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Impact of Same Red Blood Cell Infusion at Different Intervals on Premature Infants' Hemoglobin Levels

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Purpose: Blood transfusions are performed in small amounts in premature infants. Few studies have focused on the effect of the same red blood cell (RBC) package at different intervals on increasing hemoglobin(Hb) concentration. We aimed to determine the effect of infusion of the same RBC package at different time intervals on Hb levels in premature infants.

Patients and Methods: Data were collected about premature infants who received the same package of RBC transfusion at two different intervals. Venous blood Hb levels before and within 24 hours after transfusion were measured for the first and second transfusions. Overall, 196 premature infants with anemia were included in the study. The data were categorized into four groups (Group I, Group II, Group III and Group IV) based on the varying intervals between transfusions of the same red blood cells.

Results: Hb levels of the first and second transfusions with the same RBC package showed a significant difference pre and posttransfusion. Hb increments varied among groups: Group I (43.00 g/L), Group II (34.50 g/L), Group III (32.00 g/L), and Group IV (32.50 g/L), with Group I demonstrating a significant difference compared to Groups II, III, and IV ($P<0.05$), while no differences were noted among the latter groups.

Conclusion: In premature infants with anemia, hemoglobin levels significantly increased after infusion of the same RBC package at different intervals. An interval of 1 week had the most significant effect.

What is New: There are differences in the effect of infusion of the same RBC at different time intervals on hemoglobin levels in premature infants. An interval of 1 week had the most significant effect.

Keywords: preterm infants, interval time, transfusion, hemoglobin, RBC

Introduction

Premature infants are at a high risk for anemia and often need blood transfusions. However, there are risks involved with blood transfusions, and the effects of the transfusion may vary depending on the features of the donor and the length of blood storage. Many studies have examined the safety of transfusions and unfavorable outcomes (such as mortality) related to the duration of red blood cell storage.

After birth, the hemoglobin of the term infants gradually decreases to 9.5–11 g/dL between 6 and 12 weeks, known as physiological anemia of infancy.[1] In preterm neonates, anemia occurs earlier and more severe.[2] Severe anemia may lead to hypoxia in tissues and organs, growth retardation, susceptibility to infectious diseases, and an increased risk of death.[3] Retrospective studies in preterm infants have shown that red blood cell (RBC) transfusions alleviate the compensatory

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increase in cardiac output of infants with anemia and reduce organ damage.[4–7] However, blood transfusions are associated with risks, and donor characteristics and blood storage time may impact its effects.[8]

In most blood banks, RBC units are allowed up to 42 days of storage.[9] With the prolonged storage time, the RBCs undergo various physiochemical changes that impair RBC capacities and are often called "storage lesions".[10] Numerous studies have looked at transfusion safety and adverse consequences (including mortality) based on RBC storage time.[11–13] However, few studies have evaluated the relationship between RBC storage time and transfusion effectiveness. A retrospective study reported that in patients who underwent major abdominal surgery, transfusion of older RBCs increased the hemoglobin concentration less effectively than transfusion of fresher RBCs.[14] Similar results were reported in a cohort study of patients with myelodysplastic syndromes.[15] However, the effect of transfusion of the same RBC package at different intervals in premature infants is unknown.

In this study, data on preterm infants with anemia were used to study the effect of infusion of the same RBC at different intervals on hemoglobin levels.

Methods

Setting

This retrospective study was conducted in the Department of Neonatology, Fujian Maternity and Child Health Hospital College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University from January 2018 to June 2023. Data on premature infants with anemia were collected, among which 392 transfusions of RBCs from 196 cases met the inclusion criteria. Among them, 120 were male and 76 were female. Their gestational age was 24.4 to 36.5 weeks and their birth weight was 0.6 to 3.3 kg. Based on the recommendations from Difference Test, the minimum sample size required is 52 subjects.

Inclusion and Exclusion Criteria

Inclusion criteria: (a) Preterm infants with gestational age <37 weeks, (b) admission within 24 hours of birth, hospital stay> 1 week after transfusion treatment, and (c) hemoglobin detection at 24 hours before and within 24 hours after transfusion. Exclusion criteria: (a) patients with blood system diseases such as hemolytic anemia or dyserythropoiesis, (b) patients with immunodeficiency, (c) patients with hemorrhagic diseases such as traumatic hemorrhage and intracranial hemorrhage,(d) Patients suffer from severe conditions that affect hemoglobin levels, such as respiratory distress and sepsis and(e) patients with incomplete data.

Data Sources and Equipments

Preterm infants diagnosed with anemia and treated with blood transfusions were included in the analysis during the study period. Diagnostic criteria for anemia: According to the 5th edition of Practice of Neonatology,[16] the hemoglobin concentration in newborns is as low as 71 (65–90) g/l at 4 to 8 weeks of life (birth weight less than 1.2 kg), and 90 (80–100) g/L at 8 to 10 weeks of life (birth weight of 1.2 to 2.5 kg) (Table 1). The instrument used for hemoglobin was the Sysmex XN-3000 (Sysmex Corporation, Kobe, Japan).

Table 1 Hemoglobin Levels in Premature Infants at Different Stages` (S±SD g/L)

Weight (Gestational week)	3 days	1weeks	2weeks	3weeks	4weeks	6weeks	8weeks
<1500g (28~32W)	175±15	155±15	135±11	115±10	100±9	85±5	85±5
1500~2000g (32~34W)	190±20	165±15	145±11	130±11	120±20	95±8	95±5
2000~2500g (34~36W)	190±20	165±15	150±15	140±11	125±10	105±9	105±9

Study Design and Statistical Analyses

The RBCs used in the transfusion were all allogeneic leucocyte free suspension red blood cells. 1 unit RBCs were prepared from 200 mL whole blood and divided into 2 parts of 0.5 unit according to needs. Blood packaging is uniformly designed by the blood centers in accordance with national regulatory standards. The transfusion volume was 15mL/kg. The time between the first transfusion and the second transfusion is defined as the interval time. Venous blood hemoglobin levels before and within 24 hours after transfusion were measured both in the first and second transfusions.

All statistical analyses were performed using computer software (SPSS 27.0). Summary statistics were described as medians with interquartile ranges, represented by M (Q1, Q3) and the Mann–Whitney *U*-test was used to make comparisons between the two groups. Qualitative data were expressed as percentages. A P-value below 0.05 was considered statistically significant. GraphPad Prism v.8.0.2 was used for plotting.

Results

We identified 2291 transfusions of RBCs from 1006 newborns in the study time. Individuals without interval infusion of the same RBC (n=684), without complete information (n=88), with hemorrhagic diseases (n=31) and non-preterm infants (n=31) were excluded. Finally, 392 transfusions of RBCs from 196 infants met the inclusion criteria (Figure 1).

We created a histogram of distribution according to RBC infusion intervals (Figure 2). Transfusion data were divided into Group □, □, □ and □ four groups according to the different interval time, of which Group □ 65 patients (1 to 7 days), Group □ 78 patients (8 to 14 days), Group □ 41 patients (15 to 21 days) and Group □ 12 patients (22 to 28 days).

There was no statistically significant difference in gender, birth weight (PI, II=0.339, PI, III=0.446, PI, IV=0.204, PII, III=0.958, PII, IV=0.469, PIII, IV=0.537) and age at diagnosis (PI, II=0.171, PI, III=0.783, PI, IV=0.950, PII, III=0.129, PII, IV=0.178, PIII, IV=0.710) among each group (Table 2).

The median hemoglobin concentration before the first RBC transfusion was 85.5(78.00, 94.00) g/L, increasing by 38.5 (727.25, 51.00) g/L to a median posttransfusion hemoglobin of 124.0(112.00, 138.75) g/L. The median hemoglobin concentration after the second RBC transfusion was 122.0 (111.00, 132.00) g/L, with an increase of 36.0(25.00, 45.00) g/L to a median pretransfusion hemoglobin of 86.0 (78.00, 95.00) g/L (Table 3). The elevated hemoglobin levels of the first and the second transfusion with the same RBC both had a significant difference before and after transfusion (Figure 3).

We evaluated the effect of RBC transfusion in preterm infants. After the first transfusion, Hb levels of Group I, II, III, IV showed a significant increase compared with those before transfusion respectively (Group I, 115.00 vs 85.00g/L, Group II 127.00 vs 86.00g/L, Group III, 122.00 vs 85.00g/L, Group IV, 133.50 vs 87.00g/L). Hemoglobin levels followed a similar trend after the second transfusion (Group I, 125.00 vs 96.00g/L, Group II 121.50 vs 84.00g/L, Group III, 119.00 vs 82.00g/L, Group IV, 120.50 vs 76.00g/L), with statistically significant differences (Figure 4a and b).

The increments of hemoglobin concentration before blood transfusion and after the two transfusions were 43.00 (27.00 to 53.50) g/L in Group I, 34.50 (21.00 to 45.00) g/L in Group II, 32.00 (17.50 to 40.00) g/L in Group III and 32.50 (20.75 to 38.00) g/L in Group IV, respectively. When compared in pairs, the Hb increment in Group I showed a significant difference with those in Group II, III and IV, and there was no significant difference between the other three groups (Table 3, Figure 5).

Discussion

To the best of our knowledge, this is the first study to investigate the effects of multiple transfusions of the same blood bag on preterm infants. Our study found that after two transfusions of the same package of RBCs, hemoglobin levels were significantly higher in both retests than before the transfusion. Preterm infants were divided into four groups according to the interval between the two transfusions, and hemoglobin increments after the second transfusion in each group were compared in pairs. The results showed that an interval of 1 week between transfusions had the most significant increase of hemoglobin after the second transfusion compared with the other intervals. No difference was observed between groups at other time intervals.

"The Global Action Report on Preterm Birth" released by the World Health Organization showed that in 2010, prematurity incidence in China was 7.1% after adjustment, similar results were found in a later study.[17,18] After birth, the

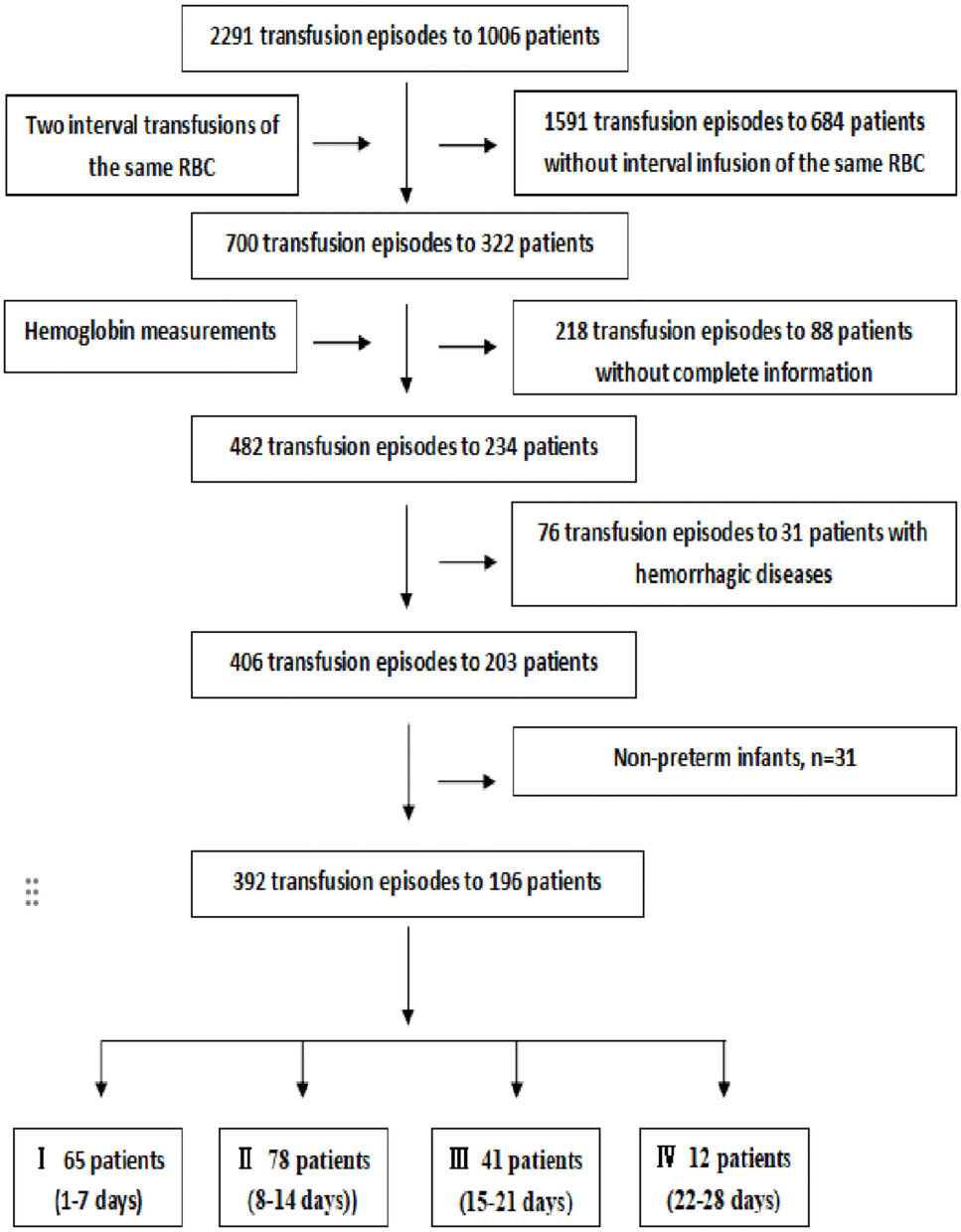

Figure 1 Flow chart of included patients, RBC transfusions, and hemoglobin measurements.

newborn's (term or preterm) hemoglobin level gradually decreases, with the lowest between 6 and 12 weeks in term infants.[16] In preterm infants, anemia appears earlier and is more severe. Phlebotomy losses, decreased iron stores, and low erythropoietin levels are thought to be the major causes.[2] RBC transfusion is the primary method used to treat premature anemia, and most infants weighing ≤1 kg receive transfusions.[19] Van Marter et al[4] found that RBC transfusions alleviated compensatory increases in cardiac output in infants with anemia. Retrospective studies in preterm infants have shown that RBC transfusion can increase circulating hemoglobin levels, improve the oxygenation index and arterial/alveolar (a/A) ratio within 24 hours after transfusion in mechanically ventilated patients,[5] and enhance cerebral tissue oxygen saturation (rSO2) and abdominal and renal rSO2 at 24 hours after transfusion.[6,7] Our study also found that after transfusion, hemoglobin levels were significantly higher than those before transfusion.

However, blood transfusions are associated with risks, including both infectious (eg, Zika.[20]) and noninfectious serious complications, such as bronchopulmonary dysplasia, retinopathy of prematurity, necrotizing enterocolitis, and adverse

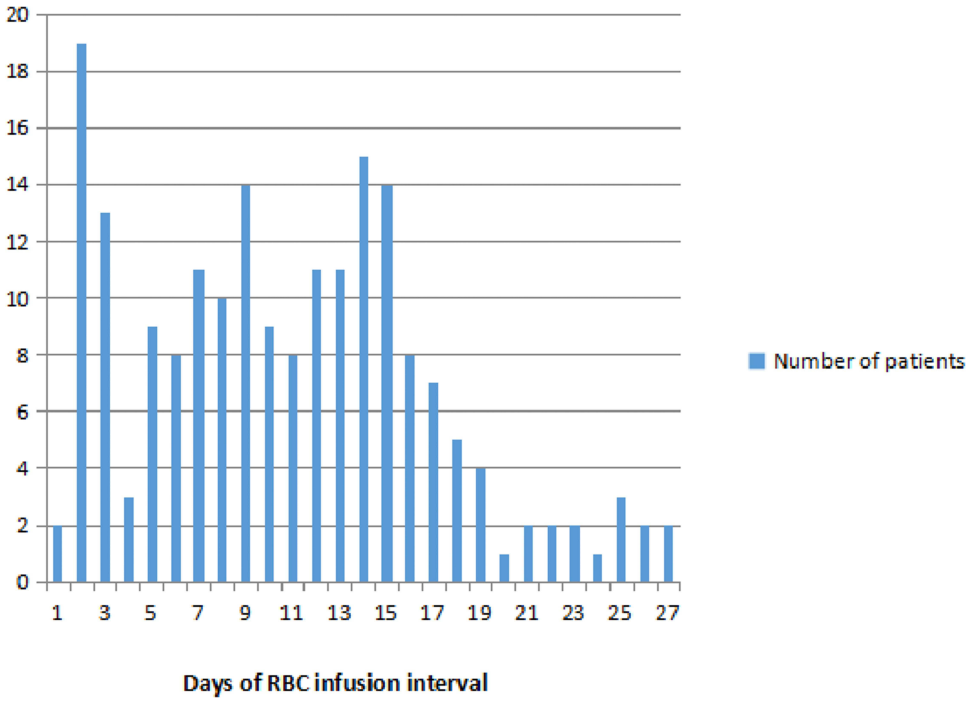

Figure 2 Histogram of distribution of RBC infusion interval (days).

neurological outcomes.[21–24] Oxidative stress, inflammatory substances in RBC units, and liberal transfusions may play roles in the pathophysiology of these complications.[25] Therefore, reducing the number of blood transfusions and minimizing blood donor exposure may be effective. For physiological reasons, transfusions in premature infants usually require a smaller volume, with a recommended volume of 10–20 mL/kg per transfusion.[26] Our study hospital has the largest neonatology ward and the largest number of newborn patients in the region, uses a uniform protocol for transfusion therapy (15 mL/kg), and has standardized equipment for fractioning RBC units into multiple smaller aliquots. These methods have enabled the study of the effectiveness of injections of the same RBC at different intervals in preterm infants.

In addition, RBC storage time may impact transfusion effects. Stored RBCs show diminished flexibility and metabolic changes called "storage lesions", which may affect its oxygen delivery capability.[27] However, most studies have focused on the relationships between RBC storage time, transfusion safety, and adverse transfusion outcomes. Several large randomized trials involving neonates, critically ill patients, and patients undergoing cardiac surgery have found that the infusion of fresh RBCs did not improve clinical outcomes.[12,28,29] Few studies have investigated the effect of blood transfusion therapy on improving hemoglobin.[14,15] This is the first study to evaluate the effects of the same blood transfusion bag on preterm infants. Similar to previous results, hemoglobin was most significantly elevated after two transfusions with a 1 week interval compared to other time intervals.

Table 2 Baseline Characteristics of the Patients

	Total (%)	I	II	III	IV
Patients, (%)	196 (100.00)	65 (33.16)	78 (39.80)	41 (20.92)	12 (6.12)
Median age at diagnosis, weeks	28.57 (27.14, 30.43)	29.14 (27.00, 30.93)	28.86 (27.07, 30.47)	28.29 (27.43, 29.86)	28.22 (27.57, 29.00)
Sex					
Female, (%)	76 (38.78)	21 (32.31)	37 (47.44)	14 (34.15)	4 (33.33)
Male, (%)	120 (61.22)	44 (67.69)	41 (52.56)	27 (65.85)	8 (66.67)
Birth weight, kg	1.10 (0.92, 1.31)	1.12 (0.90, 1.41)	1.03 (0.89, 1.23)	1.13 (0.99, 1.28)	1.19 (0.96, 1.31)

Notes: Data were presented as n (%) or median (Q1, Q3).

Table 3 Hemoglobin Before and After Two Transfusions of RBC

	Total (%)	I	II	III	IV
Transfusion episodes, (%)	392 (100.00)	130 (33.16)	156 (39.80)	82 (20.92)	24 (6.12)
Duration of interval days, days	10.78	4.02	11.14	16.71	24.75
First pretransfusion Hb, g/L	85.50 (78.00, 94.00)	85.00 (76.00, 92.50)	86.00 (77.00, 94.25)	85.00 (80.50, 91.50)	87.00 (84.25, 97.75)
First posttransfusion Hb, g/L	124.00 (112.00, 138.75)	115.00 (105.50, 129.00)	127.00 (118.00, 143.00)	122.00 (115.50, 137.50)	133.50 (118.25, 147.50)
Second pretransfusion Hb, g/L	86.00 (78.00, 95.00)	96.00 (85.00, 105.50)	84.0 (77.75, 90.00)	82.00 (75.00, 89.00)	76.00 (74.00, 82.50)
Second posttransfusion Hb, g/L	122.00 (111.00, 132.00)	125.00 (117.00, 135.50)	121.50 (109.00, 131.25)	119.00 (109.00, 128.00)	120.50 (115.25, 125.00)
Final increase in Hb, g/L	35.00 (23.25, 47.00)	43.00 (27.00, 53.50)	34.50 (21.00, 45.00)	32.00 (17.50, 40.00)	32.50 (20.75, 38.00)

Notes: Data were presented as n (%) or median (Q1, Q3). Hb, hemoglobin.

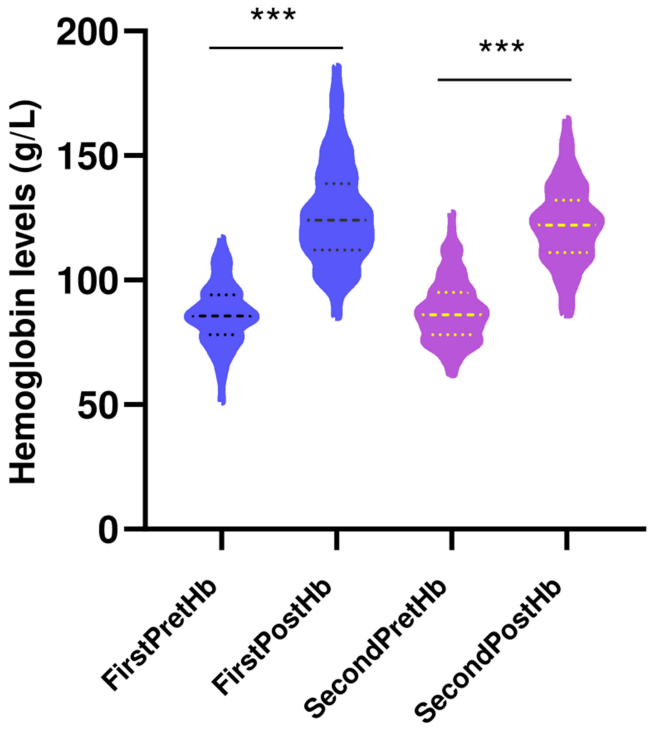

Figure 3 The effect of two transfusions of the same package of blood in preterm infants.
Note: The elevated hemoglobin levels of the two transfusions both had a significant difference before and after transfusion. Bean-plots represent the median and interquartile range, ***p<0.001.

Our study design had some limitations. First, the study was not prospectively designed, and there were no statistics on coexisting diseases or treatment plans. The influence of certain diseases and treatments on the efficacy of blood transfusion cannot be excluded. Second, we excluded many patients with incomplete information, which may have affected the study results.

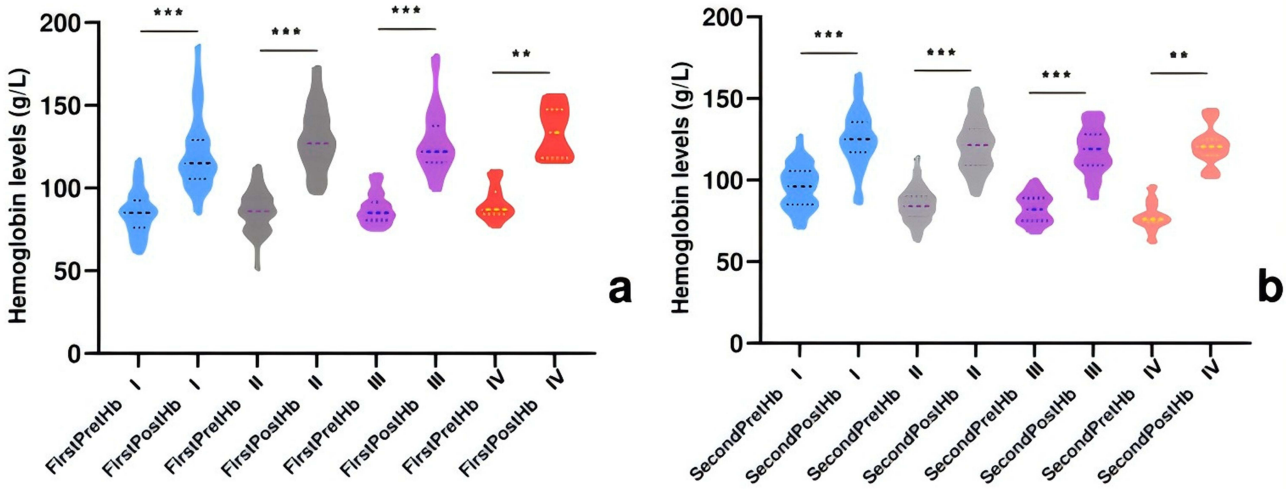

Figure 4 The hemoglobin levels before and after (**a**) the first transfusion, (**b**) the second transfusion.
Note: There were significant increases in Hb levels after the first and the second transfusion in Group I, II, III, IV. Bean-plots represent the median and interquartile range, ***p<0.001, **p<0.01.

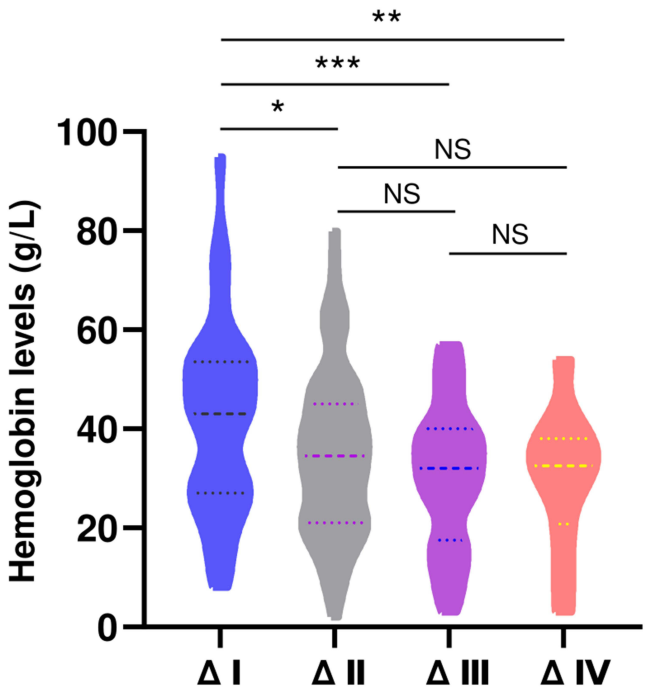

Figure 5 The comparison of hemoglobin increases after the second RBC transfusion.
Note: ΔI, ΔII, ΔIII, ΔIV represent the hemoglobin incremental concentrations in group I, II, III, IV, patients after the second transfusion, respectively. Bean-plots represent the median and interquartile range,***p<0.001 **p<0.01, *p<0.05, NS Not significant.

Conclusion

Our retrospective study discovered that a significant increase in hemoglobin levels after infusion of the same RBC package at different intervals in premature infants with anemia, and an interval of 1 week had the most significant effect. In the future, more research will be conducted to investigate the possible mechanisms of this difference.

Abbreviations

RBC, red blood cell; rSO2, cerebral tissue oxygen saturation.

Data Sharing Statement

The data are anonymous, and the requirement for informed consent was therefore waived by the Fujian Maternity and Child Health Hospital College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University of the Ethics committee. Data will be made available on reasonable request.

Ethics Approval

This study was approved by the Ethics Committee of Fujian Maternity and Child Health Hospital College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University (ethics approval number: 2023KY159). This article was a retrospective study, patient parental consent to review their medical records was not required by the ethics Committee. This study strictly kept the patients' information confidential. The study complied with the Declaration of Helsinki.

Consent for Publication

All authors consent for publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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