Red Cell Transfusion Practices in Neonatal Intensive Care Unit: An Experience from Tertiary Care Centre

Kanchan Dogra¹ · Gagandeep Kaur² · Sabita Basu³ · Deepak Chawla⁴

Received: 19 December 2017 / Accepted: 7 April 2018 / Published online: 12 April 2018
© Indian Society of Hematology and Blood Transfusion 2018

Abstract Red cells are the most often transfused blood components during the neonatal period. The aim of the present study was to obtain information regarding the relationship of red cell transfusion with clinical outcomes and to evaluate red cell transfusion practices in neonatal centre of a tertiary care centre. The clinical history, blood component details and laboratory parameters were evaluated with clinical outcomes. The neonates requiring transfusion of red cells were then followed up in the Blood bank for various laboratory parameters. Clinical parameters and clinical outcome were noted from case files. During the study period, 291 neonates were admitted in NICU. 2 neonates were excluded as they were congenitally malformed. Out of 289 admitted neonates, 61 neonates (21.1%) received blood and blood component transfusions. Out of 61 neonates, 20 received red cell transfusions. Mean donor exposure of red cells was 1.2. The mean volume of transfused red cell was 39.6 ml with mean age of red cells

was 3.6 days. The mean pre- and post-transfusion Hct was 25.3 and 30.4%, respectively. The most common indication for red cell transfusion was low haemoglobin. There was a significant increase in lactate level and decrease in base excess in transfused neonates. However, no statistically significant correlations were found between transfusions and neonatal weight gain, apnoea, respiratory support and mortality. Transfusion of red cells has significant effect on laboratory parameters as compared to clinical parameters such as weight gain, episodes of apnoea and respiratory support.

Keywords Red cell transfusions · Neonatal intensive care unit · Clinical outcome

Introduction

Transfusion practice in neonates differs from that in adults. During the transition from a foetus to a neonate, several physiologic changes occur, involving blood volume, haematologic parameters and other organ systems in the neonate. In preterm neonates, there is lack of development and adaptation to extra-uterine life that leads to diminished capacity of neonate to produce red cells, platelets and neutrophils, especially during periods of stress. The blood volume in a full term new born is approximately 85 ml/kg, while that in a preterm new born is about 100 ml/kg and that in an adult is about 70 ml/kg [1, 2]. The small blood volume and immature organ systems in the neonate necessitate special approaches in neonatal transfusion practice.

Physiological causes for the anaemia of prematurity include; (1) diminished erythropoietin secretion (2) decrease in survival of foetal red cells (3) increasing blood

✉ Gagandeep Kaur
docvpsingh@yahoo.co.in

Kanchan Dogra
galaxxyy@gmail.com

Sabita Basu
drsabitabasu@gmail.com

Deepak Chawla
drdeepakchawla@gmail.com

¹ Department of Transfusion Medicine, AIIMS, New Delhi, India

² Department of Transfusion Medicine, GMCH, Sector-32, Chandigarh, India

³ Department of Transfusion Medicine, Tata Medical Center, Kolkata, India

⁴ Department of Paediatrics, GMCH, Chandigarh, India

volume due to rapid growth. This is usually self-limited and well tolerated; however in certain situations like blood loss due to repeated phlebotomy, sepsis and severe anaemia, intervention may be required in the form of transfusion of blood and blood components [1].

The most commonly used blood components in neonates are red blood cells. Red cell transfusion could be exchange transfusion for hyperbilirubinemia, or top-up transfusion for correction of anaemia. Red cell transfusions are given to maintain the haematocrit (Hct) at a level judged best for the clinical condition of the infant [3]. Several guidelines have been published over the last two decades for red blood cell transfusion in neonates [4–6]. Most of the recommendations are based on clinical experience rather than on evidence. Although clinical trials have been conducted in the past, they are not mutually supportive and questions still remain. An unresolved controversy is the use of restrictive guidelines (low pre-transfusion Hct) versus liberal guidelines (high pre-transfusion Hct) for red cell transfusions [4, 5].

Hence, due to the physiological changes occurring in the neonatal period, transfusion of blood and blood components in neonates requires special considerations. Though neonatal transfusion guidelines exist, many issues pertaining to transfusion triggers, dosage and clinical outcomes still remain debatable. There are no similar kind of published Indian studies describing neonatal transfusion practice. The aim of this study was to get an insight into the laboratory parameters and clinical outcomes in neonatal transfusion practice.

Materials and Methods

This prospective cohort study was conducted by Department of Transfusion Medicine in collaboration with the Department of Paediatrics over a period of 18 months from 1st November, 2011 to 30th April, 2013. The study was undertaken with approval by the Institute Ethics Committee, after obtaining written informed consent. All newborns admitted to Neonatal intensive care unit (NICU) were included in the study after taking into consideration the inclusion and exclusion criteria as described below.

Inclusion criteria

- Gestation at birth ≥ 26 completed weeks.
- Birth weight ≥ 700 g.
- Duration of stay in NICU > 6 h

Exclusion criteria

Major congenital malformation.

Methodology

The clinical history, blood product details, laboratory parameters and clinical outcomes were evaluated.

The neonates requiring transfusion of red cells were then followed up in the Blood bank for various laboratory parameters. Clinical parameters and clinical outcome were noted from case files.

Laboratory Parameters

The requisition for red blood cells was assessed for product type i.e. whether whole blood, packed red blood cells (PRBC) or saline adenine glucose mannitol (SAGM) red cells. In addition, the indications for transfusion were assessed i.e. anaemia, exchange transfusion, sepsis or other indications.

- The requisition was assessed for product details i.e. volume of the product, age of the unit, and product blood group. In addition, pre- and post-transfusion serum bilirubin, pre- and post-transfusion Hct and total number of donor exposures were also noted.

Clinical parameters

All neonates receiving red cell transfusions were assessed for general clinical parameters i.e. gestational age (GA) at birth and birth weight. In addition, APGAR score at 1 and 5 min; and growth status whether appropriate for gestational age, low for gestational age or large for gestational age were assessed.

- Subjects in need of red cell transfusion were also assessed for indication for admission whether prematurity, respiratory distress, jaundice or suspected sepsis. Morbidities like respiratory distress syndrome, intraventricular haemorrhage, bronchopulmonary dysplasia and retinopathy of prematurity were also noted.
- The other observations noted were requirement of Continuous positive airway pressure (CPAP) and/or ventilation and number of exchange transfusions. Adverse reactions to the transfusion, whether febrile, allergic, circulatory overload or other type of reaction were also noted. General parameters of subjects were assessed for outcome of admission whether discharged, referred to other hospital or died.

Observations after red cell transfusion

- PRBC transfusion was assessed before and after transfusion for mode of respiratory support i.e. whether Oxygen, CPAP or ventilation. Episodes of apnoea and base excess were also noted from the cardiopulmonary monitor. In addition, Fraction of inspired Oxygen (FiO_2), lactate and average weight gain were also noted.
- Subjects in need of PRBC transfusion were assessed for respiratory distress, Hct and packed cell volume transfused and pre- and post-transfusion details were also noted.

Statistical Analysis

The various laboratory and clinical parameters were analysed and correlated statistically for red cells transfusions. For all quantitative variables, mean, median and standard deviation were calculated. Means were compared using paired or unpaired Student's *t*-test for the two groups, i.e., transfused patients and non-transfused patients, and pre-transfusion and post-transfusion: laboratory and clinical parameters. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared using Chi square test. Statistical tests were performed at a significance level of $p \leq 0.05$.

Results

During the study period, 291 neonates were admitted in NICU. 2 neonates were excluded as they were congenitally malformed. Out of 289 admitted neonates, 61 neonates (21.1%) received blood and blood component transfusions. Only 20 (32.7%) neonates received 25 PRBC transfusions. Total donor exposure of 20 neonates was 1.2. The APGAR score for neonates ranged from 2–9 at 1 min and 5–9 at 5 min.

The neonates, who were transfused, belonged to age group ranged from 27 to 41 weeks of GA. The mean age was 32.4 ± 3.4 weeks of GA. Neonates with GA less than 37 weeks were 19, who received total 24 transfusions and those with GA more than 37 weeks was 1, who received only 1 transfusion.

The birth weight of neonates who received PRBC transfusion ranged from 750 g to 2300 g with mean birth weight was 1374 ± 390.9 g. Neonates with birth weight less than 1500 g were 15, who received total 19 transfusions while those with birth weight more than 1500 g were 5, who received total 6 transfusions. Neonates who were premature and weight less than 1500 g required more number of transfusions ($p < 0.05$).

The main indication for red cell transfusion was shown in Table 1. The mean volume of transfused red cell was

Table 1 Indication for PRBC transfusion

Indication	No. of neonates
Anemia	15
Bleeding	2
Shock	2
NNJ	1

39.6 ± 57.55 ml and stratification of neonates w.r.t. volume of RBC transfused was shown in Fig. 1. The mean age of red cells was 3.6 ± 1.7 days. The mean pre transfusion Hct was $25.3 \pm 4.4\%$ and the post transfusion Hct was $30.4 \pm 4.6\%$ ($p < 0.05$).

The mean pre-transfusion FiO_2 and post transfusion FiO_2 was $55.3\% \pm 16.8$ and $68.8\% \pm 16.5\%$ respectively. The difference was statistically significant i.e. FiO_2 demand was increased significantly ($p < 0.05$) after transfusion. We did not find statistically significant ($p > 0.05$) relationship of mode of respiration with transfusion.

The pre-transfusion lactate levels ranged 2.20–10.3 mmol/l with mean of 5.6 ± 2.1 mmol/l. The post-transfusion lactate levels ranged 2.3–10.2 mmol/l with mean of 6.3 ± 2.4 mmol/l. The mean difference between post-transfusion and pre-transfusion lactate levels was significant ($p < 0.05$) i.e.; after transfusion lactate level was increased. The pre-transfusion base excess value -9.3 ± 3.3 mmol/l and post-transfusion -13.4 ± 10.2 mmol/l in neonates ($p < 0.05$).

The mean weight gain per neonate per week before red cell transfusion was 6.3 ± 12.8 g/week. The mean weight gain after red cell transfusion was 7.3 ± 21.2 g/week. The difference of weight gain per week before transfusion and after transfusion was not significant ($p > 0.05$).

Episodes of apnoea were assessed before and after 24 h of transfusion. 4 neonates experienced episodes of apnoea before transfusion. Out of these 4 neonates, 3 neonates still had episodes of apnoea even after transfusion. Hence, we could not find any relationship of apnoea with transfusion.

Out of 15 neonates who were on nasal cannula ($n = 4$), CPAP ($n = 9$) or room air ($n = 2$), only 1 required more

Fig. 1 Volume of red cells transfused (ml/kg)

respiratory support after transfusion (CPAP advanced to mechanical ventilation) and 14 remained in same mode of respiratory support. For infants already receiving mechanical ventilation ($n = 4$), 3 remained on the same mode of support and only 1 did not required mechanical ventilation. The neonatal transfusions bore no statistically significant relationship with the CPAP ($p > 0.05$).

Of the 20 neonates who received PRBC transfusions, 10 (50%) neonates expired and 10 (50%) neonates were discharged. Out of these 10 expired neonates, only one neonate received more than one transfusion and 9 received only one time transfusion. We could not find any association between mortality and number of transfusions ($p > 0.05$).

There were no incidences of any transfusion reactions in any of the neonates during the study period. None of the neonates enrolled in this study underwent any exchange transfusions as the only neonate with NNJ (treated with photo-therapy) received a top-up PRBC transfusion only.

Discussion

During initial weeks of infancy, red cell transfusions are frequently indicated to correct anaemia which thereby improves oxygen support and cardio-respiratory status. In our study, 21.7% (61/289) of patients received transfusion of either single component or more than one component. A total of 32.7% (20/61) neonates received PRBC transfusions and 75% received 15 ml to 25 ml of PRBC. The incidence of transfusions as reported by Portugal et al. [7] was 20.9%. The incidence of transfusions found in our study was very low as compared to 55.9% in Santos et al.; 85% and 90% in studies by Fabres et al. and Valieva et al., respectively [8–10]. The difference could be explained by the fact that their study included only very low birth weight infants.

On analysing the most commonly reported indication to red cell transfusions was anaemia followed by sepsis and shock. The most common reason for red cell transfusion reported by Portugal et al. [7] was sepsis and prematurity. While Kasat et al. [11] described the most common indication as desaturation episodes, tachycardia, pallor and apnoea.

In our study, 20% (4/20) neonates received multiple PRBC transfusions. Santos et al. and Portugal et al. reported that over half of neonates received more than one transfusion during their hospital stay [7, 8]. The most recent publication of Santos et al. [12] reported higher number of transfusions.

We found a lower mean number of transfusions per newborn (1.2) than what is reported in literature. Portugal et al. reported mean number of transfusions per newborn was 2.27 ± 2.16 [7]. The mean number of transfusions per

new born in liberal group was 1.59 ± 1.63 and in the restrictive group was 1.08 ± 1.51 . As the mean number of transfusion per newborn were approximately the same in their study, hence they concluded that the option to transfuse using restrictive criteria does not reduce the number of transfusions per new born. Bell et al. also reported higher incidence of intra-ventricular haemorrhages and more apnoea for a restrictive group [5]. There are no other studies reporting a higher incidence of death when using restrictive transfusion regimens. Kirpalani et al. [4] showed that maintaining a higher haemoglobin level in ELBW babies results in more number of infants receiving transfusions without any additional benefit. These same authors followed up the neurodevelopment outcome of this cohort of preterm at 18 and 21 months and concluded that there was no statistically significant difference in the combined death or severe adverse neurodevelopmental outcome between the restrictive and the liberal transfusion groups.

The most frequently transfused neonates were between 31 and 35 weeks of gestation closely followed by those between 27 and 30 weeks of gestation and those less than 1500 g closely followed by those weighing 700–1000 g. Thus, a gestational age of less than 35 weeks and weight of less than 1500 g are the major risk factors for transfusion. Conti et al. [13] also reported that the most heavily transfused neonates were between 24 and 29 weeks of gestation and less than 1000 g.

When we examined the relationship between transfusions and weight gain, the average weight gain per week was not significant between pre- and post-transfusion period. There was also no difference in the mean weight gain per day between the transfused and non-transfused groups. Stockmann et al. [6] reported improvement in weight gain after transfusion and was greatest when the pre transfusion Hb was less than 7.5 g/dl. Improvements in weight gain were associated with a decrease in metabolic rates as determined by declines in oxygen consumption while Valieva et al. [10] did not report average weight gain per week being significant after transfusion.

FiO₂ significantly changed after transfusion in our study ($p < 0.05$). No significant change in FiO₂ was reported in both liberal (32%) and restrictive (31%) group after transfusion by Fredrickson et al. [14].

Serum lactate levels can be an additional laboratory indicator of impaired oxygenation, as it correlates significantly with oxygen delivery. A significant lower oxygen delivery in patients in whom blood transfusion is indicated and an increase in oxygen induced by transfusion demonstrates the value of these criteria in identifying preterm infants who benefit from transfusion. In our study, the average pre-transfusion and post-transfusion lactate was 5.6 ± 2.4 and 6.3 ± 2.4 mmol/l. We observed that there was an increase in lactate levels. In contrast to our study,

Fredrickson et al. found that blood lactic acid level was significantly lower following transfusion in restrictive as well as liberal group groups, suggesting that tissue hypoxia may have been present before transfusion [14]. The average pre-transfusion level in both groups was 1.1 and post-transfusion level in both groups was 0.9 and 0.7 mmol/l respectively. We could not correlate blood lactate levels as an indicator of impaired oxygenation. However, we did find a significant lowering of base excess values in relation to PRBC transfusions in neonates.

Apnoea and respiratory pauses during neonatal period is generally ascribed to unstable respiratory control. Two proposed mechanisms may underlie the beneficial effect of RBC transfusions on intermittent hypoxia (IH). The first suggests that anaemia decreases oxygen delivery to the respiratory control network leading to hypoxic ventilator depression. Thus, RBC transfusions may decrease apnea frequency by improving oxygen delivery to the immature brainstem. The second underlying mechanism is that RBC transfusions increase oxygen stores resulting in greater stability of oxygenation in the presence of apnea. Our study did not demonstrate significant effect of RBC transfusion on apenic episodes. Jawdeh et al. in a recent report concluded that the benefit of RBC transfusion on intermittent hypoxemia is age dependent as improvement in the frequency and severity of IH after transfusion only occurs beyond the first week of life and these observations may aid clinicians by clarifying the benefit of RBC transfusions on patterns of oxygenation in preterm infants [15]. Zagol et al. showed sustained improvement in apnea associated with oxygen desaturation after RBC transfusions [16]. Joshi et al. found that the duration of periodic breathing decreased significantly after transfusion, as did the duration of the longest periodic breathing episode [17]. In contrast, Westkamp et al., Poets et al. and Valieva et al. found no change in the incidence of IH events post RBC transfusion [10, 18, 19].

The present study found no difference in respiratory support after transfusion ($p > 0.05$). Valieva et al. also found that respiratory support modes did not change significantly after transfusion, although the percent of patients requiring mechanical ventilation and oxygen supplementation increased after PRBC transfusions [10].

No neonate underwent exchange transfusion rather received a top-up PRBC transfusion for anaemia management; as the neonate admitted with NNJ was managed with phototherapy only. The transfusions were administered to neonates with no reported occurrences of adverse reactions which may be attributed to chance only and may also be due to the small study population.

The present study has its own limitations. The study had a very small sample size and various confounding factors. In our NICU, restrictive policy was used for red cell

transfusion in most of neonates, so we could not compare the mean number of transfusions per infant with liberal group. The study design didn't have any neonatal follow-up protocol as a result of which we failed to obtain the long-term adverse effects of neonatal RBC transfusions. This study has its own strength as it was a prospective study as most of literature was based on retrospective study. Thus, the results from this study give additional insight on transfusion practices of neonates admitted in NICU. However, still further studies are required to have better insight of the long term effects of PRBC transfusions on neonates.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical Approval Institutional. All procedures performed in studies involving human participants were in accordance with ethical standards of the institution committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individuals.

References

1. Josephson CD (2008) Neonatal and pediatric transfusion practice. In: Roback JD, Combs MR, Grossman BJ, Hillyer CD (eds) AABB technical manual, 16th edn. AABB Press, Bethesda, pp 640–641
2. Pescod D (2011) Haemorrhage [cited on 16 May 2005]. <http://www.developinganaesthesia.org>. Accessed 7 Oct 2011
3. Strauss RG (2001) Managing the anemia of prematurity. Red blood cell transfusions versus recombinant erythropoietin. *Transfus Med Rev* 15:213–223
4. Kirpalani H, Whyte RK, Anderson C, Asztalos EV, Heddle N, Blajman MA et al (2006) The premature infants in need of transfusion (PINT) study: a randomised, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr* 149:301–307
5. Bell EF, Strauss RG, Widness JA, Mahoney LT, Mock DM, Seward VJ et al (2005) Randomised trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. *Pediatrics* 115:1685–1691
6. Stockman JA, Graeber JE, Clark DA, McClellan K, Garcia JF, Kavey RE et al (1984) Anemia of prematurity: determinants of the erythropoietin response. *J Pediatr* 105:786–792
7. Portugal CAA, de Paiva AP, Feire ES, Chaoubah A, Duarte MC, Neto AEH (2014) Transfusion practices in a neonatal intensive care unit in a city in Brazil. *Rev Bras Hematol Hemoter* 36:245–249
8. Santos AM, Guinsburg R, Procianny RS, Sadeck LS, Netto AA, Rugolo LM et al (2010) Variability on red cell transfusion practices among Brazilian neonatal intensive care units. *Transfusion* 50:150–159
9. Fabres J, Wehrli G, Marques MB, Philips V, Dimmitt RA, Westfall AO et al (2006) Estimating blood needs for very low birth weight infants. *Transfusion* 46:1915–1920

10. Valieva OA, Strandjord TP, Mayock DE, Juul SE (2009) A retrospective study: effects of transfusion in extremely low birth weight infants. *J Pediatr* 155:331–337
11. Kasat K, Hendricks- Munoz KD, Mally PV (2011) Neonatal red cell transfusions searching for better guidelines. *Blood Transfus* 9:86–94
12. Santos AM, Guinsburg R, Prociandy RS, Sadeck LS, Netto AA, Rugolo LM et al (2010) Red cell transfusions are independently associated with intra-hospital mortality in very low birth weight preterm infants. *J Pediatr* 159:371–460
13. Conti VS, Azzopardi E, Parascandalo R, Soler P, Montalto SA (2013) Overview of blood transfusion policy in preterms on neonatal intensive unit care unit. *Malta Med J* 25:46–50
14. Fredrickson LK, Bell EF, Strauss RG (2011) Acute physiological effects of packed blood cell transfusion in preterm infants with different degrees of anemia. *Arch Dis Child Fetal Neonatal* 96(4):249–253
15. Jawdeh EGA, Martin RJ, Dick TE, Walsh MC, Di Fiore JM (2014) The effect of red blood cell transfusion on intermittent hypoxemia in ELBW infants. *J Perinatol* 34:921–925
16. Zagol K, Lake DE, Vergales B, Moorman ME, Paget-Brown A, Lee H et al (2012) Anemia, apnea of prematurity, and blood transfusions. *J Pediatr* 161(417–421):e411
17. Joshi A, Gerhardt T, Shandloff P, Bancalari E (1987) Blood transfusion effect on the respiratory pattern of preterm infants. *Pediatrics* 80:79–84
18. Poets CF, Pauls U, Bohnhorst B (1997) Effect of blood transfusion on apnoea, bradycardia and hypoxaemia in preterm infants. *Eur J Pediatr* 156:311–316
19. Westkamp E, Soditt V, Adrian S, Bohnhorst B, Groneck P, Poets CF (2002) Blood transfusion in anemic infants with apnea of prematurity. *Biol Neonate* 82:228–232