

Risk factors for the failure to achieve normal albumin serum levels after albumin transfusion in neonates

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Abstract

Background Albumin transfusion for the treatment of neonatal hypoalbuminemia may reduce morbidity. In conditions with disrupted endothelial integrity (e.g., sepsis and critical illness), the administered albumin may leak into the interstitial space, hence, serum albumin levels may fall below expected levels after transfusion. To date, few studies have been done to evaluate the risk factors for failure to achieve normal neonatal albumin levels after transfusion.

Objectives To determine the risk factors for failure to achieve normal neonatal albumin levels after transfusion.

Methods We performed a case-control study in the Neonatal Ward of Dr. Sardjito Hospital from 2007 to 2012. Normal albumin level was defined as above 3 g/dL. The case group included neonates with post-transfusion albumin levels <3 g/dL and the control group included those with post-transfusion albumin \geq 3 g/dL. Subjects received intravenous transfusions of 25% or 20% albumin according to the clinical standard of the Neonatal Ward of Dr. Sardjito Hospital. Neonates with very low birth weight, severe birth trauma, burn injuries, severe bleeding, or incomplete medical records were excluded. The data were analyzed with logistic regression test.

Results From January 2007 to December 2012, 124 neonates were enrolled in the study. Multivariate analysis showed that low albumin levels before transfusion (OR 12.27; 95%CI 2.17 to 69.30), presence of critical illness (OR 4.01; 95%CI 1.49 to

10.79), diagnosis of sepsis (OR 3.56; 95%CI 1.36 to 9.32), and the >24-hour interval between albumin examination and transfusion (OR 0.06; 95%CI 0.01 to 0.37) were significant risk factors affecting the failure to achieve normal albumin levels.

Conclusions Failure to achieve normal albumin levels after transfusion in neonates was significantly associated with low albumin level prior to transfusion, critical illness, sepsis, and >24-hour interval between transfusion and post-transfusion albumin examination. [Paediatr Indones. 2016;56:67-].

Keywords: neonates, albumin transfusion, albumin level

Neonatal hypoalbuminemia occurs in several clinical conditions including prematurity, critical illness, respiratory distress syndrome, necrotizing enterocolitis, intracranial hemorrhage, hydrops fetalis, and edema.^{1,2} In neonates with hypoalbuminemia,

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clinical benefits from albumin transfusion were observed in neonates who attained albumin levels >3 g/dL. The neonatal group experienced a shorter time to regain birth weight, improved nutritional status, early enteral feeding tolerance, fewer hospital complications, as well as lower incidences of pneumonia and sepsis.^{2,5}

Albumin levels after transfusion are attributable to the combination of accumulated intrinsically-synthesized endogenous albumin within a neonate, and exogenous albumin obtained from transfusion. The endogenous albumin concentration is influenced by gestational age, birth weight, and nutrition. In the first week of life, preterm, low birth weight, and small-for-gestational age infants have lower albumin levels than full term, normal birth weight, and appropriate-for-gestational age neonates.^{2,6,8} Exogenous albumin concentration (human derivate) is affected by its distribution, catabolism, and half-life. Conditions that disrupt endothelial function, such as sepsis and critical illness, may cause accelerated albumin leakage into the interstitium.^{9,10} In addition, conditions that require increased catabolism of albumin, such as surgery, make restoring normal albumin levels more difficult.¹¹ All such conditions, in turn, contribute to lower than expected post-transfusion albumin concentrations. However, the large majority of such studies were conducted in adult subjects.⁵

The aim of this study was to determine the risk factors for failure to achieve normal neonatal albumin levels after transfusion.

Methods

We performed a case-control study involving infants from the Neonatal Ward of Dr. Sardjito Hospital, Yogyakarta, between January 2002 and December 2012. The data were collected from medical records. Subjects in the case group were neonates with post-transfusion albumin levels of <3 g/dL, whereas the control group consisted of neonates with post-transfusion albumin levels ≥ 3 g/dL.

Neonates received intravenous transfusions of 25% or 20% albumin, at appropriate doses¹² according to clinical standard of the Neonatal Ward of Dr. Sardjito

Hospital,¹³ were included in this study. We excluded neonates with very low birth weight ($<1,500$ g), severe birth trauma, burn injuries, severe bleeding, or incomplete medical records. We identified the case and control group subjects, then retrospectively obtained risk factors for low, post-transfusion albumin level. The case group included neonates with post-transfusion albumin levels <3 g/dL and the control group included those with post-transfusion albumin ≥ 3 g/dL. The suspected factors were low birth weight (1,500 g - 2,500 g), prematurity (gestation <37 weeks), small-for-gestational age (birth weight $<10^{\text{th}}$ percentile for gestational age based on the Lubchenco Table), enteral nutrition, sepsis, critical illness (neonates with multi-organ failure requiring cardiopulmonary assistance), surgery, low albumin levels prior to transfusion, and <24 -hour interval time between transfusion and post-transfusion albumin level examination.

The minimum required number of the subjects was 64 per group (type I error of 5% and power of 80%). Data were analyzed separately for each factor by bivariate analysis. Multivariate analysis was performed using backward stepwise logistic regression. The results were presented in the form of odds ratio (OR) with 95% confidence interval (CI) and a significance value of $P < 0.05$. All analyses were performed using the SPSS version 17 software. This study was approved by the Medical Ethics Committee, Gadjah Mada University Faculty of Medicine and Dr. Sardjito Hospital, Yogyakarta.

Results

During the study period, 181 neonates fulfilled the inclusion criteria. We excluded 53 neonates due to very low birth weight (21 neonates), incomplete medical records (18 neonates), birth trauma (3 neonates), and bleeding (11 neonates). Hence, 128 neonates were eligible for the study, which consisted of 64 subjects per group. Baseline characteristics of subjects are shown in **Table 1**. The case and control groups had similar characteristics, with the exception of sepsis and critical illness.

Table 1. Baseline characteristics of subjects

Characteristics	Case group (n=64)	Control group (n=64)
Gender, n (%)		
Male	44 (68.7)	45 (70.3)
Female	20 (31.3)	19 (29.7)
Twin, n (%)	6 (9.4)	2 (3.1)
Delivery method, n (%)		
Caesarean	19 (29.7)	16 (25.0)
Vaginal	45 (70.3)	48 (75.0)
Sepsis, n (%)	40 (31.3)	23 (18.0)
Critical illness, n (%)	47 (36.7)	25 (19.5)

Univariate and multivariate analyses of possible influential factors in achieving normal albumin levels after transfusion are shown in **Table 2**.

Table 2. Risk factors of post-transfusion albumin levels

Multivariate analysis revealed that critical illness, sepsis, low albumin levels prior to transfusion, and albumin examination greater than 24 hours after transfusion were influential factors in failure to achieve normal albumin levels (**Table 2**).

Discussion

Our study showed that the significant risk factors for failure to achieve normal albumin levels after transfusion were low albumin levels prior to transfusion, sepsis, critical illness, and albumin examination time of >24 hours post-transfusion. However, birth weight, prematurity, small-for-gestational age, nutrition type, and surgery were not risk factors for low albumin level after transfusion.

Lower albumin level in the case group was related to greater clinical disease severity in this group. Although we did not use a neonatal severity scoring system, the severity was reflected in the higher incidence of sepsis and critical illness in the case group (**Table 1**). Similarly, a retrospective study in adult intensive care unit patients reported that those with albumin levels less than 3 g/dL had more severe clinical conditions.¹⁴

Our study demonstrated that sepsis was a risk factor for lower post-transfusion albumin levels. Previous studies conducted in adult patients reported that cytokines released during

sepsis were involved in an underlying mechanism causing low post-transfusion serum albumin levels. This cytokine release causes an increased transcapillary escape rate of albumin of up to 300%.^{8,9} Our results were also consistent with a study which showed that increased level of albumin only occurs transiently. Approximately 33% of intravenous albumin reportedly leaked into the interstitial space in 5 minutes and almost all of the albumin escaped from circulation after about 4 hours post-transfusion.¹⁵

Critical illness increased the risk of failure in restoring normal albumin levels in our study. The main pathophysiological mechanism is similar to that of sepsis, with the addition of an increased catabolism rate. Increased amounts of transfused albumin results in increased leakage and catabolism of circulating albumin.¹⁶ Thus, albumin levels fall beyond expected levels post-transfusion.^{10,11}

In addition to clinical conditions, the interval between albumin transfusion and albumin examination influenced post-transfusion albumin levels. This result corresponded with different plasma half-lives of endogenous and exogenous albumin. Endogenous albumin has a serum half-life of approximately 21 days, while human albumin derivatives last only 12-16 hours in circulation.¹⁷ Thus, if the albumin examination is done more than 24 hours after transfusion, the albumin levels after transfusion may be up to 16 times lower than that of examinations within 24 hours.

Birth weight was not correlated with post-transfusion albumin levels in this study. An Indian study reported significantly lower serum albumin level in low birth weight than in normal birth weight neonates.¹⁸ The low albumin levels were correlated with reduced albumin synthesis in low birth weight neonates with intrauterine growth retardation due to a lower availability of amino acids in utero.⁶

We also found that prematurity was not significantly associated with post-transfusion albumin levels. In contrast, Cartledge *et al.*⁷ and Zlotkin *et al.*¹⁹ reported that albumin level in neonates was influenced by gestational age, due to transfer of albumin across the placenta that mostly occurred at 38-40 weeks of gestational age. Preterm neonates

generally have lower albumin level than full term neonates.²⁰ Thus, in this study it was assumed that prematurity and birth weight were associated with low levels of albumin prior to transfusion, but were not associated with the successful achievement of albumin transfusion. Similar to birth weight and prematurity, small-for-gestational age was not associated with low post-transfusion albumin levels. Bunt *et al.* also reported that small-for-gestational age affected the synthesis of albumin only on the first day of life.⁶ This SGA phenomenon during the first day of life was associated with decreased albumin synthesis capacity due to the low availability of amino acids to the fetus.²⁰

There were no significant differences in post-transfusion albumin levels between groups of neonates who received enteral and parenteral nutrition. Nutritional schemes for neonates are aimed at improving albumin synthesis in the liver.² In acute conditions, hypoalbuminemia that occurs before and after transfusion was not associated with nutritional or metabolic components, but appeared to affect the redistribution and dilution of endogenous or exogenous albumin.^{10,11}

Major surgery may cause post-operative hypoalbuminemia in neonates. The loss of albumin from the circulation is caused by blood loss during surgery and redistribution of albumin as a result of the inflammatory process. Seven hours after surgery, there may be an increased transcapillary escape rate of albumin by as much as 100%. There was massive leakage of albumin into the interstitial space causing albumin levels to remain low.^{8,11} In **Table 2**, we found that surgical cases increased the risk of failure to achieve normal post-transfusion albumin levels upon bivariate analysis, however, this result was not statistically significant in the multivariate analysis.

The limitations of this study were that we did not consider the interval between administration of intravenous albumin and the time of surgery, or the interval between pre-transfusion albumin examination and the albumin level re-examination. We also did not determine the composition of post-transfusion albumin, as to whether it comprised low endogenous albumin (synthesis) or exogenous (intravenous albumin solution) albumin.

In conclusion, failure to achieve normal albumin levels after albumin transfusion in neonates is significantly associated with low albumin level prior to transfusion, critical illness, sepsis, and >24-hour post-transfusion albumin examination time. Further studies are warranted to confirm these results.

Conflict of interest

None declared.

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