Serum albumin perturbations in cyanotics after cardiac surgery: Patterns and predictions

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ABSTRACT

Introduction: Hypoalbuminemia is a well-recognized predictor of general surgical risk and frequently occurs in patients with cyanotic congenital heart disease (CCHD). Moreover, cardiopulmonary bypass (CPB)-induced an inflammatory response, and the overall surgical stress can effect albumin concentration greatly. The objective of his study was to track CPB-induced changes in albumin concentration in patients with CCHD and to determine the effect of hypoalbuminemia on postoperative outcomes. **Materials and Methods:** Prospective observational study conducted in 150 patients, Group 1 ≤18 years ($n = 75$) and Group 2 >18 years ($n = 75$) of age. Albumin levels were measured preoperatively (T1), after termination of CPB (T2) and 48 h post-CPB (T3). Primary parameters (mortality, duration of postoperative ventilation, duration of inotropes and duration of Intensive Care Unit [ICU] stay) and secondary parameters (urine output, oliguria, arrhythmias, and hemodynamic parameters) were recorded. **Results:** The albumin levels in Group 1 at T1, T2, and T3 were 3.8 ± 0.48, 3.2 ± 0.45 and 2.6 ± 0.71 mg/dL; and in Group 2 were 3.7 ± 0.50, 3.2 ± 0.49 and 2.7 ± 0.62 mg/dL respectively. All patients showed a significant decrease in albumin concentration 48 h after surgery ($P < 0.01$). Analysis between the groups, however, showed no statistical difference. Eleven patients expired during the study period, and nonsurvivors showed significantly lower serum albumin concentration 48 h after surgery 2.3 ± 0.62 mg/dL versus 3.7 ± 0.56 mg/dL in the survivors ($P < 0.05$). Receiver operating characteristic curve showed that a baseline albumin cut-off value of 3.3 g/dL predicts mortality with a positive predictive value 47.6% and a negative predictive value of 99.2% ($P < 0.05$). A strong correlation was seen between albumin levels at 48 h with duration of CPB ($r^2 = 0.6321$), ICU stay ($r^2 = 0.7447$) and incidence of oliguria ($r^2 = 0.8803$). **Conclusions:** The study demonstrated similar fall in albumin concentration in cyanotic patients (both adult and pediatric) in response to CPB. Low preoperative serum albumin concentrations (<3.3 g/dL) can be used to identify and prognosticate subset of cyanotics predisposed to additional surgical risk.

Key words: Albumin; Cardiac biomarkers; Cardiopulmonary bypass; Cyanotic congenital heart disease; Prognosis; Risk-prediction; Tetralogy of Fallot

INTRODUCTION

Besides dietary intake, nonnutritional factors such as chronic inflammation, recurrent infections, hepatic failure, renal dysfunction, altered gastrointestinal function, increased right-sided heart pressures, dilution from fluid overload, and medications can influence serum albumin concentration. Such states are frequently encountered in patients with long-standing cyanotic congenital heart disease (CCHD).[1-3] Worsening of cyanosis brings about a deterioration in their

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nutritional status. In these subset of patients with the acute-phase response and metabolic stress, the certainty of serum albumin as a nutritional index marker has been questioned in the past.[4]

Despite the controvery, serum albumin has been extensively evaluated as a biomarker for predicting adverse outcomes and mortality in patients undergoing high-risk surgery.[5,6] Various studies have shown that low blood levels of albumin can indicate malnutrition and a poorer prognosis in terms of increased morbidity and mortality[7-10] Cardiac surgery and cardiopulmonary bypass (CPB) induced inflammatory response syndrome leads to endothelial dysfunction and edema secondary to capillary leak across all major organ systems all of which manifest in the immediate postoperative period. As most of the early interventions are based on clinical findings, blood gas analysis, and serum lactate, there is a need to incorporate some readily available biochemical parameters, which can predict morbidity associated with organ dysfunction earlier, thereby taking steps to decrease the same.

Cyanotic patients develop chronic hypoxia-induced physiological changes which make them behave differently under stress and otherwise. Long standing hypoxia influences multiorgan systems and entities like cyanotic glomerulopathy are now well established.[11] The results of studies conducted in general population thus cannot be portrayed directly on this subset of population. Mortality and outcomes based on prospective serum albumin measurements in cyanotic patients undergoing corrective surgery are also lacking. Data are also lacking on perioperative comparative evaluation of pediatric and adult cyanotics.

The study was thus aimed to quantify and compare the perturbations in serum albumin concentration in response to CPB in pediatric and adult cyanotics undergoing intracardiac repair for tetralogy of Fallot. We also sought to assess the impact of perioperative variations in serum albumin concentration in predicting early morbidity and mortality after cardiac surgery in cyanotics.

MATERIALS AND METHODS

Institutional Ethics Committee approval was obtained and written informed consent was undertaken from patients/parents (in cases of children with age <18 years). This prospective observational study was conducted in 163 patients with tetralogy of Fallot scheduled to undergo elective intracardiac repair by a single surgeon from September 2012 to August 2013. During the enrollment process, patients with preexisting renal failure ($n = 4$) (serum creatinine >2.0 mg/dL, anuria or oliguria requiring peritoneal/hemodialysis), cardiac failure ($n = 3$), liver dysfunction (aspartate aminotransferase/alanine aminotransferase >40 U/L), immune or central nervous system dysfunction ($n = 2$), local or systemic infection or inflammation (fever, leukocytosis, tachycardia or tachypnea) ($n = 4$), or on immune-suppressive/anti-inflammatory therapy/albumin replacement were excluded from the analysis. The final study group comprised 150 patients, which were equally divided into two groups of 75 patients each based on age. Group 1 included patients <18 years of age and the Group 2 included adults of more than 18 years of age.

Clinical management

Anesthetic and surgical management were standardized in all patients including the anesthesia and surgical team members. Patients were premedicated with phenargan 0.5 mg/kg and morphine 0.1 mg/kg intramuscular 30 min before shifting to the operation theater. Anesthesia was induced with ketamine (1–2 mg/kg), fentanyl (2–3 mcg/kg), and rocuronium bromide (0.8–1 mg/kg) to facilitate tracheal intubation. Maintenance of anesthesia was then carried out with sevoflurane (0.5–1%) in the oxygen-air mixture and intermittent doses of fentanyl, midazolam, and vecuronium. Baseline activated clotting time (ACT) was noted before systemic heparinization with 4 mg/kg unfractionated heparin to achieve a target ACT of more than 480 s. Monitoring included five lead electrocardiogram, SpO_2, invasive blood pressure, central venous pressure, and urine output. Transesophageal echocardiography was performed in patients weighing more than 5 kg. A membrane oxygenator was used for all patients during CPB. The conventional CPB circuit was used which was primed with lactated Ringer's solution 20 ml/kg, sodium bicarbonate (7.5%) 1 ml/kg, and mannitol (20%) 0.5 g/kg and 100 U/kg of unfractionated heparin. Packed red blood corpuscles were added to pump volume during CPB, to maintain a target hematocrit of 25% ±5%. All the patients underwent corrective surgery for tetralogy of Fallot under CPB with temperatures brought down till 28°C. Circulatory arrest and myocardial preservation were achieved by administering del Nido cardioplegia for all the cases using cardioplegia delivery system.[12] Arterial blood gas analyses and ACT were performed at 30 min intervals during the surgery. Systemic pump flows were maintained between 120 and 200 ml/kg/min.

At the end of the surgery, systemic heparinization was reversed with protamine 1.3 mg/mg of heparin, the sternum was closed and patients were shifted to Intensive Care Unit (ICU) for elective postoperative ventilation. All the patients were started on infusion dopamine and if required on infusion dobutamine was started to maintain hemodynamics.

Albumin

2.5 ml of arterial blood sample was taken at three different time intervals to monitor the serum albumin levels which included preoperative (T1), after the termination of CPB (T2) and 48 h post-CPB (T3). Samples were collected in ethylenediamminotetraacetic acid vials and plasma was recovered immediately from these samples by centrifugation at 3000 g for 10 min at 4°C, divided into aliquots and frozen at −70°C until use.

Parameters evaluated

Demographic data were noted in all the patients. A preoperative baseline echocardiography and the routine hematological investigations were also performed. A baseline heart rate, blood pressure, and central venous pressure were also recorded. Albumin levels at three different time intervals as mentioned above were recorded. Intraoperative CPB duration was noted. Once the patients were shifted to the ICU, the primary parameters recorded were the duration of postoperative ventilation, duration of the requirement of inotropes and duration of stay in the ICU. Secondary parameters included urine output, oliguria, and hemodynamic parameters. Oliguria and renal failure were defined as per RIFLE criteria.[13]

Statistical analysis

The statistical analysis was carried out using SPSS version 20 (IBM corporation, USA) and techniques applied were Chi-square for comparing categorical data. Assuming that the baseline values of albumin in two group (age ≤18 or age >18) are same and after two follow-ups the mean level of albumin was 3.85 ± 0.9 and 3.6 ± 0.4 respectively. Further with alpha taken as 5% and power 90%, with 1:1 ratio and by the method of change, we needed to enroll 148 cases, i.e., 74 in each group. The continuous data was compared between two groups using Student's *t*-test. To see the changes in albumin levels over a period repeated measure analysis followed by *post hoc* comparison by Bonferroni method. Correlations between serum albumin concentration and continuous clinical variables were performed using Pearson's correlation method. Nonparametric Mann–Whitney test was used to correlate mortality.

Mortality percentages are presented with 95% confidence interval. $P < 0.05$ was considered as significant. To further assess the association between mortality and the serum albumin concentration recorded at various time frames, subsequently testing for accuracy with a receiver-operating characteristics (ROCs) analysis was done, with the area under the curve as a measurement of accuracy, according to the methodology used and validated in other studies. From the ROC analysis, the best cut-off values for serum albumin concentration was identified at the point where the sum of sensitivity and specificity was the highest according to the Youden index ([sensitivity + specificity] − 1). Sensitivity, specificity, and positive and negative predictive values for each cut-off value in each risk score were calculated.

RESULTS

The patient demographic data and various secondary parameters have been enlisted in Table 1. Duration of mechanical ventilation, duration of inotropes, ICU length of stay and hospital stay were significantly longer in the younger subset. Adult cyanotics however had a higher incidence of postoperative oliguria. Serum albumin levels showed a significant decrease from baseline to 48 h post-CPB [Table 2] in both groups. Analysis between the groups however showed no statistically significant difference between them at all time frames.

Strong positive correlation was seen between the serum albumin levels 48 h after CPB and postoperative measures such as duration of cardiopulmonary bypass

Table 1: Patient demographic data and postoperative parameters in the two groups

Parameters	Group 1 (*n*=75)	Group 2 (*n*=75)	P
Age (years)	4 (0.11-14)	31 (16-55)	<0.001
Weight (kg)	12 (2-56)	48 (30-85)	<0.001
Males/females (*n*)	42/33	48/27	0.73
Females (*n*)	33	27	0.81
Serum creatinine (mg/dl)	1.1±0.3	1.2±0.2	0.23
CPB duration (minutes)	90.2±8.18	87.9±9.77	0.12
Mortality, *n* (%)	7 (9.33)	4 (5.33)	0.59
Mechanical ventilation (h)	16.7±3.21	10.9±3.15	<0.001
Duration of inotropes (days)	3.6±1.27	2.0±1.02	<0.001
ICU stay (days)	4.5±1.19	3.0±1.19	<0.001
Hospital stay (days)	7.7±1.65	5.8±1.62	<0.001
Oliguria (*n*)	12.6±5.58	21.5±5.17	<0.001
Reoperation for bleeding, *n* (%)	4	6	0.87

Data expressed as mean±SD or median (range) in the two groups. CPB: Cardio pulmonary bypass, SD: Standard deviation, ICU: Intensive Care Unit

($r^2 = 0.6321$), duration of ICU stay ($r^2 = 0.7447$), incidence of oliguria ($r^2 = 0.8803$) [Table 3]. In all 11 patients expired during the study period. Seven patients were from Group 1 with age ≤18 years and four patients were from Group 2 with age >18 years ($P > 0.05$). Analysis of serum albumin levels in the 11 patients who had expired showed that serum albumin at the termination of CPB and 48 h post-CPB was lower in nonsurvivors, and the difference was statistically significant [Table 4].

The ROC curve depicts the relationship between the albumin levels taken at the three-time frames and mortality [Figure 1]. The area under the ROC curves of the serum albumin levels analyzed at baseline was 93.5% with a sensitivity and specificity of 90.9% and 92.1%. A cut-off value of 3.3 g/dL predicted mortality

Figure 1: Receiver operating characteristic curve depicting the relationship between the albumin levels at the three time frames and mortality in the sample population. ALB1, ALB2, ALB3 = albumin concentration at T1, T2, and T3 respectively

Table 2: Serum albumin levels in the two groups at the three time frames

	T1	T2	T3	*P* value T1 versus T3
Group 1 (g/dL)	3.8±0.48	3.2±0.45	2.6±0.71	<0.01
Group 2 (g/dL)	3.7±0.50	3.2±0.49	2.7±0.62	<0.01
P value Group 1 versus Group 2	0.89	0.62	0.79	

Data expressed as mean (g/dL)±SD. T1: Baseline/preoperative, T2: After termination of cardiopulmonary bypass, T3: 48 h postcardiopulmonary bypass, SD: Standard deviation

with a positive predictive value 47.6% and a negative predictive value of 99.2% [Table 5].

DISCUSSION

Hypoalbuminemia in patients with CCHD may be attributed to a combination of malnutrition and homeostatic disorders, which account for the physiologic adaptation to cardiac disease and is an added area of concern due to the associated increased the risk of complications. Exposing these debilitated patients to corrective cardiac surgery is associated with an additional impaired synthesis, catabolic stress, decreased amino acid supply, water retention, and loss of proteins to the extravascular space due to the alteration of the endothelial permeability.[14,15]

Albumin is a better prognostic indicator than anthropomorphic markers of nutritional status and can detect protein-energy malnutrition, which may be clinically unrecognizable and not necessarily accompanied by a fall in body weight, but is associated with significantly increased the risk of morbidity and mortality.[16,17] Decreased albumin levels have been associated with high concentrations of procalcitonin, C-reactive protein, α1-antitrypsin, and interleukin-6 after cardiac surgery.[18] Despite its prognostic ability, Gibbs *et al*. reported wide variation in the rate of preoperative serum albumin testing, ranging from 20% to 98% of cases, with a median testing rate of 60%. With analysis restricted only to cases with an ASA score of 3 or higher (59% of all cases), the variation in the proportion of patients tested remained large (from 27% to 97% of cases, with a median of 72%).[19]

A sudden decline in the concentration of serum albumin seen in the postoperative period in our study is unlikely to have been caused by a decreased synthesis alone owing to the long half-life of albumin in plasma. After cardiac surgery, extracorporeal circulation induced systemic inflammatory response leading to endothelial injury causes microcapillary leak, which is the main underlying mechanism for the trans-capillary flow of plasma proteins into the extravascular space causing hypoalbuminemia.[20,21]
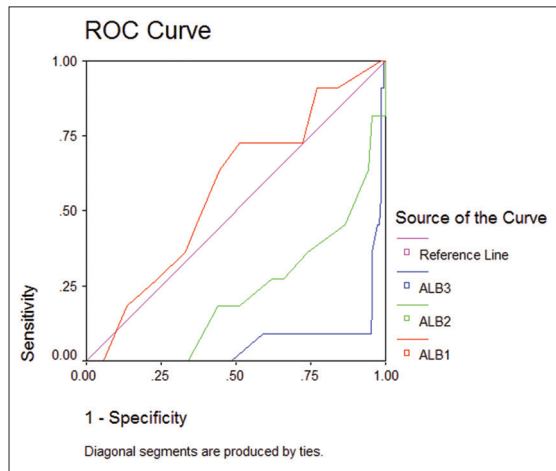
Table 3: Correlation between albumin at T3 and various postoperative outcomes

	Hospital stay	Oliguria	Duration of CPB	Duration of ventilation	Duration of ICU stay	Duration of inotropes
Pearson correlation coefficient	0.117	−0.1239	0.0393	0.1131	−0.0268	−0.0982
r²	0.1525	0.8803	0.6321	0.1680	0.7447	0.2318

CPB: Cardio pulmonary bypass, ICU: Intensive Care Unit

In our study, albumin concentration at 48 h after surgery had a positive correlation with the duration of CPB ($r^2 = 0.632$) establishing the role of the extracorporeal circuit in systemic inflammatory response activation and causation of endothelial cell injury [Table 3].[22] The patients exposed to longer durations of CPB progressively developed lower serum albumin levels 48 h after the surgery. Also noted in our study was the fact that fall in serum albumin was more severe in the younger subset of the population in comparison to the older patients, but the difference was not statistically significant. Besides the numerous factors that predispose to a longer hospital stay in pediatric population, somewhat lower serum albumin concentration in the pediatric population could have contributed to the increased ICU/hospital stay, increased requirement of inotropes and mechanical ventilation in them.

Baseline albumin concentration lower than 3.3 g/dL (cut-off value) was associated with adverse outcome in comparison to Caucasian children (cut-off value 3.0 g/dL) probably reflecting the greater magnitude and persistence of the systemic metabolic response to surgical stress in our population subset.[5] In the presence of unmet dietary requirements, visceral protein stores are metabolized and depleted, causing organ malfunction, which may present as gastrointestinal malabsorption, impaired immunological response, and impaired production of albumin and other proteins in the liver.[22,23] Moreover, the nonsurvivors showed significantly lower levels of serum albumin, perhaps proposing the contributory role of hypoalbuminemia in multiorgan failure.

Postcardiac surgery hypoalbuminemia is a result of the pathological state, and albumin administration is uncalled for unless associated with severe hypoalbuminemia with intolerance to enteral feeding, protein-losing enteropathy and fluid resuscitation aftershock. System inflammatory response associated trans-capillary leakage of plasma proteins may prevent serum albumin levels from increasing despite therapeutic albumin transfusion in these patients. A strong positive correlation exists between hypolabuminemia and acute renal failure after open heart surgery.[24,25] Our study also showed a strong correlation between the incidence of oliguria and serum albumin levels [r^2 of 0.88, Table 4]. Furthermore, the incidence of oliguria was significantly higher in patients more than 18 years age than in younger patients. This differential inflammatory response found in the adult cyanotics may be attributed to the chronic hypoxia-induced development of cyanotic glomerulopathy, characterized by diminished glomerular filtration rate, proteinuria, and large hypercellular congested glomeruli with segmental sclerosis.[26]

CONCLUSION

To conclude, we demonstrated a fall in serum albumin levels in cyanotic patients undergoing intracardiac repair on CPB, which correlated well with adverse clinical outcomes, more commonly in younger patients. Serum albumin is a simple, but useful risk marker and routine monitoring of serum albumin levels can be used to identify within a group of cyanotic undernourished patients at high surgical risk, a subgroup of patients with additional postoperative morbidity in addition to the factors that have commonly been used to define the condition of high surgical risk and predict early morbidity following cardiac surgery for total correction of CCHDs.

Limitations
A multitude of factors may affect serum albumin levels in patients undergoing cardiac surgery. Subjects were not well matched for baseline demographic data like height and weight. Preexisting malnutrition, infection, fluid overload may have been some factors that influenced the serum albumin levels besides the inflammatory effects of CPB. We studied the relationship of serum albumin

Table 4: Serum albumin levels in nonsurvivors versus survivors at various time frames

	Nonsurvivors	Survivors	*P*
T1 (g/dL)	3.8±0.46	4.7±0.49	0.432
T2 (g/dL)	3.3±0.36	4.2±0.45	0.101
T3 (g/dL)	2.3±0.62	3.7±0.56	<0.05

Values expressed as mean (g/dL)±SD. T1: Baseline/preoperative, T2: After termination of cardiopulmonary bypass, T3: 48 h postcardiopulmonary bypass, SD: Standard deviation

Table 5: Receiver operating characteristic curve data for baseline serum albumin concentration

Albumin								
Cut off point	AUC in %	*P*	Sensitivity	Specificity	PPV	NPV	OR (95% CI)	Correctly classified
≤3.3	93.5	<0.001	90.9	92.1	47.6	99.2	116.35 (13.6-994.9)	92

AUC: Area under the curve, PPV: Positive predicitve value, NPV: Negative predictive value, OR: Odds ratio, CI: Confidence interval

with nonspecific outcome variables such as hospital stay, ICU stay, and mechanical ventilation which can have confounding influences from other factors.

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Conflicts of interest

There are no conflicts of interest.

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