A study to assess the outcome of critically ill children with hypoalbuminemia admitted in a tertiary care center

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ABSTRACT

Introduction: Albumin is a major plasma protein, constituting around 55% of total protein load of the plasma. Hypoalbuminemia is commonly found in patients with heart failure, cirrhosis, nephrotic syndrome, severe malnutrition, thermal injuries, and protein-losing enteropathy. **Objectives:** The objectives of the study were to assess the outcome of critically ill children with hypoalbuminemia admitted in a tertiary care center. **Materials and Methods:** A total of 80 patients, who were diagnosed to be having hypoalbuminemia, were admitted in the pediatric intensive care unit (PICU) in Bengaluru. 80 patients with similar characteristics to cases and with normal levels of serum albumin were included in the study as "controls." The study was undertaken over the duration of 1 year. **Results:** The mean serum albumin in cases at admission was 2.5±0.5 mg/dl and in controls was 4.3±0.6 mg/dl. Mean length of PICU stay among cases was 7.8±5.1 days and among controls was 5.1±3.2 days ($p<0.001$). Among cases 32.5% died and 67.5% survived, similarly among controls 35% died and 65% survived ($p=0.73$). **Conclusion:** The level of albumin in the children plays a very important role in determining the treatment options and the outcome of the treatment in the form of an increased rate of mortality and morbidity.

Key words: *Albumin, Critically ill, Paediatric, Pediatric intensive care unit*

Albumin is a major plasma protein, constituting around 55% of total protein load of the plasma and is synthesized in the liver. Albumin plays major role in maintaining plasma oncotic pressure and acts as carrier protein for various hormones, metabolic intermediates, drugs, etc. It also plays role in inhibition of platelet aggregation, acts as anti-inflammatory antiapoptotic antioxidant [1], as such; it transports certain hormones (egg, thyroid, estrogenic, and cortisol), unconjugated bilirubin and other organic anions, and many drugs (e.g., penicillin and warfarin).

Hypoalbuminemia is commonly found in patients with heart failure, liver cirrhosis, nephrotic syndrome, severe malnutrition, thermal injuries, and protein-losing enteropathy. Typically, hypoalbuminemia is ascribed to diminished synthesis (e.g., malnutrition, malabsorption, or hepatic dysfunction) or increased losses (e.g., urinary losses with nephropathy or protein-losing enteropathy). Diversion of synthetic capacity to other proteins (acute-phase reactants) is another cause of hypoalbuminemia. Inflammatory disorders can accelerate the catabolism of albumin while simultaneously decreasing its manufacture. During critical illness, capillary permeability increases dramatically and alters albumin exchange between intravascular and extravascular compartments.

The prognostic value of serum albumin extends to critically ill patients [2]. A low serum albumin concentration correlates with increased length of stay in the intensive care unit (ICU) and with complication rates, such as ventilator dependency and the development of new infection [3]. Patients who were in the ICU for 7 days or more and survived and were able to recover to a higher mean serum albumin concentration than non survivors [2,3]. Hypoalbuminemia is associated with poor outcomes in adult critical illness, but whether this association exists in pediatric patients remains unclear. There is a paucity of data evaluating serum albumin level on admission as a predictor of outcome in critically ill children [4,5]. The objective of this study was to evaluate the frequency of hypoalbuminemia and its outcome in critically sick children admitted to pediatric ICU (PICU) in a tertiary care center.

MATERIALS AND METHODS

This prospective comparative study was conducted in a tertiary care center in Bengaluru for the duration of 1 year, i.e., from March 2014 to March 2015. The study was undertaken after obtaining the consent from the Institutional Ethics Committee and informed consent from the patients. Patients aged >1 year and <12 years admitted in the PICU and diagnosed with hypoalbuminemia were included as "cases." Hypoalbuminemia was defined as serum albumin levels below the reference values of 3.5–4.5 g/dL [6]. Patients admitted in the PICU with similar characteristics to cases, but with normal

serum albumin levels, were included as "controls." Chronically immunosuppressed patients (patients on steroids, neutropenic patients, and immunosuppressive agents); patients hospitalized within previous 14 days; patients with alternate diagnosis during follow-up; and patients diagnosed with the chronic obstructive pulmonary disease were excluded from the study.

The sample size was calculated using the following formula where z_{crit} and z_{pwr} are cutoff points along the X-axis of a standard normal probability distribution that demarcate probabilities matching the specified significance criterion and statistical power, respectively, p1 and p2 are pre-study estimates of the two proportions to be compared. D = (p1-p2) (i.e., the minimum expected difference) and p = (p1+p2)/2. A significance criterion of 5% and a power of 90% were chosen.

$$N=2[Z_{crit}\sqrt{2\bar{p}(1-\bar{p})}+z_{pwr}\sqrt{\bar{p}_1(1-\bar{p}1)+\bar{p}_2(1-\bar{p}_2)}]^2/D^2$$

A questionnaire with demographic information, clinical signs and symptoms, laboratory and radiographic findings, was completed for each patient. At the time of initial evaluation, a thorough history (including birth, dietary, family, past, and current treatment) was taken into care and detailed examination of each child including anthropometry (weight, height, BSA, and according to Indian Association of Paediatrics classification) was done. Following investigations were done on each patient: Chest radiograph (poster-anterior or anterior-posterior view) at presentation; electrocardiogram; arterial blood gas analysis and serum electrolyte measurement; complete blood counts, blood urea, and serum creatinine; and fasting blood glucose and serum albumin on admission and day 3 of admission. The patients' clinical outcome in terms of mortality was recorded and analyzed. Multiple organ dysfunction syndrome (MODS) is defined as the presence of altered organ function in acutely ill patients such that homeostasis cannot be maintained without intervention. It usually involves two or more organ systems [7].

Data were entered into Microsoft excel data sheet and were analyzed using SPSS 19 version software. Categorical data were represented in the form of frequencies and proportions. Chi-square test was used as test of significance for qualitative data.

RESULTS

A total of 160 study subjects were included in the study among which 80 subjects were taken as cases, and 80 subjects were taken as controls. The mean age of children in cases was 6.5±3.6 years and in controls was 6±3.3 years with no significant difference in age distribution between two groups. Nearly 42.5% of females were in cases and 47.5% of females in the control group with no significant difference between the two groups.

Among cases, 26.2% had pedal edema and 23.8% had anasarca, among controls 16.2% had pedal edema and 2.5% had anasarca (p<0.001). The most common illness was related to nervous system in cases and AFI in controls. There was no significant difference in system affected between two groups as shown in Table 1.

Mean serum albumin in cases at admission was 2.5±0.5 mg/dl and in controls was 4.3±0.6 mg/dl (p<0.001). At day 3, increase in serum albumin level was observed in both cases and controls; however, difference in both the groups was still significant as shown in Table 2. Mean hemoglobin among cases was 7.7±1.8 g% and among controls was 8.0±2.1 g% (p=0.462).

The mean PRISM III score among cases was 28.3±12.9 and among controls was 27.7±19.7 with no significant difference between two groups as shown in Table 3. Mean length of PICU stay among cases was 7.8±5.1 days and among controls was 5.1±3.2 days and the difference was statistically significant (Table 3). In cases, 58.8%

Table 1: Clinical features of study participants

Clinical features	Group		p value
	Cases	Controls	
	Count (%)	Count (%)	
Edema			
Absent	40 (50.0)	65 (81.2)	χ^2=21.59, df=2, P<0.001*
Pedal edema	21 (26.2)	13 (16.2)	
Anasarca	19 (23.8)	2 (2.5)	
System affected			
AFI	23 (28.7)	20 (25.0)	χ^2=4.542, df=5, P=0.474
Nervous system	24 (30.0)	17 (21.2)	
Cardiovascular system	14 (17.5)	12 (15.0)	
Respiratory system	8 (10.0)	14 (17.5)	
Renal system	7 (8.8)	10 (12.5)	
Hematology	4 (5.0)	7 (8.8)	

Table 2: Laboratory findings of study participants

Laboratory findings	Group		p value
	Cases	Controls	
	Mean±SD	Mean±SD	
Serum albumin on admission	2.5±0.5	4.3±0.6	<0.001*
Serum albumin day 3	2.8±0.6	4.4±0.5	<0.001*
Hemoglobin	7.7±1.8	8.0±2.1	0.462

SD: Standard deviation

Table 3: Outcome of study participants

Outcome of the treatment	Group		p value
	Cases	Controls	
	Count (%)	Count (%)	
Length of PICU stay (days)	7.8±5.1	5.1±3.2	<0.001*
PRISM III score	28.3±12.9	27.7±19.7	<0.05
Ventilation required			
No	33 (41.2)	36 (45.0)	χ^2=0.229, df=1, P=0.632
Yes	47 (58.8)	44 (55.0)	
MODS comparison			
No	50 (62.5)	51 (63.7)	χ^2=0.027, df=1, P=0.870
Yes	30 (37.5)	29 (36.2)	
Outcome			
Death	26 (32.5)	28 (35.0)	χ^2=0.112 df=1, P=0.73
Survived	54 (67.5))	52 (65.0)	

PICU: Pediatric intensive care unit, MODS: Multiple organ dysfunction syndrome

required ventilator support and in controls 55% required ventilator support. Among cases, 37.5% had MODS while 36.2% controls had MODS. Among cases 32.5% died and 67.5% survived, similarly among controls 35% of them died and 65% survived. There was significant difference in the outcome between two groups (Table 3).

DISCUSSION

A total of 160 patients with 80 patients in each group were analyzed and the mean age of patients in our study with hypoalbuminemia was 6.5±3.6 years and 6 years among normal groups. The mean age of children in our study was much higher when compared to the study findings of Tiwari *et al.* [8] and Aharon K *et al.* [9]. The gender was found to be statistically not significant in our study but Tiwari *et al.* [8] showed that male had more predominance of low albumin in critically ill patients than female patients.

The incidence of pedal edema and anasarca was seen more among the cases with hypoalbuminemia than normal patients. The role of albumin, in the maintained normal oncotic pressure, is well recognized by many literatures. The loss of albumin leads to decrease in oncotic pressure leading to edema and anasarca. The involvement of various systems in our study was also similar to the findings of the study done by Tiwari *et al.* [8]. The critical illness among the children changes the distribution of albumin level in both intravascular and extravascular, due to changes in the capillary permeability leading to increased vascularity and loss of albumin in the body. It is further aggravated by the damage in the endothelial lining of the vessels due to the increase in the free radicals due to infection and further septic shock increases the rate of excretion of albumin. It is also well known that severe illness and inflammation among the children leads to increased production of inflammatory mediators such as Interleukin 6 and tumor necrosis factor which has an adverse effect on transcription of albumin mRNA and even the synthesis of albumin [5,10,11].

The albumin level was very low and common among the children admitted to PICU in our study which is seen in other studies done by Kumar *et al.* [12] and Horowitz and Tai [4]. In our study, the mean serum albumin level on admission in cases was 2.5 g/dl which was comparatively less than in the controls (4.3 g/dl). The mean albumin level of cases in our study was much lower than the other studies done by Horowitz and Tai [4] and Durward *et al.* [10] but similar to the study findings of Tiwari *et al.* [8] and Kumar *et al.* [12].

The albumin level gradually increased with duration of stay in PICU with the standard treatment. In our study, the hypoalbuminemic patients had a prolonged PICU stay, and majority required ventilation support for survival when compared to the control group. The results of our study were largely consistent with the findings of other studies done by Horowitz and Tai [4], Durward *et al.* [10], and Murray *et al.* [13]. The progression of critically ill children toward MODS was seen in nearly one-third of the patients. The progression of illness toward MODS in hypoalbuminemia was also seen in the study done by Tiwari *et al.* [8] and Yap *et al.* [14].

The significant association between mortality and the level of albumin in the critically ill children was found in our study as shown in previous studies done by Tiwari *et al.* [8] and Kumar *et al.* [12]. However, our study has few limitations. Results of the study cannot be generalized as the study was conducted in a tertiary care hospital where the cases are admitted at the severe stages of the disease with many complications. The albumin level could be measured daily until the time of discharge, but we could not do it due to various financial and feasibility issues, and this is a major study limitation.

CONCLUSION

The level of albumin in the children plays a very important role to determine the outcome of the disease and children with low albumin need to be treated with high priority. The pediatrician should look for all the causes of hypoalbuminemia and plan the treatment for the better outcome for the patient.

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