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RISK FACTORS FOR NOSOCOMIAL INFECTIONS IN MECHANICALLY VENTILATED NEONATES AT INTENSIVE CARE UNIT

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ФАКТОРИ РИЗИКА ЗА НАСТАНАК БОЛНИЧКИХ ИНФЕКЦИЈА КОД НОВОРОЂЕНЧАДИ НА МЕХАНИЧКОЈ ВЕНТИЛАЦИЈИ У ЈЕДИНИЦИ ИНТЕНЗИВНОГ ЛЕЧЕЊА

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ABSTRACT

Introduction. Neonatal nosocomial infection (NIs) is defined as the occurrence of infection 48 hours after birth, which is caused by a nosocomial pathogen. Newborns admitted to neonatal intensive care units (NICU) are at increased risk for developing Nis. The aim of our study was to describe risk factors for NIs at mechanically ventilated (MV) neonates in a NICU.

Materials and methods. The study was designed as a case/control study nested in the prospective cohort study. The study population consisted of the neonates supported by MV and admitted at the NICU. Risk factors were identi-

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fied and their influence quantified by logistic regression.

Results. Our study showed that MV neonates in the NICU, who were longer carrying peripheral venous catheter (PVC) and spend more time in hospital, were more likely to get NIs (OR=1.091, CI=1.035-1.151). The neonates having an infection on admittance were less likely to acquire NIs.

Conclusions. Development of NIs in MV neonates could be prevented by education of hospital staff and shortening of hospitalization. Rate of nosocomial infections will drop if exposure of newborns to pathogens from hospital environment and to invasive devices is decreased.

Keywords: nosocomial infections, mechanic ventilation, neonates, intensive care unit.

САЖЕТАК

Увод и циљ. Неонатална нозокомијална инфекција (ННИ) дефинисана је као појава инфекције 48 часова након порођаја која је узрокована патогеном из болничке средине. Новорођенчад примљена у јединице за интензивну негу новорођенчади (НЈИН) су под посебно великим ризиком за развој ННИ. Циљ наше студије био је откривање фактора ризика за ННИ код механички вентилиране (МВ) новорођенчади у НЈИН.

Материјал и методе. Студија је дизајнирана као студија случај/контрола садржана у проспективној кохортној студији. Испитанике студије чине новорођенчад на механичкој вентилацији, смештена у НЈИН. Помоћу логистичке регресије идентификовани су фактори ризика за ННИ и њихов утицај квантификован.

Резултати. Наша студија показује да новорођенчад у НЈИН на механичкој вентилацији, која дуже носе периферни венски катетер и проводе више времена у болници, чешће имају ННИ (OR = 1,091, CI = 1,035-1,151). Новорођенчад која имају инфекцију приликом пријема ређе добијају болничке инфекције.

Закључак. Развој ННИ у новорођенчади на МВ може се спречити едукацијом болничког особља и смањењем дужине хоспитализације. Учесталост ННИ се смањује ако су новорођенчад краће изложена болничкој средини и инвазивним средствима.

Кључне речи: нозокомијалне инфекције, механичка вентилација, новорођенчад, јединица интензивне неге.

INTRODUCTION

Nosocomial infection (NIs) is an infection during hospitalization that was not present or a patient was in incubation at the time of admission[1]. Neonatal NIs are defined as the occurrence of infection 48 hours after birth, and in mechanically ventilated newborns pneumonia with onset more than 48 hours from start of mechanical ventilation could be classified as nosocomial pneumonia. However, rigid applying of fixed cut-off time limit of 48 hours could overestimate true incidence of NIs, if we do not take into account differences in localization of infection, sensitivity of various diagnostic methods and ways of establishing diagnosis[2,3]. Physicians usually start with antibiotic therapy if infected newborn has positive body fluid culture[2]. The incidence varies from 6% to 32% in the United States and from 8% to 10% in Europe-based studies[1]. Neonatal infection rates are 3-20 times higher in developing countries than in developed countries, causing 40% of all neonatal deaths in the former[1,4]. Incidence of neonatal sepsis in developing countries ranges from 5 to 17%[5].

Signs and symptoms of Nis may vary significantly in population of newborns, usually becoming atypical or semi-hidden. Characteristic signs of infection as seen in older children and adults (redness, swelling, pain, increased temperature and loss of function) are rarely obvious in the newborns. They react rather more often with feeding difficulties, vomiting, lethargy, crying, tachypnea, rash, frequent stools, abdominal distention, increased body temperature or hypothermia[1,2,3,4].

NIs become a growing concern in the neonatal intensive care units (NICU), with increased morbidity, mortality and treatment costs. Infants with NIs that require treatment in the NICU are the most vulnerable, due to their immature immune system, weak barrier functions of the skin and gastrointestinal tract and other medical treatments[1,6]. Newborns admitted to NICU are especially at high risk for developing NIs because of the exposure to invasive medical devices such as mechanical ventilators (MV) and central venous catheters (CVCs) which may harbor resistant microorganisms[7,8,9]. Mechanical ventilation is one of the most common medical procedures administered within NICU and it was proven as an independent risk factor for NIs in the NICU

(p< 0.01, OR 3.42; 95% CI 2.17-5.41)[4]. Prolonged hospital stay with the low gestational age also carries the risk of introducing resistant hospital pathogens[1,10]. The other factors that contribute to easier pathogenic transmission are poor hand-hygiene practices, re-use of single-use medication vials and devices, inadequate sterilization of medical equipment and also institutional factors, such as inadequate resources to fund infection-control programs[11,12,13]. The following risk factors were also associated with NIs: low birth weight, gestational age, total parenteral nutrition, umbilical catheter, use of antibiotics, and intubation in the delivery room[14,15]. Overuse of empirical antibiotic therapy is simultaneously a consequence of and a contributing factor to transmission[15,16]. These factors were recognized as important by the International Nosocomial Infection Consortium which gave the following recommendations for decreasing frequency of NIs: education, process surveillance for hand hygiene, adequate care of central lines, ventilator, and urinary catheter and feedback of local epidemiological situation and performance[9].

There is little information in the literature regarding usefulness of assessing correlation of infection rates with duration of exposure of newborns to hospital environment or to invasive devices, such as peripheral venous catheters (PVCs) or MV. The studies that are already published were conducted only on small cohorts of neonates admitted to NICU in developed countries[7]. True effect of invasive devices on NIs in neonates in developing countries remain unclear, taking into account that umbilical or PVC use is major risk factor for infection[17].

The aim of our study was to describe risk factors for Nis at mechanically ventilated (MV) neonates in a NICU.

MATERIALS AND METHODS

Our study was conducted at the Neonatology Department of the Pediatric Clinic, Clinical Center Kragujevac. The population that was studied consisted of all the neonates supported by MV, admitted at the NICU of the Neonatology Department. The study was conducted during the time period from January 1st 2012 to December 31st 2014.

The NICU consists of 15 beds for intensive care and 15 beds for special care. Patients are treated by 8 residents with subspecialty in neonatology. Each nurse cares for 3 newborns. All nurses are licensed and have a secondary or higher level of education. The newborns are thoroughly examined and laboratory tests are performed, in order to exclude the existence of infection at admission. The most common reasons for neonates to be on MV are: respiratory distress, apnea, aspiration syndrome, persistent pulmonary hypertension of newborn, congenital heart disease, severe infections, intracranial hemorrhage, congenital malformations, postoperative treatment and pneumonia. Parents are not involved in the care of newborns, but they insist on maintaining lactation during the hospital stay. Hand hygiene consists of using 0.75% povidone iodine solution and a rapid disinfection is done with alcoholic solutions as recommended by WHO.

Data that was used for the study were collected from the patient's files. The Ethics Committee of the Clinical Center had approved the study. The study was designed as a case/control study nested in the prospective, cohort study. The study outcome (dependent variable) by which the cases were defined was occurrence of NIs in mechanically ventilated newborns. The controls were all other newborns on mechanical ventilation. Diagnosis and site of NIs were determined according to the Serbian translation of the standard diagnostic criteria from the U.S. Centers for Disease Control and Prevention (18).

During the study period there were 1230 neonates in total in the NICU (367 in 2012, 454 in 2013 and 409 in 2014). Out of them, 258 neonates who were on MV were chosen to participate in the study.

The following variables (potential risk factors) were taken into account for this study: socio-demographic data (age of the mother, sex of neonates and city where the delivery took place), pregnancy data (existence of membrane ruptures and twin pregnancy), delivery data (premature delivery, caesarean section, existence of placental abruption), data about a neonate (gestational age, body weight at birth, Apgar score at 1st and at 5th minute, existence of: respiratory distress, asphyxia, aspiration, necrotizing enterocolitis (NEC), infection on admission, PVC, MV, thoracic drain and number of days with these devices, number of interventions, breast-feeding, fever, result of treatment, duration of hospitalization), laboratory test results (white cells count, C-reactive protein), use and choice of antibiotic therapy: penicillins G, 1st, 2nd, 3rd and 4th generation cephalosporins, carbapanems, glycopeptides, aminoglycosides, clindamycin and/or imidazole.

The study data were analyzed by descriptive statistics. Tests used to explore possible differences among the cases and controls in regard to the study variables were Student t-test (where the data were distributed normally) and Mann Whitney U-test for continuous variables, and the χ^2-test for frequencies. The differences were considered significant if the probability of null hypothesis was less than 0.05. Multivariate logistic regression was performed with variables showing significant influence on outcome by the univariate analysis. Interaction between factors which proved to be significant after adjustment, was tested by constructing new logistic regression model where combination of two factors was taken as new, separate factor. The software used for calculations was the SPSS version 18 statistical software (SPSS Inc., Chicago, IL).

RESULTS

Baseline characteristics and differences among the cases and controls are displayed in Tables 1 and 2.

Table 1. Risk factors for nosocomial infection in mechanically ventilated neonates on intensive care unit related to characteristics of the patients and how they were managed

Variables	**With NI (n=148)**	**Without NI (n=109)**	**Test value and P value**	**Crude OR 95% (CI)**	**Exp(B) (95% CI for ExpB)**
Age of mother	29.49±6.220	29.31±6.015	p=0.822	1.005 (0.96-1.04)	1.02 (0.96-1.07)
Age groups of mothers(years)			χ^2=8.586 p=0.03	1.01 (0.76-1.36)	
≤19	0 (0.0%)	5 (4.6%)			
20-24	37 (25.0%)	19 (17.4%)			
25-29	41 (27.7%)	33 (30.3%)			
≥30	70 (47.3%)	52 (47.7%)			
Existence of membrane rupture			χ^2=0.45 p=0.09	1.23 (0.79-1.92)	1.19 (0.67-2.09)
none	113 (76.4%)	92 (84.4%)			
≤24 h	26 (17.6%)	9 (8.3%)			
≥24 h	9 (6.1%)	8 (7.3%)			
Premature labor	117 (79.1%)	83 (76.1%)	χ^2=0.31 p=0.57	1.18 (0.65-2.14)	
Cesarean section	69 (46.6%)	57 (52.3%)	χ^2=0.81 p=0.37	0.79 (0.48-1.30)	
Ablation of placenta	9 (6.1%)	4 (3.7%)	χ^2=0.76 p=0.38	1.70 (0.50-5.67)	
Male sex	94 (63.5%)	6 (60.6%)	χ^2=0.23 p=0.63	1.13 (0.68-1.88)	
Gestational age of the newborn	2.74±1.006	2.91±0.99	p=0.14 Z= -1.45 WRS=7244.500	0.84 (0.65-1.08)	
Body weight of the child at birth	2.89±1.011	3.02±1.08	p=0.22 Z= -1.22 WRS=7384.000	0.89 (0.69-1.13)	
Apgar score at1stminute			χ^2=2.28 p=0.32	0.82 (0.60-1.12)	
≤3	39 (26.4%)	20 (18.3%)			
4-6	41 (27.7%)	34 (31.2%)			
7-10	68 (45.9%)	55 (50.5%)			
Apgar score in the 5th minute			χ^2=7.15 p=0.028**	0.68 (0.48-0.98)	1.112 (0.62-1.99)
≤3	23 (15.5%)	14 (12.8%)			
4-6	57 (38.5%)	27 (24.8%)			
7-10	68 (45.9%)	68 (62.4%)			
Over two days in another department	4 (2.7%)	1 (0.9%)	χ^2=1.05 p=0.31	3.00 (0.33-27.22)	
Twin pregnancy	16 (10.8%)	15 (13.8%)	χ^2=0.51 p=0.47	0.76 (0.39-1.61)	
Preterm delivery	119 (80.4%)	79 (72.5%)	χ^2=2.23 p=0.13	1.55 (0.87-2.79)	
Respiratory distress in the	105 (70.9%)	68 (62.4%)	χ^2=2.09	1.47 (0.87-2.49)	

newborn			p=0.15		
Neonatal asphyxia	85 (57.4%)	47 (43.1%)	χ^2=5.15 p=0.023**	1.78 (1.08-2.93)	1.62 (0.79-3.34)
Aspiration of gastric contents	9 (6.1%)	2 (1.8%)	χ^2=2.76 p=0.096	3.46 (0.73-16.37)	
NEC	3 (2.0%)	6 (5.5%)	χ^2=2.25 p=0.13	0.35 (0.087-1.453)	
Infection on admission	4 (2.7%)	23 (21.1%)	χ^2=22.59 p=0.000**	0.104 (0.03-0.31)	0.104 (0.03-0.36)
Insertion of peripheral venous catheter	148 (100%)	109 (100%)		1358	
Number of day patients had PVC	24.47±13.606	13.54±6.656	p=0.000** Z= -7.65 WRS=3565.000	1.16 (1.10-1.21)	1.09 (1.03-1.15)
Mechanical ventilation of neonates	148 (100%)	109 (100%)		1.36	
Number of days on mechanical ventilation	12.84±10.213	7.06±4.09	p=.000** Z= -6.35 WRS=4345.000	1.18 (1.11-1.27)	0.97 (0.89-1.06)
Thoracic drainage	13 (8.8%)	14 (12.8%)	χ^2=1.10 p=0.29	0.65 (0.29-1.45)	
Number of days patients had thoracic drainage	5.77±2.386	4.36±2.09	p=0.05 Z= -1.93 WRS=52.000	1.35 (0.91-2.00)	
Number of interventions performed on neonates			χ^2=1.55 p=0.21	0.56 (0.26-1.35)	
2	136 (91.9%)	95 (87.2%)			
3	12 (8.1%)	14 (12.8%)			
Breastfeeding	2 (1.4%)	1 (0.9%)	χ^2=0.10 p=0.75	1.48 (0.13-16.52)	
The number of leukocytes	19.11±12.68	17.77±9.298	p=0.96 Z= -0.05 WRS=8034.500	1.01 (0.99-1.03)	
The value of CRP	10.49±19.44	7.64±11.494	p=0.48 Z= -0.69 WRS=7661.500	1.01 (0.95-1.02)	
High body temperature	62 (41.9%)	14 (12.8%)	χ^2=25.43 p=0.000**	4.892 (2.55-9.36)	5.48 (2.33-12.87)
The total duration of hospitalization	6.16±1.315	4.35±1.992	p=0.000** Z= -7.72 WRS=3768.500	1.87 (1.56-2.24)	1.40 (1.12-1.77)

Note. Results are presented as mean ± SD, n (%), or as otherwise indicated.

NI (nosocomial infection) N/A (not applicable)

***** For the sake of clarity, variables with frequency of an event less than 2% and some less important variables with insignificant differences between the cases and the controls are not shown in the table;

** Significant difference; OR – odds ratios; CI – confidence interval.

Table 2. Risk factors for nosocomial infection in mechanically ventilated neonates on intensive care unit related to treatment of the patients

Variables	**With NI (n=148)**	**Without NI (n=109)**	**Test value and P value**
Antibiotics	148 (100%)	109 (100%)	
Penicillin	38 (25.7%)	11 (10.1%)	χ^2=9.88 p=0.002**
First-generation cephalosporin	0 (0.00%)	0 (0.00%)	
Second-generation cephalosporin	0 (0.00%)	0 (0.00%)	
Third-generation cephalosporin	120 (81.1%)	84 (77.1%)	χ^2=0.62 p=0.43
Fourth-generation cephalosporin	0 (0.00%)	0 (0.00%)	

Carbapenem	125 (84.5%)	81 (74.3%)	χ^2=4.06 p=0.04**
Glycopeptides	54 (36.5%)	28 (25.7%)	χ^2=3.37 p=0.06
Aminoglycosides	139 (93.9%)	98 (89.9%)	χ^2=1.41 p=0.236
Clindamycin	4 (2.7%)	1 (0.9%)	χ^2=1.05 p=0.31
Imidazole	4 (2.7%)	0 (0.0%)	χ^2=2.99 p=0.08

Note. Results are presented as mean ± SD, n (%), or as otherwise indicated.

NI (nosocomial infection) N/A (not applicable)

* For the sake of clarity, variables with frequency of an event less than 2% and some less important variables with insignificant differences between the cases and the controls are not shown in the table;

** Significant difference; OR – odds ratios; CI – confidence interval.

DISCUSSION

The results of this study show that mechanically ventilated neonates admitted to a NICU, who are longer exposed to PVC and spend more time in hospital, are more likely to have NIs, as shown in the Table 3. This also applies to those with penicillin therapy, having elevated body temperature, having asphyxia or receiving carbapenem treatment. On the other hand, the neonates having an infection on admittance are less likely to have NIs. Our results are mostly in accordance with the results of other studies of NIs among neonates.

Peripheral venous catheters are necessary to treat neonates with serious medical conditions at a NICU. The results of a multi-center study conducted in the United States by Milstone and associates confirmed that neonates with PVC placed for 2 weeks have higher risk of NIs, and that the risk didn't change after 2 weeks, all the way until removal. The authors also stressed that it is important to check if the PVC is still needed on daily basis, and to improve and investigate new ways of use and maintenance of PVC in the future[19]. The study from Mulago hospital, Uganda, conducted on children admitted to general pediatric department showed that prevalence of infection related to PVC was significant (20.72% for tips and 11.3% for hubs)[20]. Another study from pediatric intensive care unit (ICU) at Lima, Peru, showed that different techniques of catheter insertion and consequent care, bad hand hygiene, low numbers of employed nurses and obsolete medical equipment contribute to greater frequency of NIs[21]. Frequency of NIs represent quality of care[12]. Avoiding unnecessary hospitalizations, providing optimal staffing, purchasing new medical equipment and training aseptic techniques of catheter insertion and care are some of corrective measures that may decrease prevalence of NIs in NICUs[22].

Studies from European countries came to similar conclusions as our study. The study from Lithuania conducted at pediatric ICU showed that duration of hospitalization and mortality rate were higher in patients with NIs[23]. The study from Poland confirmed that prevalence of NIs is greatly influenced by duration of hospitalization[6]. Majority of NIs in newborns with PVC are caused by coagulase-negative staphylococci, and originate from the catheter lumen, which was previously contaminated by improper insertion technique or poor catheter care[14]. Much more should be done on prevention of PVC-related NIs, including avoidance of unnecessary catheterizations in newborns and improvements of quality of catheter care.

Our study was conducted in one center, and on relatively small number of patients, which are the main limitations. Besides, some other important parameters could not be followed due to the lack of the financial support.

Prolonged hospitalization is an important risk factor for NIs because it increases exposure to large number of possible causative agents of infections. Insertion of PVC additionally contributes to increased incidence of NIs, due to poor insertion technique and errors in care which inevitable accumulate with increasing number of days with PVC. In conclusion, it is important to

prevent development of NIs in mechanically ventilated neonates by continuous education of hospital staff on proper insertion and care of PVCs and by shortening of hospitalization.

Table 3. Crude and adjusted odds ratios (OR) of the risk factors for neonatal hospital infection

Risk factors	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Age of mother (≤19 years/ 20-24 years/ 25-29 years / ≥30 years)	1.01 (0.96-1.05)	1.02(0.96-1.07)
Asphyxia	1.78(1.08-2.93)	1.63(0.79-3.34)
Infection on admission	0.10(0.03-0.31)	0.10(0.03-0.36)
Number of days patient had PVC	1.16(1.11-1.22)	1.09(1.03-1.15)
High body temperature	4.89(2.55-9.36)	5.48(2.33-12.88)
The total number of days spent in hospital (≤5/ 6-10/ 11-15/ 16-20/ 21-25/ 26-30/ ≥31)	1.88(1.57-2.25)	1.41(1.12-1.77)
Penicillin therapy	3.08(1.49-6.35)	1.39(0.56-3.46)
Carbapenem therapy	1.88(1.01-3.49)	0.57(0.23-1.41)

Note. PVC (peripheral venous catheter)

* Crude and adjusted odds ratios are not shown in the table for the sake of clarity.

Table 4. Interactions between the number of days that patient had peripheral venous catheter and the total number of days spent in hospital

Variables	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
No difference in: "number of days patient had PVC"	1.0 (reference)	1.0 (reference)
Only one factor: „number of days patient had PVC"	1.16(1.11-1.22)	1.09(1.03-1.15)
Only one factor: „the total number of days spent in hospital (≤5/ 6-10/ 11-15/ 16-20/ 21-25/ 26-30/ ≥31) "	1.88(1.57-2.25)	1.41(1.12-1.77)
Both factors: „ number of days patient had PVC and the total number of days spent in hospital"	1.02 (1.01-1.03)	1.02 (1.01-1.03)

Note. PVC (peripheral venous catheter)

* Crude and adjusted odds ratios are not shown in the table for the sake of clarity.

** Adjusted for: age of mother, asphyxia, infection while admitting, number of days patient had PVC, high body temperature, the total number of days spent in hospital, penicillin therapy and carbapenem therapy

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