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Early and Late Onset Neonatal Sepsis in Very Low Birth Weight Infants in a Tertiary Center in Saudi Arabia

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Abstract

Background: Incidences and causative organisms of neonatal sepsis in the developing countries are underreported. The aim of the study was to determine the overall incidence of neonatal sepsis in very low birth weight (VLBW) infants born at one of university hospitals in Riyadh, Saudi Arabia for the period 1999 to 2007, and identify the incidences and commonest isolated pathogens in both early and late onset episodes of sepsis in this group of infants.

Methods: A retrospective study of all very low birth weight (500grams to 1500 grams) infants born at King Khalid University Hospital (KKUH) in Riyadh over a 9-year period from January 1999 to December 2007 were included. Data were collected from medical records and NICU database after obtaining ethics approval. All cultures were taken (blood and/or CSF) prior to initiation of antibiotics. Only first episodes of sepsis were considered in this study. The main outcomes are total incidences of sepsis, incidence of early and late onset sepsis, and the causative pathogens for each type of sepsis.

Results: 48% of included infants (225/468) had positive blood cultures. The incidence of early onset sepsis (EOS) was 10.9% and of late onset sepsis (LOS) was 37.1%. Gram positive pathogens were the commonest causative organisms in both early and late onset sepsis (74.5% and 87.4% respectively). Staphylococcus epidermis was the commonest single pathogen isolated in both groups (45% in EOS, and 63.8% in LOS).

Conclusion: The rate of neonatal sepsis in VLBW infants was high (48%) with high rates of EOS as well as LOS which necessitates a high priority to prevent and control sepsis in our unit.

Keywords: Neonatal sepsis; Very low birth weight infants; Incidence; Organism

Introduction

Neonatal sepsis continues to be a major cause of mortality and morbidity in newborns. This condition is more profound in Very Low Birth Weight (VLBW) infants (weighing between 500 grams and 1500 grams), despite many advances in obstetrical and neonatal care [1]. The incidence of neonatal sepsis in developed countries ranges from 10-25% for all infants and reached up to 50% in VLBW infants [2].

Early onset neonatal sepsis (EOS), defined by the Center for Disease Control and prevention (CDC) as blood or cerebrospinal fluid culture-proven infection occurring in the first three days of life, is typically caused by organisms transmitted vertically from the mother to the infant before or at the time of birth [3]; while Late Onset Neonatal Sepsis (LOS), an infection occurring after day 3 of life, is more likely to be caused by pathogens acquired during the course of hospital care. The overall incidence of EOS in the United States of America, for instance, reported to be 1-2 cases per 1000 live births and was 10-fold higher in VLBW infants. Nonetheless, the mortality rate due to neonatal sepsis in VLBW infants is also higher in comparison to term infants or VLBW infants with no sepsis. A study showed that 35% of VLBW newborns with sepsis died compared with overall 11% mortality rate among uninfected VLBW newborns in large cohort study [4].

Besides higher risk of mortality caused by neonatal sepsis, survivors of neonatal sepsis may develop severe morbidity secondary to concomitant meningitis or from hypoxemia resulting from persistent pulmonary hypertension, septic shock, and respiratory failure [5].

Recently, it has been documented that low gestational age and reduced birth weight in preterm infants contributed to increased risk of developing cardiovascular changes that may lead to death even among adults who were born prematurely [6].

In regards to the causative pathogens, gram-positive bacteria are found to be the most common pathogens isolated in VLBW infants diagnosed with LOS [7]. While in VLBW infants with EOS, gram-negative pathogens are reported more frequently as the causative organisms. Fewer studies showed that gram-positive bacteria are still common pathogens in VLBW infants with EOS relating that to nosocomial infection [8-14].

Although previous reports of sepsis in VLBW infants represent relatively large, multicenter cohorts, most data are coming from neonatal intensive care units (NICUs) within hospitals in developed countries. Developing countries have higher incidence of EOS and

LOS than developed countries (44-53%, and 46-56% respectively) with gram negative organisms being the most common causative organisms in both groups [15,16]. Incidence of neonatal sepsis in India based on National Neonatal Perinatal Database (NNPD) 2000 is 30 per 1000 admissions. The aim of this study is to estimate the incidence of early and late neonatal sepsis in VLBW infants born at University hospital in Riyadh, Saudi Arabia and to re-examine causative pathogens involved in each group.

Materials and Methods

We evaluated retrospectively a collected data of all live VLBW infants (birth weights between 500 grams and 1500 grams) admitted to the neonatal intensive care unit in a University hospital in Riyadh City, regardless of the gestational age, from 1999 to 2007.

At least one blood culture was obtained from all live-born VLBW infants admitted to the unit, as per unit protocol, and more cultures were obtained at later times (with or without cerebrospinal fluid culture) in infants with clinical pictures suggestive of sepsis and before initiation of antibiotics. After insertion of umbilical arterial catheters under aseptic technique, 1.5 ml of blood was taken by treating physician via umbilical line and sent for blood culture before commencing antibiotics for all admitted VLBW infants. The unit protocol was to treat all VLBW newborns with intravenous Ampicillin and gentamicin up to five days if cultures are negative, otherwise is to continue according to condition of infant. In addition, Ampicillin and gentamicin were routinely prescribed to women presenting with preterm labor and particularly those with premature rupture of membranes. Data were retrieved from the unit database including all related variables and known risk factors for the mothers and the newborns. We labeled the infant to have EOS if blood culture taken within the first 72 hrs of life was positive, and LOS as positive culture if specimen obtained after the age of 72 hrs of life. In LOS, only the first positive culture was considered in this study (we excluded recurrent sepsis).The Institutional Ethics Board (IRB) approved the study prior to reviewing any data.

Descriptive statistics were calculated to describe the study population, using SPSS (Statistical Product and Service Solutions). We evaluated the incidence and causative pathogens for EOS and LOS among VLBW infants. Incidence of neonatal sepsis was calculated as the number of VLBW neonates with neonatal sepsis over total number of all live VLBW infants.

Results

A total of 468 VLBW infants were admitted to our NICU during the study period (1999-2007). Included infants had a mean birth weight of 992 grams (+/- 287) and range of 500 grams to 1483 grams. There was an equal gender distribution with 51.5% male infants and 48.5% female infants).The total number of infants with culture-proven diagnosis of neonatal sepsis (both EOS and LOS) was 225 making the overall incidence of sepsis in VLBW infants in this sample 48% (95% C.I: 43.5, 52.5). Fifty one infants (10.9%) of total sample developed EOS, and 174 infants (37.1%) developed LOS (Table1). The mean gestational age for infants with and without EOS was 26.6 weeks (95% C.I: 26.4, 26.8) and 28.3 weeks (95% C.I: 28.2, 28.3), respectively (Table 2). Mortality for infants with EOS was 12.3% compared to 6.3% for infants with negative cultures ($p<0.001$). Gram positive pathogens were the most common causative organisms in both EOS and LOS (74.5% and 87.4% respectively). Staphylococcus epidermidis was the commonest single pathogen isolated in both groups (45% in EOS and 63.8% in LOS). Among cultures with gram-negative pathogens, Klebsiella pneumoniae was the commonest pathogen in LOS (6.9%) followed by Escherichia coli (3.4%).

Birth weight in g, mean (range)	**922 (500-1483) Number (%)**
Booked mothers	328 (70.0)
Antenatal antibiotics	363 (77.5)
Prolonged rupture of membranes ≥ 24 hrs	16.0 (3.5)
Small for gestational age	58 (12.5)
Total number of VLBW* infants	468 (100)
Total number of Infected infants	225 (48.0)
Infants with early onset sepsis (EOS)	51 (10.9)
Infants with late onset sepsis (LOS)	174 (37.1)

Table 1: Demographic data and rate of sepsis for a total population of 468 VLBW* infants (*Very low birth weight)

The same organisms (Klebsiella pneumoniae and Escherichia coli) were the predominant gram negative organisms isolated in EOS contributing for 11.8% and 9.8% respectively of all EOS episodes (Table 2).

Pathogen	**Early onset sepsis N/51 (%)**	**Late onset sepsis N/174 (%)**
Gram positive pathogens	38 (74.5)	152 (87.4)
Gram negative pathogens	13 (25.5)	22 (12.6)
Staphylococcus epidermidis	23 (45.0)	111 (63.8)
Staphylococcus aureus	6.0 (11.8)	12 (11.8)
MRSA*	2.0 (3.9)	18 (10.3)
Group B streptococcus	5.0 (9.8)	5.0 (2.9)
Group D streptococcus	2.0 (3.9)	6.0 (3.4)
Klebsiella pneumoniae	6.0 (11.8)	12 (6.9)
Escherichia coli	5.0 (9.8)	6.0 (3.4)
Enterobacter cloacae	1.0 (2.0)	2.0 (1.2)
Acinetinobacter	1.0 (2.0)	2.0 (1.2)

Table 2: Causative organisms (*Methicillin-resistant Staphylococcus aureus)

Discussion

Two hundred and twenty five of our VLBW infants in this study developed neonatal sepsis with an overall incidence of 48%. This high figure is similar to that reported by Haque et al [17], 2 decades ago done in VLBW infants in the same unit. This might be alarming because we expected lower incidence due to the advancement in our unit in terms of technology and therapies. However, the survival rate of our infants with EOS, which is around 88%, is comparable to

international figures [18], reflecting the good quality of care provided to those infants. The rate of neonatal sepsis in our unit, which exceeds the reported figures in developed countries, may represent the situation in other developing countries. Our study is limited by being retrospective in nature which is a major limitation factor, but we believe that an important reason for such high rate of sepsis (EOS in particular) is the overcrowding in relation to bed capacity. At the time of study, we had 24 beds but the occupancy was reaching up to 32-35 babies most of the time. Periodic overcrowding (high bed occupancy) and understaffing (low nurse to patient ratio of 1:3) are reported risk factors that increased the rate for nosocomial infections and occurrence of outbreaks [19-22]. Despite that the rates of prolonged rupture of membranes (PROM) for 24 hrs or more are within average reported rates in other studies, only 77.5% of affected mothers were antenataly covered with antibiotics because the rest came in advanced labor with insufficient time to receive appropriate antibiotics coverage.

In this study, gram positive pathogens were the leading organisms retrieved in 87.4% of LOS which matched with most published reports all over the world. Staphylococcus Epidermidis was the most common single infecting organism in LOS (63.8%). We did not report fungal sepsis in our study because we considered only the first positive culture in LOS and discarded recurrent episodes which may include fungal infections.

Unlike most of the reports regarding EOS commonest pathogens (which are gram negative organisms representing maternal flora), we had more gram positive pathogens as the leading cause for EOS (74.5%) and again Staphylococcus Epidermidis being the commonest isolated organism (45%). Although previously published data by Kilani RA et al. done in our unit in 2000 [23], concluded that gram negative bacteria were the infecting organisms in 50% of EOS and Escherichia coli being the leading organism (29%) we believe this is because that study had a smaller number of infants. In 2012, our unit was expanded to 36 beds and recruited more nursing staff with improvement in available spaces. Those changes along with the improvement and increased awareness of hand hygiene could lead to reduction of the rate of neonatal sepsis in general and in VLBW infants in particular in our unit. This improvement could only be proven by conducting of well-designed prospective study.

Conclusion

Neonatal sepsis is a well-recognized cause of neonatal mortality and morbidity and more pronounced in VLBW infants. Our study confirmed the presence of major concern about the high rate of sepsis among VLBW infants. Having gram positive organisms as the leading pathogen in EOS raises more concerns towards hand hygiene and proper patient safety practices in our unit.

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