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Study of Clinical and Outcome Profile of Neonatal Sepsis with Thrombocytopenia Patients Admitted at Tertiary health care Centre Nanded

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ABSTRACT

Background: Thrombocytopenia is a frequent problem in neonatal sepsis and is among the most predictive, independent risk factors for sepsis-associated mortality. The present study was undertaken to correlate neonatal sepsis and thrombocytopenia in terms of severity, clinical course, organism specificity and outcome. **Method:** Total 384 neonates age <28 days with sepsis and thrombocytopenia were studied and analyzed with their clinical profile, symptoms, lab findings and outcomes. **Results:** Male babies (55.86%), age <72 hrs (80.35%), preterm (68.70%) and LBW babies (85.58%) were more prone to sepsis. Maternal fever (67.44%), foul smelling liquor (53.79%) and PROM >18 hrs (66.74%) make babies more prone to neonatal sepsis. The Commonest clinical features were not accepting feed (69.95%), lethargy (67.85%) and breathing difficulty (79.04%). Early onset sepsis (82.54%) and probable sepsis (40.26%) were more common and associated with preterm and LBW babies. Leucocytosis was seen in 64.57%, thrombocytopenia moderate degree 45.67% and severe degree 34.65%, MPV >12 69.11%, ANC <1800 47.50%, micro ESR >15 mm 72.16% and CRP positivity 28.60%. Severe degree thrombocytopenia (<50000) was more common with PROM >18 hrs (83.02%), maternal fever (83.09%) and gram-negative organism(61.29%). Leucopenia (<4000) was more common with maternal fever (75.79%), proven sepsis (43.16%) and gram-negative organism (70.31%). Severe degree thrombocytopenia (61.29%), leucopenia (70.31%) and mortality (64.51%) were more commonly associated with gram-negative organism. Outcome was bad with severe degree of thrombocytopenia (62.32%), leucopenia (73.91%), and gram-negative organism (64.51%). **Conclusion:** Proper antenatal mother care, hygiene and early evaluation for illness can prevent early onset of sepsis in neonates. Severity of degree of thrombocytopenia directly proportional to the worst outcome.

KEYWORDS: Thrombocytopenia, Neonates, Sepsis, Organism, Leucocytosis, Leukopenia, Severity

INTRODUCTION

Neonatal sepsis continues to be the major reason of substantial morbidity and mortality in neonates worldwide. It is amongst one of the three primary causes of about 2.7 million deaths every year [1]. The infection can be contracted from the mother through trans-placental route, ascending infection, during an infected birth canal passed or exposure to infected blood at delivery [2]. It is responsible for approximately 30-50% of the total neonatal deaths in developing countries [3]. As per the data from National Neonatal Perinatal Database 2002-03, the incidence of neonatal sepsis in India was 30/1000 live births and sepsis remains one of the commonest causes of neonatal mortality contributing to 19% of all neonatal deaths [4].

Many factors, which are contributing to the susceptibility of the neonate to sepsis, can also influence the incidence of neonatal sepsis. Also, from nursery-to-nursery incidence varies depending on conditions predisposing neonates to infection [5]. Neonatal sepsis is most common in the low birth weight and premature infants, in whom the clinical presentation can be subtle and nonspecific. Neonates may present with lethargy, vomiting, breathing difficulty, not accepting to feed, convulsion etc. It may be secondary

to septicemia, pneumonia, meningitis, arthritis, metabolic disorder. Septicemia was the most common clinical category, with an incidence of 24 per 1000 live births [6].

Neonatal thrombocytopenia is a frequent problem in neonatal age group. A major cause of thrombocytopenia in newborns is sepsis and thrombocytopenia can become very serious within start infection by quickly drop count, reaching the lowest platelet count within 24-48 hrs [7]. Thrombocytopenia has been used as an early marker of sepsis but as a nonspecific marker [8]. However, thrombocytopenia in neonatal sepsis increases the mortality risk almost four times, with a further six times the mortality in gram-negative sepsis [9]. The death rate was higher in sepsis with thrombocytopenia. The importance of the association between thrombocytopenia and sepsis was emphasized by identifying thrombocytopenia as one of the foremost predictive, independent risk factors for sepsis-associated mortality in very low-birth weight neonates [10]. Moreover, the pathogenesis of thrombocytopenia in neonatal sepsis in not completely understood. It has been suggested that neonatal sepsis endothelial damage activates reticulo-endothelial removal of platelets causing thrombocytopenia ultimately. Hence, the present study was undertaken to correlate neonatal sepsis and thrombocytopenia in terms of severity, clinical course, organism specificity and outcome.

MATERIAL AND METHODS

After obtaining Institutional Ethical Committee approval and written informed consent from parents/guardian, this hospital based observational study was conducted in the Department of Pediatrics, at Tertiary Care Centre, Nanded during a period from April 2020 to September 2021. A total 384 neonates, age 0-28 days with clinical suspicious of septicemia admitted in NICU during the study period were included. Neonatal sepsis with coagulation disorder, thrombocytopenia cause other than neonatal sepsis, mother with history of ITP, SLE, other autoimmune disorders, on medication during pregnancy (sulphonamides, quinine / quinidine) (thiazides, tolbutamide, vancomycin, hydralazine, and heparin), neonate with history of bleeding disorder in family, trisomy's, Turner/Noonan syndrome, TAR syndrome and conditions associated with sequestration of platelets were excluded from the study.

All newborn babies admitted in NICU screened fort depressed activity, sclerema, mottling and cyanosis and all these clinically suspected cases of neonatal sepsis subjected to detail history, clinical examination, and laboratory evaluation (Laboratory Test: CBC, CRP, Micro ESR, Blood Culture, Urine Culture, CSF, and other test when required). All relevant information were recorded in Case record form (CRF). Outcome were expressed as discharge, failure of treatment, need of change in antibiotics and death.

RESULTS

Total 384 neonates were enrolled in the study, of them 44.14% were female and 55.86% male. The mean gestational age (GA) was 34.980 weeks, ranged from 27to 39.6 weeks. However, the mean age of neonates was 67.68 hrs with the lowest age 1.15 hrs and highest age 648 hrs (27 day). Low birth weight (LBW) (<2.5 KG) neonates with 85.58% (323) had neonatal sepsis compared to 14.42% (61) had normal birth weight (NBW). Mean birth weight was 1.762±0.571 kg, ranged from 0.8 to 3.5 kg. Caesarean section was the most common mode of delivery (71.98%). Majority of neonates i.e., 51.48% were delivered at our hospital (inborn) as shown in Table 1 .

Characteristics		No.	%
Sex	Male	205	55.86
	Female	179	44.14
Gestational age	Preterm	260	68.70
	Term	124	31.30
Age on admission	DOL <72 hrs	313	80.35
	DOL >72 hrs	71	19.65
Birth weight	ELBW (<1kg)	27	6.86
	VLBW (<1.5 kg)	154	39.82
	LBW (<2.5 kg)	142	38.85
	NBW (≥2.5 kg)	61	14.42
Mode of delivery	Caesarean section	273	71.98
	Normal vaginal	111	28.02
Place of delivery	Home	04	1.46
	Inborn	208	51.48
	Outborn	172	47.05

Table 1: Neonatal characteristics

Maternal factors like maternal fever (67.44%), foul smelling liquor (53.79%) and PROM > 18 hrs (66.74%) makes babies more prone to neonatal sepsis, especially early onset sepsis.

The clinical manifestations are non-specific and vague, not accepting feed (69.95%), lethargy (67.85%), hypothermia (45.03%), breathing difficulty (79.04%), grunting (48.12%), CRT> 3sec (43.45%) and cyanosis (31.64%) were more common symptoms and signs while convulsion (7.8%) less commonly seen.

Out of 384 neonates possible, probable and proven sepsis were seen in 36.68% (132), 40.26% (165) and 23.06% (87) of neonates respectively. 82.54% (322) neonates were diagnosed as early onset sepsis (EOS) and 17.46% (62) as late

onset sepsis (LOS).

Lab investigation play important role in early diagnosis and management of neonatal sepsis. In present study, leucocytosis was seen in 64.37%, thrombocytopenia moderate degree 45.67% and severe degree 34.65%, MPV >12 in 69.11%, ANC <1800 in 47.50%, micro ESR >15 mm 72.16% and CRP positive in only 28.60%, (Table 2). Out of peripheral smear of 384 neonates, 1.22% (10) neonates were showing band cells and 7.58% (36) toxic granules. Table 2

Parameters		No.	%
TLC Count (per cmm)	<4000	95	21.48
	4000-11500	62	14.16
	>11500	227	64.37
Degree of thrombocytopenia (per cmm)	Severe (<50000)	136	34.65
	Moderate (50000-100000)	179	45.67
	Mild (>100000)	69	19.68
MPV (fl)	<12	111	30.89
	>12	273	69.11
ANC (Absolute neutrophil count)	<1800	182	47.40
	>1800	202	52.60

Table 2: Laboratory investigation

Out of 384 neonates, 148 (38.54%) neonates culture reports were shown organism growth, and of which 73 (49.32%) neonates were shows gram positive organism growth and 75 (50.67%) shown gram negative organism growth. However, out of 148 neonates,106 (29.11) neonates show growth on blood culture, 35 (10.56%) neonates show growth on CSF and 7 (1.59%) neonates show growth on urine culture.

Severe degree thrombocytopenia (<50000) was more common with PROM >18 hrs (83.02%), maternal fever (83.09%) and with gram negative organisms (61.29%). Whereas 20% (249) neonates had MPV >12 ft with moderate to severe degree thrombocytopenia. The association of duration of PROM (p=0.002744), MPV (fl) (P<0.00001) and organism growth (p=0.028302) with degree of thrombocytopenia was statistically significant Table 3.

The association between maternal risk factors and incidence of EOS and LOS in neonates was statistically not significant (P=0.2032) while the association of gestational age (P<0.003078) and birth weight (P=0.000117) with the incidence of EOS and LOS in neonates was statistically significant.Table 4

Leukopenia (<4000) was more common with maternal fever (75.79%), proven sepsis (43.16%) and gram-negative organism (70.31%). Association of type of sepsis (P<0.00001) and organism (P=0.000141) with degree of thrombocytopenia was statistically significant.

Outcome was worst in neonates with grunting (75.36%), CRT>3 sec (63.77%), CRP positive 75.36%), severe degree thrombocytopenia (62.32%), leukopenia (73.91%), proven sepsis (55.07%) and gram-negative growth (64.51%) which was statistically significant, (P value < 0.0001 as shown in Table 5 .

DISCUSSION

In the present study, male was predominantly involved in neonatal sepsis as compared to female with male to female ratio of 1.14: 1 which is comparable with the study done by Hisamuddin E et al. [11]. Bias for male sex, place of study, sample including other factors may be responsible for increased number of male cases in these studies. Preterm neonates, prematurity (lowest GA), lower age group and low birth weight babies were predominately involved in neonatal sepsis which is consistent with the study by Barbara J Stoll [12]. Caesarean section (71.98%) and hospital stay (51.48%) were the risk factors causing neonatal sepsis. This may be bias as this study done at a tertiary care hospital where most mothers were high risk pregnancies and referred from outside.

Maternal factors like maternal fever (67.44%), foul smelling liquor (53.79%) and PROM > 18 hrs (66.74%) makes babies more prone to neonatal sepsis, especially early onset sepsis. These findings are consistent with the study done by Gupta S et al [13] and Bayih WA et al [14]. Though the clinical manifestations were non-specific and vague, not accepting feed (69.95%), lethargy (67.85%), breathing difficulty (79.04%) and grunting (48.12%) were more common symptoms and signs while convulsion (7.8%) less commonly seen. All these findings are correlated with the other studies [15, 16].

Early onset sepsis (82.54%) and probable sepsis (40.26%) were more common. It may be due to preterm, LBW babies with maternal risk factors. The association between maternal risk factors and incidence of EOS and LOS in neonates was statistically not significant (P=0.2032) while the association of gestational age (P<0.003078) and birth weight (P=0.000117) with the incidence of EOS and LOS was statistically significant. This result is consistent with the study conducted by El-Amir et al. [17]. ANC <1800 more commonly associated with probable sepsis 92 (55.76%). The association between ANC and possible, probable and proven sepsis was statistically significant (P=0.000137). Probable sepsis shows sensitivity 55.76%, specificity 58.90%, PPV 50.55% and NPV 63.86% while in proven sepsis sensitivity 54.02%, specificity 54.55%, PPV 25.82% and NPV 80.20%. Similar results are reported in Arif SA et al. study [18].

Lab investigation play important role in early diagnosis and management of neonatal sepsis. Leucocytosis was seen

Risk factor		Thrombocytopenia*		
		Severe No. (%)	Moderate No. (%)	Mild No. (%)
PROM duration	Less (<18 Hr)	18 (16.98)	32 (33.33)	14 (43.75)
	More (>18 Hr)	88 (83.02)	64 (66.67)	18 (56.25)
MPV (fl)	<12	13 (9.56)	53 (29.61)	45 (65.22)
	>12	123 (90.44)	126 (70.39)	24 (34.78)
Organism	Gram +VE	24 (38.70)	49 (56.97)	
	Gram -VE	38 (61.29)	37 (43.02)	

*Severe - 50000, Moderate - 50000-100000, Mild - > 100000.

Table 3: Correlation of PROM duration, MPV (fl) and organism growth with degree of thrombocytopenia

Factors		EOS No. (%)	LOS No. (%)
Maternal Risk Factors	Maternal Fever	217 (85.77)	36 (14.23)
	Foul Smelling Liquor	142 (83.53)	28 (16.47)
	PROM <18 HRS	145 (81.46)	33 (18.54)
	PROM >18 HRS	177 (85.92)	29 (14.08)
Gestational Age	Preterm	228 (70.81)	32 (51.61)
	Term	94 (29.19)	30 (48.39)
Birth Weight	LBW (<2.5KG)	281 (87.00)	42 (13.00)
	NBW	41 (67.21)	20 (32.79)

Table 4: Association of maternal risk factors and neonatal factors with the incidence of EOS and LOS in neonates

in 64.57%, thrombocytopenia moderate degree 45.67% and severe degree 34.65%, MPV >12 IN 69.11%, ANC 15 mm 72.16% and CRP positive in only 28.60%. Association between possible, probable, and proven sepsis and leukopenia in neonates was statistically significant with P< 0.00001. However, the association between gram positive and negative organisms and TLC count in neonates was statistically significant with P value =0.000141. These findings are in accordance with the study conducted by Gowda H et al. [19]. In the present study, 34.65% (136) neonates had severe degree of thrombocytopenia, 45.67% (179) had moderate degree of thrombocytopenia and 19.68% (69) had mild degree of thrombocytopenia. Mean platelet count was 72368.612. The association of duration of PROM, gram positive and negative organisms, MPV with degree of thrombocytopenia was statistically significant which is comparable with the Parmar D et al. study [20].

Fluid culture including blood culture, CSF culture and urine culture done in present study. Shows 48 neonates (38.54%) culture positive of these gram-negative organisms were 75 (50.67%) while gram positive was 73 (49.32%). Similar findings are reported in other studies [21, 22]. Blood culture is gold standard investigation in diagnosis of neonatal sepsis. In current study out of 384 neonates 106 neonates (29.11%) blood culture came positive. In this gram-positive organism (15.26%) were more common than gram negative organism (13.85%). In gram positive organism, most common growth MRSA 17 (4.58%) followed by streptococcus agalactiae 16 (4.21%), pseudomonas aeruginosa 9 (2.05%), staphylococcus aureus 5 (1.67%) and listeria monocytogenes 3 (0.75%). In gram negative bacteria, klebsiella pneumoniae 4.70% (17) was more common followed by Cons 4.05% (15) Escherichia coli 13 (3.56%), Enterobacter Citrobacter 6 (1.95%), and Acinetobacter species 5 (1.58%). These findings are comparable with the previous studies [23, 24]. CSF culture was done on 88 (24.48%) neonates of which 35 (10.56%) neonates shows growth. Gram negative bacterial growth 18 (5.64%) slightly more than gram positive bacterial growth 17 (4.92%). In gram negative growth more common growth was pseudomonas aeruginosa 11 (3.29%) followed by Escherichia coli 6 (2.00%) Acinetobacter species 1 (0.35%) while in gram positive bacteria more common growth MRSA 7 (2.00%) fol-

Parameters		Death No. (%)	Discharge No. (%)	P value
Grunting	No	17 (24.64)	186 (59.05)	< 0.001
	Yes	52 (75.36)	129 (40.95)	
CRT	More (>3ESC)	44 (63.77)	129 (40.95)	0.001
	Normal (<3SEC)	25 (36.23)	186 (59.05)	
Degree of thrombocytopenia	<50000	43 (62.32)	93 (29.52)	<0.001
	50000-100000	19 (27.54)	160 (50.79)	
	100000-150000	7 (10.14)	62 (19.68)	
TLC count	<4000	51 (73.91)	44 (13.97)	<0.001
	4000-11500	4 (5.80)	58 (18.41)	
	>11500	14 (20.29)	213 (67.62)	
CRP	Negative	17 (24.64)	244 (77.46)	<0.001
	Positive	52 (75.36)	71 (22.54)	
Sepsis Types	Possible	8 (11.59)	124 (39.37)	<0.001
	Probable	23 (33.33)	142 (45.08)	
	Proven	38 (55.07)	49 (15.56)	
Organism	Gram + VE	22 (35.48)	51 (59.30)	0.004
	Gram –VE	40 (64.51)	35 (40.69)	

Table 5: Association between study parameters and outcome in neonates

lowed by listeria monocytogenes 5 (0.90%), streptococcus agalactiae 3 (1.36%) and cons 2 (0.66%). These findings are in consisting with Rahman S et al study [25]. In urine culture all growth i.e., 7 (1.59%) were gram negative with most common growth was Escherichia coli 4 (0.99%) followed by klebsiella pneumoniae 2 (0.46%) and pseudomonas aeruginosa 1 (0.14%). The above result is consistent with Behmadi H et al. study [26].

Out of 384 neonates, 69 (17.82%) were death while 315 (82.18%) were discharged. Outcome was worst in neonates with grunting (75.36%), CRT>3 sec (63.77%), CRP positive 75.36%), severe degree thrombocytopenia (62.32%), leukopenia (73.91%), proven sepsis (55.07%) and gram-negative growth (64.51%). Severe degree thrombocytopenia increases6-fold risk of mortality compared to mild degree thrombocytopenia. Various studies [27, 28] shows leukopenia associated with more neonatal mortality. In current study also leukopenia associated with increased neonatal mortality. Association of grunting, CRT, CRP, degree of thrombocytopenia, TLC count, type of sepsis, gram positive and negative organisms with outcome was statistically significant with P value <0.0001 which is comparable with the earlier studies [29, 30].

CONCLUSION

Proper antenatal mother care, hygiene and early evaluation for illness can prevent early onset of sepsis in neonates. Severity of degree of thrombocytopenia directly proportional to the worst outcome. Early detection of symptoms and signs and early onset of treatment may improve outcomes.

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