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ORIGINAL ARTICLE

Risk Factors for Central Line-Associated Bloodstream Infection in Critically Ill Neonates

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Abstract

Objective To identify independent risk factors to develop a central line- associated bloodstream infection (CLABSI) in critically ill neonates with major underlying diseases.

Methods A nested case-control study was conducted in a neonatal intensive care unit (NICU). Patients with a central venous catheter (CVC) were included. Cases were neonates who developed a CLABSI and controls were patients without CLABSI. Variables included: perinatal history, characteristics of the catheter, installation and catheter use, surgical interventions, and hospital stay. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. X^2, Fisher exact, and Mann-Whitney U tests were used when appropriate. Variables with a p value ≤0.10 in the univariate analysis were introduced in a non-conditional logistic regression model.

Results Seventy four cases and 105 controls were analyzed. Univariate risk factors were: any surgery, abdominal surgery, length of hospitalization (≥14 d), double-lumen CVC, surgical cut-down technique, complications, CVC placement in internal jugular vein, dressing type, blood transfusions, parenteral nutrition, and number of CVC manipulations (>200). In the logistic regression analysis, independent risk factors with a p value <0.05 were: double-lumen catheter (OR 5.8, 95% CI 1.2–30), length of hospitalization ≥14 d (OR 4.6, 95% CI 1.8–11.4), abdominal surgery (OR 2.7, 95% CI 1.2–6.2) and blood transfusions (OR 2.5, 95% CI 1.2–5.3).

Conclusions One risk factor was related to the catheter itself. Management of underlying diseases in specialized NICU contributes to a greater extent to the development of a central line-associated bloodstream infection.

Keywords Bloodstream infection · Central line-associated infections · Critically ill neonates · Nosocomial infections

Introduction

Newborns in neonatal intensive care units (NICU), in particular preterm neonates, are at high risk to develop healthcare associated infections, mainly due to a greater number of invasive procedures required for their management, with consequent higher morbidity, mortality and costs [1].

The use of central venous catheters (CVCs) is mandatory, but it is usually accompanied by the risk of several complications [1, 2]. Central line-associated bloodstream infection (CLABSI) is the most common complication of the CVCs in intensive care units in developing countries. Frequency of CLABSI in neonates has been reported between 1.4% to 49%,with an incidence rate of approximately 0.93–13.6 cases/1000 catheter-days [3–11].

In newborns, most common microorganisms causing CLABSIs are Gram-positive bacteria, mainly coagulase-negative *Staphylococcus (*CoNS*), Staphylococcus aureus*, and *Enterococcus faecalis*, followed by gram-negative bacteria: *Klebsiella pneumoniae, Escherichia coli, Enterobacter cloacae* and *Pseudomonas aeruginosa* [4, 8–11].

Several studies have reported the association between patient characteristics, and the catheter itself, both linked to the development of infection. Some of the risk factors include: low birth

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weight [12], prolonged dwell-time [5, 13], catheter manipulations [14], use of total parenteral nutrition [12, 15–17], exposition to blood products [18–20], catheters inserted in the femoral vein in comparison with other sites [21], intra-abdominal pathology [22], and catheter with three lumens in comparison with one-lumen catheters [23].

Multiple factors can contribute to the development of CLABSI in patients in NICU, therefore the aim of the present study was to identify independent risk factors in critically ill neonates with major underlying diseases.

Material and Methods

This nested case-control study was conducted in a third-care level NICU in Mexico City, located in a pediatric reference hospital. The unit has 24 radiating heat cribs, the average number of admissions is 30 patients per month; 65 % of the newborns are admitted for a surgical procedure, and approximately 40% of them require at least one CVC. Patients were included from January 2014 through December 2015.

Local Research and Ethics Committee Hospital de Pediatría, Centro Medico Nacional SXXI, Instituto Mexicano del Seguro Social approved the study with the number R-2013-3603-38.

To calculate the sample size, a formula for cases and control studies was used, using the following parameters: 95% confidence level; 80% power; a 53% of exposure frequency in the cases, using the presence of congenital malformations as an independent variable, according to a previous study conducted in authors' Neonatal Intensive Care Unit; [4] with an odds ratio of 2.7, obtaining a minimum sample size of 148 (74 cases and 74 controls).

Cases were neonates diagnosed with CLABSI, and controls were those neonates with a CVC during the same period but who did not develop a CLABSI. Patients with installation of a CVC during their hospital stay at the NICU were included; only the patients with first CVC installation and those with CVC duration ≥48 h were selected for inclusion. Exclusion criteria was patients who had a catheter installed in another hospital.

Central line-associated bloodstream infection (CLABSI) was defined according to the criteria by the CDC (LCBI 3) [24]:

1. Patient ≤1 y of age has at least *one* of the following signs or symptoms: fever (>38.0 °C), hypothermia (<36.0 °C), apnea, or bradycardia, and
2. Organism(s) identified in blood is (are) not related to an infection at another site, and
3. The same common commensal is identified by a culture or non-culture based microbiologic testing method, from two or more blood specimens collected on separate occasions. Common commensal organisms include, but not are not limited to, diphtheroids (*Corynebacterium* spp. (not *C. diphtheria*), *Bacillus* spp. (not *B. anthracis)*, *Propionibacterium* spp., coagulase-negative staphylococci (including *S. epidermidis)*, *Viridans* group streptococci, *Aerococcus* spp. *Micrococcus* spp., and *Rhodococcus* spp.

CLABSI mortality-related is defined as a death directly related to the infection which occurred during active infection event and no other underlying cause of fatal outcome was present.

The study variables included

Newborn factors: birth weight, gestational age, gender, diagnoses of main disease, congenital malformations, comorbidities, surgery, type of surgery, chronological age and days of hospital stay previous to CVC installation and
CVC factors: CVC indication, insertion technique (surgical cut-down or percutaneous access), shift (morning, evening or night), number of lumens, time required to install the catheter (minutes), person who installed the catheter (resident *vs.* neonatologist), complications during procedure; catheter handling, number of CVC manipulations, blood transfusions through the CVC, administration of parenteral nutrition, type of dressing, interval between dressing changes (days), CVC indwelling time (days) before the development of bacteremia, microorganism detected in blood cultures, death related to the CLABSI and total duration of CVC.

In patients with a suspected infection, a two-set of blood cultures were obtained. Disinfection with 2% iodine-povidone were performed. One peripheral blood culture was obtained along with a catheter-drawn blood culture. The minimum volume for a blood culture inoculated in the aerobic bottle was 1.5 ml (Bac/Alert PF plus, BioMerieúx, USA) [25].

A daily follow-up was carried out to register the use of the catheter, manipulations and incidents. Catheter manipulation data were recorded by one of the researchers (BRC) using a standardized form.

Catheter manipulations were stratified into 5 categories.

1. Connection of an infusion line to the catheter (intravenous solutions, parenteral nutrition, drugs in continuous infusion)
2. Administration of IV drugs in bolus
3. Transfusions (blood, plasma, platelets, cryoprecipitates)
4. Calibrated fluid chamber manipulation (electrolyte administration)
5. Blood sampling

The follow-up of each patient was carried out until the development of bacteremia or until discharge from the NICU.

Statistical analysis was performed by using SPSS version 20. Relative frequencies and percentages for categorical variables were calculated, and medians and interquartile ranges (IQR) for quantitative variables. Univariate analysis was performed to identify variables associated with CLABSI; odds ratio (OR), and 95% confidence intervals (95% CI) were obtained. Chi-square test, Fisher exact test, and Mann-Whitney U test were used when appropriate, according to the type of variable. Those variables with a value of $p \leq 0.10$ in the univariate analysis were introduced in a non-conditional logistic regression model and adjusted ORs (aORs) were obtained.

Results

During the 24-mo period, CVC catheter was placed in 250 critically ill newborns, of them, 179 fulfilled the inclusion criteria and were analyzed in this study. Seventy-four developed CLABSI (Cases) and 105 constituted the control group.

In both groups there was a higher proportion of male patients. The most frequent diseases affecting the neonates were congenital heart defects (CHD), and malformations of the gastrointestinal tract. Seventy five percent of the cases and 64% of controls underwent a surgical procedure during hospitalization. There were no significant differences between cases and controls regarding perinatal variables. The significant differences were a longer hospital stay and the placement of the catheter in the internal jugular vein in the CLABSI group, and the catheter installed at a younger chronological age and the placement of the catheter in the upper limb in the control group (Table 1).

CVC was mainly used for the administration of fluids, vasoactive agents, antibiotics, blood transfusions, and parenteral nutrition.

A total of 38 (21.2%) patients died during their stay in NICU; 16 patients of the group with CLABSI. In five of them, death was directly related to CLABSI.

Table 1 Characteristics of the study population

Study variables	Patients with CLABSI ($n = 74$) Median (IQR)[a]	Patients without CLABSI ($n = 105$) Median (IQR)	P value[*]
Gestational age (weeks)	36 (33–38)	37 (23–38)	0.77
Birth weight (grams)	2355 (1687–3000)	2270 (1450–2922)	0.94
Age at NICU admission (days)	8 (1–22)	6 (1–25)	0.57
Age at CVC installation (days)	17 (5–45)	8 (2–26)	0.002
Weight at CVC installation (grams)	2310 (1746–3000)	2490 (1730–2890)	0.94
Total stay in NICU (days)	57 (30–76)	19 (9–42)	0.0001
Sex			0.72[**]
Male (n, %)	41 (55.4)	61 (58.1)	
Female (n, %)	33 (44.6)	44 (41.9)	
Any surgery (n, %)	56 (75.6)	67 (64.0)	0.09
Cardiac surgery (n, %)	23 (40.4)	29 (42.6)	0.79
Abdominal surgery (n, %)	27 (36.5)	19 (18.1)	0.006
Other surgeries (n,%)	6 (10.5)	13 (19.1)	0.18
Placement site of CVC			
Internal jugular (n, %)	43 (58.1)	35 (33.3)	0.001
Subclavian[b] (n,%)	17 (23)	27 (25.7)	0.67
Saphenus (n,%)	7 (9.5)	16 (15.2)	0.25
External jugular (n, %)	4 (5.4)	7 (6.7)	0.98
Upper limb[b] (n,%)	1 (1.3)	12 (11.4)	0.01
Brachial[b] (n,%)	1 (1.3)	5 (4.8)	0.21
Lower limb[b] (n,%)	1 (1.3)	3 (2.8)	0.64

[a] IQR: Interquartile range

[b] Percutaneous insertion

[*] Mann-Whitney U test

[**] Chi-square

CLABSI Central line-associated bloodstream infection; *CVC* Central venous catheter; *NICU* Neonatal intensive care unit

The most frequent microorganisms causing bacteremia were Gram-positive cocci (56.7%) and Gram-negative rods (37.8%), mainly, *Staphylococci epidermidis* and *Klebsiella pneumoniae*, respectively (Table 2). In two patients, polymicrobial infection was reported.

In the univariate analysis, statistical significant risk factors associated to the development of CLABSI were: abdominal surgery, length of hospitalization for ≥14 d previous to catheter installation, double-lumen CVC, surgical cut-down technique, CVC site (internal jugular vein), dressing with gauze and surgical tape, blood transfusions, parenteral nutrition, CVC number of manipulations (≥ 200) and CVC indwelling total time (≥ 21 d) (Table 3).

Twelve variables were included in the logistic regression analysis, four risk factors independently associated with CLABSI were: double-lumen catheter (OR 5.8, 95% CI 1.2–30.0), length of hospitalization ≥14 d (OR 4.6, 95% CI 1.8–11.4), abdominal surgery (OR 2.7, 95% CI 1.2–6.2) and blood transfusions (OR 2.5, 95% CI 1.2–5.3). (Table 4).

Discussion

Newborns with congenital malformations and underlying diseases are at higher risk to develop complications associated to healthcare. CLABSI is one of the main complications in the NICU. Prevention strategies are enforced due to the higher morbidity and mortality [2, 6].

According to a previous study and surveillance hospital epidemiology data, CLABSI is the most frequent nosocomial infection in authors' NICU. Incidence rate of CLABSI is 14.1 × 1000 catheter days, with a frequency of 35.5% [4], higher than reported in the literature, which varies between 0.93 and 13.6/1000 catheter days [2, 6, 7, 26–28].

Of the microorganisms causing bacteremia, coagulase-negative *Staphylococcus* were the most frequently isolated, similar to other publications [4, 10–12, 26, 27]. Some authors have questioned the relevance of these infections, as the origin of the bacteria is the microbiota of the skin, and different strategies to decrease the colonization have not entirely succeeded [29].

The participation of Gram-negative rods was important, mainly *Klebsiella pneumoniae*. The critical condition of the patients, along with the abdominal surgeries to correct the gastrointestinal tract malformations, and prolonged fasting could account for some of the infections, with a probable endogenous origin. However, patients with congenital heart defect also, had bacteremia due to Gram-negative rod.

The length of hospital stay previous to CVC installation as an independent risk factor can be explained due to the characteristics of patients in authors' NICU; most of the newborns have complex congenital malformations, mainly congenital heart diseases, and gastrointestinal malformations, along with comorbidities, requiring one or more surgeries and long fasting periods. In the NICU, colonization by resistant bacteria is common; Mahieu [12] also reported prolonged hospital stay before insertion of the CVC as a risk factor associated to infectious complications of the device. Other authors have reported a longer hospital stay as one of the main risk factor

Table 2 Microorganisms isolated in blood cultures

Microorganism	*n*	%
Gram-positive	42	56.7
Coagulase-negative Staphylococci	36	48.6
Staphylococcus epidermidis	26	35.1
Staphylococcus hominis	8	10.8
Staphylococcus haemolyticus	2	2.7
Staphylococcus aureus	5	6.8
Enterococcus faecalis	1	1.4
Gram-negative	28	37.8
Klebsiella pneumoniae	15	20.3
Escherichia coli	6	8.1
Pseudomonas aeruginosa	3	4
Enterobacter cloacae	3	4
Serratia marcescens	1	1.4
Polymicrobial infections		
Escherichia coli and *S. epidermidis*	1	1.4
Staphylococcus epidermidis, Candida albicans and *Klebsiella pneumoniae*	1	1.4
Candida albicans	2	2.7

Table 3 Univariate analysis of risk factors associated with CLABSI in critically ill neonates

Variables	Cases ($n = 74$)	Controls ($n = 105$)	OR	95% CI	p value*
Newborn factors					
Male	25	60	0.71	0.36–1.41	0.33
Congenital malformations	36	69	1.2	0.60–2.66	0.53
Postmenstrual age (< 32 wk)	5	13	0.51	0.17–1.5	0.21
Birth weight (<1500 g)	10	22	0.58	0.26–1.3	0.20
Any surgery	56	67	1.7	0.90–3.4	0.09
Abdominal surgery	27	19	2.6	1.3–5.1	0.006
Length of hospitalization (≥14 d)[a]	25	14	3.3	1.5–6.9	0.001
CVC factors					
Double lumen CVC	72	82	10.0	2.3–44.3	0.0001
Surgical cut-down technique	54	58	2.1	1.1–4.1	0.01
Complications during installation	9	5	2.7	0.88–8.6	0.06
CVC site (internal jugular vein)	43	35	2.7	1.5–5.1	0.001
Time of procedure (>30 min)	38	41	1.6	0.90–3.0	0.10
Day shift other than morning	43	51	1.5	0.80–2.7	0.28
Person performing the procedure (resident)	66	90	1.4	0.55–3.4	0.49
Dressing type (gauze and surgical tape)	56	62	2.1	1.2–4.1	0.02
Interval between dressing changes (≤ 5 d)	58	81	1.0	0.5–2.2	0.85
Blood transfusions	38	24	3.6	1.87–6.78	0.0001
Parenteral nutrition	64	69	3.3	1.53–7.27	0.002
Days of parenteral nutrition (≥14 d)	31	24	1.7	0.88–3.5	0.10
Number of CVC manipulations (>200)	42	34	2.7	1.5–5.0	0.001
CVC indwelling total time (>21 d)	37	27	2.9	1.5–5.4	0.001

[a] Previous to CVC installation

* Chi-square

CVC Central venous catheter; *OR* Odds ratio; *95% CI* 95% confidence interval

for the development of sepsis and nosocomial infections in general [30, 31].

Of the risk factors in this study and also reported by other authors, Elward and Fraser [19] found that multiple transfusions of red blood cells were an independent risk factor for CLABSI (OR 1.2, 95% CI 1.1–1.4). Martínez et al. [20] also reported that transfusions were independent risk factors for CLABSI (OR 2.06, 95% CI 1.18–3.58). Costello et al. [18], in a study conducted in patients with congenital heart defects, reported that exposure to more than three units of blood products had a risk of 3.88 (95% CI 1.28–11.76) for systemic infection associated with CVC.

In general, surgical procedures are considered risk factors for the development of any type of healthcare associated infections. In the pediatric population, the study of Londoño et al. [32] reported this finding (RR = 1.99, 95% CI1.0–3.7). In the PICNIC study [22], the attention focused on abdominal conditions (not only those that required surgical procedures), as the authors reported active abdominal pathology (OR, 5.9; 95% CI, 2.5–14.1) as one of the main independent risk factors for CLABSI, maybe due to bacterial translocation and secondary bacteremia.

Table 4 Independent risk factors associated to CLABSI in the regression logistic multivariate analysis

	OR	95% CI	p value*
Double-lumen catheter	5.8	1. 2–30.0	0.03
Length of hospitalization (≥14 d)	4.6	1.8–11.4	0.001
Abdominal surgery	2.7	1.2–6.2	0.02
Blood transfusions	2.5	1.2–5.3	0.01

* Mantel-Haenzel Chi-square

OR Odds ratio; *95% CI* 95% confidence interval

A systematic review reported that multiple-lumen catheters are associated with a higher CLABSI rate, compared to single-lumen catheters [23]. Stoll et al., [33] found a risk of 3.8 (95% CI 2.2–6.6) for late-onset sepsis in newborns with an indwelling CVC time from 8 to 14 d. Meanwhile, Njere [13] reported a risk of 3.1 (95% CI 1.64–5.87) when CVC in dwelling lasted 9 d or more. In the present study, indwelling CVC time was not an independent significant risk factor, and of the multiple catheter factors, only double-lumen catheter was independently associated with CLABSI.

One of the limitations of present study is the population included. The newborns in the referral NICU have multiple underlying diseases, birth defects and comorbidities. So, the extrapolation to other critically ill neonates may not be accurate. Present studies are focused on evaluation of enhanced prevention strategies. Characterization of associated risks factors in special populations of newborns, different from preterm and low-weight birth neonates are needed to apply specific policies to prevent device related infection in specialized neonatal intensive care units.

Only one risk factor was related to the catheter itself. Necessary care of morbidity conditions contributes to a greater extent to the development of CLABSI.

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Compliance with Ethical Standards

Conflict of Interest None.

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