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Original Research Article

A study of clinico-bacteriological profile and to determine incidence of meningitis in late onset sepsis in newborn unit of tertiary care teaching hospital in Northern India

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ABSTRACT

Background: The daily risk of mortality in first 4 weeks of life is almost 30-fold higher than post-neonatal period. Late onset sepsis (LONS) and meningitis still continue to be major causes of mortality and morbidity in newborn period. Our study was done to study clinical profile of enrolled newborns with LONS along with incidence of meningitis in them. The objective of this study was to study clinico-bacteriological profile and to determine associated incidence of meningitis in neonates with late onset sepsis (LONS) in a hospital setting in Northern India.
Methods: It was a hospital based prospective observational study conducted over a period of 12 months enrolling 122 newborn with >72 hours of age fulfilling inclusion criterias.
Results: Out of total 122 enrolled newborn, 37 (30.3%) neonates had meningitis. 71 (58.20%) were of term gestation with majority 61 (50.0%) in age group of 4-7days of life. Incidence of LONS in low birth weight and very low birth weight were 54% and 13.5%. Most commonly seen symptoms in at admission were lethargy, refusal to feed and fever. Blood culture was positive in 45 (36.88%) in neonates with Acinetobacter baumanii, klebsiella pneumonia and Escherichiae coli being most commonly seen organisms. Cerebrospinalfluid (CSF) culture was positive in 4 (10.81%) newborns. Mean duration of hospital stay was 24.75±13.96 days. Mortality in neonatal meningitis was 3 (3.2%).
Conclusions: Our study proved that about one third of newborn admitted with LONS also had coexistent meningitis. Thus CSF analysis is a must and it should not be missed as untreated meningitis can be devastating for newborn. Antibiotics must be added as per antibiogram of specified institute.

Keywords: Late onset sepsis, Meningitis, Newborn, Blood culture, Northern India

INTRODUCTION

The neonatal period constituting first 28 days of life carries highest risk of mortality per day than any other period during childhood. With increase in neonatal care, there has been a slow decline in Neonatal Mortality Rate (NMR).[1]

Worldwide neonatal mortality accounts for approximately 5 million deaths each year, 96% of which occurs in developing countries.[2,3] Neonatal sepsis is responsible for approximately 30%-50% of total neonatal deaths.[2] Neonatal sepsis is defined clinically as a clinical syndrome characterized by signs and symptoms of infection with/without accompanying bacteremia in first 28 days of life and microbiologically by positive blood and/or cerebrospinal fluid cultures. It encompasses various systemic infections of newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections.[4]

Neonatal sepsis is mainly categorized as Early Onset Sepsis (EONS) and Late-Onset Sepsis (LONS) depending upon onset of symptoms. EONS is primarily due to

bacteria acquired before and during delivery and LONS due to bacteria acquired after delivery (nosocomial or community sources).[5] EONS presents within first 72 hours of life and neonate may be symptomatic at birth. The common clinical presentation is respiratory distress and pneumonia. The risk factors associated with an increased risk of EONS include low birth weight (<2500 g), maternal fever, UTI, premature rupture of membranes, prolonged labour and perinatal asphyxia.[6]

LONS presents after 72 hours of age with septicaemia, pneumonia, or meningitis. Factors that predispose to nosocomial sepsis include low birth weight, prematurity, caesarean section, mechanical ventilation, invasive procedures, and poor maintenance of hygiene in neonatal care.[6] Neonatal meningitis is a serious consequence of LONS with a mortality of 33%-48% in developing countries.[5]

Thus it is important to differentiate a neonate with meningitis from one with septicaemia alone as meningitis is associated with much higher morbidity and mortality. Thus lumbar puncture should be performed in all neonates before starting antibiotics. This study was performed to estimate the incidence of meningitis in neonates with late-onset sepsis.

METHODS

It was a hospital-based observational cross-sectional study performed at Neonatal care unit of Dr. Rajendra Prasad Government Medical College, a tertiary care teaching hospital in northern India. The study was conducted between December 12, 2019 through December 11, 2020 through a self-designed semi structured interview schedule.

All the male and female neonates older than 72 hours of life with signs and symptoms suggestive of sepsis reporting to NCU during the study period and whose parents were willing to participate in study were enrolled. In each newborn admitted with signs/symptoms of sepsis, a detailed antenatal, natal and postnatal history was taken. Sepsis screen was done and blood culture, CSF analysis including CSF culture were sent. Diagnosis of Meningitis was made according to National Neonatal Forum Guidelines.[7]

Statistical analysis

All data was recorded into Microsoft® Excel workbook 2019 and exported into Statistical package for social sciences (SPSS) v21.0 (IBM, USA). Quantitative variables were expressed as mean and standard deviation. Categorical variables were expressed as frequency, percentages and were compared using Chi-square test. P-value <0.05 was considered significant.

Inclusion criteria

All neonates older than 72 hours with signs and symptoms suggestive of sepsis viz: a) Clinical features of sepsis and physical examination demonstrating either circulatory (CVS), respiratory, Central Nervous System (CNS) dysfunction or other features of sepsis. b) CVS signs and symptoms as evident by presence of tachycardia (heart rate more than 160/min) or bradycardia (heart rate less than 100/min) or capillary refill time of more than 3 seconds. c) Respiratory signs and symptoms as evidenced by presence of grunting, flaring, retractions, tachypnoea (respiratory rate more than 60/min), or apnoea lasting more than 20 seconds. d) CNS signs and symptoms as evidenced by the presence of excessive crying, high-pitched cry, bulging fontanelle and history of convulsions. e) Other symptoms/signs of sepsis included were lethargy, reduced feeding ability, no spontaneous movement, temperature more than 38°C, hypothermia, cyanosis, abdominal distension, increased pre-feed aspirates in preterm/LBW neonates, pustular lesions and umbilical sepsis. f) Positive C-reactive protein (CRP>6 mg/l)

Exclusion criteria

Exclusion criteria included neonates less than 72 hours of life, newborn with neural tube defects, very sick neonates with evidence of coagulopathy and parents not willing to participate in study.

RESULTS

A total of 2697 neonates were admitted during study period in nursery unit for various indications. Out of these neonates, 135 neonates were having symptoms/signs suggestive of LONS. A total of 122 eligible neonates were included for study.

Table 1: Demographic profile of enrolled newborns with LONS with and without meningitis (n=37).

Parameters		Meningitis (n=37) Yes (%)	Meningitis (n=85) No (%)	Total n=122 (%)	P value
Sex	Male	30 (63.82)	47 (55.30)	77 (63.11)	0.006
	Female	7 (36.18)	38 (44.70)	45 (36.89)	
Birth weight (kg)	<1.5	5 (13.51)	11 (12.95)	16 (13.11)	0.06
	1.5-2.49	20 (54.05)	28 (32.94)	48 (39.34)	
	>2.5	12 (32.44)	46 (54.11	58 (47.55)	
	Preterm	21 (56.75)	30 (35.30)	51 (58.20)	0.004
	Term	16 (43.25)	55 (64.70)	71 (41.80)	

Table 2: Age at presentation of study group (n=122).

Age of presentation in days	N	%
4-7	61	50.0
8-14	25	20.49
15-21	23	18.85
22-28	13	10.65

Out of total 122 neonates with LONS, 37 (30.32%) had meningitis. The incidence of LONS in low birth weight (LBW) and very low birth weight (VLBW) neonates were 54 (52.45%) and 16 (13.11%) respectively. Overall male /female ratio observed was 1.7:1, whereas in neonates with meningitis it was 4.2:1. 51 (58.20%) of enrolled newborn with LONS were preterms with 21 (56.75%) having coexistent meningitis. The mean age of presentation was 6.2±2.8 days.

Table 3: Presenting features in enrolled newborn with LONS with/without meningitis (N=122).

Parameters	Meningitis		Total (n=122) %	P value
	Yes (n=37) %	No (n=85) %		
Lethargy	29 (78.37)	63 (74.11)	92 (75.40)	0.615
Refusal to feed	24 (64.86)	59 (69.41)	83 (68)	0.557
Fever	21 (56.75)	42 (49.41)	63 (51.63)	0.455
Convulsion	7 (18.91)	11 (12.94)	18 (14.75)	0.409
Respiratory signs (grunt, chest retractions)	9 (24.32)	8 (9.41)	17 (13.93)	0.033
Shock	3 (8.10)	8 (9.41)	11 (9.01)	0.817
Abdominal distension	4 (1.08)	6 (7.05)	10 (8.19)	0.487

Table 4: Blood culture in enrolled newborn with and without meningitis (n=122) and microorganisms isolated from blood and CSF cultures of neonates with LONS (n-45).

Parameters	Meningitis		Total (%) n=122	P value
	Yes n=37 (%)	No n=85 (%)		
Positive	16 (43.24)	29 (34.11)	45 (36.88)	0.002
6=-terile	21 (56.76)	56 (65.89)	77 (63.12)	
Name of micro-organism	**Number (n=45)**		**Percentage (%)**	
Acinetobacter baumannii	16		35.55	
Klebsiella Pneumoniae	11		24.44	
E. coli	7		15.55	
Coagulase negative *Staphylococcus aureus*	5		11.11	
Pseudomonas	4		8.88	
Staphylococcus aureus	2		4.44	
Klebsiella pneumoniae	2		5.4	
Staphylococcus aureus	1		2.7	
Acinetobacter baumannii	1		2.7	

Table 5: Micro-organisms isolated from cerebrospinal fluid cultures of neonates (with table 7 i.e., antibiogram of enrolled newborns with LONS (n=127).

Antibiotics	*Acinetobacter baumannii* (n=16) %	*Klebsiella pneumoniae* (n=11) %	*E. coli* (n=7) %	*Coagulase Negative Staphylococcus aureus* (n=5) %	*Pseudomonas* (n=4) %	*MRSA* (n=2) %
Ampicillin	S (56.25)	R	S (42.78)	R	R	R
Amikacin	S (43.75)	S (63.63)	S (71.42)	R	S (25)	S (50)
Ceftazidime	S (81.25)	S (36.36)	S (57.14)	R (20)	S (75)	N
Ciprofloxacin	S (43.75)	S (51.,4)	S (14.28)	N	S (50)	N
Cefoperazone	S (81.25)	S (54.54)	S (71.4)	R (20)	S (75)	N
Colistin	S (87.5)	S (72.72)	S (85.71)	S (80)	S (100)	N
Clindamycin	N	N	N	S (100)	N	S (100)
Cefotaxim	R	S (18.18)	R	S (60)	R	S (50)

Continued.

Antibiotics	*Acinetobacter baumannii* (n=16) %	*Klebsiella pneumoniae* (n=11) %	*E. coli* (n=7) %	*Coagulase Negative Staphylococcus aureus* (n=5) %	*Pseudomonas* (n=4) %	*MRSA* (n=2) %
Meropenem	S (12.5)	R	R	R	R	R
Piperacillin	S (43.75)	S (63.63)	S (42.85)	S (20)	S (25)	S (50)
Linezolid	N	N	N	S (100)	N	S (100)
Vancomycin	N	N	N	S (100)	N	S (100)

N-not done, R-resistant, S-sensitive. Antibiogram revealed resistance of micro organisms to cefotaxime, ampicillin and meropenem.

Out of 122 neonates with sepsis, 92 (75.40%) had lethargy at admission, 83 (68%) had refusal to feed, 63 (51.63%) had fever and 18 (14.75%) had neonatal seizures. Similarly in neonates with coexisting meningitis, lethargy 29 (78.34%), refusal to feed 24 (64.86%), fever 21 (56.75%) and seizures 7 (18.91%) were observed. Respiratory signs had a significant association with sepsis (p<0.033).

Table 6: CSF Changes in meningitis neonates (n=37).

CSF components	Mean	Range (Min-Max)	
Proteins (mg/dl)	120.68	86	220
Glucose (mg/dl)	51.14	25	88
Cell count (permm$^{3)}$	46.16	11	160

Table 7: Data regarding blood analysis in newborn with LONS (n=122).

Parameters	Mean	Range (min-max)
Total leucocyte count	9563	(2109-27012)
Absolute neutrophil count	2312	(712-8192)
Platelet count	156000	(5200-523000)
C reactive protein	8.41	(6-48)
Serum glucose	132.65	(76-198)

Table 8: Association between meningitis and recovery/mortality outcome.

Parameters	Meningitis		Total (n=122) %
	Yes (%) n=37	No (%) n=85	
Survived	34 (91.9)	75 (90.2)	109 (89.35)
Non-survived	3 (8.1)	10 (11.8)	13 (10.65)

Blood culture was positive in 45 (36.88%) newborns in LONS and 16 (43.24%) newborns with meningitis. P value was statistically significant (0.002). Commonest isolate recovered from blood culture were *Acinetobacter* 35.55%, *Klebsiella* 24.44% followed by *E. coli* 15.55%. Commonest micro organisms isolated from CSF cultures were *Klebsiella* (5.4%), *Staphylococcus aureus* (2.7%) and *Acinetobacter baumani* (2.7%).

CSF analysis showed that mean CSF protein level amongst newborns with meningitis was 120.68 mg/dl with a mean cell count of 46.16 cell/mm3. Mean CSF glucose level was 51.14 mg/dl.

Table 9: Association between meningitis and duration of stay in hospital (n=122).

Parameters	Meningitis		P value
	Yes (n=33)	No (n=85)	
Duration of stay (days)	24.75±13.96	15.76±9.54	0.0001

Overall mean total leucocyte count was 9563 (with range 2109-27012). The mean absolute neutrophil count was 2312 (with range 712-8192). C reactive mean value was 8.41 with range of 6-48. and Mean serum glucose level was 132.65 mg/dl.

Overall mortality rate was 10.65% in LONS and 8.1% in meningitis.

The median duration of stay was 17 days ranging from 0 day to 85 days. Neonates with meningitis had a significantly higher duration of stay in comparison to neonates without meningitis (24.75±13.96 versus 15.76±9.54; p=0.0001).

DISCUSSION

Neonatal sepsis is a common cause of neonatal morbidity and mortality in our country. As clinical symptoms/signs of septicemia and meningitis overlap, it is very difficult to differentiate these two entities in a septic neonate. To miss meningitis in a newborn with LONS may be devastating. Thus it is always better to have a high index of suspicion for meningitis while treating neonates with septicemia. Nearly about 0.3-3% of neonates with sepsis do have meningitis but in case of LONS, the incidence of meningitis has been reported to be higher even upto 30%.[8,9] Our study revealed a slightly higher incidence

(30.33%) of meningitis in LONS as compared to other Indian observational studies done by Kaul et al (22.5%) and Bhagat et al (16%).[10,11] The reason can be attributed to various geographical factors in community acquired infection. However frequency of our results are in agreement with many international studies.[12,13]

Our study revealed male predominance in neonates with LONS and meningitis which is similar with the observations made by Kaul et al.[10] LBW and VLBW accounted for about half (52.45%) of enrolled newborn with sepsis. Out of these, 13.51% newborns of VLBW group and 54.05% of LBW group were having meningitis. Gestation wise 58.20% of enrolled newborns having LONS were preterm and meningitis was observed in 56.75% of these newborns. This high incidence of LONS and meningitis in LBW and preterm has also been reported by Jiang et al, Kaul et al and Bhagat et al.[10,11,14]

The mean age at onset of symptoms was 6.2±2.8 days which is slightly less as compared to a study by Bhagat et al.[11] This can be explained by increase in awareness amongst parents and more institutional deliveries.

The major presenting symptoms/signs observed in present study amongst neonates with LONS were lethargy (75.40%), refusal to feed (68.0%), fever (51.63%) and convulsions (14.75%). Also in newborns with meningitis, lethargy (78.37%), refusal to feed (64.86%), fever (56.75%) were observed. These observations were similarly reported by Hoque et al and Bhagat et al.[11,15] Thus most of symptoms of sepsis and meningitis are same and are co existent in a newborn.

Blood culture was positive in 36.88% septic neonates overall and 43.24% in neonates with meningitis amongst them ($p<0.002$) which is slightly lower than studies done by Bhagat et al and Mehta et al.[11,16] Both of them reported 42.6% and 49.6% positive blood culture in neonates with sepsis respectively. Commonest isolate recovered from blood culture were *Acinetobacter, Klebsiella pnemoniae* followed by *E. coli. Klebsiella* and *Staphlococcus aureus* have been commonly reported micro organisms in blood culture in LONS by Mehta et al and Bhagat et al.[11,16] Also *Klebsiella* and *Acinetobacter* have reported to be very commonly associated with LONS by Kuruvilla et al and Zhu et al.[17,18] Our antibiotic sensitivity panel revealed resistance of these organisms to ampicillin, cefotaxime, meropenem which are most commonly used drugs for LONS.

CSF analysis showed that mean CSF protein level amongst meningitis patients was 120.68 mg/dl with a mean cell count of 46.16 cell/mm3. Mean CSF glucose level was 51.14 mg/dl. CSF culture was positive in 4/37 newborns only. These finding were similar to findings of study done by Abdulla et al (1/13).[19] CSF analysis revealed high protein count and low sugar in CSF were consistent with meningitis.

Overall mean total leucocyte count was 9563 (with range 2109-27012). The mean absolute neutrophil count was 2312 (with range 712-8192). C reactive mean value was 8.41 with range of 6-48. Our study revealed leukocytosisis more frequently seen than leukopenia in LONS. Mean serum glucose level was 132.65 mg/dl. These findings are consistent with studies done by Thermiany et al and Zawar et al who reported about 51% neonated had leucocytosis, 6% had neutropenia and 68 % had neutrophilia.[20,21]

Overall mortality rate in LONS was 10.65% with 8.1% mortality rate in meningitis in our study group which is lower than other studies done by Kaul et al (26.1%), Tisukumara et al (20%) and Bhagat et al (17.6%).[10,11,22] This decrease in mortality rate can be explained by early referral, awareness of parents and improved intensive neonatal care. Neonates with meningitis had a significantly higher duration of stay in comparison to neonates without meningitis (24.75±13.96 versus 15.76±9.54; $p=0.0001$).

Limitations of study

Data regarding feeding status of mothers was not assessed. Anthropometric findings and head to toe findings have not been taken.

CONCLUSION

Our study showed that about one third of newborn admitted with LONS also had coexistent meningitis. Also clinical symptomology of both are same. Most of these admitted were low birth weight and premature. Thus good antenatal care is a must in reducing admission rate with LONS. Also abnormal total leucocyte count, blood sugar levels are associated with sepsis. CSF analysis is a must and it should not be missed as untreated meningitis can be devastating for newborn. Good ante natal care and involvement of obstretician is a must to help in reduction of neonatal sepsis.

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