

Anemia and blood transfusion in children with septic shock: Does it affect outcome? A prospective observational study

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Received - 07 January 2018

Initial Review - 31 January 2018

Published Online - 07 March 2018

ABSTRACT

Background: Anemia is frequently encountered in critically ill children. Packed cell transfusion is a common therapeutic intervention in these children. The consequences of this on morbidity and mortality in children with septic shock are poorly defined and need to be explored. **Objective:** The objective of this study was to evaluate the prevalence of anemia and to explore the relationship of anemia and packed red blood cells transfusion to clinical outcomes in children with septic shock. **Materials and Methods:** A prospective observational study was conducted in a tertiary care hospital in pediatric intensive care unit between July 2013 and July 2014. Children between 1 month and 16 years of age with septic shock were enrolled in the study. The clinical profile including outcomes was noted in recruited patients. **Results:** The prevalence of anemia in children with septic shock was 63%. Among them, 13% were severely anemic. No significant differences were found in the Pediatric Risk of Mortality score, length of intensive care unit (ICU) stay, duration of inotropic requirement, hours of ventilation, and mortality rates between anemic and non-anemic children. Similar findings were observed between the transfused and non-transfused groups. However, the duration of inotropic requirement was longer among the transfused group (72 [6,120] vs. 48 [3, 72], $p=0.025$). A higher mortality rate was observed among transfused group with an odds ratio of 2.168 (95%, confidence interval [CI] 0.9–5) but was not statistically significant [$p=0.08$]. **Conclusion:** More than half of our children with septic shock were anemic at presentation. Anemia was not associated with increased mortality or morbidity. The transfused group had a higher mortality rate.

Key words: Anemia, Outcome, Prevalence, Septic shock

Anemia is a commonly encountered clinical problem in critically ill patients. The etiology of anemia is multifactorial and includes diminished erythropoietin activity, poor iron use by the body, and blood loss (both iatrogenic and non-iatrogenic) [1]. In various studies, the prevalence of anemia at the time of admission into the intensive care unit has been reported up to 77%. The incidence of anemia in patients with septic shock has not been well established globally. In addition, many adult studies in critically ill patients have shown that anemia is associated with worse outcomes, due to diminished oxygen delivery to the tissues. The impact of anemia on the outcome of children with septic shock is not well understood [2,3]. There is a paucity of information on the prevalence, severity, and immediate outcome of anemic children with septic shock in India. Hence, our primary objective was to estimate the prevalence and analyze the impact of anemia on morbidity and mortality in children with septic shock in a tertiary care hospital.

Transfusion of blood products, especially packed red blood cell (PRBC), is an important therapeutic intervention in such patients. The outcomes are not always beneficial and one must weigh the risk:benefit ratio before transfusion [4]. Many studies in heterogeneous groups of critically ill adults showed that

RBC transfusions are independently associated with increased morbidity and mortality [3,5,6]. The data related to this is relatively scarce. In 2007, Lacroix *et al.* provided evidence that the lower threshold of Hb 7.0 g/dL was safe for transfusion in stabilized critically ill patient population [7]. A similar threshold was considered safe for children with sepsis based on a study by Karam *et al.* in 2011 [8]. Hence, the secondary objective of our study was to explore the relationship between blood transfusion and clinical outcomes in critically ill pediatric patients with septic shock.

MATERIALS AND METHODS

This prospective observational single-center study was conducted in the pediatric ICU (PICU) of a tertiary care teaching hospital in South India. The enrolment period was from July 2013 to July 2014. The inclusion criteria were children from 1 month to 16 years of age admitted to the PICU and diagnosed with septic shock. Septic shock was defined as sepsis with cardiovascular dysfunction (i.e., hypotension, reliance on vasoactive drug administration to maintain a normal blood pressure, or two of the following: Prolonged capillary refill, oliguria, metabolic acidosis,

or elevated arterial lactate) that persists despite the administration of ≥ 40 mL/kg of isotonic saline in one hour [9].

Patients with cyanotic heart disease, chronic lung disease, chronic renal failure, preexisting chronic anemia, and active bleeding, and patients undergoing chemotherapy were excluded from the study. Patients were followed for either 30 days or until hospital discharge or death if these occurred before day 30. The study was approved by the institutional ethics committee. Informed written consent was obtained from the parent(s)/guardian(s) of each patient before enrollment. Data related to age, gender, Pediatric Risk of Mortality (PRISM III) score, and primary and secondary admitting diagnoses were recorded. The PRISM III score is based on clinical and laboratory parameters assessed during the first 12 h. Hemoglobin (Hb) level on capillary, venous, or arterial blood sample was collected within 24 h. Additional information was recorded subsequently (duration of inotropes and mechanical ventilation, PRBC transfusion, duration of PICU, and length of hospital stay). Routine and specific investigations including cultures done in all cases were also recorded. Anemia was defined according to the WHO nutrition information system based on hemoglobin levels at admission - Hb concentration < 11 g/dl in younger children is described as anemia and severe anemia when Hb was lower than 7 g/dl [10]. The children were treated as per standard protocol guidelines.

The following categories - anemia (Hb 7–11 g/dl), severe anemia (< 7 g/dl), and non-anemic group (Hb > 11 g/dl) were created based on Hb at admission for subsequent analysis to assess the impact on severity of anemia on outcome in children with septic shock. Similarly, to explore the relationship between blood transfusion and clinical outcomes, we compared transfused versus non-transfused group.

Indications for RBC transfusion in these children with septic shock were persistent shock, metabolic acidosis ($BE > -5$), elevated lactate, or a central venous saturation ($S_{cv}O_2$) of $< 70\%$, to optimize hematocrit to 30. The primary outcome was mortality at 30 days. The secondary outcome measures were the duration of PICU, hospital stay, inotropic support, and ventilation hours.

Sample Size Calculations

For estimating the prevalence of anemia, the confidence level is set at 95%, proportion of interest is 60%, and confidence interval is 0.05 (upper and lower interval set at 0.15 and 0.05). The standard error is set at 0.0255. Using these estimates, the sample size for recruitment is set at 132 eligible children. For analyzing the outcomes due to anemia and blood transfusion, the estimates are the same as above, and the proportion of interest is 50%; thus, the sample size calculation is 130. We planned to enroll a convenience sample of 150 children.

Statistical Analysis

Data were entered into the Microsoft Excel spreadsheet. SPSS software for Windows (version 23.0, Chicago, Inc.) was used

for all the analyses. Continuous variables were reported using mean \pm standard deviation for the normally distributed variables otherwise median and interquartile range was used. Categorical variables were expressed as percentage/proportions and analyzed using the Chi-square test. Mann–Whitney U-test was used to compare the differences between the anemic and non-anemic groups and also between the transfused and non-transfused groups. Multivariate logistic regression analysis was used to find the association between PRBC transfusion and outcome. All the analysis was statistically significant at 5% level ($p < 0.05$).

RESULTS

During the study period, a total of 150 children diagnosed with septic shock admitted to our PICU were found to be eligible. Baseline characteristics of the study group are summarized in Table 1 and Fig. 1 and 2.

The median age of our children was 11 months (IQR 4, 37). The male:female ratio was 1.1:1. 66% of the children required invasive ventilation. The median duration of inotropic requirement in children with septic shock was 48 h (4, 96). The overall mortality in children with 90% of cases was community-acquired sepsis and only 8% were secondary to nosocomial infections septic shock was 16% (Table 1).

The number of children with culture-positive sepsis was 36%. 32% children had blood culture positive sepsis and 14% had other body fluid/site samples such as endotracheal tube secretions, urine, cerebrospinal fluid, ascitic fluid, stool, and pleural fluid positive for organism growth. 10% have cultures positive in both blood and other sites.

Of 150 children with septic shock, 95 were found to be anemic at admission. Among them, severe anemia (Hb < 7 g/dl) was detected in 19% of these cases with a higher PRISM III score 9 (3.7, 13.25). Majority of the anemic children were found to be < 1 year of age ($p < 0.05$). 15 children (17%) died in anemic group,

Table 1: Baseline characteristics of children with septic shock: (n=150)

Age, months, median (IQR)	11 (4,37)
Male:female	1.1:1
PRISM III score, median (IQR)	7 (3,12)
Catecholamine resistant shock% (n)	40 (60)
Prevalence of anemia % (n)	63 (95)
Prevalence of severe anemia% (n)	19 (20)
Admission Hb (g/dl), mean (SD)	9.9 (2.5)
Culture positive sepsis (%)	36
Number of children requiring mechanical ventilation (%)	99 (66)
Hours of mechanical ventilation median (IQR)	96 (60,192)
Hours inotropic duration median (IQR)	48 (4,96)
Length of hospital stay, median (IQR)	9 (4,13)
Length of ICU stay, median (IQR)	5 (3,8)
Mortality rate (%)	16 (24)

IQR: Interquartile range, ICU: Intensive care unit, SD: Standard deviation

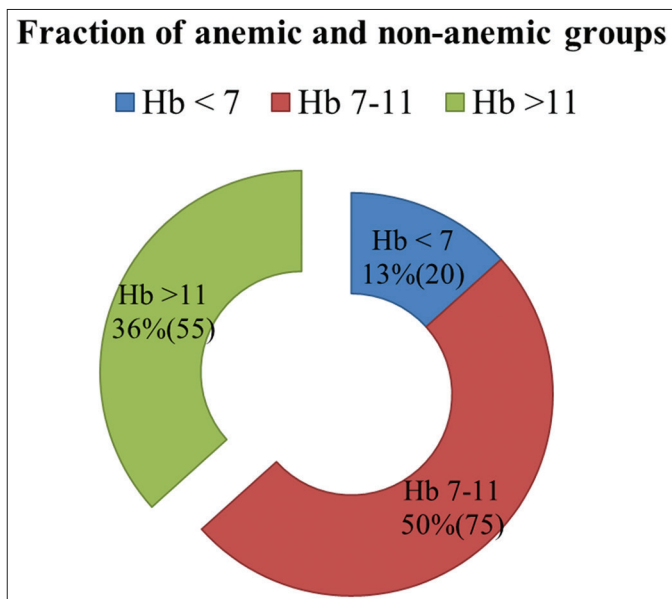


Figure 1: Distribution of children with septic shock based on hemoglobin (Hb) levels (Hb-g/dl)

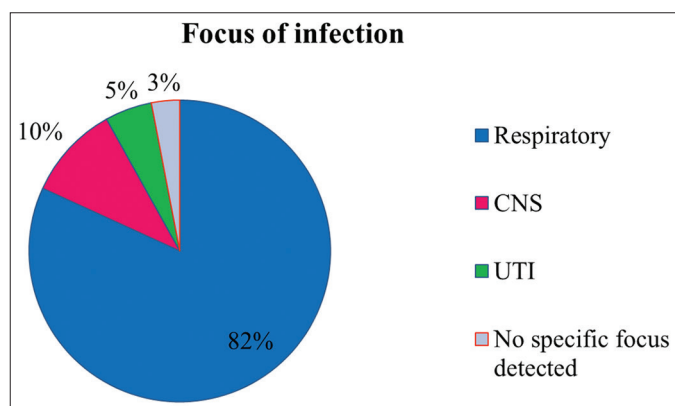


Figure 2: The percentage distribution of the primary diagnosis/system involved at admission in children with septic shock

and only 4 were found to be severely anemic. Length of PICU and hospital stay, inotropic requirement, and hours of ventilation did not vary with the severity of anemia (Table 2). There was no statistically significant difference in the ICU mortality rates among different Hb% groups ($p = 0.9$).

Subgroup Analysis: PRBC Transfusion and Outcome in Children with Septic Shock

In our study, out of 150 children with septic shock, 42 (28%) received blood transfusion. Among 42 children, 20 were severely anemic at admission, hence, received transfusion and the remaining 22 children were transfused in view of ongoing hemodynamic instability to optimize hematocrit to 30. We compared the outcome between the transfused and non transfused group to explore the impact of transfusion on outcome. We noticed that the children requiring transfusion had a significantly longer duration of inotropic requirement ($p=0.025$). The length of PICU stay and hours of ventilation did not vary between the two groups. The transfused group had 24% mortality. The PRISM

III score was higher in the transfused group but not statistically significant. On multivariate analysis, the transfused group had a higher PRISM III score ([odds ratio [OR] - 1.13 [1.05–1.205] $p < 0.01$). Similarly, the relative odds of mortality after adjusting for the severity of illness were higher as compared to the non-transfused group ([OR - 2.168] $p = 0.08$) (Table 3).

DISCUSSION

Critically ill pediatric patients have a high incidence of anemia at the time of admission. This was observed in our study as the prevalence of anemia was 63% at admission in our cohort of children with septic shock [11].

Critically ill patients will develop anemia at some point in their intensive care unit course. Anemia is associated with worse outcomes in critically ill pediatric patients, due to diminished oxygen delivery to the tissues [12]. A global review on pediatric septic shock reported an overall mortality rate up to 23% shock, but studies correlating anemia and outcomes in children with septic shock were very few [13]. We found anemia is common in the PICU, but lower Hb concentrations were not associated with higher mortality and poorer outcomes.

Many studies in critically ill adults in medical and surgical ICU revealed poor patient outcomes among the anemic, but only few pediatric studies showed clinical outcomes of anemia in critically ill children. Worse outcomes including higher mortality, extubation failures, and longer length of ICU stay were observed in anemic patients in various cohorts of critically ill adults across regions [5,14,15]. Severe anemia was associated with higher mortality in a Nigerian study of critically ill children [16]. Our study reflected no significant risk of death with severe anemia. There were no worse outcomes in terms of duration of ICU stay, hours of invasive ventilation, and inotrope duration among those with anemia. The possible explanation could be as majority of the children were chronically anemic due to nutritional deficiency, so their adaptive mechanisms might have helped to compensate during their illness [17]. The results of our study did not support the hypothesis that anemia is associated with worse outcomes. Studies in children have supported the hypothesis that blood transfusion is associated with worse outcomes in critically ill patients. The rationale is based on the concept that blood transfusion tends to increase oxygen delivery to the tissues but as no role on tissue consumption. These factors are critical in conditions such as septic shock and acute respiratory distress syndrome. Thus, the benefit may not be as significant as compared to the varied risks due to transfusion [18].

A review of three key studies done in three different population groups (critically ill adults, children, and neonates) all favored “restrictive transfusion strategies” that showed better clinical outcomes among those who were transfused at a lower Hb threshold than those who were more “liberally” transfused [19]. Karam *et al.* showed similar results in children with sepsis where a Hb level of 7 g/dl was not associated with worse outcomes and considered a safe threshold for transfusion in stabilized children with sepsis [8].

Table 2: Comparing clinical outcomes based on severity of anemia at admission and outcomes (Severe anemia [<7 g/dl], Moderate and mild [7–11 g/dl], No anemia- > 11 g/dl])

Parameter	<7 g/dl	7–11 g/dl	>11 g/dl	p value
Age, months, median (IQR)	6 (2,20)	10 (3,23)	12.5 (5,79.5)	0.049*
Male:female	1:1	1:1	0.8:1	0.868
Prism score, median (IQR)	9 (3.7,13.25)	6 (2,11)	8 (4,15)	0.16
ICU mortality rate (%)	20	16.8	16	0.9
Multiorgan dysfunction % (<i>n</i>)	63 (60)	63 (60)	70 (39)	0.8
Hospital length of stay, median (IQR)	9 (4.7,14.2)	9 (3.5,12)	9.5 (4,12.8)	0.5
ICU length of stay, median (IQR)	7 (4,8.7)	5 (3,7)	6 (3,9)	0.3
Hours of ventilation, mean (SD)	133 (91)	12 (92)	150 (123)	0.7
Hours of inotropic requirement, median (IQR)	72 (5,108)	48 (2,80)	48 (4,96)	0.4

*p value <0.05 is statistically significant. IQR: Interquartile range, ICU: Intensive care unit, SD: Standard deviation

Table 3: Characteristics and outcomes between the transfused and those non-transfused

Parameter	Transfusion <i>n</i> - 42	No Transfusion <i>n</i> - 108	p value	Adjusted analysis OR (95% CI) p-value
Age, month, median (IQR)	9 (4,30)	11.5 (3,46.5)	0.47	-
Male (%)	0.8:1	1:1	0.6	-
ICU LOS, median (IQR)	6 (3,9)	5 (3,8)	0.3	-
Hours of ventilation, mean (+ SD)	141 (98)	131 (107)	0.3	-
PRISM score median (IQR)	9 (3.5,16.5)	6 (3,11)	0.096	1.13 (1.05-1.205) p value <0.01 *
Hours of inotropic requirement, median (IQR)	72 (6,120)	48 (3,72)	0.025*	
ICU mortality rate (%)	10 (24%)	14 (13%)	0.17	2.16 (0.9–5.1) p=0.08

*p value <0.05 is statistically significant. IQR: Interquartile range, ICU: Intensive care unit, SD: Standard deviation, OR: Odds ratio, CI: Confidence interval

Our data were analyzed for clinical outcomes in the transfused and non-transfused groups. We observed a higher mortality rate among transfused but were not statistically significant [p=0.08]. A large retrospective study in critically ill children found PRBC transfusion to be an independent risk factor for mortality after adjusting for severity of illness [20]. One of the reasons for higher mortality in our study population could be because those who were transfused had more severe illness. Inotrope requirement was significantly longer among transfused children and supported the results of Kneyber *et al.* [4]. The probable reason for this could be as transfused children were sicker as reflected by the higher PRISM score. However, there was no significant difference in ICU stay and duration of ventilator requirement among the two groups. Other studies showed significantly worse outcomes with regard to all the above variables among those transfused [3,5,21]. We cannot conclude that PRBC transfusion is responsible for worse outcomes. Further, research and multicentric studies are required to evaluate the risk factors for mortality in children with septic shock.

Limitations of the Study

Anemia is a widespread public health problem in India which affects children. To the best of our knowledge, our study is the largest to date investigating the impact of anemia and possible risks of blood transfusion in pediatric intensive care patients in our country.

However, some limitations should be considered. First, our analysis is single center in nature, and our results are only hypothesis-generating study. A larger sample size is required to generalize the prevalence of anemia in pediatric patients with septic shock. Second, the multivariable analysis does not take into account unmeasured variables and cannot establish a cause-effect relation between PRBC transfusion and outcome. The confounding effect of unmeasured variables cannot be excluded. Nevertheless, many relevant variables were considered. Third, clinical outcomes of patients transfused at lower pretransfusion levels of hemoglobin were not assessed. Finally, the results of our study may not be extrapolated to patients with other types of shock case, such as cardiogenic or dengue shock.

CONCLUSION

Anemia is common in children with septic shock and is not a risk factor for mortality or morbidity. PRBC transfusion is associated with higher mortality. Conclusions on outcomes with regard to blood transfusion need further research. Our data should be regarded as being hypothesis generating and randomized controlled studies are warranted to reassess transfusion practice in the ICU.

ACKNOWLEDGMENTS

We thank Ms. Sumithra and Ms. Vinodha from the department of statistics for their contribution in statistical analysis.

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Lalitha AV, Joy ST, Sumithra S. Anemia and blood transfusion in children with septic shock: Does it affect outcome? A prospective observational study. *Indian J Child Health*. 2018; 5(2):68-72.

Doi: 10.32677/IJCH.2018.v05.i02.001