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Mupirocin for the reduction of colonization of internal jugular cannulae—a randomized controlled trial

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Summary: In a prospective study, 218 cardiothoracic patients, in whom 'Abbocath-T" cannulae had been inserted preoperatively into the internal jugular vein, were randomized to receive skin preparation of the insertion site with tincture of iodine (108 controls) or tincture of iodine followed by application of sterile 2% calcium mupirocin ointment (110 test patients). Cannulae were usually removed within 48 h of the operation. Patients receiving mupirocin were less likely to develop significant colonization of one or more of their cannulae as judged by Maki's criterion of a yield of >15 colony forming units (cfu) from a cannula segment rolled on an agar plate (17% of mupirocin treated patients compared with 54% of the controls, $P < 0{\cdot}001$). Coagulase-negative staphylococci, micrococci, or both, were the commonest isolates and were cultured from 70% of the 186 control cannulae compared with 24% of 172 cannulae inserted through mupirocin-treated skin ($P < 0{\cdot}001$). A count of more than 15 cfu was found on the tips of 25% control cannulae compared with 5% of the cannulae from mupirocin-treated patients, an effect which was independent of *in-situ* time ($P < 0{\cdot}001$). For cannulae with colonized tips, the same species was isolated from the skin of the insertion site in 67%, from the exterior of the hub in 61% and from the lumen in only 15%. There were no side effects attributed to mupirocin or superinfection with resistant organisms. We conclude that in cardiothoracic patients the application of mupirocin after standard skin preparation with tincture of iodine significantly reduces the colonization of central venous cannulae by organisms derived from the skin insertion site.

Keywords: Mupirocin; jugular cannulae; skin preparation.

Introduction

Although modern medicine and surgery are often dependent on the use of intravascular cannulae, colonization of cannulae, particularly with staphylococci derived from the skin of the insertion site, may progress to local sepsis and episodes of life-threatening septicaemia (Maki, 1982; Elliot,

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1988). In a European survey of 10 616 surgical patients, 4·48% of those with central venous lines acquired a bacteraemia (Nystrom *et al.*, 1983). In the USA up to one-third of all hospital-acquired bacteraemias are derived from vascular cannulae (Maki, 1982) and in one UK hospital, infection of central venous cannulae was the commonest focus for bacteraemia with *Staphylococcus aureus* (Gransden, Eykyn & Phillips, 1984).

Appropriate antimicrobial chemoprophylaxis may reduce the risk of cannula-related infection (Pezzarossi *et al.*, 1986; Maki & Ringer, 1987) but once an infection is established, systemic therapy may be ineffective and the cannula has to be removed (Peters & Pulverer, 1984; Young & Sugarman, 1985; Editorial, 1988). Application of a topical antibiotic to the skin of the insertion site has in general not been of benefit (Norden, 1969; Zinner *et al.*, 1969;) although ointment containing polymyxin, neomycin and bacitracin reduced colonization of cannulae in one study by about two-thirds (Maki & Band, 1981).

The recent introduction of mupirocin, a non-systemic antibiotic with high in-vitro anti-staphylococcal activity (Casewell & Hill, 1985; White *et al.*, 1985) and efficacy in the anterior nares (Casewell & Hill, 1986; Hill, Duckworth & Casewell, 1988) and on skin (Casewell & Hill, 1987) prompted us to evaluate its efficacy when applied directly to the cannula insertion site.

Materials and methods

Patients and skin preparation

Between January and September 1987, 244 patients undergoing elective cardiothoracic surgery at King's College Hospital routinely had two, but occasionally one or three, internal jugular cannulae inserted percutaneously into different but adjacent puncture sites, immediately after induction of anaesthesia. Preoperatively, all patients had one to five baths and skin cleansing with 'Triclosan' (Hough, Hoseason & Co Ltd). Routine perioperative chemoprophylaxis consisted of gentamicin (80 mg) plus flucloxacillin (500 mg) or erythromycin (500 mg), both given before cannulation and then 8-hourly for 48 h.

By means of randomization tables, patients were assigned on a weekly basis as 'test' or 'control' for skin preparation of the cannula insertion site; the microbiologists processing the specimens were unaware of the patient's allocation. Control patients received only standard skin preparation of the cannula site with tincture of iodine (2·5% in 90% methyl alcohol). After the tincture had dried the test group received, in addition, a bolus (approximately 10 mm squeezed from a 15 g tube) of sterile 2% calcium mupirocin in a white soft paraffin base (SmithKline Beecham) applied directly to the cannulation skin site. The internal jugular vein was then cannulated through the prepared skin area with two or three 16 gauge, 5·5 inch (12·3 cm) 'Abbocath-T' (Abbott Laboratories Ltd) cannulae using a no-touch technique, but without sterile drapes, gowns or gloves. Test

patients then received a second application of mupirocin to the puncture site. A further application of test or control treatments was made whenever cannulae were re-dressed. For all patients, the cannulation site, cannula hub and giving-set connections were covered and immobilized with 'Op-site' dressing (Smith and Nephew Ltd).

A dedicated research infection control nurse assessed cannula sites for inflammation or the presence of pus at redressing and at decannulation which was usually within 48 h of surgery. Other clinically evaluable data that were recorded included the indications for cardiothoracic surgery, difficulty of cannula insertion, *in-situ* time, antibiotic therapy and all information pertaining to infection including the results of blood cultures and other specimens taken for clinical indications.

Microbiology

The skin of the cannulation site was sampled before the application of antiseptics with a cotton-wool tipped swab moistened in nutrient broth (Oxoid CM1) which was rubbed over an area of approximately 2·5 cm^2. At decannulation, the exterior of the hub and skin adjacent to the cannula and puncture site were sampled with an alginate-tipped swab (Medical Wire Co. Ltd) moistened in nutrient broth. Immediately before decannulation, residual mupirocin adjacent to the insertion site was removed with sterile gauze and an alcohol-impregnated swab. After cannula withdrawal, 5 ml of double-strength nutrient broth from a syringe was flushed through the lumen into 5 ml of double-strength Robertson's cooked meat broth (Oxoid CM81). The sheath was then cut aseptically from the hub and transported to the laboratory in a sterile test tube.

In the laboratory, approximately 50 mm of the intravenous section of the cannula tip and the intracutaneous part of the cannula were rolled back and forth five times across separate blood agar plates according to the semi-quantitative method of Maki (Maki, Weise & Saraffin, 1977) and then placed in cooked meat broths (Oxoid CM81) for enrichment culture. Lumen flush broth (0·005 ml) was inoculated on blood agar and the remainder incubated for enrichment. Semi-quantitative cultures and those of the skin swab and lumen flush were incubated aerobically for 18–24 h. Enrichment broths were sub-cultured after 18–24 h on blood agar plates and incubated aerobically for 18–24 h and anaerobically for 72 h. All incubations were at 37°C. Isolates were identified using standard methods (Cowan, 1974), (API/Bio Merieux UK Ltd). Cannulae yielding organisms by enrichment culture only were defined as contaminated, and those yielding > 15cfu from semi-quantitative cultures of the intracutaneous segment or the tip were considered to be significantly colonized, in accordance with Maki's criterion (Maki, 1982). Antibiotic sensitivities were determined by a controlled disc-diffusion method using 5% lysed horse-blood DST agar (Oxoid CM 261). Methicillin sensitivity was determined at 30°C. Minimum inhibitory concentrations (MICs) of mupirocin were determined as previously described (Casewell & Hill, 1985).

Statistical analysis

The significance of differences between test and control groups was determined with the χ^2 or Fisher's two-sided exact test for categorical data.

Results

Of the 244 patients receiving cardiothoracic surgery, 26 were excluded from the analysis: four patients in the mupirocin group and two controls died of unrelated causes before cannulae were obtained. Ten other patients in each group were excluded because no cannulae were obtained for culture. For the 218 patients studied, the features of the 110 mupirocin patients and the 108 controls were very similar (Table I). In both groups there was a predominance of males aged 50–60 yrs, most of whom underwent coronary artery bypass graft operations. A slightly higher proportion of mupirocin patients (13% compared with 2% controls) received non-standard prophylaxis, mostly because of concern about possible gentamicin- and methicillin-resistant *Staphylococcus aureus* (MRSA) in the hospital for about 10 days. No significant difference for the outcome of cannulae for this subgroup could be detected when compared with the patients in the mupirocin group who had received standard prophylaxis. The majority of patients in both treatment groups had two cannulae inserted into the internal jugular vein—88% in the mupirocin group and 94% in the control group. All patients had at least one cannula cultured and complete data was obtained for 358 cannulae. The cannula-related risk factors including ease of cannulation, *in-situ* time, and the presence of other cannulae at decannulation, were similar for mupirocin and control groups (Table II).

Table I. *Features of patients in mupirocin and control groups*

	Controls	Mupirocin
Number studied	108	110
Median age (range) in yrs	55 (14–75)	58 (30–87)
Male (%)	81	82
Operation (%)		
Coronary artery by-pass graft alone	79	80
Valve replacement	15	16
Both	2·8	1·8
Congenital anomaly correction	9·2	9·8
Aneurysm	0·9	2·7
Prophylaxis (%)		
Gentamicin + flucloxacillin/ erythromycin	98	87
Other	2	13
Number of cannulae (%)		
One	0	3
Two	94	88
Three	6	9

Table II. *Features of cannulae in mupirocin and control groups*

Cannulae cultured	Mupirocin	Controls
Total number	172	186
Cannulation (%)		
Easy	73	79
Difficult	18	18
Unknown	9	3
In situ time (%)		
< 24 h	60	57
24–48 h	29	38
48–120 h	11	5
At decannulation, % from patients:		
with one other cannula in-situ	64	87
with two other cannulae in-situ	0	1
receiving systemic antibiotics	100	100

Although cannula-related bacteraemia was not detected in any of the mupirocin or control patients, and there was no significant difference in the incidence of erythema or pus at the insertion site (Table III), the application of mupirocin was consistently associated with a reduction in the proportion of patients with contamination or colonization of cannulae. As judged by positive enrichment or semiquantitative cultures, there was more than a two-fold reduction in the proportion of patients with one or more contaminated or colonized cannulae: 36% of the mupirocin-treated patients compared with 77% of the controls (Table III; $P < 0{\cdot}001$). The reduction in the proportion of patients with significant colonization of any cannula, as judged by the culture of > 15 cfu from any cannula segment, was even greater: 18 (17%) of the 110 mupirocin patients compared with 58 (54%) of the 108 controls ($P < 0{\cdot}001$).

Figure 1 shows that the proportion of cannulae with colonization (> 15 cfu) of the intracutaneous segment or cannula tip, or with > 15 cfu from 0·005 ml of the cannula lumen flush, increased with *in-situ* time, and that patients were most likely to have positive intracutaneous segments.

Table III. *Patient outcome in mupirocin and control groups*

	No. of patients (%)		
Patients	Mupirocin n = 110	Controls n = 108	*P*-value
Any cannula			
Contaminated or colonized	39 (36)	83 (77)	< 0·001
Colonized (> 15 cfu)	18 (17)	58 (54)	< 0·001
Erythema but no pus	24 (22)	22 (20)	NS*
Pus	1 (1)	3 (2·7)	NS
Cannula-related bacteraemia	0	0	

*NS = not significant.

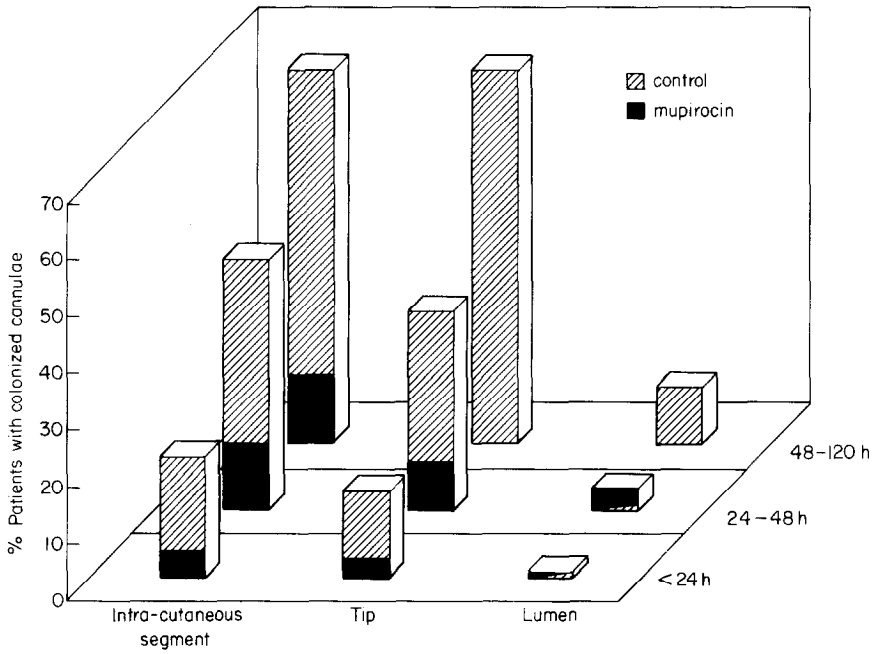

Figure 1. Effect of mupirocin on proportion of patients with one or more colonized cannulae related to *in-situ* time. Colonization defined as > 15 cfu from intracutaneous segment or tip, or from 0·005 ml of lumen flush.

Mupirocin significantly reduced the proportion of patients with culture-positive intracutaneous segments and cannula tips and this was significant ($P < 0{\cdot}001$) regardless of whether the patient had the cannula *in-situ* for < 24 h, 24–48 h or 48–120 h. Only six patients, three in each group, had cannulae with positive luminal cultures.

All species isolated by semi-quantitative or enrichment techniques from any part of the 358 cannulae from the control and mupirocin groups are shown in Table IV. Overall, species considered to be skin flora, i.e. coagulase-negative staphylococci, micrococci, corynebacteria and *Acinetobacter* species accounted for more than 90% of all isolates from both mupirocin and control cannulae. More than one species was isolated from different parts of the same cannula for 24 control and 10 mupirocin cannulae. Cultures, including enrichment, of the cannula tip, intracutaneous segment, and lumen all yielded no growth significantly more often for cannulae that had been inserted through mupirocin treated skin: 64% of 172 cannulae from mupirocin patients compared with 23% of the 186 from the controls ($P < 0{\cdot}001$). If only cannulae from patients who had all their cannulae cultured were considered, the level of significant difference was unaltered as 53% of 119 cannulae from mupirocin patients yielded no growth compared to 12% of 133 control cannulae ($P < 0{\cdot}001$).

Table IV. *Organisms isolated from 358 cannulae*

Organisms	% of Cannulae	
	Controls (n = 186)	Mupirocin (n = 172)
No growth	23	64*
Coagulase-negative staphylococci	62	19
Micrococci	8	5
Corynebacteria	8	5
Ent. aglomerans	2	0
A. calcoaceticus	3	1
Staph. aureus	2	2
Other enterobacteriaceae	2	0
Ps. testosteroni	0·5	0
Moraxella sp.	0·5	0
Strep. lactis	0·5	0

*$P < 0{\cdot}001$

Organisms isolated by enrichment or semi-quantitative techniques from the cannula tips were usually sensitive to the prophylactic systemic antibiotics although 4% of the tip isolates were resistant to both gentamicin and flucloxacillin. All Gram-negative organisms were sensitive to gentamicin. Mupirocin-resistant coagulase-negative staphylococci, with MICs of 8 to $>128\ mg\ l^{-1}$, were isolated from 10/84 (12%) of colonized cannula tips in the control group and from 2/20 (10%) of those from the mupirocin-treated patients; for these two mupirocin-treated patients the resistant isolates were also detected in skin swabs taken before the application of mupirocin. MICs for mupirocin-sensitive isolates of coagulase-negative staphylococci and corynebacteria ranged from $0{\cdot}015–0{\cdot}5\ mg\ l^{-1}$ of mupirocin.

Table V shows that using Maki's criteria for significant colonization, > 15 cfu were isolated from only 8 (5%) of the tips of 172 cannulae inserted through mupirocin-treated skin insertion sites, compared with 46 (25%) of the 186 controls ($P < 0{\cdot}001$). The organisms isolated from significantly colonized tips corresponded most often with those from the exterior of the hub, or the skin of the insertion site. Of the 46 colonized cannula tips in the control group, indistinguishable isolates were found from the skin for 67%, from the exterior of the hub for 61%, and from the lumen for only 15% of cannulae. For the eight colonized cannulae from the mupirocin group, the tip isolate was identified on the skin, from the hub exterior, and from the lumen once only in three different cannulae ($P < 0{\cdot}001$). Using Maki's criteria, significant colonization of cannula tips was more common with longer *in-situ* times but mupirocin significantly reduced the colonization for all *in-situ* times (Table V). None of the 19 cannulae inserted through mupirocin-treated skin that were *in-situ* for 48–120 h were colonized compared with six of the 10 controls.

Table V. *Significant colonization of cannula tips as judged by Maki's criteria according to* in-situ *time*

In-situ time (h)	Number colonized (%)		*P*-value
	Controls · n = 186	Mupirocin n = 172	
< 24	105 (15)	103 (3)	< 0·001
24–48	71 (34)	50 (10)	< 0·025
> 48–120	10 (60)	19 (0)	< 0·001
All cannulae	186 (25)	172 (5)	< 0·001

Discussion

Our results show clearly that the application of mupirocin to the skin of the cannula insertion site reduces the subsequent contamination and significant colonization of cannulae. Our patients and their cannulae were well matched in the test and control groups. All patients underwent cardiothoracic surgery, and had 'Abbocath-T' cannulae inserted preoperatively under standard conditions by the same group of anaesthetists. Previous studies have usually reported results on more heterogeneous groups of patients and cannula types (Norden, 1969; Zinner *et al.*, 1969; Maki & Band, 1981).

In this study, we concentrated on the earliest events in patients with central venous cannulae in the light of Maki's work which showed that contamination and established colonization of the cannula (> 15 cfu) is widely accepted as a predictor of subsequent cannula-related sepsis and bacteraemia (Maki *et al.*, 1977; Maki, 1982; Moyer, Edwards & Farley, 1983; Elliot, 1988). As judged by enrichment culture mupirocin increased to 64% the proportion of patients who yielded sterile cannulae from 23% in the controls. More importantly, by the semi-quantitative technique only 17% of patients receiving mupirocin had any cannulae that yielded > 15 cfu, compared with 54% of the controls. The cannula tip is probably the most important site for colonization with > 15 cfu and consideration of all 358 cannulae showed that there was a five-fold reduction of tip colonization to 5% in the mupirocin group; this effect was found regardless of *in-situ* times up to 120 h. We have not been able to find reductions of this magnitude in the published literature although the application of an ointment containing neomycin, bacitracin and polymyxin resulted in the colonization rate of mainly peripheral lines being reduced from 6·5% to 2·2% compared to 3·6% for povidone-iodine ointment (Maki & Band, 1981). More recently Maki, by using a biodegradable collagen subcutaneous cannula cuff that released silver ions, achieved a reduction in colonization rate of central venous lines from 28·9% to 9·1% (Maki *et al.*, 1988).

The organisms isolated from colonized cannula tips corresponded most often to isolates from the insertion-site skin or the intracutaneous segment

rather than to the infrequent isolates from the cannula lumen. For our cardiothoracic patients at least, this, taken with the efficacy of topical mupirocin, supports the view that it is the skin of the insertion site, rather than the lumen, that serves as the major source of organisms for colonization of the cannula tip (Bjornson *et al.*, 1982; Snydman *et al.*, 1982; Jakobsen, Grabe & Damm, 1986; Cercenado *et al.*, 1988; Conly, Grieves & Peters, 1988; Maki, 1988). Indeed, Cooper & Hopkins (1985) have shown by Gram staining that organisms are found on the surface of the cannula rather than in the lumen and that these organisms may reach the tip by capillary action (Cooper, Schiller & Hopkins, 1988). In-line filtration, which could potentially prevent contaminants being introduced into the lumen via a hub, does not significantly reduce sepsis (Murphy & Lipman, 1987). Nevertheless, the junction between the cannula and the 'giving set' may assume importance (Deital *et al.*, 1983; Linares *et al.*, 1985) particularly for long-term lines which have frequent 'make and break' connections, for example during parenteral nutrition (Sitges-Serra *et al.*, 1983 & 1984) or haemodialysis (Cheesbrough, Finch & Burden, 1986; Jakobsen *et al.*, 1989). The presence of another cannula has been suggested as a risk factor for the development of cannula-related sepsis but its significance has not been proved (Petersen *et al.*, 1985).

In addition to the reduction in the mupirocin group of cannula contamination and colonization with coagulase-negative staphylococci and micrococci, there were fewer cannulae yielding species of corynebacteria, *Acinetobacter* and Enterobacteriaceae. Although the low numbers do not reach statistical significance we wonder whether this reflects a useful effect of 2% (20 000 mg l^{-1}) mupirocin against these species that are usually considered 'resistant' (White *et al.*, 1985). A trial of mupirocin, applied to the insertion site of cannulae left *in-situ* for more than 48 h, would indicate whether, with more prolonged use, mupirocin-resistant strains of staphylococci emerge (Baird & Coia, 1987; Rahman, Noble & Cookson, 1987; Smith & Kennedy, 1988) and whether super-infection with Gram-negative bacilli, yeasts or other fungi ultimately occurs. None of these theoretical complications were found in the first few days of cannulation in our cardiothoracic surgical patients and there were no adverse local effects attributed to mupirocin.

We conclude that 2% calcium mupirocin applied to the insertion site, in addition to standard skin disinfection with tincture of iodine, significantly reduces the risk of the earliest events in the pathogenesis of cannula-related sepsis in these patients.

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