Randomized trial

Randomized clinical trial of preoperative intranasal mupirocin to reduce surgical-site infection after digestive surgery

Y. Suzuki, T. Kamigaki, Y. Fujino, M. Tominaga, Y. Ku and Y. Kuroda

Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kobe University, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

Correspondence to: Dr Y. Suzuki (e-mail: szk@med.kobe-u.ac.jp)

Background: **Compromised patients subjected to major digestive surgery frequently develop infective complications caused by methicillin-resistant *Staphylococcus aureus* (MRSA), which may have dangerous consequences. This was a prospective randomized study to determine whether intranasal mupirocin could reduce postoperative infective complications in patients having digestive surgery.**

Methods: **A total of 395 patients who underwent abdominal digestive surgery were assigned randomly into two groups: a treated group (193 patients) and controls (202). Patients in the treated group were given 30 mg mupirocin calcium hydrate ointment topically to each nostril three times a day on each of the 3 days before operation. The untreated group received no mupirocin treatment.**

Results: **Most infections were due to Gram-negative bacteria in both groups. There were 21 Gram-positive infections detected at the surgical site, ten in the treated group and 11 in control patients. The incidence of pneumonia was significantly different between the groups (none in the treated group and five in control patients; $P = 0{\cdot}028$). Four of five patients with pneumonia had a sputum culture containing MRSA.**

Conclusion: **Intranasal mupirocin treatment had no significant impact on surgical-site infection after digestive surgery.**

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Introduction

Digestive surgery is more frequently associated with postoperative surgical-site infection than cardiopulmonary surgery. Most infections are caused by Gram-negative bacteria. However, immunocompromised patients and those who need aggressive perioperative antibiotic treatment tend to develop infections caused by Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), which is a serious and increasing complication in most centres[1].

In 1959 Williams *et al.*[2] and Weinstein[3] reported the correlation between nasal *S. aureus* carriage and wound infection after surgery. More recently, Kluytmans *et al.*[4] reported that nasal carriage of *S. aureus* correlated with sternal wound infection after cardiac surgery. This wound infection rate was reduced by eradicating *S. aureus* from the nasal passage with intranasal mupirocin in a series of cardiac patients[5].

This aim of this randomized clinical trial was to determine whether intranasal mupirocin could reduce postoperative sepsis rates, including wound infection, after digestive surgery.

Patients and methods

Patients

The trial design was approved by the local ethics committee. Informed consent was obtained from all participants. A total of 395 consecutive patients who underwent abdominal digestive surgery between June 1998 and December 2000 in Kobe University Hospital were enrolled. Colorectal and laparoscopic procedures were excluded. The patients were randomly assigned into two groups by drawing lots in sealed envelopes within 1 week of surgery. One hundred and ninety-three patients in the treated group were given 30 mg mupirocin calcium hydrate ointment (Bactroban®; SmithKline and Beecham Pharmaceuticals, Tokyo, Japan)

Table 1 Randomized trial of perioperative intranasal mupirocin: clinical details

	Mupirocin ($n = 193$)	Control ($n = 202$)
Age (years)*	63(12) (15–84)	62(13) (19–91)
Sex ratio (M : F)	127 : 66	135 : 67
Preoperative morbidity	59	61
Diabetes	34	42
Liver cirrhosis	25	19
Prophylactic antibiotics		
Cefotiam	78	76
Cefazolin sodium	51	55
Flomoxef	49	53
Cefmetazole	12	10
Others	3	8

*Values are mean(s.d.) range.

via Q-tip swab to each nostril three times a day on each of the 3 days before operation. The control group of 202 patients received no intranasal mupirocin prophylaxis. The two groups were well matched with respect to age, sex, and preoperative diabetes and liver cirrhosis (*Table 1*).

Perioperative management

All patients had an antiseptic shower with chlorhexidine (Hibitane gluconate solution®; Sumitomo Pharmaceuticals, Osaka, Japan) either the evening before, or on the morning of surgery. Hair removal was performed in the ward on the day before surgery using a safety razor. The abdomen was prepared with 10 per cent aqueous povidone–iodine solution in the operating room before surgery. Immediately after laparotomy, the abdominal wounds were covered with a plastic wound ring drape[6,7]. Immediately after surgery, and once during each 8-h shift until removal of drains and sutures, all incisions were painted with 10 per cent aqueous povidone–iodine. Prophylactic intravenous antibiotics were started during operation, followed by the same regimen every 12 h for 4–5 days after surgery. The antibiotics used were mostly cefotiam, cefazolin sodium or flomoxef, and their use was comparable between the groups (*Table 1*).

Surgical techniques

There were no significant differences in the type and magnitude of the operations between the groups (*Table 2*). In 12 patients who had two operations simultaneously, such as total gastrectomy with cholecystectomy, only the bigger procedure was listed in *Table 2*.

Most of the operations included in this study were performed by one of four senior surgeons using standard procedures. Patients had a laparotomy through a midline incision except those undergoing liver resection, most of whom had subcostal or transverse incisions with a midline extension.

Table 2 Operations performed in randomized trial of perioperative intranasal mupirocin

Operations	Mupirocin ($n = 193$)	Control ($n = 202$)
Gastrectomy	95	100
Total	31	30
Distal	58	67
Partial	6	3
Liver resection	33	31
Major	19	17
Segmental/partial	14	14
Pancreas resection	31	33
Total	10	9
Whipple	17	18
Distal	4	6
Open cholecystectomy	10	15
Gastrojejunostomy	7	6
Hepaticojejunostomy	3	5
Exploratory laparotomy	3	2
Others	11	10

Diagnosis of postoperative infection

The diagnosis of infective complications was made by a trained infection team consisting of digestive surgeons and radiologists with an assessor-blinded technique. Surgical-site infections were diagnosed according to standard criteria developed by the Centers for Disease Control and Prevention[8]. Briefly, a superficial wound infection was diagnosed within 30 days of operation, based on purulent drainage from the wound and a positive bacterial culture, but without evidence of intraperitoneal abscess. Intraperitoneal abscesses diagnosed within 30 days of surgery by computed tomography (CT) and with positive cultures from percutaneous aspiration or drainage were classified as a deep infection, regardless of whether superficial infection was also present. Systemic infections included pneumonia, urinary tract infection and liver abscess, and were diagnosed by the same team based on clinical symptoms and findings from chest radiography, sputum and urinary culture, and CT respectively. Pneumonia was defined as the presence of patchy bronchopneumonic infiltrates or consolidation on chest radiography, with at least one clinical symptom (fever, productive cough, pleuritic chest pain or dyspnoea), and was confirmed by a positive sputum culture. All pneumonias were diagnosed within 14 days after surgery. Three of four patients with liver abscesses underwent percutaneous drainage.

Table 3 Postoperative infections in the randomized trial of perioperative intranasal mupirocin

	Mupirocin ($n = 193$)				Control ($n = 202$)			
	Gram −	Gram +	Mixed	Total	Gram −	Gram +	Mixed	Total
Surgical site	18	4	6	28 (11)	11	5	6	22 (8)
Superficial	3	2	1	6 (1)	2	5	2	9 (1)
Deep	15	2	5	22 (10)	9	0	4	13 (7)
Systemic	3	1	0	4	1	5	0	6
Pneumonia	0	0	0	0	0	5*	0	5
Urine	0	1	0	1	0	0	0	0
Liver	3	0	0	3	1	0	0	1
Total	21	5	6	32	12	10	6	28

Values in parentheses are number of secondary infectious complications following anastomotic leakage or pancreatic fistula. *$P = 0{\cdot}028$ *versus* mupirocin group (χ^2 test).

Statistical analysis

Data were analysed with the χ^2 test. $P < 0{\cdot}050$ was considered statistically significant.

Results

A total of 60 infective complications were diagnosed after surgery (*Table 3*). There were 28 surgical-site infections (six superficial and 22 deep) in the mupirocin group and 22 (nine superficial and 13 deep) in controls. There was no significant difference between the groups. Nine of 35 deep surgical-site infections occurred as secondary complications following an anastomotic leak (seven bile leaks and two gastrojejunostomy leaks); eight were due to pancreatic fistula. This profile did not differ significantly between the groups. Most surgical-site infections were caused by Gram-negative bacteria in both groups. Twenty-one Gram-positive infections were detected at surgical sites, ten in the mupirocin group and 11 in controls. Among them, 12 were concomitant infections with Gram-negative bacteria. Infection was caused by Gram-positive bacteria alone in four (2·1 per cent) of 193 patients treated with mupirocin and five (2·5 per cent) of 202 control patients.

Regarding systemic infection, there were three liver abscesses and one urinary tract infection in the mupirocin group, and five pneumonias and one liver abscess in the control group. Only the difference in incidence of pneumonia reached statistical significance ($P = 0{\cdot}028$). Two of the patients with pneumonia had received antibiotics for a preceding intra-abdominal abscess.

Infective complications were more common after major surgery including pancreas, liver and gastric resections in both groups. Total pancreatectomy and pancreaticoduodenectomy, in particular, were followed by a high incidence of infection.

Altogether 27 bacteria, including methicillin-sensitive *S. aureus* (MSSA), MRSA, *Staphylococcus epidermidis* and *Streptococcus* spp., were identified (11 in the mupirocin group and 16 in controls; $P = 0{\cdot}382$). The incidence of *S. aureus* in the treated group was four (2·1 per cent) of 193 compared with nine (4·6 per cent) of 202 ($P = 0{\cdot}185$) in the control group. Sputum cultures from all patients with pneumonia revealed Gram-positive bacteria, including MRSA in four patients and MSSA in one.

Discussion

Seriously ill patients who require major surgery and perioperative antibiotics often develop infective complications caused by Gram-positive bacteria, including MRSA. Bacterial resistance has dangerous consequences after digestive surgery. To control the emergence and spread of antimicrobial-resistant bacteria, represented by MRSA, is of importance in a digestive surgery unit.

Mupirocin is an antibiotic produced by fermentation of *Pseudomonas* bacteria, resulting in a naturally occurring drug that is very active against staphylococci, including MSSA and MRSA. Mupirocin can, however, only be used topically[9].

Nasal bacterial cultures were not taken in the present study because of limitations of health insurance coverage, a limitation to the study. Nasal *S. aureus* carriage and its eradication with intranasal mupirocin have been reported widely in the literature. Previous studies have suggested that nasal carriage rates of *S. aureus* are approximately 20 per cent[5,9]; intranasal mupirocin can eradicate *S. aureus* in the nose in at least 90 per cent of patients and healthcare workers[10–12]. Long-term follow-up has confirmed that the eradication persists. Recurrence rates of *S. aureus* nasal carriage have been reported as 26, 41, 58 and 62 per cent

at 1, 3, 6 and 12 months respectively after simple intranasal prophylaxis[13].

In previous series, intranasal mupirocin has been shown to reduce postoperative infection after cardiac surgery[4,5]. In the present series of patients having digestive surgery, the rate of superficial and deep abdominal wound infections caused by Gram-positive pathogens was not affected by mupirocin treatment. The only positive result was that postoperative pneumonia caused by *S. aureus* was significantly reduced in the group that had mupirocin. Eradication of intranasal Gram-positive bacteria might have prevented postoperative pneumonia caused by pathogens spreading into the intrapulmonary bronchi or alveoli. Covering the wounds with a ring drape[6,7] and postoperative dressing might have been as effective in preventing Gram-positive infection via the operating air and patients' own skin. Substantial Gram-negative surgical-site infections seen in this series were probably caused by contamination of surgical sites with endogenous bacteria originating from the digestive tract.

Most patients in this series received prophylactic antibiotics for 4 days after surgery; patients who had high-risk surgery, including major hepatectomy and pancreatectomy, had antibiotics for 5 days. Although the optimal duration of antibiotic prophylaxis in clean-contaminated surgery is still debated, the authors recently reduced the duration of administration to 3 days in such surgery, according to recent advice on good practice.

The mechanisms and routes of surgical-site Gram-positive infection seem to be more complex in digestive surgery. Infection with Gram-positive bacteria frequently occurs in conjunction with Gram-negative infection, and subsequent prolonged antibiotic therapy tends to be overused. In such patients, alteration of host defence, bacterial flora and immune responses contribute to the susceptibility to Gram-positive infection. In fact, 12 of 21 Gram-positive bacterial infections were identified synchronously or metachronously in patients with Gram-negative surgical-site infections. Two of five patients with pneumonia had received antibiotics for a preceding intra-abdominal abscess. This makes analysis difficult and complex, although the incidence of Gram-positive infection alone was comparable between the groups (2·1 *versus* 2·5 per cent).

From the present results, it is concluded that intranasal mupirocin treatment had no significant impact in prevention of surgical-site infection after digestive surgery.

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