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Impact of treating *Staphylococcus aureus* nasal carriers on wound infections in cardiac surgery

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Summary *Staphylococcus aureus* is a common cause of postoperative wound infections, and nasal colonization by this organism is an important factor in the development of infections. Treatment with mupirocin can eradicate the organism in the short term, and prophylactic treatment of colonized patients may prevent postoperative *S. aureus* infections. A double-blind, randomized, placebo-controlled trial was performed to determine whether nasal mupirocin administered pre-operatively to *S. aureus* carriers reduces the rates of sternal and leg wound infections after cardiac surgery. The study enrolled 263 patients with nasal *S. aureus* undergoing elective cardiac surgery at St. Michael's Hospital, Toronto, Canada. Patients were assessed for infections in the immediate postoperative period and two months later. Two hundred and fifty-seven patients were included in the intention-to-treat analysis and re-analysed according to the actual treatment applied. Wound infections occurred in 17 (13.5%) mupirocin recipients and 11 (9.1%) placebo recipients ($P = 0.319$), with seven (5.4%) and six (4.7%) sternal infections, respectively. Two (1.6%) wound infections were acquired postoperatively in the mupirocin group, neither of which were caused by *S. aureus*. The placebo group had three (2.4%) nosocomial wound infections, with two (1.6%) *S. aureus* bacteraemias ($P = 0.243$). Among patients receiving mupirocin, 106 (81.5%) cleared *S. aureus* compared with 59 (46.5%) patients receiving placebo ($P < 0.0001$). There was no significant difference between intention-to-treat and actual treatment groups. Prophylactic intranasal mupirocin administered to *S. aureus* carriers did not reduce the rates of overall surgical site infections by

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S. aureus, and only showed a trend towards decreased incidence of nosocomial *S. aureus* infections.

Introduction

Wound infections contribute substantially to morbidity and mortality following cardiothoracic surgery,[1–3] and deep chest infections have a mortality of 10–40%.[4–6] The Centers for Disease Control and Prevention estimate that surgical infection risk associated with cardiothoracic procedures is 1–33%.[7] Deep and superficial chest infections are implicated in 0.5–5% of cases,[3,5–10] and leg wound infections may complicate 6.8% of cases.[10] The economic impact of postoperative wound infections is substantial.[11–13]

Staphylococcus aureus is the most common microorganism responsible for wound infections, causing up to 80% of deep sternal infections.[14,15] *S. aureus* is found in the anterior nares, and while asymptomatic carriage is common, colonization appears to be a major factor in the development of infections.[16–20] Studies examining the effects of nasal colonization on cardiothoracic wound infection have suggested that this was a major independent risk factor for infection.[21] The authors have previously reported similar results showing that 10.8% of *S. aureus* carriers developed sternal wound infection (90% due to *S. aureus*) compared with 1.8% of non-carriers (47% due to *S. aureus*) ($P < 0.001$).[22]

It is possible that eradication of nasal *S. aureus* may prevent surgical wound infections. Topical mupirocin is the agent of choice for elimination of nasal *S. aureus*.[23] A clinical trial was conducted to determine whether pre-operative intranasal mupirocin applied to colonized patients would decrease the rates of *S. aureus* wound infections and affect the overall infection rates after cardiothoracic surgery.

Methods

Study design and patients

This randomized, double-blind, placebo-controlled trial was approved by the ethics board. Patients undergoing elective open-heart surgery at St. Michael's Hospital, Totonto, Canada between March 1997 and March 2003 were screened for *S. aureus* nasal carriage two weeks before surgery.

Only colonized patients were enrolled in the study after giving their informed consent. Patients were randomized to receive either 2% mupirocin ointment or an identical-appearing placebo administered intranasally (with a Q-tip cotton applicator to the vestibule of both nares) twice daily for seven days before surgery. Mupirocin 2% was contained in a base of polyethylene glycol 400 and polyethylene glycol 3350, and placebo contained the base only. The randomization numbers were computer generated with a 1:1 ratio for mupirocin and placebo, and the code was available to the research pharmacist. A research assistant contacted the patients directly to screen for side effects. Standard pre-operative clinical practice included a full shower or bath with chlorhexidine antiseptic soap (2%) 12 h pre-operatively, surgical site cleansing with 4% chlorhexdine solution with 4% isopropyl alcohol pre-operatively, and administration of routine antibiotic prophylaxis starting just before surgery. Antibiotic prophylaxis consisted of cefazolin 1 g every 8 h (or clindamycin in those with penicillin allergy) for 24 h.

Microbiology and follow-up

A sterile cotton swab (Starswab, Starplex Scientific, Ontario, Canada) moistened with sterile water was rubbed along the entire inner surface of both nostrils and plated on to blood agar for *S. aureus* culture, using standard laboratory techniques. Nasal cultures were obtained two weeks before surgery and again at admission just prior to surgery. Wound swabs or aspirates were obtained postoperatively under aseptic conditions from any wound with evidence of inflammation (redness, tenderness, swelling or fluctance). Intra-operative wound cultures were obtained from patients having surgical wound drainage or debridement and blood cultures were obtained from all febrile and septic patients. Prospective wound surveillance was carried out by a research assistant, who reviewed microbiology logs and nursing reports to detect potential wound infections on a bi-weekly basis. All patients were treated equally, as the research assistant was unaware of the randomization assignment. Each surgeon completed a formal postdischarge surveillance six to eight weeks after surgery. General

practitioners (GPs) and patients were contacted by telephone twice monthly to ensure the absence of wound infections following discharge. Additionally, patients were asked to telephone the investigators if they developed signs of infection. Wound infections were classified as superficial, deep or deep organ space infections according to the Nosocomial Infection Surveillance System definitions.[7] A surgical site infection (SSI) was defined by the occurrence of one of the following within eight weeks of surgery: the presence of exudate from the wound, the edges of the wound were erythematous beyond 2 cm margin the wound culture yielded a pathogen with signs of inflammation, or a physician stated in the medical record that the surgical site was infected as corroborated by one or more of the listed criteria.

Statistical analysis

The authors' previous study showed that the risk of *S. aureus* sternal infection in untreated carriers was 8.2% [95% confidence intervals (CI) 4.3—14.7%], whereas the risk in mupirocin-treated patients was 0% (95% CI 0—6.3%).[24] Thus, in order to achieve an alpha error of <0.05 and a power of 0.8, 95 patients would be needed in each group for a one-tailed test and 115 patients would be needed for a two-tailed test. The rate of any wound infection at surgical sites was the primary endpoint. The secondary endpoints were the rates of *S. aureus* infections, the rates of overall nosocomial infections and nosocomial *S. aureus* infections, the rates of nasal *S. aureus* clearance, and the rates of deaths and complications due to infections. The patients were initially analysed according to intention-to-treat and the actual treatment applied. Data were analysed using SPSS. Categorical variables were compared in univariate analysis using Chi-squared test or Fisher's exact test. Continuous variables were analysed using Student's *t*-test or the Mann-Whitney test. Variables deemed to be clinically important were used as covariates in a logistic-regression analysis to evaluate their effect on outcome. All tests were two-tailed and a *P* value of less than 0.05 was considered to be clinically significant. Blinding was maintained until after analysis by the pharmacist, who divided the treatment groups into A and B.

Results

Two hundred and sixty-six patients were eligible for the study, three of whom were eliminated prior to randomization as no study drug was dispensed. The remaining 263 patients were randomized to mupirocin or placebo. Of these, five were excluded from analysis due to cancellation of surgery (four in the mupirocin group and one in the placebo group). One patient was excluded from the intention-to-treat analysis alone, as it was not clear to which treatment he was randomized; he used mupirocin on his own initiative. Of the 257 patients included in the intention-to-treat analysis, 130 received mupirocin and 127 received placebo. The patients in the placebo group who used mupirocin as well as, or instead of, placebo (three patients), were then re-analysed in the mupirocin group (actual treatment analysis). One patient in the placebo group did not use the dispensed therapy and was re-analysed in the same group. Follow-up was complete.

Patients in the two groups were similar with respect to demographic characteristics, premorbid illnesses, and pre- and postoperative complications and care (Table I). Only chronic obstructive pulmonary disease (COPD) was significantly more prevalent in the mupirocin group compared with the placebo group (10% vs 1.6%; $P = 0.006$).

Overall, nasal carriage of *S. aureus* was eliminated in 81.5% of patients receiving mupirocin and 46.5% of patients receiving placebo ($P < 0.0001$) (Table I).

In the initial intention-to-treat analysis, the overall rates of infection were 18 (13.8%) and 11 (8.6%) ($P = 0.319$), with seven (5.4%) and six (4.7%) sternal infections in the mupirocin and placebo groups, respectively (Table II). The odds ratio for infection when adjusted for diabetes, smoking, hypertension, COPD, immunosuppression and obesity was 1.61 (95%CI 0.69—3.75). The total number of nosocomial wound infections was two (1.6%) in the mupirocin group and three (2.4%) in the placebo group ($P = 0.243$). The total number of *S. aureus* infections was five (3.8%) and four (3.2%) in the mupirocin and placebo groups, respectively; however, nosocomial *S. aureus* infections leading to bacteraemia and serious complications including death only occurred in the placebo group ($N = 2$, 1.6%, $P = 0.243$) (Tables II and III). Most infections ($N = 11$, 65% of all infections in this group) in the mupirocin group were leg infections reported by GPs on follow-up, with no microbiology data and no significant morbidity (Table III). Infections developed in eight of the 59 patients who were colonized with *S. aureus* at the time of surgery (10.9%) compared with 17 of the 156 patients who cleared *S. aureus* (13.6%). This was not a statistically significant difference. Of the patients who did not have repeat nasal swabs, four (12.5%) had infections.

When patients who took mupirocin on their own initiative were re-analysed in the mupirocin group,

Table I Characteristics of the patients in the intention-to-treat population according to study group[a]

Characteristics	Mupirocin	Placebo
Sex — N (%)		
Male	111 (85.4%)	109 (85.8%)
Female	19 (14.6%)	18 (14.2%)
Age — years	62.5 ± 10.8	62.5 ± 10.5
Body mass index	28.7 ± 4.6	29.4 ± 4.0
Diabetes — N (%)	37 (28.5%)	36 (28.3%)
Hypertension — N (%)	70 (53.8%)	78 (62.4%)
Smoking — N (%)		
Current	41 (31.5%)	50 (39.4%)
Ex-smoker	69 (53.1%)	54 (42.5%)
Never smoked	19 (14.6%)	21 (16.5%)
COPD — N (%)[b]	13 (10%)	2 (1.6%)
Obesity — N (%)	47 (36.2%)	51 (40.2%)
Cancer/immunosuppression — N (%)	12 (9.2%)	9 (7.1%)
Renal disease — N (%)	8 (6.2%)	7 (5.5%)
Prior sternotomy — N (%)	4 (3.1%)	7 (5.5%)
Duration of pre-operative stay — days:		
0	103 (79.2%)	95 (74.8%)
1	24 (18.5%)	25 (19.7%)
>1	3 (2.3%)	7 (5.5%)
Duration of surgery — min		
Median (25th–75th percentile)	160 (145–180)	160 (140–190)
Valve replacement — N (%)	24 (18.5%)	26 (20.5%)
CABG surgery — N (%)	113 (86.9%)	107 (84.3%)
Blood product transfusion — N (%)	72 (55.4%)	59 (46.5%)
Re-exploration — N (%)	12 (9.3%)	8 (6.3%)
Duration of postoperative ventilation — h		
Median (25th–75th percentile)	12.5 (8.3–20)	14 (8.8–21)
Postoperative nasal carriage of *S. aureus* — N (%)[c]	6 (4.6%)	54 (42.5%)

COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft.
[a] Numbers indicate mean $\pm$ standard deviation.
[b] $P = 0.006$ for comparison of the mupirocin and placebo groups.
[c] $P < 0.0001$ for comparison of the mupirocin and placebo groups (postoperative nasal culture was not obtained for 18 patients in the mupirocin group and 14 patients in the placebo group).

no significant difference was noted. The only independent predictor of infection, when adjusted for age, sex, diabetes, hypertension, cancer, renal disease, smoking and COPD, was obesity ($P = 0.034$). When *S. aureus* colonization status at the time of surgery was included in the multivariate regression analysis, it was not predictive of infection. Patients undergoing operations during the outbreak of severe acute respiratory syndrome in Toronto had significant delays between treatment and surgery. These patients were not re-screened pre-operatively.

There were four deaths in the mupirocin group and five deaths in the placebo group. None of the deaths in the mupirocin group were attributable to an infection, whereas one death in the placebo group was directly related to *S. aureus* infection and one death was a result of pneumonia escalating to multi-organ failure. None of the *S. aureus* isolates from either nasal or wound cultures were meticillin resistant. No adverse effects were reported for either mupirocin or placebo.

Discussion

Colonization with *S. aureus* is associated with subsequent infection.[25] Mupirocin is a topical antibacterial ointment with demonstrated benefits in eradicating colonization with *S. aureus*.[26–28] A recent meta-analysis of topical mupirocin in patients undergoing dialysis indicated that use of this therapy reduced the rate of *S. aureus* infections by 68%.[29] The efficacy of mupirocin in preventing *S. aureus* postoperative infections, however, remains controversial. Several retrospective or case–control studies have reported lower rates of SSIs among patients receiving pre-operative mupirocin

Table II   Overall and site-specific rates of infection in intention-to-treat analysis according to study groups

Variable	Mupirocin	Placebo	*P* value	Odds ratio	95% CI
Total infections	18 (13.8%)	11 (8.6%)	0.266	1.61	0.69–3.75
Sternal infections	7 (5.4%)	6 (4.7%)	1.00	1.14	0.37–3.50
Leg infections	11 (8.5%)	5 (3.9%)	0.196	2.25	0.76–6.66
NNIS wounds:					
Superficial	17 (13%)	9 (7.1%)	–	–	–
Deep	1 (0.8%)	1 (0.8%)	–	–	–
Deep space occupying	0 (0%)	1 (0.8%)	–	–	–
In-hospital wound infections	2 (1.6%)	3 (2.4%)[a]	0.672	0.65	0.10–3.93
Nosocomial *S. aureus* infections	0 (0%)	2 (1.6%)[b]	0.243	–	–
Total *S. aureus* infections	5 (3.8%)	4 (3.2%)	1.00	1.23	0.32–4.69

S. aureus, *Staphylococcus aureus*; NNIS, Nosocomial Infection Surveillance System; CI, confidence interval.

[a] Two of these infections were due to *S. aureus* (and listed in the row below) and the rest were leg wounds either not cultured or yielding no organism.

[b] Both patients had *S. aureus* bacteraemia.

compared with historical controls.[30–32] Randomized, controlled studies have not confirmed these results.[33,34]

In this randomized, controlled, double-blind study, there was no significant reduction in the total number of SSIs or *S. aureus*-related infections in the mupirocin group. However, the two cases of *S. aureus* bacteraemia occurred in the placebo group. These results are similar to two recent randomized-controlled studies, with a caution that these studies enrolled all consecutive patients, whereas only those colonized with *S. aureus* were enrolled in the present study.[33,34] Perl *et al.*[33] enrolled 4030 patients undergoing different types of surgery. Prophylactic intranasal mupirocin did not reduce *S. aureus* SSIs significantly, but it decreased the rate of nosocomial *S. aureus* infections among patients who were *S. aureus* carriers.[31] Similarly, Kalmeijer *et al.*[34] enrolled 614 patients undergoing orthopaedic surgery, but only

181 patients were colonized with *S. aureus* at baseline. Although the *S. aureus* infection rate was five times lower in the mupirocin group, the SSI rate and the duration of hospitalization were not reduced significantly.[34]

The present study had some limitations. The SSI rates with *S. aureus* are probably too low to detect a difference with the sample size enrolled, and this is also true of the other randomized studies. In retrospect, the expected SSI rate in subjects colonized with *S. aureus* was overestimated. Another factor of importance is that some of the wound infections reported by GPs were not confirmed by any of the investigators or corroborated by microbiological cultures. Moreover, it was surprising that 46% of the placebo patients cleared nasal *S. aureus* colonization before surgery, which could have resulted in low *S. aureus* SSI rates. These results are in contrast to other randomized studies. Nasal carriage of *S. aureus* was eliminated in 83.4% of patients treated with mupirocin and 27.4% treated with placebo in the study by Perl *et al.*[33] In residents of long-term-care facilities, mupirocin eradicated *S. aureus* colonization in 93% of patients compared with 15% in the placebo group.[28] The reason for the high rate of nasal *S. aureus* elimination in the placebo group in the present study is unclear. It should be noted that mupirocin could be purchased without a prescription in Ontario prior to 2000, thus raising the question of compliance with the assigned treatment regimen.

One of the main concerns with widespread use of prophylactic mupirocin is the development of resistance. This has been reported mainly with long-term use in patients on dialysis.[35,36] Short-term use did not select for mupirocin-resistant *S. aureus*.[33]

Table III   Microbiology of wounds cultured according to study group

Variable	Mupirocin	Placebo
Staphylococcus aureus infections		
Sternal	4 (3.1%)	4 (3.2%)[a]
Leg	1 (0.8%)	0
Blood	0	2 (1.6%)
Total *S. aureus* infections	5 (3.8%)	4 (3.2%)
Other infections	12 (9.2%)	7 (5.5%)
Pseudomonas aeruginosa	1 (0.8%)	0
Enterobacter cloacae	0	1 (0.8%)
Coliforms	0	1 (0.8%)
Unknown	11 (8.5%)	5 (3.9%)

[a] Two of the four patients with sternal infection had bacteraemia and are included under 'Blood *S. aureus* infections'.

A possible source of bias in trials with subjective endpoints is the lack of blinding during analysis of the results. The present study maintained blinding until analysis was completed.

In conclusion, this study failed to show benefit of mupirocin in reducing SSIs or *S. aureus* infections in subjects with nasal *S. aureus* colonization undergoing cardiothoracic surgery. Future randomized studies should be performed on high-risk patients with *S. aureus* colonization (i.e. those with established risk factors such as diabetes, obesity, smoking, etc., in whom eradication may be effective in preventing infections) in large multi-centre trials. Current evidence does not support mupirocin use for routine surgical prophylaxis.

Acknowledgements

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