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Original Article

Paediatrics Section

The Risk Factors for Development of Sepsis in Newborns with a Central Venous Catheter and their Association with the Serum Zinc Levels

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ABSTRACT

Introduction: Neonates with indwelling central venous catheters are at risk of developing the infection. Serum zinc plays a major role in mounting an immune response.

Aim: To analyse the risk factors for development of sepsis in hitherto aseptic neonates with a centrally inserted venous catheter and to study their association with the serum zinc levels.

Materials and Methods: After Institutional Ethics Committee Approval, 132 neonates were included who required Neonatal Intensive Care Unit (NICU) admission and had an indwelling central venous catheter and their serum zinc levels were measured. Only neonates who were proven aseptic at admission were included and were followed up for development of signs of sepsis using the Clinical Sepsis (CSEP) criteria, baseline septic screen parameters and blood culture, at admission and on the Day 5 along with catheter site culture. This was then correlated with their serum zinc levels and analysed by Mann-Whitney's test using SPSS 17.0.

Results: Out of 132 neonates, 19 had low and 113 neonates had normal zinc levels respectively (Zn<55 µg/dL and Zn>55 µg/dL). A total of 25% neonates developed clinical sepsis by day 5 and 23.5% of neonates had positive catheter site culture. Neonates without clinical sepsis had slightly higher levels of zinc as compared to neonates who had clinical sepsis (147 µg/dL and 141 µg/dL respectively). Neonates born to mothers without risk factors and neonates without perinatal asphyxia had higher zinc levels. Neonates with perinatal asphyxia showed statistically significant association with serum zinc levels (94.2 mcg/dL in asphyxiated newborns as compared to 131 mcg/dL in nonasphyxiated newborns). Neonates with significant band-neutrophil ratio on Day 5 had lower zinc levels than those with normal band-neutrophil ratio (107 µg/dL and 111 µg/dL).

Conclusion: The risk factor for sepsis in neonates with indwelling catheters associated with zinc deficiency was perinatal asphyxia. Prematurity, low birth weight, maternal risk factors and clinically septic newborns had lower zinc levels, though statistically not significant.

Keywords: Clinical sepsis, Indwelling intravenous line, Perinatal asphyxia

INTRODUCTION

The neonatal period carries the highest risk of mortality per day than any other period during childhood. The daily risk of mortality in the first 4 weeks of life is ~30-fold higher than the post-neonatal period, that is, from 1 month to 59 months of age, [1]. The Neonatal sepsis accounts for 25% of neonatal deaths. Neonatal mortality rate in 2017 was 25.4 deaths per 1000 newborns [2]. Among these neonatal sepsis is one of the commonest preventable causes of mortality. In a recent study by Muthukumaran N, sepsis remained the commonest cause of death followed by respiratory distress syndrome and asphyxia [3]. Immediate complications of neonatal sepsis are systemic inflammatory response syndrome, disseminated intravascular coagulation, septic shock and multiple organ dysfunction syndromes which is why it contributes to neonatal mortality. Long-term complications are many and include respiratory, gastrointestinal complications, growth retardation and neurological sequelae [4].

In the NICU, the appropriate management of newborns who require intensive care indicates the need for insertion of an indwelling central venous catheter for fluid, drug and blood component administration. Maintaining a sterile central venous catheter during prolonged stay is a challenge in itself and the line itself getting colonised and eventually becoming the source of nosocomial sepsis is becoming increasingly common. Neonates in the NICU have delayed initiation of breastfeeding and have poor supplemental nutrition during the intensive care. This too contributes to poor defence against infection. Micronutrients play an important role in fighting against infection, and among them, zinc is one micronutrient that is known for its role in immunity and gastrointestinal health.

MATERIALS AND METHODS

This was a prospective hospital-based observational study, conducted in the NICUs of the Government Hospital of Dakshina Kannada, Karnataka, India from February 2016 to September 2017. Institutional Ethics Committee approval was obtained (IEC number: IEC KMC MLR 01-16/03) to include the newborn including both inborn and outborn admitted at the Government NICU, in the study. Written, informed consent was taken from the parents prior to the recruitment of babies in the study. The sample size was calculated using the below formula, to be 132.

$$N=4pq/D^2$$

where, p=proportion of interest (i.e., 18%), q=1-p and D=relative precision

A minimum sample size of 128 was calculated assuming a confidence level of 95%, power of 80%, relative precision of 7% and Central Venous Catheter (CVC) tip colonisation to be 18% and a non-response rate of 10% [5].

Inclusion criteria: All neonates with a central venous catheter whose initial septic parameters are negative on admission to NICU (clinical sepsis and lab parameters).

Exclusion criteria: Neonates who were positive for sepsis at admission and those who did not require a central venous catheter were excluded from the study.

Methodology

In all the study neonates, their birth details, including maternal details were filled in a semi-structured proforma. Maternal risk factors like chorioamnionitis, maternal fever, urinary tract infection, foul-smelling

liquor/vaginal discharge, prematurity and mode of delivery were recorded. Neonatal details like birth weight, perinatal asphyxia and indication requiring NICU admission was recorded. Once admitted in NICU, the following parameters were sent on Day One and again repeated on Day Five:

1. Total count, Differential count and Immature to total neutrophil (I:T) ratio was calculated
2. C-Reactive Protein (CRP)
3. Blood culture and sensitivity
4. Catheter site culture and sensitivity (drawn from the central venous catheter)

Positivity of total count, differential count (with I:T ratio) and/or CRP were considered as positive for sepsis parameters. All the neonates were observed for the development of sepsis using the Clinical Sepsis Criteria as this was a study planned in a resource limited setting of the government hospitals [6]. The definition of clinical sepsis (CSEP) includes:

Patient ≤1 year of age has at least one of the following clinical signs or symptoms with no other recognised cause: fever (>38°C), hypothermia (<36°C), apnoea or bradycardia/clinical symptoms or signs of sepsis.

AND

Blood culture not done or no organism or antigen detected in blood.

AND

No apparent infection at any other site.

AND

Physician institutes treatment for sepsis.

With the development of sepsis, the treatment for the same for instituted and the blood from the catheter site was sent for culture and sensitivity. The serum zinc levels were measured on Day 5 for all newborns in the study using the colourimetric method using Zinc Kit (Tulip, Coral Clinical Systems, Goa, India). The newborns were considered septic if they qualified for clinical sepsis according to the CSEP criteria. Blood parameters (total count, differential count, I:T ratio and CRP) were considered as additional supportive evidence for sepsis, a positive blood culture as confirmed sepsis and all these factors analysed against their serum zinc levels.

STATISTICAL ANALYSIS

The results were then analysed for the maternal and/or perinatal risk factors causing development of neonatal sepsis and/or catheter site sepsis and correlated with their serum zinc levels. Data were analysed using SPSS version 17.0 by the Mann Whitney test, Wilcoxon W test. The Z score and p-value were calculated. (p-value of <0.005 was considered statistically significant).

RESULTS

A total of 132 newborns were included in the study and they were classified as per their gestational age, birth weight, maternal risk factors and perinatal asphyxia to tabulate their demography as in [Table/Fig-1]. Serum zinc levels in the newborns were calibrated as >55 µg/dL being normal and <55 µg/dL as deficiency [5] following which 19 newborns (14.3%) were found to be zinc deficient. The newborns who were proven aseptic on Day 1 were followed-up on Day 5 for the signs of clinical sepsis along with the sepsis markers. Out of 132 newborns, 51 developed clinical sepsis as per the above mentioned CSEP criteria.

When the sepsis markers were tabulated, 68 showed a positive CRP and 28 a positive I:T ratio, as detailed in [Table/Fig-2]. The blood culture reports sent showed positivity in 32 cases. The blood culture positivity in the study was 24.24%. The organisms

Demographic Characteristics		Frequency (Percentage)
Gender	Male	72 (54.5%)
	Female	60 (45.5%)
Gestational age	Term	46 (34.8%)
	Pre-term	86 (65.1%)
Weight	Small for Gestational Age (SGA)	12 (9%)
	Appropriate for Gestational Age (AGA)	103 (78%)
	Large for Gestational Age (LGA)	17 (12%)
Zinc levels (Normal 60-110 mcg/dL)	<55 (µg/dL)	19 (14.4%)
	>55 (µg/dL)	113 (85.6%)
Perinatal Asphyxia	Present	86 (65.1%)
	Absent	46 (43.9%)
Maternal risk factors for early onset neonatal sepsis	No risk factors	85 (64.4%)
	Risk factors for neonatal sepsis present	47 (35.6%)

[Table/Fig-1]: Demographic Characteristics of the study population.

Sepsis/sepsis marker on Day five		Number	Percentage
Clinical Sepsis (CSEP criteria)	Present	51	38.3%
	Absent	81	61.3%
CRP (normal <6 mg/dL)	Positive	68	51.5%
	Negative	64	48.5%
I/T Ratio	<0.2	108	81.8%
	>0.2	24	18.2%
Blood Culture	Positive	32	24.2%
	Negative	100	75.8%
Catheter site C/S	Positive	31	23.5%
	Negative	101	76.5%

[Table/Fig-2]: Details of clinical sepsis and sepsis markers on Day 5.

that were cultured were variable, hence could not be correlated with the other parameters (*Klebsiella, Staphylococcus aureus, Candida sps, Acinetobacter, Pseudomonas, Escherichia coli, Streptococcus* and *Enterococcus*). The catheter site culture also grew similar organisms (31 cases), with a catheter site culture positivity of 23.4% but the same organism was cultured from both blood and catheter in only 15 cases (6 being *Candida*, 5 *Acinetobacter*, 4 showing *staphylococcus* growth). 12 of the cases had either one (blood or catheter site) showing positive growth, and in five cases, the cultures yielded different organisms wherein the catheter site culture was considered as the colonised organism as it grew nosocomial organisms like *Acinetobacter* and *Candida*. The newborns were treated for sepsis and the haematological parameters were correlated with their serum zinc levels. The zinc level in the study population was low in 19 (14.4%) newborns, the cut-off was taken as 55 µg/dL as per a study done by Terrin G et al., [5].

Upon comparing the parameters of sepsis with the serum zinc levels [Table/Fig-3], newborns born to mothers with risk factors for sepsis showed a lower serum zinc level (134 µg/dL) as compared to those born to mothers without any such risk factors; however, this was not statistically significant. Similarly, the gestational age of the baby did not show any difference in the zinc levels of term and preterm newborns. Clinical sepsis positive newborns had also lower serum zinc values (138 µg/dL) as against clinically aseptic newborns (145 µg/dL) but without statistical significance. The presence of perinatal asphyxia in the newborn along with the development of sepsis had lower serum zinc values as compared to non-asphyxiated newborns and this showed statistical significance. Among the haematological markers, I:T ratio in the septic newborns, blood culture positivity

Parameter		Number/Percentage	Zn levels	Mann Whitney Test			
				Median IQR values	Z-value	p-value	Statistical significance
Maternal risk factors	Normal mothers	85 (64.4%)	152.87	118.5 (77.16-163.95)	-0.684	0.494	Not significant
	High risk mothers	47 (35.6%)	132.1	99.83 (81.4-168.3)			
Gestational age	Term	46 (34.8%)	147.86	NA	NA	0.329	Not significant
	Pre-term	86 (65.2%)	145.29	NA			
Clinical sepsis	Present	51 (38.6%)	138.7	NA	NA	0.454	Not significant
	Absent	81 (61.3%)	145.6	NA			
Perinatal Asphyxia	Present	86 (65.1%)	126.3	94.2 (69.13-118.82)	-3.009	0.003	Significant
	Absent	46 (34.8%)	156.8	131.75 (87.3-172.02)			
CRP	Positive	68 (51.5%)	130.8	NA	NA	0.679	Not significant
	Negative	64 (48.5%)	138.7	NA			
I:T ratio	>0.2	24 (18.2%)	123.1	107.9 (67.81-149)	-0.861	0.389	Not significant
	<0.2	108 (81.8%)	130.23	111.25 (80.83-168.3)			
Blood culture	Culture positive	32 (24.2%)	142.4	NA	NA	0.776	Not significant
	Culture negative	100 (75.8%)	153.9	NA			
Catheter site C/S	Positive	31 (23.5%)	146.1	NA	NA	0.893	Not significant
	Negative	101 (76.5%)	140.9	NA			

[Table/Fig-3]: Correlation between the risk factors for development of neonatal sepsis along with the serum zinc levels.

and central catheter site culture positivity also showed similar lower zinc levels but did not exhibit statistical significance.

DISCUSSION

In this study, 132 newborns were included who required NICU care and had an indwelling central venous catheter. The demography of the present study population was similar to a study done by Tsuzuki S and Morimoto N, where 44 newborns were included; serum zinc was measured at birth and on Day 5 [6]. There was no correlation between the zinc levels and the birth weight in that study. The prevalence of zinc deficiency in newborns in this study was 14.4%. The risk factors for the development of sepsis in newborns that were analysed were the presence of maternal risk factors, perinatal asphyxia and gestational age. The presence of maternal risk factors for early neonatal sepsis were not found to be statistically significant with serum zinc levels in the study and no specific references could be found for this, though study by Terrin G et al., have shown that supplementation of zinc has been beneficial in reducing the sepsis rates in the presence of maternal risk factors [7]. In this study, mean birth weight was 2.17 kg and mean Zinc level of preterm neonates (145.29 µg/dL) was nearly same as that of term neonates (147.86 µg/dL). In a study conducted by Iqbal AS et al., showed no significant correlation between gestational age and serum zinc levels [8]. Other study done by Terrin G et al., state that serum zinc levels in cord blood of preterm neonates is higher than term neonates and falls rapidly thereafter, which could explain the similar values that were noted in the present study on day 5 [5].

Similarly, when the occurrence of perinatal asphyxia was analysed with the serum zinc levels, it was found that neonates with perinatal asphyxia had lower zinc levels as compared to neonates without perinatal asphyxia. This association is statistically significant with a p-value of 0.003. However, authors could not find any similar reference articles with this co-relation. Development of clinical sepsis and serum zinc levels did not show statistical significance though in the study it was observed that aseptic newborns had higher zinc levels than clinically septic newborns. However, the role of zinc in immunity has been elaborated by Terrin G et al., and this can give scope to further studies on supplementation of zinc in the NICU and analysing the development of sepsis [5]. Upon analysing the haematological parameters, Low I:T ratio and positive CRP were found associated with lower serum zinc levels. This can be explained by the concordance of clinical sepsis with a positive sepsis screen.

When culture positivity was analysed, numerous organisms had grown in the blood cultures of the septic newborns and hence could not be analysed with respect to the organism. The culture positivity in the study was 24.24%. In other studies, blood culture positivity ranges from 25% to 42% but this value is dependent on multiple factors like volume of blood inoculated, the bacteraemia in the blood, empirical antibiotic usage and laboratory issues [9]. In low levels of bacteraemia the culture shows as less as <1 CFU/mL and hence this explained the low culture yield in this study [10]. Catheter site cultures showed similar positivity of 23% however there was concordance in only 15 cases (50%). The serum zinc levels in newborns who showed positive blood culture and catheter cultures were lower than those with sterile cultures, though statistically not significant. These findings imply the possibility of another study with zinc supplementation and neonatal sepsis.

LIMITATION

The analysis of sepsis could not be done with specific organisms in view of the varied culture growths. This study had a small sample size. Larger sample size with age-matched controls will be useful in deciding the need for zinc supplementation in asphyxiated newborns to reduce sepsis.

CONCLUSION

The risk factors for the development of sepsis in newborns with indwelling catheters were the presence of perinatal asphyxia in the presence of zinc deficiency. Other risk factors like the presence of maternal risk factors, gestational age, birth weight had lower zinc levels, as did newborns who developed signs of clinical sepsis, however, this was not statistically significant. Culture positivity (blood/catheter site) was found to be 24% and did not show any statistical significance with zinc deficiency. Further studies are needed to establish the role of zinc in neonatal sepsis.

REFERENCES

[1] Sankar MJ, Neogi SB, Sharma J. State of newborn health in India. Journal of Perinatology. 2016;36(Suppl 3):S3-S8. doi:10.1038/jp.2016.183.
[2] https://knoema.com/atlas/India/topics/Health/Health-Status/Neonatal-mortality-rate.
[3] Muthukumaran N. Mortality profile of neonatal deaths and deaths due to neonatal sepsis in a tertiary care center in southern India: a retrospective study. Int J Contemp Pediatr. 2018;5:1583-87.
[4] Du Pont-Thibodeau G, Joyal JS, Lacroix J. Management of neonatal sepsis in term newborns. F1000 Prime Reports. 2014;6:67. doi:10.12703/P6-67.
[5] Terrin G, Berni Canani R, Di Chiara M, Pietravalle A, Aleandri V, Conte F, et al. Zinc in early life: a key element in the fetus and preterm neonate. Nutrients. 2015;7(12):10427-46. Published 2015 Dec 11. doi:10.3390/nu7125542.

[6] Tsuzuki S, Morimoto N. Associations of maternal and neonatal serum trace element concentrations with neonatal birth weight. Public Library of Science. 2013;8(9):1-4.
[7] Terrin G, Canani RB, Passariello A, Messina F, Conti MG, Caoci S. Zinc supplementation reduces morbidity and mortality in very-low-birth-weight preterm neonates: a hospital-based randomized, placebo-controlled trial in an industrialized country. The American Journal of Clinical Nutrition. 2013;98(6):1468-74. https://doi.org/10.3945/ajcn.112.054478.
[8] Iqbal AS, Shahidullah M, Islam MN, Akhter S, Banu S. Serum zinc and copper levels in the maternal blood and cord blood of neonates. Indian J Pediatr. 2001;68(6):523-26.
[9] Kayange N, Kamugisha E, Mwizamholya DL, Jeremiah S, Mshana SE. Predictors of positive blood culture and deaths among neonates with suspected neonatal sepsis in a tertiary hospital, Mwanza-Tanzania. BMC Pediatr. 2010;10:39. Published 2010 Jun 4. doi:10.1186/1471-2431-10-39.
[10] Zea-Vera A, Ochoa TJ. Challenges in the diagnosis and management of neonatal sepsis. J Trop Pediatr. 2015;61(1):1-13.

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