ORIGINAL ARTICLE

Cardiovascular responses to blood transfusion in children with anemic heart failure

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Abstract

Introduction: This study evaluated the cardiovascular responses to blood transfusion in children with anemic heart failure using mostly clinical parameters.

Materials and Methods: Consecutive patients with anemic heart failure presenting to a children's emergency room and requiring blood transfusion were assessed for heart rate (HR), respiratory rate (RR), systolic blood pressure (SBP), liver size, and oxygen saturation (O_2 sat) pre-transfusion, 1–2 h into transfusion (intra-transfusion), immediate post-transfusion, and at late post-transfusion (24 h later).

Results: A total of 75 patients were recruited of which 46 (61.3%) were males. Their mean age was 43.8 ± 40.3 months while their mean PCV at presentation was 15.0 ± 4.5%. There was a significant mean net reduction of 10 beat per minute (bpm) between the pre (139.7 ± 25.2 bpm) and intra–transfusion (129.6 ± 22.0 bpm) HR, $P = 0.0004$. The mean net reduction of 4 cycles/ min between the pre and intra-transfusion RR was also significant, $P = 0.0033$. The two parameters declined in values subsequently.

Conclusion: The HR and RR are two easily measurable indices with reduction in HR and RR by 10 bpm and 4 cycles/ min, respectively, from pre-transfusion to intra-transfusion observations.

Key words: Blood transfusion, cardiovascular, heart failure, severe anemia

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Introduction

Severe anemia is a common pediatric emergency and is reported to be the commonest cause of childhood heart failure in sub-Saharan Africa.[1-7] In cases of severe anemia, blood transfusion has been known to be life saving.[8] However, there are reports of cardiac failure, pulmonary edema, and mortality following blood transfusion with whole blood or packed cells in adults and older children.[8,9] These untoward effects have been ascribed to acute hypervolemia, necessitating the use of isovolumetric exchange blood transfusion, a procedure that causes little change in blood.[9,10] This has also led to the search for a safe transfusion regimen in non-isovolumetric transfusion with respect to rate of transfusion.[11,12] However, in a study involving adult patients with severe anemia, no untoward cardiovascular effects were reported following 800 mL of packed cells transfused at 18 mL/min.[13]

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In severe anemia, both hemodynamic and non-hemodynamic mechanisms are activated to compensate for the declining oxygen carrying capacity.[14] Notably, the increase in 2,3 diphosphoglycerate levels and increased erythropoiesis are important non-hemodynamic responses.[14] The hemodynamic mechanisms involve the vasodilation-mediated high-output state brought on by enhancement of endothelium-derived relaxing factors activities[15] and activation of neurohormonal activities of the renin-angiotensin-aldosterone mechanism.[14] When the compensatory mechanisms become overwhelmed, cardiovascular decompensation and heart failure will manifest clinically as tachycardia, tachypnea, respiratory distress, and tender hepatomegaly.[16] These clinical features

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may also be caused by the underlying disease causing anemia. Amelioration of these features may occur following treatment of the underlying conditions. However, in severe anemia causing heart failure, treatment of the underlying condition like malaria without transfusion is unlikely to completely resolve the clinical manifestations. Tachycardia and tachypnea are also caused by febrile illnesses. The contribution of fever to tachycardia and tachypnea for every degree rise in temperature can be determined because it is known that 10 beat per minute (bpm) of heart rate and 5–7 cycles/min of respiratory rate are due to 1 degree rise in temperature for tachycardia and tachypnea, respectively.[17,18]

There is a growing concern of the morbidity and mortality with transfusion-associated circulatory overload (TACO), usually caused by large volume loading during transfusion. The resulting hydrostatic pulmonary edema increases the work of the heart, which is already compromised by the heart failure.[19] Our practice has been to give blood transfusion to patients with anemic heart failure. No study to the authors' knowledge has specifically evaluated cardiovascular responses to blood transfusion in children with anemic heart failure.

This work was therefore carried out to determine the cardiovascular responses of children with anemic heart failure to non-isovolumetric blood transfusion using the clinical parameters of heart rate (HR), respiratory rate (RR), the size of liver enlargement, systolic blood pressure (SBP), and oxygen saturation (O_2 sat). Although the cardiac output, cardiac index, peripheral vascular resistance, etc, are the best indices for assessing hemodynamic changes, the parameters used in this study represent a low-technology approach to evaluating cardiovascular response to blood transfusion in children with anemic heart failure in resource-poor setting. The study also set out to identify factors that may contribute to adverse cardiovascular responses during transfusion.

Materials and Methods

This descriptive observational study was carried out at the Children's Emergency Room (CHER) of a tertiary hospital in Nigeria. The subjects were consecutive children admitted into the CHER with anemic heart failure requiring blood transfusion. The patients were diagnosed with anemic heart failure if they fulfilled the following diagnostic criteria for congestive heart failure.[20]

- Significant tachycardia for age (>160 bpm in infancy, >140 bpm at 2 years, >120 bpm at 4 years, and >100 bpm above 6 years.) Where fever was present, a 10 bpm for every 1° C rise in temperature was allowed for.
- Significant tachypnea for age (>60 cycles/min in the newborn, >40 cycles/min <24 months, 30 cycles/min in 2–5 years, >28 cycles/min in 5–10 years, and >25 cycles/min in >10 years)
- Cardiomegaly (displaced apex beat with a central trachea or cardiothoracic ratio >60% in <5 years and >50% in >5 years)
- Tender hepatomegaly of at least 3 cm size below the right costal margin.

The fulfillment of at least three of the four criteria above was diagnostic of anemic heart failure. In addition, the patients also had severe anemia (packed cell volume of <15%). Patients with less severe anemia who had congestive heart failure were included. The protocol for blood transfusion in the study center was to transfuse when the hematocrit was ≤15% or when the hematocrit was 15% and above with signs of cardiovascular decompensation (tachycardia, tachypnea, and tender hepatomegaly).

The following information was obtained at admission: the age, sex, and the socioeconomic status (SES) using the methods described by Olusanya *et al*.[21] The patient's weight was measured using an appropriate weighing scale. The Z scores of the weight for age was then determined using the World Health Organization (WHO) growth chart.[22] Patients whose weight for age Z score was less than 2 standard deviations were classified as malnourished. The cause of anemia was determined using standards methods.

Children with severe malaria anemia received whole blood while those with anemia from other causes had sedimented cells. The children with severe malaria anemia received whole blood to also correct the attendant hypovolemia associated with the condition in line with the WHO recommendation.[23] The amount of blood to be transfused was calculated based on the maximum allowable volume of 20 mL/kg for whole blood given over 4 h (5 mL/kg/h) and 15 ml/kg of sedimented cells infused over 4 h (3.75 mL/kg/h). Children who were malnourished were given a maximum of 10 ml/kg of sedimented cells or whole blood over 4 h (2.5 ml/kg/h) to reduce the volume loading on the compromised heart. The pre-transfusion packed cell volume (PCV) was noted. The HR, RR, and SBP were measured on the right arm in the recumbent position with a mercury sphygmomanometer. The HR and RR were counted over 1 minute. The O_2 sat was measured with a pulsox 300, pulse oximeter (Konica Minolta Optics, Inc. Osaka, Japan). The size of the hepatomegaly was determined by measuring the liver edge from the lowest rib in the mid-clavicular line in the right hypochondrium, using a non-distensible measuring tape. The clinical diagnosis of anemic heart failure was made by a senior registrar while subsequent measurements were made by registrars. As much as possible, one registrar made all the measurement in a given patient.

The HR, RR, BP, O_2 sat, and the liver size below the costal margin were all determined pre-transfusion (first

observation), between the first and second hour into the transfusion (second or intra-transfusion observation), again within the 4th and 6th hour from commencement of transfusion (third or immediate post-transfusion observation), and between the 20th and 24th hours from commencement of the transfusion (fourth or late post-transfusion observation). The duration of admission and outcome of the patients were documented. Exemption from ethical approval was obtained from the institution's ethics committee.

Statistical analysis

The data were coded and entered in a computer and analysis was done using SPSS 13.0. The parametric variable such as HR, RR, SBP, etc, were presented as mean ± SD while the difference in the mean changes of variables between evaluations were computed with Student's *t*-test or one-way ANOVA, as appropriate. Turkey-Cramer multiple comparison tests were done where ANOVA was significant. The difference in proportions was computed with Chi-square tests. Significant *P* value at 95% confidence interval was set at 0.05.

Results

Characteristics of study population

During the study period, 75 patients with anemic heart failure were recruited. There were 46 (61.3%) males and 29 (38.7%) females. The mean age at presentation was 43.8 ± 40.3 (range 3–180) months. The proportion of patients less than 12 months was 13 (17.3%), the patients aged 12 to 59 months were 45 (60.0%), and the patients that were older than 60 months were 17 (22.7%). The Z scores of the weight for age of the study population showed that most of them (60 [80.0%]) had normal nutrition while 14 (18.7%) were underweight and 1 (1.3%) was overweight.

Most of the patients 52 (69.3%) were from low socioeconomic Class, 12(16.0%) from the middle SES, and 11 (14.7%) were from high SES. The distribution of maternal level of education of the patients showed that the majority of the mothers (29 [38.7%]) had up to primary and 37 (49.3%) had secondary level of education. Only 5 (6.7%) had tertiary level of education and 2 (2.7%) had no education.

There were 52 (69.3%) patients who were transfused with whole blood and 14 (18.7%) patients who were malnourished and received 10 mL/kg of sedimented cells or whole blood over 4 h.

Cause of anemia, and hematocrit and mean values of parameters

Severe malaria anemia was the commonest cause of anemia and accounted for 51 (68.0%) of the patients, followed by sickle cell anemia in crisis 8 (10.7%). The other causes are as shown in Table 1. The average PCV at presentation was 15.0 + 4.5 (range 4–23) %. There were 47 (62.7%) who had PCV <15% on presentation and 28 (37.3%) whose PCV was ≥ 15%. The mean HR of the study population was 139.7 ± 25.2 bpm, 129.6 ± 22.0 bpm, 133.7 ± 20.2 bpm, and 122.4 ± 19.8 bpm at the pre-transfusion, intra-transfusion, immediate post-transfusion, and late post-transfusion observations, respectively. The difference in the mean HR between the various observations was statistically significant, $P = 0.0004$. Specifically, on multiple comparison, the pre-transfusion HR was higher than the late post-transfusion HR observation and the HR at immediate post-transfusion observation was significantly higher than the late post-transfusion observation, $P = 0.05$ and 0.01, respectively [Table 2].

The mean RR was 45.9 ± 12.2 cycles/min, 42.1 ± 12.8 cycles/min, 43.4 ± 13.4 cycles/min, and 37.5 ± 10.0 cycles/min at the pre-transfusion, intra-transfusion, immediate post-transfusion, and late post-transfusion observations, respectively. The difference in the mean RR values between observations was statistically significant, $P = 0.0033$. On multiple comparison, the pre-transfusion mean RR was found to be significantly higher than the late post-transfusion observation, $P = 0.05$ [Table 2]. Although there was a

Table 1: Causes of anemia in study population

Diagnosis	Number	Percentage
Severe malaria anemia	51	68.0
Sickle cell anemia	8	10.7
Pediatric AIDS	5	6.7
Hemolytic anemia	4	5.3
Septicemia	3	4.0
Tuberculosis	2	2.7
Acute lymphoblastic leukemia	1	1.3
Bleeding peptic ulcer disease	1	1.3

Table 2: The mean values of the parameters evaluated at each observation

Parameter	First evaluation	Second evaluation	Third evaluation	Fourth evaluation	*P* value
Heart rate (Beats per minute)	139.7±25.2	129.6±22.0	133.7±20.2	122.4±19.8	0.0004
Respiratory rate (Cycles/minute)	45.9±12.2	42.1±12.8	43.4±13.4	37.5±10.0	0.0033
Liver size (cm)	5.8±2.4	5.6±2.4	5.0±1.8	3.9±1.5	0.1615
Systolic BP (mmHg)	90.3±8.8	92.6±10.0	97.0±11.2	95.1±11.2	0.1276
Oxygen saturation (%)	93.2±16.1	94.8±16.2	94.7±16.3	98.2±2.4	0.8994

gradual decline in the liver size and the oxygen saturation over time, the differences were not statistically significant, $P = 0.1615$ and $P = 0.8994$, respectively. The mean SBP values showed a steady increase between observations, but the difference was not significant, $P = 0.1276$ [Table 2].

The difference in the mean HR in the patients who received whole blood compared with those who received sedimented cells in the first, second, and third observations were significant, $P = 0.002$, 0.001, and 0.042, respectively. The differences in the mean RR, liver size, SBP, and O_2 sat between the two groups were not significant. There were no statistically significant differences in the parameters between those who had 10 mL/kg and those who had either 15 mL/kg or 20 mL/kg of blood over 4 h.

Mean changes in heart rate, respiratory rate, blood pressure, and liver size

There was a mean reduction of 10 bpm in the HR between the pre-transfusion and the intra-transfusion observation while a mean of 13 and 24 bpm reductions were recorded between the pre-transfusion observation and the immediate and late post-transfusion observations, respectively. Similarly, there was a mean reduction in the RR of 4 cycles/min between the pre-transfusion and the intra-transfusion observations. The RR reduced by about 10 cycles/min between the pre-transfusion and the late post-transfusion observations.

The liver size decreased by a mean of 0.15 cm between the pre-transfusion and the intra-transfusion observations and by 0.39 cm between the intra-transfusion and immediate post-transfusion observations. The children with normal weight for age had a mean 2 cm reduction in liver size between the pre-transfusion and intra-transfusion observations compared with the undernourished children with 0.23 cm, $P = 0.013$.

Outcome

None of the patients had deterioration of their cardiovascular status during or post transfusion. Most of the patients (68 [90.7%]) were discharged home, 4 (5.3%) were discharged against medical advice (DAMA), and 3 (4.0%) died. The three mortality cases had severe malaria anemia. Of those that DAMA, 1 (25.0%) had acute lymphoblastic leukemia and 3 (75.0%) had severe malaria anemia.

There was no significant association between mortality and sociodemographic variables as shown in Table 3. The patients that died were all from low socioeconomic class. None of the children of mothers with tertiary level of education died. No mortality was recorded among children <12 months of age and all the deaths were children with normal weight for age. There was no significant difference in the mean values of all the parameters between those who died and those who survived. The duration of hospitalization was 8.8 ± 8.1 (range 1–48 days). The longest staying patient had severe anemia and pulmonary tuberculosis.

Table 3: Relationship of mortality and socioeconomic class, maternal education and severity of anemia

Characteristics	Discharge	Death	*P* value
Sex			
Male	44	2	1.000
Female	28	1	
Age categories			
<12 mo	13	0	0.697
12–59 mo	43	2	
≥ 60 mo	16	1	
Socioeconomic class			
High and middle	21	0	0.551
Low	48	3	
Maternal level of education			
Tertiary education	5	0	1.000
>Tertiary	63	3	
Z score of weight for age			
Undernourished (<2 SD)	14	0	0.677
Normal weight for age	57	3	
>2 SD	1	0	
Severity of anemia			
PCV <15%	45	2	1.000
PCV ≥ 15%	27	1	

Discussion

The cardiovascular response to volume loading in transfusion was assessed in this study using the parameters of HR, RR, size of the hepatomegaly, blood pressure, and levels of oxygen saturation. These parameters are also the same used for determining the presence of heart failure. These parameters except for oxygen saturation do not require sophisticated equipments and can easily be done at the patient's bedside.

In this study, the response to blood transfusion was in reduction in HR, RR, and the liver enlargement; this response is similar to the one obtained in the study by Jayobose *et al*.[12] where they evaluated the response to packed cell transfusion of 2 cc/kg/h in children with gradual-onset anemia; whereas in the present study, we evaluated the response to transfusion in children with acute anemia complicated with congestive heart failure. It is to be expected that there might be untoward transfusion reaction such as TACO considering that the heart is in failure and might be unable to cope with volume loading because blood transfusion is known to increase the blood volume and increase the work of the heart.[24] The absence of TACO in the study would seem to suggest that the transfusion regimen of 2.5–5 mL/kg/h was tolerated by

the different groups of children with anemic heart failure in this study. It is important to note that transfusion of the prescribed volume is important in preventing TACO as earlier documented by previous workers.[19,25] That the heart coped with volume loading in this study may be due to the fact that in severe malaria anemia (the major cause of anemia in this study), there is associated volume depletion and relative hypotension.[26] The blood transfusion partially or wholly corrects the volume depletion. The rate of transfusion in this study is higher than that of Jayabose *et al*. Tolerance to higher rates of blood transfusion has been demonstrated in an earlier study.[27]

The reduction in the parameters except O_2 sat and blood pressure in response to blood transfusion in this study is consistent with previous reports in adult and children. [11,12,28,29] The HR and RR had the most easily measurable reduction compared with change in liver size. This easily measured difference in HR has been reported in previous works.[28,29] In contradistinction, the reduction in liver size became more measurable post transfusion. This may be due to the fact that the increase in HR and RR activated by neurohumoral mechanisms in response to decrease in oxygen carrying capacity (anemia) are easily reversed following blood transfusion. In contrast, fluid accumulation in the liver in hepatomegaly takes more time to build up and reversal of the process is similarly slow. Thus, changes in HR and RR are early indicators of response to blood transfusion. The statistically significant difference in the pre-transfusion and subsequent measurements in the HR, RR, and liver size shows a trend that can be employed in clinical setting. A deviation from this trend could be an early sign of circulatory overload. Such signs as worsening tachycardia, tachypnea, and accumulation of fluid as in hepatomegaly are signs of TACO and indicate the need to institute measures to reduce the volume overload.

It is of note that the pre-transfusion hematocrit did not seem to significantly influence the cardiovascular response to volume loading. It would have been expected that patients with very low PCV would have had adverse reaction to volume loading because of the greater stress to the heart and vessels, which may possibly result in TACO.[19] It is possible that the small number of patients with very low PCV and the limit of volume of blood transfused may have led to this finding. The mortality recorded in this study was small and was not an immediate transfusion outcome, further attesting to the ability of the patients to handle the prescribed volume of blood. This study did not identify any factors that may have contributed to adverse outcomes. The small mortality may have contributed to the insignificant relationship of mortality with the age, socioeconomic status, etc. Perhaps another study with a bigger sample size would provide more valid inferences.

One limitation of this study is that the diagnosis of heart failure was entirely based on clinical evaluation. The estimation of brain atrial natriuretic factor or echocardiographic evaluation may have strengthened the diagnosis of heart failure in these children.

Conclusion

The cardiovascular response to volume loading in blood transfusion in anemic heart failure is towards resolution of the decompensation. The HR and RR are two easily measurable indices with reduction in HR and RR by 24 bpm and 10 cycles/min, respectively, from pre-transfusion observations to values obtained 1–2 h into the transfusion.

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