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Transfusion support in preterm neonates <1500 g and/or <32 weeks in a tertiary care center: A descriptive study

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Abstract:

BACKGROUND: Lack of recent studies focusing on indications, pattern, and benefits of transfusions in low birth weight (B.Wt) and low gestational age (GA) preterm neonates prompted us to undertake this study.

AIM: To estimate the transfusion requirements and outcomes in preterm neonates <1500 g and/or <32 weeks.

SETTINGS AND DESIGN: This is a cross-sectional study conducted over a period of 2 years in a tertiary care center.

MATERIALS AND METHODS: This study was conducted with 101 preterm neonates <1500 g and/or <32 weeks who received blood transfusions in the Neonatal Intensive Care Unit. Restrictive pattern of transfusion was followed. Demographic details and antenatal, neonatal, laboratory, and transfusion parameters were collected.

STATISTICAL ANALYSIS USED: Statistical analyses were performed using SPSS 16.

RESULTS: The study participants received 311 transfusions. Transfusion requirements decreased with increasing GA and B.Wt. Majority of blood transfusions occurred during the first 2 weeks of life. Packed red blood cells (PRBCs) were the most frequent blood components transfused. Ninety-six percent of the study population had an uneventful transfusion. Mean hemoglobin improvement after PRBC transfusions was 2.3 ± 2.1 g/dl. Improvement in apnea occurred in 76% PRBC transfusions. Infants with sepsis, patent ductus arteriosus, bronchopulmonary dysplasia, disseminated intravascular coagulation, and dyselectrolytemia received more number of transfusions.

CONCLUSION: This study would serve as an audit for neonatal blood transfusion therapy. Close adherence to neonatal transfusion policy and restrictive transfusion guidelines helps reduce inappropriate use of blood products and adverse transfusion reactions.

Keywords:

Blood component, preterm neonates, restrictive, transfusion

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Introduction

India ranks first with 23.6% of preterm births in the world.[1] Preterm neonates are the most heavily transfused group of patients and about 85% of extremely low birth weight (ELBW) newborns receive transfusion by the end of their hospital stay.[2,3] The reasons for increased transfusion in preterm neonates are immature hematopoiesis, poor compensatory hematological mechanisms, blood losses from frequent laboratory testing, sepsis, necrotizing enterocolitis (NEC), bleeding, and consumptive coagulopathy.[4]

Lack of studies in our country focusing on transfusion needs, patterns, indications,

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and short-term outcomes in preterm neonates <1500 g and/or <32 weeks prompted the need for this study.

Materials and Methods

This cross-sectional study was conducted from 2014 to 2016 after obtaining approval from the Institutional Ethics Committee. Preterm neonates <1500 g and/or <32 weeks receiving transfusion support in the Neonatal Intensive Care Unit (NICU) were included in the study as these infants have the greatest need for transfusion and also require multiple transfusions.[4-6] Preterm infants who got discharged against medical advice during the study period were excluded from the study. Data were collected from case sheets, blood bank records, and hospital information systems.

The study population (n = 101) was divided into five groups based on the definitions for gestational age (GA) and birth weight (B.Wt)[7] [Figure 1]. Infants belonging to GA ≥32 weeks and B.Wt <1000 g and meeting the inclusion criteria were not admitted during the study period (n = 0). Infants belonging to GA <28 weeks, B. Wt ≥1500 g and to GA 28–32 weeks, B. Wt ≥1500 g were included in Groups 2 and 3, respectively.

Antenatal parameters such as obstetric and medical complications, multiple/singleton gestation, antenatal steroid administration, and intrapartum parameters such as time of cord clamping and mode of delivery were collected. Neonatal data such as GA, B.Wt, APGAR score, diagnosis, indication for transfusion, day of life of transfusion, comorbid illness such as bronchopulmonary dysplasia (BPD), NEC, retinopathy of prematurity (ROP), sepsis, metabolic disturbances, and patent ductus arteriosus (PDA) were noted. Transfusion details such as transfusion outcome and time and volume of transfusion were recorded.

Hematocrit, platelet count, prothrombin time (PT), international normalized ratio (INR), and fibrinogen were noted before and 24 h after transfusion. B.Wt at discharge, changes in apneic episodes, length of hospital stay, and discharge status were also noted. Type and time of blood component issued, transfusion reaction, results of direct and indirect Coomb's test, immunohematological discrepancies, and red cell antibody screening were noted.

Decision to transfuse blood component was at the discretion of an attending physician. Packed red blood cells (PRBCs) <5 days old were issued to NICU infants. Aliquots from a parent blood bag were not reserved for a single infant. ABO and Rh blood components identical to neonate's blood group were issued based on request. Only in case of serological discrepancies with baby blood samples, mother's serum was used for cross-match. All PRBC and platelet units were irradiated with 25 Gy gamma irradiation just before issue.

Blood components were transfused within 30 min of release from blood bank. Babies were kept nil per oral 4 h before and after transfusion. PRBCs were transfused at the rate of 4–20 ml/kg over 4 h; platelets and fresh frozen plasma (FFP) were transfused at the rate of 10–15 ml/kg over 30 min. During transfusion, preterm infants were monitored for signs of transfusion reaction. Restrictive pattern of transfusion protocol adapted

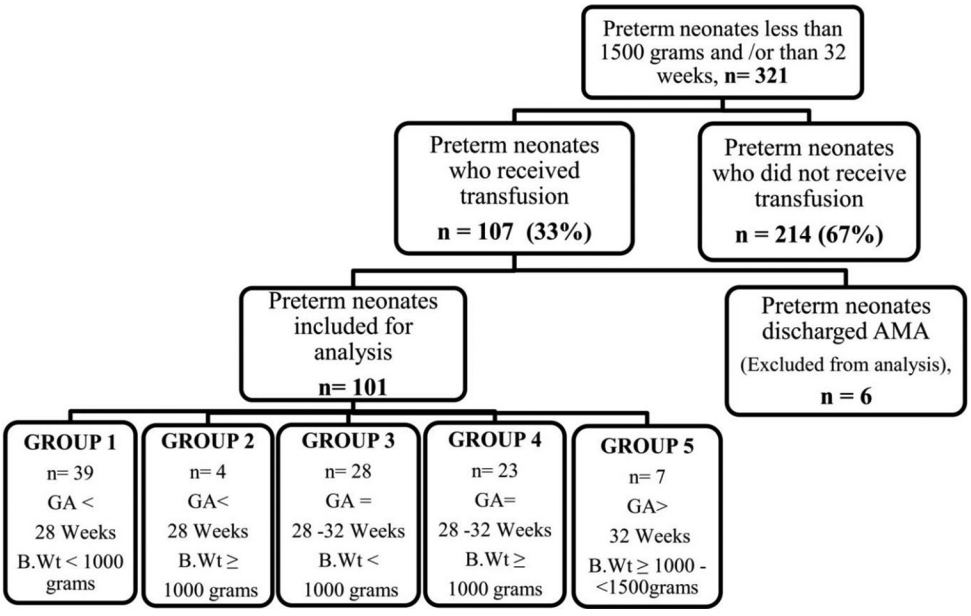

Figure 1: Schematic representation of study groups

from the National Neonatology Forum guidelines was followed[8] [Table 1]. Volume of transfusion was determined using the formula.[8]

Volume of blood for transfusion in ml = Weight in kg × hemoglobin deficit × 6

Statistical analyses were performed using SPSS 16 (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). Mean and standard deviation were used to express values in groups. Pearson's correlation coefficient was calculated to see the relationship between the variables. Chi-square test and Fisher's exact test were used to measure the differences in categorical variables. Student's *t*-test was used for analyzing differences in normally distributed data. Statistical significance was set at $P \leq 0.05$.

Table 1: Transfusion protocol in our tertiary care

Indications for PRBC transfusion
Transfuse at hematocrit <20% - If asymptomatic with reticulocytes <1%
Transfuse at hematocrit <30%-35%
If receiving >35% supplemental oxygen
If on CPAP or mechanical ventilation with MAP >6 cmH_2O
If significant apnea or bradycardia persist despite respiratory stimulants and/or oxygen (>9 episodes in 12 h or 2 episodes requiring bag and mask ventilation)
If heart rate >180 beats/min or respiratory rate >80 breaths/min persist for >24 h
If weight gain <10 g/day is observed over 4 days while receiving >100 kcal/day
If undergoing surgery
If recovering from serious illness such as septicemic shock
If: oxygen-dependent/clinically significant PDA/apneic episodes/or ill
Transfuse at hematocrit<40% if hypotension/shock
Do not transfuse
To replace blood removed for laboratory tests alone
For low hematocrit alone, unless the hematocrit is <20%
Indications for platelet transfusion
If active bleeding and platelet count <100,000/cu.mm
Consider prophylactic platelet transfusion in sick neonates - if platelet count <20,000-50,000/cu.mm
DIC maintain platelet count >100,000 cu.mm
If NAIT/platelet function defects: Discuss with consultant
Failure of platelet production - maintain 20,000-30,000/cu.mm; if active bleeding maintain platelet >100,000/cu.mm
Indications for FFP transfusion
For active bleeding and
DIC
Vitamin K deficiency
If specific coagulation factors not available
Liver disease
Other indications
Altered coagulation profile in a sick neonate
Along with PRBCs in exchange transfusion
Indications for cryoprecipitate transfusion
Fibrinogen levels <100 mg/dl in bleeding neonate/sick neonate
Altered coagulation profile and or persistent bleeding not responding to FFP

CPAP = Continuous positive airway pressure, MAP = Mean airway pressure, PDA = Patent ductus arteriosus, DIC = Disseminated intravascular coagulation, NAIT = Neonatal alloimmune thrombocytopenia, FFP = Fresh frozen plasma, PRBCs = Packed red blood cells

Results

In the study, 65% were male and 35% were female. 62.3% infants were delivered by lower segment cesarean section (LSCS) and 37.7% infants by normal vaginal delivery. 36.6% infants were twins and 63.4% were singletons. Seventy-four percent infants were born to mothers with various obstetric complications [Figure 2]. Thirty percent infants were born to mothers with certain medical complications [Figure 3]. Delayed cord clamping (DCC) was done in 46.5% infants. For need of resuscitation procedures, immediate cord clamping was done in 53.5% infants. Ninety-three percent infants had an APGAR score ≥7/10 at 5 min. Mothers of 26% infants received antenatal steroids at least once. Mean number of transfusion ($n = 3$) was set as cutoff value for assessing statistical significance [Table 2].

The study population received 311 blood component transfusions, with a mean of 3 ± 2.5 transfusions. PRBC was the most frequent blood component transfused. Platelet and FFP transfusions were higher (80%) in infants <1000 g. Cryoprecipitate utilization was higher in infants weighing >1000 g. Male infants received more transfusions (64.6%) than female infants. However, there was no significant difference ($P > 0.05$) between mean number of transfusions received by the male (3.09 ± 2.185) and female (3.06 ± 2.976) infants.

Mean day of life while receiving the first transfusion was 15 ± 12 days. Infants in Group 1 received more number of blood transfusions (49%) than those in other groups. All the infants received highest number of blood transfusion during their 1st and 2nd weeks of life and the

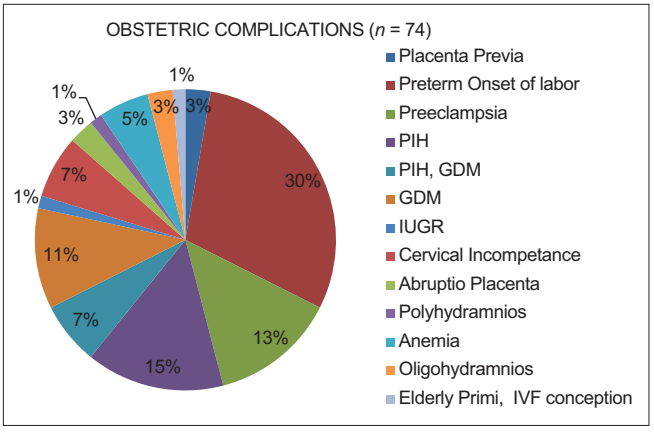

Figure 2: Incidence of obstetric complications in mothers of preterm infants (%)

most common indication was anemia. Highest number of PRBC transfusions (23%) was given when infants were on respiratory support with hematocrit <30%. Platelet counts < 20,000–50,000 cells/cu.mm was the most common indication for platelet transfusion. FFP (58%) and cryoprecipitate (80%) were indicated for bleeding infants [Figure 4].

In this study, 68.3% infants received multiple transfusions. Multiple transfusions were higher among Group 1 infants. Pearson's correlation coefficient showed a weak negative correlation between GA (r = −0.170, P = 0.09) and B.Wt (r = −0.190, P = 0.06) and the number of transfusions. Mean donor exposure was 2.9 ± 2.3 per infant. Mean time interval between time of issue and transfusion to infants in NICU was 23 ± 12 min. Mean volume of PRBC transfused was 16 ± 4.2 ml/kg.

Table 2: Factors associated with need for transfusion

Variables	Number of transfusions		*P*
	<3	≥3	
Delayed cord clamping			
Yes	26	21	0.276
No	24	30	
Maternal medical complications			
Yes	31	40	0.071
No	19	11	
Obstetric complications			
Yes	12	15	0.539
No	38	36	
APGARm <7/10 at 5 min			
Yes	5	4	0.741*
No	45	47	
Mode of delivery, LSCS			
Yes	31	32	0.938
No	19	19	
Multiple births			
Yes	30	34	0.487
No	20	17	
Antenatal steroid administration			
Yes	16	10	0.154
No	34	41	

*P value from the Fisher's exact test. LSCS = Lower segment cesarean section

At discharge, 85% infants showed mean increase in weight of 596.40 ± 464 g, while 13% showed decrease in weight, and 2% infants showed no change in weight. Seventy percent preterm infants recovered, while 30% infants succumbed due to various reasons such as sepsis, respiratory failure, and shock. There was no statistical significance between mean number of transfusions received by the infants who survived and the infants who did not survive.

Ninety-nine infants received a total of 253 PRBC transfusions. Among them, 90% infants showed an improvement while 10% infants showed a decline in mean hemoglobin percentage (Hb%). The mean pre- and post-transfusion Hb% was 8.1 ± 1.9 g/dl and 10.4 ± 1.8 g/dl, respectively. Mean Hb% improvement was 2.3 ± 2.1 gm/dl. Mean transfusion trigger was 7.7 ± 2.1 g/dl. Among ten infants who received 24 platelet transfusions, 90% infants showed an increase and 10% showed a decrease in platelet count. Mean platelet count increase was 30,000 ± 20,000 cells/cu.mm.

In 18 preterm infants who received 24 FFP transfusions, 66.7% infants showed a decrease and 33.3% infants showed an increase from pretransfusion PT and INR value. Mean decrease from pretransfusion PT and INR values was 31 ± 8.3 s and 0.3 ± 0.6, respectively. Among eight preterm infants who received 10 cryoprecipitate transfusions, 90% showed mean increase in fibrinogen of 134.8 ± 112.6 mg/dl, while 10% infants showed decrease in mean fibrinogen postcryoprecipitate transfusion.

Effect of PRBC transfusion on the apneic episodes is shown in Table 3 and incidence of metabolic complications posttransfusion is shown in Table 4. The incidence of

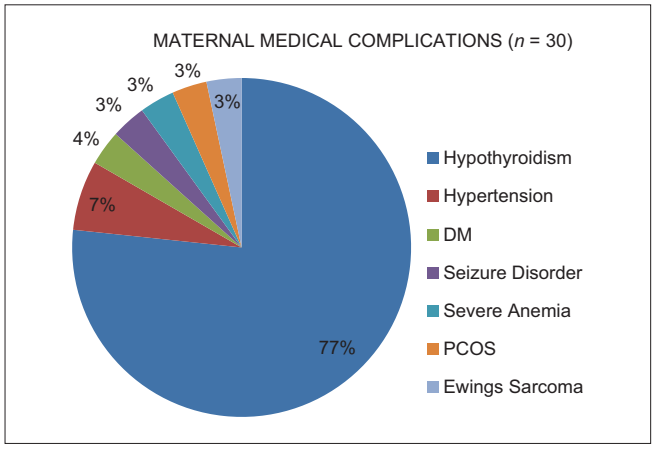

Figure 3: Incidence of maternal medical complications

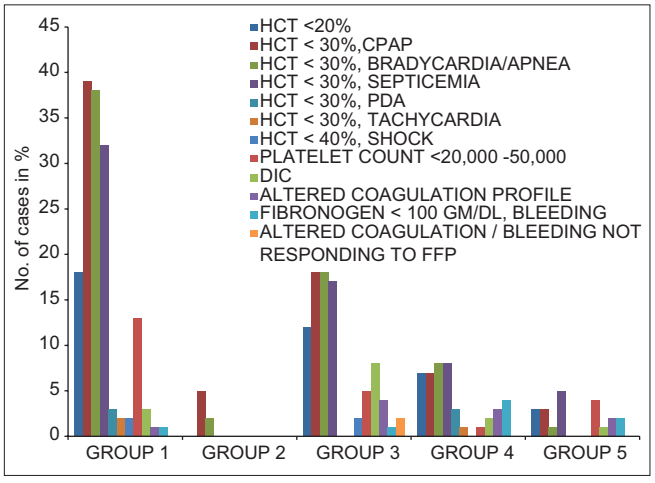

Figure 4: Group-wise breakup of indication for transfusio

comorbid conditions and mean number of transfusions in the comorbid conditions are shown in Tables 5 and 6, respectively. Infants with sepsis, PDA, disseminated intravascular coagulation (DIC), and dyselectrolytemia showed increased requirements for transfusion. There was no statistical significance between the number of transfusions and the occurrence of NEC, ROP, and BPD.

Discussion

Evidence from the literature has demonstrated various benefits of transfusion, has helped in formulating or selecting a particular transfusion guideline for neonates, but gives conflicting results. This cross-sectional study was carried out to observe the actual benefits of transfusion while following restrictive transfusion guideline in preterm babies <1500 g and/or <32 weeks. We evaluated the pattern, indications, and short-term outcomes of blood transfusion along with factors associated with the need for blood transfusion.

Transfusion requirements were highest among infants whose GA was <28 weeks and B.Wt <1000 g, which is similar to the findings in a study by O'Riordan *et al*.[6] In the present study, transfusion requirements were inversely proportional to the infant's GA and B.Wt. Many studies from the developed countries show similar results.[5,9-11] Male infants received more transfusions (64.6%) than the female infants (35.4%). A study by Giridharan and Ramalingam shows similar result.[12] All the preterm infants received highest number of blood component transfusion during their 1st and 2nd weeks of life. Bell *et al*. reported a similar finding in their study.[13]

Factors such as DCC, maternal medical complications, obstetric complications, APGAR <7/10 at 5 min, mode of delivery by LSCS, multiple births, and antenatal steroid administration in mother were not found to influence the need for transfusions statistically. Similarly, Strauss *et al*. reported no change in RBC transfusion requirements due to DCC[14] and Freitas and Franceschini Sdo found that LSCS, intrauterine growth retardation (IUGR), and multiple births did not make a difference in transfusion requirements of infants.[15] However, many studies have demonstrated that DCC has resulted in reduced blood transfusions[16,17] and pregnancies complicated by placental insufficiency, IUGR, maternal hypertension, perinatal asphyxia have increased the transfusion requirements in preterm neonates.[4,18]

PRBC was the most frequent blood component transfused in preterm neonates under study. Literature reviews have shown PRBC to be the most common blood product transfused to sick neonates.[19,20] Platelet transfusions were higher in infants <1000 g, which was similar to a study conducted by Giridharan and Ramalingam.[12] FFP transfusion was also higher in infants <1000 g, but cryoprecipitate utilization was higher in infants weighing >1000 g.

In this study, mean number of transfusions was 3 ± 2.5, while Chen *et al*. reported an average of five transfusions

Table 3: Outcome of apnea status postpacked red blood cell transfusion

Apnea-24 h before transfusion (*n*=253)		Apnea-24 h after transfusion	Number of transfusions (%)
Present	93 (37%)	Resolved	71 (76)
		Present	22 (24)
Absent	160 (63%)	Not applicable	

Table 4: Metabolic complications of transfusion in preterm neonates

Infants with transfusion complications		Types of transfusion complication	Number of cases (%)
Present	4	Hypoglycemia	1 (25)
		Hyperglycemia	2 (50)
		Hyperkalemia	1 (25)
Absent	97	Not applicable	

Table 5: Comorbid illness in preterm infants

Comorbid illness present in study population	Group 1 (*n*=39)	Group 2 (*n*=4)	Group 3 (*n*=28)	Group 4 (*n*=23)	Group 5 (*n*=7)
Sepsis	22	2	14	8	2
RDS	33	2	24	16	4
NEC	4	1	2	0	0
ROP	9	0	9	9	3
PDA	11	0	8	8	5
IVH	13	3	7	0	1
BPD	5	0	1	0	2
DIC	4	2	0	1	0
Metabolic acidosis	2	1	2	4	2
Dyselectrolytemia	10	1	1	0	0
AOP	21	4	17	15	5
Perinatal asphyxia	3	0	0	7	0

RDS = Respiratory distress syndrome, NEC = Necrotizing enterocolitis, ROP = Retinopathy of prematurity, PDA = Patent ductus arteriosus, BPD = Bronchopulmonary dysplasia, DIC = Disseminated intravascular coagulation, IVH = Intraventricular hemorrhage, AOP = Apnea of prematurity

Table 6: Analysis of transfusion in comorbid conditions

Comorbid illness	Number of transfusions (mean±SD)	*P*
Sepsis		
Present	3.94±2.41	0.010
Absent	2.62±2.41	
RDS		
Present	3.05±2.55	0.828
Absent	3.18±2.26	
NEC		
Present	4.00±1.63	0.311
Absent	3.01±2.53	
ROP		
Present	3.20±2.53	0.752
Absent	3.02±2.47	
PDA		
Present	4.21±3.04	0.001
Absent	2.55±1.98	
BPD		
Present	5.00±4.21	0.022
Absent	2.91±2.23	
DIC		
Present	5.14±2.96	0.022
Absent	2.92±2.38	
Metabolic acidosis		
Present	4.27±2.76	0.091
Absent	2.93±2.42	
Dyselectrolytemia		
Present	5.00±3.41	0.004
Absent	2.82±2.23	
AOP		
Present	3.21±2.61	0.508
Absent	2.87±2.27	
Perinatal asphyxia		
Present	2.40±1.26	0.364
Absent	3.15±2.57	

RDS = Respiratory distress syndrome, NEC = Necrotizing enterocolitis, ROP = Retinopathy of prematurity, PDA = Patent ductus arteriosus, BPD = Bronchopulmonary dysplasia, DIC = Disseminated intravascular coagulation, AOP = Apnea of prematurity, SD = Standard deviation

in >90% of ELBW infants.[21] In other studies, 85% ELBW infants received transfusion,[2,3] while in the present study only, 71% of ELBW preterm infants received transfusion by the end of hospital stay. This decrease in our study is probably due to restrictive pattern of transfusion. Mean Hb% transfusion trigger was 7.7 ± 2.1 g/dl in our study, which is closer to restrictive guideline value in a study by Kirpalani *et al*.[22]

Most common indication for PRBC transfusion was anemia. Majority (23%) of PRBC transfusions were given to infants who were on respiratory support with hematocrit <30%. According to the previous studies, neonatal cardiorespiratory illness, laboratory blood testing, oxygen requirement, and need for respiratory support are important factors for deciding administration of blood transfusion.[13,23] Platelet counts <20,000–50,000 cells/cu.mm were the most common indications for platelet transfusion, which is similar to a study conducted by Murray *et al*.[18] FFP (58%) and cryoprecipitate (80%) transfusions were indicated for bleeding infants and to increase fibrinogen, respectively.

No adverse transfusion reactions were recorded. This could be because of the meticulous care in selection, collection, processing, and issue of blood components in our blood bank and use of leukofiltered, irradiated PRBC. This has been proved in many other studies also.[24-28] Metabolic complications in 4% infants could have been due to multiple transfusions given on subsequent days and exchange transfusion.[4] However, the infant's underlying disease condition contributing to metabolic complications could not be ruled out. Adhering to a transfusion guideline has helped us restrict unnecessary transfusions in the infants. According to many studies, transfusion guidelines help decrease donor exposure in very low birth weight (VLBW) neonates.[29,30]

Number of blood transfusions received by the preterm neonates did not make any significant difference in the length of hospital stay. Similar observation was made by Ohls *et al*. in their study.[31] In the present study, mean donor exposure was higher. Although the ideal goal is one donor exposure/infant, previous studies state that reducing donor exposure below 1.1 is difficult in VLBW infants.[32,33]

Hume recommended the use of pedipacks up to expiration date of red blood cells (RBCs).[34] Similarly, using aliquoted blood products until expiry might reduce donor exposure in infants. Another study has recommended the use of old stored blood in small volume transfusions.[35] Alternatively, minimizing phlebotomy losses, better phlebotomy techniques, DCC, use of autologous umbilical cord blood red cells, and recombinant human erythropoietin are recommended as complementary strategies to reduce erythrocyte transfusions in LBW infants by many studies.[36-40]

Few studies found an increase in weight gain as a result of PRBC transfusion.[41,42] In this study, although there was no statistical significance, a negative correlation existed between number of transfusions and weight gain. Therefore, increased transfusion requirements might be an indication of severity of clinical illness. Valieva *et al*. and Chen *et al*. found that transfusions had no effect on rate of infant's weight gain.[11,21] Mean pre- and post-transfusion Hb% in our study was comparable with pre- and post-transfusion hemoglobin values in a study conducted by Stockman and Clark.[43] Mean Hb% improvement in our study was closer to the suggested Hb% improvement of 3 g/dl.[44]

Although previous studies in preterm neonates have reported improvement in apneic episodes post-PRBC transfusions,[45,46] we were not able to establish a statistical significance between blood transfusions and improvement in apnea. Similar results were recorded by many authors.[11,42,43,47] Abu Jawdeh *et al*. demonstrated a significant improvement in incidence and severity of intermittent hypoxemia after RBC transfusion only beyond the 1st week of life.[48] This probably might explain the absence of statistical significance in our study as majority of transfusions occurred during the 1st week of life. It can also be due to susceptibility of apnea to influence from confounding factors, which was also demonstrated by Keyes *et al*. in their study.[47]

Infants who exhibited a negative response with PRBC, platelet, FFP, and cryoprecipitate transfusions belonged to <28 weeks and <1000 g group. It might have been due to underlying disease conditions and ongoing bleeding episodes. Thus, outcomes of transfusion are influenced not only by underlying disease condition but also by GA and B.Wt.

Incidence of various comorbid illnesses such as sepsis, respiratory distress syndrome, NEC, ROP, PDA, intraventricular hemorrhage, BPD, and anemia of prematurity was higher in the infants who were <28 weeks and 1000 g. Infants with sepsis, PDA, BPD, DIC, and dyselectrolytemia received significantly more number of transfusions. Our findings were similar to the studies conducted by Freitas and Franceschini Sdo and Silvers *et al*.[15,49] There was no statistical significance between the number of transfusions and the occurrence of NEC, ROP, and BPD. Similarly, Fortes Filho *et al*. did not find any significant association between number of transfusions and incidence of ROP.[50] However, other studies have found an association between number of transfusions and incidence of ROP, BPD, and NEC.[48,51,52]

Conclusion

GA, B.Wt, and underlying disease of preterm neonates influence their transfusion needs. Transfusion requirements decrease with increasing GA and B.Wt. Majority of blood transfusions occur during the first 2 weeks of life. Increased transfusion requirement might be an indication of severe clinical illness. Adherence to neonatal transfusion policy and restrictive guidelines of transfusion reduces inappropriate blood product utilization. Appropriate management of sepsis, PDA, BPD, DIC, and dyselectrolytemia might help reduce transfusion needs of preterm infants.

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Conflicts of interest

There are no conflicts of interest.

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