J Infect Chemother (2008) 14:399–403
DOI 10.1007/s10156-008-0637-9

ORIGINAL ARTICLE

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Risk factors for central venous catheter-related bloodstream infection: a 1073-patient study

Received: August 15, 2007 / Accepted: August 8, 2008

Abstract We intended to evaluate the risk factors for catheter-related bloodstream infection (CR-BSI) with central venous (CV) catheters. For the hub of the CV line, we used three-way stopcocks in the first year of the study and closed needleless connectors (NCs) in the second year. Background factors included the age and sex of patients; the ward; the specialty service; the CV catheter and its days of placement; and the staff compounding the intravenous infusion, i.e., either nurses, who disinfect hands-free, or pharmacists using clean benches. Outcome factors included positive culture from the blood-related samples and the body temperature estimate. Of a total of 29 221 device-days in 1073 patients, positive cultures showed an overall incidence of 2.26 per 1000 device-days. Multivariate analysis showed a higher odds ratio of positive cultures for the ICU (odds ratio [OR], 4.415; 95% confidence interval [CI], 2.054–9.490]) and for CV catheter placement for more than 30 days (OR, 7.529; 95% CI, 4.279–13.247), but no significance for male sex (OR, 1.752; 95% CI, 0.984–3.119) or for pharmacists' compounding (OR, 2.150; 95% CI, 0.974–4.749). Univariate analysis showed no significance for the following factors: age more than 70 years (OR, 0.968; 95% CI 0.561–1.641), the surgery service (OR, 1.029; 95% CI, 0.582–1.818), double-lumen CV catheters (OR, 0.841; 95% CI, 0.465–1.521), or the NC (1.107; 95% CI, 0.673–1.821). We conclude that the theoretical benefit of the NC, the abolished dead space in the hub, contributed little to the outcomes of blood-related culture. The hands-free disinfection may have resulted in comparable odds ratios for the nurses and the pharmacists compounding the infusions.

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Key words Bloodstream infection · Needleless connector · Three-way stopcock

Introduction

Among the studies carried out to reduce catheter-related bloodstream infection (CR-BSI), the microbiological data are supportive,[1] but the clinical data remain controversial[2,3] in regard to the use of a closed connector in the central venous (CV) line. Because of the possible seasonal fluctuations in the incidence of CR-BSI, before and after the customary changes of staff in April in Japan, we carried out a 2-year study, before and after implementation of the use of closed needleless connectors (NCs) in a teaching hospital.

Patients and methods

Clinical setting

Our institution is a 430-bed teaching hospital in Japan. In principle, every ward has its specialty service but allows admission of patients under other medical disciplines.

Design

During December 2004 to November 2005, the hub of the CV line was a three-way stopcock, whereas from December 2005 to November 2006, the hub was altered to an NC (SurePlug; Terumo, Tokyo, Japan; Fig. 1). In detail, during the first year of the study we used three-way stopcocks with caps (Nipro, Osaka, Japan) and a bacterial filter in the CV line. During the second year, we used a CV line equipped with the NC and a bacterial filter.

Throughout the 2 years' study, at infusion via the hub, the staff disinfected the hub with a sterilized swab containing 76.9%–81.4% ethanol (EthaCotton Stick; Yoshida Pharmaceuticals, Sayama, Japan). Every 7 days, the staff replaced the CV line together with the bacterial filter con-

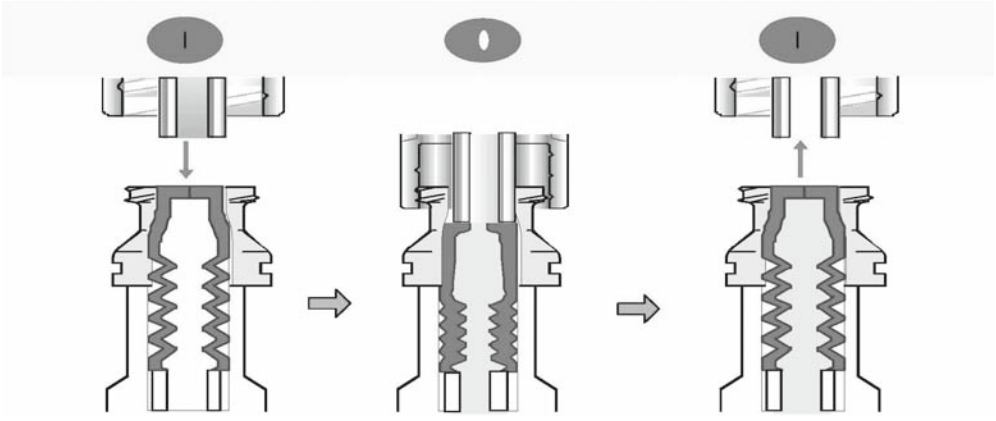

Fig. 1. Cross-sections of the needleless connector as it opens and closes. The authors obtained the approval to reproduce the electronic data from the manufacturer (Terumo, Tokyo, Japan)

nected next to the infusion bottle. The CV catheters were of two luminal types, either a single-lumen catheter (CV Catheter; Kawasumi, Shizuoka, Japan and CV Kit; Nippon Sherwood, Tokyo, Japan) or a double-lumen catheter (EXCV; Nippon Sherwood).

When inserting the CV catheters, physicians' personal protective equipment included sterilized gloves and they used a wide sterile drape of the field. They submitted the tip of the CV catheter and/or blood for culture whenever they suspected CR-BSI or bacteremia. The specific signs included a fever of 38°C or higher, typically with sudden onset, in the presence of the CV catheter for more than 48 h,[4] and in the absence of septic foci other than the bloodstream. In the presence of spiking fever, physicians removed the CV catheter whenever possible.

The blood sample was either arterial or venous. The staff wore sterilized gloves and disinfected the patient's skin with povidone iodine; 3 min later, they applied disinfection-level ethanol and withdrew the blood sample. In our study, positive bacteriologic results and the above clinical signs met the criteria of CR-BSI.

In Japan, nurses prepare intravenous drugs in the ward without clean benches, whereas pharmacists prepare intravenous drugs in laboratories with clean benches. During the 2 years of the study, both nurses and pharmacist carried out disinfection without touching the sterilized swab. In detail, the pharmacists compounded infusions for patients admitted for longer periods in designated general wards. In the intensive care unit (ICU), however, the nurses prepared the infusions. Thus, some patients received infusions prepared by a nurse in the ICU but after their transfer to another ward, they received infusions compounded by a pharmacist. The data were, however, documented by device-days and analyzed for the day when a positive culture was harvested, warranting multivariate analysis for respective days.

Background factors

For every device-day, we collected data on the age and the sex of the patients, the ward (ICU or not), the specialty (Department of Surgery or not), the CV catheter lumen, the hub (the three-way stopcock or the NC), and the staff compounding the infusion.

Outcome factors

We excluded samples submitted within 48 h[4] after placement of the CV line and positive cultures obtained for the second time or later while the same CV line was placed. We divided culture sources into the categories of blood, CV catheter, and blood+catheter when both were submitted on the same day.

To estimate a febrile episode before and after the sample submission, we intended to collect the electronic chart data of the body temperature as far as 3 days prior to and 3 days after the submission. For the body temperature estimate, we calculated the area under the curve and above 37°C per day in the body temperature graph, which we termed AUC37/day. The formula is as follows:

$$\text{AUC37/day} = \Sigma(\text{hourly area above } 37^\circ\text{C})/\text{Days} \ [\text{h } ^\circ\text{C/day}]$$

where a negative sign indicates the area below 37°C. The interval of sampling was 4 to 12 h. This index of body temperature was calculated in an attempt to estimate fever, within the limitation that patients with severe sepsis may show low body temperature.

Data analysis

For statistical analysis to compare the 2 years, we used either Pearson's χ^2 analysis or one-way analysis of variance. Our study being a historical control one, a direct comparison between the 2 years would have been meaningless. A multivariate analysis over the 2 years, however, would elaborate all the factors, including that of the hub (either the closed NC or not) that may contribute to CR-BSI. To analyze the odds ratios of the background factors, we used logistic regression analysis. First we performed a univariate

analysis, the significant factors in which we used for the multivariate analysis. We defined a P value of less than 0.05 as indicating statistical significance. For computation, we used the SPSS statistical software (SPSS, Chicago, IL, USA).

Ethics

Should any hazardous effect of the NC be detected during the study period, we were to discontinue the NC and to resume the open system. For this purpose, we continued the surveillance of CR-BSI, as we participate in the Japanese National Surveillance System. We submitted the study to the internal review board and received their approval.

Results

During the study period, the number of device-days totaled 29221 and the number of patients amounted to 1073, of whom 613 were male patients and 460 were female patients. The sex distribution as well as the mean age was comparable in the first and second years (Table 1).

Analysis of differences between the 2 years

No clinical factors showed significant differences between the 2 years (Table 2), except for the catheter hub (either the open or the NC type). A total of 66 samples were positive and these were the subjects of the outcome analysis.

Table 1. Patients' profiles in the 2 years of the study

Period	1st year	2nd year	Total	P value
Age, in years (mean ± SEM)	71.48 ± 0.63	71.24 ± 0.70		0.795
Sex (n)				
Male	316	297	613	
Female	246	214	460	0.537
Total	562	511	1073	

Analysis of variance was performed for age; otherwise the χ^2 test was used

Table 2. Background factors in the 2 years of the study

Variables Catheter hub	1st year Open (n)	2nd year Needleless (n)	Subtotal (n)	n	P value
Ward					
ICU	43	32	75		
Others	519	479	998	1073	0.403
Service					
Surgery	154	117	271		
Others	408	394	802	1073	0.092
CVC					
Two-lumen	158	118	276		
One-lumen	404	393	797	1073	0.069
Days (mean ± SEM)[a]	28.10 ± 1.60	26.11 ± 1.49			0.366
Drug					
Pharmacist	37	32	69		
Nurse	525	479	1004	1073	0.901
Sample					
Blood	16	15	31		
CVC	14	16	30		
Blood + CVC	3	2	5	66	0.823

Analysis of variance was performed for numerical data, otherwise the χ^2 test was used
n, number of patients; ICU, intensive care unit; CVC, central venous catheter
[a]Days of catheter placement

Table 3. Half-year results of the culture-positive incidents and the body temperature in culture-positive patients

Year	1st year		2nd year		Total	P value
Half year	First half	Second half	First half	Second half		
Subtotal (device-days)	9236	6724	7188	6139	29 221	
Culture-positive patients (n)	17	16	15	18	66	
CR-BSI rate (per ml)	1.84	2.39	2.09	2.94	2.26	0.551
AUC 37/day (h °C/day; mean ± SEM)	4.03 ± 2.28	5.46 ± 3.13	3.04 ± 2.59	4.20 ± 1.15		0.917

Analysis of variance was performed comparing the four half-year groups
CR-BSI, catheter-related bloodstream infection

Table 4. Predominant microbes isolated from the bloodstream infection over the 2 years of the study period, permitting repetition

Species	1st year	2nd year	(Subgroup)		(Subgroup)	
			1st year	2nd year	Total	*P* value
CNS	14	14			28	
(*Staphylococcus epidermidis*)			(8)	(11)		(19)
S. aureus	7	5			12	
(MRSA)			(6)	(4)		(10)
(MSSA)			(1)	(1)		(2)
Bacillus cereus	2	4			6	
Pseudomonas aeruginosa	1	3			4	
Enterococcus faecalis	2	1			3	
Klebsiella pneumoniae	2	1			3	
Candida albicans	2	0			2	
Enterobacter cloacae (D group)	1	1			2	
Proteus mirabilis	2	0			2	
12 Others	6	6			12	
Total	39	35			74	0.611

CNS, coagulase-negative staphylococci; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*

Table 5. Factors for positive bloodstream culture (66 patients) as opposed to others (1007 patients)

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age (years): <70 vs ≧70	0.968	0.561–1.641	0.904			
Sex: male vs female	2.086	1.197–3.637	0.010*	1.752	0.984–3.119	0.057
Ward: ICU vs others	2.947	1.471–5.905	0.002*	4.415	2.054–9.490	<0.001*
Service: surgery vs others	1.029	0.582–1.818	0.923			
CVC: two-lumen vs one-lumen	0.841	0.465–1.521	0.566			
Hub: needleless vs open	1.107	0.673–1.821	0.690			
Drug: pharmacist vs nurse	2.492	1.177–5.275	0.017*	2.150	0.974–4.749	0.058
CVC days: ≧31 vs <31	7.115	4.129–12.262	<0.001*	7.529	4.279–13.247	<0.001*

*Significant difference (less than 0.05)
CI, confidence interval of odds ratio; ICU, intensive care unit; CVC, central venous catheters

The number of positive cultures showed no difference between the 2 years, nor did AUC37/day. Furthermore, neither of these outcomes showed any difference among a total of four half-year divisions (these divisions were made to determine the presence or absence of seasonal fluctuation within a year; Table 3). Overall, we detected positive cultures at an average of 2.26 per 1000 device-days (Table 3).

From the 66 positive cultures, a total of 74 microbial species were isolated, including coagulase-negative staphylococci (CNS) and others (Table 4). In terms of species causative of the CR-BSI, we found no significant difference between the 2 years.

Main outcome analysis

Defining the main outcome as the 66 culture-positive patients as opposed to the other 1007 patients, univariate analysis showed higher odds ratios for male sex, the ICU, the pharmacists' compounding, and for CV catheter placement for more than 30 days. The univariate analysis showed, however, no significance for the following factors: age more than 70 years (0.968; 95% confidence interval [CI], 0.561–1.641), the surgery service (1.029; 95% CI, 0.582–1.818), the double-lumen CV catheter (0.841; 95% CI, 0.465–1.521), and the NC (1.107; 95% CI, 0.673–1.821).

The subsequent multivariate analysis showed higher odds ratios for positive culture in the ICU (4.415; 95% CI, 2.054–9.490) and for CV catheter placement for more than 30 days (7.529; 95% CI 4.279–13.247) but no significance for male sex (1.752; 95% CI 0.984–3.119) or the pharmacists' compounding (2.150; 95% CI, 0.974–4.749; Table 5).

Medicoeconomics

The three-way stopcock line system with its bacterial filter cost ¥670, while the NC line system with its bacterial filter cost ¥650, or 3% less than the other.

Discussion

The current 2-year study on CR-BSI showed no significance for the NC against the open three-way stopcock. The theoretical benefit of bacterial reduction in the dead space produced by the NC did not affect CR-BSI. This conclusion may partly be due to the methodological drawbacks of our

study, i.e., that it was a historical control study. To offset this shortcoming, we carried out multiple regression analysis. In fact, the preliminary univariate analysis showed a higher odds ratio for the pharmacists' compounding, but the multivariate analysis revealed that the days of catheter placement overtook the factor of the compounding staff. Another hypothesis, that of seasonal fluctuation, was rejected (Table 3), indicating that the staff change had little effect on CR-BSI.

When inserting the CV catheters, the maximal barrier precaution was not observed. If there had been cases using this precaution, this variable as opposed to the standard barrier precaution would have been analyzed.

Yebenes et al.[2] described that in critically ill patients, a needle-free connector prevented CR-BSI. McDonald et al.,[5] however, reported an increased risk of CR-BSI associated with a needleless device in a pediatric ICU. Likewise, Cookson et al.[6] described increased CR-BSI associated with inappropriate use after implementation of a needleless device in surgical patients. For a new mechanical valve intravenous access port, as well, Maragakis et al.[7] reported increased CR-BSI in ICUs after its introduction. Our study showed no such untoward effects.

The failure of the NC to reduce CR-BSI in our study may have resulted from the low CR-BSI rate of use of the three-way stopcock. When disinfecting the hub, we have been using a sterilization-level swab with ethanol, never using alcohol on a cotton swab by hand. The use of alcohol on cotton swabs may invite the implantation of *Bacillus* species, an example of alcohol-resistant microbes. Late in 2006, a Japanese hospital experienced an outbreak of *Bacillus cereus* where the manner of disinfection with cotton swabs was alleged to have caused the infection. Our study showed, however, a rate of 8.1% for *B. cereus* in the species isolated from the blood-related sources (Table 4).

As for the preparation of intravenous infusions in Japan, nurses often prepare intravenous drugs in the wards, but the government now advises that pharmacists should prepare the infusions on clean benches. This factor of pharmacists' compounding was significantly detrimental in the preliminary univariate analysis, but was not significant in the multivariate analysis, where the duration of CV catheter placement had a greater influence on CR-BSI. The hands-free disinfection at infusion compounding and at the injection via the hub may have played a role in controlling the CR-BSI.

Our study showed that the NC reduced the cost of the line system by 3%. We continue with the use of the NC at this reduced cost. Another reason that we abolished the open system was because of its polyvinyl chloride (PVC)-containing material, as this material is contraindicated for use with some chemotherapeutic agents. Apart from the consideration of CR-BSI, the PVC-free lines cost ¥652 000 in the first year of using the NC system, with the cost being ¥0 in the second year. Thus we await future studies to investigate the clinical as well as medicoeconomic benefits of the NC.

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