The Efficacy of Erythrocyte Transfusion in Very Low Birth Weight Infants with Premature Anemia

Prematüre Anemisi Olan Çok Düşük Doğum Ağırlıklı Bebeklere Eritrosit Transfüzyonunun Etkisi

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ABSTRACT

Objective: This study aimed to determine the clinical efficacy of erythrocyte transfusion (ET) in premature infants.

Material and Methods: Very low birth weight (VLBW) infants with gestational age (GA) < 32 weeks and/or birth weight (BW) <1500 g and hospitalized in neonatal intensive care unit (NICU) between 2012-2018 were retrospectively evaluated. ET was performed according to Ohls 2007 and Turkish Neonatalogy Society Blood Products Transfusion Guidelines.

Results: 72 infants included in this study. Mean BW was 1325 g (680-2290 g), GA was 30 weeks (25-32), median postnatal age was 36.7±26.9 days (8-129), number of ET during hospitalization was 2±1.2 (1-6). There were no significant changes in mean heart rates (p=0.183) and median respiratory rates before and after ET (p=0.123). Weight gain (16 g/day-11 g/day) was statistically similar before and after ET (p=0.861). A significant decrease in apnea, non-invasive ventilation (NIV) and caffeine therapy requirements after ET was determined (p<0.001, p=0.016 and p=0.016). Serum lactate (2.9-1.5) levels were decreased by ET (p=0.017).

Conclusion: Premature infants should closely follow-up for anemia and related symptoms during NICU stay. ET may help to decrease frequency of apnea of prematurity, requirements of caffeine therapy and NIV. ET improves tissue oxygenation in VLBW infants with anemia. Decision of ET should be made according to severity of symptoms, and should be performed according to international, national or local transfusion guidelines.

Key Words: Anemia, Erythrocyte transfusion, Premature

ÖZ

Amaç: Bu çalışmada prematüre bebeklerde eritrosit transfüzyonunun (ET) klinik etkisinin araştırılması amaçlandı.

Gereç ve Yöntemler: 2012-2018 yılları arasında yenidoğan yoğun bakım ünitesinde (YYBÜ) takip edilen ve gestasyonel haftası (GH)< 32 hafta ve/veya doğum ağırlığı (DA) < 1500 g olan çok düşük doğum ağırlıklı (ÇDDA) bebekler retrospektif olarak değerlendirildi. ET, Ohls 2007 ve Türk Neonatoloji Derneği Kan Ürünleri Transfüzyon Rehberi'ne göre yapıldı.

Bulgular: 72 hasta çalışmaya dahil edildi. Ortalama DA 1325 g (680-2290 g), GH 30 hafta (25-32), ortanca postnatal yaş 36.7±26.9 gün (8-129), hastanede yatış sırasındaki ET sayısı 2±1.2 (1-6)'dı. ET öncesi ve sonrası ortalama kalp hızlarında (p=0.183) ve medyan solunum hızlarında (p=0.123) anlamlı bir değişiklik yoktu. Kilo alımı (16 g/gün-11 g/gün), ET'den önce ve sonra istatistiksel olarak benzerdi (p=0.861). ET sonrası apne, non-invaziv ventilasyon (NIV) ve kafein tedavisi gereksinimlerinde anlamlı azalma saptandı (p<0.001, p=0.016 ve p=0.016). Serum laktat (2.9-1.5) seviyeleri ET ile azaldı (p=0.017).

Sonuç: Prematüre bebekler, YYBÜ'de kaldıkları süre boyunca anemi ve ilgili semptomlar açısından yakın takip edilmelidir. ET prematüre apne sıklığını, kafein tedavisi ve NIV gereksinimlerini azaltmaya yardımcı olabilir. ET anemili ÇDDA

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bebeklerde doku oksijenasyonunu düzeltir. ET kararı semptomların şiddetine göre verilmeli ve uluslararası, ulusal veya yerel transfüzyon rehberlerine göre yapılmalıdır.

Anahtar Sözcükler: Anemi, Eritrosit Transfüzyonu, Prematüre

INTRODUCTION

Increased tissue oxygenation following onset of postnatal breathing causes closure of ductus arteriosus, suppression of erythropoietin (EPO) production and reduction of erythropoiesis (1-3). In premature infants, anemia develops earlier than term babies and causes more clinical symptoms. Blood loss due to phlebotomy, low erythrocyte life expectancy and decreased iron contribute to the development of anemia in premature infants. Volume of blood for laboratory analysis increases according to severity of infant's disease and low gestational age (4-7).

Approximately, 50-95% of low birth weight (<1500 g) and 95% of extremely low birth weight (<1000 g) infants receive erythrocyte transfusion (ET) at least once during their stay in neonatal intensive care unit (NICU) after birth (8,9). ET administered to 90% of extremely low birth weight and 58% of premature infants with gestational age <32 weeks (10-13). Tranfusion increases amount of circulating hemoglobin, improves tissue oxygenation, maintains same oxygen level by decreasing cardiac output (10, 14). It is also associated with increased morbidity and mortality in infants with bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and intraventricular hemorrhage (IVH) (15-18).

In this study, evaluating benefits of ET on clinical findings and it's relation to BPD, ROP, NEC and IVH in very low birth weight (VLBW) infants with gestational age (GA) equal or below 32 weeks and/or birth weight (BW) equal or below 1500 g were aimed. Improvement of symptoms secondary to anemia particularly heart rate (HR), apnea, respiratory rate (RR) and daily weight gain were analysed before and after ET. Indications of ET and factors affecting number of transfusion were also reviewed.

MATERIALS and METHODS

All of VLBW infants with GA ≤32 weeks and/or BW ≤1500 g and hospitalized in our unit between 2012-2018 were retrospectively evaluated (Health Sciences University, Ankara Children's Hematology Oncology Research Hospital). As there is no maternity unit in our hospital, all of patients were transported from other NICUs. Congenital anomalies (esophageal atresia 11, hydrocephalus 4, sacrococcygeal teratoma 2, anal atresia 8, gastroschisis 3, gonadal dysgenesis 4), congenital genetic (trisomy 21 5, trisomy 18 2, Pierre robin syndrome 2, trisomy 13 1, arthrogryposis multiplex congenita 2, Smith-lemli-opitz syndrome 1), cardiac (congenital aortic stenosis 1, atrioventricular malformation 1, tetralogy of fallot 2) and metabolic disease (congenital lactic acidosis 2) were excluded. Infant's BW, GA, Apgar score, SNAP-PE II score, postnatal age, umbilical vein catheterization (UVK), number of ET, indication for ET, length of hospitalization, requirement of respiratory support [invasive mechanical ventilation, non-invasive ventilation (NIV)], RDS, ROP, BPD, NEC, patent ductus arteriozus (PDA), IVH, sepsis, problems encountered during transfusion, mother's concomitant disease and hemoglobin (Hb) level were recorded. Infant's concurrent body weight, apnea, caffeine therapy, arterial blood gases, Hb - hematocrit (htc) levels, HR and RR before and after ET during 72 hours were determined.

Indications for ET classified as low Hb level (only anemia), recurrent apnea of prematurity, continuous tachycardia, low oxygen saturation, respiratory failure and suspected sepsis. An apneic episode was defined as a pause in breathing for more than 20 seconds. Severe apnea episodes required bag-mask ventilation, placement on continuous positive airway pressure, or reintubation during management of the episode (19). Tachycardia was defined as HR> 180 beat/minute at least 24 hours. Low oxygen saturation was defined as the infant's increasing oxygen requirement or oxygen saturation lower than target (<88%). Respiratory failure was defined as infant's pressure requirement to maintain target saturations. If infant was hypotonic, hypoactive and had low tissue perfusion at any time, we suspected sepsis. Than, blood culture, hemogram, peripheral smear, acute phase reactants were analysed and empirical antibiotics were administered. Diagnosis of NEC was based on systemic, laboratory and radiographic findings. It's severity was assessed by modified Bell's staging (20). Diagnosis of IVH was made by ultrasound and graded according to Papile's classification (21). ROP screening was performed by ophthalmologist and classified according to International Classification of Retinopathy of Prematurity (22). Diagnostic criteria of BPD were based on those described in National Institutes of Health Workshop (23). Diagnosis of PDA was made by echocardiography within first 24-72 hours with presence of significant PDA (left atrium / aortic root ≥ 1.5 and/or ductus diameter ≥ 1.5 mm) and presence of clinical findings (24). Ibuprofen and/or paracetamol were applied for PDA closure.

Erythrocyte transfusion was performed according to Ohls 2007 and Turkish Neonatalogy Society Blood Products Transfusion Guidelines (25,26). Transfusion decision was made by attending neonatologist according to infant's postnatal age, clinical findings and htc level. All infants were provided daily energy intake higher than 100 kcal/kg and at least 70% by enteral nutrition. ABO and Rh appropriate, leukocyte reduced and irradiated erythrocyte suspension was administered at a dose of 15-20 cc/kg in between 2-4 hours. Patients were divided into single or multiple transfused groups, to determine factors effecting number of ET. The patients transfused only once were defined as group 1, and multiple transfused patients were defined as group 2.

The study was approved by the Clinical Research Ethics Committee of Ankara Pediatrics Hematology Oncology Training and Research Hospital (2019-016/18.02.2019).

Statistical Analysis

Statistical analysis was performed by SPSS (Statistical Package for the Social Sciences) computer pocket program (21.0). Distribution of the numerical variables was investigated with Levene and Kolmogorov-Smirnov tests. Descriptive statistics were shown as mean ± standard deviation or median (minimum-maximum) for continuous numerical variables, as number of cases and % for categorical variables. If parametrical test statistic assumptions were not provided between groups, significance of the difference for continuous numerical variables was examined by Kruskal Wallis test. Spearman's sequence numbers were investigated by correlation test, whether there was a statistically significant correlation between continuous numerical variables. Categorical variables were analysed by means of Exact Test of probability with Chi-Square or Fisher's Continuity Correction.

Significance of change in Hb and hct levels after transfusion was evaluated by dependent t-test. Improvement in apnea, decrease in requirements of NIV and caffeine therapy after transfusion were investigated by McNemar test. A statistically significant change in mean HR and RR, between periods of 72 hours before and after ET, was evaluated by Variance Analysis in Repetitive Measurements using Wilks' Lambda test. Data were analysed by IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA). Results for $p<0.050$ were considered statistically significant.

RESULTS

During study period, there were 135 VLBW infants. Twelve infants died within 21 days of age (sepsis 3, NEC 3, respiratory failure 4, IVH 1 and renal failure 1). Infants with congenital anomalies and inborn error of metabolism were excluded, 72 infants were included in the study. Among them, 33.6% was female and 66.4% was male. Ratio of patients born by spontaneous vaginal delivery was 18.1%. Ratios of mothers with single and multiple pregnancies were 69.4%, 30.6% respectively. Mean BW was 1325 g (680-2290 g), GA was 30 weeks (25-32), median postnatal age was 36.7±26.9 days (8-129), number of ET during hospitalization was 2±1.2 (1-6). Antenatal steroid therapy had not been administered to 79.2% of mothers, besides 1 and 2 doses had been administered to 12.5% and 8.3% of mothers respectively. There was no statistically difference between number of ET and mother's gestational diabetes mellitus, preeclampsia, cervical insufficiency, thyroid disease, anemia, oligohydroamnios, urinary tract infection, premature rupture of membranes, placental detachment and in-vitro fertilization pregnancy ($p> 0.050$), except hypertension during pregnancy ($p=0.026$), (Table I).

Results of laboratory analysis (Hb, htc, lactate, HCO_3), weight changes, apnea of prematurity, HR and RR were examined before and after ET. There was statistically significant increase in hemoglobin (8.47±1.31/12.22±2.17) and hematocrit levels (25.09±3.85/35.99±6.78) after ET ($p<0.001$, $p<0.001$). Weight gain (16 g/day - 11 g/day) was statistically similar before and after ET ($p=0.861$). There was statistically significant decrease in lactate (2.9-1.5) and statistically significant increase in HCO_3 levels (20.2-22.3) after ET ($p=0.041$, $p=0.017$). There was statistically significant decrease in apnea, NIV and caffeine therapy requirements after ET ($p<0.001$, $p=0.016$ and $p=0.016$) (Table II).

Patient's mean HR and RR were recorded during 0-72 hours before and after ET. There was no significant changes in mean HRs ($p = 0.183$) and median RRs before and after ET ($p=0.123$) (Table III).

Table I: The relation between the maternal characteristics and the number of transfusions.

Maternal characteristics	Absent		Present		p‡
	n	Number of ET* Mean±SD†	n	Number of ET* Mean±SD†	
Gestational diabetes mellitus	69	2.1±2	3	2±0	0.466
Hypertension	63	1.9±2	9	218±1.39	0.026
Preeclampsia	65	2.1±2.1	7	2±0.8	0.448
Cervical insufficiency	70	2.1±2	2	1.5±0.7	0.704
PROM§	61	2.2±2.1	11	1.5±0.5	0.188
Thyroid disease	67	2±1.9	5	2.8±1.8	0.297
History of maternal anemia	70	2.1±2	2	2.5±0.7	0.268
Oligohydramnios	69	2.1±2	3	1.7±1.2	0.689
Urinary infection	67	2.1±2	5	1.6±0.9	0.561
Plasental abruption	70	2.1±2	2	2±0	0.570
Invitro fertilization	65	2.1±2	7	2.1±1.3	0.559

***ET:** Erythrocyte transfusion, †**SD:** Standard deviation, ‡Spearman's rank-order correlation test, §**PROM:** Premature rupture of membrans.*

Table II: The clinical and laboratory findings of the patients before and after erythrocyte transfusion.

Finding	Before transfusion	After transfusion	Difference	p
Hemoglobin	8.47±1.31	12.22±2.17	3.75±1.93	<0.001*
Hematocrit	25.09±3.85	35.99±6.78	10.9±6.35	<0.001
Weight gain	16 (-75 – 80)	11 (-90–130)	0 (-110 – 200)	0.861*
Lactate	2.9 (1.0-5.6)	1.5 (0.7-7.3)	-0.85 (-4.9 – 2)	0.041*
HCO_3	20.2 (14.8-26.1)	22.3 (15.8-25.2)	1 (-0.9 – 6.4)	0.017*
Apnea of prematurity	12 (17.1)‡	1 (1.4)‡	11 (15.7)‡	<0.001†
NIV§	9 (12.7)‡	2 (2.8)‡	7 (9.9)‡	0.016†
Caffeine therapy	23 (32.4)‡	16 (22.5)‡	7 (9.9)‡	0.016†

Wilcoxon Signed test, †McNemar test, ‡: (%), §NIV:** Non-invasive ventilation*

Table III: The heart and respiratory rates before and after erythrocyte transfusion.

Time	Heart rate	p	Respiratory rate	p
Before transfusion		0.183†		0.123‡
48-72. hours	144±10.6		41 (40-57)	
24-48. hours	147.2±11.2		45 (40-59)	
0-24. hours	148.8±13		47 (40-64)	
After transfusion				
0-24. hours	147.7±11.4		46 (40-70)	
24-48. hours	145.3±11.2		44 (40-72)	
48-72. hours	141.6±10.6		43 (40-72)	

†Mean±standard deviation, ‡Median (minimum-maximum), †Variance Analysis, Wilks's Lambda test, ‡Friedman test

Table IV: The relation between patient's clinical characteristics and number of erythrocyte transfusion.

Clinical characteristics	Correlation Coefficient	p*
Birth weight	-0.401	<0.001
Gestational age	-0.368	<0.001
Apgar score at 1st minute	-0.428	<0.001
Apgar score at 5th minute	-0.328	0.011
Duration of hospitalization	0.568	<0.001
Bronchopulmonary dysplasia	0.336	0.004
Necrotizing enterocolitis stage 2-3	0.273	0.020
Intra-ventricular hemorrhage grade 2-4	0.032	0.789
Retinopathy of prematurity stage 2-5	0.255	0.031
SNAP-PE II score	0.222	0.063
Additional oxygen duration	0.380	<0.001
Respiratory support	0.369	0.032
Hemoglobin at birth	-0.123	0.390
Hematocrit at birth	-0125	0.383

**Spearman's sequence numberscorrelation test*

Most common cause of ET was only anemia without accompanying symptoms (45.8%). These patient's Hb and/or htc levels were below limits suggested by Ohls 2007 and Turkish Neonatalogy Society Blood Products Transfusion Guidelines. Other indications for ET were recurrent apnea of prematurity (16.7%), suspected sepsis (16.7), low oxygen saturation (13.9%), continuous tachycardia (4.2%) and respiratory failure (2.8%), respectively. Mean duration of respiratory support after ET was 6 days (1-40 days). Decrease of BW, GA, and Apgar scores increased number of ET significantly (p <0.050). Besides, number of ET was significantly increased by advanced stages of BPD, NEC and ROP, prolonged hospital stay, oxygen and mechanical ventilation (MV) supports (p <0.050). However, there was no significant correlation between Hb and htc levels at birth, SNAP-PE II score, IVH degree and number of ET (p <0.050) (Table IV).

Table V: The number of erythrocyte transfusion and patient's clinical features.

Clinical feature	n	Absent Mean±SD*	n	Present Mean±SD*	p†
Apnea of prematurity	36	1.5±0.6	36	2.7±2.6	<0.001
Bronchopulmonary dysplasia	59	1.7±0.9	13	3.6±3.9	0.007
Necrotizing enterocolitis 2-3	48	1.7±0.8	24	2.8±3.1	0.031
Intra-ventricular hemorrhage 2-4	57	2.1±2.1	15	1.9±1.1	0.817
Retinopathy of prematurity 2-5	62	1.7±0.8	10	4.2±4.5	0.032
Suspected sepsis	18	1.3±0.6	54	2.3±2.2	0.004
Patent ductus arteriosus	37	1.5±0.8	35	2.6±2.6	0.003
Umbilical vein catheter	40	1.6±0.8	32	2.7±2.7	0.003

***n:** Number of patient, ***SD:** Standard deviation, †Mann Whitney U test*

There was no significant association between number of ET and sex, delivery route, single/multiple pregnancy (p> 0.050). Number of ET and nutritional content (breast milk and fortification, formula or mixed feeding) was also not related (p>0.050, Kruskal Wallis test). The presence of apnea, BPD, NEC, ROP, suspected sepsis, PDA and UVK was significantly increased with number of ET (p<0.050). There was no significant difference between number of ET and spontaneous or drug induced closure of ductus arteriosus (Table V).

Although incidence of BPD, NEC, IVH and ROP was higher in multiple transfused infants; relation was statistically insignificant between the groups (p> 0.050) (Table VI).

Table VI: The relation between significant prematurity related disorders and the number of erythrocyte transfusion.

Disease	Single transfusion (n=31)	Multiple transfusion (n=41)	P
Bronchopulmonary dysplasia,*	2 (6.5)	11 (26.8)	0.055†
Necrotising enterocolitis 2-3,*	8 (25.8)	16 (39)	0.355†
Intra-ventricular hemorrhage 2-4,*	6 (19.4)	9 (22)	>0.999†
Retinopathy of prematurity 2-5,*	3 (9.7)	7 (17.1)	0.499‡

***:** *n(%), †Chi-square Exact test of Probability, ‡Fisher's Continuity Correction*

DISCUSSION

Premature infants born ≤32 weeks or birth weight ≤1500 g and administered erythrocyte transfusion with diagnosis of premature anemia during hospital stay in our neonatal intensive care unit were analysed to determine clinical efficacy of ET transfusion. Frequency of apnea of prematurity, requirements of caffeine therapy and respiratory support were decreased following ET. Besides, serum lactate levels were decreased and HCO_3 levels were increased after ET. Heart and respiratory rates during 72 hours before and after ET were not changed. Although, optimal nutritional support was provided, weight gain of infants were not different before and after transfusion. There were more infants with advanced stages of NEC, BPD, IVH and ROP in multiple transfusion group, but this was statistically insignificant.

Physiologic anemia develops much earlier in premature infants due to physiological and iatrogenic factors. Erythropoietin (EPO) levels in premature infants are low and their responses to EPO are insufficient. Besides, short life of erythrocytes, rapid growth of infant, frequent blood sampling, accompanying diseases such as sepsis and malnutrition are factors that increase the risk of premature anemia (1,5,27). HbF level is high and 2.3 diphosphoglycerate level is low in premature infants. As HbF has a high affinity to oxygen, tissue hypoxia can be more pronounced. For all these reasons, most of premature infants have been were transfused before 3 months of old (28). We thought that VLBW infants should be monitored in the NICU. It is important to reduce the number of phlebotomies, because the most common cause of ET in VLBW infants is frequent blood samplings. Blood sampling should be collected in microcollection tube, blood gas analysis in capillary tube.

Anemia of prematurity can cause tachycardia, inadequate weight gain, increase oxygen need and apnea or bradycardia (13,27,29). n premature infants, anemia becomes symptomatic when imbalance develops between it's distribution and consumption. For that reason, symptoms appear at different Hb levels in each premature infant (30). Higher Hb values may be required in infants with cardio-pulmonary or severe diseases. Kasat et al. (31) noticed that tachycardia was the most sensitive predictor of anemia and ET improved apnea, bradycardia, desaturation, tachycardia and oxygen requirements. In this study, indication for ET was only anemia, determined by routine blood sampling for 45.8% of the patients. Other causes of transfusion were apnea of prematurity (16.7%), suspected sepsis (16.7%), low oxygen saturation (13.9%), tachycardia (4.2%) and respiratory failure (2.8%). Priya also reported that the most common indication of ET was anemia (32). Although maternal factors were not found to be effective on ET in Priya's study, maternal hypertension was found to be effective on ET in our study.

Lowest hemoglobin value in which tissue oxygenation can normally be maintained is defined as critical or threshold of hemoglobin value. Transfusion decision is frequently made according to this value and accompanying clinical findings. Therefore, lower limits of Hb for transfusion should be individualized according to the patient's symptoms, requirements of respiratory and circulatory support. Since there is no clear marker of tissue oxygenation, it is important to know clinical symptoms (3,33). Premature infants should be closely monitored for symptoms related to anemia. ET should be performed in case of clinical necessity and in accordance with transfusion guidelines. Due to increased lactate level and reduction of lactate following ET in infants with premature anemia; we proposed that lactate is a good marker for tissue perfusion in infants with premature anemia.

We determined that ET decreased frequency of apnea of prematurity, NIV and caffeine requirements in VLBW infants. This might be explained by improved tissue oxygenation in central nervous system. There are studies with and without improvement of apnea of prematurity by ET (6,14). We found that HR and RR were not different throughout 72 hours before and after ET. Although nutritional support was adequate, there was no difference in weight gain of VLBW infants followed by ET. There were conflicting results related to weight gain following ET in premature infants. Studies reported both increment and no increment in weight gain following ET (34,35). Nelle et al. (35) described a significant HR drop (from 161 to 149 beats per min) in 33 premature infants followed by ET. Lachance et al. (36) also reported HR drop (from 155±10 to 146±7 beats per min) in 12 premature infants after ET. Similar to our results, Dani et al. (37) (n=14) and Alkalay et al. (38) (n=32) found no difference in HR of premature infants followed by ET. We proposed ET should be individualised and considered according to severity of clinical symptoms in VLBW infants with premature anemia.

Erythrocyte transfusion increases amount of circulating Hb, improves tissue oxygenation, decreases cardiac output, improves blood pressure of infants on MV and improves oxygenation (2,14,30). Studies stated the less BW and GA, the higher need of ET (28). We showed as BW, GA and Apgar scores were decreased, number of ET was increased. We found a positive correlation between ET number and length of hospitalization, supplemental oxygen and respiratory support. Mimica identified increased number of ET with duration of MV (39). Santos determined an association between in number of ET and SNAP-PE II score, moderate-severe IVH, NEC and BPD (40). We determined that apnea, BPD, NEC, ROP, suspected sepsis, PDA and UVC increased number of ET. We thought that increased hospital stay might be related to severity of infant's diseases, lower BW, increased blood sampling and energy requirement due to rapid growth. Both degree of prematurity and iatrogenic causes might be more evident in extreme premature infants. It should be emphasized that unnecessary blood sampling should be avoided.

Besides benefits, there are risks and concerns that erythrocyte transfusion causing development of BPD, ROP, NEC, IVH in premature infants with high morbidity and mortality (2,11,12). The risk-benefit profile for red cell transfusions to treat anaemia is uncertain. It has been suggested that there is frequent iron overload with ET, increasing oxidative stress, developing free radicals and damaging premature lung, intestine and retina (16,28). On the other hand, ET and BPD, ROP, NEC were reported to be irrelevant (6). In some studies, infant's ROP and cranial USG findings in the liberal and restricted groups had not been different (41). Similarly, we found that BPD, NEC, IVH and ROP were not different in the single and multiple ET groups. The implementation of neonatal blood transfusion guidelines should reduce number of transfusion in VLBW infants.

CONCLUSION

Premature infants should closely follow-up for anemia and related symptoms during hospital stay. Erythrocyte transfusion may help decrease frequency apnea of prematurity, requirements of caffeine therapy and respiratory support. ET improve tissue oxygenation in VLBW infants with anemia. However, we found that ET has no effect on weight gain, HR and RR. Infant's disease severity, GA and BW should increase number of ET. Nevertheless BPD, NEC, IVH and ROP were not related to ET. As the potential risks, decision of ET should be individualised. Infant's clinical findings, diseases, treatments, oxygen/pressure support, Hb and/or htc levels, BW, GA and postnatal age should be carefully considered. Decision of ET should be made according to severity of symptoms, and should be performed according to international, national or local transfusion guidelines.

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