A Prospective Study Of Serum Ferritin As A Diagnostic And Prognostic Marker Of Neonatal Sepsis

Dr.Alok Himanshu[1], Dr. Priti Rani[2], Dr. Sanni Kumari[3], Dr. Rishu Kumar[4*], Dr. Ram Kinker[5]

[1]Senior Resident, Department of Biochemistry, Darbhanga Medical College, Laheriasarai, Darbhanga, Bihar.
[2]Senior Resident, Department of Biochemistry, AIIMS, Patna.
[3]Senior Resident, Department of Biochemistry, ESIC Medical College, Bihta, Patna.
[4*]Senior Resident, Department of Pharmacology, Nalanda Medical College, Patna.
[5]Consultant Orthopaedics, Shankar Ortho Clinic, Daltonganj, Jharkhand.
Corresponding Author: Dr. Rishu Kumar
Senior Resident, Department of Pharmacology, Nalanda Medical College, Patna.
G mail: dr.rishu.kumar@gmail.com

Abstract

Introduction: Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Severe sepsis is defined as sepsis plus one of the following: Cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions (renal, neurologic, hematologic, or hepatic). In 2017, almost half (20 million) of all estimated sepsis cases worldwide occurred in children under 5 years of age. The study estimated that 41.5% (20.3 million) of incident sepsis cases and 26.4% (2.9 million) deaths related to sepsis worldwide were among children younger than five years.

Materials and Methods: Present prospective and observational study was conducted in Department of Biochemistry, Darbhanga Medical College, Laheriasarai, Darbhanga, Bihar. Study duration was of 1 year (April 2021 to March 2022). Detailed history regarding symptoms, past/medical history was collected from parents/relatives. All children underwent anthropometric measurements, detailed general/systemic examination. Relevant laboratory investigations were done at admission, such as total white blood cells count, differential count, erythrocyte sedimentation rate, platelet count and serum ferritin levels.

Results: In present study 120 children satisfying study criteria were studied. Boys (63.3 %) were more than girls (36.7 %) and mean age was 36.46 ± 13.63 months. Mean duration of illness before admission and duration of fever before admission was 5.36 ± 1.26 days and 4.21 ± 3.48 days respectively. 58.3 % children received antibiotics before admission and 18.3 % children had malnutrition. Common suspected source of infection was pneumonia (35.0 %), Urinary tract infection (18.3 %), Meningitis (18.3 %), Intra-abdominal infection (6.7 %) and from other focus

(21.7 %). Blood culture was positive in 23.3 %. Mean serum ferritin levels were 172.56 ± 118.3 ng/mL and ferritin ≥ 300 ng/mL was noted in 26.7 %.

Conclusion: Serum Ferritin levels can be helpful predictive marker of mortality in severe sepsis and higher ferritin is associated with increasing organ dysfunction. Serum ferritin levels >300 ng/ml can be useful in predicting outcome in children with severe sepsis.

Key Words: Sepsis, acute respiratory distress syndrome, mortality.

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Severe sepsis is defined as sepsis plus one of the following: Cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions (renal, neurologic, hematologic, or hepatic).[1] In 2017, almost half (20 million) of all estimated sepsis cases worldwide occurred in children under 5 years of age. The study estimated that 41.5% (20.3 million) of incident sepsis cases and 26.4% (2.9 million) deaths related to sepsis worldwide were among children younger than five years.[2]

The three most common causes of sepsis-related deaths among children were infections related to neonatal disorders (for example, preterm birth, encephalopathy, hemolytic disease), lower respiratory infections and diarrheal diseases.[3] The increase in plasma ferritin concentration paralleled the increase in plasma CRP during acute pneumonia, tuberculosis, rheumatoid arthritis and neutropenic sepsis, suggesting that ferritin was acting as an acute phase protein.[4]

Ferritin is an iron storage protein. In inflammatory conditions there is a great production of ferritin which leads to a decrease in serum iron, believed to minimize the availability of iron to microorganisms. For this reason, ferritin in critically ill patients may be elevated, and it is associated with severity in some diseases.[5] This study was planned to evaluate serum ferritin as a diagnostic and prognostic marker of neonatal sepsis.

MATERIALS AND METHODS

Present prospective and observational study was conducted in Department of Biochemistry, Darbhanga Medical College, Laheriasarai, Darbhanga, Bihar. Study duration was of 1 year (April 2021 to March 2022).

Inclusion Criteria:

Children 1-5 years age group with severe sepsis. Severe sepsis was defined as sepsis plus one of the following: Cardiovascular organ dysfunction OR acute respiratory distress syndrome or two or more other organ dysfunctions (renal, neurologic, hematologic, or hepatic).

Exclusion Criteria:

Non-infective causes that alter the levels of inflammatory markers, such as chronic inflammatory conditions (including rheumatoid arthritis, inflammatory bowel disease, and Wilson's disease). Conditions with iron overload whether primary, e.g., hereditary hemochromatosis or secondary, e.g.,transfusion overload, porphyria cutanea tarda, and ineffective erythropoiesis (in sideroblastic anemia or thalassemia), and hematological malignancy. Study was explained to parents/relatives and written consent was taken.

Detailed history regarding symptoms, past/medical history was collected from parents/relatives. All children underwent anthropometric measurements, detailed general/systemic examination. Relevant laboratory investigations were done at admission, such as total white blood cells count, differential count, erythrocyte sedimentation rate, platelet count and serum ferritin levels. Serum ferritin level was considered raised if the result was >300 mg/L. 5 ml of blood was collected with aseptic precautions and blood culture was performed by using agar based growth mediums and into bile broth using standard techniques. All children received antibiotics and ICU care as per standard operating procedures of department.

Treatment details, clinical course were noted in proforma. Follow up was kept till 1 month of discharge. Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

RESULTS

In present study 120 children satisfying study criteria were studied. Boys (63.3 %) were more than girls (36.7 %) and mean age was 36.46 ± 13.63 months. Mean duration of illness before admission and duration of fever before admission was 5.36 ± 1.26 days and 4.21 ± 3.48 days respectively. 58.3 % children received antibiotics before admission and 18.3 % children had malnutrition. Common suspected source of infection was pneumonia (35.0 %), Urinary tract infection (18.3 %), Meningitis (18.3 %), Intra-abdominal infection (6.7 %) and from other focus (21.7 %). Blood culture was positive in 23.3 %. Mean serum ferritin levels were 172.56 ± 118.3 ng/mL and ferritin ≥ 300 ng/mL was noted in 26.7 %.

Patient characteristics	No of cases/ mean ± SD	Percentage
Age (Months)	36.45±13.63	
Gender		
Male	76	63
Female	44	37
Duration of illness before admission (days)	5.36±1.26	

Duration of fever (Days)	4.21±3.48	
Receipt of antibiotics before admission	70	
Malnutrition ≤2SD of Z-score	22	
Suspected source of infection		
Pneumonia	42	
Meningitis	22	
Intra-abdominal infection	8	
Urinary tract infection	22	
Other focus	26	
Blood culture		
Positive	28	23
Negative	92	77
Leukocytes/µL	16942±6218	
CRP mg/dL	16.32±11.20	
Ferritin ng/mL	170.51±118.2	
Ferritin ≥300 ng/mL	32	27

Table 1: Over all characteristics

Criteria	No of cases (N=120)	Percentage
Cardiovascular organ dysfunction	78	65
Hypotension	46	38
Need for vasoactive drug to maintain blood pressure;	24	*20*
Unexplained metabolic acidosis: Base deficit>5 meq/L	20	16.7
Increased arterial lactate: >2 times upper limit of normal	10	8.3
Oliguria: Urine output <0.5 ml/kg/hour	42	35
Prolonged capillary refill: >5 sec	30	25
Core to peripheral room temperature gap >3°C	16	13.3

Acute respiratory distress syndrome (ARDS)	44	36.7
PaO2/FiO2 ratio ≤300	24	20
Need for non-elective invasive or noninvasive mechanical ventilation	44	36.7
Organ dysfunctions	48	40
Neurological,	24	20
Renal,	36	30
Hepatic	28	23.3
Hematologic	16	13.3

Table 2: severe sepsis criteria

Variables	Serum ferritin < 300 ng/ml (n=92) No. of cases / mean ± SD	Serum ferritin ≥ 300 ng/ml (n=28) No. of cases/ mean ± SD	P Value
Survivors	14 (15.2%)	10 (35.7%)	0.001
Non-survivors	78 (84.8%)	18 (64.3%)	0.001
Multiorgan dysfunction syndrome (MODS)	34 (37%)	22 (78.6)	0.001
Need of Mechanical Ventilation on Day 1	42 (45.7%)	12 (42.9%)	0.53

Table 3: Serum ferritin levels

DISCUSSION

Among the biomarkers, commonly used are leukocyte count, C-reactive protein (CRP) and ferritin levels, the last two had limited studies in pediatrics correlating serum levels with unfavorable outcomes. Assessment of severity of illness at admission is important for effective patient management, prognostication, and optimum utilization of resources. Simple interventions such as early rapid fluid administration, early antibiotics therapy, oxygen supplementation, and early use of inotropes through peripheral intravenous access have shown to improve the outcome of pediatric sepsis.[6]

In a global study, the prevalence of severe sepsis was 8.2% among children in ICU (<18 years old) with the associated hospital mortality of 25%, which was not different by age and between developed and developing countries. Ferritin is an iron-storing protein, in inflammatory

processes, a great production of this protein occurs, inducing a decrease in serum iron, believed to minimize the availability of iron to microorganisms. For this reason, ferritin in critically ill pediatric patients may be elevated, and it is associated with severity in some diseases. Elevate serum ferritin is associated with several inflammatory conditions, such as sepsis, multiorgan dysfunction syndrome (MODS), and Macrophage Activation Syndrome.[7]

Pedro Celiny et al.,studied 36 children aged 1 month-16 years with severe sepsis or septic shock requiring intensive care. Ferritin was <200 ng/mL in 13 children, 200–500 ng/mL in 11 children and >500 ng/mL in 12 children. The mortality associated with these groups was 23%, 9% and 58%, respectively. A ferritin >500 ng/mL was associated with a 3.2 (1.3–7.9) relative risk of death (p = 0.01). Ferritin Index of 1.7 was the best cutoff value for identifying those who died. Ferritin was raised in children with septic shock and high ferritin level was associated with poorer outcome. In study by Sarkar M et al., they studied 132 children of 1 month to 12 years with a diagnosis of septic shock or severe sepsis, mortality rate was 22.7%. PRISM III and PELODS-2 were significantly high in non-survivors (P ≤ 0.001 and 0.006, respectively). The cutoff value of ferritin at 2375 ng/dl had sensitivity 96.7% and specificity 88% to predict mortality.[8]

Serum ferritin values ≥2375 ng/mL in children with septic shock, and severe sepsis was significantly associated with mortality. Arnab Nandy et al., studied 47 children with sepsis who progressed to 2375 ng/dl had sensitivity 96.7% and specificity 88% to predict mortality.[9]

Serum ferritin values ≥2375 ng/mL in children with septic shock, and severe sepsis was significantly associated with mortality. State of MODS; 32 recovered from MODS. Significant differences in serum ferritin level were observed with severity of sepsis. There was clear demarcation of ferritin levels between sepsis severity stages. The proportion of death among the 47 MODS cases was 31.9%. ROC analysis in the MODS group indicated that serum ferritin >1994.3 ng/mL predicts mortality with sensitivity 66.7% and specificity 100%.[10]

CONCLUSION

Serum Ferritin levels can be helpful predictive marker of mortality in severe sepsis and higher ferritin is associated with increasing organ dysfunction. Serum ferritin levels >300 ng/ml can be useful in predicting outcome in children with severe sepsis.

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