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Invasive devices as risk factors for neonatal sepsis in neonatal intensive care units

Dispositivos invasivos como fatores de risco para sepse neonatal em unidades de terapia intensiva neonatal

Dispositivos invasivos como factores de riesgo de sepsis neonatal en unidades de cuidados intensivos neonatales

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Abstract

This study aimed to evaluate the impact of invasive devices as risk factors for the development of neonatal sepsis in Neonatal Intensive Care Units**.** Hospital-based retrospective cohort study performed in two Neonatal Intensive Care Units in Ponta Grossa, Paraná, Brazil. Documentary data were collected through consultation of electronic medical

charts of all patients admitted to two hospitals and of the patients with diagnosis of sepsis in another hospital. Health conditions at admission and outcomes were evaluated. Frequencies of the reasons for admission and the outcomes were calculated. In the association analysis, exposure variables were calculated with odds ratio and confidence intervals (95%). The frequency of sepsis was 39%, and 45.7% of the cases were of early-onset sepsis and 54.3% of late-onset sepsis. The mortality rate associated with sepsis was 9.9%. The use of invasive devices was observed to increase by 6 times the risk of neonatal sepsis. Peripherally inserted central catheter and phlebotomy were the devices causing higher risk. The high incidence of late-onset sepsis, its association with the use of invasive devices and the higher mortality rate among newborns with sepsis suggest the presence of fragilities in neonatal care and the need to seek alternatives of neonatal approach to avoid new cases of neonatal sepsis and consequent death.

Keywords: Sepsis; Pregnancy complications; Infectious; Child health services.

Resumo

Incluir o resumo. Este estudo teve como objetivo avaliar o impacto dos dispositivos invasivos como fatores de risco para o desenvolvimento de sepse neonatal em Unidades de Terapia Intensiva Neonatal. Estudo de coorte retrospectivo de base hospitalar realizado em duas Unidades de Terapia Intensiva Neonatal de Ponta Grossa, Paraná, Brasil. Os dados documentais foram coletados por meio de consulta a prontuários eletrônicos de todos os pacientes internados em dois hospitais e dos pacientes com diagnóstico de sepse em outro hospital. As condições de saúde na admissão e os resultados foram avaliados. Foram calculadas as frequências dos motivos de admissão e os desfechos. Na análise de associação, as variáveis de exposição foram calculadas com odds ratio e intervalos de confiança (95%). A frequência de sepse foi de 39%, sendo 45,7% dos casos de sepse precoce e 54,3% de sepse tardia. A mortalidade associada à sepse foi de 9,9%. Observou-se que o uso de dispositivos invasivos aumenta em 6 vezes o risco de sepse neonatal. Cateter central de inserção periférica e flebotomia foram os dispositivos de maior risco. A alta incidência de sepse tardia, sua associação com o uso de dispositivos invasivos e a maior mortalidade entre os recém-nascidos com sepse sugerem a presença de fragilidades na assistência neonatal e a necessidade de buscar alternativas de abordagem neonatal para evitar novos casos de sepse neonatal e consequente morte.

Palavras-chave: Sepse; Complicações infecciosas na gravidez; Serviços de saúde da criança.

Resumen

Incluir o resumo em espanhol. Este estudio tuvo como objetivo evaluar el impacto de los dispositivos invasivos como factores de riesgo para el desarrollo de sepsis neonatal en Unidades de Cuidados Intensivos Neonatales. Estudio de cohorte retrospectivo de base hospitalaria realizado en dos Unidades de Cuidados Intensivos Neonatales en Ponta Grossa, Paraná, Brasil. Los datos documentales se recogieron mediante consulta de historias clínicas electrónicas de todos los pacientes ingresados en dos hospitales y de los pacientes con diagnóstico de sepsis en otro hospital. Se evaluaron las condiciones de salud al ingreso y los resultados. Se calcularon las frecuencias de los motivos de ingreso y los resultados. En el análisis de asociación, las variables de exposición se calcularon con razón de probabilidades e intervalos de confianza (95%). La frecuencia de sepsis fue del 39% y el 45,7% de los casos fueron de sepsis de inicio temprano y el 54,3% de sepsis de inicio tardío. La tasa de mortalidad asociada a la sepsis fue del 9,9%. Se observó que el uso de dispositivos invasivos aumentaba en 6 veces el riesgo de sepsis neonatal. El catéter central de inserción periférica y la flebotomía fueron los dispositivos de mayor riesgo. La alta incidencia de sepsis de inicio tardío, su asociación con el uso de dispositivos invasivos y la mayor tasa de mortalidad entre los recién nacidos con sepsis sugieren la presencia de fragilidades en la atención neonatal y la necesidad de buscar alternativas de abordaje neonatal para evitar nuevos casos de sepsis neonatal y consecuente muerte.

Palabras clave: Sepsis; Complicaciones infecciosas del embarazo; Servicios de salud del niño.

1. Introduction

About 36% of the 4 million neonatal deaths estimated annually are caused by infections (Shane & Stoll, 2014). One of the major concerns in Neonatal Intensive Care Units (NICU) is the development of neonatal infections and sepsis, the latter being the main cause of mortality and morbidity in these units. Characterized by signs and symptoms of infection and bacteremia in the first 28 days of life (Silveira & Procianoy, 2012), sepsis has a direct impact on neonatal mortality and can implicate neurodevelopmental disorders, especially in cases of extremely low birth weight (Shindler et al., 2017). Incidence and mortality rates are higher in developing countries such as Brazil.

The neonatal period is characterized by vulnerability due to the immaturity of the immunological system and the first major exposures to microorganisms, starting from the

moment the newborn leaves the intra uterine cavity and gets in contact with maternal blood, the birth canal, people and eventual extreme situations such as admission to intensive care units and use of invasive devices (Rosa et al., 2020; Shane & Stoll, 2014). The incidence of neonatal sepsis varies according gestational age and the risk is higher in preterm infants, in whose cases can be around 60% (Wynn, 2016).

Much progress has taken place in neonatal care in the last 30 years, such as the development of successful ventilation strategies for the management of pulmonary hypertension and hyaline membrane disease, therapeutic hypothermia for hypoxic-ischemic encephalopathy, and improvement in parenteral nutrition care. However, the treatment of neonatal sepsis and outcomes of neurodevelopmental disorders remain the same despite all efforts to decrease the burden of infection (Wynn et al., 2014).

Early-onset sepsis arises in the first 72 hours of life, is mostly caused by Group B Streptococci or Escherichia coli, and accounts for about 8% of neonatal deaths. On the other hand, late-onset sepsis starts after 72 hours of life, is caused by healthcare-associated pathogens, and has a four-fold greater impact on neonatal mortality (Global Maternal and Neonatal Sepsis Initiative Working Group, 2017).

Late-onset neonatal sepsis appears from the fourth day of life onwards and although it can be associated with childbirth-related factors, in general, postnatal factors have a greater influence (Silveira & Procianoy, 2012). Cross-contamination via the hands of health care professionals plays an important role in increasing the risk of infection, which reinforces the importance of proper hand hygiene (Shane; Sánchez; Stoll, 2017). Premature infants are at greater risk of developing late-onset sepsis in view of their immunological immaturity and the multiple procedures they are subjected to during their stay in the NICU and prolonged length of hospitalization (Hornik et al., 2012). Prolonged parenteral nutrition, intravascular catheters, orotracheal intubation and invasive mechanical ventilation are predisposing factors to the onset of infection (Alcock et al., 2017).

In view of the national and worldwide relevance of neonatal sepsis, this study aimed to evaluate the impact of invasive devices as risk factors to the development of neonatal sepsis at two NICU in Ponta Grossa, Paraná, Brazil. Both are tertiary care hospitals, the first being a reference to high risk pregnancy, the second did not have an obstetric ward at the time of the study, and newborns came from other Hospitals in the region.

2. Methodology

Hospital-based cohort retrospective study conducted at the NICU of two hospitals in Ponta Grossa, Paraná, Brazil, after approval from the ethics committee of the State University of Ponta Grossa (UEPG) (Protocol 2.414.044/2017). The NICU of the first hospital (hereafter Hospital 1) was inaugurated in 2004 and had 14 beds, offering services to the Unified Health System (SUS) and private health plans. The NICU of the second hospital (hereafter Hospital 2) was inaugurated in 2013, with 4 beds for neonatal care and 4 for pediatric care in the same unit, and offered services only to SUS users.

Newborns admitted to the two NICU were included in the study. This corresponded to all infants admitted from January 1st, 2015, to December 31st, 2017, in Hospital 1, and all infants diagnosed with sepsis from January 1st, 2013, to December 31st, 2017, in Hospital 2. Regarding the years encompassed in this study, a limited period of time was adopted for data collection because it represented the short period of study in one of the hospitals. Electronic charts of patients were consulted for a retrospective analysis of gestational age, birth weight, maternal pathologies, maternal age, maternal use of antibiotics and steroids, use and time of use of invasive devices, prenatal care, method of delivery, late rupture of membranes,- and chorioamnionitis.

This study was performed in South Brazil, state of Paraná, which is the fifth-largest economy of the country. The South region has the lowest maternal mortality and child mortality rates in the country.

In this study, three criteria were considered for the diagnosis of sepsis: 1 - Abnormal laboratorial analysis (Rodwell hematologic score ≥ 3 and/or elevated C-reactive protein); 2 - Presence of any non-specific sign/symptom of infection (respiratory distress, apnea, lethargy or irritability, thermic instability, hypotonia, persistent gastric stasis, pulmonary hemorrhage); 3 - Prescription of antimicrobial treatment by the medical team. All newborns who presented the three diagnostic criteria in the first 28 days of life were classified as presenting neonatal sepsis. Automatized blood cultures were not available at the time; thus, less than 5% of the blood cultures tested positive and they were not enough to diagnose neonatal sepsis. Aiming to increase specificity to the diagnosis, we adopted the three abovementioned criteria, i.e. laboratorial, clinical, and medication parameters.

Early-onset sepsis was considered when sepsis was manifested within the first 72 hours of life, and late-onset sepsis when manifested after 72 hours of life (Shane & Stoll, 2014). Birth weight classification followed the World Health Organization (WHO)

recommendations: low birth weight (LBW) < 2500 g; very low birth weight (VLBW) < 1500 g, and extremely low birth weight (ELBW) < 1000 g. Newborns were classified as to prematurity according to the following categories: extremely preterm (< 28 weeks), very preterm (28 to < 32 weeks), and moderate/late preterm (32 to < 37 weeks) (World Health Organization, 2012).

Crude frequencies and 95% confidence intervals (95% CI) of early- and late-onset neonatal sepsis in all individuals, and in individuals from each hospital, were estimated. Crude frequencies estimate the real absolute number of the events and the rates at which they happened in the patients.

The frequency of presence and absence of sepsis was calculated for each one of the risk factors. The Chi-square test was used to check differences in proportions for all the risk factors. In order to evaluate the association between neonatal sepsis and variables of a binary outcome, the odds ratios (95% CI) were calculated. The Chi-square statistic is tool designed to analyze group differences between categorical variables and reveals if the observed distribution occurred at random, when compared to a theoretical distribution.

Means, medians, standard deviations and interquartile ranges of numerical variables were calculated to investigate the differences between presence *versus* absence of sepsis, and early- *versus* late-onset neonatal sepsis according exposure variables (birth weight, gestational age, maternal age, time of membranes rupture, and number of prenatal medical consultations). The association between numerical independent variables and neonatal sepsis were tested with the Student's t-test or Mann-Whitney test, depending on the compliance with normal distribution. The Student's t-test is a tool for quantitative variables that compares the sample mean with the population, and the Mann-Whitney test is a non-parametric version of the Student's t-test when the variables do not have a normal distribution.

All variables with p-value <= 0.20 in the bivariate analysis were included in a logistic regression model. The logistic regression is a statistical multivariate method that allows the construction of a predictor model to explain the outcome based on a series of binary explanatory variables. Data were analyzed with SPSS®, 20th version. All the notes of this study were extracted by the main researcher in both hospitals through consultation of the medical charts of the patients.

3. Results

The number of newborns analyzed in the study was 520. These children were hospitalized in both institutions in the period of study, and 226 had neonatal sepsis (Table 1). Hospital 2 had a higher number of cases of late-onset sepsis (Table 2).

Table 1 – Frequency of neonatal sepsis in NICU, Paraná, Brazil, 2013-2017.

Neonatal sepsis	**Nº (%)**	**95% CI**
Both hospitals	226 (39.0)	35.3-43.0
Hospital 1	161 (32.9)	28.7-37.1
Hospital 2	65 (72.2)	64.4-82.2

Source: Authors (2020).

Table 2 – Number and percentage of early and late-onset neonatal sepsis in NICU, Paraná, Brazil, 2013-2017.

Neonatal sepsis	**Classification**	**Nº (%)**	**95% CI**
Both hospitals	Early-onset	100 (45.7)	38.8-51.6
	Late-onset	119 (54.3)	48.4-61.2
Hospital 1	Early-onset	79 (49.1)	41.0-56.5
	Late-onset	82 (50.9)	43.5-59.0
Hospital 2	Early-onset	21 (36.2)	23.3-50.0
	Late-onset	37 (63.8)	50.0-76.7

Source: Authors (2020).

In the crude analysis, risk factors for the development of neonatal sepsis were vaginal delivery, birth weight, admission of the mother to the ICU, use of invasive devices such as endotracheal intubation, bi-level positive airway pressure (BiPAP), peripherally inserted central catheter (PICC), phlebotomy, and total parenteral nutrition (TPN) (Table 3). Surfactant use appeared as a protection factor and the risk of death in septic patients were 2.81-fold greater than that of non-septic patients (Table 3).

Table 3 – Risk factors for neonatal sepsis in NICU, Paraná, Brazil, 2013-2017.

Conditions		Septic		Non-septic		Total		OR 95% CI	*p*-value
		N	%	N	%	N	%		
Sex	Male	125	40.6	183	59.4%	308	100.0	1.14	0.243
	Female	226	37.4	169	62.6%	270	100.0	(0.82 – 1.59)	
Weight classification*	ELBW	43	60.6	28	39.4%	71	100.0	0.50 (0.28-0.90)	0.021
	VLBW	45	42.5	61	57.5%	106	100.0	1.05 (0.63-1.75)	0.849
	LBW	71	28.1	182	71.9%	253	100.0	1.99 (1.29-3.05)	0.002
	Above 2500g	62	43.7	80	56.3%	142	100.0	1	
Membranes rupture	Yes	49	32.0	104	68.0%	153	100.0	0.82	0.358
	No	122	36.5	212	63.5%	334	100.0	(0.54 – 1.23)	
Gestational age (weeks)	≥ 38	43	60.6	28	39.4%	71	100.0	1	
	< 28	45	42.5	61	57.5%	106	100.0	1.45 (0.77 – 2.73)	0.249
	28 - 32	71	28.1	182	71.9%	253	100.0	0.77 (0.45 – 1.32)	0.335
	32 - 37	62	43.7	80	56.3%	142	100.0	0.41 (0.26 – 0.65)	<0.001
Twin pregnancy *	Yes	15	27.3	40	72.7%	55	100.0	0.568	0.070
	No	206	38.8	312	60.2%	518	100.0	(0.31 – 1.06)	
Prenatal care*	Yes	167	33.9	326	66.1%	493	100.0	0.448	0.118
	No	8	53.3	7	46.7%	15	100.0	(0.16 – 1.26)	
Method of delivery *	Cesarean section	141	34.4	269	65.6%	410	100.0	0.517	<0.001
	Vaginal delivery	78	50.3	77	49.7%	155	100.0	(0.36 – 0.75)	
Outcome*	Death	50	58.8	35	41.2%	85	100.0	2.819	<0.001
	Cure	148	33.6	292	66.4%	440	100.0	(1.75 – 4.53)	
Gestational Diabetes	Yes	11	32.4	23	67.6%	34	100.0	1.00	0.989
	No	137	32.2	288	67.8%	425	100.0	(0.48 – 2.12)	
Hypertension	Yes	41	34.7	77	65.3%	118	100.0	1.17	0.490
	No	108	31.3	237	68.7%	345	100.0	(0.75 – 1.82)	
Admission of the mother to the ICU *	Yes	23	47.9	25	52.1%	48	100.0	2.05	0.018
	No	127	31.0	283	69.0%	410	100.0	(1.12 – 3.75)	
Placental diseases	Yes	7	29.2	17	70.8%	24	100.0	0.83	0.688
	No	154	33.1	311	66.9%	465	100.0	(0.34 – 2.05)	

Maternal pathologies	Yes	137	32.5	284	67.5%	421	100.0	0.89	0.697
	No	19	35.2	35	64.8%	54	100.0	(0.49 – 1.61)	
Maternal use of antibiotics	Yes	10	41.7	14	58.3%	24	100.0	0.95	0.955
	No	3	42.9	4	57.1%	7	100.0	(0.17 – 5.23)	
Maternal use of steroids	Yes	80	30.9	179	69.1	259	100.0	0.82	0.315
	No	71	35.3	130	64.7	201	100.0	(0.55 – 1.21)	
Invasive devices*	Yes	223	42.2	306	57.8	529	100.0	11.17	<0.001
	No	3	6.1	46	93.9	49	100.0	(3.43 -36.39)	
Endotracheal intubation*	Yes	148	54.0	126	46.0	274	100.0	3.43	<0.001
	No	78	25.5	228	74.5	306	100.0	(2.42 – 4.87)	
CPAP*	Yes	90	43.5	117	56.5	207	100.0	1.34	0.097
	No	136	36.5	237	63.5	373	100.0	(0.95 – 1.90)	
BiPAP*	Yes	33	73.3	12	26.7	45	100.0	4.87	<0.001
	No	193	36.1	342	63.9	535	100.0	(2.46 – 9.66)	
Umbilical catheter*	Yes	202	40.6	295	59.4	497	100.0	1.66	0.050
	No	24	29.3	58	70.7	82	100.0	(1.00- 2.75)	
PICC*	Yes	137	71.0	56	29.0	193	100.0	8.19	<0.001
	No	89	23.0	298	77.0	387	100.0	(5.54 – 12.10)	
Phlebotomy*	Yes	20	90.9	2	9.1	22	100.0	17.087	<0.001
	No	206	36.9	352	63.1	558	100.0	(3.95 – 73.85)	
TPN*	Yes	85	63.9	48	36.1	133	100.0	3.84	<0.001
	No	141	31.5	306	68.5	447	100.0	(2.56 – 5.77)	
Surfactant*	Yes	84	47.7	92	52.3	176	100.0	1.35	<0.001
	No	117	37.9	250	68.1	367	100.0	(1.35 – 2.82)	

*Variable selected for logistic regression analysis. Source: Authors (2020).

In the multivariate model (Table 4), the use of invasive devices, birth weight and the outcome were considered independent risk factors for development of neonatal sepsis. that the presence of any invasive device, phlebotomy and PICC increased the risk for neonatal sepsis, respectively by 5.84 ($p = 0.019$), 11,53 ($p = 0.025$) and 8.26 ($p < 0.001$) times, respectively, while the other risk factors increased it by approximately twice such risk.

Table 4 – Independent risk factors for neonatal sepsis in NICU, Paraná, Brazil, 2013-2017.

Variable	**Adjusted OR**	**IC 95% OR**	***p*-value***	**R^2**
Invasive devices	5.84	1.33 – 25.56	0.019	0.386
PICC	8.26	4.96 – 13.75	< 0.001	
Phlebotomy	11.53	1.35 – 98.28	0.025	
Outcome	2.87	1.51 – 5.45	0.001	
Very low birth weight	2.91	1.49 – 5.66	0.002	
Low birth weight	2.48	1.46 – 4.21	< 0.001	

*Logistic regression analysis. Source: Authors (2020).

4. Discussions

Neonatal sepsis causes 3 million deaths per year. Early detection and treatment of maternal conditions during prenatal care may avoid 1/3 of these deaths (Black et al., 2016). Almost half of the patients analyzed in this study had sepsis. Late-onset sepsis was more frequent. The higher incidence of late-onset sepsis worldwide point to the impact of the fragilities in healthcare, because this condition is mostly caused by healthcare-associated pathogens and is particularly related with NICU care (Giannoni et al., 2018).

Low, very low and extremely low birth weight preterms are more prone to develop sepsis due to their immunological immaturity, constant handling by healthcare professionals, prolonged hospital stay, and use of invasive devices. At this study, VLBW and LBW had statistically significant higher risk of neonatal sepsis.

Different approaches can be successful to prevent this severe condition. A first measure is to implement interventions during prenatal and delivery care for adequate detection and treatment of the mother's infections (Silveira & Procianoy, 2012).

Regarding the method of delivery, vaginal delivery showed a higher risk of neonatal sepsis. However, the maternal information available in the charts was not complete and as neonatal sepsis has a multifactorial etiology, the association of sepsis with method of delivery has not enough support.

Since 2011, a healthcare strategy called the "Rede Cegonha" was introduced in Brazil aiming to provide assistance to family planning of reproductive health and humanized care during gestation, labor and puerperium. In the state of Paraná, this program is called "Mãe Paranaense". Initially, there was a decrease in maternal and child mortality rates, but in 2017, these rates started to rise again. Brazil has a wide range of economic and social inequality.

Providing proper assistance in rural areas and extremely poor regions can be very challenging, and better governmental strategies are needed for a comprehensive national coverage (Frank et al., 2016).

Regarding late-onset sepsis, admission to NICU is necessary to avoid this condition. This study shows evidence of flaws in local hospital care: individuals using invasive devices, PICC and with phlebotomy had 6-fold, 8-fold and 11-fold higher risk for sepsis. The impact of invasive devices on the increase of risk of sepsis and, consequent mortality is noteworthy. Septic patients were 3-foldmore prone to die.

Bundle implementation to control the use of invasive devices is likely to be effective to reduce morbidity and mortality. Gocke et al. (2018) noted a 63% reduction of ventilator-associated pneumonia (VAP) after application of care bundles for prevention of VAP at a NICU in Turkey. Adherence to hand hygiene guidelines, oral care, bed head elevation to 10–13 degrees, ventilator circuit evaluation and changing the circuit when visibly soiled or malfunctioning, periodical draining and discarding of ventilator circuit condensate were included in the bundle checklist (Gocke et al., 2018). Regarding central line-associated infections, Resende and Do Ó (2011) reported a reduction from 24.1/1000 to 14.9/1000 catheter day after bundle implementation at a NICU in Brazil. The bundle included hand hygiene, maximum barrier protection, skin cleansing with clorhexidine 0.2%, avoiding femoral insertion and early withdrawal. The impact of the bundle application demonstrates that preventing infection is feasible. In the units studied, the bundles applied include hand hygiene and VAP prevention. Bundle implementation alone is not enough though; constant updating and actions of professionals up committed to such measures are also necessary.

The limitations of this study include the retrospective cohort approach and the analysis of medical charts which can provide incomplete information. On the other hand, these methods chosen made the research easier to follow up the individuals. Chart analysis was also considered to reduce the bias of non-response and loss of follow up. Moreover, information bias was reduced because information loss was equally distributed among patients with and without neonatal sepsis. At the end, to minimize analysis bias, data were examined by a statistical expert blinded for the neonatal sepsis risk factors already described by the literature. Also, as this was a hospital-based study, the newborns had more severe infectious conditions.

Further studies in NICU should be performed, such as clinical trials, and should compare intervention strategies aiming at reducing exposure to the risk factors found in the present study. Finally, we stress that researchers of neonatal sepsis, especially in developing

countries, should investigate the role of educational practices for the healthcare team and families so as to reduce neonatal sepsis.

5. Conclusion

The high incidence of late-onset sepsis, its association with the use of invasive devices and the higher mortality rate among newborns with sepsis suggest the presence of fragilities in the neonatal care and the need to seek alternatives of neonatal approach to avoid new cases of neonatal sepsis and consequent death. Other studies in NICU should be performed to compare intervention strategies aiming to reduce neonatal sepsis.

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