Blood Component Transfusion in Tertiary Care Neonatal Intensive Care Unit and Neonatal Intermediate Care Unit: An Audit

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Abstract

Background

Neonates admitted in a tertiary neonatal intensive care unit (NICU) require multiple blood transfusions because of extended NICU stay and repeated sampling. The rookie organ systems and minute blood volumes in the neonate call for regular audits in neonatal blood transfusion practice. Sharing component usage data with the blood bank will prepare them to store components according to demand, thus limiting wastage of components as well as make banks ready to face a shortage in case of ramped up requirements.

Objective

Auditing neonatal blood transfusion indications and identifying the most commonly used component.

Methodology

This retrospective cohort study was conducted by the department of pediatrics over 22 months from February 20, 2017, to December 30, 2018. Any preterm and term neonates admitted to the NICU and Neonatal Intermediate Care Unit (NICU) and receiving any transfusion, i.e., fresh frozen plasma (FFP), red cell concentrate (RCC), platelets, and exchange transfusion were included in our study. We collected data from the medical records of NICU and NICU admitted patients receiving blood component transfusions from 2011 to 2016. Patients were categorized according to the classification of neonatal conditions by the International Classification of Diseases 11th Revision (ICD-11). There were no exclusion criteria. A descriptive statistical analysis was done, and a Chi-square test was applied.

Results

Out of 340 neonates, 249 (73.2%) were low birth weight, 139 (40.9%) were small for gestational age (SGA), and 277 (81.5%) neonates required transfusion during the first week of life. The majority of neonates require multiple transfusions. Fourteen (4.12%) neonates required up to 10 transfusions, two neonates required up to 22 transfusions, and 58 neonates required more than five blood transfusions. The majority required transfusion due to neonatal sepsis, Disseminated intravascular coagulopathy, low birth weight, respiratory distress syndrome, and unconjugated hyperbilirubinemia. Thirty-seven point eighty-two percent (37.82%) transfusions were fresh frozen plasma, 31.34% transfusions were red cell concentrate, 28.14% transfusions were platelet concentrate, and 2.70% were whole blood. Out of 340 neonates, 317 survived and were discharged.

Conclusion

The most commonly transfused component was fresh frozen plasma, the indication was neonatal sepsis, and the group was preterm. Whole blood is still being used and needs to be stopped.

Introduction

Neonates admitted in a tertiary neonatal intensive care unit (NICU) require multiple blood transfusions as a consequence of extended NICU stay and repeated sampling. Neonate refers to an infant in the first 28 days after birth. A neonate's blood volume is tiny compared to the large transfusion bags they frequently receive [1]. For a 2.5 kg neonate, the total blood volume is approx 210 ml [2]. Multiple physiological changes occur
when a fetus becomes a neonate. These changes refer to an alteration in their blood volume, hematological parameters, and other body systems. Stress to adapt in an extrauterine environment leads to a blunted capacity of premie to produce erythrocytes, thrombocytes, and immune cells, i.e., neutrophils. The blood volume in a full-term newborn is approximately 85 ml/kg while that in a preterm newborn is about 100 ml/kg and that in an adult is about 70 ml/kg. The miniature blood volume and rookie organ systems in the neonate call for novel proposals in neonatal blood transfusion practice. The physiological puerility of different organ systems can put at peril those very low birth weight babies (VLBW) to metabolic imbalance following transfusion and their additives, and infectious and immunological hazards such as graft-versus-host disease (GVHD). However, with advanced transfusion medicine, the risk of getting infectious diseases and other adverse events related to blood transfusion is reduced significantly. Neonates are often transfused based on expert clinical opinion rather than specific documented guidelines. Lack of statistically valid clinical trials put neonatal transfusion practice in controversy. This study aims to delineate the neonatal blood transfusion indications and the most commonly used component. Sharing of component usage data with the blood bank will prepare them to store components according to demand, thus limiting the wastage of components as well as make banks ready to face a shortage in case of ramped up requirements.

Materials And Methods
This retrospective cohort study was conducted over 22 months from February 20, 2017, to December 30, 2018. The study was undertaken with approval by the Institute Ethics Committee. Any preterm and term neonates admitted to the NICU and NIMC at Shree Krishna Hospital, who received any transfusion, i.e., fresh frozen plasma (FFP), red cell concentrate (RCC), platelet concentrate (PC), and exchange transfusion, is included in our study. We have collected data from the medical records of NICU and NIMC admitted patients receiving blood component transfusions from 2011 to 2016. Table 1 shows the case study form used for data collection. Patients were categorized according to the classification of neonatal conditions by the International Classification of Diseases 11th Revision (ICD-11) [7]. There are no exclusion criteria. The analysis was done by descriptive statistics with the chi-square test.

| Serial No. | Blood Group of neonates |
|------------|-------------------------|
| Name of Patient | Blood group of mothers |
| Age (in days) | Diagnosis |
| Gender | Blood component used (RCC/FFP/Platelet Concentrate/Exchange Transfusion) |
| Religion | Histogram and differential count: pre-transfusion and post-transfusion |
| Hospital No. | Volume transfused (approximately) |
| Date of Admission | The time between birth & transfusion received/day of transfusion |
| Type of Delivery | Complication due to transfusion |
| Birth Weight | Previous blood transfusion history |
| Preterm (<37 weeks)/Full term | Maternal diseases during pregnancy |

TABLE 1: Case study form

Results
We studied a total of 340 neonates, 256 (75.3%) were male and the rest were female. Out of 340 neonates, 249 (73.2%) were low birth weight. Two-hundred eighty-three (283; 83.2%) belonged to the Hindu community, which is predominant in the Anand locality. Two-hundred fifty (205; 60.3%) delivered via spontaneous vaginal delivery, whereas 135 (39.7%) delivered by cesarean section. The blood group of neonates was as follows: B+ 110 (32.4%) > O+ 109 (32.1%) > A+ 76 (22.4%) > AB+ 27 (7.9%), and the rest 18 neonates had a negative blood group. Twenty-one (6.2%) were twin pregnancies, and 319 (93.8%) were a singleton pregnancy. Three-hundred thirty-eight (338; 99.4%) cried immediately after birth. Three-hundred thirty-five (335; 98.5%) were delivered at the hospital. Two-hundred one (201; 59.1%) neonates were appropriate for gestational age (AGA), and 139 (40.9%) were small for gestational age (SGA). Out of 249 patients, 33 (9.7%) were extremely low birth weight, 77 (22.6%) were very low birth weight, and 139 (40.9%) were low birth weight. Two-hundred seventy-seven (277; 81.5%) neonates require transfusion during the first week of life. The majority of neonates require multiple transfusions. Fourteen (4.12 %) neonates required up to 10 transfusions, two neonates required up to 22 transfusions, and 58 neonates require more than five blood transfusions. Fifteen (15) out of 53 extremely low birth weight babies required ≥ five transfusions, 40 out of 139 low birth weight neonates required ≥ five transfusions, and 18 term neonates...
required ≥ five transfusions. A statistically significant correlation is found between neonatal birth weight and multiple transfusion needs (p = 0.01). Low birth weight neonates required more transfusions. The majority required transfusion due to neonatal sepsis, disseminated intravascular coagulopathy, low birth weight, respiratory distress syndrome, and unconjugated hyperbilirubinemia. No transfusion-related complications were observed in our study. Three-hundred seventy-nine (379) bags of fresh frozen plasma, 314 bags of red cell concentrate, 282 bags of platelet concentrate, and 27 bags of whole blood were transfused. Out of a total of 1002 transfusions, 37.82% transfusions were fresh frozen plasma, 31.34% transfusions were red cell concentrate, 28.14% transfusions were platelet concentrate, and 2.70% were whole blood. Out of 340 neonates, 317 survived and were discharged.

Out of 340 neonates, 240 neonates received fresh frozen plasma (Figure 1). The pre-transfusion and post-transfusion comparison show significant improvement in neonates. Post-transfusion increase in hemoglobin, hematocrit, and platelet count was noted. Post-transfusion decrease in coagulation parameters was noted. Transfusion data for all of the components yielded a statistically significant result (Table 2).

**FIGURE 1**: Graph showing the proportion of neonates who received component transfusion

RCC = Red Cell Concentrate, FFP = Fresh Frozen Plasma, PC = Platelet Concentrate
### TABLE 2: Changes in hematological parameters before and after blood transfusion

*values in ×1,00,000

| Component name                  | No. of neonates | Mean  | SD    | P-value   |
|---------------------------------|----------------|-------|-------|-----------|
| Hemoglobin before giving RCC    | 154            | 12.35 | 3.65  | <0.001    |
| Hemoglobin after giving RCC     | 154            | 14.14 | 2.78  |           |
| Hematocrit before giving RCC    | 154            | 37.51 | 10.60 | <0.001    |
| Hematocrit after giving RCC     | 154            | 42.43 | 8.45  |           |
| Platelet count before giving PC | 105            | 0.96* | 0.95  | 0.004     |
| Platelet count after giving PC  | 105            | 1.36* | 1.26  |           |
| Hemoglobin before giving WB     | 22             | 12.95 | 3.42  | >0.05 (0.770) |
| Hemoglobin after giving WB      | 22             | 13.55 | 2.22  |           |
| PT before giving FFP            | 189            | 33.74 | 15.77 | <0.001    |
| PT after giving FFP             | 189            | 18.7  | 8.8   |           |
| aPTT before giving FFP          | 231            | 81.67 | 30.04 | 0.002     |
| aPTT after giving FFP           | 231            | 39.43 | 24.54 |           |
| INR before giving FFP           | 222            | 2.74  | 1.28  | <0.001    |
| INR after giving FFP            | 222            | 1.61  | 0.71  |           |

Infections of the newborn is the category consuming the most red cell concentrate, fresh frozen plasma, and whole blood, whereas, hemorrhagic or hematologic disorders of the newborn received the most platelets (Table 3). Although the number of neonates receiving transfusions is higher, the analysis done in Table 3 only includes those neonates whose pre-transfusion and post-transfusion laboratory parameters were available.
TABLE 3: Classification of neonatal conditions according to ICD-11 and requirement of blood components

| Broad diagnostic categories | Sub-categories | No. of patients receiving blood products |
|-----------------------------|----------------|-----------------------------------------|
| A) Certain conditions originating in the perinatal period | Low birth weight | 116 |
| a) Disorder of newborn related to the length of gestation or fetal growth | Very low birth weight | 59 |
| | Extremely very low birth weight | 31 |
| | Intrauterine growth retardation | 4 |
| | Respiratory distress syndrome | 93 |
| | Birth asphyxia | 78 |
| | Apnea of newborn | 44 |
| | Neonatal aspiration of meconium | 29 |
| b) Respiratory disorder specific to the neonatal period | Pulmonary hemorrhage | 11 |
| | Pneumothorax | 11 |
| | Pneumonia | 10 |

In our study, the top five conditions chewing blood products are sepsis (293), low birth weight (116), respiratory distress syndrome (95), neonatal hyperbilirubinemia (85), and disseminated intravascular coagulopathy (50) (Table 4).
| Category                                                                 | Condition                          | Frequency |
|------------------------------------------------------------------------|------------------------------------|-----------|
| Bronchopulmonary dysplasia                                             | 5                                  |
| Transient tachypnoea of the newborn                                    | 2                                  |
| c) Cardiovascular disorder present in the neonatal period              | Persistent pulmonary hypertension of the newborn | 40        |
| d) Hemorrhagic or hematological disorders of newborn                    | Neonatal hyperbilirubinemia       | 85        |
|                                                                         | Disseminated intravascular coagulopathy | 50        |
|                                                                         | Anemia of prematurity              | 28        |
|                                                                         | Intracerebral hemorrhage           | 9         |
|                                                                         | Blood incompatibility              | 6         |
|                                                                         | Acute bilirubin encephalopathy(kemicterus) | 6         |
|                                                                         | Intraventricular hemorrhage        | 6         |
|                                                                         | Vitamin k deficiency               | 5         |
|                                                                         | Hypoglycemia                       | 22        |
| e) Transitory endocrine or metabolic disorders specific to newborn     | Electrolyte imbalance              | 18        |
|                                                                         | Hyperglycemia                      | 6         |
|                                                                         | Metabolic acidosis                 | 4         |
| f) Disturbances of temperature regulation of newborn                   | Hypothermia                        | 8         |
| g) Infections of the newborn                                           | Sepsis                             | 293       |
|                                                                         | Meningitis                         | 32        |
| h) Neurologic disorders specific to the perinatal or neonatal period   | Hypoxic ischemic Encephalopathy    | 76        |
|                                                                         | Neonatal Seizures                  | 12        |
| i) Digestive system disorders of the fetus or newborn                  | Gastro-oesophageal reflux disease  | 4         |
|                                                                         | Intestinal perforation             | 3         |
|                                                                         | Necrotizing enterocolitis          | 2         |
| j) Certain Disorders originating in the perinatal period; unspecified  | Underfeeding of newborn            | 12        |
|                                                                         | Failure to thrive                  | 6         |
|                                                                         | Birth depression                   | 5         |
| k) Genitourinary system disorders specific to the perinatal or neonatal period | Acute Renal Failure               | 37        |
| B) Diseases of the visual system                                       | a) Retinopathy of prematurity      | 10        |
| C) Symptoms, signs or clinical findings, not elsewhere classified      | a) Multi-organ failure             | 11        |
| D) Developmental anomalies                                             | a) Septal defects                  | 26        |
|                                                                         | b) Patent ductus arteriosus        | 16        |
|                                                                         | c) Imperforate anus                | 2         |
|                                                                         | d) Spina bifida                    | 2         |
|                                                                         | e) Renal agenesis                  | 1         |
Our study demonstrated that the rate of transfusion was higher in the neonate with a below-normal birth weight (Table 5).

**TABLE 4: Few most frequent ICD-11 diagnoses**  
ICD-11 = International Classification of Diseases 11th Revision

| Diagnosis                  | Frequency |
|----------------------------|-----------|
| f) Down syndrome           | 1         |
| g) Tracheoesophageal fistula| 1         |
| h) Meningomyelocele        | 1         |

Table 5 shows that preterm neonates needed transfusions more often than full-term neonates.

**TABLE 5: Need for blood components in comparison to the birth weight of the neonate**  
RCC = Red Cell Concentrate, FFP = Fresh Frozen Plasma, PC = Platelet Concentrate, WB = Whole Blood

| Birth weight              | RCC (%) | FFP (%) | PC (%) | WB (%) |
|---------------------------|---------|---------|--------|--------|
| Normal Birth Weight       | 27 (16.5%) | 72 (30%) | 21 (18.8%) | 8 (32%) |
| Low Birth Weight          | 58 (35.4%) | 98 (40.8%) | 46 (41.1%) | 15 (60%) |
| Very Low Birth Weight     | 51 (31.1%) | 47 (19.6%) | 30 (26.8%) | 1 (4%) |
| Extremely Low Birth Weight| 28 (17.1%) | 23 (9.6%) | 15 (13.4%) | 1 (4%) |
| Total                     | 164 (100%) | 240 (100%) | 112 (100%) | 25 (100%) |

Table 6 shows that preterm neonates needed transfusions more often than full-term neonates.

**TABLE 6: Need for blood components in comparison to the gestational age of the neonate**  
RCC = Red Cell Concentrate, FFP = Fresh Frozen Plasma, PC = Platelet Concentrate, WB = Whole Blood

| Gestational age | RCC (%) | FFP (%) | PC (%) | WB (%) |
|-----------------|---------|---------|--------|--------|
| Preterm         | 108 (65.9%) | 118 (49.2%) | 69 (81.6%) | 7 (28%) |
| Full term       | 56 (34.1%) | 122 (50.8%) | 43 (38.4%) | 18 (72%) |
| Total           | 164 (100%) | 240 (100%) | 112 (100%) | 25 (100%) |

**Discussion**

The results of the current audit highlight inconsistencies in practice vis-a-vis guidelines available. We show that many of the blood products given are at high levels of indications and readers are right in concluding that many were not needed. The audit is intended to bring a realization among practitioners in this field about the need to audit their own practices regularly. It is likely that due to various providers involved, many practices may not be in line with global recommendations. Using the quality improvement route may improve their practices in many areas.

Hematocrit is the primary determinant for transfusing RCC to a neonate. Opinion-based practice is favored widely in the absence of evidence-based protocols [6]. Many audits have identified several clinical scenarios, including the prevention of hemorrhage in critically ill neonates based on their coagulation profile. Neonatologists often transfuse plasma in the neonate with a deranged coagulation profile without any clue of active hemorrhage, despite a lack of data to prove the effectiveness of this practice [8]. Coagulation
protein levels keep fluctuating depending on the gestational age of the neonate. This should be taken into account while interpreting prothrombin time (PT) and activated partial thromboplastin time (aPTT) [9]. Prolonged PT and aPTT are seen in premature infants due to the decreased synthetic function of hepatocytes. But prematurity itself is not an indication for transfusing fresh frozen plasma. Unless there is bleeding, FFP should not be used to restore a prolonged international normalized ratio (INR). Disseminated intravascular coagulation (DIC) without active bleeding does not justify the use of FFP. The use of FFP in liver disease is controversial, as you don't always get a full reversal of the coagulation defect [10]. Severe hyperbilirubinemia can be corrected rapidly with the use of whole blood exchange transfusion (WBET). WBET has the advantage of removing partially hemolyzed RBCs, antibody-coated RBCs, and circulating immunoglobulin [11]. One of the major causes of neonatal mortality is necrotizing enterocolitis (NEC) arising as a complication of red cell concentrate transfusions [12]. Blood transfusion practice depends solely on blood component availability, recipient's epidemiology, and their response to therapy. A comparison between international transfusion practice differences and their impact on the recipient's prognosis can help to construct a clear guideline for neonatal transfusion [13]. As compared to normal birth weight neonates, extremely low birth weight neonates required more frequent platelet transfusions when they were diagnosed with thrombocytopenia [14]. One cannot extrapolate adult transfusion data to fill gaps in neonatal transfusion cutoff [5]. Hemoglobin level in neonates differs from adults because they are age-dependent. Neonates have a hemoglobin level of 19 g/dl at birth, which dips down to 11.2 g/dl when they reach infancy. At one point in time, the child's hemoglobin reaches 13 g/dl. At birth, 70% of the total blood is made up of fetal hemoglobin or HbF (and at six months of age, very less amount of HbF remains). In neonates, the oxyhemoglobin dissociation curve is shifted to the left secondary to shortened RBCs lifespan (90 days of neonate vs. 120 days of an adult). A higher blood transfusion/unit volume ratio in neonates threatens them to metabolic derangements with transfusion. These occur due to donors' RBCs and preservatives used in blood bags. Hypothermia, hypocalcemia, hyperkalemia, acidosis, and hypomagnesemia are risks related to transfusion. Hyperkalemia arising due to blood transfusion poses a significant threat in the neonate and potassium levels should be actively monitored in neonate receiving >20 ml/kg transfusion volume (or lower if the neonate has kidney problems or hyperkalemia at the beginning of transfusion). Cardiac arrest is associated with large blood volume transfusion due to hyperkalemia, especially neonate receiving exchange transfusion. The risk for cardiac dysfunction is raised with hypocalcemia, as neonates have limited sarcoplasmic reticulum. Transfusion effects depend on the environment. Hypothermia can occur in neonates due to large body surface areas. Coagulopathy can be exacerbated by hypothermia [15].

Anemia poses a major health threat for extremely low birth weight babies. Among them, RCC transfusion was associated with increased mortality [16]. Preterm neonates, especially those born before 30 weeks are often anemic. The current study showed that 83.6% of RCC transfusions were done among below-normal birth weight babies. Gestational age and birth weight are inversely proportional to the number of RCC given [17].

Delayed cord clamping increases hemoglobin levels at birth, which may have a favorable effect on developmental outcomes [18]. The World Health Organization (WHO) recommends delaying cord clamping for a minimum of 30 seconds [19]. In comparison to early cord clamping, delayed cord clamping results in fewer RCC transfusions and a reduced chance of necrotizing enterocolitis and intraventricular hemorrhage compared with early cord clamping [20]. However, strict adherence to guidelines cannot be judged due to a lack of documentation about the time allowed before cord clamping. Improved outcomes occur with platelet transfusions for hemorrhage secondary to thrombocytopenia [21]. But, the majority of platelet transfusion in neonates are done prophylactically in a bid to prevent hemorrhage, even if the neonate is not actively bleeding [22].

Limitations
The study has several potential limitations. First, the data was obtained from one urban hospital, which may not accurately represent overall transfusion practices in India. A future prospective multicenter study, which incorporates hospitals in all states at different locations, will provide a better picture of the patterns of blood consumption throughout the country. Iatrogenic anemia occurring due to repeated blood sampling in the NICU is a major cause of anemia. Our hospital records lacked documentation regarding the number and amount of blood samples collected. So we cannot establish it as a cause of anemia that required RCC. Although this study presents data from a single tertiary care hospital and a small chunk of neonates who got a blood transfusion in India, the analysis of data provides a perception of the traits of blood transfusion recipients and generate the platform for planning more ecumenical blood utilization studies in India. This heralds more exploration in various settings targeted at yielding proof necessary to communicate policies and practices.

Conclusions
Low birth weight and prematurity are the two risk factors identified that lead to multiple blood transfusions. Fresh frozen plasma was the most commonly transfused component, and the indication was neonatal sepsis. Whole blood is still used and must be avoided. Neonate's varying body mass ratio, age-related physiology, immature heart, and weak immunity make transfusion requirements complex. This study presents a chance
for measuring the use of and adherence to guidelines on prescribing blood in India. Findings from these types of audits will ensure a base for determining adherence to policies, guidelines, and practices in the proper clinical use of blood, leading to effective auditing and improvement in transfusion practices across neonatal intensive care units.

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue.
Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.
Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:
Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work.
Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.
Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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