FACTORS ASSOCIATED WITH MORTALITY AMONG PATIENTS WITH CENTRAL VENOUS CATHETER-RELATED BLOODSTREAM INFECTION IN AN INTENSIVE CARE UNIT

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ABSTRACT

Central venous catheterization is a common practice in the management of critically ill patients and is associated with various complications, such as Bloodstream Infections (BSI), which are major determinants of increased morbidity, mortality and healthcare expenses. Few studies have addressed factors that predict mortality in patients with this complication. The aim of this study was to investigate factors associated with mortality in patients with Central Venous Catheter (CVC)-related BSI in an intensive care unit of a tertiary care hospital in the Federal District, Brazil. This was a retrospective and observational study, in which all CVC-related BSI that occurred between January 2008 and December 2010 were reviewed. We obtained demographic, clinical, biochemical and microbiological data from medical records and investigated its association with mortality during ICU stay. There were 4,504 ICU admissions during the study period and 68 were complicated by CVC-related BSI (4.09 per 1000 catheter-days), most due to gram-negative organisms (45.6%). Overall mortality was 59.7%. Death risk was significantly associated with mechanical ventilation (OR 27.8, 95% CI 3.28-250, p<0.001), the mean number of invasive devices other than the CVC (1.44 Vs 2.37 in controls Vs cases, p<0.001) and increased serum levels of urea (mean value of 44.2 mg dL^{-1} in survivors vs. 73.9 mg dL^{-1} in non-survivors, p = 0.001). Mortality was not associated with other clinical or biochemical features, neither with microbiological variables, although lethality was high among patients with gram-positive infections (77% Vs 58.33% for fungi and 54.83% for gram-negative). CVC-related BSI was associated with high absolute mortality, which was predicted by mechanical ventilation and a higher number of invasive devices other than the CVC. Knowledge of local factors predictive of mortality is critical for planning strategies to reduce death risk associated with this complication.

Key words: Bloodstream Infection, Central Venous Catheter, Intensive Care Unit, Mortality

1. INTRODUCTION

Central venous catheterization is a common practice with unquestionable benefits in the management of critically ill patients (Mcgee and Gould, 2003). However, it is also associated with potentially serious complications (McGee and Gould, 2003; Garnacho-Montero *et al*., 2008). One of the main complications is Central Venous Catheter (CVC)-related Bloodstream Infection (BSI) (O'Grady *et al*., 2011), which is a major determinant of increased morbidity, mortality, hospitalization length and health care expenses in the Intensive Care Unit (ICU) (Pittet *et al*., 1994; Garrouste-Orgeas *et al*., 2006).

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In the United States, 80,000 new cases of CVC-related BSI are estimated to occur in ICUs each year (Mermel *et al*., 2009). In South America, there are fewer studies addressing this issue. In an Argentinian 5 year study involving 6 hospitals, it was reported that CVC-related BSI complicated 2.92% of all ICU admissions, increased hospitalization length by 11.9 days and resulted in a 24.6% excess mortality (Rosenthal *et al*., 2003). A Brazilian study carried out over a period of 11 months in 7 public ICUs in the Federal District found a 6.4% frequency of overall BSI and a 1.5% frequency of CVC-related BSI. This complication increased 3.5 times the duration of hospitalization (Mesiano and Merchan-Haman, 2007).

There are a number of interventions to attempt reducing the incidence of CVC-related BSI, mostly involving CVC insertion and care, such as barrier precautions, hand hygiene, skin antisepsis and careful CVC insertion site choice (O'Grady *et al*., 2002). Nevertheless, rationale and effective interventions to reduce CVC-related BSI rates and its associated mortality remain a major focus of research (Vincent *et al*., 2009) and identifying the factors that predict the occurrence of these infections and its associated mortality might contribute to improvement of these interventions. The aim of this study was to investigate factors associated with mortality in patients with central venous catheter CVC-related BSI in an intensive care unit of a tertiary care hospital in the Federal District, Brazil.

2. MATERIALS AND METHODS

2.1. Study Design

This study was carried out in a 40-bed medical-surgical ICU of a tertiary care hospital in Brasília, (Federal District, Brazil). All occurrences of CVC-related BSI from January 2008 to December 2010 were prospectively investigated. The diagnosis of CVC-related BSI was defined according to the local protocol, which follows the recommendations from the Centers for Disease Control and Prevention, CDC (O'Grady *et al*., 2002; Mermel *et al*., 2009).

Patients aged over 18 years were included in the study and only the first episode of CVC-related BSI was considered if there was more than one episode of infection per patient during ICU stay. Exclusion criteria were CVC insertion prior to ICU admission, pregnancy and patients who were transferred to another ICU.

The following data were collected: age, gender, admission APACHE II score, reason for ICU admission, comorbidities, need for mechanical ventilation and renal replacement therapy, need for glucocorticoid or insulin therapy during ICU stay, need for other invasive devices,

length of ICU stay and time period between admission and CVC-related BSI diagnosis. Biochemical (serum urea, creatinine, glucose and lactate levels), CVC-related (insertion site) and microbiological (microbiological isolate causing the infection: gram-positive, gram-negative or fungi) data were collected from medical records.

The study was approved by the local ethics committee, which required no written informed consent because it was an observational and retrospective study based on routinely obtained information in the ICU.

2.2. Statistical Analysis

Continuous variables were reported as the appropriate measures of central tendency and categorical variables, as percentages. CVC-related BSI rate was reported as incidence density (number of case per 1000 catheter-days). The patient status (survivor or non-survivor) at the end of ICU stay was considered as the outcome variable. The association of the outcome variable with the categorical variables analyzed was expressed as the Odds Ratio (OR) with 95% Confidence Intervals (95% CI). The frequency of these variables in survivors and non-survivors groups was compared using simple logistic regression. For continuous variables showing normal distribution, mean values were compared using t-Student test. For those not showing normal distribution, median values were compared using Mann-Whitney and Kruskal-Wallis tests. Statistical significance was set at p-value <0.05. Statistical analyses were done using the 17th version of the Statistical Package for the Social Sciences (Chicago, IL, US) and R Statistics softwares.

3. RESULTS

3.1. Study Population

A total of 4,504 patients were admitted to the ICU during the study period and CVC-related BSI was diagnosed in 68 patients (1.53%). The corresponding incidence density of this infection was 4.09 per 1000 catheter-days. All cases were included in the study.

Patients with CVC-related BSI had a mean age of 72.20 ± 17.0 years and 54.4% were male. Mean APACHE II score on admission was 16.4 ± 5.6 and the mean duration of ICU stay was 91.22 ± 77.40 days. The most common reason for ICU admission was medical conditions associated with infection (50.0%) and the most frequent comorbidity was diabetes (27.9%), as shown in **Table 1**.

The most commonly needed invasive procedure was mechanical ventilation (82.1%) and 22.4% of patients needed hemodialysis as renal replacement therapy.

Table 1. Demographic and clinical features of patients with CVC-related BSI

	Total study period (2008-2010) N = 68
Demographic data	
Age (mean ± SD)	72.20±17.0
Male gender (%)	54.4
Clinical data	
APACHE II at admission (mean ± SD)	16.4±5.6
Length of ICU stay in days (mean ± SD)	91.22±77.40
ICU admission reason	
Clinical without infection (%)	16.6
Clinical with infection (%)	50.0
Surgical without infection (%)	22.1
Surgical with infection (%)	11.8
Comorbidities	
Diabetes mellitus (%)	27.9
Oncologic disease (%)	10.3
Chronic renal disease (%)	10.3
Need for mechanical ventilation (%)	82.1
Need for dialysis (%)	22.4
Mean number of invasive devices other than the CVC	2.0
Time period between ICU admission and diagnosis of CVC-related BSI (mean ± SD)	38.2±28.8
Insulin therapy (%)	94.0
Glucocorticoid therapy (%)	31.3
CVC insertion site	
Subclavian vein (%)	91.0
Internal jugular vein (%)	7.5
Femoral vein (%)	1.5
Outcome	
Mortality (%)	59.7

SD: Standard Deviation; APACHE II: Acute Physiology and Chronic Health disease Classification System II; CVC: Central Venous Catheter; BSI: Bloodstream Infection; ICU: Intensive Care Unit

Table 2. Demographic and clinical features and death risk among patients with CVC-related BSI

	Survivors N = 27	Non-survivors N = 41	OR (95% IC)	p-value
Mean age ± SD	69.3±15.0	74.1±18.3		0.080
Male gender	13 (48.14%)	24 (58.3%)	1.52 (0.57-4.04)	0.277
Apache II at admission (mean ± SD)	15.7 ± 4.9	16.9±6.0		0.700
ICU admission reason				
Clinical without infection	4 (14.8%)	7 (17.1%)	0.84 (0.22-3.2)	0.542
Clinical with infection	11 (40.7%)	23 (56.1%)	1.86 (0.69-4.9)	0.161
Surgical without infection	7 (25.9%)	8 (19.5%)	0.69 (0.22-2.2)	0.369
Surgical with infection	5 (18.5%)	3 (7.3%)	2.9 (0.63-13.2)	0.154
Comorbidities				
Oncologic disease	1 (3.7%)	6 (14.6%)	4.46 (0.50-40.0)	0.148
Diabetes mellitus	7 (25.9%)	12 (29.3%)	1.18 (0.4-3.52)	0.494
Chronic renal disease	4 (14.8%)	3 (7.3%)	0.45 (0.09-2.2)	0.275
Need for mechanical ventilation	16 (59.3%)	40 (97.6%)	27.8 (3.28-250)	< 0,001
Need for dialysis	6 (22.2%)	9 (22%)	1.02 (0.31-3.3)	0.603
Glucocorticoid therapy	8 (29.6%)	13 (31.7%)	1.10 (0.38-3.2)	0.537
Insulin therapy	26 (96.3%)	38 (92.7%)	0.49 (0.05-4.9)	0.478
CVC insertion site				
Subclavian vein	25 (92.6%)	37 (90.2%)	1.35 (0.23-7.9)	0.551
Internal jugular vein	1 (3.7%)	4 (9.8%)	2.8 (0.29-26.3)	0.334
Femoral vein	1 (3,7%)	A0	-	-
Mean number of invasive devices other than the CVC	1.44±1.0	2.37±0.8		< 0.001
Mean length of ICU stay in days ± SD	87.6±6.8	93.6 ±78.7		0.878

CVC: Central Venous Catheter; ICU: Intensive Care Unit; SD: Standard Deviation; OR: Odds Ratio, 95% IC: 95% confidence interval

Table 3. Biochemical features and death risk among patients with CVC-related BSI

	Survivors N = 27	Non-survivors N = 41	p-value
Urea, mg/dL (mean ± SD)	44.2±42.1	73.9±45.0	0.001
Creatinine, mg/dL (mean ± SD)	1.2±1.3	1.4±1.5	0.411
Glucose, mg/dL (mean ± SD)	123±34.6	148.2±70.2	0.125
Lactate, mmol/L (mean ± SD)	1.2±0.97	2.1±2.7	0.093

SD: Standard Deviation

Table 4. Microbiological diagnosis and death risk among patients with CVC-related BSI

	N (%)	Mortality N (%)	Lethality (%)	OR (95%IC)	p-value
Gram-positive	13 (19.1)	10 (14.7)	77.00	2.6 (0.64-10.4)	0.147
Gram-negative	31 (45.6)	17 (25)	54.83	0.65 (0.23-1.7)	0.277
Fungi	24 (35.3)	14 (20.58)	58.33	0.88 (0.32-2.4)	0.504

OR: Odds Ratio, 95% IC: 95% confidence interval

The mean number of invasive devices other than the CVC was 2.0 and the mean time period between ICU admission and diagnosis of CVC-related BSI was 38.2±28.8 days. The need for insulin (94%) and glucocorticoid (31.3%) therapy was frequent. The most common CVC insertion site was the subclavian vein (**Table 1**). Biochemical data collected within a 5 day period of CVC-related BSI diagnosis showed mean serum levels of urea of 62.1±46.5 mg dL^{-1} (reference range, RR 10-46), creatinine of 1.3±1.4 mg dL^{-1} (RR 0.6-1.1), glucose of 138.2±59.7 mg dL^{-1} and lactate of 1.7±2.3 mmol/L (RR 0.4-2.0). Most cases of CVC-related BSI were due to gram-negative organisms (45.6%), followed by fungi (35.3%) and gram-positive (19.1%) organisms. There were no cases of polymicrobial CVC-related BSI.

3.2. Factors Associated with Mortality among Patients with CVC-Related BSI

In the study period, there were 41 deaths among patients with CVC-related BSI, corresponding to a mortality of 59.7%. There was a significant association between death risk and the need for mechanical ventilation (OR 27.8, IC 95% 3.28-250.00, p<0.001) and the mean number of invasive devices other than the CVC (1.44 Vs 2.37 in the survivors vs. non-survivors group, p<0.000). There was a trend towards association between mortality and the presence of oncologic disease (OR 4.46), although not statistically significant (IC 95% 0.50-40.0, p = 0.148). There was no association between death risk and the other demographic and clinical variables analyzed such as admission APACHE II score, diabetes, chronic renal disease, the need for hemodialysis and the mean length of ICU (**Table 2**).

Interestingly, serum levels of urea, but not those of creatinine, were significantly associated with death risk

(mean urea serum levels of 44.2 mg dL^{-1} in survivors Vs 73.9 mg dL^{-1} in non-survivors, p = 0.001). Other biochemical variables were not associated with mortality, as shown in **Table 3**. Mortality was higher (25.0%) in patients with CVC-related BSI due to gram-negative organisms, although patients with gram-positive infections showed the highest lethality (77%). However, no association was found between microbiological diagnosis and death risk in patients with CVC-related BSI (**Table 4**).

4. DISCUSSION

Nosocomial BSIs are primarily associated with intravascular devices, such as CVCs and represent a major determinant of morbidity and mortality among critically ill patients (Laupland *et al.*, 2002; Vincent, 2003; Garrouste-Orgeas *et al.*, 2006; Vincent *et al.*, 2009). We studied 4,504 ICU admissions over a period of three years; 1.53% of them were complicated by CVC-related BSI and the correspondent incidence density was 4.09 per 1000 catheter-days. Patients with CVC-related BSI in our study were old (mean age of 72.20 years) and there was a slight male preponderance (54.4%). We found a high overall mortality in patients with this complication (59.7%).

There is a large variation in the incidence and mortality rates of CVC-related BSI in the ICU setting worldwide. These reasons for these discrepancies are not completely defined, but are believed to reflect at least in part the diversity of local clinical practices, distinct patient characteristics and the different designs of epidemiological studies from which these data are derived (Tacconelli *et al.*, 2009; O'Grady *et al.*, 2011). Data from the SCOPE (Surveillance and Control of Pathogens of Epidemiologic Importance) study,

comprising 49 hospitals in the United States, indicated an incidence of 60 cases of nosocomial BSI per 10,000 hospital admissions, 50.5% of which occurred in the ICU and a crude mortality of all BSI of 27% (Wisplinghoff et al., 2004). In France, the National Nosocomial Infection Survey estimated an incidence rate of CVC-related BSI of 1.23 per 1000 catheters-days (Tacconelli et al., 2009) and another European study reported a 43.9% mortality of BSI in the ICU (Pratikaki et al., 2009). In South America, an Argentinian study found a 2.92% incidence of CVC-related BSI in the ICU, with a crude mortality of 52.4% (Rosenthal et al., 2003). A Brazilian study also conducted in the ICU setting reported a 1.5% frequency of CVC-related BSI with a 40% overall mortality (Mesiano and Merchan-Haman, 2007). We found an incidence of CVC-related BSI similar to the latter study, although mortality in our study population was considerably higher. This finding might be attributable to some of the patient's features, which are predictive of increased overall mortality, such as advanced age, illness severity on ICU admission as indicated by a high APACHE II score (mean of 16.4), serious underlying diseases (malignancy, diabetes and chronic renal disease) and the common need for other invasive procedures (Garnacho-Montero et al., 2008; Stoeckle et al., 2008; Son et al., 2010).

In addition, in this study death risk was associated with the need for mechanical ventilation and with a higher mean number of invasive devices other than the CVC. It was also associated with urea but not creatinine serum levels and this may reflect the advanced age of our study population. No significant differences were found for other variables analyzed. In other studies, several factors have been described as predictive of mortality in patients with CVC-related BSI, such as adult respiratory distress syndrome, shock, multiorgan failure, mechanical ventilation, chronic hepatic failure, acute renal failure and APACHE II score greater than 14 (Rello et al., 1994; Valles et al., 1997; Garrouste-Orgeas et al., 2006). Unlike these studies, we could not find an association of mortality with admission APACHE II score. It is also noteworthy that factors associated with mortality risk, including those found in our study, may all be viewed as surrogate markers of illness severity, rather than specific etiologic factors for mortality.

We found a predominance of CVC-related BSI infections due to gram-negative organisms over fungi and gram-positive. Although this is in disagreement with the more recent reports indicating an increased incidence of gram-positive organisms in patients with BSI in the ICU setting (Wisplinghoff et al., 2004), it may be explained by local factors and also by the increased age of our study population and the severity of their clinical status, which have been found to be associated with increased risk for gram-negative infections (Waterer and Wunderink, 2001; Kohlenberg et al., 2008; Vincent et al., 2009). Mortality was higher among patients with CVC-related BSI due gram-negative bacteria (25%), in agreement with data from the Extended Prevalence of Infection in Intensive Care (EPIC II) study, which comprised 75 countries and found that mortality was higher among ICU patients with infections due to gram-negative organisms (Vincent et al., 2009). Lethality, however, was higher among patients with infections due to gram-positive organisms (77%) in our study.

This study has some limitations, including the relatively small absolute number of CVC-related BSI occurrences and the high absolute mortality in patients with this complication, which may have precluded us from finding differences between survivors and non-survivors. Moreover, our study did not include a control group of patients submitted to CVC insertion but without CVC-related BSI and it was limited to only one ICU facility.

5. CONCLUSION

We found a high mortality in patients with CVC-related BSI, which was associated with need for mechanical ventilation, with a higher mean number of invasive devices other than the CVC and with a higher serum level of urea. This suggests that in addition to rigorous infection control measures to reduce the incidence of this complication in the ICU setting, it is important to develop strategies to improve patient outcome when CVC-related BSI infection occurs and these strategies should focus specially on severely ill patients.

5.1. Competing Interests

The authors declare that they have no competing interests. Authors' contributions: All authors contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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