12-2021

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Scientific Research Publishing

Open Journal of Pediatrics, 2021, 11, 786-796
https://www.scirp.org/journal/ojped
ISSN Online: 2160-8776
ISSN Print: 2160-8741

# Categorization and Frequency of Indications for Packed Cell Transfusion in the Preterm Newborn during the Initial Hospital Stay at a Tertiary Care Hospital: A Cross-Sectional Study

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**How to cite this paper:** Surani, S., Lohana, H., Ahmed, S., Hassan, R., Kewalani, S. and Ahmed, K. (2021) Categorization and Frequency of Indications for Packed Cell Transfusion in the Preterm Newborn during the Initial Hospital Stay at a Tertiary Care Hospital: A Cross-Sectional Study. *Open Journal of Pediatrics*, **11**, 786-796.
https://doi.org/10.4236/ojped.2021.114073

**Received:** September 6, 2021
**Accepted:** December 19, 2021
**Published:** December 22, 2021



## Abstract

**Introduction:** Packed cell transfusion is a lifesaving procedure in premature babies as they have more complications as compared to babies who are born at term. Complications related to prematurity increase as gestational age decreases and anemia is one of the complications of prematurity which needs packed cell transfusions. To date, when to transfuse preterm babies and what would be the threshold for hemoglobin and hematocrit is still a point of argument as well as liberal versus restrictive transfusion protocols have been developed but what should be followed still needs more data. In our study, we have observed frequencies of different indications of packed cell transfusion in the neonatal intensive care unit of a tertiary care hospital. This endeavor will help in the establishment of guidelines regarding transfusion and the threshold on which any intervention should be done also it would be a step towards the identification of preventable causes that lead to transfusion and transfusion-related risks and hazards. **Objective:** To determine the indication of packed cell transfusion and their frequencies in preterm neonates. **Study Design:** This was a cross-sectional study. **Setting:** The study was carried out in the neonatal intensive care unit (NICU). **Study Duration:** The duration of the study was 1 year. **Material and Methods:** A total of 246 preterm neonates admitted to Aga Khan University Hospital (AKUH) neonatal intensive care unit in the tenure of 1 year, fulfilling the inclusion criteria and requiring packed cell transfusion were included. After the approval from ethical review committee, charts were reviewed for gestational age, birth weight, mode of delivery (normal vaginal or Cesarean-section) were recorded. Indications of packed cell transfusion (intraventricular hemorrhage, infection or sepsis, anemia of prematurity, phlebotomy losses, increase oxygen requirement, he-

matological causes, other causes of hemorrhage and other causes) were observed and recorded. Pre-transfusion hemoglobin levels (g/dL) and hematocrit levels were also recorded. Other information like number and volume of transfusion and day of life on which transfusion was administered was also documented. **Results:** A total of 246 critically ill children were enrolled in this study. Of the total, 52.8% were baby boys and 47.2% were baby girls. 57% of babies were born via cesarean section and 43% were born via vaginal delivery. Out of total preterm newborns admitted in NICU, 22.8% were extremely preterm, 35.4% were very preterm and 41.9% were late preterm. Mean gestational age was observed to be 31 (±4) weeks and the mean birth weight of newborns was 1500 (±600) grams. Indications of packed cell transfusion observed in our study are intraventricular hemorrhage 10%, 26% sepsis/infection, 4% hematological disorders, 12.8% anemia of prematurity, 25.2% was related to increase in oxygen requirement, 13% other hematological causes and 9.3% other causes. **Conclusion:** An increase in oxygen requirement and anemia of prematurity were the indications that were observed in the extremely preterm and very preterm groups. Sepsis and increase oxygen requirement are some of the major causes of transfusions observed in the late preterm group. Preventable indications can be one of the areas that can be worked on and will reduce the need for transfusion in preterm babies with subsequent prevention of transfusion-associated risks.

## Keywords

Packed Cell Transfusion, Preterm, Neonatal Intensive Care Unit, Anemia of Prematurity, Phlebotomy Losses

## 1. Introduction

About 15 million babies are born prematurely worldwide every year. Out of these 1 million children are dying each year due to complications of preterm birth. Globally, prematurity is the leading cause of death in children under the age of 5. And in almost all countries with reliable data, preterm birth rates are increasing. Globally from the year 2000, the incidence of preterm was 9.7% which has risen to 10.4% in the year 2014 [1]. More than 60% of preterm deliveries are from Africa and South Asia. Pakistan is 4$^{th}$ out of 10 countries with the greatest number of preterm births and 8$^{th}$ with the highest rate of preterm birth per 100 live births *i.e.*, 15.8/100 live births [2].

Packed red blood cell transfusion is a life-saving procedure in preterm neonates admitted to the neonatal intensive care unit. Approximately 90% of extremely low birth weight neonates of less than 1000 g will require at least one red blood cell transfusion [3]. 50% of all RBC transfusions administered to VLBW infants are given in the first 2 weeks after birth, and 70% are administered within the first month [4]. Anemia can also be one of the causes which can decrease oxygen delivery to tissues so to increase oxygen delivery packed RBC transfusion

is an important measure.

A study done in 2008, evaluated the pathophysiology of anemia and showed that anemia of prematurity along with other factors like infection/sepsis (89.1%) [5], malnourishment, intraventricular hemorrhage grade II and IV (10.9%] [5] and cardiorespiratory disease are contributing factors. Phlebotomy losses (36.7%) are also one of the main culprits [2].

A multicenter study carried out in seven neonatal units found that phlebotomy blood loss of 10 mL/kg increased the number of RBC transfusions by 27% [5]. Another study done in 2010 elaborated that blood hemoglobin concentration falls to approximately 8 g/dL in infants with birth weights of 1000 g to 1500 g and to approximately 7 g/dL in infants with birth weights < 1000 g [3].

Neonatal specialists have long debated the indications and merits of strategies for use of transfusions to preserve oxygen delivery or to address a variety of adverse clinical associations with transfusion [6].

Delay of 30 - 120 seconds in umbilical cord clamping is also one of the contributing factors in reducing the need for transfusion in the preterm neonate [7]. There is a certain risk associated with transfusions and known complications, which can be due to: 1) storage associated (due to reduced adenosine triphosphate, adenosine, potassium leak, increased hemolysis, free hemoglobin, formation of micro-particles, activation of white cells, and release of pro-inflammatory cytokines), 2) reduced red blood cells (RBC) deformability and increases in viscosity (altered rheology) as well as RBC lysis, 3) decreased (2,3-diphosphoglycerate) levels and reduced $O_2$ binding, 4) reduced capacity to transport and release nitric oxide, 5) oxidative injury due to free radicals and iron release, and 6) transmission of viral or bacterial infections. Complications that are associated with red blood cell transfusions in neonatal group are transfusion-associated gut injury, increased risk of necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity and intraventricular hemorrhage [4] [6] [8].

It has been observed that transfusion with packed red blood cells at a dose of 20 mL/kg is well tolerated and results in an overall decrease in the number of transfusions compared to transfusions done at 10 mL/kg. There is also a higher rise in hemoglobin with a higher dose of packed red blood cells.

The expected response after each transfusion of 9 mL/kg of body weight hemoglobin level should increase by 3 g/dL. Meticulous monitoring of input, output and vital signs are mandatory during blood transfusion [9].

## 2. Material and Methods

### 2.1 Study Setting

The study was conducted at the neonatal intensive care unit of the Aga Khan University Hospital, Karachi, Pakistan.

#### 2.1.1. Duration of Study

This study was carried out over a period of 1 year from 1st January 2018 till 31st December 2018, after the approval from the College of Physicians and Surgeons

Pakistan (CPSP).

#### 2.1.2. Sample Size

50% - 80% of the preterm babies admitted in a neonatal ICU receive red blood transfusion during their stay (3). The sample size was calculated to be 246 with a frequency of 80% with 5% precision and 95% confidence interval[1].

#### 2.1.3. Sampling Technique

Non-probability purposive sampling technique was used for the enrolment of the study participants.

#### 2.1.4. Sample Selection

Inclusion Criteria*:*

All newborn preterm babies > 24 weeks of gestation and less than 37 weeks require admission in the neonatal intensive care unit and red blood cell transfusion.

Exclusion Criteria:

All neonates receiving packed cell transfusion outside AKUH will be excluded and whose code status has been decided as DNR for any reason will be excluded.

#### 2.1.5. Study Design

Descriptive, cross-sectional study.

### 2.2. Data Collection

Preterm neonates admitted to AKUH neonatal intensive care unit, fulfilling the inclusion criteria and requiring packed cell transfusion were included. After ethical review committee approval from the hospital, charts were reviewed for gestational age, gender, birth weight, as well as pre-transfusion hemoglobin and hematocrit levels were documented. Mode of delivery (normal vaginal and C-section) and indications of packed cell transfusion in terms of frequencies was recorded (Intraventricular Hemorrhage, Infections/sepsis, Hematological disorder, Anemia of prematurity, Increase in oxygen requirement in last 48 hours of >4 fold increase in nasal cannula flow (*i.e.* 0.25 L/min to 1 L/min) or increase in nasal CPAP > 20% from previous 48 hours (*i.e.* 5cm to 6 cm of $H_2O$), Phlebotomy losses in mL/kg (>15 mL/kg were taken as an indication) in last 48 hours before transfusion, Other causes of hemorrhage and other causes). Number and volume of blood transfusion and day of life on which transfusion was administered were also documented.

### 2.3. Data Analysis

Collected data on proforma was entered, described and analyzed statistically in SPSS 22. For continuous variables like Gestation age, birth weight, hemoglobin levels and phlebotomy losses (mL/kg), number of transfusion and day of life; mean and standard deviation are calculated. Categorical variables like gender, mode of delivery, categories of preterm, indications of transfusion (intraventri-

[1]https://www.openepi.com/SampleSize/SSPropor.htm.

cular hemorrhage, hematological disorder, anemia of prematurity, phlebotomy losses and increase in oxygen requirement) are reported as frequencies and percentages. p-values reported as < 0.05 were taken as positive.

## 3. Results

A total of 246 critically ill children were enrolled in this study. Of the total, 52.8% (n = 130) were baby boys and 47.2% (n = 116) were baby girls (Figure 1). 57% (n = 140) babies were born via cesarean section and 43% (n = 106) were born via vaginal delivery (Figure 2). Out of total 246 preterm newborns, 22.8% (n = 56) were extremely preterm, (35.4% n = 87) were very preterm and 41.9% (n = 103) were late preterm (Figure 3). Mean gestational age was observed to be 31 (±4) weeks and the mean birth weight of newborns was 1500 (±600) grams (Table 1).

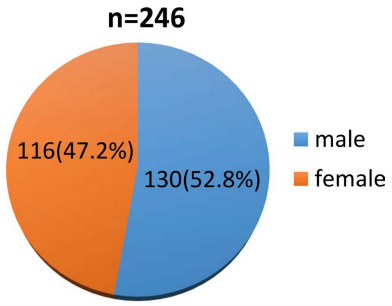


Figure 1. Gender distribution of total preterm babies with transfusion.

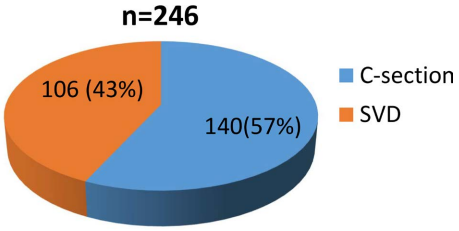


Figure 2. Mode of delivery of total newborns with transfusion.

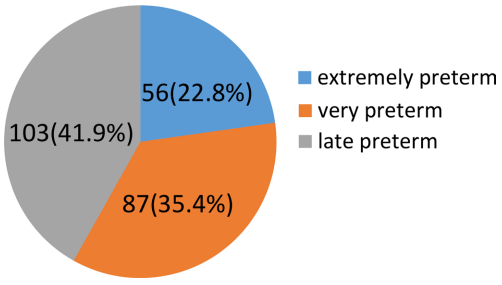


Figure 3. Categories of preterm newborns.

Table 1. Mean gestational age and birth weight of study population.

| Demographics | Mean ± SD |
|---|---|
| Gestational Age | 31 ± 4 week |
| Birth weight | 1500 ± 600 gram |

Out of total 246 preterm babies admitted in NICU who were transfused. Indications of packed cell transfusion was observed and 10% (n = 25) were attributed to intraventricular hemorrhage, 26% (n = 64) sepsis/infection, 4% (n = 10) hematological disorders, 12.8% (n = 30) anemia of prematurity, 25.2% (n = 62) was related to increase in oxygen requirement, 13% (n = 32) other hematological causes and 9.3% (n = 23) other causes (Figure 4).

Characteristics of blood transfusions include mean pre-transfusion hemoglobin which was found to be 9.06 ± 2.07 g/dL in extremely preterm newborns whereas 9.83 ± 2.06 g/dL and 10.05 ± 2.07 g/dL were observed in very preterm and late preterm respectively (p-value of 0.017). Mean transfusion volume was 15.61 ± 4.09 mL/kg ($p < 0.001$) and average number of transfusions during the hospital stay was 3.59 ± 2.38 (p-value < 0.000). Our study revealed that preterm neonates were transfused mostly in the second week of life with average of 16.22 ± 13 days of life ($p < 0.001$) (Table 2).

Gestational Age categorized into extremely preterm, very preterm and late preterm. In extremely preterm babies, packed cell transfusions were done secondary to intraventricular hemorrhage (17%, n = 10), sepsis/infection (17%, n = 10), anemia of prematurity (21%, n = 12), increase in oxygen requirement (32%, n = 18), other sources of hemorrhage (5.3%, n = 3) and other causes (5.3%, n = 3). No transfusions were done following phlebotomy losses or hematological causes.

In very preterm newborns, Increase in oxygen requirement (27%, n = 24) and infection/sepsis (27%, n = 24) were the most common causes of transfusion followed by intraventricular hemorrhage (12%, n = 11), anemia of prematurity (9.1%, n = 8) and hematological causes (5.7%, n = 5). Other causes were 11% (n = 10) and other sources of hemorrhage were 5.7% (n = 5). Phlebotomy losses more than 15 mL/kg were also not a cause in this group of neonates.

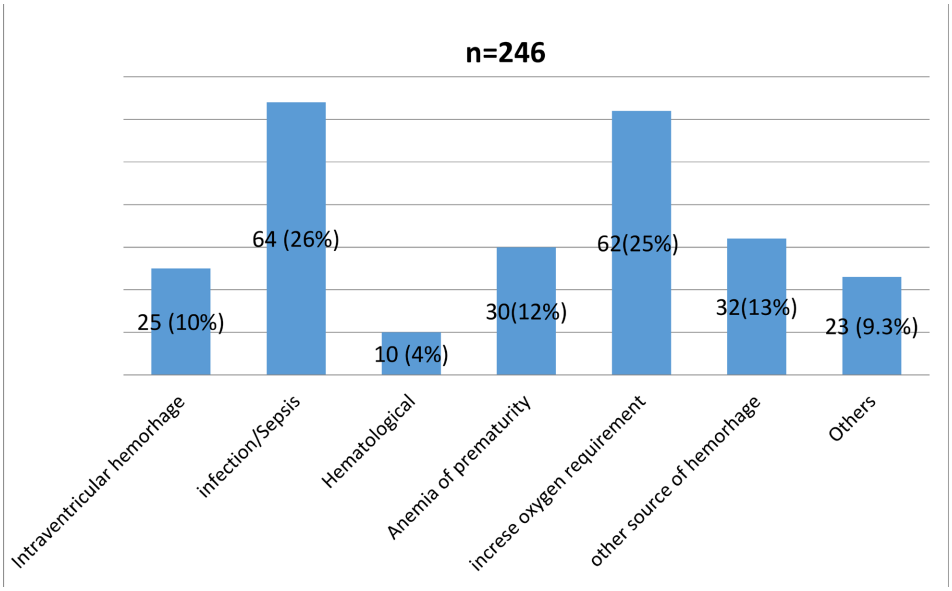


**Figure 4.** Indications of transfusion.

Transfusions in late preterm babies were mainly secondary to infections which were found to be in 29% (n = 30) of patients. Increase in oxygen requirement and other sources of hemorrhage were also important causes in this category and are observed in 19.4% (n = 20) and 23.3% (n = 24) respectively. Intraventricular hemorrhage (3.8%, n = 4), hematological disorders (4.8%, n = 5), anemia of prematurity (9.7%, n = 10) and other causes (9%, n = 10) were included in other indications in this category. No indications were attributed to phlebotomy losses (Figure 5).

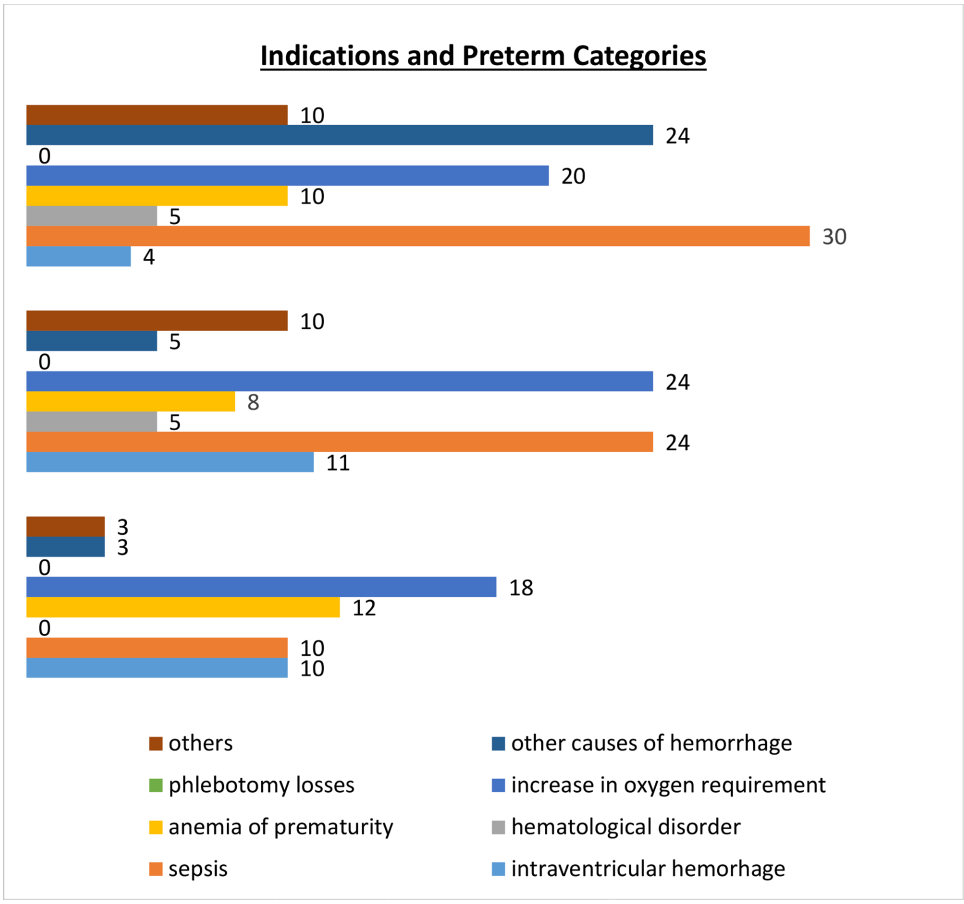


Figure 5. Indications of transfusion in preterm categories.

Table 2. Characteristics of transfusions.

| | Extremely preterm | Very Preterm | Late preterm | p-value | Total |
|---|---|---|---|---|---|
| | Mean ± SD | | | | |
| Pre-transfusion Hb | 9.06 ± 2.07 | 9.83 ± 2.06 | 10.05 ± 2.07 | 0.017 | 9.75 ± 2.09 |
| Volume of blood (mL/kg) transfused | 16.5 ± 3.85 | 16.74 ± 4.3 | 14.14 ± 3.52 | <0.001 | 15.61 ± 4.09 |
| Number of transfusions (mean number) | 5.61 ± 2.38 | 3.43 ± 1.94 | 2.64 ± 1.37 | <0.001 | 3.59 ± 2.38 |
| Day of life of transfusion | 15.09 ± 14.8 | 19.14 ± 14.5 | 14.36 ± 9.8 | 0.031 | 16.22 ± 13 |

## 4. Discussion

In Pakistan, a total of 8.39% of preterm babies were born in the year 2014 [1] Packed cell transfusion is a lifesaving procedure in newborns especially in extremely preterm newborns in whom the rate of complication of prematurity is more as compared to other preterm babies. In Asia in the year 2014, the incidence of extremely preterm babies was 3.4%, 10.8% were observed to be very preterm and 85.9% of babies were late preterm [1]. In our study, out of a total of 246 preterm babies, 22.8% (56) were extremely preterm, 35.4% (87) were very preterm and 41.9% (103) were late preterm. Of all the preterm newborns under study, we have observed that 43% (106) babies were delivered via normal vaginal delivery and 57% (140) were delivered via cesarean section. The rate of cesarean section was similar as compared to other developing countries as [10] analyzed national data of Brazil in the year 2015 and observed Prevalence of cesarean section (CS) was 55.5%, preterm prevalence (<37 weeks' gestation) was 10.1% and early-term births (37 - 38 weeks of gestation) represented 29.8% of all births.

It was observed in multiple studies that as gestational age decreases, the rate of complications related to prematurity increases so gestational age is significantly related to administration of transfusions which was also evident in our study.

In our study, we have observed that mean pre-transfusion hemoglobin was 9.7 g/dL (range 2.0 g/dL- 28 g/dL) and mean pre-transfusion hematocrit was 29.5 (range 12 - 60). Large multicenter trials were done to assess whether preterm newborns need liberal packed cell transfusion or restrictive transfusion. In The Premature Infants in Need of In transfusion (PINT) study, [11] did a randomized controlled trial in 450 extremely preterm newborns weighing less than 1000 g and their thresholds for pre-transfusion hemoglobin and hematocrit in restrictive transfusion group were for infants requiring respiratory support (ventilation, CPAP, or oxygen): 115 g/L or 11.5 g/dL in the first post-natal week and in the liberal group were 135 g/L or 13.5 g/L. In another trial, [12] transfused 78 preterm babies according to clinical indication but in liberal group pre-transfusion hemoglobin threshold was <10 g/dL. [13] kept pre-transfusion hemoglobin in restrictive group to be less than 70 g/L but in the liberal group, the threshold was 100 g/L. In some studies level of respiratory support was important like a study done by [11] and [14]. low thresholds for packed cell transfusion were kept for intubated babies as compared to higher thresholds for babies who did not require any respiratory support [11] [14]. In our study, no guidelines for restrictive or liberal transfusions were followed.

As per WHO, the global prevalence of LBW is 15.5%, which amounts to about 20 million LBW infants born each year, 96.5% of them in developing countries. The mean birth weight of all the preterm newborns under study was observed to be very low birth weight (1500 ± 600 grams). [15] observed in their study that at their facility inborn delivery rate is approximately 1500 births per year with 32% of these being of LBW (<2500 gm) and approximately 13% of these being of very low birth weight (<1500 g) as observed in our study as well.

We have observed that in all preterm babies observed indications of transfusions were intraventricular hemorrhage 10% (25), sepsis/infection 26% (64), hematological disorders 4% (10), anemia of prematurity 12% (30), increase in oxygen requirement 25% (62), other causes of hemorrhage 13% (32) and 9.3% (23) were other causes. No transfusions were observed secondary to phlebotomy losses of more than 15 mL/kg. on evaluation of category-based indications, extremely preterm and very preterm babies were being transfused after an increase in oxygen requirement followed by anemia of prematurity, however, in late preterm babies most frequently observed cause was sepsis and hematological causes.

In a prospective study, indications of transfusions with packed red cells are post-hemorrhagic and hemolytic anemia as well as anemia due to reduced or altered red blood cell production. In the first week of life, transfusion is advised for severe anemia (Hb < 8 g/dL) with hypovolemic shock (loss of blood volume > 20%) following bleeding from a placenta Previa, abruptio placentae, ruptured cord, etc. Transfusion therapy is also necessary for the presence of severe cardiorespiratory difficulty or surgery to maintain the Hematocrit more than 35. In newborns, late-onset anemia (after the first week of life) transfusion is advised with the presence of any symptoms suggesting inadequate tissue oxygenation, such as apathy, difficulty in suckling, poor growth, tachycardia, and tachypnea [16]. In another study, anemia of prematurity which is an exaggeration of physiological anemia was also an important cause of packed red cell transfusion in premature babies [3] and a similar finding was evident in our study as well.

One of the established complications in extremely low birth weight neonates is anemia secondary to phlebotomy losses [13] [17]. In one report, withdrawal of blood in excess of that required for laboratory studies contributed to iatrogenic blood loss by 2 to 4 mL/kg per week [18].

## 5. Limitations

It was a single-center study so we cannot generalize its findings.

## 6. Conclusions

As more newborn babies are born preterm, the rate of complications rises and the need for packed cell transfusion also increases. To reduce the number of packed cell transfusion, we need to work on its respective indications. It was evident from our study that in extremely preterm and very preterm newborns increase in oxygen requirement and anemia of prematurity were major causes of transfusion and in late preterm infections are the leading cause of red blood cell transfusion.

Preventable indications under study are infection and phlebotomy losses, therefore, we recommend endeavors for infection control and use of phlebotomy protocols in neonatal intensive care units.

Variability was observed in all three preterm categories so there is a need for a proper guideline to be followed.

## Ethics Approval and Consent to Participate

Aga Khan University Hospital's ethical review committee approved the study in 2018 with ERC number 5268-Ped-ERC-18.

## Funding

The study was self-funded by Dr. Shirin Surani

## Authors' Contributions

SS, SA, and HL contributed to drafting the article. SS, RS and SK collected the data from the hospital. SS and HL managed and analyzed data. KA and HL supervised the study. All authors approved the final version of the article for submission.

## Acknowledgements

We would like to acknowledge mothers of enrolled children for providing us with time and data for this study. We would also like to thank all our nursing staff for conducting this study under stressful conditions.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References

[1] Chawanpaiboon, S., *et al.* (2019) Global, Regional, and National Estimates of Levels of Preterm Birth in 2014: A Systematic Review and Modelling Analysis. *The Lancet Global Health*, **7**, e37-e46. https://doi.org/10.1016/S2214-109X(18)30451-0

[2] World Health Organization (2012) Born Too Soon: The Global Action Report on Preterm Birth. World Health Organization, Geneva.

[3] Strauss, R.G. and Widness, J.A. (2010) Is There a Role for Autologous/Placental Red Blood Cell Transfusions in the Anemia of Prematurity? *Transfusion Medicine Reviews*, **24**, 125-129. https://doi.org/10.1016/j.tmrv.2009.11.003

[4] Widness, J.A. (2008) Pathophysiology of Anemia during the Neonatal Period, Including Anemia of Prematurity. *NeoReviews*, **9**, e520. https://doi.org/10.1542/neo.9-11-e520

[5] Dos Santos, A.M., *et al.* (2015) Factors Associated with Red Blood Cell Transfusions in Very-Low-Birth-Weight Preterm Infants in Brazilian Neonatal Units. *BMC Pediatrics*, **15**, 113.

[6] La Gamma, E.F. (2012) Introduction to Transfusion Practices in Neonates: Risks, Benefits, and Alternatives. *Seminars in Perinatology*, **36**, 223-224. https://doi.org/10.1053/j.semperi.2012.04.001

[7] Rabe, H., Gyte, G.M., Diaz-Rossello, J.L. and Duley, L. (2019) Effect of Timing of Umbilical Cord Clamping and Other Strategies to Influence Placental Transfusion at Preterm Birth on Maternal and Infant Outcomes. *The Cochrane Database of Systematic Reviews*, **9**, CD003248. https://doi.org/10.1002/14651858.CD003248.pub4

[8] Christensen, R.D., *et al.* (2014) Association, among Very-Low-Birthweight Neo-

nates, between Red Blood Cell Transfusions in the Week after Birth and Severe Intraventricular Hemorrhage. *Transfusion*, **54**, 104-108. https://doi.org/10.1111/trf.12234

[9] Jain, R., *et al.* (2008) Blood and Blood Component Therapy in Neonates. *Indian Journal of Pediatrics*, **75**, 489-495. https://doi.org/10.1007/s12098-008-0076-8

[10] Barros, F.C., *et al.* (2018) Caesarean Sections and the Prevalence of Preterm and Early-Term Births in Brazil: Secondary Analyses of National Birth Registration. *BMJ Open*, **8**, e021538. https://doi.org/10.1136/bmjopen-2018-021538

[11] Kirpalani, H., *et al.* (2006) The Premature Infants in Need of Transfusion (PINT) Study: A Randomized, Controlled Trial of a Restrictive (Low) versus Liberal (High) Transfusion Threshold for Extremely Low Birth Weight Infants. *The Journal of Pediatrics*, **149**, 301-307. https://doi.org/10.1016/j.jpeds.2006.05.011

[12] Blencowe, H., *et al.* (2012) National, Regional, and Worldwide Estimates of Preterm Birth Rates in the Year 2010 with Time Trends since 1990 for Selected Countries: A Systematic Analysis and Implications. *The Lancet* (*London*, *England*), **379**, 2162-2172. https://doi.org/10.1016/S0140-6736(12)60820-4

[13] Tooley, W.H. (2003) Intensive Care Nursery; HOUSE STAFF MANUAL the Regents of the University of California ed., San Francisco: UCSF Benioff Children's Hospital, 2003 *Very Low and Extremely Low Birthweight Infants*.

[14] Blank, J.P., *et al.* (1984) The Role of RBC Transfusion in the Premature Infant. *American Journal of Diseases of Children* (1960), **138**, 831-833. https://doi.org/10.1001/archpedi.1984.02140470031010

[15] Iannucci, T.A., Tomich, P.G. and Gianopoulos, J.G. (1996) Etiology and Outcome of Extremely Low-Birth-Weight Infants. *American Journal of Obstetrics and Gynecology*, **174**, 1896-1900. https://doi.org/10.1016/S0002-9378(96)70226-0

[16] Girelli, G., *et al.* (2015) Recommendations for Transfusion Therapy in Neonatology. *Blood Transfusion*, **13**, 484-497.

[17] Strauss, R.G. (2010) Anaemia of Prematurity: Pathophysiology and Treatment. *Blood Reviews*, **24**, 221-225. https://doi.org/10.1016/j.blre.2010.08.001

[18] Lin, J.C., *et al.* (2000) Phlebotomy Overdraw in the Neonatal Intensive Care Nursery. *Pediatrics*, **106**, E19. https://doi.org/10.1542/peds.106.2.e19