Original Research Article

Prognostic Factors and Clinical Outcome in Children Hospitalized with Severe Lower Respiratory Tract Infection: A Nested Case Control Study

Pallavi Agarwal[1], A. K. Niswade[2]

[1]Junior Resident, [2]Professor,
Department of Pediatrics, Government Medical College, Nagpur, India

Corresponding Author: Pallavi Agarwal

ABSTRACT

Introduction: Severe LRTI is one of the leading causes of death in children especially below the age of 5 years. Hyponatremia is the most common electrolyte disturbance occurring in such patients. This study aims to explain the impact of hyponatremia on the course of disease and explore other associated risk factors which may worsen the clinical outcome.

Materials and methods: A nested case control study was conducted at a tertiary care hospital for a period of 2 years. Study comprised of 150 children aged 1 month to 5 years. The subjects were divided into cases and controls based upon presence or absence of hyponatremia. Continuous variable (age) was presented as Mean± SD. Other variables (Gender, TLC, CRP, Hypoglycemia, Acidosis) were expressed in numbers and percentages. Categorical variables (duration of hospital stay, need for mechanical ventilation and mortality) were compared between cases and controls using Pearson's Chi square test.

Results: Hyponatremia in severe LRTI was inversely proportional to the duration of hospital stay. There was a statistically significant increase in the rate of mechanical ventilation (odds ratio-3.03 with 95%CI of 1.44-6.42 and p value-0.0014) and mortality (odds ratio-3.03 with 95%CI of 1.44-6.42 and p value-0.001) in patients having hyponatremia. In univariate analysis, SAM, hypoglycemia and acidosis were found to be poor prognostic markers. However, in multivariate analysis, SAM and hypoglycemia emerged as independent risk factors. A change in microbiological profile was also reported.

Conclusion: Regular estimation of electrolytes is necessary to guide appropriate fluid and electrolyte management in severe LRTI. Presence of SAM and hypoglycemia in severe LRTI is predictor of worsened outcomes, hence needs to be addressed with caution. The changing trend of infectious organisms and increasing antibiotic resistance highlights the importance of judicious use of antibiotics.

KEYWORDS: LRTI (lower respiratory tract infection), TLC (total leukocyte count), CRP (C-reactive protein), SAM (severe acute malnutrition)

INTRODUCTION

Globally pneumonia is responsible for high morbidity and mortality among children under 5 years of age. The World Health Organization (WHO) has estimated an incidence of 0.37 episodes per child per year for clinical pneumonia, India accounts for 36% of the total WHO South East Asia regional burden. [1,2] In the most recent estimate of Acute Lower Respiratory

Infections associated mortality in India(2014), pneumonia was held responsible for 369,000 deaths (28% of all deaths), making it the single most important killer in this age group. [3] The national level surveys of India reported the prevalence of ARI, which was found to be 2.4–8.9% for the state of Maharashtra. [4,5] Reduction of these risk factors is suggested as a primary strategy to protect against pneumonia.

Electrolyte abnormalities are known to occur in severe LRTI with hyponatremia being the most common electrolyte abnormality detected in such cases. There is a lot of literature to prove the correlation between hyponatremia and severe LRTI (the reason for it being SIADH). [6-9] However, not many studies have been conducted to explore the significance of other factors that might worsen the outcome, if coexists with hyponatremia in severe LRTI. Hence this study was conducted to explore the significance of hyponatremia on the course of disease and to look for presence of such coexisting factors which might independently or in relation to hyponatremia worsen the outcome of children hospitalized with severe LRTI. Early recognition of these factors will allow implementation of early interventions and can significantly decrease morbidity and mortality associated with it.

MATERIALS AND METHODS

A nested case control study was conducted in the wards and ICU under Department of Pediatrics at a tertiary care center in central India on a heterogenous population from October 2014-2016.The study group consisted of 150 children between the age of 1 month to 5 years admitted to the tertiary care hospital with severe LRTI.

A written informed consent was obtained from parents or guardians of each enrolled subject who were willing to get enrolled in the study after getting briefed about the nature of study. Ethical clearance for conducting the study was obtained from the Institutional Ethics Committee. Baseline characteristics of children including age, weight on admission, gender and other characteristics including nutritional status, type of fluid received before hospitalization in case of referrals, blood glucose levels on admission, weight on admission as well as discharge were recorded. Subjects who were enrolled for the study were evaluated with relevant investigations like complete blood count, differential counts, random blood sugar, CRP, serum electrolytes, kidney function test, blood culture, and ABG analysis. Relevant imaging studies including chest X-ray were done as well. The subjects were then divided into cases and controls based upon presence or absence of hyponatremia (cases- with hyponatremia and controls-without hyponatremia).

Data was collected on structured data collection forms and all the findings were coded and entered in Excel master sheet. Continuous variables (age on admission) was presented as Mean ± SD using Mann Whitney U test. Categorical variables like gender and presence of risk factors like TLC, CRP, SAM, Hypoglycemia and Acidosis were expressed in actual numbers and percentages. Categorical variables (outcome variables i.e., duration of hospital stay, need for mechanical ventilation and mortality) were compared between cases and controls by performing Pearson's chi square test. Odds ratio and 95% confidence interval were calculated to determine the correlation of various risk factors (hyponatremia, SAM, hypoglycemia and acidosis) with the outcome variables (duration of hospital stay, need for MV and death) in severe LRTI. Multiple logistic regression analysis was performed using STATA software to determine the independent risk factors affecting morbidity and mortality in severe LRTI. In statistical test analysis, p value of <0.05 was considered significant.

RESULTS

In our study, maximum numbers of subjects (both cases and controls) were infants with mean age of 9 months in cases

and 11 months in controls, and interquartile range in both cases and controls was 5-24 months. 61.33% of the subjects were males and 38.67% were females, however there was no statistically significant difference observed in the two groups based upon sex (p value-0.314).

Table 1. Distribution based on age

Age (in months)	Cases	Controls
1 month-12months	47	38
12-24 months	2	13
24-36 months	8	6
36-48 months	7	8
48-60 months	11	10
Chi square-9.41; df-4 and p value-0.051		

Among cases, 33.33% had mild hyponatremia, 13.33% had moderate and 53.33% had severe hyponatremia. As far as the duration of hospital stay is concerned, the difference between cases and controls was statistically significant (p value-0.010). Cases had lesser duration of hospital stay due to greater mortality. And mortality in cases was inversely proportional to the degree of hyponatremia. The odds of need for mechanical ventilation was more in subjects with hyponatremia (odds ratio-2.04 with 95% CI of 1.01-4.16 and a p value of 0.0322). Additionally, as the severity of hyponatremia increased, the need for mechanical ventilation increased. The odds of death were higher in subjects with hyponatremia (odds ratio-3.03 with 95% CI of 1.44-6.42 and p value-0.0014). Also, as the severity of hyponatremia increased, mortality increased significantly (p value-<0.01).

Table 2. Risk factors associated with hyponatremia in LRTI

Risk Factor	Odds ratio	95% Confidence interval	p value	Result
TLC	2.22	1.08-4.62	0.019	NS
CRP	1.997	1.01-3.91	0.042	NS
SAM	2.19	1.06-4.53	0.031	NS
Hypoglycemia	-	-	0.616	NS
Acidosis	-	-	0.235	NS
NS- not statistically significant				

As seen in table 2, none of the biochemical markers or clinical markers had statistically significant association with hyponatremia in severe LRTI.

Table 3. Other risk factors affecting morbidity and mortality in severe LRTI (Univariate analysis)

Risk Factor	Duration of hospital stay (p value)	Need for mechanical ventilation (OR,95% CI, p value)	Mortality (OR,95%CI, p value)	Result
SAM	<0.01	3.26,1.56-6.79, <0.01	12.26, 5.28-28.50, <0.01	S
Hypoglycemia	<0.01	11.41,5.23-24.85, <0.01	12.52, 5.32-29.85, <0.01	S
Acidosis	<0.01	6.46, 3.09-13.5, <0.01	10.42, 4.79-22.65, <0.01	S
OR- Odds ratio, CI- confidence interval, S- statistically significant				

Univariate analysis was done, and severe acute malnutrition, hypoglycemia and acidosis emerged as risk factors affecting the outcome in severe LRTI. All the three factors showed inverse relation with the duration of hospital stay and increased the mechanical ventilation rates and mortality significantly (p value<0.01). Stepwise multiple logistic regression analysis was applied to identify independent risk factors that worsen the outcome. Taking the need for mechanical ventilation as the outcome, hypoglycemia (OR=7.48) was found to be an independent risk factor, whereas taking death as outcome, hypoglycemia (OR=9.73) and severe acute malnutrition (OR=4.83) were identified as independent risk factors. Among the culture positive subjects, maximum showed Acinetobacter baumannii (non-lactose fermenter) growth in their blood culture reports (10.67%) followed by 7.33% showing Pseudomonas aeruginosa; 4% showed Staphylococcus aureus; 4% showed Klebsiella pneumonia growth and 2.67% subjects showed E. coli growth in blood culture. This shows the changing trend of microbiological profile in cases of severe LRTI where gram negative organisms (particularly non-lactose fermenters) and

Staphylococcus aureus are emerging as main culprits.

DISCUSSION

The results in present study indicate that hyponatremia is common in children with severe LRTI and its development is associated with age of 1-12 months with median of 9 months and interquartile range of 5-24 months. Similar results were reported by Cheryl Kay Zogg et al [10] in their study, where they found that there is an increased risk of hyponatremia in pneumonia with a mean age of 14.7 months. The results in present study can be explained based on the fact that development of hyponatremia in severe LRTI requires the presence of both an increased ADH level and a source of electrolyte free water. Infants with severe LRTI frequently meet both the requirements. [11]

There was no difference between both the groups in present study as far as sex of the subject is concerned. Similar result was reported in the study by Afroditi Sakellaropoulou et al. [12]

In present study, we didn't find any statistically significant association between hyponatremia and raised total leukocyte count as was found in the study conducted by Afroditi Sakellaropoulou et al [12] wherein they reported that TLC as an independent predictor of hyponatremia. Since our study population had many other associated comorbidities like SAM which can independently affect the cell counts, our results deviated.

In present study, we found no statistically significant association of CRP with hyponatremia in severe LRTI, however, Hiroaki Kanai et al [13] reported that fever severity and CRP levels on admission are early markers of hyponatremia. We used qualitative measure of CRP not quantitative which could affect the results, which is why our study results deviated from the reported study.

In present study, using chi square for trend, the relation of degree of hyponatremia with duration of hospital stay was demonstrated i.e., as the severity of hyponatremia increases, duration of hospital stays decreases (p value-0.010). Similar results were reported by Afroditi Sakellaropoulou et al [12] in their study where they found negative association between the degree of hyponatremia and duration of hospital stay (z= -3.398, p value-0.001).

In present study, we found that the need for mechanical ventilation increased by association of hyponatremia with severe LRTI. Similar results were reported by Marya D Zilberg et al [14] in their study where they found that mechanical ventilation rates were increased when hyponatremia was associated with pneumonia (3.9% v/s 2.3%, p-0.01).

In present study, we found that mortality was more among cases, similar results were reported by S. Singhi et al [15] i.e., 3.5 times increase in mortality in hyponatremic patients as compared to their normonatremic controls.

SAM was found to be an independent risk factor in increasing mortality in severe LRTI, similar results were reported by Mohammad Jobayer Chisti et al [16] They found that SAM increased mortality in cases of severe pneumonia (20% v/s 4%; p value<0.001). This finding in our study can be explained by understanding the different pathophysiological mechanisms operating in body of severely malnourished children resulting in inability to carry out routine operations of normal pathways. These reductive adaptations described in the work by Collins et al [17] may help explain findings in present study, suggesting that as the severity of nutritional insult increases, reductive adaptations progressively limit the body's ability to respond to stresses such as infection.

In present study we found that hypoglycemia is an independent risk factor for both increasing mechanical ventilation rates as well as mortality in severe LRTI. Eric M Mortensen et al [18] also found that

unadjusted mortality for those who were hypoglycemic was 27.3% v/s 8.6% for those who were not (p= 0.0003). These results can be explained by understanding the pathophysiology of hypoglycemia. Infections may cause hypoglycemia by increased glucose utilization by macrophage-rich tissues including liver, lung etc. and from depressed hepatic gluconeogenesis that may result from decreased sensitivity to stress hormones and/or adrenal failure. This suggests that patients with pneumonia who present with hypoglycemia require a higher level of care. [19]

In present study we found that acidosis increased mortality and morbidity in severe LRTI but was not found to be an independent risk factor for the same. Our results are comparable with the results of a study by Rakesh Bhadade et al, [20] but they found metabolic acidosis as independent predictor of mortality in ARDS.

In present study we observed that new organisms are emerging as culprits in causing bacteremia in cases of severe LRTI. Similar results were reported by Sagar Khadanga et al [21] where they observed that Gram-negative bacilli (GNB) as a group exceeded marginally over S. pneumoniae. This change can be attributed to overuse and inappropriate prescription of antibiotics even for viral infections and due to increasing usage of pneumococcal vaccine in developing countries leading to decline in incidence of pneumococcal infection in children. [21,22]

CONCLUSION

As we have shown that hyponatremia among hospitalized children with severe LRTI is associated with worsened clinical outcomes as well as with an increase in the utilization of mechanical ventilation and hospital resources. Hence regular estimation of serum electrolyte concentration is necessary to guide appropriate fluid and electrolyte management of children with severe LRTI requiring hospitalization. Therefore, the use of isotonic fluids is recommended for the parenteral therapy of patients with severe lower respiratory tract infection. Our findings suggest that presence of severe acute malnutrition, hypoglycemia and acidosis in children with severe lower respiratory tract infection warrants implementation of protocolled management to mitigate the myriad of devastating consequences associated with symptomatic and advanced disease. Also, the observation of changing trend of infectious organisms and increasing antibiotic resistance underscores the importance of judicious use of antibiotics in clinical practice.

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