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Incidence of Thrombocytopenia and Changes in Various Platelet Parameters in Neonates with Blood Culture Positive Sepsis

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Abstract

Introduction

The aim of this study was to assess the incidence of thrombocytopenia and changes in various platelet parameters in neonates with blood culture positive sepsis.

Materials and Methods

This was prospective study conducted over a period of one year in Neonatal Intensive Care Unit of Deen Dayal Upadhyay Hospital (DDUH), in Delhi, North India. All babies who were admitted during the study period were evaluated prospectively for evidence of sepsis.

Results

Among 560 neonates, 80/560 (14.28%) had culture positive sepsis. Gram- positive sepsis occurred in 21/80 (26.25%), gram- negative sepsis in 54/80 (67.5%), and fungal sepsis in 5/80 (6.25%). Incidence of thrombocytopenia in gram- negative sepsis was (35/54) 64.81%, in gram- positive sepsis (15/21) 71.41%, and in fungal sepsis was (3/5) 60%. Mean platelet count at the onset of sepsis in all the patients was 123287.5± 49428.68. The mean duration of thrombocytopenia in gram- positive sepsis was 4.66 ±2.6 days, in gram- negative sepsis 4.39 ± 2.22 days and in fungal sepsis 5.2±1.3 days. Mean platelet volume (MPV) at the time of onset of sepsis was high in gram- positive sepsis than in gram- negative sepsis (11.57±0.88 Vs 11.29 ± 0.76). The MPV of thrombocytopenic neonates was significantly higher than of non-thrombocytopenic neonates (P< 0.01).

Conclusion

In this study, incidence of culture positive sepsis in neonates was 14.28%; thrombocytopenia was present in 66.25% of neonates with sepsis. Thrombocytopenia had 66.25% sensitivity and 87% specificity in predicting sepsis among culture positive patients.

Key Words: Culture positive sepsis, Gram- negative sepsis, Gram- positive sepsis, Thrombocytopenia.

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Introduction

Throughout the world, 1.6 million neonates die even year from infections(1). Although most of these deaths are in developing countries, where neonatal mortality from sepsis may be as high as 60% (2), the incidence of infection in developed world is also very high at 2.2 to 8.6 per 1000 live births(3). Neonatal deaths account for half of deaths of children less than 5 years of age and two thirds of infant deaths (4). The Millennium Development Goal-4 includes a reduction of childhood mortality by two-thirds between 1995 and 2015 and a major component is reduction of neonatal mortality (5). Immunological defence mechanisms in neonates are immature and/or deficient, which predispose them to serious and opportunistic infection (6). Signs of sepsis in neonates are non-specific, subtle and inconspicuous but the clinical course may be alarmingly fulminant leading to septic shock Disseminated Intravascular Coagulation (DIC) and death within hours of onset (7). Thrombocytopenia affects up to 35% of all patients admitted in neonatal intensive care unit (8). The causes of thrombocytopenia in neonates are very diverse and include immune and non-immune disorders. Sepsis and Necrotizing Enterocolitis (NEC) are among the most common cause of severe thrombocytopenia in NICU (8). The etiology of thrombocytopenia in neonates can be categorized into several broad categories including increased platelet destruction, decreased platelet production, mixed etiology and unknown cause. Also, mechanism of thrombocytopenia in septic neonates is multifactorial (9).

Platelets interact with invading micro-organisms and are critically linked to pro inflammatory innate immune response. Platelets express Toll Like Receptors (TLR) especially Toll-like receptor 4 is (TLR-4) and this expression significantly modulates Lipopolysaccharides (LPS), induced thrombocytopenia and TNF-alpha Production in vivo (10). This explains the clinical observation of severe thrombocytopenia associated with sepsis (10). Thus platelets may play an important role in host defence by acting as circulating pathogen sentinels to initially alert cells of innate immune system. Most studies indicate that with onset of systemic bacterial infection the first complete blood count change is leukocyte shift to left. By the time sepsis is diagnosed, 25% neonates have thrombocytopenia and by 36-48 hours later majority of neonates develop thrombocytopenia (11). Fungal sepsis is associated with greater degree of thrombocytopenia than is seen with either gram positive or gram negative organisms and outcome in these neonates is poor (12).

There is paucity of literature regarding the organism specific platelet response in neonates with sepsis. Hence we decided to study the incidence of thrombocytopenia in neonates with blood culture positive sepsis and also the effect of different organisms on various platelet parameters in neonates.

Materials and Methods

The study was conducted over a period from December 2009 to November 2010 in neonatal intensive care unit of Deen Dayal Upadhyay Hospital (DDUH), a tertiary care hospital in New Delhi, North of India. This study was approved by Ethics Committee of Deen Dayal Upadhyay hospital.

All babies who were admitted during this period were evaluated prospectively for evidence of sepsis. Sepsis was defined according to international sepsis definition conference (13) as "Clinical syndrome characterized by presence of both infection and systemic inflammatory response syndrome". Systemic inflammatory

response syndrome in case of neonates is defined as two or more of the following:

1. Tachypnea (more than 60 breaths per minute).
2. Temperature instability < 36°C or more than 37.9°C;
3. Capillary refill time more than 3 seconds;
4. White blood cell count < 5000/µl or more than 34000/µl;
5. C-reactive protein (CRP) greater than 10 mg/dl IL-6 more than 70 pg/ml;
6. Procalcitonin more than 8.1 mg/dl or more than 2 Standard deviation (SD) above normal values.

Sepsis is defined as one or more systemic inflammatory response syndrome criteria with signs of infection (14). Only first episode of sepsis in a patient was included to avoid any confounding effect of earlier sepsis on platelets. Sepsis evaluation was based on clinical signs and symptoms and rapid screen tests for sepsis, including changes in complete blood counts and positive blood culture. In case of Coagulase-negative staphylococci (CoNS) sepsis repeat blood culture was taken to rule out contamination. Babies with congenital malformations, and chromosomal anomalies were excluded. Near term and term babies with weight appropriate for gestation ages were included in this study.

Blood for culture (1 ml of blood) and complete blood counts was obtained by means of venipuncture. Platelet count and MPV determinations were carried out on coulter counter. Initial platelet count used for the study was the one obtained either with the blood culture or the one closest to the time the positive blood culture was drawn. Nosocomial sepsis was defined as an infection that occurs 48 hours after admission in a baby who did not have any evidence of infection on admission characterized by growth of a pathogen not related to infection at another side from 1 blood culture in presence of clinical features of infection. Early onset sepsis was defined as infection during the 1st 72 hours of life and late onset sepsis as infection occurring after 72 hours of life. The platelet parameters studied include total platelet count, incidence of thrombocytopenia, duration of thrombocytopenia, platelet nadir, change in platelet count and MPV. Thrombocytopenia was defined as platelet count less than 150 x $l0^3$/µl. Incidence of thrombocytopenia was the number of sepsis episodes with a platelet count less than 150 x $l0^3$/µl. The duration of thrombocytopenia was the number of continuous days during which platelet count remained below 150 x $l0^3$/µl. Platelet nadir was the lowest platelet count obtained for that neonate starting from the period in which blood culture was drawn. Outcome in the form of mortality and multiorgan failure was analyzed. Mortality was defined as death before discharge. Infants discharged to home were considered survivors. The data was analysed using SPSS software, version 16 and P- value <0.05 was significant.

Results

During the study period, out of total 2,240 admissions sepsis was diagnosed in 560 (25%) neonates. Among these 560 neonates 80 near term and term neonates with weight appropriate for gestational age had at least one episode of positive blood culture. Other 480 neonates had clinical features as well as biochemical evidences of sepsis, but there blood cultures were persistently sterile. Out of 80 blood culture positive neonates 73 were term neonates and 7 were near term. Among these males were 43 (53.75%) and females were 37 (46.25%). Gram positive sepsis occurred in 21/80 (26.25%), gram negative sepsis occurred in 54/80 (67.5%), and fungal sepsis was diagnosed in 5/80 (6.25%).

Among gram negative organisms the most common pathogen was Klebsiella pneumonia seen in 32/80 (40%). The second common organism isolated was Acinetobacter in 12/80 (15%), followed by Escherichia Coli in 6/80 (7.5%) and Pseudomonas in 4/80 (5%). Among gram positive organisms the most common pathogen was Staphylococcus aureus in 13/80 (16.25%). Enterococcus was seen in 6/80 (7.5%) and Coagulase negative Staphylococcus in 2/80 (2.5%) patients. The most common fungal isolate was Candida albicans (Table.1).

Table 1: Organisms Causing Neonatal Sepsis

Variables	Organism	Number	Percent
Gram- Negative (67.5%)	Klebsiella	32	40
	Acinetobacter	12	15
	E coli	6	7.5
	Pseudomonas	4	5
Gram- Positive (26.25%)	Staph Aureus	13	16.2
	Enterococcus	6	7.5
	Coagulase-negative staphylococci(CoNS)	2	2.5
Yeast (6.25%)	5	12	6.2
Total	80	280	100

The demographic details of the septic neonates are shown in Table.2. The average gestational age of all babies was 37.84 ± 1.68 weeks. Average age at admission in all neonates was 92.89±24.57 hours. In gram negative sepsis it was 88.70±23.13 hours, in gram positive sepsis it was 93.10±19.62 hours. Average age at onset of fungal sepsis was 137.20±14.80. The difference was statistically significant ($p< 0.01$). Average duration of stay in hospital in all patients was 15.96±5.24 days. The average mortality in all septic neonates was 14/80 (17.5%). The difference between the groups was statistically insignificant (P=.961).

Table 2: Demographic Data of Septic Neonates

Variables	All patients	Geram-negative	Gram-positive	Fungal	P value
Gestation(weeks)	37.83±1.68	38.09±1.59	37.33±1.93	37.20±1.09	.148
Birth weight (kgs)	2.49±0.23	2.49±0.26	2.52±0.16	2.41±0.15	.595
Caesarean section	21(26.25%)	14(17.5%)	5(6.3%)	2(2.5%)	.532
Age(in hour)	92.88±24.57	88.70±23.13	93.10±19.62	137.20±14.80	<.01
Stay in hospital(days)	15.96±5.15	16.39±5.15	15.14±5.56	14.80±5.40	.579
Mortality	14(17.5%)	9(11.3%)	4(5.0%)	1(1.3%)	.961

Results showed, thrombocytopenia (defined as < 150 x 10^3/µl) was seen in 53/80 (66.25%) of babies with blood culture positive sepsis. Among these babies 28/53 (52.8%) were having mild thrombocytopenia, 18/53(33.9%) were having moderate thrombocytopenia and 7/53 (13.52%) were having severe thrombocytopenia. Thrombocytopenia had 66.25% sensitivity. Incidence of thrombocytopenia in Gram negative sepsis was (35/54) 64.81%, in gram positive sepsis the incidence was (15/21) 71.41% and in fungal sepsis the incidence was (3/5) 60%; however correlation among these was not statistically significant.

Among all patients 35/80 (43.75%) gram negative organisms, 15/80(18.75%) gram positive and 3/80 (3.75%) fungal sepsis had thrombocytopenia (Table. 3). This Table depicts that thrombocytopenia occurs in 43.45 neonates with klebsiella sepsis.

Table 3: Organism distribution of thrombocytopenia neonates

Variables	Organism	N	%
Gram-negative 35/53 (66.03%)	Klebsiella	23/53	43.4%
	Acinetobacter	6/53	11.32%
	E. Coli	3/53	5.66%
	Pseudomonas	3/53	5.66%
Gram-positive 26/53 (49.05%)	Staph. Aureus	9/53	16.98%
	Enterococcus	4/53	7.54%
	CONS	2/53	3.77%
Yeast 3/53 (5.66%)		3/53	5.66%

Mean platelet count at the onset of sepsis in all the patients was 123287.5±49428.68, in males it was 119534.8± 45750.53 and in females it was 127648.64± 53694.72. Platelet nadir in gram negative sepsis was 34000/µl compared to 20000/µl in gram positive sepsis and 104000/µl in fungal sepsis(P = 0.05) (Figures 1, 2). The mean duration of thrombocytopenia in gram positive sepsis was 4.66 ±2.6 days, in gram negative sepsis 4.39 ± 2.22 days and in fungal sepsis 5.2±1.3 days. There was a significant difference in the average duration of thrombocytopenia between groups (P<0.02) (Figure.3).

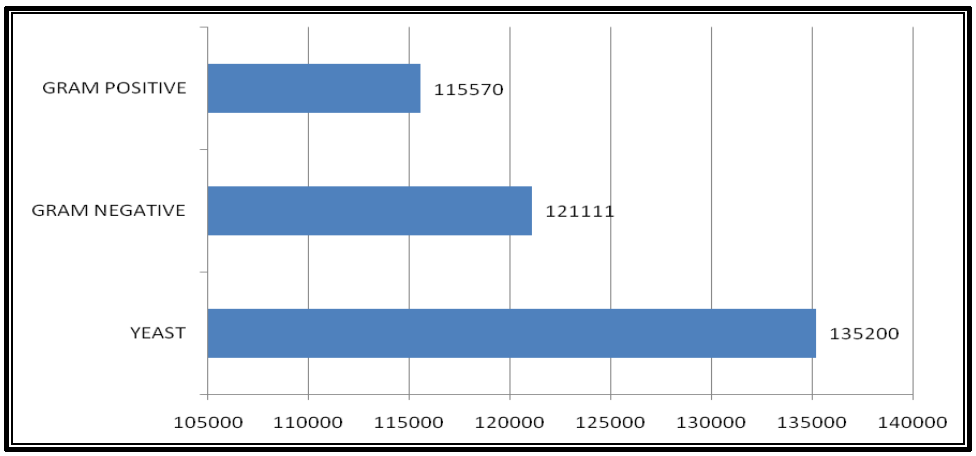

Fig. 1: Platelet Count (Per µl) at Onset of Sepsis in three Groups

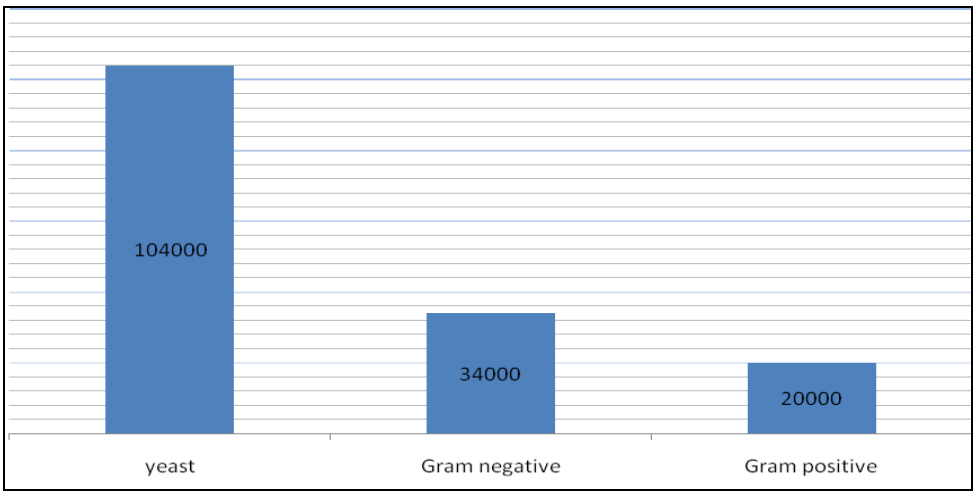

Fig. 2: Lowest Platelet (Per µl) Reached by three Groups of Organism

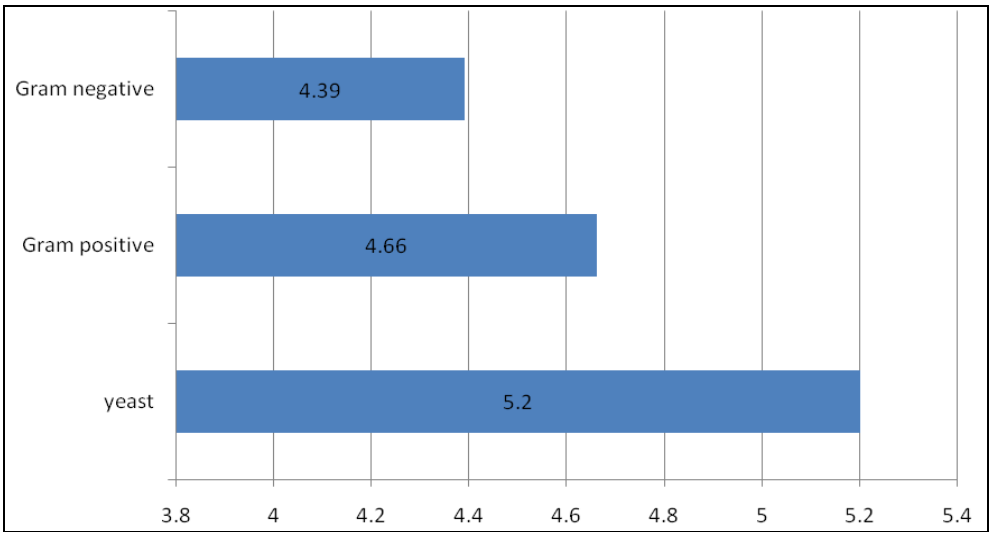

Fig.3: Duration of Thrombocytopenia (in days) with three Groups of Organisms

There was statistically insignificant (P=0.7) difference in the platelet count at the time of onset of sepsis between the organisms with in respective groups. The lowest platelet count for Klebsiella was (34,000/µl). CONS 20,000/µl. Platelet nadir of Klebsiella, staph. aureus, Acinetobacter, Enterococcus and CONS was significantly lower than (P<0.01) the other organisms.

The mean duration of thrombocytopenia in all thrombocytopenic patients was 4.75 days. The difference between the groups was statistically significant (p<0.02). The average mortality in all thrombocytopenic patients with sepsis was 12/53(22.64%). Higher incidence was seen with Klebsiella 6/53(11.32%) (Table.4). The average mean platelet volume of patients with thrombocytopenia was 11.74 ± 1.08 and in patients without thrombocytopenia was 9.59 ± 1.04 fl. The MPV of thrombocytopenic neonates was significantly higher than that of non-thrombocytopenic neonates (p < 0.01).

Results also showed patients having duration of thrombocytopenia ≤5 days had 9.30% mortality and those with ≥6 days duration had 27.02% mortality (P < 0.05).

Table 4: Effect of different organisms on platelet indices in thrombocytopenia neonates

Organism		Number of Patients	Platelet Count at onset of sepsis (per µl)	Lowest Platelet count (per µl)	Mean duration of Thrombocytopenia	MPV (Fl)	Mortality
1	Klebsiella	23/53	96000	34000	5.09	11.71	11.32%
2	Staph. Aureus	9/53	95444.44	40000	4.23	11.38	1.88%
3	Acinetobacter	6/53	97166	42000	3.08	11.61	3.77%
4	E. Coli	3/53	121666.66	90000	2.83	12.13	0%
5	Enterococcus	4/53	102000	44000	4.00	11.85	1.88%
6	pseudomonas	3/53	99333.33	68000	5.00	11.96	0%
7	(CONS)	2/53	38000	20000	9.50	1 1.85	1.88%
8	Yeast	3/53	118000	104000	5.20	11.43	1.88%

Discussion

About 1.6 million neonatal deaths occur worldwide every year, 40% of which occur in developing countries, particularly Asia and Africa (15). Infections such as pneumonia, septicemia, meningitis, and diarrhoea account for 30-50% of neonatal deaths in developing countries (16). Neonatal sepsis is a life threatening emergency and a delay in treatment may result in death. Thrombocytopenia affects up to 20-50% of all neonates admitted in neonatal intensive care unit (17). In our study thrombocytopenia was present in 66.25% of neonates with sepsis. Thrombocytopenia had 66.25% sensitivity and 87% specificity in predicting sepsis among culture positive patients. Guida et al. (18) had reported that 54% septic Very Low Birth Weight (VLBW) neonates developed thrombocytopenia. Akarsu et al. (19) had shown higher initial platelet count in gram positive sepsis compared to gram negative sepsis.

Platelet nadir reached in our study was lowest $36xl0^3$/µl in gram negative sepsis, in fungal sepsis it was $104xl0^3$/µl and in gram positive sepsis $20xl0^3$/µl. Mean platelet Count was lower in gram negative sepsis ($P = 0.05$). Guida (18) had similarly reported significantly low platelet nadir in gram negative and fungal sepsis. Akarsu (19) also reported lowest platelet count in gram negative sepsis than in gram positive sepsis. Bhat et al. (15) had reported significantly low platelet count at the onset of sepsis arid low platelet nadir in gram negative and fungal sepsis than gram positive sepsis. In our study we had included both low birth weight and normal birth weight babies that influenced the degree of fall in platelet counts.

Klebsiella pneumoniae caused maximum effect on various platelet parameters. There was statistically significant ($P < 0.02$) difference in the lowest platelet nadir reached between Klebsiella and other organisms. Klebsiella pneumoniae expresses a smooth lipopolysaccharide (LPS with O antigen) and capsular polysaccharide (K antigen) and both are important for virulence. There is a variation in genetic makeup of O antigen between Klebsiella pneumoniae and other gram negative organisms, which allow Klebsiella pneumoniae strains to constitutively express a polysaccharide capsule critical for organisms ability to resist compliment mediated opsonophagocytic killing (20).

These genetic variations in Klebsiella pneumoniae may be responsible for persistent bacteremia and maximum effect on various platelet parameters as seen in our study.

The mean duration of thrombocytopenia in gram positive sepsis in our study was 4.66 days. In gram negative sepsis 4.39 days and in fungal sepsis 5.2 days. The difference between the bacterial and fungal sepsis was statistically significant ($p< 0.02$). Similar findings were reported by Bhat et al. (15), Guida (18) had reported the mean duration of thrombocytopenia in gram positive sepsis 0.4 days and in gram negative and fungal sepsis 2 days. The greater duration in gram negative sepsis may be attributed to the fact that gram negative sepsis causes severe thrombocytopenia gram negative and fungal sepsis induced thrombocytopenia is very severe, and takes more than 7 days for platelet count to return to baseline (21).

Maximum percentage decrease in platelet count was seen with gram negative sepsis compared to gram positive sepsis and in fungal sepsis in our study ($p>0.05$), Bhat et al. (15) had shown similar findings. Study by Akarsu et al. (19) had shown statistical difference between gram positive agents (26%) and gram negative agents (53.9%) in terms of percentage change ($p<0.05$). Guida et al. (18) had reported significantly greater percentage decrease in platelet count with cases of fungal infection than in gram positive infection. The average mean platelet volume of septic patients without thrombocytopenia in our study was 10.1 ± l.94 fl and average MPV of septic thrombocytopenic babies was greater (12.5 ± 1.08) ($P<0.05$). The MPV at the onset of sepsis in gram negative organisms was 11.29± 1.2, in gram positive sepsis 11.57±0.9 although it was higher in gram positive sepsis the difference was statistically insignificant ($P > 0.05$). Guida et al. (18) had shown a statistically significant increase in MPV with sepsis from baseline but had not shown any significant difference between the two groups. Bhat et al. (15) had reported higher MPV in gram negative and fungal sepsis than gram positive sepsis. Akarsu et al. (19) had demonstrated elevation of MPV during sepsis but did not find any statistical difference between the groups. While considering the affect of individual organisms we found the MPV of Klebsiella and pseudomonas was greater than (11.3fl and 12.1fl) the MPV of other organisms (MPV =11 – 11.85 fl). These two organisms were also having lowest platelet nadir and persistent bacteraemia especially Klebsiella. Akarsa et al. (19) had reported MPV over 10.8 significantly associated with bacteremia.

In thrombocytopenic neonate the platelet transfusion rate was 52.83%. 71.4% patients with severe thrombocytopenia and 50% of neonates with moderate thrombocytopenia had received platelet transfusion ($p <0.01$). Bonifacio et al. (22) had reported the incidence of platelet transfusion rate in 85% babies with severe thrombocytopenia and 64% babies with moderate thrombocytopenia. Murry et al. (23) had reported that 51% of babies with severe thrombocytopenia received platelet transfusion.

The mortality of thrombocytopenic babies receiving platelet transfusion was 42.85% compared to (0%) mortality in babies who had not received transfusion ($P <0.01$). Bonifacio (22) had mentioned that in babies with gestation of 28-32 weeks the mortality rate was not significantly different in platelet transfused vs. non transfused group. However among infants with gestational age <28 weeks a higher proportion of platelet transfused died as compared to non-transfused group. Christen et al. (24), had mentioned that mortality rate of those receiving platelet transfusion was twice than those babies receiving none.

In our study among 7 neonates with severe thrombocytopenia (71.42%) babies had received platelet transfusion. Mortality in babies with severe thrombocytopenia who had received platelet transfusion was 100%. In contrast severely thrombocytopenic babies who were not transfused had no mortality 0% (P <0.01). We have also found, with increase in number of platelet transfusions the mortality increased (P <0.01) babies received only one transfusion each had (40%) mortality in comparison to babies having received three transfusions 100% died. Therefore we found that the mortality of babies with late onset sepsis induced thrombocytopenia is significant (14/53). Study from Khassawneh et al. (25) had found similar high mortality in gram negative sepsis. Akarsu et al. (19) had shown more mortality in gram negative sepsis. Mortality in our study was 16.66% in gram negative, 19.04% in gram positive and 20% in fungal sepsis (P> 0.05). The overall mortality in all septic neonates was 17.5%. It was 22.64% in neonates with sepsis induced thrombocytopenia and 7.40% in neonates with sepsis but without thrombocytopenia (P < 0.01). The mortality was more with gram negative organisms. Similar high mortality was reported by Bhat et al. (15). Vankateshan et al. (26) had documented 42% mortality in neonatal sepsis in 1996 which gradually decreased to 20% in 2006.

As the duration of thrombocytopenia increased the mortality also increased in our study. Patients having thrombocytopenia of ≤5 days duration had 9.30% mortality compared to thrombocytopenia ≥6 days 27.02% (P <0.05). Bhat et al. (15) had reported that incidence of death is directly related to duration of thrombocytopenia.

Conclusion

To conclude it is important to look for and appropriately manage thrombocytopenia in all babies admitted to NICU even in apparently low-risk babies as incidence and mortality associated with this condition is high.

Conflict of interest: None.

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