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Original Article

Analysis of correlative risk factors for blood transfusion therapy for extremely low birth weight infants and extreme preterm infants

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Abstract: Objective: To analyze the related risk factors in blood transfusions for extremely low birth weight infants and extreme preterm infants, and to explore the prevention strategy of anemia. Methods: A total of 60 infants with gestational age < 28 weeks or birth weight < 1000 g admitted to our hospital from January 2017 to December 2020 were retrospectively analyzed. The infants with a birth weight of less than 1000 g were divided into the blood transfusion group and the non-blood transfusion group according to whether they received a blood transfusion. The general health situation, disease occurrence and treatment measures during hospitalization were compared between the two groups, and the risk factors of blood transfusion were analyzed. Results: There were significant differences in maternal anemia during pregnancy, birth weight, gestational age, hemoglobin and hematocrit at birth, blood collection within 2 weeks after birth, length of hospital stay, bronchopulmonary dysplasia and patent ductus arteriosus between the transfusion group and the non-transfusion group ($P < 0.05$). Multivariate logistic regression analysis and ROC curve analysis showed that the younger the gestational age (OR=0.385, 95% CI: 0.212~0.705, P=0.002), the lower the birth weight (OR=1.004, 95% CI: 0.967~0.998, P=0.001), the longer the hospitalization time (OR=2.178, 95% CI: 1.172~4.049, P=0.014) and a larger blood collection within 2 weeks after birth (OR=1.269, 95% CI: 1.084~1.489, P=0.003) would induce higher the blood transfusion rates. Conclusion: The transfusion indications of extremely low birth weight infants and extreme preterm infants are affected by many factors, among which gestational age, length of hospital stay, blood collection within 2 weeks after birth and birth weight are independent predictors of transfusion. Blood transfusion in extremely low birth weight infants and extreme preterm infants is associated with an increased risk of apnea, neonatal respiratory distress syndrome, bronchopulmonary dysplasia and patent ductus arteriosus.

Keywords: Extremely low birth weight infants and extreme preterm infants, blood transfusion, risk factors

Introduction

Anemia in preterm infants refers to when hemoglobin (HB) in the venous blood is ≤ 130 g/L, and peripheral HB ≤ 145 g/L within 2 weeks of birth, peripheral HB < 110 g/L from 2 weeks to 1 month of birth, and peripheral HB < 90 g/L after 1 month of birth [1]. The smaller the preterm infants are, the more likely they need a blood transfusion [2, 3]. The main clinical manifestations of neonatal anemia include pale skin and mucous membranes, low reaction, apnea, feeding difficulties, weight loss and other symptoms [4]. At present, blood transfusion is still the most common and effective treatment. The Canadian neonatal network (CNN) survey showed that more than 75% of extremely low birth weight infants and extreme preterm infants received at least one blood transfusion during hospitalization [5]. Blood transfusion in preterm infants may also produce serious side effects, such as bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), pulmonary hemorrhage, intracranial hemorrhage (IVH) and retinopathy of prematurity (ROP), etc [6-10]. Whyterk et al. [11] suggested that the inhibition of the erythropoietin response in preterm infants after birth, and the large amount of iatrogenic blood loss are the causes of anemia in preterm infants. Jeannette S [12] indicated that low erythropoietin levels and low iron storage are the causes of anemia

in premature infants, and studies have pointed out that the younger the gestational age and more iatrogenic blood loss could induce greater anemia in premature infants.

In our study, we analyzed the related risk factors of blood transfusion for extremely low birth weight infants and extreme preterm infants.

Data and methods

Clinical data

This is a retrospective study, With 60 extremely low birth weight infants and extreme preterm infants in our hospital from January 2017 to December 2020 who were divided into two groups: the observation group (n=36 cases) and the control group (n=24 cases). The study was approved by the institutional ethics committee of Huizhou Municipal Central Hospital and was conducted in accordance with the Declaration of Helsinki.

Inclusion and exclusion standards

Inclusive standards: ① Admission within 24 hours after birth; ② Gestational age < 28 weeks or birth weight < 1000 g; ③ Stay in hospital ≥ 7 days; ④ The basic information and laboratory examination data are complete.

Exclusion standard: ① Had a history of erythropoiesis disorders; ② Had a history of hemolytic anemia; ③ Had a history of thalassemia and other blood system diseases; ④ Had a history of immunodeficiency at birth.

Methods

The infants in the control group had no blood transfusion (n=24 cases). The infants were didn't receive blood transfusion.

The infants in the observation group for did have a blood transfusion (n=36 cases). The blood transfusion indication conformed to standards of Practical Neonatology [13] and were as follow: ① Infants needed moderate mechanical ventilation, and hemoglobin (HB) ≤ 110 g/L, or hematocrit (HCT) ≤ 0.35; ② Infants needed mild mechanical ventilation, and hemoglobin (HB) ≤ 100 g/L, or hematocrit (HCT) ≤ 0.30; ③ Infants needed oxygen, but they did not need mechanical ventilation, moreover, Infants had anemia symptom, and hemoglobin (HB) ≤ 80 g/L, or hematocrit (HCT) ≤ 0.25; ④ Infants were asymptomatic, but hemoglobin (HB) ≤ 70 g/L, or hematocrit (HCT) ≤ 0.20.

Observation index

① Collection of clinical data: The general data of infants, such as birth weight, gestational age, gender were collected; high risk factors of pregnant females: mode of delivery, pregnancy induced hypertension, gestational diabetes mellitus, premature rupture of membranes; related risk factors of infants such as times of administration of surfactant, duration of mechanical ventilation, duration of oxygen use, Hb and HCT before blood transfusion, apnea before blood transfusion, neonatal sepsis, IVH, NEC, length of hospital stay, etc.

② Recorded related complications: 1) Bronchopulmonary dysplasia (BPD). 2) Necrotizing enterocolitis (NEC). 3) Intraventricular hemorrhage (IVH). 4) Patent ductus arteriosus (PDA).

Statistical analysis

All data were analyzed by SPSS 25.0. Among them (n, %) refers to the calculated data. The comparison of relevant data between groups and within groups was performed by chi square test, and the measurement data was applied (Mean ± sd). The comparison between groups was conducted by t test. $P < 0.05$ indicated the difference had statistical significance. Analyses were performed using Graph Pad Prism 7 Software (Graph Pad Prism, San Diego, CA).

Results

Clinical data of the infants

The research included 60 infants with extremely low birth weight and that were extremely preterm. This involved 36 infants in the observation group, with a mean gestational age (30.6±2.2) weeks, while in the control group, there was a mean gestational age (32.9±2.5) weeks. The birth weight in the observation group was (1268.1±196.2) g, and in the control group it was (1373.2±136) g, there was a statistical significance between two groups ($P < 0.05$). The level of Hb value at birth in the observation group was (173.5±21.4) g/L, and that in the control group was (188.9±21.1) g/L. The Hct value at birth in observation group was (52.7±5.5)%, and in control group was

Table 1. Comparison of clinical data between the two groups

	Observation group (n=36)	Control group (n=24)	t/x^2	*P*
Gestational age (weeks)	30.6±2.2	32.9±2.5	4.25	0.00002
Sex			0.68	0.418
Male (n, %)	19 (52.8%)	13 (54.2%)		
Female (n, %)	17 (47.2%)	11 (45.8%)		
Birth weight (g)	1268.1±196.2	1373.2±136	2.39	0.008
Delivery modes			5.52	0.37
Cesarean section	23 (63.9%)	15 (62.5%)		
Natural labor	13 (36.1%)	9 (37.5%)		
Hb value at birth (g/L)	173.5±21.4	188.9±21.1	4.55	0.0004
Hct value at birth (%)	52.7±5.5	56.4±5.7	3.29	0.005
Stay in hospital (d)	41±16.9	18±7.4	9.95	0.0003
Maternal anemia during pregnancy	26 (72.2%)	5 (20.8%)	14.45	0.0009
Blood collection within 2 weeks after birth (mL/Kg)	24.4±8.6	16.6±7.4	5.57	0.0002

Note: Compared with the control group, significant difference as $P < 0.05$.

(56.4±5.7)%, there was statistical significance between two groups ($P < 0.05$). The time of stay in hospital in observation group was (41±16.9) days, and in control group was (18±7.4) days. The number of pregnant women who maternal anemia during pregnancy in the observation group was 26 (72.2%), and the control group was 5 (20.8%). The blood collection within 2 weeks after birth in observation group was (24.4±8.6) mL/Kg, and in the control group it was (16.6±7.4) mL/Kg. There was statistical significance between the two groups ($P < 0.05$) (**Table 1** and **Figure 1**).

Clinical features of the mothers of the infants

The number of pregnant women who had cesarean section in the observation group was 23 (63.9%) cases, and that in the control group was 15 (62.5%) cases. The number of pregnant women with natural labor in the observation group was 13 (36.1%) cases, and that in the control group was 9 (37.5%), there was no statistical significance between two groups ($P > 0.05$). The rate of premature rupture of membranes in the observation group was 27.8% (10/36), and that in the control group was 16.7% (4/24). The number of pregnant women who had pregnancy-induced hypertension in the observation group was 12 (33.3%), and that in the control group was 7 (29.1%). The number of pregnant women who had gestational diabetes in the observation group was 7 (19.4%), and that in the control group was 4 (16.7%). The two groups were similar in demographics, clinical characteristics of the mothers of the infants, and there was no statistical significance between two groups (**Table 2**).

Clinical complications in infants

The incidence of tracheal intubation, asphyxia, apnea, NRDS, BPD, sepsis and PDA after birth in blood transfusion group was higher than those in non-blood transfusion group ($P < 0.05$). However, there was no significant difference in the incidence of pulmonary hemorrhage, NEC and IVH between the two groups ($P > 0.05$). In the blood transfusion group, 13 cases of NEC occurred after blood transfusion, and 7 cases occurred within 48 hours after blood transfusion (**Table 3**).

Analysis of related risk factors of blood transfusion

Multivariate logistic regression analysis and ROC curve analysis showed that the younger the gestational age (OR=0.385, 95% CI: 0.212~0.705, P=0.002), the lower the birth weight (OR=1.004, 95% CI: 0.967~0.998, P=0.001), the longer the hospitalization time (OR=2.178, 95% CI: 1.172~4.049, P=0.014) and a larger the blood collection within 2 weeks after birth (OR=1.269, 95% CI: 1.084~1.489, P=0.003) would induce a higher blood transfusion rate. Therefore, gestational age, length of hospital stay, birth weight and blood collection

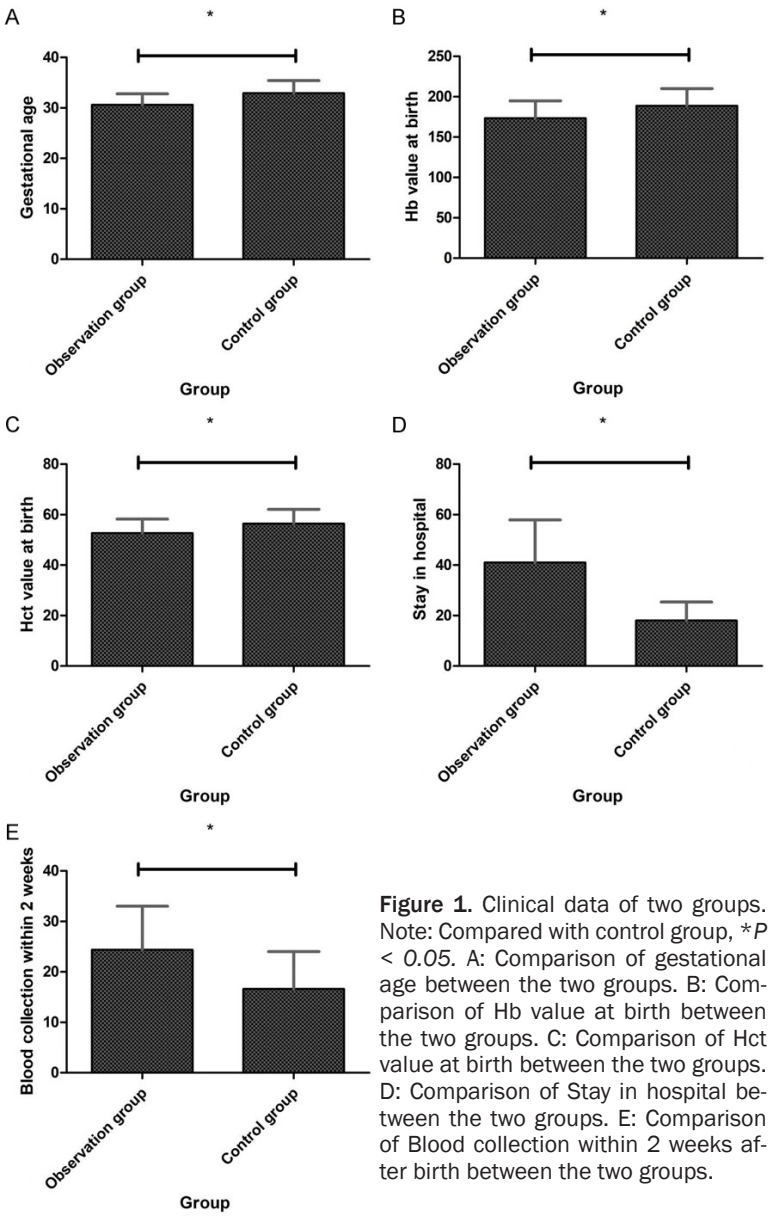

Figure 1. Clinical data of two groups. Note: Compared with control group, *$P < 0.05$. A: Comparison of gestational age between the two groups. B: Comparison of Hb value at birth between the two groups. C: Comparison of Hct value at birth between the two groups. D: Comparison of Stay in hospital between the two groups. E: Comparison of Blood collection within 2 weeks after birth between the two groups.

within 2 weeks after birth were independent predictors of blood transfusion (**Table 4** and **Figure 2**).

Discussion

Anemia of extreme low birth weight and extreme preterm infants is one of the most common complications of many complications in preterm infants. It is affected by many factors, such as physiological factors and pathological factors. Severe anemia can aggravate disease and even endanger life [14]. As shown in our results, maternal anemia during pregnancy, birth weight, gestational age, hemoglobin and hematocrit at birth, blood collection within 2 weeks after birth, length of hospital stay, need for tracheal intubation after birth, neonatal respiratory distress syndrome, apnea, bronchopulmonary dysplasia and patent ductus arteriosus were the risk factor for anemia of extremely low birth weight infants and extreme preterm infants. Multivariate logistic regression analysis and ROC curve analysis showed that blood transfusion in extremely low birth weight infants and extreme preterm infants is associated with increased risk of apnea, neonatal respiratory distress syndrome, bronchopulmonary dysplasia and patent ductus arteriosus.

Currently, the cause and mechanism of hemorrhage anemia in small and low birth weight newborns has not been clarified. The main reasons for anemia are low level of cytopoietin, short life span of red blood cells, gastrointestinal feeding intolerance and other factors [15]. As is consistent with our results, the gestational age and birth weight of the blood transfusion group were less than those of the non-blood transfusion group. A younger gestational age, has greater risk of blood transfusion, especially for premature infants with gestational age < 28 weeks and birth weight < 1000 g.

Our study showed that the incidence rate of tracheal intubation and BPD, ARDS, apnea and asphyxia in the transfusion group is high. This is related to the young gestational age, low birth weight, relatively immature lung development and relatively severe disease in the blood transfusion group. Some studies suggest that the amount of red blood cells needed in transfusion is closely related to the occurrence of BPD. With the increase of red blood cell transfusion volume, the occurrence of BPD increas-

Table 2. Comparison of clinical features of the mothers of the infants between the two groups [n (%)]

	Observation group (n=36)	Control group (n=24)	t/x^2	*P*
Delivery modes			5.52	0.37
Cesarean section	23 (63.9%)	15 (62.5%)		
Natural labor	13 (36.1%)	9 (37.5%)		
Premature rupture of membranes	10 (27.8%)	4 (16.7%)	17.8	0.23
Pregnancy-induced hypertension	12 (33.3%)	7 (29.1%)	6.69	0.15
Gestational diabetes	7 (19.4%)	4 (16.7%)	4.48	0.28

Note: Compared with the control group, significant difference as P < 0.05.

Table 3. Comparison of *clinical complications* of the infants between the two groups [n (%)]

	Observation group (n=36)	Control group (n=24)	t/x^2	*P*
Asphyxia	27 (75%)	6 (25%)	27.52	0.0003
Apnea	22 (61.1%)	5 (20.8%)	19.94	0.010
NRDS	15 (41.7%)	4 (16.7%)	9.38	0.002
Pulmonary hemorrhage	6 (16.7%)	1 (4.2%)	22.8	0.07
BPD	13 (36.1%)	4 (16.7%)	9.69	0.006
NEC	13 (36.1%)	4 (16.7%)	2.48	0.342
PDA	12 (33.3%))	3 (12.5%)	15.23	0.023
IVH	6 (16.7%)	3 (12.5%)	5.58	0.414
Septicemia	11 (30.6%)	5 (20.8%)	7.27	0.007
Tracheal intubation is required	21 (58.3%)	2 (8.3%)	27.77	0.00001

Note: Compared with the control group, significant difference as P < 0.05. NRDS: Neonatal respiratory distress syndrome; BPD: bronchopulmonary dysplasia; NEC: Necrotizing enterocolitis; IVH: Intraventricular hemorrhage; PDA: patent ductus arteriosus.

Table 4. Multivariate logistic analysis of blood transfusion risk

Factors	β	Wald	OR	95% CI	*P*
Gestational age (weeks)	-0.962	9.632	0.385	0.212-0.705	0.002
Birth weight (g)	-0.004	0.857	1.004	0.967-0.998	0.001
Stay in hospital (d)	0.779	6.037	2.178	1.172-4.049	0.014
Blood collection within 2 weeks after birth (mL/Kg)	0.239	8.653	1.269	1.084-1.489	0.003

Note: Significant difference as P < 0.05.

es significantly, which may be due to the oxidative stress reaction caused by the increase of non-transferrin bound iron in stored blood [16, 17].

At present, there are still many controversies about the indications of blood transfusions in premature infants. A blood transfusion study involving 1018 newborns in 11 countries found that only 51% of neonatal intensive care units follow strict blood transfusion indications [18]. The two transfusion strategies are limited transfusion and non-limited transfusion. They are relative concepts, which are still clearly defined in the clinic. Restrictive blood transfusion is relatively conservative and the blood transfusion threshold is relatively high, while the relatively low blood transfusion threshold is called a non-restrictive blood transfusion [19]. In the past, there was a tendency for limited blood transfusion to significantly reduce the amount of neonatal red blood cell transfusion, but some scholars suggest that anemia related complications may increase the risk of blood transfusion. Non limited blood transfusions can reduce the time of mechanical ventilation and nosocomial infection, which is more conducive to the recovery of the disease [20]. Jayanta et al. [21] suggested that restrictive blood transfusions increase the risk of pulmonary hemorrhage, IVH, apnea and bradycardia. However, Wang et al. [22] concluded that restrictive

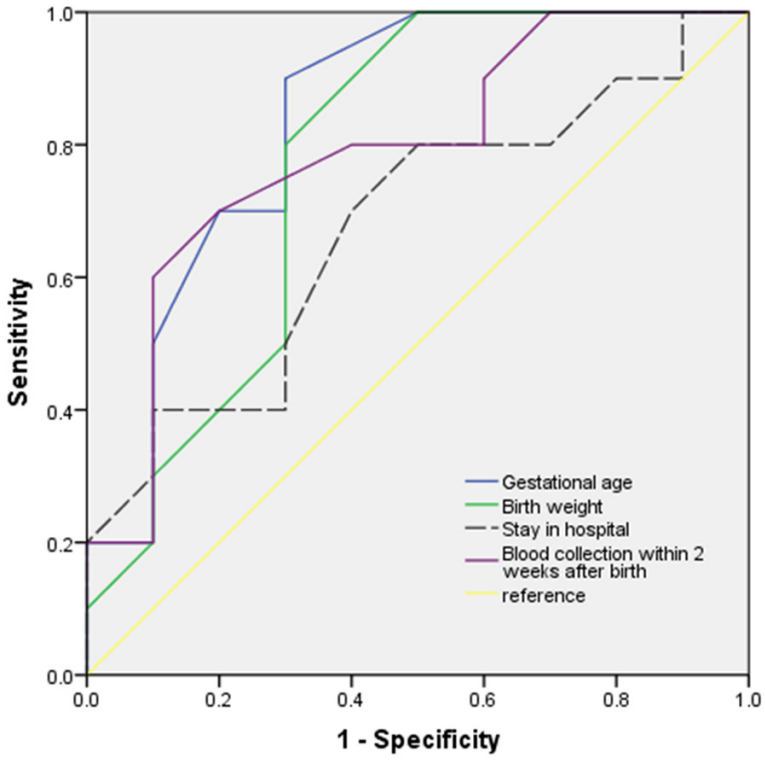

Figure 2. ROC curve of related risk factors of blood transfusion.

blood transfusions do not increase death, pulmonary hemorrhage, IVH, apnea and BPD. The risk of non-restrictive blood transfusion does not bring significant benefits to children.

In conclusion, the transfusion indications of extremely low birth weight infants and extreme preterm infants are affected by many factors, among which gestational age, length of hospital stay, blood collection within 2 weeks after birth and birth weight are independent predictors of transfusion. Blood transfusion in extremely low birth weight infants and extreme preterm infants is associated with increased risk of apnea, neonatal respiratory distress syndrome, bronchopulmonary dysplasia and patent ductus arteriosus. Furthermore, our study is a retrospective study with a small sample size. Prospective and multicenter studies are still needed to evaluate the advantages and disadvantages of blood transfusions.

Disclosure of conflict of interest

None.

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References

[1] Howarth C, Banerjee J and Aladangady N. Red blood cell transfusion in preterm infants: current evidence and controversies. Neonatology 2018; 114: 7-16.

[2] Goldstein GP, Rao A, Ling AY, Ding VY, Chang IJ and Chock VY. Influence of enteral feeding and anemia on tissue oxygen extraction after red blood cell transfusion in preterm infants. Transfusion 2020; 60: 466-472.

[3] Whitehead HV, Vesoulis ZA, Maheshwari A, Rao R and Mathur AM. Anemia of prematurity and cerebral near-infrared spectroscopy: should transfusion thresholds in preterm infants be revised? J Perinatol 2018; 38: 1022-1029.

[4] Ozdemir H, Akman I, Demirel U, Coşkun S, Bilgen H and Ozek E. Iron deficiency anemia in late-preterm infants. Turk J Pediatr 2013; 55: 500-5.

[5] Keir AK, Yang J, Harrison A, Pelausa E and Shah PS; Canadian Neonatal Network. Temporal changes in blood product usage in preterm neonates born at less than 30 weeks' gestation in Canada. Transfusion 2015; 55: 1340-6.

[6] Duan J, Kong X, Li Q, Hua S, Zhang S, Zhang X and Feng Z. Association between anemia and bronchopulmonary dysplasia in preterm infants. Sci Rep 2016; 6: 22717.

[7] Yeo KT, Kong JY, Sasi A, Tan K, Lai NM and Schindler T. Stopping enteral feeds for prevention of transfusion-associated necrotising enterocolitis in preterm infants. Cochrane Database Syst Rev 2019; 2019: CD012888.

[8] Hasanbegovic E, Cengic N, Hasanbegovic S, Heljic J, Lutolli I and Begic E. Evaluation and treatment of anemia in premature infants. Med Arch 2016; 70: 408-412.

[9] Elguazzar S, Alaoui AM and Izgua AT. Evaluation of the practice of transfusion in the anemia in preterm infants. Rev Med Brux 2013; 34: 4-11.

[10] Jain D, D'Ugard C, Bancalari E and Claure N. Cerebral oxygenation in preterm infants receiv-

ing transfusion. Pediatr Res 2019; 85: 786-789.
[11] Whyte R and Kirpalani H. Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. Cochrane Database Syst Rev 2011; 15: CD000512.
[12] von Lindern JS and Lopriore E. Management and prevention of neonatal anemia: current evidence and guidelines. Expert Rev Hematol 2014; 7: 195-202.
[13] Levine E, Beroul N, Cortey A, Damais Cepitelli A, Gouezec H, Pujol S, Wibaut B and Marti B. Blood transfusion in neonatology: study of practical aspects in 2016 in France, excluding acute bleeding or surgical care. Transfus Clin Biol 2018; 25: 249-256.
[14] Stripeli F, Kapetanakis J, Gourgiotis D, Drakatos A, Tsolia M and Kossiva L. Post-transfusion changes in serum hepcidin and iron parameters in preterm infants. Pediatr Int 2018; 60: 148-152.
[15] Moreno-Fernandez J, Ochoa JJ, Latunde-Dada GO and Diaz-Castro J. Iron deficiency and iron homeostasis in low birth weight preterm infants: a systematic review. Nutrients 2019; 11: 44-53.
[16] Zhang Z, Huang X and Lu H. Association between red blood cell transfusion and bronchopulmonary dysplasia in preterm infants. Sci Rep 2014; 4: 4340.
[17] Gao S, Xiao T, Ju R, Ma R, Zhang X and Dong W. The application value of lung ultrasound findings in preterm infants with bronchopulmonary dysplasia. Transl Pediatr 2020; 9: 93-100.
[18] Guillén U, Cummings JJ, Bell EF, Hosono S, Frantz AR, Maier RF, Whyte RK, Boyle E, Vento M, Widness JA and Kirpalani H. International survey of transfusion practices for extremely premature infants. Semin Perinatol 2012; 36: 244-7.
[19] Friedman N, Yochpaz S, Zirkin S, Herzlich J and Marom R. Iron homeostasis after blood transfusion in stable preterm infants - an observational study. J Perinat Med 2016; 44: 919-923.
[20] Balasubramanian H, Malpani P, Sindhur M, Kabra NS, Ahmed J and Srinivasan L. Effect of umbilical cord blood sampling versus admission blood sampling on requirement of blood transfusion in extremely preterm infants: a randomized controlled trial. J Pediatr 2019; 211: 39-45, e2.
[21] Banerjee J, Leung TS and Aladangady N. Effect of blood transfusion on intestinal blood flow and oxygenation in extremely preterm infants during first week of life. Transfusion 2016; 56: 808-15.
[22] Wang YC, Chan OW, Chiang MC, Yang PH, Chu SM, Hsu JF, Fu RH and Lien R. Red blood cell transfusion and clinical outcomes in extremely low birth weight preterm infants. Pediatr Neonatol 2017; 58: 216-222.