidine gluconate has been shown.[27] Chlorhexidine gluconate is virtually devoid of adverse effects.[27] Indeed, an adverse effect was observed only once in our study population. Results from long-term clinical studies have indicated no adverse alterations in microbial resistance.[34] Although some studies describe decreased susceptibility to chlorhexidine gluconate in some bacteria, an increase in the minimum inhibitory concentration for a biocide in a microorganism does not necessarily result in a failure of the biocide to effectively kill the organism.[35,36]

In our trial, we found an incidence of LRTI in 119 patients (12.5%). An SSI was found in 92 patients (9.6%). We achieved relative risk reductions of more than 60% in patients decontaminated with chlorhexidine gluconate. Because our study group is a large population containing surgical patients of all ages, with a wide range of surgical procedures and risk factors present, we believe these results are generalizable to other surgical disciplines. Analysis showed it is sufficient to decontaminate 1 day preoperatively, and the protocol is simple enough that it could be accomplished in an ambulatory setting for patients who are hospitalized on the day of surgical procedures. According to our NNT analysis, 1 extra nosocomial infection can be prevented if 16 patients are decontaminated with chlorhexidine gluconate. Thus, with this inexpensive preventive measure (daily cost price, €6 [US $7.20]; average duration of decontamination, 2 days), the cost to prevent 1 nosocomial infection is only €192 or US $230.

For our study, we excluded patients receiving selective decontamination of the digestive tract. This high-risk population would be of interest for further research to compare chlorhexidine gluconate with a more expensive selective decontamination of the digestive tract protocol, which uses antibiotics, having an increased risk of developing microbial resistance.

Over time, 3 patterns of *S aureus* nasal carriage can be distinguished. Approximately 20% of the general population chronically carries *S aureus* in their nares. Approximately 60% are intermittent carriers. In the remaining 20%, *S aureus* is never isolated.[13] In the general population, a mean carriage rate of 37% is reported.[13] In our trial, a mean *S aureus* nasal carriage of 33.7% was found. After decontamination of the nose with chlorhexidine gluconate, positive cultures for *S aureus* were reduced by 57.5%. In the placebo group, the prevalence of positive cultures remained at a comparable level (Figure 2).

Figure 2. *Staphylococcus aureus* Nasal Carriage Over Time for Chlorhexidine Gluconate and Placebo Groups



For the chlorhexidine gluconate group, the within-group comparisons of nasal culture positive for *S aureus* taken at admission (36.5%) and at surgery (15.5%) was significant ($P<.001$). For the placebo group, the within-group comparisons of nasal culture positive for *S aureus* taken at admission (30.7%) and at surgery (24.5%) was not significant ($P=.21$). For the analysis of nasal cultures within patients in time, a general linear model (repeated measures) was used.

Although we found an important reduction in deep SSI, prevention of superficial SSI was not achieved. Possibly, prevention of superficial SSI could be accomplished if nasal decontamination with chlorhexidine gluconate were continued for a longer period. To determine if this hypothesis is correct, further studies should be performed with large sample sizes to obtain sufficient power. An alternate explanation for the lack of effect on superficial SSI is in the trend of more *S aureus* isolates in deep than in superficial SSI (73% vs 57%, respectively).

Our study does have potential limitations. A method that would decontaminate both the nose and the oropharynx simultaneously was used. It could be argued that it is not possible to iden-

tify the reason for the reduction in nosocomial infection because it is not possible to discriminate between the decontaminated regions. However, it is known that potentially pathogenic microorganisms located in the nose are associated with SSI, whereas oral health is associated with LRTI.

Decreased colonization rates of the oral cavity after administrating chlorhexidine gluconate have been extensively reported in literature.[14,18,19,21] Decontamination of the nose by chlorhexidine gluconate has not been previously studied in an adequate fashion. The clinical relevance of oral and nasal decontamination has not yet been proven by well-designed research; therefore, we designed this clinical trial and included culturing of the nose to evaluate the effectiveness of chlorhexidine gluconate in decontaminating the nares and not to take cultures from the oropharynx.

In conclusion, we found significant risk reductions of nosocomial infection in patients undergoing cardiac surgery and treated with chlorhexidine gluconate. This safe and inexpensive disinfectant is effective in decontaminating the nasopharynx and oropharynx, resulting in less LRTI and SSI, and should be considered in the preoperative preparation of a patient undergoing cardiac surgery.

Author Contributions: Dr Segers had full access to all of the data and takes full responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition of the data: Segers, Speekenbrink, de Mol.
Analysis and interpretation of the data: Segers, Speekenbrink; Ubbink, de Mol.
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Statistical analysis: Segers, Ubbink.
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Independent Statistical Analysis: Dr Segers had full access to all of the data used in the study and performed an independent analysis in close supervision with Dr Ubbink, from the Departments of Clinical Epidemiology, Biostatistics, and Bioinformatics and Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.
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