CLINICAL PROFILE AND ROLE OF SEPTIC SCREEN IN EARLY ONSET SEPSIS IN A TERTIARY CARE HOSPITAL OF WESTERN NEPAL-A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

INTRODUCTION

Neonatal sepsis is an important cause of neonatal mortality and morbidity with wide range of clinical manifestations. This study was aimed to study the clinical characteristics of sepsis along with the role of septic screen for early diagnosis of septicemia.

MATERIAL AND METHODS

A prospective observational hospital-based cross-sectional study was conducted in 113 screen positive newborns over a 12-month period at Universal College of Medical Sciences, Teaching Hospital, Bhairahawa, Nepal.

RESULTS

Out of 489 cases admitted to the NICU during the study period, 113 babies with screen-positive sepsis were included in the study. Poor feeding (46%, n=52), respiratory distress (38.9%, n=44) and lethargy (30.1%, n=34) were top three clinical presentations in neonates with sepsis followed by seizures, jaundice, vomiting, fever, and hypothermia respectively. 57.5% (n=65) of clinical sepsis cases enrolled had culture positivity with *Staphylococcus aureus* in 41.5% (n=27) and coagulase negative *Staphylococcus* (CONS) in 27.7% (n=18). *Klebsiella* was the third common organism isolated in blood culture (23.1%, n=15).

The sensitivities and specificities of two-test and three-test combinations in proven sepsis was calculated. Two-test combination showed sensitivities between 33-100% and specificities between 30-90% whereas three-test combination showed the sensitivities and specificities between 60-100% and 20-90% respectively.

CONCLUSION

Poor feeding, respiratory distress and lethargy were common presentations in early-onset neonatal sepsis. Three-test combination of septic screen had no overall advantage over two-test combination in the present study.

KEYWORDS Neonatal sepsis, Septic screen, CRP

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INTRODUCTION

Neonatal sepsis is a significant cause of neonatal morbidity and mortality in the newborn.[1] Globally, the estimated neonatal morbidity and mortality cases range between 2.53 million annually.[2] It is estimated that 20% of all neonates develop sepsis and it is responsible for 30-50% of total neonatal deaths in developing countries.[3] In Nepal, septicemia and emergence of drug resistant bacteria have been found to be important predictors of neonatal mortality. According to Nepal Demographic and Health Survey (2011), 85% of total death is accounted to neonatal sepsis which is higher than the previous surveys, 70% in 2006 and 69% in 2001.[4] NMR is higher in rural areas (34 deaths per 1000 live-births) than in urban areas (23 deaths per 1000 live births).

The fate of a neonate with sepsis largely depends on early detection and treatment accordingly. The diagnosis of neonatal sepsis may not be easy clinically. Many risk factors are associated with neonatal sepsis, and clinical features of neonatal sepsis are often non-specific. Though blood culture is the gold standard in the diagnosis of neonatal sepsis, it is not always positive even if clinical features of sepsis are present in the neonates. Also, a positive blood culture report is only obtained in 25-40% of cases and requires a period of about 48-72 hours.[3] Therefore, high index of suspicion is necessary for early diagnosis of sepsis, and when blood culture tests are negative. In these conditions, a combination of septic screen tests may help in the diagnosis. In developing countries like Nepal where the culture facilities are not available in many district hospitals, it becomes more essential to consider septic screening tests.[5]

Hence, there is a role of sepsis screen (a battery of rapid diagnostic test) for early diagnosis of septicemia and identification of culture negative cases. This study was, therefore, conducted to study the clinical profile of septic babies along with the role of septic screen for early diagnosis of septicemia to identify culture negative sepsis and compare rapid diagnostic tests with blood cultures.

MATERIAL AND METHODS

A hospital-based prospective observational study was carried out in Neonatal ward at Universal College of Medical Sciences, Bhairahawa, Nepal from July 2013 to July 2014. The study was approved by the Institute`s ethics committee. All inborn and out born neonates of either sex from birth to 72 hours of life having clinical symptoms of sepsis and maternal risk factors such as (prolonged rupture of membranes, fever, meconium stained liquor, prolonged duration of labor, chrioamnionitis) were screened and neonates with screen positive sepsis were included in the study. Babies who received antibiotics prior to the enrollment and patients not willing to give consent were excluded from the study. Sample size of 113 babies was calculated assuming absolute precision of 5% corresponding to a confidence interval of 50%±5%) at type 1 error of 5%. Prevalence rate of 8%was considered for the sample size calculation which was obtained from a study done by Nepal et al.[6]

Blood investigations were sent from all neonates with clinically suspected sepsis. Total leukocyte count (TLC), differential leukocyte count (DLC), immature to total neutrophil ratio (I/T ratio), peripheral smear for band cells and toxic granules,C-reactive protein (CRP) by latex agglutination technique and μ ESR using standardized non-heparinized capillaries were sent. Blood culture was sent after obtaining blood samples (approximately 2 ml) from peripheral vein after proper cleaning with iodine and spirit. Chest x-ray was considered whenever necessary. The cut-off values for positive tests were TLC <5000/mm^3 or >20000 /mm^3, I/T ratio ≥ 0.20, CRP positive or negative and μ ESR ≥15 mm in first hour. Clinical sepsis was considered in babies with two or more parameters positive for septic screen also called "screen positive sepsis".

Data was entered into excel sheet and analysis was done by using SPSS 21 software. All screen positive sepsis were subjected to analysis with comparison to culture positive cases by application of appropriate statistical tools. Descriptive analysis was done using mean and percentage as statistical tools. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for the septic screen parameters. Sensitivities and specificities were also calculated for two-test and three-test combinations.

RESULTS

Out of 489 cases admitted to the NICU during the study period, 113 babies had screen positive sepsis and were included in the study. Out of 113 screen positive babies included in the study, the proportion of male babies were more than female babies (n=77, 68.1% versus n=36, 31.9%). Majority of babies (n=83, 73.5%) were born by lower segment cesarean section (LSCS). 45.1% (n=51) were low birth weight (< 2500 gm) and 31% (n=35) were preterm. About 62.8% of mothers were in between 20-25 years with 23.9% in between 26-30 years and 9.7% above >30 years of age. Only 3.5% mothers were less than <20 years.

Table 1 presents the baseline characteristics of maternal distribution according to clinical examination. Fever was only present in 6.2% (n=7) mothers. Per vaginal examination more than 3 times was found to be done in 57.5% (n=65) of mothers. 20.4% (n=23) mothers had meconium stained liquor (Table 1)

Table 1. Maternal distribution according to clinical examination

Clinical examination	Number (n=113)	Percentage (%)
Fever	7	6.2
Per vaginal examination>3 times	65	57.5
FHR>160bpm	2	1.8
Duration of PROM>12 hours	30	26.5
Meconium stained liquor	23	20.4
Duration of labor>24 hours	11	9.7

bpm- beats per minute, PROM- prolonged rupture of membranes

CRP was positive among 50.4% neonates and toxic granules present in peripheral smear werefound in 37.2% of neonates. The mean values of Hb, TLC, immature/total neutrophil, micro ESR (mm) was found as shown in the table (Table 2).

Table 2. Biochemical parameters of enrolled neonates

Biochemical parameters	Mean±SD (n=113)
Hb (gm/dl)	16.49±2.32
TLC (cells/mm^3)	17960.65±9745.55
Immature/Total neutrophil ratio (I/T ratio)	0.22±0.10
µESR (mm in 1st hour)	11.27±5.49

Poor feeding (46%, n=52), respiratory distress (38.9%, n=44) and lethargy (30.1%, n=34) were top three clinical presentations in neonates with sepsis followed by seizures, jaundice, vomiting, fever and hypothermia respectively (figure 3).

Table 3. Clinical profile of septic babies (n=113)

Clinical Features	Number (N)	Percentage (%)
Poor feeding	52	46
Fever	14	12.4
Lethargy	34	30.1
Seizures	26	23
Jaundice	23	20.4
Vomiting	16	14.2
Respiratory distress	44	38.9
Hypothermia	4	3.5
Poor cry	41	36.3
Diminished activity	34	30.1

The sensitivity and specificity of CRP in detecting culture positive neonatal sepsis was found to be 64.6% and 68.8% with positive predictive value (PPV) and negative predictive value (NPV) of 73.7% and 58.9% respectively. The accuracy of CRP was 66.3%. The sensitivity, specificity, PPV, NPV and accuracy of micro-ESR were 67.7%, 81.2%, 83%, 65% and 73% respectively whereas of I/T ratio were 60%, 68.7%, 72%, 55%, and 63.7% respectively as shown in Table 4.

The sensitivity and specificity was calculated combining two or three septic screen parameters. Two-test combination viz CRP+TLC, CRP+I/T ratio, TLC+I/T ratio TLC+ANC, TLC+µESR, I/T ratio+ANC, I/t ratio+µESR, ANC+µESR showed sensitivities and specificities of 100% and 40%, 73% and 90%, 80% and 80%, 67% and 90%, 100% and 70%, 73% and 90%, 100% and 30%, 93%, and 40% respectively whereas three-test combination viz TLC+I/T ratio+ANC, TLC+I/t ratio+CRP, TLC+I/T ratio+ANC, TLC+ANC+CRP, TLC+ANC+µESR+ TLC+CRP+µESR, I/T ratio, ANC+CRP, I/T ratio+NC+µESR, I/T ratio+CRP+ANC showed the sensitivities and specificities of 60% and 80%, 80% and 80%, 100% and 20%, 87% and 70%, 73% and 30%, 73% and 90%, 100% and 30%, 100% and 30%, 80%, and 90% respectively.

Table 4. Sensitivity, specificity, PPV, NPV and accuracy of septic screen parameters

Septic Screen parameters	Culture		Sensitivity	Specificity	PPV	NPV	Accuracy
CRP	Positive	Negative					
Positive	42	15	64.6	68.8	73.7	58.6	66.3
Negative	23	33					
µESR							
Positive	44	9	67.7	81.2	83	65	73
Negative	21	39					
I/T ratio							
Positive	9	15	60	68.7	72	55	63.7
Negative	26	33					

57.5% (n=65) of clinical sepsis cases enrolled had culture positivity with *Staphylococcus aureus* in 41.5% (n=27) and coagulase negative *Staphylococcus* (CONS) in 27.7% (n=18). *Klebsiella* was the third common organism isolated in blood culture (23.1%, n=15) (Table 5).

Table 5. Bacteriological profile of organisms isolated

Blood culture	Number (N=113)	Percentage (%)
Positive	65	57.5
Negative	48	42.5
Isolates detected	(n=65)	
Citrobacter	1	1.5
Coagulase negative *Staphylococcus* (CONS)	18	27.7
E. coli	3	4.6
Klebsiella	15	23.1
Proteus mirabilis	1	1.5
Staphylococcus aureus	27	41.5

DISCUSSION

Neonatal sepsis is an important cause of neonatal mortality and morbidity in low and middle incomes countries like Nepal. It is extremely important to make an early diagnosis of sepsis, because early institution of empirical antimicrobial therapy may be life saving.[7]

Out of 489 babies admitted in the NICU during the study period, 23% (n=113) had screen positive early onset sepsis. A retrospective study conducted by Shrestha et al in Nepal found 20% cases to be culture positive (103 cases culture positive out of 513 screen positive).[1] In contrast to his study, the present study had culture positivity in 57.5% (n=65) cases which was higher than the study conducted by him. A study done by Lakhey et al found culture positivity of 66.3% (n=65) out of total 98 screen positive newborns which was even more than the present study. They also concluded that 90.35% of total culture positive sepsis had screen positive sepsis.[8] Another study done at a tertiary care hospital of Nepal showed culture positivity rate of 6.1% (54 cases culture positive out of 1349 cases.[9] The high incidence of culture positivity in the present cases could be due to inclusion of only screen positive cases whereas the low incidence of culture positivity in some studies were most probably due to inclusion of all suspect cases of clinical cases in its calculation.

The clinical features of early onset neonatal sepsis are often subtle and non-specific which necessitates the high index of suspicion. Poor feeding (46%, n=52), respiratory distress (38.9%, n=44) and lethargy (30.1%, n=34) were top three clinical presentations in neonates in the present study followed by seizures, jaundice, vomiting, fever and hypothermia respectively. A study conducted by Khinchi et al (2010) also concluded refusal to feed (74%, n=160) and respiratory distress (75%, n=161) being two major clinical presentations in neonates with sepsis. In their study, fever was present in 69% (n=148) cases which was higher than in the present study.[10] A recent study done in Nepal also concluded respiratory distress (56%, n=84), fever (26%, n=39) and feeding difficulty (12.7%, n=19) being the major manifestations of sepsis in newborn.[8] A study conducted in a tertiary care hospital in Bangladesh concluded fever (44.4%), respiratory distress (27.8%) and poor feeding (22.2%) to be the major manifestations of neonatal sepsis. In the same study, they documented hypothermia in 11.1%, apnea in 16.7%, cyanosis in 11.1%, convulsions in 11.1% and jaundice in 50%.[11] This variation in clinical features of neonatal sepsis may probably be due to different influencing factors like birth weight, delivery site, age of the newborn, and referral timing.

In the present study, 57.5% (n=65) neonates of early onset sepsis had culture positivity where *Staphylococcus aureus* (41.5%, n=27), coagulase negative *Staphylococcus* (27.7%, n=18) and *Klebsiella* (23.1%, n=15) were three predominant isolated organisms. Lakhey et al (2015-2016) in their study, also found similar proportions of *Staphylococcus aureus* isolated in newborns (41.7%, n=30).[8]

The sensitivity, specificity, PPV and NPV of CRP in the present study were 64.6%, 68.8%, 73.7%, and 58.6%. In a study done by Lakhey et al[8], these parameters were comparatively more than the present study (sensitivity-77.8%, specificity-66.7%, PPV-68.2%, and NPV- 76.5%). Bhale et al[12] found that these parameters were even more (sensitivity-84.62%, spscificity-78%, PPV-77.78 and NPV-84.78) than the study done by Lakhey et al and the present study. In contrast, Swarnakar et al (2012) found the sensitivity, specificity, PPV and NPV of 52.3%, 56%, 89% and 14.3% respectively which were less than the present study and the previous studies.[13]

The sensitivity, specificity, PPV and NPV of µESR in the present study were 67.7%, 81.2%, 83%, and 65% which was almost similar as in the study conducted by Bhale et al.[12] In contrast, these parameters were less in a study conducted by Lakhey at al (sensitivity-51.4%, specificity- 60.2%, PPV-54%, and NPV- 57.3%).[8]

The sensitivity, specificity, PPV, and NPV of I/T ratio in the present study were 60%, 68.7%, 72%, and 55% respectively. The findings were almost comparable in a study conducted by Lakhey et al (sensitivity- 73%, specificity- 61.5%, PPV-63.8% and NPV- 71.6%).[8] Jadhav et al (2013)[14] and Bhale et al (2015)[12] found the sensitivity of I/T ratio (80% and 75.82% respectively) to be more than the present study whereas the specificity was less (65% and 66.35% respectively).

Lakhey at al[8] found the sensitivity and specificity in two-test combination to be 90.3% and 75.6% whereas it was 100% and 83% respectively in a study done by Chirico et al.[15] On two-test combination, the sensitivities in the present study ranged from 33%-100% with specificities in between 30%-90%. Three-test combination revealed sensitivities and specificities in between 60%-100% and 20%-100%. We could not find any added benefit in diagnosing sepsis on three-test combination in comparison to the two-test combination.

This study had few limitations. Firstly, we only included early- onset sepsis cases in the present study. Inclusion of late-onset sepsis cases along with the early onset septic cases would have given a clearer picture on the clinical profile and laboratory findings of septic newborns. Secondly, this was a hospital-based study which may not give a true picture of septic cases in the community. Therefore, multicentric trials with large sample size should be considered.

CONCLUSION

Poor feeding, respiratory distress and lethargy were top three clinical presentations in neonates. Combining two or more parameters increased the sensitivity and specificity of the septic screen in comparison to the individual parameter. Three-test combination did not reveal any additional benefit in comparison to two-test combination in the diagnosis of sepsis.

CONFLICT OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

BKG (Binod Kumar Gupta) conceptualized the study, performed the literature search, analyzed the data, drafted the manuscript, revised it and supervised the study. RK performed the literature search, analyzed the data and drafted the manuscript. BPK collected the data and helped in analysis, drafting and revision of the manuscript. BKG (Badri Kumar Gupta) drafted the manuscript, revised it and supervised the study.

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