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Correlation of serum zinc levels with the outcome of neonatal sepsis

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Abstract
Background and Objective: Sepsis, defined as a "life-threatening organ dysfunction caused by a dysregulated host-response to infection" is a major health issue worldwide and still lacks a fully elucidated pathobiology and uniform diagnostic tests. The trace element zinc is known to be crucial to ensure an appropriate immune response. During sepsis a redistribution of zinc from serum into the liver has been observed and several studies imply a correlation between zinc and sepsis outcome. Therefore the alterations of zinc concentrations in different tissues might serve as one part of the host's defense mechanism against pathogens during sepsis by diverse mechanisms. It has been suggested that zinc is involved in nutritional immunity, acts as a hepatoprotective agent, or a differentiation signal for innate immune cells, or supports the synthesis of acute phase proteins. Limited studies are available on zinc in neonatal sepsis and also zinc deficiency as a predisposing factor of neonatal sepsis. This prompted us to assess zinc levels in neonatal sepsis and its outcome. The primary outcome was treatment failure which was a need to change antimicrobial treatment, or death at any time. Secondary outcome was time to clinical recovery. Moreover, the changes in zinc homeostasis are substantial and correlate with the severity of the disease, suggesting that zinc might also be useful as a diagnostic marker for evaluating the severity and predicting the outcome of sepsis.
Methods: A cross sectional prospective study was undertaken at SIMS, Hyderabad during, January 2016 TO June 2017. A total of 50 neonates with clinical suspicion of sepsis were included in our study. Maternal clinical history, risk factors and detailed history of neonate was taken followed by a detailed general and systemic examination. Sepsis screen and Serum Zinc levels were obtained. Based on Sepsis Score, the neonates were categorized as Possible, Probable and High Probable Sepsis. Serum Zinc levels were correlated with Onset of Sepsis, Sepsis Score, CRP levels, upgradation of antibiotics and duration of hospital stay.
Results: We had enrolled 50 newborns as per our inclusion criteria. Among the 50 neonates in the study, we had 42 (80%) inborns and 10 (20%) were outborns. Majority of the neonates were term newborn 45(90%) and 5 (10%) were preterm. Of the 50 neonates in our study, majority were term (45, 90%) and 5 (10%) were preterm. Mean gestational age was 39.2 ± 3.2 weeks. Mean birth weight was 2.85 ± 0.517 kg. In our study, we found that majority (70%) of neonates admitted to NICU with suspicion of neonatal sepsis had fever. 30% neonates presented with respiratory distressed birth and 87% with perinatal depression. Majority of our subjects had Probable Sepsis (50%). Possible Sepsis and High Probable Sepsis were seen in 40% and 10% of the neonates respectively. The overall mean Serum Zinc level was 66.0 ± 20.50 µg/dl. More than half of the neonates enrolled in our study had low Serum Zinc levels (N= 28, 56%). The mean level of serum zinc of the zinc deficient group was 44.12 ± 7.2 µg/dl. The mean Serum Zinc level in neonates with early onset sepsis was 65 ± 23.14 µg/dl and late onset sepsis was 68.20 ± 22.11 µg/dl. The mean Serum Zinc levels of neonates with Possible, Probable and High Probable Sepsis was 83.2 ± 22.22 µg/dl, 54.0 ± 14.33 µg/dl 55.02± 17.66 µg/dl respectively
Conclusion: Changes in zinc homeostasis are substantial and correlate with the severity of the disease, suggesting that zinc could be used as a diagnostic marker for evaluating the severity and predicting the outcome of sepsis or even as a starting point for therapeutic approach.

Keywords: Serum zinc, hypozincemia, sepsis screen, sepsis score, CRP, possible sepsis, probable sepsis, high probable sepsis

Introduction
The term "sepsis" in relation to a disease has already been used by Hippocrates, but to this day it remains a challenge to compile a definition comprising its complexity. The term "sepsis" in relation to a disease has already been used by Hippocrates, but to this day it remains a challenge to compile a definition comprising its complexity. Neonatal sepsis is a condition defined as a clinical syndrome characterized by signs and symptoms of infection in an infant 28 days of life or younger. This manifested by systemic signs of infection and isolation of a bacterial or other pathogen from the bloodstream 1 results in an estimated 750,000 annual deaths worldwide [1, 2]. The term "sepsis" in relation to a disease has already been used by Hippocrates, but to this day it remains a challenge to compile a definition comprising its complexity.

The term “sepsis” in relation to a disease has already been used by Hippocrates, but to this day it remains a challenge to compile a definition comprising its complexity. To diagnose organ dysfunction in the clinical setting, Singer *et al*. recommend the Sequential Organ Failure Assessment (SOFA) score. It includes parameters to evaluate the functions of respiration, the liver, the cardiovascular system, the central nervous system, the kidneys, and coagulation. An elevation of the total SOFA score of 2 points or more indicates organ dysfunction. Sepsis is the second major cause of mortality among neonates 4 and globally, it is still one of the major causes of morbidity and mortality in neonates, despite recent advances in healthcare units.

The estimated global burden for neonatal sepsis was 2,202 (95% CI: 1,099–4,360) per 100,000 live births, with mortality between 11% and 19%. More than 40% of under-five deaths occur in the neonatal period, resulting in 3.1 million newborn deaths each year. According to the Global Sepsis Alliance, infections leading to sepsis are responsible for about one-fifth of the world’s annual 2.7 million neonatal deaths, and in South Asia and sub-Saharan Africa, it was about 25% of all neonatal deaths. Incidence of neonatal sepsis is around 40 times higher and mortality rates are two times higher in middle- income countries than in high-income countries.5 Globally, of the three million annual neonatal sepsis cases (2202/ 1,00,000 live births), India has the highest incidence of clinical sepsis (17,000/ 1,00,000 live births). The case fatality rate of sepsis among neonates ranges between 25% to 65% in India. These rates are likely to be underestimated, and more accurate data is expected from the ‘Global Maternal and Neonatal Sepsis Initiative’ [1, 2].

Neonatal sepsis includes septicaemia, pneumonia, meningitis, osteomyelitis, arthritis and urinary tract infections.14 Neonatal sepsis, pneumonia and meningitis together result in up to a quarter of all newborn deaths. Besides the high mortality in the acute phase of sepsis there is growing evidence that survivors of sepsis are more susceptible to infections, resulting in an increased re-hospitalization rate, higher morbidity and consecutively higher mortality [7, 8].

Zinc is an essential trace element. In the body it functions, for example, as a co-factor for a high number of enzymes or as a structural element for a variety of proteins. Zinc deficiency can result in growth retardation, dermatitis, and hypogonadism, or symptoms such as delayed wound healing, thymic atrophy or lymphopenia, and high incidence of infection; the latter points are due to its particular importance for the immune system. Consequently, zinc deficiency results in multiple immunological changes, including what seems to be a shift toward a predominantly innate immune response when the availability of zinc is limited. One particularly important effect of zinc is a modulation of the production of inflammatory cytokines [4, 5]. Zinc is an essential trace element and has been shown to be crucial for ensuring an adequate immune response. In the context of sepsis the host’s zinc homeostasis is altered. Various study results imply some of the alterations to be part of the host’s defense mechanism against pathogens. There are indications that a patient’s zinc supply and serum zinc concentration is associated with severity, outcome, and recurrence of sepsis. Zinc seems to have potential to be used as a biomarker or even as a starting point for a therapeutic approach. The results of our preliminary study showed that the zinc supplementation might modulates the relative expression of immune-related genes involved in sepsis pathway among neonates [9, 10].

Aims and objectives

To study the role of Serum Zinc levels in the outcome of neonatal sepsis. The primary outcome was treatment failure which was a need to change antimicrobial treatment, or death at any time. Secondary outcome was time to clinical recovery.

Materials and Methods

Design of the study

We conducted a cross sectional prospective study at the Department of Paediatrics, Shadan Institute of Medical Sciences over a period of 18 months during January 2016 to June 2017.

Inclusion Criteria

All term and preterm neonates admitted in SIMS/Hospital, Neonatal Intensive Care Unit with clinical suspicion of septicaemia are included in the study.

Exclusion Criteria

Congenital anomalies, inborn errors of metabolism, Neonates already treated with antibiotics and Neonates who have received Zinc supplementation.

We included 50 term and preterm neonates suspected to have sepsis. Informed consent was taken from the parents. The gestational age in our study was calculated using the maternal dates and the Modified Ballard scoring system. The day of admission to NICU was noted. We categorized the study population in to Early Onset (<72hrs), and Late Onset (>72 hrs) Sepsis. Maternal clinical history and risk factors were sought out. Detailed history of neonate was taken followed by a detailed general and systemic examination. Baseline blood investigations were done on the day of admission to NICU for Sepsis Screen. Complete blood count, C - reactive protein (CRP) and Serum Zinc levels were performed. •White blood cells count (WBC), Absolute Neutrophil Count (ANC), Platelet Count (PLT) and Ratio of immature to total neutrophils (I/T ratio). Serum Zinc levels were estimated by Colorimetric method.

The neonates were then categorized according to Sepsis Score in to Possible Sepsis (POS), Probable Sepsis (PRS) and High Probable Sepsis (HPS).

Results

This is a prospective observational study conducted at Neonatal Intensive Care Unit, over a span of 18 months. We had enrolled 50 newborns as per our inclusion criteria. Among the 50 neonates in the study, we had 42 (80%) inborns and 10 (20%) were outborns. Majority of the neonates were term newborn 45(90%) and 5 (10%) were preterm. Amongst the 10 outborns, 1 was preterm and rest were term AGA. Of the 42 inborns, 6 were preterm, and amongst the rest i.e 36, were term babies of which 4 were IUGR and 32 were AGA.

Table 1: Maternal Demographics

Age of mother (years)	Number (N=50)	Percentage (%)	Mean(SD)
18-20	20	40%	24.8 ± 5.2
21 – 25	20	40%	
26-30	5	10%	
>30	5	10%	
Parity			
Primi	28	56%	
Multi	22	44%	
Gestational Age			
Term	45	90%	39.2 ± 3.2
Pre Term	5	10%	

In our study, most of the mothers were in the age group 21-25 years and 26-30 years (40%) with mean maternal age of 24.8 ± 5.2 years. Majority (28, 56%) were primigravida. Amongst all the neonates included in our study, 41 (59%) were males and 29 (41%) females. Of the 50 neonates in our study, majority were term (45, 90%) and 5 (10%) were preterm. Mean gestational age was 39.2 ± 3.2 weeks. Mean birth weight was 2.85± 0.517 kg. In our study, 20 (40%) mothers had no risk factors. Of the remaining 30(60%) who had risk factors, like 12 had hypothyroidism, 8 anemia, 4 had premature rupture of membranes (PROM), Pregnancy Induced Hypertension (PIH) and candidiasis were seen in 5% each, Meconium Stained Amniotic Fluid (MSAF) in 4%, Gestational Diabetis Mellitus (GDM) and Antepartum Haemorrhage (APH) in 2% each.

In our study, we found that majority (70%) of neonates admitted to NICU with suspicion of neonatal sepsis had fever. 30% neonates presented with respiratory distressat birth and 87% with perinatal depression. The other associated symptoms like poor feeding, lethargy, icterus, and excessive cry were seen in 10%, 12%, 10%, 8% respectively. 6% of the study population had convulsions.

36 neonates (72%) had early onset sepsis and 14 (28%) late onset sepsis.

Table 2: Sepsis Types

Sepsis Clinical Features		
Fever	35	70%
Respiratory Distress	15	30%
Poor feeding	5	10%
Lethargy	6	12%
Icterus	5	10%
Excessive cry	4	8%
Convulsions	3	6%
Onset of sepsis		
Early onset sepsis	36	(72%)
late onset sepsis	14	28%)
Sepsis Score		
Probable Sepsis	25	50%
Possible Sepsis	20	40%
High Probable Sepsis	5	10%

According to the Sepsis Score, the neonates in our study were grouped under Possible Sepsis, Probable Sepsis and High Probable Sepsis. Majority of our subjects had Probable Sepsis (50%). Possible Sepsis and High Probable Sepsis were seen in 40% and 10% of the neonates respectively.

The overall mean Serum Zinc level was 66.0 ± 20.50 µg /dl.

More than half of the neonates enrolled in our study had low Serum Zinc levels (N= 28, 56%). The meanlevel of serum zinc of the zinc deficient group was 44.12 ± 7.2 µg /dl.

Table 3: Mean Serum Zinc levels of neonates

Zinc levels	N	Percentage	Mean (SD) g/dl
Normal	22	44	89.25± 12.66
Low	28	56%	44.12 ± 7.2
Total	50	100	66.0 ± 20.50

The mean Serum Zinc level in neonates with early onset sepsis was 65 ± 23.14 µg /dl and late onset sepsis was 68.20 ±22.11 µg /dl. This shows that there was a marginal difference in the mean Zinc levels between early onset and late onset sepsis.

Table 4: Mean Serum Zinc levels of Neonates with relation to Onset of Sepsis

Onset of sepsis	N	Mean (SD) µg /dl
Early onset	36	65 ± 23.14
Late onset	14	68.20 ± 22.11
Total	50	66.0 ± 20.50

Table 5: Mean Serum Zinc Levels of neonates in relation to Sepsis Score

Sepsis score	N	Mean (SD)g/dl
Possible Sepsis	20	83.2 ± 22.22
Probable Sepsis	25	54.0 ± 14.33
High Probable Sepsis	5	55.02 ± 17.66
Total	50	66.58 ± 23.53

In our study, neonates with Probable Sepsis and High Probable Sepsis had low mean Serum Zinc levels.

The mean Serum Zinc levels of neonates with Possible, Probable and High Probable Sepsis was 83.2 ± 22.22 µg/dl, 54.0 ± 14.33 µg/dl 55.02±17.66 µg/dl respectively.

Table 6: Spearman Correlation of Neonatal Serum Zinc levels, Onset of Sepsis and Sepsis Score

Parameters	ρ value	*p* value
Onset of Sepsis	0.0555	0.622
Sepsis Score	- 0.555	0.001*

* $p < 0.05$ significant

In our study, there was no significant correlation between Serum Zinc levels and onset of sepsis but there was a

significant moderate negative correlation between Serum Zinc levels and Sepsis Score. The *p value* of 0.001* and Spearman Correlation Coefficient rho (ρ) of – 0.55 was statistically significant.

Table 7: CRP levels Versus Sepsis Score

Sepsis score	N	Mean (SD)(mg/dl)
Possible Sepsis	20	0.131 ± 0.115
Probable Sepsis	25	1.770 ± 1.944
High Probable Sepsis	5	2.284 ± 1.084
Total	50	1.158 ± 1.656

The mean CRP level was 1.158 ± 1.656 mg/dl. We observed that the mean CRP concentration was the highest in the High Probable Sepsis group (2.284 ± 1.084 mg/dl), followed by Probable Sepsis (1.770± 1.944 mg/dl). The mean CRP level was low in the Possible Sepsis group (0.131 ± 0.115 mg/dl).

In our study, we observed that overall 42 (60%) neonates had high CRP levels of which83% had low serum zinc levels and 17% had normal zinc levels. Amongst the neonates with low CRP levels, majority (89%) had normal and only 11% had low serum zinc levels.

Discussion

Sepsis, defined as a "life-threatening organ dysfunction caused by a dysregulated host-response to infection" is a major health issue worldwide and still lacks a fully elucidated pathobiology and uniform diagnostic tests [10, 11]. It is widely accepted as a major cause of high mortality and morbidity in neonates despite the progress in neonatal treatment modalities. The neonatal immunity against infections is immature especially in premature neonates, and this makes the neonates especially the premature ones more susceptible to multiple recurrent infections. The trace element Zinc is known to be crucial to ensure an appropriate immune response. During sepsis, a redistribution of zinc from serum into the liver has been observed and several studies imply a correlation between zinc and sepsis outcome [10, 11].

Hypozincemia is a well observed phenomenon in sepsis patients [10]. The alterations of zinc concentrations in different tissues might serve as one part of the host's defence mechanism against pathogens during sepsis by diverse mechanisms. It has been suggested that zinc is involved in nutritional immunity, acts as a hepato-protective agent, or a differentiation signal for innate immune cells, or supports the synthesis of acute phase proteins. Further knowledge about these events could help in the evaluation of how zinc could be optimally applied to improve treatment of septic patients.

Changes in zinc homeostasis are substantial and correlate with the severity of the disease, suggesting that zinc might also be useful as a diagnostic marker for evaluating the severity and predicting the outcome of sepsis or even as a starting point for a therapeutic approach.

Of the 50 neonates included in our study, majority of them were term, males born through LSCS. Bhatnagar *et al*. [8] had 700 including both neonates and infants with probable sepsis enrolled of which majority were males. Wang *et al*. [14] had included 46critically ill neonates in their study, most of which were males. In their study conducted by Newton *et al*. [16] on the effect of zinc supplementation on outcome of neonatal sepsis, had included 88 neonates of which majority were preterm and males delivered by vaginal delivery. Another study by them had 150 neonates, preterm and males being predominant. A similar study was conducted by El Frargy *et al*. [18] where they had included 200 neonates, majority were males and delivered through LSCS.

Another study by Mehta *et al*. [17] who included 614 neonates with probable neonatal sepsis had majority males through vaginal delivery. Almost half of their neonates were intramural similar to our study.

Almost half of the babies had early onset sepsis and late onset sepsis which were closeto studies conducted by El Frargy *et al*. [18] and Newton *et al*. [16]. Majority of neonates had early onset sepsis in a study by Mehta *et al*. [17] and all late onset sepsis neonates where enrolled in a study conducted by Bhatnagar *et al*. [8]

Majority of our subjects had Probable Sepsis (50%). Possible Sepsis and High Probable Sepsis were seen in 40% and 10% of the neonates respectively, unlike study by El Frargy *et al*. [28] where all the neonates enrolled had high probable sepsis and Mehta *et al*. [17] where all had probable sepsis. In our study, majority of the neonates enrolled had fever, followed by respiratory distress. This was in disparity with study conducted by Newton *et al*. [16], where majority of the enrolled neonates had respiratory distress and Bhatnagar *et al*. [8] where most of the neonates had respiratory distress and refusal to feed. The overall mean Serum Zinc level was 66.0 ± 20.50 μg/dl. More than half of the neonates enrolled in our study had low Serum Zinc levels (N= 28, 56%). The mean level of serum zinc of the zinc deficient group was 44.12 ± 7.2 μg/dl. The mean Serum Zinc level in neonates with early onset sepsis was 65 ± 23.14 μg/dl and late onset sepsis was 68.20 ± 22.11 μg/dl. This shows that there was a marginal difference in the mean Zinc levels between early onset and late onset sepsis.

This shows that serum zinc levels tend to be low with the severity of infection which is well evident in our study which showed a significant moderate negative correlation (ρ –0.55, *p value* 0.001*) between serum zinc levels and Sepsis Score.

In our study, neonates with Probable Sepsis and High Probable Sepsis had low mean Serum Zinc levels. The mean Serum Zinc levels of neonates with Possible, Probable and High Probable Sepsis was 83.2 ± 22.22μg/dl, 54.0 ± 14.33μg/dl 55.02 ± 17.66 μ g/dl respectively. The *p value* of 0.001* and Spearman Correlation Coefficient rho (ρ) of – 0.55 was statistically significant. In our study, there was no significant correlation between Serum Zinc levels and onset of sepsis but there was a significant moderate negative correlation between Serum Zinc levels and Sepsis Score. The *p value* of 0.001* and Spearman Correlation Coefficient rho (ρ) of – 0.55 was statistically significant.

The mean CRP level was 1.158 ± 1.656 mg/dl. We observed that the mean CRP concentration was the highest in the High Probable Sepsis group (2.284 ± 1.084 mg/dl), followed by Probable Sepsis (1.770 ± 1.944 mg/dl). The mean CRP level was low in the Possible Sepsis group (0.131 ± 0.115 mg/dl).

Bhatnagar *et al.* [27] in their study had enrolled only neonates with high concentrations of CRP at baseline. They observed low baseline serum zinc levels in 44% of the subjects. In our study, 60% neonates had high baseline CRP levels of which majority of them had low serum zinc levels and there was

weak negative correlation between serum zinc and CRP levels (r = - 0.388, *p value* 0.001*) which was statistically significant. This shows that low serum Zinc levels was a marker of sepsis.

In their study, Wang *et al.* [14] reported that Serum Zinc levels were significantly low in critically ill neonates and still lower in the extremely critical ones. Similar findings were reported in studies conducted by Besecker *et al.* [12], Mertens *et al.* [15], Negm F *et al.* [13] Animal studies done by Hoeger *et al.* [18] and Wessels *et al.* [19] showed continuous decline of serum serum zinc concentration in mice after induction of sepsis. Hoeger *et al.* [18] in their study reported significantly decreased serum zinc levels in surgical sepsis patients which was also associated with a higher susceptibility to a recurrent sepsis episode. In our study of the 50 neonates enrolled, 42 were started on antibiotics and 8 were not. In view of worsening of the clinical status and persistence of infection on repeat investigations, antibiotics were upgraded in 46 neonates of which majority had low serum zinc levels. Amongst the neonates who had low serum Zinc levels, three- fourth had an upgradation of antibiotics. There was a significant association between serum zinc levels and upgradation of antibiotics (p = 0.001*). This apparently shows that sepsis was associated with low serum zinc levels which led to the upgradation of antibiotics due to increase in the severity of infection. Similar results were seen in study conducted by Bhatnagar *et al.* [8].

The mean duration of hospital stay was 6.4 ± 5.2 days and there was a significant weak negative correlation between neonatal serum zinc levels and duration of hospitalization (r is -0.28, *p value* 0.010*). This again shows that neonates with sepsis disassociated with hypozincemia which caused persistence and severity of infection leading to upgradation of antibiotics leading to a delay in recovery and prolongation of hospital stay. There were no case fatalities in our study.

In our study, we observed that overall 42 (60%) neonates had high CRP levels of which83% had low serum zinc levels and 17% had normal zinc levels. Amongst the neonates with low CRP levels, majority (89%) had normal and only 11% had low serum zinc levels. In studies conducted on Zinc supplementation in neonatal sepsis, Newton *et al,* [16]. Bhatnagar *et al.* [8], El Frargy *et al.* [11] concluded that Zinc supplementation in neonatal sepsis led to a significant reduction in the risk of treatment failure. The use of zinc as an adjuvant in treatment of sepsis in neonate is associated with better outcome.

Conclusion

Administration of zinc as an adjuvant therapy in the treatment of neonatal sepsis is associated with improvement of clinical and laboratory outcome.

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Conflict of Interest

None

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