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Original Article

The Risk Factors for the Occurrence of Late-Onset Sepsis among the Admitted Patients in Neonatal Intensive Care unit at Tishreen University Hospital

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Abstract *- Background: Late-onset sepsis remains a common complication in neonates admitted to the Neonatal Intensive Care Unit (NICU) with poor outcomes, especially in critical cases. Objective: This study aimed to evaluate the risk factors associated with the occurrence of late-onset sepsis in neonates. Materials and Methods: An analytic prospective cohort study was conducted for the period of one year (2022 – 2023) at Tishreen University Hospital in Lattakia-Syria. The study included two groups of neonates that were compared: group I consisted of 76 neonates with a diagnosis of late-onset sepsis, whereas Group II consisted of 115 neonates without sepsis. Results: The results showed that 39.8% of the study population had late-onset sepsis, which was observed at 4-22 days of life. The prevalence of sepsis was increased significantly with decreasing gestational age (p:0.03), very low birth weight (p:0.001), use of vein catheters (p:0.003), administration of intravenous antibiotic(p:0.0001), parenteral nutrition (p:0.0001), and mechanical ventilation(p:0.0001). Very low birth weight (RR 5.5), use of mechanical ventilation (RR 8.4), intravenous antibiotic (RR 5.9), total parenteral nutrition (RR 6.1), and use of vein catheters (RR 5.8) were factors that associated significantly with the risk of progression late-onset sepsis. The rate of mortality was significantly higher in the presence of sepsis (11.8% versus 0.9%, p<0.05). Conclusion: There is an important prevalence of late-onset septicemia in our health center, which was associated with significant mortality. The presence of extremely low birth weight, mechanical ventilation, intravenous antibiotics, parenteral nutrition, and vein catheters are all warning flags that may predispose to septicemia after 72 hours of neonate life.*

Keywords *- Late-onset sepsis, Very low birth weight, Risk factors, Nosocomial infection.*

1. Introduction

Neonatal sepsis is a syndrome manifested by systemic signs of infection and isolation of bacterial pathogens from the bloodstream. The frequency of sepsis during birth hospitalization varies inversely with gestational age at birth and may reach 6 the most immature infants. During recent years, no significant progress has been observed regarding the treatment of neonatal sepsis and its side effects related to the neurodevelopmental in surviving infants despite multiple failed attempts to reduce the burden of infection [1,2]. It is considered an important cause of morbidity and mortality among newborn infants. The overall incidence ranges from 1 to 5 cases per 1000 live births, which varies according to the case definition and population studied [3,4]. It may be categorized into two groups: Early-Onset Sepsis (EOS), which is defined as the onset of symptoms before 72 hours of age and results mainly from maternal factors and Late-Onset Sepsis (LOS) in which symptoms begin at ≥72 hours of age and acquired from the environment, especially during hospitalization in NICU[5,6,7,8].

Neonatal sepsis is defined as a clinical-laboratory syndrome that results from the transition of pathological organisms, their toxins, or specific antigens to the bloodstream [9,10]. Clinical manifestations of sepsis are nonspecific and range from subtle symptoms to septic shock. They include temperature instability, irritability, lethargy, respiratory symptoms, poor feeding, poor perfusion, and hypotension [11,12]. Various risk factors are known for neonatal sepsis in neonates, including very low birth weight, prematurity, male sex, use of broad-spectrum antibiotic for a longer duration, mechanical ventilation, low Apgar score, use of H2-receptor blocker or Proton Pump Inhibitor (PPI), and Total Parenteral Nutrition (TPN) [13,14,15]. It is essential to identify risk factors for late-onset sepsis in neonates and develop effective prevention strategies to improve outcomes and reduce long-term complications, especially in developing countries due to the high prevalence of sepsis compared to developed ones. Therefore, this study aimed to investigate the risk factors for late-onset sepsis in infants admitted to neonatal ICU.

2. Patients and Methods

2.1. Study Population

After approval by the local research ethics committee, an analytic-prospective cohort study was conducted on neonates admitted at the Neonate Intensive Care Unit

(NICU) of Tishreen University Hospital over a period of one year (May 2021 –May 2022).

2.1.1. Inclusion Criteria were as Follows

Neonates of both sexes, all gestational ages, and birth weight with proven diagnosis of late-onset sepsis.

2.1.2. Exclusion Criteria

Neonates with the presence of one of the following: early onset sepsis (EOS), neonates with late-onset sepsis but a referral from another hospital, and discharge or mortality before complement 72 hours of hospitalization. A complete history, review of systems, physical examination including measurements of weight, length, and head circumference, and laboratory investigations including complete blood count, C-reactive protein (CRP), and blood culture were performed. Patients were assigned to group I (76 neonates) with a diagnosis of late-onset sepsis and group II (115 neonates), which included neonates without sepsis. Characteristics of the study population were compared according to the presence of sepsis.

2.2. Statistical Analysis

IBM SPSS version 20 was used to perform Statistical analysis. Basic Descriptive statistics included means, Standard Deviations (SD), median, frequency, and percentages. The chi-square test or Fisher's test was used to examine the relationships and comparisons between the two groups. Independent t-student t-tests were used to compare 2 independent groups. Multivariate logistic regression analysis was performed to estimate independent risk factors. This model included risk factors first identified through univariate analysis. All the tests were considered significant at a 5% type I error rate ($p<0.05$), β:20%, and power of the study:80%.

Table 1. The relationship between late-onset sepsis and demographic variables of the study population

Variable	Group I late-onset sepsis (+) (76)	Group II late-onset sepsis (-) (115)	P value
Gender			
Male	42(55.3%)	63(54.8%)	0.9
Female	34(44.7%)	52(45.2%)	
Gestational age(week)			
Prematurity	25(32.9%)	22(19.1%)	0.03
Full term	51(67.1%)	93(80.9%)	
Low birth weight(g)			
Present	11(14.5%)	2(1.7%)	0.001
Absent	65(85.5%)	113(98.3%)	
5-minute Apgar score	8.94±0.5	9.05±1.01	0.5
Parenteral nutrition			
Present	21(27.6%)	6(5.2%)	0.0001
Absent	55(72.4%)	109(94.8%)	
Use of vein catheters			
Present	75(98.7%)	94(81.7%)	0.003
Absent	1(1.3%)	21(18.3%)	
Intravenous antibiotic			
Present	67(88.2%)	12(10.4%)	0.0001
Absent	9(11.8%)	103(89.6%)	
Use of proton pump inhibitors (PPI)	6(7.9%)	1(0.9%)	0.05
Present	70(92.1%)	114(99.1%)	
Absent			
Mechanical ventilation			
Present	11(14.5%)	1(0.9%)	0.0001
Absent	65(85.5%)	114(99.1%)	
Outcome			0.04
Recovery	67(88.2%)	114(99.1%)	
Death	9(11.8%)	1(0.9%)	

Table 2. Risk factors for late-onset sepsis of the study population

Variable	RR b [CI 95%]	RR a [CI 95%]	P value
Low birth weight	5.9[2.05-9.3]	5.5[2.8-7.7]	0.0001
Mechanical ventilation	9.2[2.2-13.4]	8.4[2.9-10.5]	0.0001
Use of intravenous antibiotic	6.3[1.9-10.5]	5.9[2.3-9.8]	0.0001
Parenteral nutrition	6.8[1.7-12.3]	6.1[1.8-11.1]	0.0001
Use of vein catheters	7.1[1.3-9.9]	5.8[1.9-8.7]	0.0001

In the multivariate logistic regression analysis, low birth weight (RR 5.5,95% CI 2.8-7.7, p=0.0001), using mechanical ventilation (RR 8.4,95% CI 2.9-10.5, p=0.0001), intravenous antibiotic (RR 5.9,95% CI 2.3-9.8, p=0.0001), parenteral nutrition (RR 6.1,95% CI 1.8-11.1, p=0.0001), and using of vein catheters (RR 5.8,95% CI 1.9-8.7, p=0.001 were factors that associated with the risk of progression late-onset sepsis, Table (2).

4. Discussion

Late-onset sepsis remains a serious condition among neonates admitted to NICU, especially in severe cases with increasing evidence of worsening outcomes. Prevention of sepsis, halting its progression, and reducing associated complications represent the main goal of identifying risk factors for late-onset sepsis.

Late-onset sepsis was present in 39.8% of neonates admitted to the NICU. The prevalence was lower (13.6%) in a study conducted by Hernandez et al. (16), and this difference in occurrence might be related to the presence of additional special neonate care units, early diagnostic or screen modalities, and prompt initiation of treatment. The result of the current study revealed that, compared with the control group, sepsis was associated significantly with the presence of prematurity and extremely low birth weight, which might be related to immature immune systems (low neutrophil storages) and body organs that fight infections. In addition, low birth weight neonates are mostly premature, have an immature immune system, are unable to feed, easily lose their heat, and are more likely at risk of developing hypoglycemia, which may increase the likelihood of neonatal infections. These findings are in agreement with Perlman et al. (17), Stoll et al. (18), and Dong et al. (19). Using intravenous antibiotics for a duration longer than 5 days was associated significantly with the development of sepsis which might be related to the effects of widespread use of antibiotics that lead to reduced gut microbiome diversity and increased antibiotic-specific resistance pathogens. This finding is in agreement with Kuppala et al. (20).

There was a significant correlation between the use of parenteral nutrition and the occurrence of sepsis. The exact mechanism for this association is unclear. It might be explained by the negative effect of parenteral nutrition on phagocytosis, increase in epithelial permeability, and morphological alterations in intestinal villi after the sixth day of applying parenteral nutrition. This finding is in agreement with Perlman et al. (17).

The use of mechanical ventilation was associated significantly with the progression of sepsis, which might be explained by the introduction of foreign materials into the mouth and throat of the neonates and, as a result, colonization by microorganisms that may develop sepsis. In addition, mechanical ventilation induces inflammatory response and release of factors that lead to multi-organ failure. This finding is in agreement with Perlman et al. (17). In addition, the use of peripheral vein catheters was correlated significantly with the development of sepsis, which might be explained by the following: catheters provide access for bacteria living on the body's surface to the bloodstream and make it possible for contaminated intravenous fluids and microorganisms growing on catheters to cause an infection. This finding is in agreement with Geffers et al. (21). In contrast to the current study, Hernandez et al. (16) found a significant association between central vein catheters and the development of vein catheter sepsis without any correlation with peripheral catheters.

Hernandez et al. (16) and Lidya et al. (22) demonstrated a significant correlation between the male sex and the occurrence of sepsis, which might be explained by immunoglobulin production being associated with the X chromosome and, as a result, high ability to resistance infections in females than males. There was no significant correlation between the Apgar score and the development of sepsis in the current study, in contrast to the results of Hernandez et al. (16) and Lidya et al. (22) studies, which demonstrated that an Apgar score less than 6 is a risk factor for sepsis. This association might be explained by fetal distress, associated mitochondrial alterations and release of free radicals that play an important role in the development of sepsis. The use of PPIs wasn't associated with an increased risk for the development of sepsis, in contrast to the results of the study by Guillet et al. (23). PPIs lead to impairment function of neutrophils, toxic T lymphocyte, and natural killer cells which predispose to infection. Late-onset sepsis was associated with a higher rate of mortality, 11.8%, and this finding is in agreement with Afonso et al. (24) and Freitas et al. (25).

5. Conclusion

There is an important prevalence of late-onset sepsis in our health center, which was associated with significant mortality. The presence of extremely low birth weight, mechanical ventilation, intravenous antibiotics, parenteral nutrition, and vein catheters are all warning flags that may predispose to sepsis after 72 hours of neonate life.

In summary, it is crucial to take high-quality, effective infection prevention programs in the NICU to reduce the incidence of nosocomial infection and improve outcomes.

Declaration

Ethical Consideration

After discussing the study with the parents, all of them gave complete and clear informed consent to participate in the study.

Availability of Data and Materials

Most of the data was in the article, and other data can be asked from the corresponding author.

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