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Original Research Article

A Prospective Observational Assessment of the Serum Ferritin for Predicting Outcome in Children with Severe Sepsis in the Pediatric Intensive Care Unit

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Abstract

Aim: The aim of the present study was to evaluate the prognostic ability of serum ferritin when estimated within 5 days of onset of illness in children with severe sepsis admitted to a pediatric intensive care unit.

Methods: The Present prospective and observational study was conducted in Department of Paediatrics, DMCH, Darbhanga, Bihar, India. Study duration was of 1 year. Study was started after obtaining approval from institutional ethics committee. In present study 50 children satisfying study criteria were studied.

Results: Boys (64%) were more than girls (36%) and mean age was 36.46 ± 13.64 months. Mean duration of illness before admission and duration of fever before admission was 5.37 ± 1.26 days and 4.23 ± 3.48 days respectively. 58% children received antibiotics before admission and 18% children had malnutrition. Common suspected source of infection was pneumonia (36%), Urinary tract infection (18%), Meningitis (18%), Intra-abdominal infection (6%) and from other focus (22%). 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%. According to severe sepsis criteria cardiovascular organ dysfunction (64%) was most common, followed by one or more Organ dysfunctions (40%) and acute respiratory distress syndrome (36%). We compared variables between cases with serum ferritin < 300 ng/ml (n=38) and cases with serum ferritin ≥ 300 ng/ml (n=12). We noted a statistically significant difference in cases of survivors, non-survivors, cases of multiorgan dysfunction syndrome (MODS), pediatric risk of mortality score (PRISM III) at 24 h and length of Pediatric intensive care unit (PICU) stay.

Conclusion: Serum Ferritin levels can be helpful predictive marker of mortality in severe sepsis and higher ferritin is associated with increasing organ dysfunction.

Keywords: Anemia, C-reactive protein, Infection, Mortality.

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. [1] 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. [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]

Sepsis is a major cause of morbidity and mortality in children worldwide [5], with high fatality rate. Biomarkers can diagnose, monitor, stratify, predict outcomes and aid in evaluating therapy response and recovery in sepsis. [6] C-reactive protein (CRP) and procalcitonin are the two extensively studied biomarkers. [7] Although CRP is widely available, its ability to accurately predict outcomes is yet to be established, while the use of procalcitonin is limited in developing countries. Elevated levels of serum ferritin in sepsis has been linked with poor outcome in children aged 28 days to 18 years. [8,9] Serum ferritin, when used as a biomarker to risk-stratify hospitalized children, would be helpful in clinical management.7 The role of serum ferritin as a biomarker to prognosticate severe sepsis in children with concurrent iron deficiency; however, still needs to be studied.

In critical illness due to sepsis, a systemic inflammatory response (SIR) is triggered and high levels of proinflammatory cytokines are present in early phases of illness. Because proinflammatory cytokines such as interleukin 6, interleukin 8, and tumor necrosis stimulate ferritin synthesis, ferritin level in these patients should be raised. Indeed, in critically ill adults, ferritin levels ranged from 340 to 830 ng/mL, which is much higher than the level expected in a 'normal' inflammatory response. [10,11]

The aim of the present study was to evaluate the prognostic ability of serum ferritin when estimated within 5 days of onset of illness in children with severe sepsis admitted to a pediatric intensive care unit.

Materials and Methods

The Present prospective and observational study was conducted in Department of Paediatrics, DMCH, Darbhanga, Bihar, India. Study duration was of 1 year. Study was started after obtaining approval from institutional ethics committee. In present study 50 children satisfying study criteria were studied.

Inclusion Criteria

Children 1-5 years age group with severe sepsis. Severe sepsis2 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).

1. Cardiovascular organ dysfunction - Despite >40 ml/kg of isotonic intravenous fluid in 1 hour ‑

Hypotension ≤5th percentile for age or systolic blood pressure <2 SD below normal for age; OR Need for vasoactive drug to maintain blood pressure; OR 2 of the following 5:

- Unexplained metabolic acidosis: Base deficit>5 meq/L
- Increased arterial lactate: >2 times upper limit of normal.
- Oliguria: Urine output <0.5 ml/kg/hour
- Prolonged capillary refill: >5 sec
- Core to peripheral room temperature gap >3°C

2. Acute respiratory distress syndrome (ARDS) was defined by ‑ the presence of a PaO2/FiO2 ratio ≤300 OR PaCO2 65 torr or 20 mm Hg over baseline PaCO2 OR Need for non‑elective invasive or noninvasive mechanical ventilation.
3. Organ dysfunctions (neurological, renal, hepatic or hematologic) was defined as
   i. **Neurological:** GCS score ≤ 11 or acute change in mental status with GCS of ≥ 3 points from abnormal baseline.
   ii. **Renal:** Serum creatinine >2 times upper limit of normal or 2 fold increase in baseline creatinine.
   iii. Hepatic: Total bilirubin ≥ 4 mg/dl or ALT level twice the upper limit of normal for age.
   iv. **Hematological:** Platelet count < 80,000 or a 50% decline in the platelet count from the highest value recorded over the last 3 days or INR >2.

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 was tested using chi- square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

Results

Table 1: Overall characteristics

Patient characteristics	No. of cases / Mean ± SD	Percentage
Age (months)	36.46 ± 13.64	
Gender		
Boys	32	64
Girls	18	36
Duration of illness before admission (days)	5.37 ± 1.26	
Duration of fever (days)	4.23 ± 3.48	
Receipt of antibiotics before admission	29	58
Malnutrition ≤2SD of Z-score	9	18
Suspected source of infection		
Pneumonia	18	36
Meningitis	9	18

Intra-abdominal infection	3	6
Urinary tract infection	9	18
Other focus	11	22
Blood culture		
Positive	12	24
Negative	38	76
Leukocytes/µL	16952 ± 6231	
CRP mg/dL	16.36 ± 11.27	
Ferritin ng/mL	172.56 ± 118.3	
Ferritin ≥300 ng/mL	13	26

Boys (64%) were more than girls (36%) and mean age was 36.46 ± 13.64 months. Mean duration of illness before admission and duration of fever before admission was 5.37 ± 1.26 days and 4.23 ± 3.48 days respectively. 58% children received antibiotics before admission and 18% children had malnutrition. Common suspected source of infection was pneumonia (36%), Urinary tract infection (18%), Meningitis (18%), Intra-abdominal infection (6%) and from other focus (22%). 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%.

Table 2: Severe sepsis criteria

Severe sepsis criteria	No. of cases	Percentage
Cardiovascular organ dysfunction	32	64
Hypotension	19	38
Need for vasoactive drug to maintain blood pressure	10	20
Unexplained metabolic acidosis: Base deficit>5 meq/L	8	16
Increased arterial lactate: >2 times upper limit of normal	4	8
Oliguria: Urine output <0.5 ml/kg/hour	17	34
Prolonged capillary refill: >5 sec	13	26
Core to peripheral room temperature gap >3°C.	7	14
Acute respiratory distress syndrome (ARDS)	18	36
PaO2/FiO2 ratio ≤300	10	20
Need for non‑elective invasive or noninvasive mechanical ventilation	18	36
Organ dysfunctions	20	40
Neurological	10	20
Renal	15	30
Hepatic	12	24
Hematologic	7	14

According to severe sepsis criteria cardiovascular organ dysfunction (64%) was most common, followed by one or more Organ dysfunctions (40%) and acute respiratory distress syndrome (36%).

Table 3: Serum ferritin levels

Variables	Serum ferritin < 300 ng/ml (n=38) No. of cases / mean ± SD	Serum ferritin ≥ 300 ng/ml (n=12) No. of cases/ mean ± SD	P value
Survivors	6 (15.7 %)	4 (36.36%)	0.001
Non-survivors	32 (84.21%)	7 (63.63%)	0.001
Multiorgan dysfunction syndrome (MODS)	14 (36.84%)	8 (72.72%)	0.001
Need of Mechanical Ventilation on Day 1	17 (44.73%)	5 (45.45%)	0.53

We compared variables between cases with serum ferritin < 300 ng/ml (n=38) and cases with serum ferritin ≥ 300 ng/ml (n=12). We noted a statistically significant difference in cases of survivors, non-survivors, cases of multiorgan dysfunction syndrome (MODS), pediatric risk of mortality score (PRISM III) at 24 h and length of Pediatric intensive care unit (PICU) stay. While duration of mechanical ventilation and need of mechanical ventilation on day 1 were comparable in both groups and difference was not significant statistically.

Discussion

Ferritin is an iron storage protein highly conserved and widely distributed throughout nature. [12] It has a major role in the complex process that regulates iron requirement. [13,14] Increased ferritin production is part of the acute phase reaction to infection and induces an iron-deficient milieu by reducing serum available iron. [14-16]

Clinical experience and various studies have shown that the most important measure in reducing the mortality from sepsis is early identification of the condition and prompt initiation of therapy. [17,18] 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. [19,20] 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. [5] 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. [21] 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. [22,23]

Elevate serum ferritin is associated with several inflammatory conditions, such as sepsis, multiorgan dysfunction syndrome (MODS), and Macrophage Activation Syndrome. [24] Pedro Celiny et al., [20] 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., [25] 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. Serum ferritin values ≥2375 ng/mL in children with septic shock, and severe sepsis was significantly associated with mortality.

Arnab Nandy et al., [26] studied 47 children with sepsis who progressed to a 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. [27] 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%. Major limitations of present study were single‑center study, factors such as pre-existing anemia/ liver dysfunction were not considered and investigations to estimate body iron store were not done. Multicentric large sample studies are recommended.

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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