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ORIGINAL RESEARCH

The early neurological outcome in neonates with septic shock

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ABSTRACT
The clinical manifestations of neonatal sepsis are nonspecific and have varied clinical features. The various manifestation includes decreased acceptance of feed, respiratory distress, pneumonia, apnea, delayed capillary refill time, cold peripheries, mottling, cyanosis, feed intolerance, necrotizing enterocolitis, temperature instability including hypothermia and hyperthermia, hypotonia, seizures, bulging fontanels, disseminated intravascular coagulation (DIC), bleeding manifestation, and prolonged jaundice. This was hospital based prospective observational study undertaken to study the early neurological outcome in term neonates who survived septic shock at the time of discharge and at 3 months of age. A total of 51 term neonates who met the inclusion and exclusion criteria were studied. Among the 51 neonates 2 neonates had developed sclerema, and 2 had convulsion during hospital stay and these neonates had moderate neurological impairment at 3 months of age and this association was statistically significant. Septic shock remains a major challenge in the NICU. Severe neurologic sequelae were not seen however moderate impairment was seen in our study.

Key words: Early neurological outcome, neonates, septic shock

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INTRODUCTION

Sepsis is an important cause of morbidity and mortality among newborn infants. According NNPD (Neonatal perinatal data) the incidence of sepsis is 30 per 1000 live births. Neonatal sepsis can be divided in to early onset or late onset based on onset whether less than 72 hours or more [1].

Sepsis is a major cause of morbidity and death in the neonatal period. The incidence of sepsis is higher in very low birth weight infants, ranging from 1.9% to 21% depending on age of onset of sepsis. Reported fatality rates range from 10% to 18% depending on birth weight and age at onset of sepsis. Mortality rate of 10% to 40%, account for to 7% of all deaths among neonates annually. In neonates, it is generally accepted that septic shock is also associated with high mortality and morbidity, but very few data on its epidemiology are available in the literature [2, 3].

Neonatal sepsis has been defined as the presence of bacteria in sterile body fluids, namely, blood, urine, cerebrospinal, peritoneal, and pleural fluid. It has been classified as early onset sepsis (EOS) and late onset sepsis (LOS) on the basis of time of onset after neonatal birth. EOS is defined when the onset of sepsis is within 72 h of postnatal life and the source of infection is vertical transmission of bacteria from mother to newborn. LOS has been defined as onset of sepsis after 72 h of postnatal life and the source of infection is horizontal transfer of bacteria from health care personal [4]. The importance of defining neonatal sepsis as EOS and LOS is to guide for antibiotic pattern and prognostication. The neonatal population especially very low-birth weight (VLBW) and extremely low-birth weight (ELBW) are more prone to develop neonatal sepsis secondary to immature immune system, prolonged invasive mechanical ventilation and respiratory support, prolonged duration of hospitalization, insertion of central line catheters, endotracheal tubes, and other invasive procedures. The clinical manifestations of neonatal sepsis are nonspecific and have varied clinical features. The various manifestation includes decreased acceptance of feed, respiratory distress, pneumonia, apnea, delayed capillary refill time, cold peripheries, mottling, cyanosis, feed intolerance, necrotizing enterocolitis, temperature instability

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including hypothermia and hyperthermia, hypotonia, seizures, bulging fontanels, disseminated intravascular coagulation (DIC), bleeding manifestation, and prolonged jaundice [5, 6].

METHODOLOGY

TYPE OF STUDY

PROSPECTIVE OBSERVATIONAL STUDY

INCLUSION CRITERIA

1) Neonates with positive sepsis screen with positive blood culture and have signs of shock.

EXCLUSION CRITERIA

1) Neonates with major congenital malformations.
2) Neonates who have died.
3) Neonates with Negative blood culture.
4) Neonates who have lost follow up.

SAMPLE SIZE: Based on the previous studies the proportion of adverse outcome in neonates with septic shock was 52%, so to estimate the true proportion with 95% confidence and 5% error we require minimum of 50 neonates with septic shock.

n = z2 p(1-p) /d2

z = 95% confidence

1.96

p = Proportion of adverse outcome 0.52 (52%)

d = 0.15 (15%).

METHOD OF COLLECTION OF DATA

Neonates with total leukocyte count less than 5000 cells/mm3 or more than 20000 mm3, absolute neutrophil count of less than 1800/mm3, immature to total neutrophil count (I/T ratio of more than 0.2), positive CRP, and micro ESR 15 mm or more in the first hour, presence of any two among these is taken as sepsis screen positive, neonates with positive sepsis screen taken as probable sepsis, neonate with probable sepsis and having hypotension, were included in study and later excluded if blood culture was negative, and among the neonates who developed shock 2d echo was done to rule presence of any congenital heart disease, neonates with congenital heart diseasewere excluded.

Blood culture was taken for all the neonates with probable sepsis using aseptic precautions wiping the Venepuncture site using sterilium betadine sterilium, and 1 ml of blood was taken in sterile syringe and culture was sent in BACT/ALERT culture broths.

RESULTS

Table 1: Association between Duration of Stay and Antibiotics and HNNE (N=51)

Duration (Days)	HNNE		P Value
	41-60 Mean (SD)	>60 Mean (SD)	
Antibiotics	**17.27 (3.61)**	**14.64 (1.82)**	**0.001***
Stay	19.40 (4.30)	`17.64 (4.29)	0.189

In our study subjects with moderate neurological required antibiotics for average 17.27 days, and the subjects with normal neurological outcome at 3 months the average duration of antibiotic usage in them was 14.64 days.

Table 2: Distribution of Study Subjects according to the CSF Parameters (N=51)

Parameter	No.	Percent
CSF Sugar <2/3rd	6	11.8
CSF Gram Stain Positive	2	3.9
CSF Culture Growth	9	17.6

Table 3: Association between CSF Parameters and HNNE (N=51)

Parameter	No.	HNNE 41-60	HNNE >60	P Value
CSF Sugar <2/3	6	6 (100.0)		**<0.001***
Gram Staining Showing Isolation	2	2 (100.0)		**0.025***
Culture Growth	9	8 (88.9)	1 (11.1)	**<0.001***

In our study the csf culture was positive in 9 subjects, gram staining was positive in 2 subjects and hypoglycorrhachia was seen in 6 subjects and these subjects had modearte neurological impairment and this association was statistically significant.

Table 4: Association between HNNE and Clinical Features and Complications

Parameter	No.	HNNE 41-60	HNNE >60	P Value
Hypothermia	16	4 (25.0)	12 (75.0)	0.640
		11 (31.4)	24 (68.6)	
Reduced Urinary Output	2	9 (34.6)	17 (65.4)	0.406

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	6			
		6 (24.0)	19 (76.0)	
Petechial Rash	1	1 (100.0)		0.118
		14 (28.0)	36 (72.0)	
Sclerma	**2**	**2 (100.0)**		**0.020***
		13 (26.5)	36 (73.5)	
Convulsions	**2**	**2 (100.0)**		**0.025***
		13 (26.5)	36 (73.5)	
Feeding Intolerance	4	2 (50.0)	2 (50.0)	0.347
		13 (27.7)	34 (72.3)	
Increased O2 Requirement	18	3 (16.7)	15 (83.3)	0.140
		12 (36.4)	21 (63.6)	
Requirement of Ventilation	12	3 (25.0)	9 (75.0)	0.701
		12 (30.8)	27 (69.2)	
Poor Sucking	1	6 (37.5)	10 (62.5)	0.391
	6	9 (25.7)	26 (74.3)	
Abdomen Distension	6	3 (50.0)	3 (50.0)	0.239
		12 (26.7)	33 (73.3)	
Irritability	17	4 (23.5)	13 (76.5)	0.514
		11 (32.4)	23 (67.6)	
Lethargy	17	7 (41.2)	10 (58.8)	0.192
		8 (23.5)	26 (76.5)	
Hypotonia	10	4 (40.0)	6 (60.0)	0.412
		11 (26.8)	30 (73.2)	

In our study sclerema was seen in 2 subjects and convulsion was seen in 2 subjects and al subjects who had sclerema and convulsion during hospital stay had moderate neurological impairment 3 months followup.

Table 5: Distribution of Study Subjects according to the Lab Parameters (N=51)

Lab Parameters	No.	Percent
Leucocytosis	24	47.1
Leukopenia	27	52.9
Thrombocytopenia	11	21.6
Elevated CRP	51	100.0
Hyperglycaemia	6	11.8
Hypoglycaemia	12	23.5

Table 6: Association between Lab Parameters and HINE (N=51)

Lab Parameters	No.	HINE 41-60	HINE >60	P Value
Leucocytosis	24	8 (33.3)	16 (66.7)	0.562
		7 (25.9)	20 (74.2)	
Leukopenia	27	7 (25.8)	20 (74.2)	0.562
		8 (33.3)	16 (66.7)	
Thrombocytopenia	11	4 (36.4)	7 (63.6)	0.568
		11 (27.5)	29 (72.5)	
Hyperglycaemia	6	2 (33.3)	4 (66.7)	0.906
		13 (31.0)	29 (69.0)	
Hypoglycaemia	12	2 (16.7)	10 (83.3)	0.268
		13 (33.3)	26 (66.7)	

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In our study leucocytosis was seen in 24 subjects, leucopenia was seen in 27 subjects, and 11 had thrombocytopenia, 6 had hyperglycemia, 12 had hypoglycemia.

Table 7: Distribution of Study Subjects according to the Number of Boluses (N=51)

Number of Boluses	No.	Percent
2	4	7.8
3	44	86.3
4	2	3.9
5	1	2.0

Table 8: Association between Number of Boluses and HINE (N=51)

Number	HINE	
	41-60 n (%)	>60 n (%)
2		4 (100.0)
3	15 (34.1)	29 (65.9)
4		2 (100.0)
5		1 (100.0)
Chi-Square Test, P Value = 0.337, Not Significant		

Table 9: Distribution of Study Subjects according to the Inotropes (N=51)

Inotropes	No.	Percent
No	2	3.9
Yes	49	96.1
<24 hrs	30	62.7
>24 hrs	19	37.3

Table 10: Association between Inotropes and HINE (N=51)

Inotropes	HINE	
	41-60 n (%)	>60 n (%)
Yes	14 (28.6)	35 (71.4)
No	1 (50.0)	1 (50.0)
Chi-Square Test, P Value = 0.514, Not Significant		

Table 11: Association between Duration of Inotropes used and HINE (N=51)

Duration	HINE	
	41-60 n (%)	>60 n (%)
<24 hrs	8 (25.0)	24 (75.0)
>24 hrs	7 (36.8)	12 (63.2)
Chi-Square Test, P Value = 0.370, Not Significant		

In our study inotropes were used in 49 subjects and the duration inotropesusage was less than 24 hours in 30 subjects and was more than 24 hours in 19 subjects, 8 subjects who required inotropes for less than 24 hours had moderate neurological impairment,7 subject who required inotropes for more than 24 hours had moderate neurological impairment.

Table 12: Distribution of Study Subjects according to the Duration of Antibiotics (N=51)

Duration of Antibiotics	No.	Percent
14	39	76.5
18	3	3.9
21	9	17.6

Table 13: Distribution of Study Subjects according to the Duration of Hospital Stay (N=51)

Duration (Days)	No.	Percent
11-14	7	13.7
15-21	30	58.8

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22-28	14	27.5
Mean (SD)	18.16 (4.33)	
Range	11-28	

DISCUSSION

The Hammersmith Neonatal/infant Neurological Examination (HI/NNE) is a standardized, structured assessment of the newborn first published in 1981 and revised in 1998. It is a predominantly neurological assessment, which has been widely used in clinical practice to evaluate the maturity and integrity of the nervous system of extremely, very, and late preterm and term-born infants. The HINNE has good sensitivity and high predictive value of adverse neurological outcome in high-risk populations under 5 months. The HINNE scores of < 52 at 3 months 96% predictive of cerebral palsy [7].

In our study 26 were males and 25 were females of these 7(26.9) of males and 8 (32%) of females had moderate neurological impairment, in a study conducted by Glinianaia the adverse neurological outcome was significantly higher in males (2.91 per 1000) than females (1.99 per 1000): RR 1.46 (95% CI 1.27 to 1.68.

In our study the average HINE scores were 59.6 in contrast to study conducted by Romeo *et al*. the average HINE scores were 65 between 3 and 6 months. Cosistent with a study conducted by Harriet L.S *et al*. in ghana proving that the average lower HINE scores in infants of developing country compared to caucasian infants. In our study 35 % of low-birth-weight neonates against the 26% normal weight neoantes had moderate neurodevelopmental outcomes [8].

In our study 27(52%) mothers had complicate pregnancies (PIH, anemia, gdm, hypothyroidsim) of these 8 (53%) infants had moderate neurological impairment, similary in a study conducted by Lilienfeld *et al.* of infants who had adverse neurodevelopmental outcome, 38% of the mothers had complicated pregnancies.

In our study 12 neonates had hypoglycemic episodes two manifesting as convulsions of these 2 neonates had moderate neurodevelopmental impairment at 3months, in a study by Lucas, A *et al*. Plasma glucose concentrations below 2-6 mmol/l were associated with reductions in Bayley motor and mental development scores at 18 months, even after adjustment for confounding factors known to influence development.

In our study hypoglycorrachia was found in 6 neonates and all of them had moderate neurological imapirmen, in a study conducted by Wen-Hao Yu *et al*. in the 25 infants with hypoglycorrhachia who were for folloed w-up, 4 (16%) had abnormal outcomes, of which 3 (12%) had the history of mixed-type developmental delay [9].

In our study 11 (21.5%) cases had thrombocytopenia of these 4 (36%) had adverse neurological outcome, Thrombocytopenia and disseminated intravascular coagulation have been shown to be predictors of adverse outcome in adult septic shock (1, 25). Similarly, in a study by Kermorvant-Duchemin *et al*. thrombocytopenia it was concluded that could be associated with an increased risk of adverse outcome during septic shock in neonates, even if this factor did not remain significant in the multivariate analysis [10].

CONCLUSION

Septic shock remains a major challenge in the NICU. Severe neurologic sequelae were not seen however moderate impairment was seen in our study. We have shown that the outcome of septic shock in neonates is mainly determined by weight, age of onset of sepsis, presence of meningitis, antenatal risk factors like anemia, PIH, hypothyroidism, type of infecting organism, presence of convulsions and also on the duration antibiotics usage, our data also showed that presence of a Gram-negative infection has a major impact on outcome. Efforts toward furthering our understanding the pathophysiology of neonatal septic shock and its early recognition and reversal should have a measurable effect on outcome.

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