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ORIGINAL ARTICLE

# Comparison of Hematocrit Change in Preterm Neonates with Birth Weight Based Versus Formula Based Packed Red Blood Cell Transfusion: A Randomized Control Trial

**Rajbir Kaur Cheema[1] · Suksham Jain[2] · Ravneet Kaur Bedi[1] · Gagandeep Kaur[1] · Deepak Chawla[2]**

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**Abstract** Conventionally the packed red blood cell (PRBC) transfusion volume given to neonates is 10 ml/kg to 20 ml/kg. The weight-based formulae underestimate the volume of PRBC required to achieve a target hematocrit (Hct) in preterm neonates. The study was done to compare the rise in Hct after transfusing PRBC volume calculated either based on body weight or using formula considering Hct of blood bag and Hct of preterm neonates. This prospective study included a total of 68 preterm neonates requiring transfusion for the first time having $\leq$ 34 weeks of gestational age. Neonates were randomized using block randomization, to receive 15 ml/kg of PRBC transfusion (group A) or transfusion based on the formula (group B). The primary outcome of interest was post-transfusion rise in hematocrit. The secondary outcome was the effect of transfusion on neonatal morbidities in terms of retinopathy of prematurity, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, and death. Baseline variables (birth weight, gestation age, APGAR score and score of neonatal acute physiology) pre-transfusion hemodynamics and hematocrit of the bag were comparable in both groups. The mean volume of PRBC in group A was 18.8 $\pm$ 4.9 ml, whereas in group B it was 29.6 $\pm$ 7.3 ml, p = 0.0001. Group B transfusions had a statistically significant change in 24 h post-transfusion hematocrit. Secondary outcomes were comparable in two groups. Post transfusion rise in Hct of the patient in group B was significant as compared to group A. The study needed huge sample size to establish a difference in the number of re-transfusions required across two groups. The trial was registered under the clinical trial registry of India (CTRI/2018/01/011,063).

**Keywords** Preterm neonates · Transfusion · Hematocrit

## Introduction

About 85% of extremely low birth weight newborns receive a transfusion by the end of their hospital stay [1]. Because of the need for frequent transfusions, these preterm neonates are often exposed to multiple blood donors. Red blood cell (RBC) transfusion in this group is also often associated with an increased incidence of complications such as retinopathy of prematurity (ROP), Necrotizing enterocolitis (NEC) and Intra-ventricular hemorrhage (IVH). Thus, RBC transfusion in neonates should be restricted to a minimum.

Though neonatal RBC transfusion guidelines exist, many issues about transfusion dosage and volume remain debatable. Currently, in neonatal intensive care unit

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✉ Ravneet Kaur Bedi
rkbedi15@yahoo.com

Rajbir Kaur Cheema
cheemarajbir50@gmail.com

Suksham Jain
dr.sukshamj@gmail.com

Gagandeep Kaur
docvpsingh@yahoo.co.in

Deepak Chawla
drdeepakchawla@gmail.com

[1] Department of Transfusion Medicine, Government Medical College and Hospital, Chandigarh 160030, India

[2] Department of Neonatology, Government Medical College and Hospital, Chandigarh 160030, India

(NICU) packed red blood cells (PRBCs) are transfused at a dosage of 10–20 mL/kg. Transfusion with PRBCs at a dose of 20 mL/kg is well tolerated and it results in a higher rise in hemoglobin compared to transfusions done at 10 mL/kg thereby reducing donor exposure in preterm neonates [2]. Nevertheless, several formulae have also been used to estimate the volume of PRBC that should be transfused to achieve a target hemoglobin concentration or hematocrit (also called packed cell volume) [3, 4]. These formulae are based on weight, degree of anemia and hematocrit of the newborn. Calculation of required RBC transfusion volume, using a formula based on infant weight and degree of anemia has shown to achieve desired target hemoglobin levels [5].Additionally, the blood bags with higher hemoglobin content and hematocrit decrease donor exposure and transfusion-related adverse effects [6]. Hence, the hematocrit of the blood bag can also be considered for calculating the blood volume to be transfused.

The present study was planned to know if the desired rise in hematocrit in preterm neonates can be achieved by transfusing RBC volume calculated using a formula based on hematocrit of a blood bag, hematocrit of patient and blood volume of the patient in comparison to weight-based calculated PRBC volume. We hypothesized required hematocrit is achieved early if volume of PRBC transfusion in preterm neonates is calculated considering hematocrit of blood bag and that of the patient along with blood volume of the patient.

## Materials and methods

The single centre randomized controlled trial was conducted over 18 months (January 2017 to June 2018) in a tertiary care hospital in North India after obtaining ethical clearance from the institutional ethics committee. The trial was registered under the clinical trial registry of India (CTRI/2018/01/011,063). All preterm neonates admitted to NICU, intermediate care nursery (ICN) and postnatal ward (PNW) requiring PRBC transfusion for the first time were assessed for eligibility. Infants with evidence of active bleeding, hemolysis due to ABO/Rhesus incompatibility, disseminated intravascular coagulopathy, intra-ventricular hemorrhage (grade III or more) and congestive cardiac failure were not eligible to participate. Written informed consent was taken from a parent of each eligible preterm infant in their vernacular language. The eligible infants were recruited and randomized into two groups. Group A where preterm neonates received weight based transfusion and Group B received formula based transfusions. For randomization computer generated random numbers with varying block size of 4 and 6 were used. Allocation was done by an independent observer using sequentially numbered, opaque, sealed, identical envelopes. Parents, clinician and investigators were not blinded about the intervention. However, the investigator involved in performing post-transfusion hematocrit was blinded about clinical outcomes. The blood transfusions were given only when the hematocrit level fell below the assigned value. This value was assigned using American Red Cross practice guidelines for transfusions in newborn infants [7]. Infants with $FiO_2$ requirement of $> 0.35$ were given PRBC transfusion when hematocrit fell $< 40$–$45\%$, those with chronic oxygen dependency, on CPAP were maintained at hematocrit of 30–35% and in late anemia hematocrit of 20–25% as tolerated.

**Blood transfusion protocol in preterm neonates** The average new born blood volume is 80 mL/kg, whereas that of preterm neonates is 100 mL/kg [8]. In our institution, for preterm neonates who require PRBC transfusion, transfusion protocol of 10–15 mL/kg PRBC volume is followed. American Red Cross practice guidelines are used for recognizing preterm neonates requiring PRBC transfusion in our institution.

### Preparation of PRBC Unit

Leukoreduced, nonirradiated PRBC units screened for mandatory transfusion-transmitted infections required by national regulatory authorities were used for transfusion. All PRBC units were prepared following standard operating procedures and using calibrated equipment. Each blood unit to be transfused was checked for compatibility with mother and preterm neonate sample using microcolumn gel agglutination technology (BioradDiaMed, Switzerland).

The two groups received transfusion as following protocol:

Group A Preterm neonates were transfused volume of PRBC based on the weight of neonate i.e. 15 mL/ kg of PRBC.

Group B Received volume of PRBC calculated using following formula [5].

$$\text{PRBC volume} = \frac{\text{Desired PCV } (\%) - \text{Observed PCV}(\%)}{\text{Packed cell volume of transfused blood}(\%)} \times \text{blood volume of the neonate (ml)}$$

The blood volume of the neonate was calculated using Rawlings normogram [9]. Hematocrit of selected blood bag was done using a fully automated cell counter (I.S.E Srl, Italy). PRBC volume was calculated using the formula given above. The calculated volume of PRBC for each group was transferred from mother blood bag to transfer blood bag using a sterile connecting device (T-SCD II Terumo Penpol, Japan).The maximum volume of blood

that was given to the preterm neonate did not exceed 30 mL/kg.

The duration of intervention was the maximum duration of transfusion i.e. 3 h. Extra volume transfused in the form of blood, was adjusted against total fluid, glucose, and electrolytes. All the preterm neonates were followed weekly till discharge to determine the need for subsequent transfusions and the occurrence of morbidities. Hematocrit measurement in both groups before and 24 ± 6 h post-transfusion was done after taking free-flowing venous blood of preterm neonate using capillary tube and results were read on hematocrit reader after subjecting the capillary tube to centrifugation of 10,000 rpm for 10 min. Target hematocrit to be achieved in both groups was taken as 45% in our study.

### Outcome Measures

The primary outcome measure was reaching the target hematocrit level within 24 ± 6 h post-transfusion. Secondary outcome measures were need of re-transfusion within two weeks after the first transfusion, number of donor exposure, need of diuretic during or post-transfusion, oxygen requirement, mean arterial pressure (MAP) before and after transfusion, incidence of mortality and manifestation of complications like transfusion-associated circulatory overload (TACO), NEC, ROP, PVL, IVH.

### Sample size and statistical analysis

To show a difference in hemoglobin and hematocrit of 50%, with ß being 0.1 and being 0.05, a sample size of 68 was calculated. A total of 34 preterm neonates were enrolled in each group. Categorical variables were analyzed using the chi-square test. For nominal data *t*-test was applied. One-way analysis of variance, 2, or Mann–Whitney *U* tests was used as appropriate to compare groups. SPSS software version 22 was used for statistical analysis.

## Results

During the study period, 74 preterm neonates admitted to NICU, ICN and PNW required transfusion. All neonates were assessed for eligibility. Sixty-eight preterm neonates were enrolled as they fulfilled the inclusion criteria (Fig. 1).

Neonatal characteristics in group A and group B were comparable concerning birth weight, gestation age, sex, APGAR score, and SNAP score. (Table 1).

SNAP score indicates a score for neonatal acute physiology including various parameters of newborn recorded within 24 h of birth [10].

Mean pre-transfusion hematocrit (24.9 ± 3.4) of preterm neonates of group A was comparable to that of group B preterm neonates (24.8 ± 2.9). There was no statistical difference in the mean hematocrit of the blood bags transfused to the two groups. Group B preterm neonates were transfused significantly more volume of blood (29.5 ± 7.3 mL vs 18.8 ± 4.9 mL; $p < 0.001$) (Table 2).Short term hemodynamic variables ($FiO_2$, heart rate, blood pressure, respiratory rate and mean arterial pressure) of preterm neonates immediately before and 6 h post-transfusion of both the groups were comparable (Table 3). No change was observed in the mode of ventilation in preterm neonates before and after transfusion. Synchronized intermittent mechanical ventilation (SIMV) was a major mode of ventilation (45.6%) in both the groups.

Group B preterm neonates showed a statistically significant rise in mean hematocrit after 24 ± 6 h of transfusion as compared to group A preterm neonates (Table 4).

16 preterm neonates in group A and 15 in group B needed repeat PRBC transfusions. In all, 15 preterm neonates underwent LASER (light amplification by stimulated emission of radiation) for progression of ROP (6 cases in group A and 9 cases in group B). 4 preterm neonates in group A and 1 in group B showed progression of BPD following blood transfusion. Death was observed in 4 neonates in each group. 4 deaths were attributed to sepsis. 3 preterm neonates died of respiratory distress syndrome (RDS) and 1 baby died of ventilator-associated pneumonia. No death was attributed to participation in the study, or to receiving a blood transfusion.

Incidence and progression of complications like IVH, NEC, PVL and TACO (measured using point of care echocardiography) did not arise in any of the groups following transfusion. Also, there was no need for diuretics during and after transfusion in any preterm neonate.

## Discussion

In this double blind, randomized controlled trial over 18 months, we evaluated the method of calculating PRBC volume to be transfused in preterm neonates using a formula based on hematocrit of blood unit, hematocrit, and blood volume of preterm neonate. We compared the various laboratory and clinical outcomes in two groups of preterm neonates. To the best of our knowledge, this is the first randomized controlled trial comparing the outcome of transfusion of weight-based PRBC volume with formula based volume transfusion in preterm neonates.

In our study, we also observed a statistically significant rise in hematocrit (36.3% vs 39.9%; $p = 0.002$) in a group of preterm neonates who were transfused PRBC volume

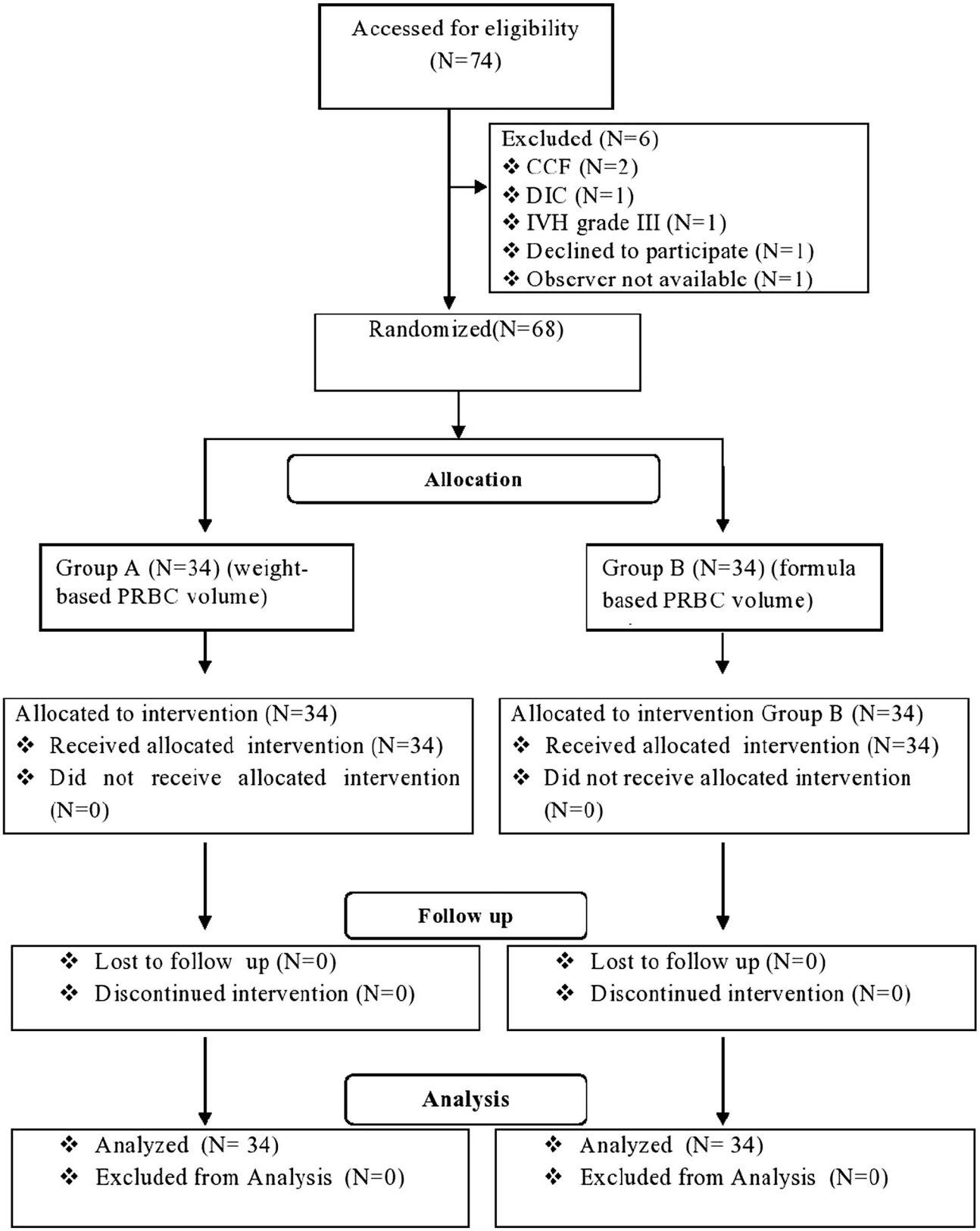


**Fig. 1** Flow chart of study

**Table 1** Neonatal characteristics in group A and group B, $N = 68$

| Characteristics | Group A $N = 34$ | Group B $N = 34$ | $p$-value |
|---|---|---|---|
| Birth weight (grams) | 1212.94 ± 323.74 | 1185 ± 410.34 | 0.76 |
| Gestation age (weeks) | 30.30 ± 1.85 | 30.19 ± 1.80 | 0.80 |
| Male sex | 15 (44.1%) | 18 (52.9%) | 0.47 |
| Immediate cry at birth | 19 (55.9%) | 21 (61.8%) | 0.62 |
| Regular respiration at birth | 19 (55.9%) | 22 (64.7%) | 0.46 |
| APGAR score (1 min) | 6* (3,9) | 5.5* (2,9) | 0.06 |
| APGAR score (5 min) | 7* (5,9) | 7* (5,9) | 0.37 |
| SNAP score | 26.29 ± 9.23 | 26.23 ± 11.53 | 0.85 |

Values are expressed in mean ± SD or *median (range) and $n$ (%). $p < 0.05$ – significant

**Table 2** Hematocrit of preterm neonates, hematocrit of blood bag and volume transfused

| Parameter | Group A ($N = 34$) | Group B ($N = 34$) | $p$ value |
|---|---|---|---|
| Pre-transfusion hematocrit of preterm neonates (%) | 24.9 ± 3.4 | 24.8 ± 2.9 | 0.88 |
| The hematocrit of blood bag (%) | 66.6 ± 3.9 | 67.4 ± 3.7 | 0.37 |
| Volume transfused (ml) | 18.8 ± 4.9 | 29.5 ± 7.3 | < 0.001 |

Values are expressed in mean ± SD. $p < 0.05$ – significant and (*) is a statistically significant value

**Table 3** Haemodynamic variables of preterm neonates

| Variable | Group A ($N = 34$) | | Group B ($N = 34$) | | $p$ value | |
|---|---|---|---|---|---|---|
| | Pre transfusion | Post transfusion | Pre transfusion | Post transfusion | Pre transfusion | Post transfusion |
| FiO2 requirement (%) | 40.3 ± 21.4 | 40.3 ± 21.4 | 34.53 ± 14.6 | 34.5 ± 14.6 | 0.20 | 0.20 |
| Heart rate (per minute) | 155.5 ± 10.6 | 155.5 ± 10.6 | 156.3 ± 9.2 | 156.3 ± 9.2 | 0.74 | 0.40 |
| Systolic blood pressure (mm Hg) | 70.9 ± 14.2 | 70.9 ± 14.2 | 69.4 ± 13.7 | 69.3 ± 13.7 | 0.66 | 0.66 |
| Diastolic blood pressure (mm Hg) | 40 ± 10.6 | 40 ± 10.6 | 41.4 ± 10.6 | 41.4 ± 10.6 | 0.61 | 0.51 |
| Respiratory rate (per minute) | 56 ± 2.3 | 56 ± 2.3 | 55 ± 4.0 | 55 ± 4.04 | 0.20 | 0.18 |
| Mean arterial pressure (mm Hg) | 52 ± 10.3 | 52 ± 10.3 | 49.8 ± 10 | 49.8 ± 10 | 0.37 | 0.96 |

Values are expressed in mean ± SD. $p < 0.05$ – significant

**Table 4** Outcome measures in both groups

| Variables | Group A ($N = 34$) | Group B ($N = 34$) | $p$ value |
|---|---|---|---|
| †Post transfusion rise in hematocrit (%) | † 36.38 ± 4.20 (95% CI 10.3–12.6, 11.5) | †39.88 ± 4.56 (95% CI 13.5–16.6, 15.1) | 0.002* |
| Repeat transfusions | 16 (47%) | 15 (44%) | 0.35 |
| ROP (requiring LASER) | 6 (17.6%) | 9(26.5%) | 0.38 |
| BPD | 4 (11.8%) | 1 (2.9%) | 0.36 |
| Death | 4 (11.8%) | 4 (11.8%) | 1.0 |

(†)Values are expressed in mean ± SD (95% Confidence Interval, mean difference)

All other values are expressed in n (%), $p < 0.05$ – significant and (*) is a statistically significant value

calculated using formula (group B). This could be because of transfusion of higher PRBC volume to this group in comparison to group of preterm neonates receiving weight based calculated PRBC volume (18.8 ± 4.9 m vs 29.5 ± 7.3 mL; $p < 0.001$).Larger volume of PRBC transfusion is associated with more rise in hematocrit [2]. In a study done by Wong et al.significant high post-transfusion hematocrit and hemoglobin values were observed in a group of neonates receiving significantly higher volume of PRBC (20 mL/kg) as compared to individual receiving standard volume (15 mL/kg) of PRBC (132 vs 148, $p < 0.01$). No adverse events were attributed to the use of high volume transfusions. Paul et al. also reported that transfusion of higher volume of PRBC (20 mL/kg) in preterm infants was associated with greater increase hemoglobin and hematocrit levels after transfusion compared with those who received PRBC transfusions of 10 mL/kg [2].

The number of re-transfusions required in our study were not significantly different in the two groups (16 vs 15; $p = 0.35$). Both groups were exposed to a similar number of donors and mean donor exposure in both groups was 1.6, despite transfusion of statistically significant more PRBC volume in group B. Higher volumes failed to reduce the episodes of re-transfusions. Similar results were seen in a study done by Wong et al. where the number of transfusions required was not significantly different between the two transfusion groups of preterm neonates receiving high volume (20 mL/kg) versus standard volume (10 mL/kg) PRBC transfusion respectively [11].

The post transfusion progression of ROP was comparable in the two groups. In a prospective observational cohort study performed by Hesse et al. the relationship between the volume of blood transfusion and the incidence of retinopathy of prematurity was studied in preterm neonates. The study confirmed the role of blood transfusions as an independent risk factor for ROP [12]. In a study done by Cooke et al. same results were seen [13]. However, Brooks at el. reported there was no significant reduction in the incidence of ROP with a more restrictive transfusion policy in preterm neonates [14].

Progression of BPD was also statistically insignificant in both groups, although literature reports the progression of BPD with successive blood transfusions in preterm neonates [15].

None of the preterm neonates in both the groups showed progression of other complications (IVH, PVL, NEC) after PRBC transfusion. There are conflicting results in the literature regarding the effect of blood transfusion on the incidence and progression of these complications. Studies by Baer et al. and Christensen et al.demonstrated the correlation between RBC transfusion and development of severe IVH (grade 3 and more) [16, 17]. But, "Premature Infants in Need of Transfusion" study demonstrated no association between IVH and transfusion policy used for such patients [18].

So still there is paucity in literature regarding the exact relationship between the volume of blood transfused and the development of these complications. Also, none of the studies in literature have ever compared the outcomes of all these transfusion-related complications among two groups of preterm neonates who are given random PRBC transfusion based either on the weight of the patient or on hematocrit of blood bag and patient.

The limitation of the study is the small sample size. Moreover, the study is not powered to detect any meaningful differences in the number of re-transfusions/donor exposure and various clinical complications of blood transfusion in preterm neonates.

In conclusion, our study demonstrates that target hematocrit can be achieved in preterm neonates by giving PRBC volumes considering hematocrit of blood bag, hematocrit and blood volume of preterm neonate. But, on the other hand, it also exposes the preterm neonates to a larger volume of PRBC as formula based PRBC volume (group B) was significantly more than PRBC volume calculated using weight (group A). No possible advantage in terms of reducing donor exposure or the number of re-transfusions was observed with formula based calculation of PRBC volume. So, we suggest the transfusion of PRBC volume using conventional volume policy of 15 mL/kg in preterm neonates [19], however, there is a need for large sample size multi-centric studies to explore the ideal PRBC volume to be transfused and its effect on various clinical outcomes in preterm neonates.

## Author Contributors Statement

Suksham Jain and Ravneet Kaur Bedi designed the study, Suksham Jain and Deepak Chawla are clinicians involved in the study. Rajbir Kaur Cheema conducted the study and collected data under the supervision of the rest of the authors. The manuscript was drafted by Rajbir Kaur Cheema and finalized by Ravneet Kaur Bedi and Suksham Jain.

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**Declarations**

**Conflict of interest** The authors declare no conflict of interest.

**Statement of Ethics** The study protocol numbrt EC/2016/0042 was approved by local institutional ethics committee of human research.

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