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Original Article

Role of sepsis screening in early diagnosis of neonatal sepsis

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ABSTRACT

Background: Neonatal sepsis, a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life is a major cause of morbidity and mortality in newborn inborn. Early diagnosis is critical, as sepsis can progress more rapidly in neonates than in adults. An attempt was made to establish correlation between early neonatal sepsis screening & blood culture in neonates presenting with features of sepsis. The aim of this study is to assess the usefulness of sepsis screen in early diagnosis of neonatal septicemia.

Materials and Methods: The study was done in Kist medical college and hospital, Nepal from October 2015 to October 2016. Statistical correlation between early indicators of sepsis screen & blood culture (considered as gold standard) was established in clinically suspicious cases of neonatal sepsis.

Results: Out of 150 cases studied, 72 were culture positive. CRP (77.8%) and immature: total neutrophils ratio (73%) showed highest sensitivity. CRP (66.7%), I/T ratio (61.5%) and micro ESR (60.2%) showed highest specificity. Positive predictive value was highest for CRP (68.2%) followed by I/T ratio (63.8%) and corrected total leukocyte count (56.2%).

Conclusion: Serum CRP is the most sensitive marker of sepsis. Use of peripheral smear study and CRP can be implicated effectively as a sepsis screen for early diagnosis of neonatal sepsis. The combination of parameters yielded better results than single tests and proved to be an invaluable tool for early diagnosis of neonatal sepsis.

INTRODUCTION

Neonatal sepsis (NS) is a clinical syndrome characterized by systemic signs of circulatory compromise caused by invasion of the blood stream by bacteria in the first four weeks of life.[1] Neonatal sepsis is one of the major causes of morbidity and mortality among the newborns in the developing world.[2] Neonatal mortality rates in Nepal as per NDHS 2011 data is 33 per 1000 live births.[3] The incidence of neonatal sepsis in India is approximately 30/1000 live births.[4] Neonatal mortality rate (NMR) is 27/1000 live birth5 and Neonatal sepsis contributes 36% of total death in Bangladesh.[6] The reported incidence of neonatal sepsis varies from 7 to 38 per 1000 live birth in Asia.[7] Sepsis is

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Table 1: Common clinical features in cases presenting with features of sepsis

Clinical features	Frequency
Resp. distress	84 (56%)
Fever	39 (26%)
Feeding difficulty	19 (12.66%)
Lethargy	8 (5.33%)
Total	150 (100%)

Table 2: Frequency of micro-organisms isolated in blood culture

Micro-organisms	Percent (Number)
Coagulase positive Staphylococcus	41.7%(30)
Coagulase negative staphylococcus (CONS)	30.6%(22)
Citrobacter	11.1%(8)
Acinitobacter	5.5%(4)
Escherichia coli	5.5%(4)
Enterobacter	5.5%(4)
Total	100.0(72)

more common in developing countries when compared with developed countries.[2] Neonatal sepsis may be classified according to the time of onset of the disease: early onset sepsis (EOS) and late onset sepsis (LOS).[8] The distinction has clinical relevance, as EOS disease is mainly due to bacteria acquired before and during delivery, and LOS disease to bacteria acquired after delivery (nosocomial or community sources).[9] Early onset sepsis usually presents within the first 72 hours of life and Late onset sepsis usually presents after 72 hours of age.[10] Infections are more common in low birth weight and preterm babies.[11] In neonates the illness can progress more rapidly than in adults; therefore early diagnosis is of utmost importance.[11] Clinical features of sepsis are nonspecific in neonates and a high index of suspicion is required for the timely diagnosis of sepsis.

Positive blood culture is a gold standard for diagnosis, but it is time consuming (requires 72 hours, atleast 24 hours in case of BacT- ALERT®) and demands a well-equipped laboratory.[12] Many investigators have evaluated various inflammatory markers such as interleukin-6, interleukin-8 and plasma elastase. But these are sophisticated and impractical for developing countries.[13-15] A good diagnostic test should have high sensitivity and specificity and should be cost effective with early availability of results.[13] Even though a positive blood culture is gold standard for diagnosis of neonatal sepsis the technique is time consuming, demands a proper laboratory setup and is positive in only 40% cases.[16]

Early treatment with antibiotics is possible with the help of certain indirect markers such as neutropenia (<1800 cells/mm^3), leucopenia (<5000 cells/mm^3), band cells, micro ESR and C-reactive protein (CRP). All these investigations are collectively known as sepsis screen and aids in early diagnosis of neonatal sepsis in absence of negative blood cultures. They together can be used as sepsis screen. Presence of two or more abnormal parameters in case of strong clinical suspicion is considered as positive sepsis screen. The results can be obtained much earlier than blood culture and early medical intervention can be issued. This can be helpful to reduce neonatal mortality and morbidity.[17]

The purpose of this study was to evaluate the early indicators of sepsis screen and their statistical correlation with blood culture (considered as gold standard) in neonatal septicemia. All these will help in early diagnosis of neonatal septicemia and its speedy management and ultimately lead to timely intervention thus leading to reduced mortality and morbidity amongst neonates afflicted with neonatal sepsis.[18]

MATERIAL AND METHODS

This was a descriptive prospective study carried out in Kist Medical College, Imadol, Kathmandu, Nepal. For ethical issues confidentiality of patient's information was considered and ethical clearance was duly taken from institutional ethics committee and progress of study was duly intimated to the ethics committee time to time. All the neonates admitted to the baby nursery between October 2015 to October 2016, with signs and symptoms of sepsis or presence of predisposing factors for development of sepsis, were included in this study.

Inclusion criteria

Neonates were enrolled on the basis of signs and symptoms of clinical sepsis (as per NNF criteria)[18] after through clinical examination and proper history taking.

The clinical criteria considered (NNF criteria) were – poor feeding, irritability / excessive cry, lethargy poor cry and reflexes, fever, hypothermia, jaundice, vomiting, abdominal distension, tachypnoea and grunting, convulsions, diarrhea, pustules, cyanosis, bulged fontanalle, DIC/bleeding, poor perfusion / shock, apnea.

Also significant predisposing factors for presumed early onset sepsis was taken into consideration (according to NNF guidelines)[18] during inclusion of cases.

Exclusion criteria

Neonates who received antibiotics before Admission, Neonates who died before work up was complete, Neonates who underwent surgery, Congenital anomalies e.g. tracheoesophageal fistula, lobar agenesis, malrotation of the gut, complex heart diseases, neural tube defects etc. Inborn errors of metabolism

Each patient was studied in a methodical manner using a

Table 3: Sepsis screening parameters in relation to blood culture

	Bloodculture positive	Blood culture negative	Total
Septic screen positive	65 (90.3%)	33 (42.3%)	98
Septic screen negative	7 (9.7%)	45 (57.7%)	52
Total	**72**	**78**	**150**

proforma. Myriads of clinical profile of neonatal septicemia amongst all cases of neonatal sepsis (with emphasis on sepsis screen positive and/or bacteriologically positive i.e. blood culture positive cases) were studied. Correlation between early indicators of sepsis screen and their statistical correlation with blood culture in neonatal septicemia was performed. Following Investigations done were included in the study:

i. Sepsis screen (according to NNF criteria)

a. Total leukocyte count
b. I/T ratio (band cell ratio)
c. Absolute neutrophil count
d. m-ESR
e. C reactive protein

ii. Blood culture

Statistical analysis and Ethical Clearance

It was done as per standard statistical tools. A 'p' value less than 0.01 was considered to be statistically significant. Some help was taken from statistical package for social sciences (SPSS, Version 21) software.

RESULTS

Out of 150 suspected neonatal sepsis patients, 56 % (84) were males and 44% (66) were females. Thus male babies were more affected by suspected neonatal sepsis than female babies. Among the patients with suspected neonatal sepsis, the most common presenting clinical feature was respiratory distress followed by fever and feeding problems. (Table 1)

Bacteriologically positive cases were found in 72(48%) of the total 150 clinically suspected neonates. Bacteriologically negative but sepsis screen positive cases were found in 33 (22%) of the total 150 neonates. Bacteriologically negative, sepsis screen negative but clinical course compatible with sepsis were found in 45 (30%) neonates. Out of the 72 culture positive cases, early onset septicemia was found in (n=54)75% cases. Late onset septicemia was present in 18(25%) cases.

Birth weight less than 2500 gms (low birth weight) was present in 51(70.8%) culture positive cases. Birth weight greater than equal to 2500 gms (normal birth weight) was present in 21(29.2%) culture positive cases. 33.33% (n=24) preterm babies were affected by septicemia whereas, 66.67% (48) term babies were affected by septicemia.

There was marked association of neonatal sepsis with coagulase positive and coagulase negative staphylococcus comprising 72.3% (n=52) cases. (Table 2)

As illustrated in table 3 significant number (n=65; 90.3%) of culture positive cases were positive for two or more septic screen parameters. On contrary, only 7 of septic screen negative cases were culture positive. Blood culture negative suspicious sepsis cases, which were positive for septic screen parameters were total 33 in number. 45 cases were both culture and septic screen negative but had strong clinical suspicion for sepsis.

Amongst all sepsis screening parameters CRP & I/T ratio had the highest predictive accuracy. (Table 4) As the single parameter CRP per se had the highest sensitivity (77.8%), specificity (66.7%), positive predictive value (68.2%) and the negative predictive value (76.5%). Although, both the CRP and I/T ratio were statistically significant as the sepsis parameters, the predictive accuracy of the screening test increased noticeably when two or more positive parameters were combined together. (Table 2)

DISCUSSION

Definitive diagnosis rests upon a positive blood culture,

Table 4: Sepsis screen parametres and their predictive accuracy

Sepsis screen parameters	Sensitivity	Specificity	PPV	NPV	P value
Neutropenia (ANC <1800 cells/mm^3)	**38**	**48.7**	**41.2**	**46**	**>0.001**
Leucopenia (TLC <5000 cells/mm^3)	62	55	56.2	61.4	>0.001
IT Ratio (>0.2)	73	61.5	63.8	71.6	<0.001
mESR (>15 mm in 1st hour)	51.4	60.2	54	57.3	>0.001
CRP Positive (>1 mg/dl)	77.8	66.7	68.2	76.5	<0.001
Two parameters	90.3	75.6	77	89	<0.001

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Table 5: Distribution of cases according to age of onset

Authors	Year	No of cases studied (n)	Culture positive cases	EOS (≤72 hrs) (%)	LOS (>72 hrs) (%)
Chacko et al.,[28]	2005	36	69	55.4	44.6
Sriram et al.,[29]	2011	115	58	77.6	22.4
Swarnakar et al.,[14]	2012	72	37	38.09	61.91
Vinay et al.,[30]	2015	60	48	90.0	10.0
Bhale et al.,[31]	2015	191	91	64.83	35.17
Present study	**2016**	**150**	**72**	**77.0**	**23.0**

to identify the pathogen and determine its antibiotic susceptibility pattern, but for better survival and outcome, simple and rapid diagnostics tests are required as adjuncts to the blood culture for early and effective initiation of treatment to the septicemia in neonates.

In this study, Coagulase positive Staphylococcus(41%), Coagulase negative staphylococcus (CONS) (29%), Citrobacter (12%), Acinitobacter (6%), Escherichia coli (6%), Enterobacter(6%) were the common organisms associated with sepsis.

In a similar study done in India most prevalent organisms were coagulase negative staphylococcus(CONS) followed by Coagulase positive staphylococcus, streptococcus fecalis, alpha- hemolytic Streptococcus, klebsiella, proteus, E.coli and Candida albicans.[19] The causative organisms in neonatal sepsis vary from place to place and the frequency of the causative organisms is different in different hospitals and even in the same hospital at different time.

The other published data in Nepal on the subject shows E.coli as the most common isolate.[20,21] The study carried out in western Nepal showed Staphylococcus aureus to be the most common isolate.[22] E.coli was the leading cause in many studies done in Nepal.[20,21] E. coli was the second most common isolate as reported from Uganda.[23] Staphylococcus aureus was the third most common isolate as in India.[24] Klebsiella pneumoniae was found to be the fourth most common isolate but the other report in Nepal and India showed Klebsiella pneumoniaeas the second most common cause[14] and in West Indies showed as the most common cause.[25] Pseudomonas spp.was isolated from one case in this study but the reports from Iran and India showed Pseudomonas spp. to be the most common cause of neonatal sepsis.

The causative organisms of neonatal sepsis vary with time and place. There is increasing trend of antibiotic resistance to the commonly used and available drugs. Continuous surveillance is needed to monitor changing epidemiology of pathogens and antibiotic susceptibility pattern.

The major presenting clinical features were respiratory distress, fever followed by feeding problems which was in concordance with the study done by Basu R[26] Neonatal Sepsis screen was considered positive if any two criteria of the following were present.[18]

• Absolute Neutrophil Count of ≤1800/cumm

• CRP ≥1 mg/dL.

• I/T ratio ≥0.2

• Micro-ESR ≥15mm at the end of 1st hour

• Serum direct bilirubin ≥ 2mg/dL

• Total Leucocyte Count (TLC) of ≤5000/cumm

The ratio of culture positive neonatal septicemia cases was higher among males than the females in the present study, showing a ratio of 1.22. The male preponderance in neonatal septicemia may be linked to the X- linked immune-regulatory gene factor resulting in the host's susceptibility to infections in males.[13] There is male preponderance, which is due to the prevalent custom of taking male babies

Table 6: Distribution of cases according to birth weight

No.	Authors	Year	No. of cases	EOS (≤72 hrs) (%)	LOS (>72 hrs) (%)	NORMALBIRTH WEIGHT(≥2.5 kgs)(%)
1	Sriram et al.29	2011	115	58	74.14	25.86
2	Mondal et al.33	2012	62	38	84.0	16.0
3	Pal et al.34	2013	238	93	71.11	28.89
4	Vinay et al30	2015	60	48	70.0	30.0
5	Bhale et al31	2015	191	91	81.32	18.68
6	Present study	2016	150	72	70.0	30.0

Table 7: Predictive accuracy of absolute neutrophil count

No.	Authors	Year	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
1	Buch et al.13	2010	66.15	90.91	89.58	69.44
2	Shirazi et al34	2010	35.0	74.0	--	--
3	Sriram et al29	2011	63.6	51.0	12.1	93.0
4	Swarnakar et al14	2012	50.0	48.23	2.2	97.0
5	Jadhave et al15	2013	20.0	87.5	75	36.8
6	Bhale et al31	2015	42.86	99.0	97.5	65.56
7.	Present study	2016	38.0	48.7	41.2	46

preferentially to healthcare institutions and also because female babies are immunologically more competent.[27]

Maximum culture positive cases were seen in neonates of age ≤72 hours (i.e. 77%) as compared to neonates aged more than 72 hours (i.e 23%). This was comparable with other studies, which is shown in table 5. The higher proportion of early onset sepsis cases may be due to the immature immunological responses of the neonates in the first week of life, making them more susceptible to infections in this period.

In present study, the percentage of culture positive cases in low birth weight neonates was 70%. According to Barbara Stoll et al.[32] the rate of infection is inversely proportional to the birth weight, and low IgG levels due to impaired cellular immunity in the very low birth weight neonates contributes to the increased susceptibility to infections in these neonates.[32] In present study, sepsis was not common in preterms. Similar finding was seen in the study done by Mondal et al.[33] However, the sepsis was more common in preterm neonates than in term babies in other studies. Preterm babies are more susceptible to infections due to inherent deficiencies of both humoral and cellular defense mechanisms. According to Barbara J. Stoll et al[32] the incidence of septicemia increased with the decreased gestational age of the neonates.[32] (Table 6)

Cut off value of absolute neutrophil count≤1800/µl was taken as diagnostic criterion for sepsis screen. Absolute neutrophil count in the sepsis screen showed low sensitivity (42.9%) and high specificity (99.0%). The positive predictive value was 97.5% and negative predictive value was 65.6% Absolute neutrophil count showed highest specificity and positive predictive value among all the other parameters of sepsis screen. (Table 7)

C-reactive protein ≥1mg/dl was considered as positive result for sepsis screen. Predictive accuracy of CRP of this study is compared with other studies (Table 8). In present study, CRP had a high sensitivity of 77.8%, specificity (66.7%), positive predictive value (68.2%) and negative predictive value (76.5%) CRP proved to be the most efficient of all the markers of sepsis. The principal ligand to CRP is phosphocholine, which is found in lipopolysaccharide, bacterial cell walls, as well as in most biological membranes.[35] CRP is part of the acute-phase response which aims to neutralize the inflammatory agent and to promote the healing of the injured tissue.[36]

During the acute-phase-response, CRP's hepatic synthesis rate increases within hours and can reach 1,000-fold levels.[35] Despite the ongoing rise (and fall) of new infection markers, its wide availability and its simple, fast, and cost-effective determination make it one of the preferred indices in many neonatal intensive care units (NICUs).[37]

In present study, immature to total neutrophils ratio≥0.2 was diagnostic criterion for sepsis screen. Sensitivity, specificity, positive predictive value and negative predictive value was acceptable with a p-value of <0.001. This was comparable to other studies. (Table 9)

Table 8: Predictive accuracy of C-reactive protein

Authors	Year	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Buch et al[13]	2010	68.466	73.64	71.83	71.43
Swarnakar et al[14]	2012	52.3	56	89	14.3
Pal et al.[35]	2013	83.33	91.89	86.21	90.07
Jadhav et al[15]	2013	90.7	37.5	73.1	68.2
Vinay et al[30]	2015	81.2	50.0	86.6	40.0
Chacha et al[38]	2014	62.9	73.3	37.5	88.6
Bhale et al[31]	2015	84.62	78.00	77.78	84.78
Present study	**2016**	**77.8**	**66.7**	**68.2**	**76.5**

Table 9: Predictive accuracy of immature to total neutrophils ratio

Authors	Year	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Swarnakar et al[14]	2012	52.63	53.3	81.0	22.8
Jadhav et al[15]	2013	80.0	65.0	81.1	63.4
Bhale et al[31]	2015	75.82	66.35	65.2	74.71
Present study	2016	73	61.5	63,8	71.6

Table 10: Predictive accuracy of micro ESR

Authors	Year	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Buch et al[13]	2010	63.08	72.73	73.21	62.5
Swarnakar et al[14]	2012	73.0	54.0	29.7	88.5
Mondal et al[33]	2012	63.0	94.0	92.0	--
Vinay BS et al[30]	2015	43.0	75.0	87.0	25.0
Bhale et. Al[31]	2015	69.23	87.0	82.89	75.65
Present study	2016	51.4%	60.2%	54%	57.3%

Table 11: Comparison of the studies according to two or more abnormal parameters of sepsis screen

Authors	Year	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Gerdes et al[37]	2004	100.0%	83.00%	27.00%	100.0%
Sriram et al[29]	2011	55.30%	91.70%	98.30%	19.30%
Swarnakar et al[14]	2012	56.0%	87.50%	97.00%	20.00%
Jadhav et al[15]	2013	100.0%	62.50%	63.30%	100.0%
Vinay et al[30]	2015	77%	41%	84%	31%
Bhale et al[31]	2015	93.4%	77.00%	78.70%	92.77%
Present study	**2016**	**90.3**	**75.6**	**77**	**89**

Micro ESR≥15 mm at the end of 1 hour was considered as positive for sepsis screen. The results in the present study for micro ESR showed lesser sensitivity, specificity, Positive predictive accuracy and negative predictive accuracy. The various studies done showed variable result for micro ESR. Micro ESR in our study didn't prove to be as efficient as other septic parameters as compared to other studies. (Table10)

Two or more abnormal parameters had a high accuracy in predicting neonatal sepsis. The results in the present study were in accordance with Gerdes et al[37] Jadhav et al[15] and Bhale et al[31] The sensitivity of two or more abnormal parameters was 90.3%, specificity was 75.6%, positive predictive value was 77.0% and negative predictive value was 89.0% as shown in table 11. The sepsis screen should be considered as a positive septic screen, If two parameters are abnormal and antibiotic therapy can be started. If there is strong clinical suspicion and sepsis screen is negative, in 12 hours the screen can be repeated. If the screen is negative even after that, then sepsis may not be present.

CONCLUSION

CRP had highest sensitivity, specificity, positive predictive value and proved to be a sensitive and responsive indicator of neonatal sepsis. The presence of two or more abnormal parameters has more sensitivity than any single abnormal parameter. The combination of tests also yielded statistically significant correlation with blood culture status than individual test. The parameters used in this study are simple, quick and cost effective.

Amongst early onset sepsis the predominant clinical features were respiratory distress (manifested by tachypnoea and grunting) followed by fever and poor feeding. The results obtained from sepsis screen cannot establish or rule out neonatal sepsis completely. The gold standard remains blood culture. False positive cases may receive unwanted antibiotic therapy.

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