Prevalence of thrombocytopenia in neonatal sepsis

Sambhaji Chate[1], Sunil Holikar[2], Suyog Nagare[3]

From [1]Associate Professor and Head, [2]Associate Professor, [3]Junior Resident, Department of Pediatrics, Swami Ramanand Teerth Medical College, Ambajogai, Maharashtra, India

Correspondence to: Dr. Sunil Holikar, Gangasagar Residency, Banglow No. 122, Near D-MART Ring Road, Latur - 413 512, Maharashtra, India. E-mail: sunilholikar@gmail.com

Received - 18 April 2019 Initial Review - 07 May 2019 Accepted - 27 May 2019

ABSTRACT

Background: The problem of neonatal sepsis is enormous in India and many hospital-based studies have revealed an incidence of 30/1000 live births. **Objectives:** The objectives of this study were to assess the prevalence of thrombocytopenia in culture-positive neonatal sepsis and to observe the outcome of these neonates. **Methods:** It was a retrospective observational study which was conducted in neonatal intensive care unit (NICU) of a Rural Medical College between September 2018 and December 2018. We have analyzed the records of all the neonates who were admitted at the hospital during this period. We have only included the cases who were culture positive for sepsis and were below 28 days of age. Data were analyzed statistically and $p<0.05$ was considered to be statistically significant. **Results:** About 54 neonates who had culture-positive sepsis and thrombocytopenia treated in NICU. Of 54 culture-positive neonates, the most common isolated microorganism was *Klebsiella pneumoniae* (21, 38.88%) followed by *Pseudomonas* (15, 27.77%), *Staphylococcus* (9, 16.66%), and *Escherichia coli* (9, 16.66%). Thrombocytopenia was present in 49/54 (90.74%) cases. As per severity grading, severe thrombocytopenia was found in 21 (42.86%) neonates, moderate in 17 (34.69%), and mild in 11 (22.45%). The mortality rate among newborns with sepsis was 32.65%. The average period for platelets to rise >100,000/mm^3 was 5.0 days (interquartile range 4.0–7.0). **Conclusion:** Severe thrombocytopenia was commonly associated with neonatal sepsis. Antibiotics covering these groups of bacteria can be started empirically after collecting the required investigations.

Key words: *Blood culture, Neonatal sepsis, Thrombocytopenia*

India contributes to one-fifth of global live births and more than a quarter of neonatal deaths [1]. The problem of neonatal sepsis is enormous in the country. Hospital-based studies have revealed an incidence of 30/1000 live births, while community-based studies indicate an incidence of 2.7–17% of all live births. About one-fifth of neonates are being diagnosed with sepsis disease in the hospital; the figure rises up to 50% for those with culture-proven sepsis. Their hospitalization period gets extended, the patients need additional resources. Such patients are also at a high risk of major neurodevelopmental disabilities at a later age [2,3].

Neonatal sepsis is a systemic infection occurring in infants at ≤28 days of life and is an important cause of morbidity and mortality of newborns [4]. In 2010 worldwide, 7.6 million children <5 years old died, predominantly due to infectious causes including sepsis, neonatal deaths (in the first 28 days of life) accounted for 40% of the total lives lost [5]. Despite major advances in neonatal care and increasing research, in developed countries, four of every 10 infants with sepsis die or experience major disability including significant permanent neurodevelopmental impairment [6]. Prematurely born neonates experience the highest incidence and mortality of sepsis among all age groups. Bacterial sepsis is a common cause of non-immune thrombocytopenia in neonatal intensive care unit (NICU) [7]. The main underlying pathology is increased destruction or decreased production of platelets. Several mechanisms are accountable for sepsis-induced thrombocytopenia, and it consists of accelerated platelet destruction, endothelial damage, and removal by the reticuloendothelial system, consumption from disseminated intravascular coagulation (DIC), binding of platelets to the bacterial products by platelet aggregation, and diminished production. Thrombocytopenia is reflected as the major sign of neonatal septicemia [8].

Thrombocytopenia is found in approximately 20–35% of babies who present to the NICU, whereas it is observed in 70% of very low birth weight (VLBW) babies with a higher rate of accompanying bleeding problems. A platelet count below 150,000/mm^3 is defined as thrombocytopenia and values below 50,000/mm^3 are defined as severe thrombocytopenia. Degrees of thrombocytopenia can be further subdivided into mild (platelet count 100,000–150,000/mm^3), moderate (50,000–99,000/mm^3), and severe (<50,000/mm^3). Thrombocytopenia occurring in the first 3 days of life is classified as early-onset thrombocytopenia, and thrombocytopenia occurring after the 4th day is classified as late-onset thrombocytopenia. The most common causes of early-onset thrombocytopenia include maternal preeclampsia,

pregnancy-induced hypertension or diabetes, intrauterine growth retardation, perinatal infections, perinatal asphyxia, and transplacental transmission of maternal allo-/auto-antibodies. Late-onset thrombocytopenia is most commonly caused by postnatal infection and necrotizing enterocolitis [9].

Severe neonatal thrombocytopenia (platelet count <50,000/mL) is associated with bleeding and, potentially, significant morbidity, although there is a poor correlation between platelet count and incidence of bleeding. As a result, it is important to identify at-risk infants, and if needed, initiate therapy to prevent associated complications. Neonatal sepsis continues to remain a leading cause of morbidity and mortality worldwide. Neonatal sepsis is divided into two groups based on the age of presentation: Early-onset sepsis (EOS) at 72 h or before 7 days of life and late-onset sepsis (LOS) is defined as sepsis occurring at or after 72 h or 7 days of life. In developing countries, sepsis is the most common cause of mortality responsible for 30–50% of total neonatal deaths each year [10]. Gram-negative organisms are more commonly reported from India [11].

Therefore, it is a known fact that the high incidence of mortality is due to thrombocytopenia and neonatal sepsis in NICUs. This study was conducted to find out the bacteriological, clinical profile and the prevalence of thrombocytopenia in culture-positive neonatal sepsis.

METHODS

This was a retrospective observational study conducted at the Department of Pediatrics of a Rural Medical College and tertiary care center, Maharashtra, India. Data were collected from previous records of NICU over 4 months from September 2018 to December 2018. Clinical and laboratory data were collected from records during admission, i.e., laboratory reports, notes/case papers of neonates. Permission from the Institutional Research and Ethical Committee was taken before commencement of the study.

In this study, neonates aged below 28 days with culture-positive sepsis were only included. Babies who were extremely low birth weight (LBW) (<1000 g), aged >28 days, neonates having maternal history suggestive of placental insufficiency, neonates with family history of bleeding manifestations, and newborn's mother with low platelets counts, were excluded from the study. The blood cultures of the neonates were collected for the information regarding isolated organism, demographic profile, type of sepsis (EOS/LOS), presentation (non-specific/systemic), and hematology. Septic screening was done according to hospital protocols, and it consists of complete blood cell, blood culture, C-reactive protein, and erythrocyte sedimentation rate.

Definitions used in this study were; (a) neonatal period was referring to age <28 days after birth. (b) Culture-proven sepsis – when an infant having clinical picture suggestive of septicemia, pneumonia, or meningitis along with isolation of pathogen from blood. (c) Normal platelets count referred to platelets count of >150,000/mm^3. (d) Thrombocytopenia was defined as newborn infants having platelets counts below 150,000/mm^3. Mild, moderate, and severe thrombocytopenia were defined as when platelet counts between 100,000 and 150,000/mm^3, 50,000 and 100,000/mm^3, and <50,000/mm^3. (e) Prevalence is the proportion of disease found to have been affecting a particular population.

The data were recorded and analyzed using the MS Excel 2010. Association and correlation of qualitative data were tested by Chi-square test and "$p<0.05$" was considered statistically significant.

RESULTS

The study population was selected as per the inclusion criteria and a total of 54 newborns were included in the study. Of these 54 newborns, 29 (53.70%) were male and 25 (46.30%) were female. Extramural neonates were 26 (48.14%) and intramural were 28 (51.86%). EOS was seen in 39 (72.22%) cases and those 15 (27.78%) had LOS. Table 1 shows the birth weight, mode of delivery, and thrombocytopenia, in the patients. Among the patients, 8 (14.81%) children had VLBW and preterm delivery was seen in 19 (35.18%), whereas term 33 (61.11%) and post-term neonates were 2 (3.7%).

The most common organism isolated in blood culture were *Klebsiella pneumoniae* in 21 (38.88%) cases, followed by *Pseudomonas* (15, 27.77%), *Staphylococcus* (9, 16.66%), and *Escherichia coli* (9, 16.66%). Thrombocytopenia was present in 49/54 patients (90.74%). As per the severity grading, severe thrombocytopenia was found in 21 (42.86%) neonates, moderate in 17 (34.69%), and mild in 11 (22.45%) neonates, respectively. As presented in Table 2, severe thrombocytopenia was found in 7/21 (33.33%) patients with *K. pneumoniae* infection, followed by 6/21 (28.57%) with *Pseudomonas* spp., 5/21 (23.80%) with *Staphylococcus aureus,* and 3/21 (14.28%) neonates with *E. coli* infection (p=0.016).

According to organism isolated in blood culture, *K. pneumoniae* was the leading cause of death in 10/21 (47.61%) newborns followed by *Pseudomonas* spp. 4/15 (26.66%), *E. coli* 1/9 (11.11%), and *S. aureus* sepsis in 1/9 (11.11%) neonates.

DISCUSSION

As per the study results, culture-positive sepsis was seen more common among male (53.70%) than the female (46.30%) neonates. This finding was similar to the previous study by Singh *et al*. and Raha *et al.*, where 62.5% were male neonates and 37.5% were female. Even though recent developments in medical expertise have enhanced the survival of LBW infants, they remain at a high risk for sepsis [12]. In this study, 29 neonates

Table 1: Birth weight, mode of delivery, and thrombocytopenia

Parameters	N (%)	Thrombocytopenia (%)
Normal	25 (46.29)	21 (84)
Low	29 (53.7)	28 (96.55)
Normal delivery	41 (75.92)	39 (95.12)
Cesarean section	13 (24.8)	10 (76.92)

Table 2: Severity of thrombocytopenia as per organism found in blood culture

Organisms found	Normal	Mild	Moderate	Severe	Total	Mortality
Klebsiella pneumoniae	0	5	9	7	21	10
Pseudomonas spp.	2	2	5	6	15	4
Staphylococcus aureus	1	1	2	5	9	1
Escherichia coli	2	3	1	3	9	1
Total	5	11	17	21	54	16

with sepsis had LBW of these 28 (96.55%) babies developed thrombocytopenia. One of the most common hematological manifestation during early sepsis is thrombocytopenia; thus, platelet count may act as an early marker for the diagnosis of septicemia [13].

The results of the present study showed thrombocytopenia in 49/54 (90.74%) neonates. The prevalence of thrombocytopenia among neonatal sepsis patients was significant in various previous studies across the globe. As per Singh *et al*., percentage of thrombocytopenia was 95.2%, while the study by Abdulla *et al.* showed 42.8% incidence of thrombocytopenia in neonatal sepsis [12]. A study by Sindhura and Reddy found that the number needed to treat (<150,000/mm^3) can be used to screen neonate with sepsis with sensitivity of 82.6% [13].

In our study, as per the severity grading, severe thrombocytopenia was found in 21 (42.86%) neonates, moderate in 17 (34.69%), and mild in 11 (22.45%) neonates. According to the study by Karne *et al.* in proven sepsis, severe thrombocytopenia was present in 57.5% of patients, while mild and moderate thrombocytopenia was seen in 22.5% and 20.0% of cases, respectively [14]. This indicates that the low platelets in newborns have important correlation with sepsis and admission in the NICU. The severity grading of thrombocytopenia also represents that it was associated with culture-positive sepsis. The majority of the study cohort had a positive blood culture for *K. pneumoniae*. As per Shukla and Rawat, high culture positivity rate was seen in LBW neonates [15].

As per blood culture test, *K. pneumoniae* was the most common organism, followed by *Pseudomonas* (15), *Staphylococcus* (9), and *E. coli* (9). Similar results were found by Singh *et al*. where *K. pneumoniae* was found in 44.8% (47/105) newborns, followed by *Pseudomonas* spp. 24.8% (26/105), *E. coli* 13.3% (14/105), *S. aureus* 10.5% (11/105), and *Candida* spp. 1.9% (2/105) [16]. Verma and Sadawarte found that *S. aureus* (58.62%) was the most common followed by *Klebsiella* (16.09%) coagulase-negative *Staphylococcus* (6.89%) [17]. Karne *et al.* found that *Pseudomonas aeruginosa* was the most common organism causing neonatal sepsis accompanying severe thrombocytopenia (64.7%) than the mild or moderate thrombocytopenia [18]. In a study by Torkman *et al.*, *Enterobacter* was the most common organism causing neonatal sepsis with thrombocytopenia [19]. Khassawneh *et al.*, from Jordan, also reported Gram-negative organisms as the most common cause of neonatal sepsis [20]. *S. aureus* colonizes skin, nasopharynx, and gastrointestinal tract and spreads through hands of health care workers. This suggests a prerequisite for better adherence to hygiene practices and isolation of health care workers.

Platelet indices in neonates with EOS and LOS, thrombocytopenia was significantly higher in LOS which is supported from a study by Kudawla *et al.* The same study also concluded that decreased platelet count was seen more frequently in LOS group [18]. Most commonly, it is the Gram-negative organisms responsible for neonatal sepsis.

The pathogenesis of thrombocytopenia in neonatal sepsis is not clear. Thrombocytopenia may just be a marker of severity of sepsis, as Gram-negative sepsis is more severe than Gram-positive ones and sepsis can cause DIC. A direct pathophysiological mechanism of endotoxins produced by Gram-negative bacteria in neonatal sepsis could also contribute. Both bacterial groups show a great inhomogeneity, with a different pathogenicity for each separate bacterial species [21]. Theoretically, the observed differences in this study could be completely attributed to the individual pathogenic effect of coagulase-negative staphylococci and E. coli, as those bacteria were the most abundant in our groups.

This study has shown the trend toward a higher occurrence of pulmonary hemorrhage and mortality in septic neonates with severe and very severe thrombocytopenia, compared to neonates with platelets >50,000/mm^3. Mortality observed in our study was 16 (32.65%) which is similar to the previous study by Kumar *et al.* where the mortality was 25%. Thrombocytopenia is also known to be of prognostic value [21]. Thrombocytopenia was found to be consistently associated with poor prognosis, confirming the finding of other studies [12-16].

The study results and interpretations do have few restrictions including that it was a retrospective study in nature and has possibility of being bias. This study was not powered to evaluate the differences in bleeding events and did not take into full account the time relation between the bleeding events and actual occurrence of thrombocytopenia, or other potential factors influencing the risk of bleeding such as hemodynamic instability.

CONCLUSION

Thrombocytopenia was common among sepsis due to *K. pneumonia*, *Pseudomonas*, *Staphylococcus*, and *E. coli* organisms. Severe thrombocytopenia shows an increased association with major hemorrhages and mortality. Ideally, a large sample-based, prospective multicenter study would be able to clarify various factors associated with and mortality in neonatal sepsis.

REFERENCES

1. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, *et al*. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: An updated systematic analysis. Lancet 2015;385:430-40.
2. National Neonatal Perinatal Database. Report for the Year 2002-03. Available from: http://www.newbornwhocc.org/pdf/nnpd_report_2002-03. [Last accessed on 2019 Feb 12].
3. Bang AT, Bang RA, Baitule S, Deshmukh M, Reddy MH. Burden of morbidities and the unmet need for health care in rural neonates-a prospective observational study in Gadchiroli, India. Indian Pediatr 2001;38:952-65.
4. Edwards MS, Baker CJ. Sepsis in the Newborn, Krugman's Infectious Diseases of Children. 11th ed. Philadelphia, PA: Mosby; 2004. p. 545-61.
5. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, *et al*. Child health epidemiology reference group of WHO and UNICEF. Lancet 2012;379:2151-61.
6. INIS Collaborative Group, Brocklehurst P, Farrell B, King A, Juszczak E, Darlow B, *et al*. Treatment of neonatal sepsis with intravenous immune globulin. N Engl J Med 2011;365:1201-11.
7. Visner M, Sallmon H, Brown R. New insights into the mechanisms of non-immune thrombocytopenia in the neonate. Semin Perinatol 2009;33:43-51.
8. Baer VL, Lambert DK, Henry E, Christensen RD. Severe thrombocytopenia in the NICU. Pediatrics 2009;124:e1095-100.
9. Deorari AK. Neonatal sepsis: Manageable daunting issue for India. J Neonatol 2009;23:7-11.
10. MacDorman MF, Minino AM, Strobino DM, Guyer B. Annual summary of vital statistics-2001. Pediatrics 2002;110:1037-52.
11. Storm W. Use of thrombocytopenia for the early identification of sepsis in critically ill newborns. Acta Pediatr Acad Sci Hung 1982;23:349-35.
12. Abdulla A, Maghayreh M, Khriesat W, Swedan S. The effect of neonatal sepsis on platelet count and their indices. Jordan Med J 2008;42:82-6.
13. Sindhura YS, Reddy KR. A study of neonatal thrombocytopenia in neonatal sepsis. Int J Contemp Med Res 2017;4:2250-2.
14. Karne TK, Joshi DD, Zile U, Patil S. Study of platelet count and platelet indices in neonatal sepsis in tertiary care institute. MVP J Med Sci 2017;4:55.
15. Shukla OS, Rawat A. Clinical profile and outcome of early onset sepsis in high risk very low birth weight neonates. Int J Contemp Pediatr 2018;5:389-94.
16. Singh S, Agrawal A, Mohan U, Awasthi S. Prevalence of thrombocytopenia in neonates admitted in NICU with culture proven sepsis. Int J Contemp Pediatr 2018;5:743-8.
17. Verma P, Sadawarte K. Neonatal septicemia: Its etiological agents and clinical associates. Indian J Child Health 2015;2:113-7.
18. Kudawla M, Dutta S, Narang A. Validation of a clinical score for the diagnosis of late onset neonatal septicaemia in babies weighing 1000-2500 g. J Trop Pediatr 2008;54:66-9.
19. Torkman M, Afsharpaiman SH, Hoseini MJ, Moradi M, Mazraati A, Amirsalari S, *et al*. Platelet count and neonatal sepsis: A high prevalence of *Enterobacter* spp. Singapore Med J 2009;50:482-5.
20. Khassawneh M, Khader Y, Abuqtaish N. Clinical features of neonatal sepsis caused by resistant gram-negative bacteria. Pediatr Int 2009;51:332-6.
21. Kumar S, Kamalarathnam C, Kumutha J, Bharathi S, Lingaldinna S. Mortality profile and incidence of deaths due to neonatal sepsis in an urban tertiary care center in South India: A retrospective study. Indian J Child Health 2017;4:415-8.

Funding: None; Conflict of Interest: None Stated.

How to cite this article: Chate S, Holikar S, Nagare S. Prevalence of thrombocytopenia in neonatal sepsis. Indian J Child Health. 2019;6(6):309-312.

Doi: 10.32677/IJCH.2019.v06.i06.012