Antibiotic Coated Catheter to Decrease Infection. Pilot Study*

Cateter Venoso Profundo Recoberto com Antibiótico para Reduzir Infecção. Estudo Piloto

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SUMMARY

BACKGROUND AND OBJECTIVES: Nosocomial catheter related bloodstream infections (CR-BSI) increase morbidity and mortality in critically ill patients. Central venous catheters (CVC) coated with rifampin and minocycline (RM) decrease rates of colonization and CR-BSI. However, recent trials challenged the clinical impact of such catheters. We designed this trial to compare rates of colonization and CR-BSI in RM catheters and controls in a cohort of critically ill patients in Brazil.

METHODS: Prospective, controlled trial conducted in one medico-surgical ICU. Patients were assigned to receive a control or RM CVC. After removal, tips were cultured in association with blood cultures. Rates of colonization and CR-BSI were recorded.

RESULTS: Among 120 catheters inserted, 100 could be evaluated, 49 in the uncoated and 51 in the coated group. Clinical characteristics of patients were similar in the two groups. Two cases of CR-BSI (3.9%) occurred in patients who received RM catheters compared with 5 (10.2%) in the uncoated group (p = 0.26). Six RM catheters (11.8%) were colonized compared with 14 (28.6%) control catheters (p = 0.036). Kaplan-Meier analysis showed no significant differences in the risk of colonization or CR-BSI. Rates of CR-BSI were 4.7 per 1000 catheter-days in the RM coated group compared to 11.4 per 1000 catheter days in the uncoated group (p = 0.45).

CONCLUSIONS: In this pilot study, we showed lower rates of colonization in RM coated when compared with uncoated catheters. Incidence and rates of CR-BSI were similar in the two groups.

Key Words: Bacteremia, catheter-related blood stream infection, colonization, minocycline, rifampin.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A bacteremia associada a cateter venoso central (CVC) aumenta a morbidade e mortalidade hospitalar em pacientes internados em unidade de terapia intensiva (UTI). Os cateteres recobertos com rifampicina e minociclina (RM) reduzem a freqüência de colonização e bacteremia. No entanto, resultados de estudos recentes questionaram o seu impacto clínico. O objetivo deste estudo foi comparar a incidência de colonização e bacteremia associada à CVC recobertos com RM e não recobertos numa coorte de pacientes admitidos em UTI.

METODO: Estudo prospectivo, controlado em UTI mista clínico-cirúrgica. Os pacientes receberam um CVC recoberto com RM ou não recoberto. Após remoção do CVC, a sua ponta foi culturada e as hemoculturas coletadas. Avaliou-se a freqüência de colonização e bacteremia.

RESULTADOS: Cento e vinte CVC foram inseridos e 100 puderam ser avaliados, 49 no grupo não recoberto e 51 no grupo recoberto. As características clínicas foram similares nos 2 grupos. Dois casos de bacteremia associada ao cateter (BAC) (3,9%) ocorreram em pacientes que receberam CVC recobertos com RM

comparado a 5 (10,2%) casos de BAC no grupo não recoberto (p = 0,26). Seis (11,8%) cateteres recobertos foram colonizados comparados a 14 (28,6%) no grupo não recobertos (p = 0,036). A análise de Kaplan-Meier não demonstrou diferença no risco de colonização ou BAC entre os dois grupos estudados. A taxa de BAC foi de 4,7 por 1000 cateteres-dia no grupo com CVC recobertos e 11,4 por 1000 cateteres-dia no grupo que recebeu cateteres não recobertos (p = 0,45).

CONCLUSÕES: Neste estudo piloto, demonstrou-se menor freqüência de colonização em cateteres recobertos com RM, quando comparados a cateteres não recobertos. A freqüência de BAC não foi diferente entre os dois grupos.

Unitermos: Bacteremia associada à cateter, bacteremia, minociclina, rifampicina

INTRODUCTION

Physicians insert central venous catheters (CVC) for measurement of hemodynamic variables, delivery of medications and nutritional support. More than 5 million catheters are inserted each year in the United States, and unfortunately this growing number is associated with adverse events that can be both hazardous and expensive, such as infectious complications[1].

Nosocomial catheter related bloodstream infections (CR-BSI) have been associated with increased morbidity and possibly increased mortality in critically ill patients. CR-BSI occurs in 3% to 5% of catheters inserted[2,3]. It is associated with an attributed mortality that varies from 3 to 35%[2,4], excess length of stay in the ICU of up to 20 days and increased costs of up to US$ 40.000 per survivor[5,6].

Several approaches have been proposed to prevent CR-BSI, including site selection (use of subclavian vein)[3,8], maximal sterile barriers[1,7,8], and more recently, antibiotic coated CVC[3,4,8-15]. CVC coated with rifampin and minocycline (RM), both in the intra luminal and extra luminal surfaces have been shown in randomized clinical trials (RCT) to decrease rates of colonization and CR-BSI when compared to controls and to chlorhexidine/silver sulfadiazine (CSSD) catheter[3,11]. When the RM catheter was compared to the CSSD type in a randomized clinical trial, the former proved to be 12 times less likely to be associated with CR-BSI than the latter[3].

However, recent randomized trials challenged the clinical impact of such catheters showing decreased rates in colonization but not in CR-BSI[14,16]. Based on these conflicting results, concerns about emergence of resistant microorganisms, potentially increased costs, and lack of original regional data, physicians and hospitals in Brazil are still reluctant to adopt the use of antibiotic impregnated catheters as a mean to decrease rates of CR-BSI.

We designed this pilot trial to compare the rates of colonization and CR-BSI in RM catheters and controls in a population of critically ill patients.

METHODS

After approval by the institutional review board (Research Ethics Committee), the trial was conducted from June 2005 to May 2006 in a 19 bed medico-surgical ICU of a private hospital in Rio de Janeiro, Brazil. All adult patients admitted to the ICU that required a double or triple lumen CVC intended to stay in place for 3 or more days, were eligible for the study. Patients with a history of allergy to one of the antimicrobial agents impregnating the catheters were excluded. All patients or their legal guardians gave informed consent.

Patients were sequentially (in groups of 5) assigned to undergo insertion of a 7 French, 15 or 20 cm long, non cuffed, double or triple lumen catheter coated with rifampin and mynociclin (Cook Spectrum, Cook Critical Care) or uncoated (Cook Critical Care). Patients were initially assigned to the control and treatment groups in sequential blocks of 20. After the fortieth catheter inserted, the study board changed to smaller alternating bocks of 5 to improve matching of the groups. Attending physicians or house staff inserted the catheters into the subclavian, jugular or femoral vein using maximal sterile barrier precautions. Catheters changed over a guide wire were not considered for the study. Study catheters could subsequently be inserted in the same patient up to three times, as long as the patient had only one study catheter at a time. At the time of insertion and at each dressing change site was disinfected with chlorhexidine 2 percent. We used transparent dressing, which was changed when needed. Insertion site was inspected and patients were evaluated by study coordinators daily. Decision to remove the catheter was made by patient's physician only, who kept it in place until it was no longer needed or until a complication, such as infection or occlusion, precipitated its removal. Two centimeter segments from the tips of the removed catheters were cultured by the roll plate method. One or two

peripheral blood samples were collected for culture before catheter removal. Recovered organisms were identified by standard microbiologic methods. Definitions adopted were those proposed by the Centers for Disease Control and Prevention, and used in previous clinical trials. Colonization was defined as growth of 15 or more colony-forming units in culture of catheter segments prepared by roll-plate method. CR-BSI was defined as the isolation of the same organism from the colonized catheter tip and from peripheral blood in a patient with clinical manifestations of sepsis and no other source of bloodstream infection.

Statistical Analysis

Continuous variables were expressed as mean or median. Categorical variables were expressed as absolute numbers and percentiles. Normal distribution was evaluated by Kolmogorov-Smirnov test and continuous variables were compared using Student's t test or Mann-Whitney U test. Categorical variables were compared using chi-square test or Fischer's exact test. Survival analysis was performed to assess the duration of catheterization free of colonization or CR-BSI using the Kaplan-Meier method, and differences were evaluated through the log-rank test. A two-sided p value of < .05 was considered to be statistically significant. Statistical analysis was done using Software Statistical Package for Social Sciences (SPSS-Chicago-IL-USA-2003).

RESULTS

A total of 120 study catheters (60 coated with minocycline and rifampin and 60 uncoated) were inserted into 81 patients. Complete data could be evaluated for 100 catheters (83%): 51 coated and 49 uncoated. Twenty were not cultured or accidentally removed and were excluded. Sixty five percent of catheters in the antibiotic coated group were inserted while another intravascular catheter was in place compared to 31% in the uncoated group (p = 0.001). The two groups were similar in all other clinical characteristics evaluated (Table 1). Study catheters were in place for a mean time of 8.2 ± 2.9 days in the antibiotic coated group and 8.9 ± 4 days in the control group (p = 0.595) (Table 1). Six of 51 catheters coated with minocycline and rifampin (11.8%) and 14 of 49 control catheters (28.6%) were colonized according to the roll-plate method (p = 0.036). Analysis of the Kaplan Meier estimates of the risk of colonization

according to time catheters were in place showed no significant differences (p = 0.14 by the log rank test). Organisms associated with colonization in coated catheters were *Escherichia coli*, coagulase-negative *Staphylococcus*, *Pseudomonas aeruginosa* and *Candida tropicalis*; while colonization in uncoated catheters involved 4 Gram-negative species (*Proteus mirabilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Acinetobacter baumanii*), 3 Gram-positive species (coagulase-negative *Staphylococus*, *Staphylococcus aureus* and *Enterococcus faecalis*) and 1 case of *Candida albicans*. There were 7 cases of CR-BSI during the study. Two cases developed among the antibiotic coated catheters group (3.9%) and 5 cases among the control group (10.2%) (p = 0.26). The rates of CR-BSI per 1000 catheter-days were 4.7 for coated catheters and 11.4 for uncoated catheters (p = 0.45). Kaplan Meier estimates of risk of CR-BSI according to duration of catheterization showed no significant differences among the two groups (log rank test, p = 0.43). The only organism associated with CR-BSI in the coated catheter group was *Candida tropicalis* in two catheters from the same patient, while CR-BSI in the uncoated group was caused by one Gram-positive species (coagulase-negative *Staphylococcus* – twice), two Gram-negative (*Escherichia coli* and *Acinetobacter baumanii*) and one yeast (*Candida albicans*).

Table 1 - Characteristics of Patients

	Coated N = 51 (%)	Uncoated N = 49 (%)	P values
Age (years)	66.3 ± 15.6	71.9 ± 14.6	0.081
Male	34 (66.7)	36 (73.5)	0.458
APACHE II	21.5 ± 8.2	21.8 ± 10.8	0.817
Days with catheter	8.3 ± 2.9	8.9 ± 4	0.595
Clinical diagnosis (non surgical)	25 (49)	22 (44.9)	0.48
Cultures taken during ATB use	24 (47)	32 (65.3)	0.06
Total parenteral nutrition	5 (9.8)	7 (14.3)	0.491
Subclavian site	24 (47.1)	25 (51)	0.692
Other CVC present	33 (64.7)	15 (30.6)	0.001
First CVC	18 (35.3)	28 (59.6)	0.016
Multiple attempts	7 (13.7)	7 (14.3)	0.93

Values expressed as Mean ± SD or Number (%)
ATB = antibiotic; CVC = central venous catheter

Table 2 – Incidence of Catheter Related Blood Stream Infection (CR-BSI) and Colonization

	Coated	Uncoated	P value
CR-BSI rate – N /1000 catheter days	4.7	11.4	0.45
CR-BSI – N (%)	2 (3.9)	5 (10.2)	0.26
Colonization – N (%)	6 (11.8)	14 (28.6)	0.036

Table 3 – Microbiology of Colonization and Catheter Related Blood Stream Infection (CR-BSI)

	Coated	Uncoated
Colonization – n (%)	6 (100)	14 (100)
Gram-positive	2 (33)	7 (50)
Gram-negative	2 (33)	6 (43)
Candida	2 (33)	1 (7)
CR-BSI – n (%)	2 (100)	5 (100)
Gram-positive	-	2 (40)
Gram-negative	-	2 (40)
Candida	2 (100)	1 (20)

DISCUSSION

Catheter related bloodstream infections (CR-BSI) remain a major concern in intensive care patients, with severe morbidity and cost implications; despite continuous efforts to reduce its burden, such as maximal sterile barriers and insertion by skilled experienced operators, some centers still have high rates of sepsis associated with CVC[8,17].

Recently, antibiotic coated CVC were included in the armamentarium available to prevent CR-BSI since landmark RCT by Maki et al.[9] and Raad et al.[11] showed reduction in CR-BSI rates with its use when compared to uncoated catheters. Later, Darouiche et al.[3] reported the superiority of RM coated over chlorhexidine and silver sulfadiazine impregnated catheters. In their last guidelines, the United States Center for Disease Control (CDC) recommended that the use of either one should be implemented if CR-BSI rates remained above 3,3 per 1000 catheter days, despite adherence to other preventive strategies[8]. However, widespread use of this technology is not a reality in most countries, especially in Brazil. This may be explained by uncertainty about cost implications, emergence of resistance and even real clinical impact. Potential financial implications were explored in a study by Shorr et al.[2], where they found that the implementation of antibiotic coated catheters to prevent CR-BSI should be cost effective and lead to significant savings. However, these results cannot be extrapolated to other settings and regional data is not available in most countries. Nevertheless, results from a recent RCT conducted in Spain raised questions about the clinical importance of antibiotic coated catheters when they failed to show significant reductions in CR-BSI, only reducing colonization rates. Emergence of resistance is another major concern and data is still conflicting on this issue. Our study was designed as a pilot trial

to compare rates of colonization and CR-BSI between antibiotic coated and non coated catheters in a population of critically ill patients, in order to plan a major RCT aiming to clarify questions on outcome and cost effectiveness of the implementation of this technology in our reality. Colonization rates, which are accepted by some authors as a surrogate for CR-BSI, were lower in the antibiotic coated group. Incidence of CR-BSI didn't differ between study groups, but our trial was underpowered to show such differences. There were 7 cases of CR-BSI and a total of 20 catheters were colonized during the study. Despite the small absolute number, the sole two cases of CR-BSI in the RM coated group were caused by *Candida tropicalis* and happened in the same patient. Also, because of the small sample size, there were few imbalances between study groups, including more patients in the coated catheter arm having another intravascular line concomitant with the study catheter; this may have introduced a bias against the effectiveness of the coated catheter. Both groups had catheters colonized by Gram-positive and Gram-negative bacteria, with coagulase-negative Staphylococcus colonizing 2 RM coated catheters. These results raise concerns about the emergence of CR-BSI caused by yeast species and the protective role of the RM catheter against gram-positive bacteria. There are some limitations in our trial including: (1) the major limitation is the small sample size; (2) but also catheter tip cultures were not submitted to the sonication method, (3) bacteria responsible for CR-BSI were not submitted to pulsed field electrophoresis, (4) permission to use more than 1 study catheter per patient, even if not at the same time (5) and no evaluation of cost savings with the use of ATB coated catheter.

Finally, as this was a small sized pilot clinical trial, it was not sufficiently powered to assess significant differences in clinical outcomes. However, since there have been no Brazilian reported studies that assess the rate of catheter colonization and CR-BSI in uncoated versus antimicrobial coated catheters, the results of this pilot trial will allow us to design a prospective randomized multicenter clinical trial in Brazilian ICU to confirm the efficacy and assess the cost savings associated with the use of endovascular antimicrobial coated catheters.

ACKNOWLEDGMENT

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