Original Research Paper

Volume - 10 | Issue - 6 | June - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Pediatrics

A STUDY ON INCIDENCE AND RISK FACTORS OF EARLY ONSET NEONATAL SEPSIS IN AN OUT BORN NEONATES IN A TERTIARY CARE CENTRE IN EASTERN BIHAR.

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ABSTRACT

Introduction: Neonatal septicemia is diagnosed when generalized systemic features of sepsis are associated with pure growth of bacteria from one or more sites. It refers to systemic infection of neonates including Septicemia, Pneumonia, Meningitis, Arthritis, Osteomyelitis and UTI. The incidence of neonatal sepsis in India is the highest in the world.

Objectives: The objective was to study the Incidence and risk factors of early-onset neonatal sepsis in an out born neonates in a tertiary care centre in Eastern Bihar.

Methods: The present study is a prospective descriptive study done over a period of 1 year from May 2019 to April 2020 in department of Pediatrics in Jawahar Lal Nehru Medical College and Hospital, Bhagalpur, Bihar. All out born neonates admitted within 72 hours of life, with clinical features of sepsis with two or more high-risk factors for sepsis were enrolled and samples for sepsis screen and cultures were taken prior to administration of antibiotics in all cases. Standard data collection form was used to collect all demographic data and clinical characteristics of neonates. Bacterial isolates were identified, and their resistance patterns were analyzed using the Vitek 2 C system.

Results: In the present study, among the 440 admissions to NICU during the study period, 82 neonates (19%) with early onset sepsis were enrolled. The mean (standard deviation) weight and hours of life at admission were 2016 ± 724.04 g and 23.05 ± 2.89 h, respectively. Incidence of early onset sepsis was 18/1000 patient. 28 (34%) neonates were home delivered. Low birth weight (68%), prematurity (46%), and poor hygiene/cord care (46%) were common risk factors while lethargy/refusal to feed (77%), hypothermia (47.5%), and respiratory distress (44%) were common clinical presentations. Sepsis screen and blood culture were positive in 57% and 18%, respectively. *Klebsiella pneumonie* (36%), *Staphylococcus aureus* (21%), and *Escherichia coli* (14%) were common organisms. Case fatality rate was 14%.

Conclusion: Clinical sepsis along with sepsis screen is a good marker of neonatal sepsis: Incidence of early onset sepsis varies in out born neonates and many factors affect it like place of delivery, perinatal risk factors, and immediate practices done in newborn. Evidence regarding its risk factors can guide clinical practice and prevention strategies.

KEYWORDS : Outborn Neonates, Early Onset Neonatal Sepsis, Sepsis Screen.

INTRODUCTION:

Sepsis is the second major cause of mortality among neonates, killing more than one million neonates annually.[1] Neonatal sepsis, pneumonia and meningitis together result in up to a quarter of all newborn deaths.[2] Approximately, 1 million deaths per year are caused by infection occurring in the neonatal period (0-28 days), accounting for over 25% of global neonatal deaths;[3] 99% of these deaths occur in developing countries.[3,4] Early onset neonatal sepsis (EONS) remains a major cause for neonatal mortality and morbidity. The case fatality in EONS ranges from 16.7% to 19.4%.[5,6]

Neonatal septicemia (NNS) is a great masquerader and can present with very nonspecific manifestations pertaining to any system of the body. More than half of neonates admitted to neonatal intensive care units (NICUs) carry a diagnosis of "suspected sepsis" and these infants account for up to 25% of NICU days in some units.[7]

In addition, many other conditions can mimic the sepsis, which leads to both over and under treatment and each has its own hazards.[8] Screening tests such as total and differential leukocyte counts, band cells, absolute neutrophil counts (ANCs), and rapid immunological techniques like C-reactive proteins (CRPs) assays may help in the diagnosis of septicemia; however, they lack the capacity to detect specific pathogens and are not available in many centers in developing countries.[9] The gold standard for diagnosis of NNS is a positive blood culture, which is positive in only 50-80% at best, however, negative blood culture does not rule out the disease.[10,11]

It is important to know the etiology, various risk factors and antimicrobial sensitivity patterns of organisms that cause neonatal infections in developing countries in order to develop effective treatment strategies and to reduce neonatal mortality.[12,13] Most of the previous studies on NNS were on hospital born neonates, however, the fact remains that the majority of childbirths in our country are occurring at home or in the community by trained or untrained birth attendants. However, data on diagnosis, severity, bacteriological profile and antibiotic sensitivity of home/domiciliary delivered and community-acquired infection s in neonates are scanty. This prompted us to conduct the present study. Our study goal was to identify the incidence and various risk factors of EONS in out born neonates and also to evaluate bacteriological profile along with sensitivity pattern of EONS in an out born NICU of India.

METHODS:

The present study is a prospective observational study, done in a referral, tertiary out born Neonatal Intensive Care Unit (NICU) of department of Pediatrics in Jawahar Lal Nehru Medical College and Hospital, Bhagalpur, Bihar from May 2019 to April 2020.

All neonates admitted within 72 hours of life, with two or more perinatal high risk factors for sepsis which includes, maternal fever more than or equal to 38°C, foul smelling vaginal discharge, premature rupture of membranes (PROM) >24 h, more than 3 vaginal examinations during delivery (done in any setting, hospital or at home), Apgar score < 4 at birth, poor cord care (cord cut by unsterile blade, ligated by unsterile thread or application of cow dung, ghee or milk), prelacteal feeds (honey, tea, water), poor hygiene during delivery and prematurity (<37 weeks of gestation) or low birth weight (LBW) neonates (<2500 g) and with one or more clinical manifestation suggestive of sepsis (lethargy, tachypnea, hypo or hyperthermia, grunting, apneic spells, shrill cry, irritability), irrespective of gestational age and birth weight were enrolled in the present study.

In this study neonates with congenital malformations and in whom clinical symptoms, on the stabilization were explained by other conditions like hypoglycemia, hypocalcemia or any other metabolic causes were excluded.

All neonates were subjected to complete examination at admission and every 12 hours. Temperature, blood sugar, and capillary refill time were recorded at the time of admission Gestation age assessment was done by using Ballard score. Sepsis screen and cultures (blood/urine/cerebrospinal fluid [CSF]) taken prior to administration of antibiotics in all cases. Sepsis screen which includes total and differential count, ANC, CRP, Immature to total neutrophil ratio were taken.

Sepsis screen was considered positive when any two of the following laboratory criteria were present: Total leukocyte count (TLC) <5000/mm ^{3} , immature/total neutrophils ratio ≥0.2, ANC <1800, and positive CRP (CRP >10 mg/dL).[10] Blood cultures were collected under aseptic precautions in BACTEC Peds Plus bottles. Bottles flagged positive by automated system (BACTEC 9120) were sub-

cultured on sheep blood agar, chocolate agar, and MacConkey agar. Bacteria thus isolated were identified, and antimicrobial susceptibility testing was done using Vitek 2 compact system. Tracheal aspirate was taken within 12 hours of intubation and CSF culture s were taken when clinically indicated, and cultured on conventional microbiologic techniques. Urine Cultures were taken under all aseptic precautions by catheterization.

In the present study organisms like *Cornybacterium,* diphtheroid, generally considered contaminants and were excluded from the analysis. Blood culture positive for coagulase-negative staphylococci was only considered positive if same species was obtained on repeat culture. A chest X-ray was performed, whenever clinically indicated and interpreted by two radiologists. Neonates were labelled as culture-positive and culture-negative sepsis, the blood culture-negative sepsis was labelled when there were one or more risk factors with two biomarkers of sepsis screen was positive.

RESULTS:

In the present study, all the data were collected in excel-8, analyzed using Epi info version 6.0. One hundred seventy-four neonates with clinical sepsis were enrolled in the study. This was about 39% of neonates admitted during the study period. EONS occurred in 82 (47%). The Incidence of EONS was 18/1000 admissions. Mean age and mean weight at admission were 23.05 (±20.89) h and 2016 (±25.72) g, respectively. Duration of hospital stay was 17.4 days.

Out of 82 neonates with EONS, 28 (34%) neonates were home delivered and 38 (46%) were preterm. Among the home delivered neonates, 19 had moderate to severe hypothermia during admission, 10 were in shock, 16 and 9 were LBW and preterm, respectively. Twelve (14.6%) received some antibiotics before admission, mainly referred from some other hospitals which were nearby.

In this study blood culture was positive in only 15 (18%) neonates. Culture positivity among hospital and home delivered neonates were nine and six neonates, respectively. Twelve (14.6%) neonates died, 8 were preterm and LBW, respectively, and four were home delivered. Death occurred in 41% (5/12) neonates with culture positive sepsis. Case fatality rate was 14%.

In the present study most common perinatal risk factor was LBW 56 (68%) followed by PROM 46 (56%). Poor cord care was present in 38 (46%), and foul smelling amniotic fluid only in 18 (22%) neonates. All the neonates who were included in the study had at least two perinatal high risk factors, while 70 (85%) neonates had 2-4 perinatal high risk factors, and 12 (15%) had more than four perinatal risk factors. More than two-third neonates presented with two or more clinical features of sepsis.

Most common presenting symptom was lethargy, poor cry, and refusal to feed in 63 (77%) followed by hypothermia 39 (47.5%) and respiratory distress/grunting 36 (44%), while 23 (28%) neonates were in shock at admission. Of the sepsis screen, CRP was positive in 33 (40%) neonates, immature/total neutrophil count (I/T) ratio more than 0.2 were in 20 (24%) neonates, TLC <5000 mm ^{3} were in 7 (8.5%) neonates and ANCs were positive only in 3 (3.5%) neonates.

Culture proven meningitis and urinary tract infection (UTI) were present in 3 and 2 neonates respectively. Total 20 (24%) neonates had pneumonia confirmed by radiological and clinical picture. Sepsis screen was positive (≥2 factors present) in 46 (56%) neonates and negative in 36 (43%) neonates. Out of total screen positive neonates, only 10 (17%) were blood culture positive and among the septic screen negative (36) neonates, only 5 (11%) had blood culture proven sepsis. Thus, the sensitivity and specificity of sepsis screen were 71% and 47%, respectively, while positive and negative predictive values were 22% and 89% respectively. *Klebsiella pneumoniae* 5 (36%), *Staphylococcus aureus* 3 (21%), and *Escherichia coli*. 2 (14%) were the common causes of bacteremia. K. pneumoniae bacteremia was the most fatal.

In the present study entire Gram-negative bacteria isolates were found to be susceptible to meropenam (80%) and piperacillin-tazobactum (75%) followed by cefotaxime (50%), imipenem (50%) and chloramphenicol (50%) while all resistant to ofloxacin and least sensitive to amikacin (25%). Interestingly, 40% of *K. pneumoniae* were found sensitive to cotrimoxazole. All the Gram-positive cocci (GPC) were found susceptible to vancomycin, linezolid, and clindamycin while they were least susceptible to penicillin. Among three isolates of *S. aureus,* one was found to be methicillin resistant *S. aureus* as confirmed by oxacillin MICs and (penicillin binding protein) kit.

DISCUSSION:

In the present study, the incidence of early onset sepsis was 18/1000 live births, various studies reported it 4.8-20.7 per 1000 births.[5,14,15] Reports from India showed 50-60% of septic neonates are premature and very LBW.[16]

In the present study, 56 (68%) of neonates were LBW; PROM was present in 46 (56%) of cases in comparison to 29.2% reported by Hossain *et al*.[17] A large Indian study in septic out born neonates showed pneumonia in 37%, meningitis in 19.6% and UTI in 0.9% neonates.[18] In our study we found pneumonia in 20 (24%), and culture-proven meningitis and UTI in 3 (4%), and 2 (2.4%) neonates, respectively.

The common clinical presentation in the present study was lethargy/refusal to feed 63 (77%), respiratory distress 36 (44%), and hypothermia 39 (47.5%). Khatua *et al.*, reported refusal to feed (92%), lethargy (74%), hypothermia (72%) and respiratory distress (24%) as common clinical presentation,[19] Whereas, Saxena *et al.*, found refusal to feed (70%), lethargy (53%), loose motions (29%), respiratory distress (24%), and hypothermia (5%).[20]

In the present study, respiratory distress at admission was associated with the highest mortality rate of 62.5%. Shock was present in 50% of neonates who died; similar association was reported by others.[21]

Our study suggests that perinatal risk factors were well-associated with mortality, as in 12 (15%) cases, ≥4 perinatal risk factors were present, out of these more than 50% (7/12) of neonates expired. In the present study, blood culture was positive in 17%, which is very low as compared to prior Indian studies.[14,22,23] This may be due to the fact that about 14.6% neonates were admitted after receiving some antibiotics from outside.

The case fatality rate in the present study was 14%, which is comparable to other studies done in out born newborns. Multi-centric data from India have revealed 17% mortality among out born neonates with 19.3% mortality in preterm neonates due to sepsis.[14,18,24] The present study suggests mortality rates among preterm, 8 (57%) neonates was significantly higher than the term 6 (43%) neonates.

In developing countries, GN sepsis remains an important cause of NNS,[14] similarly in our study, GN sepsis was the most common cause of sepsis with *Klebsiella* species (35.5%) being the most common etiological agent.[14,22,24] A decade earlier, bacteria responsible for NNS were found to be sensitive to most of the third-generation cephalosporins and aminoglycosides.[23,24,25] Emergence of antimicrobial resistance in GNB poses major therapeutic challenge. Many studies have shown resistance to third-generation cephalosporins, aminoglycosides, and carbapenems in recent years.[14,22] In the present study, GNB were highly sensitive to colistin (100%), meropenem (75%), and piperacillin tazobactam (71%) followed by imipenem (50%) while all were resistant to ofloxacin and least sensitive to cefotaxime (20%) and amikacin (20.5%).

In this study, 36.3% of *K. pneumoniae* were found sensitive to cotrimoxazole and alarmingly 25% of *Pseudomonas aeuroginosa* were resistant to colistin and 40% resistant to meropenem while all GPC were found sensitive to vancomycin, linezolid, and clindamycin which was a strange finding.

In our study many factors had substantial heterogeneity, which may be explained by the population (e.g. type of controls, twins, inborn neonates), criteria used to define and/or diagnose sepsis (e.g. culture-dependant vs hematologic sepsis paramaters), definitions of risk factors and hospital policies in place (e.g. intrapartum antibiotic prophylaxis). Though subgroup analyses did not show significant differences, this may be explained by the limited number of studies. All these factors could increase heterogeneity, and may limit comparability, as similarly discussed in other reviews.[26,27]

CONCLUSION:

We concluded from our study that incidence of early onset sepsis varies in out born neonates and many factors affect it like place of delivery, perinatal risk factors, and immediate practices done in the newborns.

Mortality and morbidity of neonatal sepsis are high in out born neonates. Guidelines for management and prevention of neonatal sepsis in developing countries are needed so that morbidity and mortality of sepsis due to highly prevalent multi-resistant GNB can be reduced. Robustly designed and reported research is urgently needed to confirm the role of other risk factors of neonatal sepsis in India. Evidence regarding its risk factors can guide clinical practice and prevention strategies.

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