The Use of Rifampicin-Miconazole–Impregnated Catheters Reduces the Incidence of Femoral and Jugular Catheter-Related Bacteremia

Leonardo Lorente,[1] María Lecuona,[2] María José Ramos,[2] Alejandro Jiménez,[3] María L. Mora,[1] and Antonio Sierra[2]

Departments of [1]Critical Care and [2]Microbiology and [3]Research Unit, Hospital Universitario de Canarias, La Laguna, Santa Cruz de Tenerife, Spain

Background. The guidelines of the Centers for Disease Control and Prevention do not recommend the use of an antimicrobial- or antiseptic-impregnated catheter for short-term use. In previous studies, we have found a higher incidence of central venous catheter–related bacteremia among patients with femoral and central jugular accesses than among patients with other venous accesses.

Objective. The objective of our study was to determine the incidence of central venous catheter–related bacteremia associated with rifampicin-miconazole–impregnated catheters and standard catheters in patients with femoral and central jugular venous accesses.

Methods. This was a cohort study, conducted in the 24-bed polyvalent medical-surgical intensive care unit of a university hospital. We included patients who were admitted to the intensive care unit from 1 June 2006 through 30 September 2007 and who underwent femoral or central jugular venous catheterization.

Results. We inserted 184 femoral (73 rifampicin-miconazole–impregnated catheters and 111 standard catheters) and 241 central jugular venous catheters (114 rifampicin-miconazole–impregnated catheters and 127 standard catheters). We found a lower rate of central venous catheter–related bacteremia associated with rifampicin-miconazole–impregnated catheters than with standard catheters among patients with femoral access (0 vs. 8.62 cases per 1000 catheter-days; odds ratio, 0.13; 95% confidence interval, 0.00–0.86; $P = .03$) and among patients with central internal jugular access (0 vs. 4.93 cases per 1000 catheter-days; odds ratio, 0.13; 95% confidence interval, 0.00–0.93; $P = .04$).

Conclusions. Rifampicin-minonazole–impregnated catheters are associated with a statistically significant reduction in the incidence of catheter-related bacteremia in patients with short-term catheter use at the central jugular and femoral sites.

In patients who require the use of central venous catheters (CVCs), the use of rifampicin-miconazole–impregnated catheters (RMCs) has been found to decrease the incidence of CVC-related bacteremia (CVCRB) [1]. The use of such catheters has not received worldwide acceptance, in large part for the following 2 reasons: first, these impregnated catheters are more expensive than standard catheters (SCs); (although in a hypothetical cohort study by Shorr et al. [2], it was estimated that the use of such catheters would reduce overall costs because of a reduction in the incidence of CVCRB). Second, the guidelines of the Centers for Disease Control and Prevention (CDC), published in 2002, recommended the use of an antimicrobial- or antiseptic-impregnated CVC for short-term catheter use only when the rate of CVCRB remained above the upper limit set by the individual institution [3].

In previous studies [4, 5], we found a higher incidence of CVCRB associated with femoral and central jugular accesses than with other venous accesses. For this reason, the objective of the present study was to determine the incidence of CVCRB associated with the use of RMCs and SCs in patients with femoral and jugular venous accesses.

PATIENTS, MATERIALS, AND METHODS

This was a historical cohort study involving patients who were admitted to the intensive care unit at the

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Reprints or correspondence: Dr. Leonardo Lorente, Dept. of Critical Care, Hospital Universitario de Canarias, Ofra s/n. La Cuesta, La Laguna 38320, Santa Cruz de Tenerife, Spain (lorentemartin@msn.com).

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Hospital Universitario de Canarias (Tenerife, Spain) from 1 June 2006 through 30 September 2007 and who underwent femoral or central jugular venous catheterization. The study was approved by the institutional review board of Hospital Universitario de Canarias.

The catheters used were the Multistar catheter (Vygon), which is an RMC that is coated with antimicrobials on both external and internal surfaces, and the Arrow catheter (Arrow), which is an SC that is not coated with antimicrobials. The decision to use an RMC or an SC was made by the patient's physician. All catheters were triple lumen and polyurethane catheters. The catheters were inserted by physicians using the Seldinger technique with the following sterile barrier precautions: use of large sterile drapes around the insertion site; surgical antiseptic hand wash; and sterile gown, gloves, mask, and cap. The skin insertion site was first disinfected with 10% povidone-iodine and anesthetized with 2% mepivacaine. After catheter insertion, the area surrounding the catheter was cleaned with a sterile gauze soaked with povidone-iodine, and a dry, sterile gauze occlusive dressing covered the site. No topical antimicrobial ointment was applied to the insertion sites.

Catheter gauze dressings were changed every 48 h or sooner, at the discretion of the nurse caring for the patient, if the dressing was contaminated. The connecting lines were changed every 72 h.

For patients in whom catheter-related infection was suspected, the catheter was removed, the catheter tip was cultured, and the insertion site for a new catheter was changed. The catheters were removed by an intensive care unit nurse with use of a sterile technique. The 5-cm distal segment of each catheter was cut with sterile scissors, placed in a sterile transport tube, and cultured with use of the semiquantitative method described by Maki et al. [6]. Microbiological surveillance included cultures of urine, tracheal aspirate, and wound samples that were performed twice weekly during intensive care unit stay.

CVCRB was defined according to the following criteria: positive results of cultures performed on blood samples obtained from a peripheral vein, signs of systemic infection (fever, chills, and/or hypotension), no apparent source of bacteremia except the catheter, and catheter tip colonization with the same organism (with significant growth of a microorganism defined as detection of >15 colony-forming units of the same species found in blood cultures, with identical antimicrobial susceptibility) [3]. The diagnosis of CVCRB was made by an expert panel blinded to the type of catheter (RMC or SC).

Statistical analysis was performed with SPSS software, version 11.0 (SPSS); LogXact software, version 4.1 (Cytel); and StatXact softwear, version 5.0.3 (Cytel). Continuous variables are reported as means and SDs, and categorical variables are reported as frequencies and percentages. First, the groups of patients (those with RMCs vs. those with SCs) were compared with respect to age, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and duration of catheter use with use of the Wilcoxon Mann-Whitney *U* test. Second, we used the Kruskal-Wallis test for singly ordered tables' row by column to compare groups (RMC group vs. SC group) with respect to sex, diagnosis group, and reason for catheter removal. Third, the coated catheter group was compared with the noncoated catheter group with respect to the order of catheter insertion, use of tracheostomy, reintubation, use of mechanical ventilation, use of antimicrobials, use of parenteral nutrition, use of paralytic agents, use of urinary catheter, use of vasoactive agents, use of propofol, percentage of CVCRB, and death rate with use of the Jonckeree-Terpstra test for doubly ordered tables' row by column analysis. Two survival analyses were performed—the first for patients with catheters at the femoral site and the second for patients with catheters at the jugular site—with the duration of catheter use as a dependent variable, the type of catheter (RMC vs. SC) as the independent variable, and CVCRB as the event. We used the log-rank test to compare the distribution of time free of CVCRB between both groups. Finally, to obtain the magnitude of the effect of the type of catheter (RMC vs. SC) on the number of CVCRB days, we performed a Poisson regression logistic analysis. The magnitude of the effect is expressed as an OR with 95% CI. A P value <.05 was considered to be statistically significant.

RESULTS

We inserted 184 femoral (73 RMCs and 111 SCs) and 241 central jugular venous catheters (114 RMCs and 127 SCs). No differences were found with respect to the clinical characteristics of the patient groups (table 1). We found a lower rate of CVCRB associated with RMCs than with SCs in the femoral access group (0 vs. 8.62 cases per 1000 catheter-days; $P = .03$). We found a lower rate of CVCRB associated with RMCs than with SCs in the central internal jugular access group (0 vs. 4.93 cases per 1000 catheter-days; $P = .04$).

The results of the survival analysis revealed that RMCs were associated with a different distribution of time free of CVCRB than were SCs for both the jugular site group (χ^2, 7.54; $P = .006$) (figure 1) and the femoral site group (χ^2, 6.35; $P = .01$) (figure 2). The variables with zero-cells in the jugular and femoral RMC groups were accounted for by the method previously reported by Metha and Pattel [7]. Thus, when the jugular SC group is used as the reference group, the lower limit for the OR in the population tends to zero (OR, 0.13; 95% CI, 0.00–0.93; $P = .04$). This means that RMCs protect against CVCRB. On the other hand, if the jugular RMC group is used as the reference group, the upper limit for the OR in the population is positive infinity (OR, 7.4; 95% CI, 1.07 to positive infinity; $P = .04$). This means that the use of SCs increases the risk of

Table 1. Characteristics of patients with either rifampicin-miconazole–impregnated catheters (RMC group) or standard catheters (SC group) placed at either the femoral or central jugular venous sites.

Variable	Femoral placement			Central jugular placement		
	RMC group (n = 73)	SC group (n = 111)	P	RMC group (n = 114)	SC group (n = 127)	P
No. of catheter-days	634	927		1107	1217	
Age, mean years ± SD	59.77 ± 17.71	58.05 ± 16.48	.24	64.10 ± 14.57	65.04 ± 14.23	.65
Male sex	47 (64.4)	78 (70.3)	.42	75 (65.8)	80 (63.0)	.69
APACHE II score, mean value ± SD	17.51 ± 5.49	17.35 ± 6.20	.77	16.55 ± 5.87	16.72 ± 7.18	.65
Diagnosis group			.97			.84
Cardiac surgery	11 (15.1)	21 (18.9)		18 (15.8)	16 (12.6)	
Cardiology	9 (12.3)	17 (15.3)		13 (11.4)	18 (14.2)	
Respiratory	17 (23.3)	22 (19.8)		27 (23.7)	37 (29.1)	
Digestive	12 (16.4)	18 (16.2)		33 (28.9)	34 (26.8)	
Neurological	10 (13.7)	15 (13.5)		15 (13.2)	16 (12.6)	
Traumatology	13 (17.8)	16 (14.4)		8 (7.0)	6 (4.7)	
Intoxication	1 (1.4)	2 (1.8)		0 (0)	0 (0)	
Order of catheter insertion			.41			.45
First	40 (54.8)	66 (59.5)		71 (62.3)	85 (66.9)	
Second	18 (24.7)	29 (26.1)		34 (29.8)	34 (26.8)	
Third	15 (20.5)	16 (14.4)		9 (7.9)	8 (6.3)	
Use of tracheostomy	25 (34.2)	36 (32.4)	.87	27 (23.7)	27 (21.3)	.76
Reintubation	9 (12.3)	10 (9.0)	.62	14 (12.3)	13 (10.2)	.68
Use of mechanical ventilation	68 (93.2)	101 (91.0)	.78	99 (86.8)	106 (83.5)	.48
Use of antimicrobial drugs	56 (76.7)	90 (81.1)	.58	92 (80.7)	98 (77.2)	.53
Use of total parenteral nutrition	7 (9.6)	12 (10.8)	.81	19 (16.7)	16 (12.6)	.46
Use of paralitic agents	9 (12.3)	13 (11.7)	.99	10 (8.8)	11 (8.7)	.99
Use of urinary catheter	71 (97.3)	106 (95.5)	.70	113 (99.1)	122 (96.1)	.22
Use of vasoactive agents	24 (32.9)	35 (31.5)	.87	41 (36.0)	41 (32.3)	.59
Use of propofol	23 (31.5)	31 (27.9)	.62	27 (23.7)	33 (26.0)	.77
Reason for catheter removal			.71			.85
Death	11 (15.1)	18 (16.2)		16 (14.0)	20 (15.7)	
Suspicion of catheter-related infection	28 (38.4)	45 (40.5)		31 (27.2)	32 (25.2)	
Catheter no longer needed	30 (41.1)	38 (34.2)		59 (51.8)	69 (54.3)	
Accidental removal	4 (5.5)	10 (9.0)		8 (7.0)	6 (4.7)	
Duration of catheter use, mean days ± SD	8.68 ± 4.90	8.35 ± 4.49	.77	9.71 ± 5.11	9.58 ± 4.55	.89
CVCRB	0 (0)	8 (7.2)	.02	0 (0)	6 (4.7)	.02
No. of CVCRB cases per 1000 catheter-days	0	8.62	.03	0	4.93	.04
Death	11 (15.1)	21 (18.9)	.56	16 (14.0)	21 (16.5)	.60

NOTE. Data are no. (%) of patients, unless otherwise indicated. APACHE, Acute Physiology and Chronic Health Evaluation; CVCRB, central venous catheter–related bacteremia.

CVCRB. When the femoral SC group is used as the reference group, the lower limit for the OR in the population tends to zero (OR, 0.13; 95% CI, 0.00–0.86; $P = .03$). This means that RMCs protect against CVCRB. On the other hand, if the femoral RMC group is the reference category, the upper limit for the OR in this population is positive infinity (OR, 7.6; 95% CI, 1.17 to positive infinity; $P = .03$). This means that the use of SCs increases the risk of CVCRB.

The following microorganisms were responsible for CVCRB in patients with catheters located at the femoral site: *Staphylococcus hominis* in 1 patient, *Enterococcus faecalis* in 3, *Escherichia coli* in 1, *Klebsiella pneumoniae* in 1, *Enterobacter cloacae* in 1, and *Candida albicans* in 1. The following microorganisms caused CVCRB in patients with catheters located at the central internal jugular site: *Staphylococcus epidermidis* in 5 patients and *S. aureus* in 1.

DISCUSSION

In previous studies of SCs, we found a rate of CVCRB among patients with catheters located at the femoral site of 8.34 cases per 1000 catheter-days [4] and a rate among patients with catheters located at the central jugular site of 2.99 cases per 1000 catheter-days [5]. In this study, the rates of CVCRB that we found in the SC group, by catheter site, were similar to those found in our previous studies [4, 5]. We found no cases of CVCRB among patients with RMCs.

The meta-analysis by Falagas et al. [1], which included data

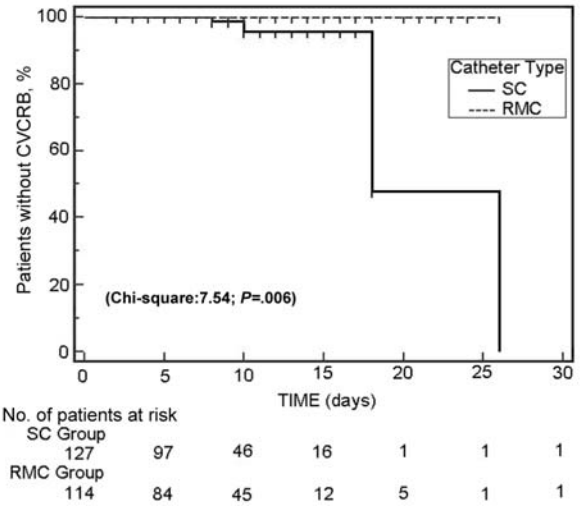

Figure 1. Comparison of the distribution of time free of central venous catheter–related bacteremia (CVCRB) in patients with either rifampicin-miconazole–impregnated catheters (RMCs) or standard catheters (SCs) placed at the central jugular site.

on 3452 patients with CVCs from 8 clinical randomized trials, showed a decrease in the incidence of CVCRB associated with the use of rifampicin-impregnated catheters; however, in the 2 studies that exclusively studied critically ill patients, a decrease in the incidence of CVCRB was not found [8, 9].

The statistically significant decrease in the incidence of CVCRB associated with the use of RMCs in critically ill patients found in our study may be attributable to the objective of our study, which was to determine whether the incidence of CVCRB associated with RMCs was lower than that associated with SCs without antimicrobial agents among patients with catheters located at femoral and central jugular venous sites. In the study by Leon et al. [9], catheters with femoral access were not used, and in the study by Fraenkel et al. [8], the femoral site was only used in 12% of cases. In the study by Chatzinikolau et al. [10], in which only the femoral site was used, a trend toward lower incidence of CVCRB was found among patients with RMCs. The difference in CVCRB incidence between groups was high (0% in the antimicrobial-impregnated CVC group vs. 11% in the control CVC group), although it was not statistically significant. The absence of a statistically significant difference may be attributable to the small sample size (140 patients with catheters).

In 7 of the 8 studies included in the meta-analysis by Falagas et al. [1], the antimicrobial combination used for the impregnation was rifampicin-minocycline, and rifampicin-miconazole was used only in the study by Yücel et al. [11]. In the study by Yücel et al. [11], it was found that RMC use was associated with a decrease in the incidence of catheter-related local infection but was not associated with a decrease in the incidence of CVCRB, probably because their patients had a lower mean APACHE II score (6.6 points) and a shorter mean duration of catheter use (7.1 days) than did our patients.

The limitations of our study included the following: (1) the use of RMCs and SCs was not randomly assigned; (2) because the number of cases of CVCRB was small, a multivariate analysis was not performed to control for confounding variables; (3) we did not evaluate the costs related to the use of RMCs versus SCs or the costs associated with CVCRB; and (4) we did not use molecular techniques to genetically relate microorganisms isolated from the catheters with microorganisms isolated from peripheral blood cultures.

On the other hand, our study had 2 strengths. First, the influence of other possible sources of bacteremia was minimized as a result of microbiological surveillance, including twice-weekly cultures of urine, tracheal aspirate, and wound samples that were performed during the intensive care unit stay. Second, the diagnosis of CVCRB was made by an expert panel that was blinded to the type of catheter used (RMC or SC).

We used 10% povidone-iodine for skin disinfection in accordance with the 2002 CDC guidelines [3]. In these guidelines, with respect to catheter site care, the CDC states that, although a 2% chlorhexidine-based preparation is preferred, a tincture of iodine, an iodophor, or a 70% alcohol solution can be used.

Controversy remains regarding the antimicrobial spectrum and the possibility of developing resistance to the antimicrobials used in the catheter. In the study by Sampath et al. [12], the catheter impregnated with rifampicin-minocycline exhibited a zone of inhibition against gram-positive bacteria >20 mm in diameter (although it was 12 mm in diameter against *E. faecalis*

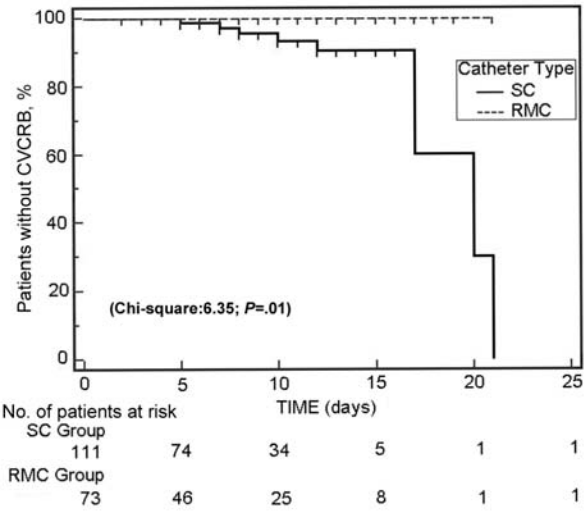

Figure 2. Comparison of the distribution of time free of central venous catheter–related bacteremia (CVCRB) in patients with either rifampicin-miconazole–impregnated catheters (RMCs) or standard catheters (SCs) placed at the femoral site.

and 1 mm in diameter against *C. albicans*) and a zone of inhibition against gram-negative bacteria that was 8–15 mm in diameter (although it was only 1 mm in diameter against *P. aeruginosa*). In the in vitro study by Schierholz et al. [13], it was found that the RMCs developed a zone of inhibition >25 mm in diameter against gram-positive bacteria (although the zone of inhibition against *E. faecalis* was 17 mm in diameter), 14 mm in diameter against *C. albicans,* and 10–15 mm in diameter against gram-negative bacteria. Zones of inhibition >10 mm in diameter are considered to be highly predictive of in vivo efficacy in prevention of colonization [14]. According to our findings, it can be assumed that the pathogens in the SC group would have been susceptible to the antimicrobials in the RMCs.

In the CDC guidelines from 2002 [3], CVC insertion at the subclavian site, rather than at a femoral or jugular site, is recommended to minimize the risk of infection. In our study, the use of RMCs decreased the incidence of CVCRB among patients with catheters with femoral and central internal jugular access, and it might be associated with incidences of bacteremia that are similar to or lower than those associated with the use of SCs that are placed at the subclavian site. Therefore, use of the subclavian site does not seem to be essential to minimizing the risk of CVCRB in patients with RMCs. Therefore, we propose the use of SCs at the subclavian site and antibiotic impregnated catheters at the central internal jugular and femoral sites.

The CDC guidelines [3] recommend tunneled catheters for patients who require long-term vascular access. There are published data that indicate a lower incidence of catheter-related sepsis among patients who require short-term vascular access at jugular [15] and femoral sites [16] when tunneled catheters are used; however, the use of tunneled catheters does not reduce the incidence of bacteremia among patients with subclavian access [17]. Therefore, the use of short-term tunnelled catheters at central jugular and femoral venous sites is another possibility that requires more research. In conclusion, RMCs are associated with a statistically significant reduction in CVCRB among patients with short-term catheter use at the central jugular and femoral sites.

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Potential conflicts of interest. All authors: no conflicts.

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