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Original Research Article

Comparative Study on Mortality in Neonates with Probable Sepsis and Neonates with Proven Sepsis in Tertiary Care Hospital, Western Up

Madhu Singh[1*], Abhishek Singh[2], Navratan Gupta[3]

[1]Senior Resident, Department of Pediatrics, SN Medical College, Agra, 282002 (U.P) India
[2]Professor, Department of Pediatrics, L.L.R.M. Medical College, Meerut, 250004 (U.P) India
[3]Assistant Professor, Department of Pediatrics, L.L.R.M. Medical College, Meerut, 250004 (U.P) India

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Corresponding Author: Dr. Madhu Singh
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Abstract:

Objective: This prospective observational cohort study was undertaken to compare the mortality in neonates with probable sepsis and neonates with proven sepsis in tertiary care hospital, LLRM medical college Meerut UP.

Method: A total of 246, 123 in each group that is probable sepsis group and proven sepsis group who are admitted in NICU over a duration of 6 month and followed till next 6 month. Neonate who are admitted in the duration of 6 month are divided in two group, one is probable sepsis and another is proven. These 2 groups are followed for next 6 month and mortality and morbidity are compared between two groups.

Result: Overall mortality rate of the neonates at the hospital was 14.2%, in our study. The mortality rate among probable sepsis neonates was 19.5% and proven sepsis was 8.9. Majority of the neonates were newborn (67.5%), males (69.1%) and term deliveries (94.3%).Proven sepsis neonates had thrombocytopenia (39.4%) than the ones who had probable sepsis. The duration of hospital stay was significantly longer among the proven sepsis than the probable sepsis neonates. None of the enrolled children reported any defect in the CVS, RS, CNS, Vision and hearing during the follow-up till 6 months. There was no significant association between the type of sepsis (probable/proven) and the incidence of diarrhoea, pneumonia, fever, re-hospitalization and feeding difficulties at 6 months of life. Klebsiella (40.7%) was the most common organism cultured.

Conclusion: Mortality is significantly high in newborn with probable sepsis in comparison to proven sepsis.

Keywords: Sepsis, Neonates, Klebsiella, Mortality, Thrombocytopenia.

Introduction

Neonatal sepsis is defined as a systemic condition which may be of bacterial, fungal or viral origin that is associated with changes in the haemodynamics as well as other clinical features and causes substantial morbidity and fatalities in new-born infants less than 28 days old [1]. As per the recent data from a global meta-analysis, the incidence of NS has been reported to be 2824 (95 percent Confidence interval 1892 - 4194) cases per 100 000 live births [2].

According to the Global Burden of Disease (GBD) Study 2016-17 it is estimated 1.3 (95% CI 0.8 to 2.3) million annual incident cases of Neonatal sepsis worldwide, resulting in 203 000 (95% CI 178 700 to 267 100) deaths attributable to sepsis [3]. In India, the case fatality rate of sepsis in neonates ranges from 25 to 65 percent [4]. National Neonatal Forum (NNF) of India has defined Neonatal sepsis into some major categories [5]. First is probable (clinical) sepsis/ Culture-Negative Sepsis, if any of the characteristics are present, probable sepsis is observed in a child with a clinical picture (no bacterial aetiology detected) indicative of septicaemia. The presence of two of the four criteria, TLC (5000/mm), band to total polymorphonuclear cells ratio >0.2, absolute neutrophil count 1800/ml, C-reactive protein (CRP) >1mg/dl, and micro ESR>10 mm-first hour, would result in a positive septic screen.

Another category is proven (Culture Positive) Sepsis, if any of the following criteria are present in a neonate with a clinical picture indicative of septicemia, pneumonia, or meningitis: Pathogen isolation from blood, CSF, urine, or abscess. Depending upon the onset of symptoms, the Neonatal sepsis was classified (6) into: Early onset sepsis (EOS): It manifests within a span of first 72 hours of life. The maternal genital tract is usually the source of infection. Group B Streptococcus (GBS), Escherichia coli, coagulase-negative Staphylococcus, Haemophilus influenzae, and Listeria monocytogenes are among the bacteria linked to EOS [7].

Based on studies conducted in Indian settings, several maternal and perinatal conditions appear to be linked to an elevated risk of Early Onset Sepsis (EOS). These conditions include infants with low birth weight (less than 2500 grams) or born prematurely.

Additionally, increased risk is associated with mothers who experienced febrile illness indicative of bacterial infection within two weeks before delivery, as well as the presence of foul-smelling and/or meconium-stained amniotic fluid. Other risk factors include membrane rupture lasting more than 24 hours, a single unclean or three sterile vaginal examinations during labor, prolonged labor exceeding 24 hours in total, and instances of perinatal asphyxia with an APGAR score below 4 at 1 minute after birth [6, 8].

In late onset sepsis (LOS), it normally appears 72 hours after birth. In infants with LOS, the source of infection is either nosocomial (hospital- acquired) or community-acquired, and septicemia, pneumonia, or meningitis are common [9, 10]. Low birth weight, preterm, admission to an intensive care unit, mechanical ventilation, invasive operations, parenteral fluid delivery, and the use of stock solutions are all variables that raise the risk of nosocomial sepsis. Inadequate sanitation, poor cord care, bottle-feeding, and prelacteal feeds are all factors that may raise the risk of community-acquired LOS. In contrast, breastfeeding helps in prevention of infections. The organisms commonly associated with LOS include coagulase-negative staphylococci, Staphylococcusaureus, Klebsiella pneumoniae, Escherichia coli, Enterobacter spp., Pseudomonas aeruginosa and Acinetobacter species [11].

In Neonatal Sepsis, the bacteriological profile varies significantly between industrialized and developing countries. In underdeveloped nations, Klebsiella pneumoniae is the predominant causal organism, while in developed countries, group B Streptococcus and coagulase-negative staphylococci are more common [12]. Regional differences in bacterial agents causing sepsis exist even among developing countries.

In underdeveloped nations, the immature immune system is a primary factor increasing vulnerability. Newborns lack a complete inflammatory response due to immature function in neutrophils, macrophages, and T lymphocytes. Additionally, limited immunoglobulins at birth hinder an effective response to pathogens. Premature infants, with reduced time in the uterus, face a higher risk of sepsis due to immunoglobulin shortage [13]. Neonatal sepsis manifests with diverse symptoms, ranging from nonspecific to hemodynamic collapse. Early signs include irritability, lethargy, and poor feeding. Laboratory abnormalities, like hyperglycemia or hypoglycemia, aid in diagnosis [14]. A septic screen, with two abnormal parameters indicating a positive result, is crucial for diagnosis, with associated sensitivity and specificity percentages [15]. Documentation of polymorphs in neonatal gastric aspirate serves as a chorioamnionitis marker and a gold standard for diagnosis. Antimicrobial therapy relies on positive blood culture results, and cultures should be monitored for at least 72 hours before declaring sterility [16]. As clinical signs are nonspecific, meningitis may coexist without distinct symptoms. The incidence of meningitis in Neonatal sepsis ranges from 0.3 to 0.5 percent [5, 17].

With this background, the present study was planned to compare the mortality rate in neonates (<28days) with probable sepsis and neonates with proven sepsis, hospitalized in a neonatal unit for sepsis and followed after dischargetill6 months of age in tertiary care Hospital, Western UP.

Material and Methods

That study is a prospective observational cohort study which was carried out in Neonatal Intensive Care Unit of Department of Pediatrics L.L.R.M. Medical College, Meerut, Uttar Pradesh, India from April 2020 to March 2021. This study was conducted as prospective cohort study of newborn infants (<28 days) hospitalized in a neonatal unit for sepsis and followed after discharge till 6 months of age. The main outcome of the study was obtained as mortality rate in probable and proven sepsis.

Sample Size: The sample size was calculated on the basis of mortality proportion of sepsis cases and assuming the null hypothesis of equality with probable sepsis using 90% power of

Study which was 123 number of study sample in each group.

Inclusion criteria: All neonates who are admitted in the NICU for sepsis either probable or proven.

Exclusion criteria

Babies with any of the following will be excluded:

1. Babies born with any major congenital anomalies
2. Babies with HIE stage 2,3.
3. Babies with weight <1.2kg or <32 weeks of gestation.
4. Babies referred from other hospital after taking treatment.
5. Babies require any surgical intervention.

Procedure

All neonate babies who will fulfill the inclusion criteria will be enrolled. Close follow up of babies need to be done at 8 days, 1 month, 3months, 6 months after discharge. Followup can also be planned with all routine Immunization or telephon-

ically connected.

Statistical analysis: Data was entered in MS Excel and the analysis was conducted in IBM SPSS v26.0 Categorical variables were expressed in frequencies and proportion. Pie charts and bar graphs were used to depict the results. Chi square test was used to test the significance between the type of sepsis and clinico-demographic variables. A p value of <0.05 was taken as statistically significant.

Sample Size Calculation: The two formulae were considered for sample size calculation for the present diagnostic efficacy study. Utilizing sensitivity and other 2. Utilizing specificity [18].

$$\text{Sample size (n) based on sensitivity} = \frac{Z^2_{1-\alpha/2} \times S_N \times (1-S_N)}{L^2 \times \text{Prevalence}}$$

$$\text{Sample size (n) based on specificity} = \frac{Z_{1-\alpha/2} \times S_N \times (1-S_P)}{L^2 \times (1-\text{Prevalence})}$$

Where

n=required sample size, S_N = Anticipated sensitivity,
S_P=Anticipated specificity,
α=size of the critical region (1-αis the confidence level),
$Z_{1-\alpha/2}$= standard normal deviate corresponding to the specified size of the critical region (α),
L = absolute precision desired on either side (half-width of the confidence interval) of sensitivity or specificity.

Using the above mentioned method, sample size was found to be=112 in each group, with sensitivity and specificity of 90 % and expected maximum prevalence of 50 %, L= absolute precision of 10%, and Z=2 (for 95% confidence interval). For the current study, anticipating 10% dropouts/ loss to follow-up/attrition, 123 patients in each group were enrolled.

Results

Among the 246 babies of study group, the neonates in our study were equally distributed between probable (50%) and proven sepsis (50%) (Figure 1).

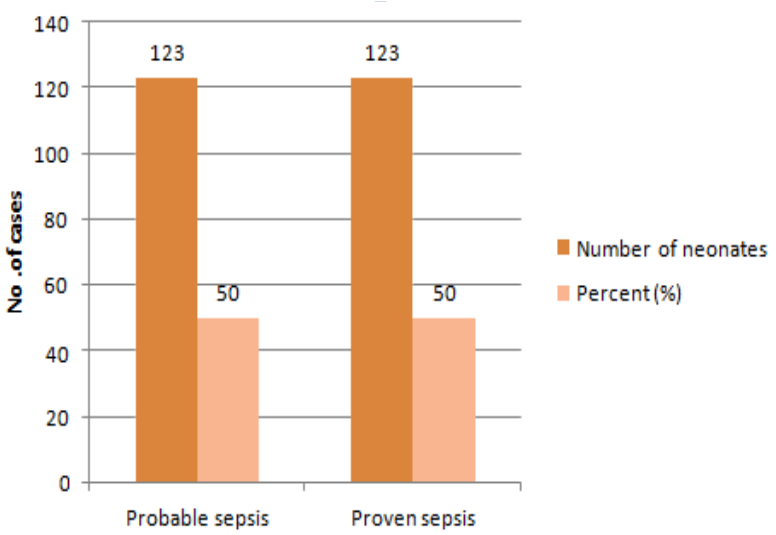

Figure 1: Distribution of neonates into probable and proven sepsis

Majority of the neonates were 166 newborn (67.5%), whereas total 80 (32.5%) were not newborn among total number of 246 babies. In terms of gender segregation, the highest number of study population were 170 male (69.1%) followed by 76 (30.9%) of females. Also the gestational age was calculated with 232 number of term deliveries (94.3%) as compared to 14 (5.7%) preterm deliveries (Table 1).

Table 1: Distribution of case of 246 study neonates among the newborns, gender and gestational age

	Number	Percentage (%)
Newborn		
Yes	166	67.5
No	80	32.5
Gender		
Male	170	69.1
Female	76	30.9
Gestational age		
Term	232	94.3
Preterm	14	5.7
Total	246	100

Thrombocytopenia among neonates: The presence of thrombocytopenia was studied in all the population study of 246 neonate's patient. Out of 246 total neonates, it was observed that total number of cases of thrombocytopenia present were 67 i.e., 27.2 %. While the total number of cases of thrombocytopenia absent were 179 i.e., 72.8 %. Therefore, among the total population of neonates majority of the study population thrombocytopenia cases were not present in the neonates (Figure 2).

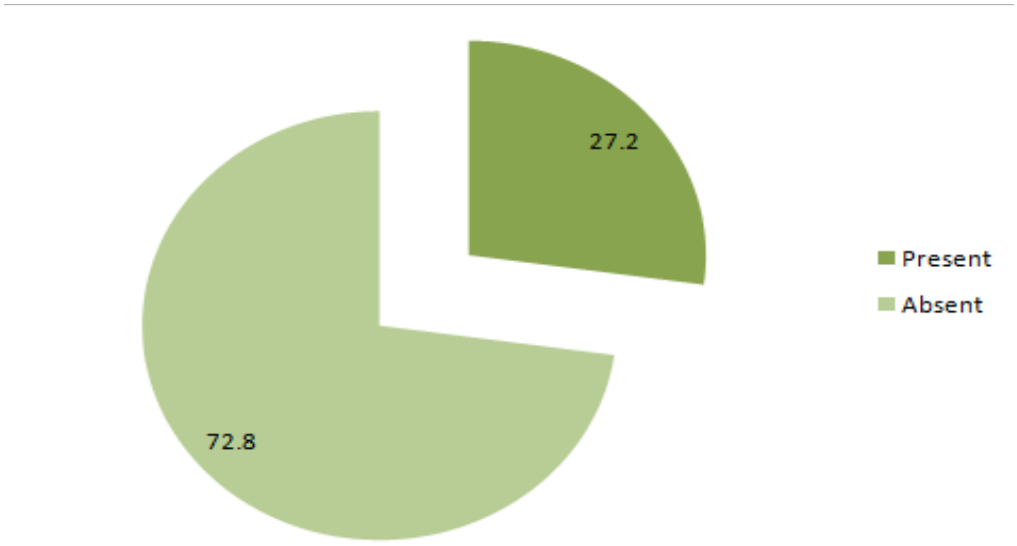

Figure 2: Distribution of cases according to Thrombocytopenia

Mortality and Duration of hospital stay of neonates

Among the total 246 neonates of study population, the Lumbar Puncture (LP) study was not done/not significant.

The mortality of neonates was also measured in this study, with highest number of 211 (85.8%) neonates were discharged from the hospital. However, among total 246 neonates, only 211 survived while 35 (14.2%) neonates were died in the hospital.

Also, the duration of the hospital stay was calculated among the total study population of the neonates in different range durations of the days. The neonates who stayed less than <7 days in the hospital were 116 (47.2%), while the neonates who stayed within 7 – 15 days were 115 (46.9%).

Also the neonates who stayed more than 15 days were also calculated which 14 were (5.9%). Therefore among the total population of the neonates, the highest number of neonates stayed for less than 7 days followed by 7-15 days of duration, while the lowest number of neonates stayed for more than 15 days. (Table 2)

Table 2: Distribution of cases of Mortality and Duration of hospital stay of neonates

	Number	Percentage (%)
Mortality at Hospital		
Discharged	211	85.8
Died	35	14.2
Duration of hospital stays		
<7 days	116	47.2

7-15 days	115	46.9
>15 days	14	5.9
Total	246	100

Causative Bacteria of Neonatal Sepsis

According to the results in Table3, positive sepsis (123 out of 246 neonates) predominated in causing newborn sepsis as compared to neonates who were not infected and tested negative. Klebsiella infected 50 neonates (40.7%), outnumbering other bacterial species in blood culture positive sepsis. Staphylococcus aureus was observed as second bacteria causing infection among 34 (27.6%) neonates followed by E. coli which caused infection in 26 (21.1%) neonates. The least causing infection were found in Group B Streptococcus with 13 (10.6%) of neonates getting infected.

Thus among the neonates with proven sepsis, Klebsiella (40.7%), followed by Staphylococcus aureus (27.6%), E. coli (21.1%) and group B streptococcus (10.6%) were the reported organisms in culture positive sepsis.

Table 3: Distribution of organism in blood culture positive sepsis

Organism in Blood culture positive Sepsis	Number	Percent (%)
Staphylococcus aureus	34	27.6
Klebsiella	50	40.7
Group B Streptococcus	13	10.6
E .Coli	26	21.1
Total	123	100

The neonates which were found positive with staphylococcus aureus (34), cefotaxime, Meropenem and vancomycin and Linezolid were the preferred sensitive first, second and third line of antibiotic, administered.

Followed by the neonates found positive with Klebsiella (50), Piperacillin+ tazobactum, minocycline and colistin were the preferred sensitive first, second and third line of antibiotic, administered.

Similarly the neonates found positive with Group B streptococcus (13), ampicillin, Piperacillin+ tazobactum, and meropenem were the preferred sensitive first, second and third line of antibiotic, administered.

Also the neonates found positive with E.coli (26), Piperacillin+ tazobactum, minocycline and colistin were the preferred sensitive first, second and third line of antibiotic, administered (Table 4).

Table 4: Table showing Antibiotic sensitivity according to the blood culture organism in proven sepsis (N=123)

Antibiotic Sensitivity	1st line		2nd line		3rd line	
Organisms	**Drug**	**N**	**Drug**	**N**	**Drug**	**N**
Staphylococcus Aureus	Cefotaxime	34	Meropenem	34	Vancomycin and Linezolid	34
Klebsiella	Piperacillin+ Tazobactum	50	Minocycline	50	Colistin	50
Group B streptococcus	Ampicillin	13	Piperacillin+ Tazobactum	13	Meropenem	13
E coli	Piperacillin+ Tazobactum	26	Minocycline	26	Colistin	26

Discussion

Mortality: Sepsis in neonates is a common complication and often mortal. Its incidence and the factors affecting the outcomes are matters of research across the world. The time of onset of the sepsis (Early vs late) has been studied extensively with related to its risk factors and outcomes.

Considering the limited resources, especially in Low and Low-Middle income countries like India, where blood culture which is the definitive diagnosis for neonatal sepsis may not be feasible in all cases, and due to various other reasons [19,20].The entity of probable sepsis, its treatment and outcomes needed to be explored. However, the literature on this is very limited. Hence in our study, we compared the outcomes in terms of mortality and other cardinal events between the probable and proven sepsis in a tertiary care referral hospital setting of North India.

The overall mortality rate of the neonates at the hospital was 14.2%, in our study. Salama et al reported a higher incidence of hospital mortality to the tune of 51.6%.21 significantly higher proportions of the probable sepsis neonates had mortality (19.5%) than the ones who had proven sepsis (8.9%) ($p<0.05$) Jatsho et al study from Bhutan and Kayange et al from Tanzania reported a diagonally opposite results wherein the culture positive neonates had higher mortality (20.5%)

[1,22]. Culture negative neonates had a lower mortality rate of 6.3%. Gamarra et al reported 23.5% mortality among confirmed sepsis from Peru [23]. The differential finding may be due to the varied management and antibiotic screening and administration protocol followed in the respective settings.

This finding may be due to the treatment part of the type of sepsis. While proven sepsis in our study was treated with the appropriate sensitive antibiotics by means of culture sensitivity, the probable sepsis was not given such specific antibiotics. This might have had the differential effect on the outcome of the probable and proven sepsis. It has been reported that among the culture negative sepsis neonates, 6 to 16 times more neonates are administered antibiotic therapy when a culture positive report is not available. This directly leads to overuse of antibiotics in NICUs. Hence, overuse of broad-spectrum antibiotics increases colonization with antibiotic resistant bacteria, development of multi-drug resistant bacterial infection as a consequences [24] and thus leading to worsening of the condition of the neonate, with added long term adverse implications as well [25]. Developing countries have shown to have such resistance pattern due to the blanket treatment with antibiotics [26].

Empirical treatment with antibiotics has been shown to reduce this mortality from the study done in Panama [27]. Yet, the differential mortality and other outcomes and its incidence remain unknown in most countries and the previous literature depicts marked heterogeneity, thus signifying the necessity to improve the number of research studies on the burden of neonatal sepsis.

Thrombocytopenia: Significantly higher proportion of the proven sepsis neonates had thrombocytopenia (39.4%) than the ones who had probable sepsis (14.6%) ($p<0.05$), while Guida et al reported 54% prevalence among the culture proven sepsis higher than our findings [28]. Thrombocytopenia is a common complication in patients who are critically ill, suffering from various diseases and is also correlated with rise in mortality [29]. Thrombocytopenia has been a significant marker for the sepsis which has been reported in many studies.

Apart from thrombocytopenia, none of the blood parameters such as TLC, Absolute neutrophil count or micro ESR, IT ratio were found to have significant association with the type of sepsis.

WBC count was comparable between the probable and proven sepsis in our study similar to Ahmad et al. and Mannan et al. [30,31]. CRP was insignificant in our study, while it had a 78.6% and 62% sensitivity and specificity in diagnosing the culture positive sepsis in Bangladesh study [30].

Hospital Stay: The duration of hospital stay was significantly longer among the proven sepsis than the probable sepsis neonates ($p<0.05$). Salama et al reported hospital stay duration of 24 ± 22 days which was longer than our study, where majority had 7-15 days of hospital stay [21]. Such longer duration of hospital stay of the neonates in whom sepsis was proven, might have been due to the time taken for the culture and antibiotic sensitivity reporting in Salama et al. [21].

Morbidity: None of the included proven sepsis cases was found to have significant lumbar puncture finding, indicating zero prevalence of meningitis. This is in contrast to the findings of previous studies that reported meningitis in neonatal sepsis cases in the range of 4-8%. The zero prevalence of meningitis in our study might due to the timing of the initiation of antibiotics, empirical or otherwise, before the Lumbar Puncture (LP) was done, as this has a potential impact on the LP findings [32,33]. The absence of neurological complications in our neonates might also be due to the absence of the meningitis [34].

Klebsiella (40.7%) was the most common organism cultured. Klebsiella was followed by Staphylococcus aureus (27.6%), E.coli (21.1%) and group B streptococcus (10.6%) were the reported organisms in our study. In our study, the neonates who were found positive with staphylococcus aureus (34), cefotaxime, meropenem, vancomycin and Linezolid were preferred. For Klebsiella (50), Piperacillin+ tazobactum, minocycline and colistin were preferred.

For Group B streptococcus (13), ampicillin, Piperacillin+ tazobactum, and meropenam were preferred .For E.coli (26), Piperacillin+ tazobactum, minocycline and colistin were preferred. Antibiotics (such as Piperacillin+ tazobactum, meropenem) as the first line of management. Thus, the antibiotic resistance profile among the proven sepsis cases, when read in tandem with the worse mortality among probable sepsis

Conclusion

The present study which compared the neonates with probable and proven sepsis concluded that mortality was significantly higher among the probable sepsis neonates. Neonates with proven sepsis had higher thrombocytopenia making it a potential differentiating factor between probable and proven sepsis. Hospital stay was longer in proven sepsis neonates, but none of them were found to have meningitis.

Culture sensitivity for the antibiotics shall be done before initiating the antibiotics for the neonatal sepsis. Loss to follow-up need to be minimised by adopting techniques such as community

based/home based follow-up to ensure till 6 months of the neonatal outcomes.

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