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Original Article

Correlation of Post-Operative Hypoalbuminemia with Outcome of Pediatric Cardiac Surgery

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Abstract

Background: *Hypoalbuminemia may be caused by liver disease, nephrotic syndrome, burns, protein-losing entropathy, malnutrition, and metabolic stress. Alterations in albumin in metabolic stress such as cardiac surgery have been previously investigated. We studied serum albumin concentration in children with congenital heart disease and also the association of hypoalbuminemia with mortality and morbidity after pediatric cardiac surgery.*

Methods: *We measured serum albumin concentration prospectively in 300 children with congenital heart disease who underwent surgery between July and September 2008 in Shaheed Rajaee hospital. Serum albumin concentration was measured before and 48 hours after cardiac surgery and was subsequently compared between 2 groups: cyanotic and acyanotic and also with normal values.*

Results: *Serum albumin concentration decreased on the second post-operative day in 70 (23.3%) patients. There was a positive correlation between the post-surgical hypoalbuminemia and cyanotic heart disease. The cyanotic children had lower serum albumin concentration than the acyanotic ones (P value <0.001). There was a significant association between post-operative serum albumin concentration and acute renal failure (P value <0.001) and death (P value <0.001). Drop in serum albumin concentration was more prominent in the males than in the females (P value=0.038) and in the cyanotic patients than in the acyanotic ones (P value <0.001) as well as in those with acute renal failure (P value <0.001), pericardial effusion (P value=0.050), seizure (P value <0.001), and death (P value <0.001). Hypoalbuminemia was not associated with longer hospital (P value=0.142) or intensive care unit stay (P value=0.199).*

Conclusion: *Post-operative serum albumin concentration was lower in the cyanotic children and male patients in our study. In addition, the post-operative decrease in albumin was associated with an increased risk of pericardial effusion, renal failure, seizure, and death.*

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Introduction

Serum albumin concentration is the most abundant blood plasma protein and is thus considered a classic parameter of nutritional assessment.[1] Serum albumin is produced in the liver and forms about 60%-70% of the total plasma protein. Other proteins that present in plasma are called globulins. The main functions of albumin are the maintenance of plasma oncotic pressure; regulation of blood volume by maintaining the osmotic pressure of blood compartment; binding

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of several molecules of low water solubility, including hormones, bile salts, bilirubin, free fatty acids (apoprotein), iron (transferin), calcium, and some drugs; tissue growth, and healing. The average biological half-life of albumin is about 18-20 days. There are two pools available for albumin distribution: intravascular and extravascular, with as much as 60% of the total body protein staying in the extravascular space.[1-3]

The long biological half-life of albumin and its broad distribution in the body prevent nutritional changes from being rapidly reflected in serum albumin concentration.[1] In the case of protein depletion, albumin is first mobilized from the extravascular space into the intravascular space and will maintain serum concentration for some time. Therefore, a decrease in serum albumin concentration develops only late in the course of malnutrition and, as a consequence, in the most severe cases.[1]

Hypoalbuminemia may be caused by various factors such as liver disease, nephrotic syndrome, inflammation, infection, protein-losing entropathy, malabsorption, malnutrition, late pregnancy, and dilution from fluid overload, thereby impairing its validity as a nutritional parameter in patients who have acute-phase response and metabolic stress.[4]

The decrease in albumin concentration during sepsis and injury is regarded as a negative acute-phase protein. In 1955, Rhoads and Alexander observed that hypoalbuminemia was a risk factor in surgical patients.[1, 5] Research on adult patients in various situations has shown the usefulness of this protein as a predictor of mortality and morbidity.[1, 6-11]

Leite et al. showed that hypoalbuminemia was common among children with congenital heart disease and that it correlated with the outcome of cardiac surgery in these patients.[1] Harvey et al. concluded that hypoalbuminemia was the best predictor of mortality.[9] Herrmann et al. while studying a large group of clinical and medical adult patients observed that the hypoalbuminemic patients had a longer duration of hospitalization, higher risk of readmission after having been discharged from the hospital, and greater in-hospital mortality.[10] Hsu concluded that hypoalbuminemia was one of the independent risk factors for hospital death in patients with end-stage heart failure operated on for heart transplantation.[12] Dittrich et al. observed that acute renal failure (ARF) was more common in cyanotic patients after cardiac operation.[13] Protein-losing entropathy (PLE), defined as loss of serum protein in to the intestine, occurred in 4%-13% of these patients.[14, 15] After the Fontan operation, protein-losing entropathy complicates the post-operative period. Rich et al.[16] and Rody et al.[17] maintained that hypoalbuminemia in the pre-operative period increased complications such as prolonged mechanical ventilation, nosocomial infections, and prolonged hospital stay and mortality after cardiovascular surgery.

For all the studies underscoring the usefulness of serum albumin concentration as a predictor of mortality and morbidity in adult patients, there is a dearth of related data in the existing literature on the pediatric age group. We, therefore, sought to quantify and compare serum albumin concentration in children with different congenital heart defects and evaluate its behavior in response to metabolic stress associated with cardiac surgery. We also assessed the correlation between hypoalbuminemia and the post-operative outcome.

Methods

This prospective study, conducted from July to September 2008, measured the serum albumin concentration of 347 children admitted for heart surgery to Shaheed Rajaee hospital. The protocol of the study was approved by the University Ethics Committee. In total, 300 patients were included in this study and 47 patients were excluded because of concomitant chronic renal failure (CRF), hepatic failure, central nervous system disorder, active infection, non-cardiac cause of growth retardation, and other severe complex diseases. Serum albumin concentration was measured before and 48 hours after surgery in the intensive care unit (ICU) or ward. The blood samples were obtained from a peripheral vein at rest with other routine tests, and the measurements were obtained in the research lab of the hospital. Post-operative mortality, post-operative length of hospital stay, and complications such as pericardial effusion, seizure, and ARF were evaluated. Biochemical analyses were carried out via the Green Bromocresol Method.[18] The standard solution was procured from Pars Azmoon factory. The pre- and post-operative serum albumin concentrations were compared with normal values in references.[19]

The interval data are expressed as mean±standard deviation. The comparison between the serum albumin concentrations of the two groups was made using the Mann-Whitney U test. The T-Test was employed to compare albumin changes (percent change between pre- and post-operative values), cyanotic or acyanotic disease, ARF, pericardial effusion, seizure, and death. Spearman's rank-order correlation was calculated to show the correlation between serum albumin levels before and 48 hours after surgery, age, height, weight, and the amount of albumin drop. All the data analyses were conducted using SPSS version 15.0.The level of statistical significance was set at 0.05.

Results

The study population was comprised of 300 patients: 142 (47.3%) were female and 158 (52.7%) were male. The mean age of the patients was 12 months (range: 1-240 months). There were 146 (48.7%) cyanotic patients with mean O_2 saturation of 82% (range: 35-92%) and 154 (51.3%) acyanotic patients. The mean height was 94±27.6 cm (range: 47-171 cm). The mean body weight was 11.6±10.3 kg (range: 3-76 kg). The mean serum albumin concentration at admission was 47.6±4.8 gr/l (range: 26-58 gr/l): 47.7±5 gr/l in the males and 47.5±4.7 gr/l in the females. The mean serum albumin concentration on the second post-operative day was 39.5±5.4 gr/l (range: 21-55 gr/l): 38.8±5.2 gr/l in the males and 40.2±5.6 gr/l in the females. The mean serum albumin at admission was 48±4.7 gr/l in the acyanotic and 47.2±4.9 gr/l in the cyanotic patients; and on the second post-operative day, it was 40.8±5.3 gr/l in the acyanotic and 38±5.2 gr/l in the cyanotic patients. The normal range of serum albumin is 35-52 gr/l. Close surgery such as PA-banding was performed in 78 (26%) patients, and cardiopulmonary bypass was performed in 222 (74%) patients with an average duration of total bypass time of 99.1±53.6 minutes (range: 24-310 minutes). ARF was seen in 4 (1.3%) patients according to clinical and laboratory data; these patients had a rise in their blood urea nitrogen (BUN) and creatinine levels and need for dialysis and they all subsequently died. Seizure was seen in 3 (1%) patients. Pericardial effusion was observed in 32 (10.7%) patients before the 7th post-operative day. Hospital death occurred in 25 (8.3%) patients, including 20 (6.6%) in the cyanotic and 5 (1.7%) in the acyanotic groups. The average length of stay in hospital was 14±12.5 days (range: 3-120 days), and the average length of stay in the ICU was 5.4±9.1 days (range: 1-100 days). The patients' general characteristics are presented in Table 1. The types of the congenital heart disease in the patients are presented in Table 2.

Post-operative hypoalbuminemia had a significant association with cyanosis (P value <0.001) (Table 3). All of the 4 (1.3%) patients with ARF had post-operative hypoalbuminemia. The association between ARF and post-operative hypoalbuminemia was significant (Table 3) (P value=0.003). There was a significant association between post-operative hypoalbuminemia and death (25 patients, 8.3%, P value <0.001) (Table 3). Sex, pericardial effusion, and seizure had no significant association with post-operative hypoalbuminemia. Post-operative hypoalbuminemia was not associated with hospital or ICU stay (P value >0.05). The associations of post-operative hypoalbuminemia with different variables are presented in Table 3.

Table 1. General characteristics of patients

Variable	Mean	SD	Range
Age (m)	12	47.4	1-240
Weight (kg)	11.6	10.3	3-76
Height (cm)	94	27.6	47-171
Pre-operative serum albumin (gr/l)	47.6	4.8	26-58
Post-operative serum albumin (gr/l)	39.5	5.4	21-55
Length of hospital stay (d)	14.8	12.5	3-120
Length of ICU stay (d)	5.4	9.1	1-100
Cardiopulmonary bypass time (m)	99.1	53.6	24-310

SD, Standard deviation; ICU, Intensive care unite

Table 2. Type of congenital heart disease in patients

Heart Disease	Frequency	Percentage
Transposition of the great arteries	29	9.7
Pulmonary atresia	4	1.3
Tricuspid atresia	10	3.3
Atrial septal defect	35	11.7
Ventricular septal defect	85	28.3
Patent ductus arteriosus	6	2
Atrioventricular septal defect	29	9.7
Pulmonary stenosis	4	1.3
Tetralogy of Fallot	53	17.7
Aortic stenosis	7	2.3
Total and partial anomalous pulmonary vein connection	7	2.3
Coarctation of the aorta	5	1.7
Double outlet right ventricle	10	3.3
Other*	16	5.3
Total	300	100

*Other, Other complex or non-common cardiac lesions

Table 3. Association of post-operative hypoalbuminemia with different variables

Variable	Patients with hypoalbuminemia (n=70)	Patients with no hypoalbuminemia (n=230)	P value
Sex			
Female (n=142)	32 (45.7%)	110 (47.8%)	0.76
Male (n=158)	38 (54.3%)	120 (52.2%)	
Age (mo)	44±53	54±45.4	0.12
Weight (kg)	12.2±10.2	15.0±10.3	0.05
Type of CHD			
Cyanotic (n=146)	46 (65.7%)	100 (43.5%)	<0.01
Acyanotic (n=154)	24 (34.3%)	130 (56.5%)	
Acute renal failure (n=4)	4 (5.7%)	-	<0.01
Pericardial effusion (n=32)	10 (14.03%)	22 (9.6%)	0.26
Seizure (n=3)	-	3 (1.3%)	0.45
Death (n=25)	14 (20%)	11 (4.8%)	<0.01

CHD, Congenital heart diseases

The amount of drop in serum albumin was more prominent in the males (Figure 1) than in the females (Figure 2) (8.9 vs. 7.3 gr/l, P value=0.038) and in the cyanotic patients than in the acyanotic ones (9.2 vs. 7.2 gr/l, P value <0.001) (Table 4). Five patients, all males, had pre-operative and post-operative hypoalbuminemia. The decrease in serum albumin was observed in 70 (23.3%) patients, (male=38, female=32). Of these 70 patients, open cardiac surgery was performed in 28 males and 20 females and close cardiac surgery in 10 males and 12 females. Human albumin (1-2 gr/kg) was administered to 222 patients after surgery (Table 4).

Significant difference in serum albumin concentration levels, before and after surgery, was prominent in the patients with ARF (4 patients 1.3%, P value=0.03), pericardial effusion (32 patients, 10.7%, P value=0.050), seizure (3 patients, 1%, P value <0.001), and death (25 patients, P value <0.001) (Table 4). The associations of the drop in serum albumin

Table 4. Drop in serum albumin levels in different subgroups

Volunteers	Pre-operative serum albumin (gr/l)	Post-operative serum albumin (gr/l)	Serum albumin drop (gr/l)	P value
Sex				
Male (n=38)	47.7±5.0	38.8±5.2	8.9	0.038
Female (n=32)	47/5±4.7	40.2±5.6	7.3	0.470
Type of CHD				
Cyanotic (n=43)	47.2±4.9	38±5.2	9.2	<0.001
Acyanotic (n=24)	48±4.7	40.8±5.3	7.2	0.158
Surgery				
Open (n=222)	48±4.5	39.5±5.4	8.5	<0.001
Close (n=78)	47±5.9	39.4±5.7	7.6	<0.001
Acute renal failure (n=4)	46±3.6	30.5±2.6	15.5	0.003
Pericardial effusion (n=32)	47.8±4.4	38±5.6	9.8	0.050
Seizure (n=3)	48±1.7	37.3±1.5	10.7	<0.001
Hospital death (n=25)	44.4±5.4	35.3±6.6	9.1	<0.001

CHD, Congenital heart disease

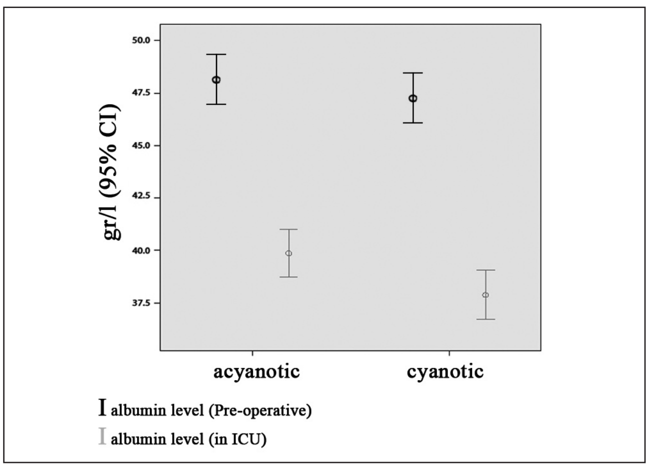

Figure 1. Pre-operative and post-operative serum albumin levels in male patients
ICU, Intensive care unit

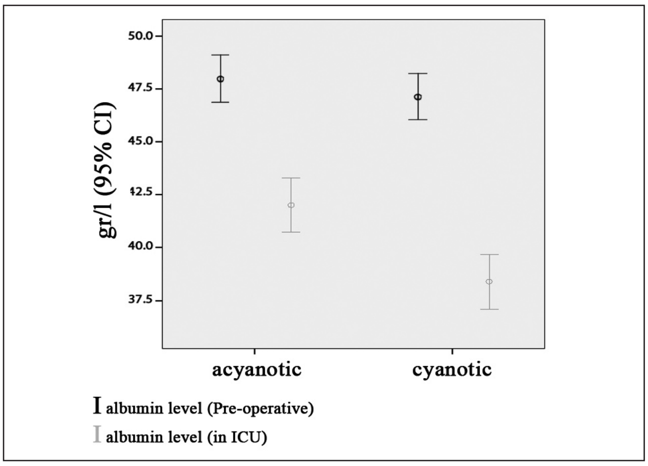

Figure 2. Pre-operative and post-operative serum albumin levels in female patients
ICU, Intensive care unit

concentration with different variables are presented in Table 4.

Discussion

Hypoalbuminemia is common amongst children who have heart disease and can affect the outcome of cardiac surgery.[1] A rapid decrease in serum albumin concentration in the post-operative period is unlikely to have been caused by diminished synthesis alone because serum albumin has a relatively long half-life. Hermann et al.[10] reported a positive correlation between hypoalbuminemia and death, which chimes in with the results of the present study as well. Dittrich et al.[13] studied the correlation between albuminuria and renal function after cardiac surgery in cyanotic congenital heart disease. Boskin et al.[20] described a positive correlation between hypoalbuminemia and ARF after open heart surgery in infants.

In the present study, there was a significant association between lower serum albumin concentrations and ARF after surgery. We found that the occurrence of post-operative pericardial effusion had a positive association with the drop in albumin serum concentration, which was not reported in previous studies. Also, there was a positive correlation between seizure and drop in albumin. The mechanisms implicated in the genesis of hypoalbuminemia are multifactorial, involving the processes of synthesis, catabolism and amino acid supply, water retention, and loss to extravascular space due to the alteration of the endothelial permeability.[1, 21-25] Therefore, hypoalbuminemia represents a symptom of the organism's adaptation to various events such as infection, liver disease and burns.

The low pre-operative values could be explained by a combination of malnutrition and homeostatic disorders, which account for physiologic adaptation to the severity of the cardiac disease.[1] Hypoalbuminemia is a result of pathologic condition and there is no agreement for albumin administration to manage low albumin concentration except in significant situations (e.g., severe hypoalbuminemia with intolerance to entral tube feeding, protein-losing entropathy, and fluid resuscitation in burn or shock).[1] After cardiac surgery, endothelial lesion is the main underlying mechanism for the transcapillary flow of plasma protein to explain hypoalbuminemia. Varrier et al.[26] discussed endothelial cell injury in cardiovascular surgery and the response of endothelial cells such as coagulation, leukocyte adhesion, and smooth muscle cell proliferation. On the second post-operative day, we observed a significant decrease in serum albumin concentration, especially in the male patients and cyanotic patients, which was related to the severity of metabolic responses. Greater decrease in albumin concentration in male patients has not been hitherto discussed in other studies. In the initial stage of the inflammatory process, there is an increase in the permeability of the microcirculation, allowing a greater transcapillary flow of plasma protein.[1, 22-25] As a result, the administration of albumin may not increase serum albumin levels in these patients. After 48 hours, concomitant with the attenuation of the post-operative inflammatory response, serum albumin concentration is likely to increase gradually. We observed that post-operative hypoalbuminemia and the difference in the albumin levels in the pre- and post-operative period had significant associations with mortality and morbidity.

Leite et al.[1] and Redy et al.[17] discussed the positive correlation between mortality and morbidity after cardiovascular surgery such as prolonged hospital stay with hypoalbuminemia. In our patients duration of stay in ICU or hospital had no correlation with hypoalbuminemia. In one study, investigators found that serum albumin concentration was lower in survivors.[27] In our study, there was a significant association between the drop in albumin and mortality.

The main limitation of our study is that the infusion of albumin to all open surgeries may mask a larger response with the decrease in albumin. A randomized trial of albumin infusion can shed further light on the issue.

Conclusion

Hypoalbuminemia after pediatric cardiac surgery is not uncommon. A decrease in serum albumin concentration was seen on the second post-operative day in our patients. The amount of albumin drop was more prominent in the male patients and in children with cyanotic congenital heart disease. Our results also suggest that hypoalbuminemia is associated with increased mortality and morbidity.

Future studies are required to delve further into hypoalbuminemia as a risk factor in pediatric patients with congenital cardiac disease undergoing cardiac surgery.

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