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Original Article

Effect of anemia and blood transfusion on tissue oxygen saturation and blood pressure in very preterm infants

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Abstract: *Objective:* This study aimed to investigate the effect of anemia and blood transfusion on tissue oxygen supple and blood pressure in very preterm infants, which may provide evidence for the clinical rational blood transfusion in the treatment of anemia in very preterm infants. *Methods:* 55 very preterm infants were divided into 4 groups: normal control group, mild anemia group, moderate anemia group and severe anemia group. The brain and intestinal oxygen saturation and blood pressure were measured. *Results:* Before transfusion, there were significant differences in the brain and intestinal oxygen saturation reduced significantly in anemia group as compared to control group ($P<0.05$). The brain tissue oxygen saturation in mild anemia group was significantly different from that in moderate and severe anemia groups ($P<0.05$). There was significant difference between mild/moderate and severe anemia groups ($P<0.05$). During blood transfusion, the brain and intestinal oxygen saturation increased gradually in moderate and severe anemia groups ($P<0.05$). After blood transfusion, significant difference was noted in the brain oxygen saturation between moderate group and severe group ($P<0.05$). Blood pressure remained unchanged during and after blood transfusion. During blood transfusion, fluctuation of intestinal oxygen saturation was larger than that of brain oxygen saturation, but the intestinal oxygen saturation recovered rapidly. After blood transfusion, both reached a high level and remained stable. *Conclusion:* Anemia of different degrees can reduce the oxygen supply to the brain and intestine of very preterm infants.

Keywords: Very preterm infant, anemia, brain, intestine, oxygen saturation, blood pressure

Introduction

The survival rate of very preterm infants increases significantly with the development of modern medicine. The anemia in very preterm infants has been a common problem in clinical practice. Anemia significantly affects the growth and development of very preterm infants, and causes poor immune function and developmental retardation. Thus, prevention and early treatment of anemia is crucial for the recovery of disease and healthy development in very preterm infants. Treatments of anemia in very preterm infant include blood component transfusion, iron supplement, and intramuscular injection of erythropoietin. Transfusion of red blood cells is the most widely used treatment for anemia with the best efficacy in clinical practice. It can rapidly increase the oxygen supply by red blood cells and improve clinical symptoms, which is helpful for the growth and development of these patients [1]. However, blood transfusion has some risks such as infection and transfusion related adverse effects. The indications for blood transfusion are very strict in clinical practice, and restrictive blood transfusion is recommended by clinicians. In asymptomatic infants with low HCT, blood transfusion is not recommended. In NICU, blood transfusion is usually subjective, and whether blood transfusion is needed and what is the volume of blood transfused mainly depend on some clinical factors including clinical manifestations. However, whether there is hypoxia before the presence of clinical manifestations and whether this has influence on the growth and development of infants are still poorly understood. In previous studies, far-infrared

Table 1. Brain and intestinal oxygen saturation in different groups before blood transfusion

Groups	Brain n (mean ± SD)	Intestine n (mean ± SD)
Controls	120 (82±5.3)$^{\#\#,\&\&}$	120 (84±5.0)$^{\#\#,\&\&}$
Mild anemia	120 (78±3.4)$^{**,\#\#}$	120 (79±4.7)$^{**,\#\#}$
Moderate anemia	120 (76±5.1)$^{**,\&}$	120 (78±3.8)$^{**,\#\#}$
Severe anemia	120 (74±3.9)$^{**,\&\&}$	120 (74±4.6)$^{**,\&\&}$
P	<0.001	<0.001

Notes: $^{*}P<0.05$, $^{**}P<0.01$ vs. control group; $^{\&}P<0.05$, $^{\&\&}P<0.01$ vs. mild anemia group; $^{\#}P<0.05$, $^{\#\#}P<0.01$ vs. severe anemia group.

Table 2. Blood pressure in different groups before blood transfusion

Group	SBP n (mean ± SD)	DBP n (mean ± SD)
Controls	120 (65±6.7)	120 (38±5.4)
Mild anemia	120 (65±7.9)	120 (38±6.4)
Moderate anemia	120 (63±7.6)	120 (36±3.5)
Severe anemia	120 (62±4.9)	120 (36±4.0)
P	0.325	0.226

Notes: *P*>0.05 vs. control group; *P*>0.05 among groups. SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 3. Effects of blood transfusion on brain oxygen saturation during and after blood transfusion

Group	During n (mean ± SD)	After n (mean ± SD)	*P*	T
Moderate anemia	180 (77±6.5)	180 (84±4.6)	0.024	-6.3
Severe anemia	180 (76±4.8)	180 (84±3.0)	0.001	-7.6
P	0.020	0.007		
T	-1.13	-0.35		

Table 4. Effects of blood transfusion on intestinal oxygen saturation during and after blood transfusion

Group	During n (mean ± SD)	After n (mean ± SD)	*P*	T
Moderate anemia	180 (81±9.3)	180 (86±5.9)	0.002	-3.49
Severe anemia	180 (80±5.4)	180 (85±3.4)	0.001	-6.25
P	0.001	0.092		
T	0.516	0.407		

cerebral oximetry showed the oxygen saturation lower than baseline level could significantly affect the clinical status of infants [2]. In the present study, far-infrared cerebral oximetry was performed to detect the tissue oxygen supply in very preterm infants with anemia of different extents, the influence of anemia on the tissue oxygen supply was further evaluated, and the effects of blood transfusion on blood pressure and tissue oxygen supply were further assessed in these patients. Our findings may provide evidence for the clinical management of anemia with blood transfusion in very preterm infants and are helpful for the development of rational and scientific guideline for blood transfusion in preterm infants.

Subjects and methods

Subjects

A total of 55 cases of very preterm infants were recruited from the Department of NICU of Bayi Children's Hospital Affiliated to the Army General Hospital of PLA between May 2015 and October 2015. The gestational age of these infants was 28-31^{+6} weeks. Patients were divided into 4 groups according to the severity of anemia: normal controls (n=10), mild anemia group (n=15), moderate anemia group (n=15) and severe anemia group (n=15).

Diagnostic criteria for anemia

Anemia in neonates was diagnosed according to the diagnostic criteria in the Textbook of Pediatrics (8th edition) [3]: 1. mild anemia: Hb=144-120 g/L; 2. moderate anemia: Hb=120-90 g/L; 3. severe anemia: Hb=90-60 g/L; 4. very severe: Hb<60 g/L.

Indications for blood transfusion

The indications for blood transfusion were adopted from those published in the Practical Neonatology (4th edition) [4].

Monitoring of oxygen saturation and blood pressure

Near-infrared cerebral oxygen saturation monitor (NIRS; CASMED, Branford, MT, USA) was used to monitor the brain and abdominal oxygen saturation from 1.5 h before blood transfusion to 2 h after blood transfusion. Blood transfusion last for 3 h. Multifunctional electrocardiogram monitor was used to monitor blood

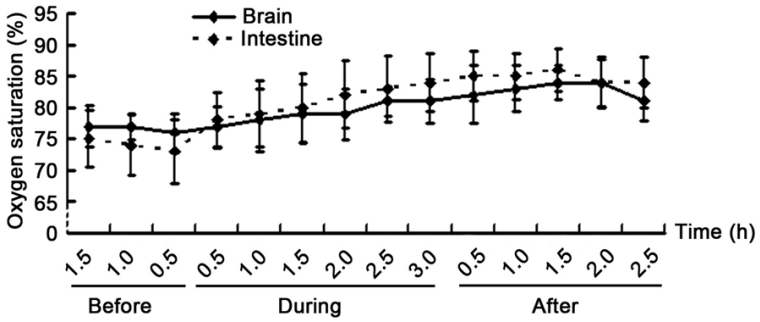

Figure 1. Brain and intestine oxygen saturation in moderate anemia patients before, during and after blood transfusion.

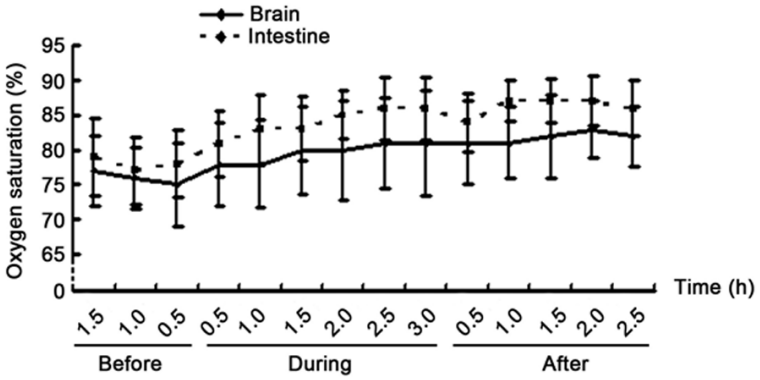

Figure 2. Brain and intestine oxygen saturation in severe anemia patients before, during and after blood transfusion.

pressure. Blood pressure was measured thrice and a mean was calculated.

Statistical analysis

Statistical analysis was performed with SPSS version 20.0. Quantitative data were compared with one way analysis of variance among groups, followed by LSD for comparisons between groups. Data are expressed as mean ± standard deviation (SD). A value of $P<0.05$ was considered statistically significant.

Results

Brain and intestinal oxygen saturation before blood transfusion

To elucidate the influence of anemia on the brain and intestinal oxygen supply in very preterm infants, the brain and intestinal oxygen saturation was monitored continuously in very preterm infants with anemia of different severities and healthy controls. Results showed the brain and intestinal oxygen saturation in anemia infants was significantly lower than that in healthy controls (P<0.05). In addition, the reduction in brain oxygen saturation was larger than that in intestinal oxygen saturation in these infants.

Moreover, one-way ANOVA were done among groups. Before transfusion, the brain oxygen saturation in healthy controls was significantly higher than that in any other group (P<0.05). Significant difference was also observed between mild anemia group and moderate/severe anemia group (P<0.05), but not between moderate anemia group and severe anemia group (P>0.05). Before blood transfusion, the intestinal oxygen saturation in healthy controls was significantly higher than that in any other group (P<0.05). There was no significant difference between mild anemia group and moderate anemia group (P>0.05), but the intestinal oxygen saturation in severe anemia group was significantly different from that in moderate and mild anemia groups (P<0.05) (**Table 1**).

Blood pressure in different groups before blood transfusion

To elucidate the change in blood pressure including systolic blood pressure and diastolic blood pressure in very preterm infants, multifunctional electrocardiogram monitor was used to monitor blood pressure. Results showed blood pressure in anemia infants was comparable to that in healthy controls (P>0.05), and there was no significant difference in blood pressure among groups (ANOVA; P>0.05) (**Table 2**).

Influence of blood transfusion on brain and intestinal oxygen saturation in different groups

During and after blood transfusion, there was significant difference in the brain oxygen saturation between moderate anemia group and severe anemia group (P<0.05), but significant

Table 5. Effect of blood transfusion on systolic blood pressure during and after blood transfusion

Group	During n (mean ± SD)	After n (mean ± SD)	*P*	T
Moderate	180 (60±7.1)	180 (66±9.5)	0.074	-4.09
Severe	180 (64±7.1)	180 (63±7.95)	0.721	0.317
P	0.421	0.233		
T	-2.699	1.81		

Table 6. Effect of blood transfusion on diastolic blood pressure during and after blood transfusion

Group	During n (mean ± SD)	After n (mean ± SD)	*P*	T
Moderate	180 (34±5.4)	180 (36±5.1)	0.573	-1.49
Severe	180 (34±4.8)	180 (35±6.1)	0.341	-1.76
p	0.260	0.620		
T	0.75	0.31		

difference in intestinal oxygen saturation was observed only during blood transfusion (P< 0.05). In a specific group of anemia infants, the brain and intestinal oxygen saturation changed significantly after blood transfusion as compared to that during blood transfusion (P<0.05; **Tables 3** and **4**). During blood transfusion, the brain oxygen saturation increased gradually and remained a stable level after reaching the peak. However, the intestinal oxygen saturation fluctuated significantly during blood transfusion, and it reached the peak and then remained relatively stable. Moreover, the restoration of intestinal oxygen saturation was more rapid as compared to that of brain oxygen saturation. It is suggested that intestinal oxygen saturation is susceptible to the influence of blood transfusion (**Figures 1** and **2**).

Effect of blood transfusion on blood pressure

Blood pressure remained unchanged in moderate and severe anemia groups during and after blood transfusion as compared to that before blood transfusion (P>0.05). In addition, blood pressure was comparable among three groups during and after blood transfusion (P>0.05) (**Tables 5**, **6**), suggesting that blood transfusion has no influence on blood pressure (**Figures 3** and **4**).

Discussion

With the introduction of neonatal intensive care unit and the improvement of medical techniques, the survival rate of very preterm infants increases over year. The very preterm infants have immature development of all the systems and thus are susceptible to complications, one of which is anemia. The presence of anemia in very preterm infants is determined by the physiological and developmental characteristics. The nutrient intake is insufficient due to poor suck and digestion, and the susceptibility to severe heart and lung diseases and infectious disease may induce the iatrogenic blood loss in very preterm infants [5]. The symptoms of anemia are caused by the poor oxygen supply of Hb. When the anemia is present, the oxygen supply reduces. Once the oxygen supply is lower than the required level, it may cause clinical manifestations. Currently, blood transfusion is still a major way for the treatment of anemia in very preterm infants [6]. However, blood transfusion has some complications such as transfusion related adverse effects, and transfusion related NEC and IVH, which significantly limits the wide application of blood transfusion in clinical practice. Thus, restrictive blood transfusion is employed in clinical practice. In recent years, NIRS is used to measure the tissue oxygen saturation which is the ratio of oxyhemoglobin to total hemoglobin in a specific organ. There is evidence showing that NIRS can objectively reflect the change in oxygenation of the brain and other visceral tissues and may provide important information for clinical treatment [7-12]. Thus, NIRS was employed to measure the brain and intestinal oxygen saturation in the present study.

The major findings of this study were as follows: 1) anemia in different severities may reduce the oxygen supply to the brain and intestine of very preterm infants: the more severe the anemia was, the more obvious the influence was. However, anemia has no significant influence on blood pressure including systolic blood pressure and diastolic blood pressure. 2) blood transfusion could increase the brain and intestinal oxygen saturation to different extents in very preterm infants with moderate or severe anemia. During blood transfusion, the intestinal oxygen saturation fluctuated significantly and increased rapidly, but the brain oxygen saturation remained relatively stable. After blood transfusion, both peaked and remained stable thereafter. In addition, our results also showed blood transfusion had no influence on blood pressure in very preterm infants, which was consistent with previous findings. Sandal

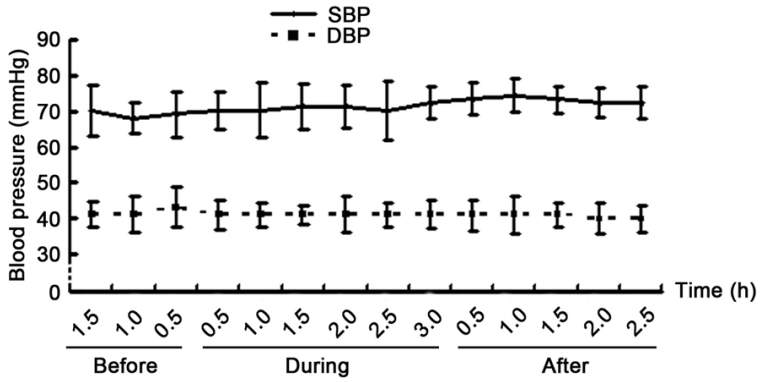

Figure 3. Blood pressure in moderate anemia patients before, during and after blood transfusion.

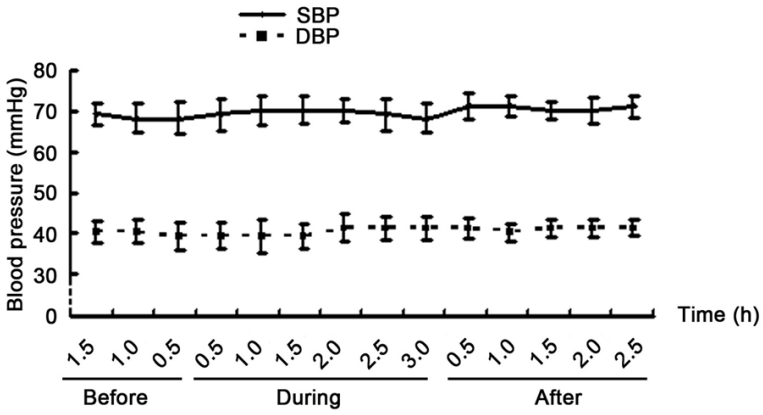

Figure 4. Blood pressure in severe anemia patients before, during and after blood transfusion.

et al investigated 23 symptomatic infants with anemia and gestational age of <30 weeks, and their results showed blood transfusion could elevate the brain and mesenteric oxygen saturation [13]. Although the actual brain oxygen saturation was not presented, results showed oxyhemoglobin increased after blood transfusion, which was consistent with the increase in brain oxygen saturation. Our results showed, during blood transfusion, the intestinal oxygen saturation fluctuated significantly, but brain oxygen saturation remained relatively stable. This might be explained as that blood perfusion and auto-regulation of intestinal vessels are poor in very preterm infants, the oxygen supply is very unstable, and thus anemia or blood transfusion may affect the intestinal blood supply and oxygen supply. This might be an important cause of anemia induced NEC. Studies have shown that blood transfusion is related to NEC. Amin et al found blood transfusion was associated with NEC, the smaller the gestational age and the lower the body weight, the higher the incidence of NEC is, and about 25-40% of patients with NEC had received blood transfusion [14]. Marin et al reported that 25%-35% of very low birth weight infants (body weight: <1500 g) receiving blood transfusion developed NEC [15], and they also found that low intestinal oxygen saturation and significant fluctuation of intestinal oxygen saturation were closely related to blood transfusion related NEC, and intestinal oxygen saturation could predict the risk for NEC in high risk infants [16]. Other studies also report that very low birth weight infants receiving blood transfusion have a low incidence of NEC [17], and there is no relationship between body weight and transfusion related NEC [18]. In our study, NEC was not found in very preterm infants, but reduced intestinal oxygen supply due to anemia and significant fluctuation of intestinal oxygen saturation during blood transfusion were found in these very preterm infants with anemia. Our results showed the intestinal oxygen saturation was similar between very preterm infants with mild and moderate anemia, but the intestinal oxygen saturation in mild anemia group was significantly different from that in severe anemia group. This suggests that mild anemia may affect the intestinal tissues. For very preterm infants, blood transfusion may be considered when moderate anemia is present, but clinicians should pay attention to the intestinal function during blood transfusion, aiming to prevent the deterioration due to the unstable blood flow in the intestine.

Taken together, anemia of different severities may reduce the oxygen supply to the brain and intestine of very preterm infants. If anemia is severe enough or it lasts for a long time, it may cause hypoxia/ischemia brain injury and necrotizing enterocolitis, but anemia has no influence on blood pressure. Blood transfusion may improve the oxygen supply to the brain and intestine, and has no impact on blood pres-

sure. During blood transfusion, the intestinal oxygen saturation fluctuates significantly, but it recovers more rapidly as compared to brain oxygen saturation. The significant fluctuation may induce NEC in very preterm infants because they have immature intestinal tissues. Thus, we recommend the indications for blood transfusion should not be strictly controlled for very preterm infant, and the transfusion rate should be monitored during blood transfusion to reduce its influence on the intestine. The optimal transfusion rate is required to be investigated in future studies.

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Disclosure of conflict of interest

None.

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