EVALUATION OF BLOOD UTILIZATION PRACTICES IN NEONATES

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ABBREVIATIONS

AABB	American Association of Blood Banks
ACOG	American Congress of Obstetricians and Gynaecologists
AITP	Autoimmune thrombocytopenia
APGAR	Appearance, Pulse, Grimace, Activity and Reflex
APTT	Activated Partial Thromboplastin Time
ARIPI	Age of Red Blood Cells in Premature Infants
AS	Additive Solution
BCSH	British Committee for Standards in Haematology
BPD	Broncho Pulmonary Dysplasia
CPD	Citrate Phosphate Dextrose
CPDA-1	Citrate Phosphate Dextrose Adenine – 1
DIC	Disseminated Intravascular Coagulation
EBT	Exchange Blood Transfusion
ECMO	Extracorporeal Membrane Oxygenation
ELBW	Extremely Low Birth Weight
EPO	Erythropoietin
ETTNO	Effects of Transfusion Thresholds on Neurocognitive Outcome
FFP	Fresh Frozen Plasma
FiO2	Fraction of inspired oxygen
G6PD	Glucose – 6 – Phosphate Dehydrogenase
HDN	Haemolytic Disease of Newborn
HFV	High Frequency Ventilation
HPA	Human Platelet Antigen
HT	High Titre
IAT	Indirect Antiglobulin Test
ICH	Intra Cranial Hemorrhage
INR	International Normalized Ration
IUGR	Intra Uterine Growth Restriction

IVH	Intra Ventricular Hemorrhage
IVIG	Intravenous Immunoglobulin
LBW	Low Birth Weight
LOS	Length Of Stay
MAP	Mean Arterial Pressure
MCV	Mean Corpuscular Volume
NAIT	Neonatal alloimmune thrombocytopenia
NEC	Necrotising Enterocolitis
NEC	Necrotizing enterocolitis
NICU	Neonatal Intensive Care Unit
NNF	National Neonatology Forum
PCV	Packed Cell Volume
PET	Partial Exchange Transfusion
PI	Pathogen Inactivation
PINT	Premature Infant in Need of Transfusion
PINTOS	PINT follow up Outcome Study
PT	Prothrombin Time
PVH	Periventricular Hemorrhage
RBC	Red Blood Cell
SAGM	Saline Adenine Glucose Mannitol
SCD	Sterile Connecting Device
TA-GvHD	Transfusion Associated Graft versus Host Disease
TOP	Transfusion Of Premature Trial
TT-CMV	Transfusion Transmitted – Cytomegalo Virus
VLBW	Very Low Birth Weight
WHO	World Health Organisation
2,3 – DPG	2,3 – Di Phospho Glycerate

INTRODUCTION

INTRODUCTION

A newborn infant or neonate, is defined as a child under 28 days of age.[1] There occurs in neonate a dramatic and rapid change in physiology in almost all organs systems. Most of this can be attributed to fast growth of the newborn infant and changes in the haematological domain. It can be manifest as erythropoietin and/or iron deficiency inherent to neonates, due to low erythropoiesis and the shorter life span of fetal haemoglobin,[2] low levels of Vitamin K dependent clotting factors and contact factor.[3] So, it bears mentioning that for the foundation of a healthy childhood and adulthood further down, special care is needed during this precarious period right from birth, to first few days of life and during the remaining neonatal period.[4]

Blood component therapy is a very common intervention practised in newborns,[4] when neonates are affected by illnesses related to destruction of blood or blood loss.[5] The different blood components used in modern day therapeutics include whole blood and a variety of other products like Packed Red Blood Cells, Platelet Concentrates, Plasma and cryoprecipitate.[6] The transfused blood and/or its components replaces the volume and the specific constituents of blood, which play specific roles in oxygen carriage, immunity and clotting all of vital importance in a neonate with immature reserves. Therefore, blood transfusion is required to maintain life, by increasing cardiac output and oxygen delivery to tissues, ensure adequate haemostasis by

increasing platelet count, increasing clotting factors and preventing irreparable organ damage by removing toxins like bilirubin from the body.[5]

The indications for transfusion in neonates may occur due to physiological or pathological causes.[5] Physiologically, healthy full-term neonates have a mean cord blood haemoglobin level of 16.9 ± 1.6 g/dL and that of preterm neonates is 15.9 ± 2.4 g/dL. The haemoglobin concentration usually falls off during the first few weeks of life, leading to physiological anaemia of infancy in newborns and physiological anaemia of prematurity in preterm infants.[7] Both these conditions are usually self-limiting and are tolerated without deleterious effects.[3] Many aspects of haematopoiesis are either incompletely developed in preterm infants or are adapted to serve the foetus. Preterm infants of very low birth weight have very little iron stores and a small circulating volume of RBCs when they exit the uterine stage, as can be expected with low reserves and small circulatory volumes, the effects of loss of even small blood volumes can be profoundly lethal for the neonates.[8]

Platelet production in the intrauterine life starts at around 5 weeks after conception and by the end of the second trimester has established the normal postnatal range of 150–450 $\times 10^9$/L. Reference ranges derived from a large population of babies having blood counts in hospital show a lower (5th centile) limit of 105× 10^9/L for those born ≤ 32 weeks of gestation and 125 $\times 10^9$/L for those >32 weeks of gestation. Postnatal infants born at 28 weeks or

earlier usually present with a lower platelet count than those infants who are more mature at birth, which is probably due to their postnatal clinical course as well as reduced marrow reserve.[9]

Physiologically, low levels of vitamin K dependent factors (Factors II, VII, IX, and X) and contact factors (Factor XI, Factor XII, prekallikrein, and high-molecular-weight kininogen) contribute to altered coagulation test results. Also, the levels of naturally occurring vitamin K dependent anticoagulants (proteins C and S) and the non-vitamin K dependent antithrombin protein are depressed at birth. Despite these deviations from adult levels of coagulation proteins, the procoagulant and anticoagulant systems are usually in balance in healthy newborns. So spontaneous bleeding and thrombosis are rare. However, the reserve capacity of both procoagulant and anticoagulant systems of neonates are limited as compared to that in an adult.[3] So, very low birth weight premature neonates are amongst the most common of all patient groups to receive extensive transfusions.[10]

The leading causes of neonatal morbidity and mortality include respiratory distress, sepsis, low birth weight, prematurity, birth asphyxia, congenital malformation, jaundice and others.[11] The most common indications for blood transfusions were sepsis and prematurity.[2] RBCs are indicated in sepsis because sepsis leads to the oxidative haemolysis and thus necessitates where transfused RBCs are necessary to maintain circulatory homeostasis.[2] Most of the extremely preterm neonates (< 28 weeks gestation)

receive at least one red cell transfusion as they frequently become anaemic, partly caused by cumulative phlebotomy losses sometimes with sample volumes larger than can be tolerated. Use of cord blood for initial blood tests for Very Low Birth Weight (VLBW) neonates has been advocated to reduce the need for transfusion, but results should be interpreted with caution if there are sampling difficulties. Neonatal transfusions are usually given as small-volume "top-up" transfusions, to maintain the haemoglobin above a critical threshold or when necessitated because of presence of surrogate markers of anaemia such as poor growth, lethargy or increased episodes of apnoea.[12] Exchange transfusion is required to rapidly remove the excess bilirubin from the blood to prevent irreversible and often debilitating brain damage (bilirubin encephalopathy).[5]

Older RBCs are associated with change in cell shape and membrane, an increase in adhesiveness, a decline in flexibility, reductions in capillary flow,[13] increase in extracellular potassium and reduction in 2,3-DPG levels.[3] To circumvent the problems posed by such biologically fragile cells, fresh RBCs are being used in neonatal set up. Recent studies have shown that age of red cells used for neonatal small volume top up transfusion does not affect the clinical outcome of the neonate. But for large volume transfusions such as exchange transfusion, fresh (<5 days old) RBCs are recommended.[3,14]

The transfusion of platelets is indicated for the prophylaxis and treatment of haemorrhage in patients with thrombocytopenia or with primary

or secondary functional disorders of platelets. The main indication for the transfusion of plasma is to correct deficiencies of clotting factors, for which a specific concentrate is not available, in patients with active bleeding.[15]

Blood transfusions are frequently life-saving. However, transfusions are not without risks, and they should be given only when true benefits outweigh potential risks. Therefore, as with any therapy used in neonates, it is essential that one considers the risk- benefit ratio and strive to develop treatment strategies that will result in the best therapeutic outcomes for ill neonates.[16] Since neonatal physiology varies with the maturity, age, weight and the presence of morbidities, it is difficult to formulate one parameter to guide all transfusion decisions.[4]

Hence to solve the problems encountered in neonatal transfusion and to address any sequelae of the same, analysis of blood usage pattern among neonates in Neonatal Intensive Care Unit (NICU) is essential. This will also help to optimize blood component utilization in situations where prohibitive costs and general unavailability of blood components can be crippling to effective neonatal care. Lending more urgency is the fact is that there are not many studies about transfusion practices among neonates in Neonatal Intensive Care Units in India. The present study would help make blood transfusion practices more rooted in peer reviewed evidences and also predict future blood demand and help maintain blood bank inventory.

AIM AND OBJECTIVE

AIM AND OBJECTIVES

AIM

A prospective study to evaluate the blood utilization practices in neonates admitted in Neonatal Intensive Care Unit (NICU) at Institute of Child Health & Hospital for Children, Chennai, Tamilnadu.

OBJECTIVES

- To evaluate the appropriateness of transfusion practices among neonates.
- To assess the relationship between gestational age, birth weight and APGAR score (5 min) with transfusion requirement of blood components.
- To evaluate the relationship between age of red blood cells and length of stay (LOS).

REVIEW OF LITERATURE

REVIEW OF LITERATURE

A newborn infant or neonate, is defined as a child under 28 days of age.[1] Depending on the gestational age of mother, the newborn can be classified into term baby and preterm baby. A preterm baby is defined as a baby born alive before 37 weeks of pregnancy is completed. Preterm babies are sub classified into various categories, based on gestational age namely extremely preterm (<28 weeks), very preterm (28 to <32 weeks) and moderate to late preterm (32 to <37 weeks).[17] Term birth or baby is defined as a baby born after 37 weeks of pregnancy.[18] According to the birth weight of the neonate, they are classified into normal birth weight (≥2500 gm), Low Birth weight neonates (2499 – 1500 gm), Very Low Birth weight (1499 – 1000 gm) and Extremely Low Birth weight (<1000 gm) neonates.[19] APGAR score was used to assess the neonatal status immediately after birth and further management. The Apgar score comprises five components namely colour, heart rate, reflexes, muscle tone and respiration, each of which is given a score of 0, 1, or 2. 5-minute Apgar score of 7–10 is considered as reassuring, a score of 4–6 as moderately abnormal, and a score of 0–3 as low in the neonates.[20]

BLOOD TRANSFUSION IN NEONATES

A very rapid change of physiology is experienced by a newborn at birth and during the first few days of life.[4] Hillman et al in their study stated

that the change from fetal to extrauterine life is the sum of several fast organ adaptations that often has redundant intermediaries. The primary intermediaries that prepare the foetus for birth and support the multi-organ transitions are cortisol and catecholamines. Pulmonary adaptation requires the coordinated clearance of fetal lung fluid, surfactant secretion, and the beginning of consistent breathing. The transition in cardiovascular system requires gross changes in blood flow, pressures and pulmonary vasodilatation. Abnormalities in adaptation are not rare following preterm birth or delivery by caesarean section at term.[21] This is the time when many infants may fall ill and may even die.[4,22] Hence care at birth and during the remaining neonatal period is of paramount importance and can lay a good foundation for a healthy life later on.[4]

Blood constitutes an integral part of the therapeutic arsenal of the neonates.[4] It has been reported that 20% of patients will, at some time during their NICU stay, receive one or more transfusions.[23] Transfusion needs are closely connected to the changes in various organ systems when a foetus transforms into a neonate, neonate to infant, and throughout childhood. Hence it is of vital significance to have a thorough understanding of blood components and their indications.[21]

Blood transfusion is the process of infusion of blood and blood products into an individual's circulatory system. Blood transfusion is used in a variety of medical conditions to replace the lost components of blood.

Component therapy whereby components of the blood such as red cell concentrate, fresh frozen plasma, cryoprecipitate, and platelet concentrate are infused as indicated, has overtaken the old practice of whole blood infusion. The blood transfusion need in the neonate is huge because of reduced marrow activity in the neonatal period.[6,24] Other indications include correction of anaemia, exchange blood transfusion or partial exchange transfusions for removal of bilirubin, removal of antibodies and replacement of red cells, replacement of losses due to blood loss during blood samples collection for various tests. Blood products such as platelets concentrates and fresh frozen plasma can also be transfused in septicaemic neonates with DIC and neonates with bleeding diathesis.[24] Newborn especially very low birth weight preterm neonates are a group most susceptible for frequent transfusions with special requirements.[4,10] The following four are the major indications for neonatal transfusion: anaemia of prematurity, neonatal sepsis, disseminated intravascular coagulation and neonatal jaundice.[24]

The best transfusion practice in neonates provide good therapeutic outcomes, especially in reducing transfusion transmitted infections due to exposure to multiple donors.[25] As can be assumed the specifications and guidelines for blood component therapy used in adults cannot be completely applied to neonates, the small size of neonates and the presence of unique physiological and immunological factors make transfusion needs in neonates uniquely different from that of adult patients.[3]

The realm of neonatal transfusion guidelines is a fast evolving one subject to new data and recent developments. Neonatal transfusion has two major criteria for transfusion namely the optimum product to use, and suitable transfusion triggers to ensure the judicious use of blood.[4] It is a continuing endeavour to define and refine the most clinically appropriate protocols for blood product use in neonates, within the limitations of the present evidence.[26] Furthermore, it is also necessary to consider alternatives to transfusion and ways to reduce the need for transfusion.[27]

NEONATAL PHYSIOLOGY PERTAINING TO BLOOD TRANSFUSION

1. PHYSIOLOGY PERTAINING TO PREMATURE NEONATES

In preterm neonate, because of the lack of complete development of haematopoiesis and adaptation to extra uterine life there is a decreased capacity to produce red blood cells (RBCs), platelets, and neutrophils — this is of increased relevance during a life-threatening illness such as sepsis, severe pulmonary dysfunction, necrotizing enterocolitis, and immune cytopenia. In the same way, liver function is immature resulting in low levels of both plasma clotting and anticoagulant factors. Thus, preterm infants begin life with low levels of RBC and other vital factors in blood. Furthermore, their ability to increase production of RBCs and other clotting factors in

severely impaired due to immature or ill developed organs systems. These conditions lead to the need for blood component transfusions.[8]

2. PHYSIOLOGICAL ANEMIA AND ANEMIA OF PREMATURITY

Healthy full-term neonates have a mean cord blood haemoglobin level of 16.9 ± 1.6 g/dL and that of preterm neonates is 15.9 ± 2.4 g/dL. The haemoglobin concentration usually falls off during the first few weeks of life, leading to physiological anaemia of infancy in newborns and physiological anaemia of prematurity in preterm infants. Both these conditions are usually self-limiting and are tolerated without deleterious effects. The rate of decline in haemoglobin depends on the gestational age at birth. At 4 to 8 weeks after birth, haemoglobin decreases to as low as 8.0 g/dL in preterm infants weighing 1000 to 1500 g and 7.0 g/dL in neonates weighing less than 1000 g at birth.[3,8,28,29] Many factors contribute to this fall in haemoglobin concentration: 1) a decrease in erythropoietin (EPO) levels resulting in diminished red cell production, 2) a decrease in life span of fetal red cells,[30] and 3) an increasing blood volume due to rapid growth. Reduced EPO production results from increased oxygen delivery to tissues because of increased pulmonary blood flow, elevated arterial pO2 levels, and increased red cell 2,3-diphosphoglycerate (2,3 DPG) and haemoglobin A levels.[3,8]

When neonates are delivered before 28weeks of gestation (birthweight <1.0kg), most of iron transport has not occurred from mother to foetus via the

placenta and marked erythropoietic activity of fetal marrow during the third trimester is yet to commence. Because of this, preterm infants of very low birth weight have very little iron stores and a small circulating volume of RBCs when they exit the uterine stage.[8]

Bowen et al[31] study and Freitas et al[32] study, there is an increase in red blood cell transfusion in neonates <32 weeks gestation. Strauss[33] in an international forum stated that transfusions were greatly influenced by birth weight. 88% of ELBW neonates are transfused with blood.

3. INFANT SIZE AND BLOOD VOLUME

A full-term newborn has a blood volume of approximately 85 mL/kg compared to 100 mL/kg in a preterm newborn.[3,34] Due to the small total blood volumes of preterm infants (100 mL or less), the size of blood components provided by blood banks should be appropriate.[3,8] Many factors, including iatrogenic blood loss from repeated venepunctures, lead to frequent transfusions.[8,28,35] Hypovolemia is poorly tolerated in newborns because their left ventricular stroke volume decreases without a corresponding increase in heart rate when >10% of their blood volume is lost. Thus, newborns must physiologically increase their peripheral vascular resistance with decreasing cardiac output to maintain systemic blood pressure. This leads to impaired tissue perfusion and oxygenation, which may end in metabolic acidosis.[3]

Although transfusion may be required, the goal of transfusion is not to replace the amount of blood lost mL for mL; rather, transfusions can be done to maintain a target haemoglobin level in neonates.[3,8,29] When ill preterm and full-term neonates receive multiple transfusions, their levels of fetal haemoglobin decreases proportionately and that of adult haemoglobin increases.[3]

4. ERYTHROPOIETIC RESPONSE

The EPO response in newborns differs from that in adults and older children. In non-neonates, oxygen sensors in the kidney recognize decreases in oxygen delivery, resulting in the release of EPO into the circulation. But in the foetus, this sensor is in the liver and is less sensitive to hypoxia, resulting in reduced EPO production and secretion in the face of hypoxia (hypo responsiveness). This obtunded response actually prevents polycythaemia of the foetus in the hypoxic intrauterine environment.

Although EPO production eventually shifts from the liver to the kidney, most premature infants produce EPO only sparingly for any degree of anaemia.[3,8,29]

5. HYPOTHERMIA

Hypothermia in the neonate can activate or amplify several responses, which includes 1) an increase in metabolic rate; 2) hypoglycaemia; 3)

metabolic acidosis; and 4) potential apnoeic events that may lead to hypoxia, hypotension, and cardiac arrest. In-line blood warmers are needed for all Red Blood Cell (RBC) exchange transfusions to counteract the effects of hypothermia. Because of the risk of haemolysis radiant heaters for blood should not be used.[3]

6. METABOLIC PROBLEMS

In infants younger than 4 months, transfusions of large volumes of reconstituted whole blood or plasma may result in acidosis and/or hypocalcaemia because their immature liver cannot effectively metabolize citrate. The immature kidneys also contribute to these complications because they have lower glomerular filtration rates and concentrating ability than older infants, thus causing difficulties in excreting excess potassium, acid, and/or calcium.[3,27]

7. PHYSIOLOGY OF PLATELETS IN NEONATES

Platelet production in the intrauterine life starts at around 5 weeks after conception and by the end of the second trimester has established the normal postnatal range of 150–450 $\times 10^9$/l.[8,9,29,36-39] Reference ranges derived from a large population of babies having blood counts in hospital show a lower (5th centile) limit of 105×10^9/l for those born $\leq$ 32 weeks of gestation and 125×10^9/l for those >32 weeks of gestation. Postnatal infants born at 28 weeks or earlier usually present with a lower platelet count than those infants

who are more mature at birth, which is probably due to their postnatal clinical course as well as reduced marrow reserve. The same study also revealed that all except the most immature infants have a postnatal increase in platelet count between 2 and 4 weeks after birth, with counts at the end of the 1st postnatal month frequently above 450×10^9/l.[38-40] Normally the neonatal platelets respond sluggishly in vitro to most agonists as opposed to adult platelets. Numerous studies have shown that full-term neonates have adequate primary haemostasis, despite their in vitro platelet hyporeactivity. This seemingly paradoxical finding is because there are compensatory factors in neonatal blood that enhance clot formation and perfectly balance the hyporeactivity of neonatal platelets, leading to normal BTs and clotting times. These compensatory factors include the high haematocrit of neonatal blood, the high MCV (mean corpuscular volume) of neonatal RBCs, and the predominance of ultra-long polymers of von Willebrand factor in neonatal plasma.[40] Thrombocytopenia occurs in neonates either due to accelerated platelet destruction or diminished platelet production or a combination of these.[3,8,29]

Bowen et al[31] study, platelet requirement is high in neonates ≥32 weeks of gestation. But in Ramanathan et al[41] study, there was no significant relationship between gestational age and neonatal thrombocytopenia & platelet transfusion. In Ramanathan et al[41] study, VLBW neonates received more platelet transfusions.

8. DEVELOPMENTAL HEMOSTASIS

The dynamic and evolving process of the haemostatic system that occurs during infancy and childhood was first described by Andrew and was termed "developmental hemostasis".[42,43] Neonates must synthesize their own coagulation factors because amounts required for proper coagulation response are not transferred from the mother via placenta. In the immediate post-natal period too, infants are unable to produce normal levels of these proteins physiologically, and so low levels of vitamin K dependent factors (Factors II, VII, IX, and X) and contact factors (Factor XI, Factor XII, prekallikrein, and high-molecular-weight kininogen) contribute to altered coagulation test results. Also, the naturally occurring vitamin K dependent anticoagulants (proteins C and S) and the non-vitamin K dependent antithrombin protein are at reduced levels at birth. Despite these variations from adult levels of coagulation proteins, the procoagulant and anticoagulant systems are usually in balance in healthy newborns, so spontaneous bleeding and thrombosis are rare. However, the reserve capacity of both procoagulant and anticoagulant systems are limited as compared to that in an adult.[3,8,42-46] So, the coagulation test results should be evaluated clinically according to the age of the neonate.[8,47]

INDICATIONS FOR TRANSFUSION

1. RBC TRANSFUSIONS

Red blood cells are the component most often transfused in sick neonates.[8,48] RBC transfusions are provided mainly to treat symptomatic anaemia and when tissue oxygenation is poor. Tissue oxygenation depends on cardiac output, oxygen saturation and haemoglobin concentration. If cardiac output and oxygen saturation are not compromised, tissue oxygenation can be increased by increasing the haemoglobin level.[48] The most common causes for RBC transfusions in neonates are sepsis, prematurity, anaemia with mechanical ventilation for severe respiratory illness, blood loss, apnea and failure to thrive.[49]

2. PLATELET TRANSFUSIONS

Thrombocytopenia, generally defined as a platelet count $<150 \times 10^9$/L,[40,41] is the second most common hematologic disorder after anaemia, in infants admitted to neonatal intensive care units (NICUs).[40] It affects 18% to 35% of all neonates admitted to NICUs[40,50] and approximately 70% of extremely low birth weight (ELBW) infants with a birth weight less than 1000 g. The incidence of thrombocytopenia is inversely proportional to the gestational age, and it is a risk factor for poor outcomes in NICUs.[40]

The etiology and natural history of thrombocytopenia are highly diverse and distinct. Clinically, a distinction is frequently made between early

onset (≤3 days of life)[40,41] and late-onset (≥4 days of life) neonatal thrombocytopenia. Intrauterine growth restriction, pregnancy-induced hypertension or diabetes, perinatal infection, and transplacental passage of maternal allo- or autoantibodies are frequently associated with early onset thrombocytopenia. Late-onset neonatal thrombocytopenia is most commonly caused by bacterial infection or necrotizing enterocolitis.[40] The neonatal factors associated with thrombocytopenia are sepsis, respiratory distress, NEC, IUGR, coagulopathy, DIC and shock.[41]

3. PLASMA TRANSFUSIONS

In neonates, plasma is mainly given to mitigate perceived bleeding risk (prophylaxis) in non-bleeding patients. However, it should be accepted that all critically ill neonates will show some features of bleeding risk, for example, oozing at sites of venepuncture. Other usages include bleeding with abnormal coagulation test results, intraoperative bleeding, sepsis, partial exchange for polycythaemia, and exchange transfusions. Bleeding complications from coagulation abnormalities in the newborn are usually the result of an acquired defect in haemostasis, although congenital disorders may be present, particularly in association with an iatrogenic insult.[46]

RATIONAL USE OF BLOOD AND ITS COMPONENTS

One of the objectives in National Blood Policy is the rational use of blood components.[51] Judicious use of blood implies the right blood product is

to be given to the right patient in the right amount.[52] Evidence based recommendations will ensure safe patient care of high quality, while also making the use of blood products cost effective with minimal wastage.[53] Indiscriminate use of blood and blood components is on the rise. The apparent reasons for inappropriate transfusions were fear of immediate risk to the patient and ignorance about the role of blood components in therapeutics.[16]

GUIDELINES FOR ASSESSING APPROPRIATE NEONATAL TRANSFUSIONS

Transfusion practices for high-risk neonates differ widely among neonatal intensive care units.[54,55] Neonatal transfusion guidelines are repeatedly changed as new data become available and remain an area of debate.[26] Because of the fragile clinical status of these small patients, it is difficult to design randomized controlled trials with enough statistical power to produce ironclad data. A great majority of the papers written about neonatal transfusion are practice oriented and derived by consensus. Therefore, adapting published literature to be used when creating transfusion audit guidelines for neonates and it should be done on an individualized basis. In certain selected clinical situations, transfusion events that deviate from the proposed guidelines may be considered appropriate. Scientific data, as well as review of the patient's chart, can be helpful in evaluating the appropriateness of transfusion events that deviate from guidelines.[56]

Table 1: RBC Transfusion Guidelines

<table>
<tr><th>NNF GUIDELINES[4]</th><th>AABB GUIDELINES[3]</th><th>BCSH GUIDELINES[12]</th></tr>
<tr>
<td>Severe anemia of antenatal onset:
Anemia occurring before birth, characterized by Hb< 8/dL at birth, requires prompt transfusion, as specified below
a. In severe anemia associated with congestive heart failure (due to immunohemolysis, chronic feto-maternal or feto-fetal hemorrhage) the most appropriate treatment is "partial" exchange transfusion (PET) with packed RBC with the aim of correcting the anemia while avoiding volume overload.
b. In severe anemia with hypovolaemic shock (placenta previa, abruption placentae, rupture of the cord), the intravascular volume must be restored and the anaemia corrected.
Early neonatal anemia:
For anemia developing after birth or in the first week of life, in which the values of Hb are moderately decreased, transfusion treatment is necessary in the case of severe cardio-pulmonary diseases, in order to maintain the PCV greater than 0.35 to 0.40.
Late neonatal anaemia:
a. Acute blood loss greater than 10% of blood volume with features of decreased oxygen delivery or greater than 20% of blood volume.</td>
<td>1. Haematocrit <20% with low reticulocyte count and symptomatic anaemia (tachycardia, tachypnea, poor feeding).
2. Haematocrit <30% and any of the following:
a. On <35% oxygen hood.
b. On oxygen by nasal cannula.
c. On continuous positive airway pressure and/or intermittent mandatory ventilation on mechanical ventilation with mean airway pressure <6 cm of water.
d. With significant tachycardia or tachypnea (heart rate >180 beats/minute for 24 hours, respiratory rate >80 beats/minute for 24 hours).
e. With significant apnea or bradycardia (>6 episodes in 12 hours or 2 episodes in 24 hours requiring bag and mask ventilation while receiving therapeutic doses of methylxanthines).
f. With low weight gain (<10</td>
<td>
<table>
<tr><th rowspan="2">Postnatal age</th><th colspan="3">Suggested transfusion threshold Hb (g/L)</th></tr>
<tr><th>Ventilated</th><th>On oxygen /NIPPV#</th><th>Off oxygen</th></tr>
<tr><td>1st 24 hours</td><td>< 120</td><td>< 120</td><td>< 100</td></tr>
<tr><td>≤ week 1 (day 1-7)</td><td>< 120</td><td>< 100</td><td>< 100</td></tr>
<tr><td>week 2 (day 8 - 14)
≥ week 3 (day 15 onwards)</td><td>< 100</td><td>< 95
< 85</td><td>< 75*</td></tr>
</table>
* Standard definition of preterm is <37 weeks gestational age at birth but table applies to very preterm neonates (< 32 weeks).
** It is accepted that clinicians may use up to 85 g/L depending on clinical situation
</td>
</tr>
</table>

b. PCV < 30%: Moderate or significant mechanical ventilator support [MAP >8 cm, FiO2 >0.40 with conventional ventilation or MAP > 14 and FiO2 > 0.40 with High frequency ventilation-HFV] c. PCV < 25%: Minimal mechanical ventilator support [MAP < 8 cm, FiO2 < 0.40 on conventional ventilation or MAP <14 and/or FiO2 0.40 on HFV] d. PCV < 20%: Supplemental oxygen not requiring mechanical ventilatory support plus the presence of one or more of the following: i. Tachycardia >180/minute or Respiratory rate > 60 for ≥ 24hours ii. Doubling of the oxygen requirement in last 48 hours iii. Lactate > 2.5 mEq/L or acute metabolic acidosis with pH <7.20 iv. Weight gain less than 10 grams/kg/day over 4 days while receiving 120 kcal/kg/day v. If the infant will undergo major surgery within 72 hours e. PCV < 18%: Consider transfusion for asymptomatic infants with absolute reticulocyte count of < $100x10^3/\mu L$ ($100x10^9/L$) or < 2 percent.	g/day observed over 4 days while receiving ≥ 100 kcal/kg/day). 3. Haematocrit <35% and either of the following: a. On >35% oxygen hood. b. On continuous positive airway pressure/intermittent mandatory ventilation with mean airway pressure ≥ 6-8 cm of water. 4. Haematocrit <45% and either of the following: a. On extracorporeal membrane oxygenation. b. With congenital cyanotic heart disease.	# NIPPV, non-invasive positive pressure ventilation

Table 2: Platelet Transfusion Guidelines

NNF GUIDELINES[4]

Platelets ($x10^9$/L)	Bleeding		Immune status	
	Yes	**No**	**AITP***	**NAIT#**
<30	Transfuse	Consider Platelet transfusion	Transfuse if bleeding/ IVIG not available	Transfuse if bleeding
30 to 49	Transfuse	Transfuse if Weight <1000grams or postnatal age <1week or Unstable (IVH Gr3-4) or associated coagulopathy or Surgery required	Transfuse, if unstable, bleeding	Transfuse if bleeding
50 to 99	Transfuse	Do not transfuse	Do not transfuse	Transfuse if bleeding
>99	Do not transfuse			

* Autoimmune thrombocytopenia
# Neonatal Alloimmune thrombocytopenia

AABB GUIDELINES[3]

With Thrombocytopenia

- Platelet count 5,000 to 10,000/μL with failure of platelet production.
- Platelet count <30,000/μL in neonate with failure of platelet production.
- Platelet count <50,000/μL in stable premature infant:
  - With active bleeding, or
  - Before an invasive procedure, with failure of platelet production.
- Platelet count <100,000/μL in sick premature infant:
  - With active bleeding, or
  - Before an invasive procedure in patient with DIC.

Without Thrombocytopenia

- Active bleeding in association with qualitative platelet defect.
- Unexplained excessive bleeding in a patient undergoing cardiopulmonary bypass.
- Patient undergoing ECMO with:
  - A platelet count of <100,000/μL, or
  - Higher platelet counts and bleeding.

DIC = disseminated intravascular coagulation; ECMO = extracorporeal membrane oxygenation.

BCSH GUIDELINES[12]

Platelet count (x 10^9/l)	Indication for platelet transfusion
< 25	Neonates with no bleeding (including neonates with NAIT if no bleeding and no family history of ICH)
< 50	Neonates with bleeding, current coagulopathy, before surgery, or infants with NAIT if previously affected sibling with ICH
< 100	Neonates with major bleeding or requiring major surgery (e.g. neurosurgery)

ICH: Intracranial hemorrhage

Table 3: Fresh Frozen Plasma Transfusion Guidelines

NNF GUIDELINES[4]	AABB GUIDELINES[3]	BCSH GUIDELINES[12]
Indication for Fresh Frozen Plasma Transfusion a. Severe clotting deficiency (including DIC) with bleeding b. Severe clotting deficiency in a neonate undergoing an invasive procedure c. Vitamin K deficiency with bleeding d. Dilutional coagulopathy with bleeding e. Severe anticoagulant protein deficiency f. Reconstitution of packed RBC for exchange transfusion Incorrect Indications: a. Prevention of intraventricular haemorrhage in premature neonates b. Volume replacement in the management of sepsis c. As an adjunct in the management of thrombocytopenia d. To "correct" prolonged indices of coagulation	Fresh Frozen Plasma (FFP) • Support during treatment of disseminated intravascular dissemination. • Replacement therapy: When specific factor concentrates are not available, including, but not limited to antithrombin; protein C or S deficiency; and Factor II, Factor V, Factor X, and Factor XI deficiencies. • During therapeutic plasma exchange when FFP is indicated (cryopoor plasma, plasma from which the cryoprecipitate has been removed). • Reversal of warfarin in an emergency situation, such as before an invasive procedure with active bleeding. Note: FFP is not indicated for volume expansion or enhancement of wound healing.	Recommendations 1. There is no evidence to support the routine use of FFP to try to correct abnormalities of the coagulation screen alone in non-bleeding neonates (1C). 2. FFP may be of benefit in neonates with clinically significant bleeding (including massive blood loss) or prior to invasive procedures with a risk of significant bleeding, and who have an abnormal coagulation profile, defined as a PT or APTT significantly above the normal gestational and postnatal age-related reference range (taking into account local reference ranges where available) (2C). 3. FFP should not be used for simple volume replacement or routinely for prevention of IVH (1B).

1. NEONATAL RBC TRANSFUSION

Table 1 describes about the various guidelines used in neonatal RBC transfusion practice. NNF guidelines with regard to transfusion trigger for RBC, it failed to explain haemoglobin threshold for cardiac patients and neonates on ECMO support which was included by AABB guidelines. NNF guidelines also failed to mention about the transfusion trigger when the neonates are symptomatic at room air even with a haematocrit of <30%. Both guidelines had not specified to which group of neonates this protocol applies because the physiology of term and preterm neonate are not similar. BCSH guideline formulated new guidelines for RBC transfusion trigger for neonates <32 weeks. WHO stated that the decision to transfuse should not be based on the haemoglobin level alone, but also on a careful assessment of the child's clinical condition.[57] RBCs are transfused to apnoeic neonates. Although apnea of prematurity has a multifactorial etiology, decreased oxygen carrying capacity may play a role. Studies have shown that RBCs transfusion had improved oxygen carrying capacity in neonates with apnea of prematurity.[58] In Wade et al study, 77% of packed red cell transfusions were appropriate.[16] In Baer et al study, 70% of packed red cell transfusions were appropriate.[23]

Liberal Versus Restrictive RBC Transfusion Practice

RBC transfusion guidelines have moved from being liberal to restrictive. Two randomized controlled trials, the Premature Infants in Need

of Transfusion (PINT)[59] and its follow up study [PINT Follow up Outcomes Study (PINTOS)][60] as well as a University of Iowa study[61] compared the outcomes of restrictive (Hb = 7 g/dL) vs liberal RBC transfusion triggers (Hb = 10 g/dL) in VLBW infants.[3,12,59-62]

The Iowa trial revealed a lower rate of transfusion events (3.3 vs 5.2; p=0.025) with the restrictive strategy compared to the liberal strategy. However, rates of periventricular leukomalacia and death were higher in the restrictive arm.[61] The PINT study found no significant difference between the two arms, which had the same thresholds as the Iowa study, with respect to complications like death or any of bronchopulmonary dysplasia, retinopathy of prematurity (Stage >3), or brain injury (periventricular leukomalacia, intracranial hemorrhage Grade 4, or ventriculomegaly).[59] The follow up PINTOS study showed that at 18 to 24 months after birth, infants in the PINT study's restrictive arm had more neuro developmental impairments than those in the liberal arm.[60] In summary, these studies concluded that maintenance of higher haemoglobin levels in low birth weight infants may provide long term neurologic protection.[3,12,59-62] It should be noted that safety of haemoglobin threshold levels below those used in the trials is not known.[12]

Given the conflicting nature and limitations of the above-mentioned trials, experts agree that further study is needed to determine the optimal RBC transfusion threshold for neonates. To address the above-mentioned concerns regarding the haemoglobin thresholds and cut-off values, two trials namely

Transfusion of Premature (TOP) trial and Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-Weight Infants (ETTNO) are currently underway.[12,62]

Despite many studies on the RBC transfusion therapies, an agreement has not been reached on various threshold values of transfusion.

2. NEONATAL PLATELET TRANSFUSION

Table 2 describes about the various guidelines used in neonatal platelet transfusion practice. NNF and BCSH guidelines had failed to explain about transfusion trigger for qualitative disorders of platelets, whereas AABB alone describes about it. AABB and NNF guidelines failed to explain about surgery when platelet count above 50×10^9/L, whereas BCSH guidelines has explained about it. In AABB guidelines, there is no clear distinction between platelet count 5,000 to 10,000/ μL and <30,000/μL as both explains the same transfusion trigger. Experts stated that during sepsis there will be a fall in platelet count and platelet transfusion is reasonable in a bleeding sick neonate with sepsis.[63]

In Wade et al study, 75% of platelet transfusions were appropriate.[16] In Baer et al study, 69% of platelet transfusions were appropriate.[23] Even though the least inappropriate transfusions to neonates are transfusion of platelets, the optimal platelet transfusion threshold for neonates is still unknown. A large-

scale randomized multicenter controlled trial (PlaNet-2 trial) may yield more precise information about the thresholds required to transfuse platelets.[40,64]

3. NEONATAL PLASMA TRANSFUSION

Table 3 describes about the various guidelines used in neonatal FFP transfusion practice. NNF and AABB guidelines doesn't explain about the coagulation parameters value in a bleeding neonate. Furthermore, the age-related changes of coagulation proteins during infancy make it hard to correctly diagnose coagulopathy in neonates and subsequently determine the time and dose of FFP administration.[43] Motta et al reported 63% of the infants receiving FFP for prophylaxis, without evidence of haemorrhage which is 60% non-compliant with established guidelines.[43,44,53] In Wade et al study, FFP transfused were 100% inappropriate.[16] In Raban et al[53] study, 75% of FFP transfused were appropriate.[53] In Baer et al study, 65% of FFP transfusions were appropriate.[23] The inappropriate use of FFP is due to absence of evidence based guidelines.[43,53] Decrease in titres in procoagulation and anticoagulation proteins has been reported in asphyxiated and hypothermic neonates, resulting in abnormal clotting tests and later progressing to coagulopathy.[65-67] However, a meta-analysis studying the consequence of therapeutic hypothermia in asphyxiated encephalopathic neonates showed no significant difference in coagulopathy, thrombosis, or hemorrhage in cooled versus non- cooled neonates. FFP administration is not advised in perinatal asphyxia neonates subject to therapeutic hypothermia, if

there is no active bleeding.[43] In sepsis related coagulopathy, the indications for FFP usage range from mild laboratory alterations to severe disseminated intravascular coagulation (DIC). Risk of bleeding increases with low levels of platelets and coagulation factors. However, plasma or platelet substitution therapy is indicated only in those patients with active bleeding or at high risk for bleeding complications. Large volumes of plasma are often required to correct the coagulation defect thus seen.[63] Experts stated that neonates with a significant coagulopathy [e.g. prothrombin time (PT) or activated partial thromboplastin time (APTT) ratio >1.5] and significant risk of bleeding (e.g. preterm and/or intubated, previous PVH) or who are about to undergo an invasive procedure should receive FFP.[68]

CRYOPRECIPITATE TRANSFUSION

Cryoprecipitate transfusions are currently being used to treat conditions resulting from decreased or dysfunctional fibrinogen (congenital or acquired) or Factor XIII deficiency. In the treatment of DIC in newborn cryoprecipitate is usually given in conjunction with platelets and FFP. Typically, 1 unit is sufficient to achieve haemostatic levels in an infant.[3,50]

AABB GUIDELINES[3]

- Hypofibrinogenemia or dysfibrinogenemia with active bleeding.
- Hypofibrinogenemia or dysfibrinogenemia while undergoing an invasive procedure.

- Factor XIII deficiency with active bleeding or while undergoing an invasive procedure in the absence of Factor XIII concentrate.
- Limited directed-donor cryoprecipitate for bleeding episodes in small children with hemophilia A (when recombinant and plasma-derived Factor VIII products are not available).
- In the preparation of fibrin sealant.
- von Willebrand disease with active bleeding, but only when both of the following are true:
    - Deamino-D-arginine vasopressin (DDAVP) is contraindicated, not available, or does not elicit response.
    - Virus-inactivated plasma-derived Factor VIII concentrate (which contains von Willebrand factor) is not available.

GRANULOCYTE TRANSFUSION

The role of granulocyte transfusion for sepsis in neonates is not clear, and this treatment is not routinely used. It is important to establish the following factors before the transfusion of granulocytes: 1) strong evidence of bacterial or fungal septicaemia; 2) absolute neutrophil count less than 500/μL, chronic granulomatous disease, or leukocyte adhesion deficiency; and 3) diminishing storage pool (such that 7% of nucleated cells in the marrow are granulocytes that are metamyelocytes or more mature).[3,56]

AABB GUIDELINES[3]

- Neonates or children with neutropenia or granulocyte dysfunction with bacterial sepsis and lack of responsiveness to standard therapy.

- Neutropenic neonates or children with fungal disease not responsive to standard therapy.

DOSAGE OF BLOOD COMPONENTS

Table 4: According to *AABB*[3], Blood Components and Dosing of Small Volumes in Neonates

Component	Dose	Expected Increment
Red Blood Cells	10-15 mL/kg	Haemoglobin increase 2-3 g/dL*
Fresh Frozen Plasma	10-15 mL/kg	15%-20% rise in factor levels (assuming 100% recovery)
Platelets [whole-blood-derived (WBD) or apheresis]	5-10 mL/kg or 1 WBD unit/10 kg (patients ≥10 kg	50,000/μL rise in platelet count (assuming 100% recovery) †
Cryoprecipitated AHF	1-2 units/10 kg	60-100 mg/dL rise in fibrinogen (assuming 100% recovery)

*Dependent on anticoagulant-preservative solution: with 3 g/dL increment for CPD and CPDA-1 and 2 g/dL for AS-1, AS-3 and AS-5.

†Assumes $\geq 5.5 \times 10^{10}$ platelets in 50 mL of plasma (whole-blood-derived) and $\geq 3.0 \times 10^{11}$ platelets in 250-300 mL plasma (apheresis).

CPD = citrate-phosphate-dextrose; CPDA-1 = citrate-phosphate-dextrose-adenine-1; AS = additive solution.

PRETRANSFUSION TESTING

1. PRINCIPLE

Fetal and neonatal ABO grouping differs from adult ABO grouping because:

- Fetal/neonatal ABO red cell antigens may be poorly expressed.
- Due to the naivety of the fetal/neonatal immune system the corresponding ABO red cell antibodies are not usually well-developed.
- Maternal IgG ABO antibodies may be detectable in the fetal /neonatal plasma.

The in-built laboratory double-check for ABO blood grouping cannot be used for fetal/neonatal samples because the red cell antigen (forward) group cannot be confirmed by the plasma antibody (reverse) group.

Fetal/neonatal antibody screening differs from adult antibody grouping because:

- Red cell antibodies are not usually produced within the first four months of life even after multiple transfusions.
- Maternal IgG antibodies are actively transported across the placenta during the second trimester onwards providing acquired immunity to the fetus and neonate. These can include clinically significant red cell antibodies and prophylactic anti-D if administered during pregnancy.

Due to these factors antibody screening of a foetus/neonate represents the maternal antibody status rather than the fetal/neonatal antibody status.[12]

2. RBC TRANSFUSION[68]

Red cells for small volume transfusion should

- be ABO compatible with mother and infant, and infant's RhD group (or RhD negative)
- be IAT compatible with maternal plasma (if available) or neonate's plasma for first transfusion (and subsequent transfusions up to four postnatal months if atypical maternal antibodies present);
- be 35 days old or less (if in SAG-M or similar additive system)
- 28 days old or less (if in CPD)
- have a haematocrit of 0.50–0.70;
- be irradiated if appropriate (in case of immunocompromised recipients)
- usually be infused in a volume of 10–20 ml/kg;
- be aliquoted donations (Pedi pack) from a single unit dedicated to one infant.

3. PLATELET TRANSFUSION[68]

Platelets for neonatal transfusion should

- be ABO identical or compatible (Table I): RhD identical or compatible;
- be HPA compatible in infants with alloimmune thrombocytopenia;
- be produced by standard techniques without further concentration;
- be irradiated if appropriate;
- usually be infused in a volume of 10–20 ml/kg

4. PLASMA TRANSFUSION[68]

Fresh frozen plasma for neonatal transfusion should

- be group AB, or compatible with recipient's ABO red cell antigens
- usually be infused in a volume of 10–20 ml/kg

Virus inactivated plasma should be used for the treatment of patients with inherited coagulation deficiencies where no pathogen-inactivated (PI) factor concentrate is available.

CYTOMEGALOVIRUS (CMV) SAFE BLOOD COMPONENT

With recent advances in the manner of blood collection and segregation the risk of infection from transfusion has decreased considerably, but still there are chances of transmission of various infections inadvertently.[8] Prevention of transfusion-transmitted infections is especially important for neonates because any gain from transfusion safety in neonates will lead to more disease-free years of life compared with adults.[62] The transmission of CMV via transfusion is of special concern in immune incompetent patients, such as preterm neonates born to CMV-seronegative mothers which can cause serious morbidity and mortality.[62,69] CMV negative blood is indicated for intrauterine transfusion of packed RBC and platelets, neonates with birth weight <1500 grams and/or gestation < 30weeks and neonates with congenital or acquired immune deficiency[4] and exchange transfusion.[70]

Proper donor screening for CMV can be effective to decrease the risk of TT-CMV; however, TT-CMV can still occur with this approach because of false-negative serology results and the window period in which a CMV-seronegative donor has been acutely infected.[62] CMV is endemic in India with seroprevalence rates greater than 95%, which severely limits the donor pool.[71] Because latently infected monocytes in the donor blood are the primary source of TT-CMV, leukocyte reduction of blood products also effectively decreases the risk of TT-CMV.[62,72] With the increasing use of filtered blood components, the need for blood from CMV-seronegative donors is decreasing because there is no known additive effect of combining both measures for preventing CMV.[73] Future steps should consider other better and more accurate donor testing, like CMV nucleic acid testing to further improve the safety of leukoreduced blood products and pathogen reduction technology.[62]

IRRADIATED BLOOD COMPONENTS

Neonates, particularly those who are extremely preterm, are at risk for transfusion associated graft versus host disease (TA-GvHD).[8] Irradiation is the only method to render the T lymphocyte nonmitogenic and prevent this reaction.[72] Irradiation is indicated for intrauterine transfusion of packed RBC and platelets, transfusion of packed RBC and platelets after intrauterine transfusion, exchange transfusion, transfusion of RBC and platelets in neonates with birth weight < 1500grams and/or gestation at birth < 30weeks, donations from first or second-degree relatives and neonates with congenital

or acquired immunodeficiency.[4,73] So, a blanket policy of irradiating blood for all neonates is not required.[72,73]

EXCHANGE TRANSFUSION

1. INDICATIONS

Neonatal hyperbilirubinemia resulting in clinical jaundice is a common problem among neonates.[74] Exchange blood transfusion (EBT) is usually done in neonatal population to manage a high or rapidly rising bilirubin not responsive to intensive phototherapy or intravenous immunoglobulin or for severe anaemia.[3,75,76] EBT is mainly used in the treatment of HDN to prevent bilirubin encephalopathy by taking away from circulation the antibody-coated red cells and excess bilirubin.[5,76] It may also be required for neonatal hyper bilirubinaemia due to other causes, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency.[3,75] Noto et al in their study stated that exchange transfusion have been used in the treatment of DIC, sepsis[77], hyper viscosity syndrome and other toxic conditions.[75]

2. GUIDELINES

The criteria used to assess the need for exchange transfusion includes total bilirubin level, haemoglobin level and subjective symptomatology of the neonate.[8] Murray et al[78] in their study stated that traditional guidelines suggest exchange transfusion in the following circumstances:

Within 12 hours of birth if:

- Cord blood bilirubin concentration exceeds 3 to 5 mg/dL (50–85μmol/L) for preterm infants, and 5 to 7 mg/dL (85–120μmol/L) for term infants, or the rate of increase is >0.5mg/dL/hour (8.5μmol/L/h); and
- Severe anaemia with haemoglobin <10 g/dL combined with hyperbilirubinemia.

After 24 hours of birth if:

- Total bilirubin concentration >20mg/dL (342μmol/L) or a bilirubin increase of >0.5mg/dL/hour (8.5μmol/L/h), or haemoglobin <10g/dL combined with hyperbilirubinemia.

EBT is not without its associated risks and is now infrequently performed in most neonatal units mainly because of the reduction in HDN following routine antenatal anti-D prophylaxis for D-negative women and the ready availability of intensive phototherapy as a safe alternative to EBT. EBT must take place in an intensive care setting with intensive clinical and biochemical monitoring, carried out by trained healthcare providers.[3,76]

A single blood volume EBT will remove 75% of the neonatal red cells, and a double volume (160-200 mL/kg depending on gestational age) up to 85-90% red cells, and up to 50% of circulating bilirubin. A double-volume

exchange transfusion can be more efficacious in removing antibody-sensitised neonatal red cells and reduce the need for a subsequent EBT, but there is little direct evidence.[3]

3. COMPONENT AND PROCEDURE

A specific red cell component for neonatal exchange transfusion is provided, usually group O, and it should be compatible with any maternal antibody. Red cell units for neonatal exchange transfusion are not available readily in institution and they require adequate notice to be made available from the hospital transfusion laboratory. The time is needed to perform irradiation of the selected component and transportation to the hospital. When HDN is caused by an unusual antibody, it may take longer for red cell units to be provided by the Blood Services, and at least 24 hours' notice should be made to the lab. In emergency situations, it is occasionally necessary to use standard antigen-negative red cells in saline, adenine, glucose and mannitol (SAGM) if red cells for specific exchange transfusion cannot be provided in time. There should be meticulous biochemical monitoring of the recipient neonate for complications e.g. for possible rebound hypoglycaemia.[3,12]

Red cells suitable for neonatal exchange are irradiated, and 'fresh' (before the end of Day 5 following donation, with a 24-hour shelf-life post irradiation in order to reduce the risk of recipient hyperkalaemia[3,12] and CMV negative.[4,12] They have a controlled Hct 0.5-0.6, in order to mitigate the

dangers of both post-exchange anaemia and polycythaemia.[3,4,12] The red cell unit must be negative for high-titre anti-A and anti-B antibodies (HT negative).[12]

EBT should not be performed with red cells straight from 4ºC storage, and an approved/CE-marked blood warming device should be used to avoid hypothermia. However, use of a blood warmer is only appropriate if the infusion is given at a constant rate (warming is not suited to the intermittent bolus nature of a single vessel EBT where the "push-pull" cycle method is used). Blood warming during EBT should not be uncontrolled (e.g. infusion lines exposed to a radiant heater) because of the risk of red cell haemolysis.[3,12]

TRANSFUSING STORED RBCs IN NEONATES

Neonatologists insist on fresh RBCs over stored RBCs generally for the following concerns:

1. The increase in extracellular potassium (K+)
2. The decrease in RBC 2,3-disphosphoglycerate (2,3-DPG) – both of which occur in RBC units during extended storage; and
3. The safety of additives such as mannitol, adenine and the relative amounts of glucose and phosphate present in extended storage preservative solutions

These are more pronounced in transfusion with large volume (>25 mL/kg) as during a surgery, exchange transfusion or extracorporeal membrane oxygenation and do not apply in the small volume transfusion setting.[14] Most of the red cell transfusions to neonates are small volume transfusions (traditionally 10-20 mL/kg, typically 15 mL/kg over 4 hours) given to replace phlebotomy losses in the context of anemia of prematurity, especially for preterm Very Low Birth Weight (VLBW) neonates.[12,56]

1. POTASSIUM

To compute the amounts added potassium due to transfusions, Strauss determined that an RBC unit (80% haematocrit) stored in an extended storage medium for 42 days would deliver 2mL of plasma containing only 0.1 mmol/L of potassium when transfused at 10 mL/kg. This amount of potassium is much less than the daily requirement of 2 to 3 mmol/L for a patient weighing 1 kg. The amount of potassium leak from cell is determined by the type of anticoagulant-preservative solution used to store RBCs. For instance, a unit of RBCs preserved in an additive solution (AS), such as AS-1, AS-3, or AS-5, delivers less extracellular potassium than RBCs stored in citrate-phosphate-dextrose adenine (CPDA-1).[3,14,79] In addition, special component processing, such as irradiation, can aggravate potassium leaks. When components with potassium leak are stored for more than 24 hours, washing may be required to remove the excess potassium before transfusion.[3,80] This washing practice is supported by several studies in which,

infants who received either older RBC units or units that had been irradiated (>1 day before transfusion), via central line or intra cardiac line had severe adverse effects, including cardiac arrest and death which were attributed to potassium.[3,81]

2. 2,3-DPG

Levels of 2,3-DPG in red cells decrease rapidly after 1 to 2 weeks of storage because of the absence of glycolysis. This deficit does not affect older children and adult recipients negatively because of they can manufacture more 2,3- DPG in vivo and they can adjust for hypoxia by increasing their heart rate. Infants younger than 4 months do not have such advanced coping mechanisms to low 2,3-DPG levels. Sick neonates are further endangered in this context because of their low intracellular 2,3-DPG levels that further reduces with respiratory distress syndrome or septic shock. The regeneration of 2,3-DPG in transfused RBCs has not been studied in infants. However, even if no 2,3-DPG were regenerated the p50 of RBCs stored to outdate is the same as that found in the blood of preterm infants at birth (18 mmHg).[3,14]

3. ADDITIVE SOLUTIONS

RBCs are routinely produced from WB collection and stored in one of several anticoagulant and/or preservative solutions, which have varying constituents and shelf lives.[3] The clinician should be made aware of the nature and ingredients of the additive solution in use, especially in neonatal

transfusions. Initially, there were concerns about the use of AS-1 in premature neonate due to the presence of mannitol with its diuretic affects (750mg/100mL AS-1 vs none in CPDA-1) and higher quantities of adenine (27 mg/100mL AS-1 vs 17.3mg/63mL CPDA-1). Both adenine and mannitol have been shown to be renal toxic in high concentrations. A variety of clinical trials and mathematical models have concluded that blood preserved in AS is safe when used for small-volume (5-15 mL/kg) transfusions and may improve blood glucose homeostasis. AS-3 has 30mg adenine per 100mL without mannitol, has been found to be safe for small-volume neonatal transfusion.[55] However, for neonates with compromised liver or kidney function, it is advised that AS solution be removed from RBC prior to transfusion, especially if there might arise a need for multiple transfusion. The safety of AS-preserved RBCs in high volume transfusion as seen in trauma-related massive transfusions, cardiac surgery, or exchange transfusions is not well studied in neonatal population. Therefore, caution should be exercised when transfusing AS preserved RBCs in neonates especially in large volumes.[3] AS-5 is also used in blood collection, but there are no studies or guidelines regarding its use in neonatal population. Because its composition is similar to the other solutions, its safety profile can be assumed to be similar to the other solutions.[56]

STRATEGIES TO REDUCE DONOR EXPOSURE IN NEONATES

The increased risk of transfusion transmitted infections including unidentified infectious agents is a major concern in neonatal transfusion practice especially in those neonates with multiple transfusion.[25] So, strategies to reduce the donor exposure were researched. The adopted measures to reduce donor exposure are dedicating specific units to neonates, while taking the advantage of longer shelf life and improved viability of RBCs stored in additive solutions, with extended RBC shelf life of 42 days. Multiple Pedi-packs/Transfer bags with the aid of Sterile Connecting Device (SCD) from a single donor unit can be used to reduce donor exposure.[56,82,83] Uezima et al in their study showed a 33% reduction of blood donor exposure in preterm infants with birth weight less than 1000g using pedi-packs.[84] Cook et al reported a 49% reduction and 27% reduction in donor exposure for neonates weighing less than 1500gm and more than 1500gm respectively.[85] Liu et al,[79] Arora et al,[86] Lee et al[87] and Wang-Rodriguez et al[88] studies showed reduction in donor exposure using Pedi-packs. The other measures to reduce donor exposure are delayed cord clamping during birth, testing initial blood investigations using cord sample of the neonate, limiting phlebotomy losses and use of erythropoietin as an alternative to red cell transfusion.[82,89]

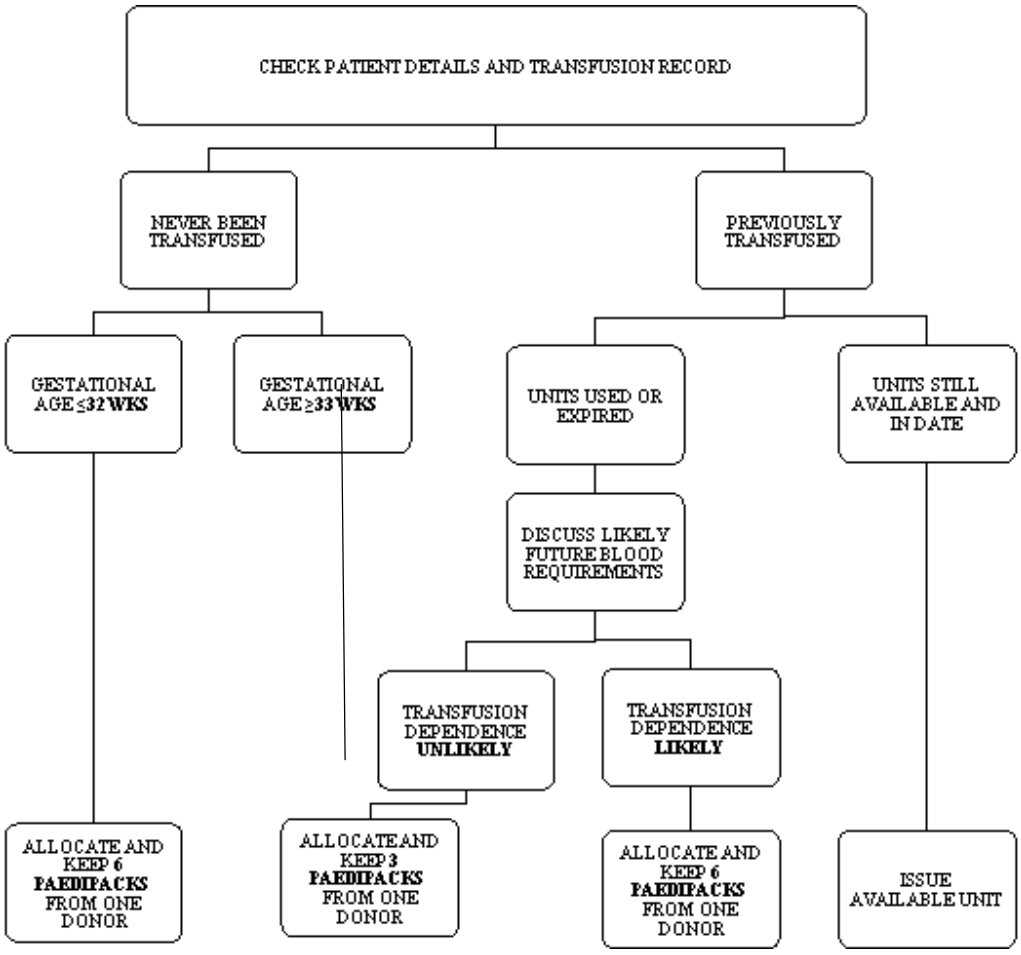


Fig. 1: Example neonatal paedipack allocation algorithm[12]

STORAGE AGE OF RED CELLS AND LENGTH OF STAY

1. AGE OF RED CELLS

Prolonged storage of RBCs leads to morphological changes that could have a deleterious impact on microvascular perfusion and thus oxygen delivery. These changes include changes to the cell shape and membrane, an increase in adhesiveness, a decline in flexibility and reductions in capillary flow. Further, older blood is associated with the release of free iron that may

predispose to vascular dysfunction, thrombosis and nosocomial infections. The storage medium could be deleterious by generating superoxides and inflammatory mediators that could result in oxidative damage.[13,62,90] Various studies have shown that prolonged RBC storage is associated with increased rates of infection, organ failure, death and increased length of stay. So, neonates are usually transfused with fresh RBCs because of the storage lesion associated with older RBCs.[90,91] But recent literatures are saying that there is no difference in outcome when transfusing with fresh or old units of red blood cells for small volume top up transfusion.[13] Fresh (<5 days old) RBCs are required in case of large volume transfusion such as exchange transfusion, during cardiac surgery and ECMO.[14]

2. LENGTH OF STAY

It has been demonstrated in various studies that blood component transfusion is associated with increased morbidity, mortality and length of stay. Prospective and retrospective observational studies in critically ill adults show that RBC transfusions have an independent association with increased morbidity and mortality rates, irrespective of disease severity.[90] RBC transfusions are associated with immunosuppressive effects and the development of multiple system organ failure. The leukocytes in the donor blood are responsible for the immunomodulatory effects seen.[92] However, it is still unclear whether the high mortality and morbidity were the direct result of

transfusions, with the sickest neonates receiving more transfusions and predictably having worse outcomes.[49]

Age of Red Blood Cells in Premature Infants (ARIPI),[91] a randomized controlled trial conducted in Canada to address the issue of the effect of RBC age on transfused neonates. In this study they randomly assigned low birth weight infants to be transfused with RBCs that were 7 days old or less (mean = 5.1 days, n = 188) and with standard issue RBCs divided into aliquots and stored for 2 to 42 days (mean = 14.6 days, n = 189). The primary composite endpoints in this trial were, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and bronchopulmonary dysplasia (BPD). The ARIPI trial found no differences in the primary endpoints between infants in the two arms, suggesting that in the study population, the age of RBCs does not affect these common morbidities of prematurity. The systematic review and meta-analysis by Alexander et al could not discern any difference in the impact of blood age across patient groups, i.e. very fresh vs fresh RBCs, or old vs very old RBCs. But they have also noted narrow confidence intervals regarding mortality thus calling into question the applicability of the conclusions of the trial.[13] Alexander et al[13] study, AABB[3] and Cochrane review,[93] the length of stay was not influenced by the storage age of red cells. But in Hassan et al[10] study and Karam et al[94] study, LOS was influenced by the storage age of red cells and found to prolonged when using >14 days old blood.

Standard operating procedures in transfusion differ widely among neonatal care units based on factors like preferences of caregivers, hospital policy and availability of resources.[26] Most neonatal transfusion practices are based more on opinions and anecdotes than on verifiable evidence.[56] The expectation of benefit that most neonatologists have while prescribing medicines, is not seen to the same degree in the administration of blood products. Recent advances have resulted in both an increased need for transfusion of blood and awareness of the possible consequences of these products in the sick newborns.[95] Identifying and eliminating any unnecessary transfusions in the NICU would be a step toward better care, lower costs and more careful preservation of blood component resources.[23] Because of the above-mentioned reasons there exists a wide diversity in the practices among clinicians and in institutions when it comes to transfusions. Such a situation is far from ideal and there is a need to find and implement best transfusion practices uniformly and cohesively. As it stands, transfusion practices pose a great challenge to the healthcare workers caring for neonates.

MATERIALS AND METHODS

MATERIALS AND METHODS

Study design

Prospective Study

Study Population

Neonates admitted and treated in the Neonatal Intensive Care unit at Institute of Child Health.

Study area

- Neonatal Intensive Care Unit (NICU) & Blood Bank at Institute of Child Health & Hospital for Children.
- Department of Transfusion Medicine, The Tamilnadu Dr. M.G.R. Medical University, Chennai.

Sample size and Study Period

Neonates admitted and treated between September 2016 and August 2017, who fulfil inclusion criteria (Purposive sampling) were included in this study.

Inclusion criteria

- All neonates (up to 28 days), who received transfusion of at least one unit of blood and its components in the Neonatal Intensive Care Unit (NICU) at Institute of Child Health & Hospital for Children, Chennai.
- Those who are willing to participate in the study.

Exclusion criteria

- Those who are not willing to participate in the study.

Informed consent

Informed consent from parents/guardian of the neonates were obtained for willingness to participate in the study.

Study Procedure

The study protocol was approved by the Ethics Committee of University and Institute. A detailed clinical and blood transfusion details were recorded in a predesigned proforma. The data were taken till the outcome of the baby.

The following variables of the study population were obtained

- Neonate demographic details such as postnatal age of the neonate on admission, sex, birth weight, gestational age and mode of delivery.
- APGAR score at 5 min.
- Blood grouping and Rh typing
- Indication for admission in NICU and Diagnosis
- Indication for transfusion
- Components requested and issued
- Age of red cell units transfused
- Number of donor exposure
- Length of stay

OPERATIONAL DEFINITION

I. APPROPRIATENESS OF TRANSFUSION

The following guidelines formulated by "National Neonatology Forum (NNF) of India",[4] "American Association of Blood Banks",[3] "British Committee for Standards in Haematology"[12] and "Evidence based Experts opinion"[43,63,68] were used to study the appropriateness of blood and its components utilized in neonates. (Refer Table 1-3). If the transfusions given were based on the above guidelines the transfusion would be considered appropriate.

Table 5: Dosage of components used in the study

COMPONENT	DOSE
Packed red cells	15 ml/kg
Platelets	10 ml/kg
Fresh Frozen Plasma	10 ml/kg

II. Classification of neonates to assess transfusion requirements:

1. Gestational age[17,18] (Table 6)

Gestational age of the neonate
Extreme preterm (<28 weeks)
Very preterm (28 to <32 weeks)
Preterm (32 to <37 weeks)
Term (>37 weeks)

2. Birth Weight[19] (Table 7)

Birth Weight
Normal birth weight (≥2500 gm)
Low Birth Weight (2499-1500 gm)
Very Low Birth Weight (1499-1000 gm)
Extremely Low Birth Weight (<1000 gm)

3. APGAR Score at 5 min[20] (Table 8)

APGAR Score at 5 min	
7 – 10	Normal
4 – 6	Intermediate
0 – 3	Low

III. Relationship between Length of Stay (LOS) and Age of Red Cells

Length of stay (LOS) is the interval between admission and discharge of the neonate from the hospital.

The age of RBC unit was determined by subtracting the date of collection from the date of transfusion.

Older RBCs are associated with storage lesion.[13] Transfusion of older RBCs are associated with multi organ failure, postoperative infections mainly due to immunomodulatory effects of blood transfusion.[90] But there is no standard definition for fresh or old RBCs.[13] So, in this study the storage age of

red cells <7 days and <14 days were considered fresh to assess the relationship between LOS and storage age of red cells.

Statistical analysis

Data entry and analysis were done using SPSS software version 21.0. Statistical analysis was done using chi square test and analysis of variance for categorical variables and Pearson correlation to find correlation. P <0.05 was considered significant.

RESULTS

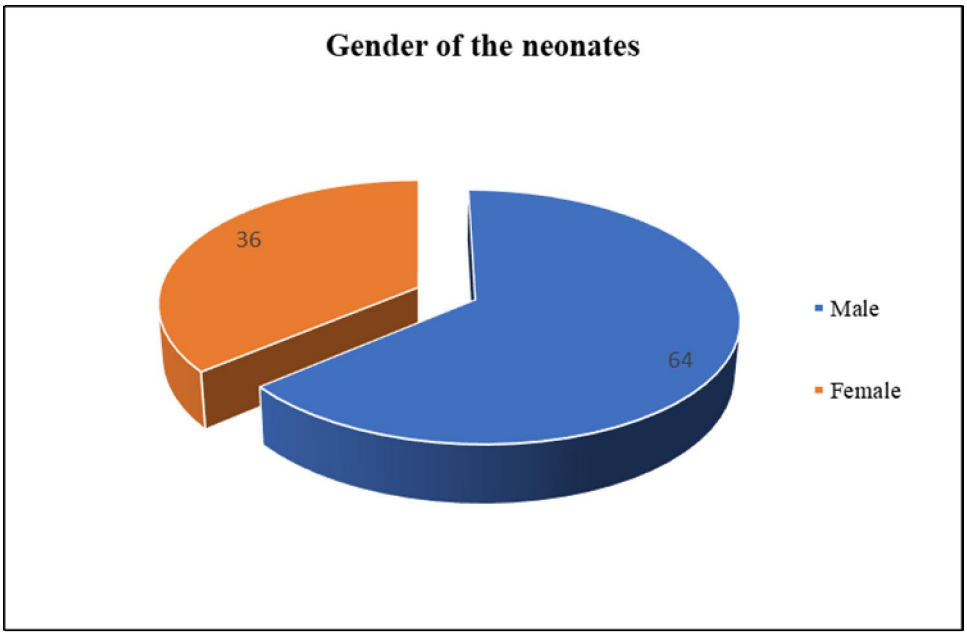
RESULTS

I. DEMOGRAPHIC CHARACTERISTICS OF NEONATES

Table 9: Distribution of gender among neonates

Gender	No of neonates	Percentage of neonates
Male	64	64%
Female	36	36%

Fig. 2: Distribution of gender among neonates

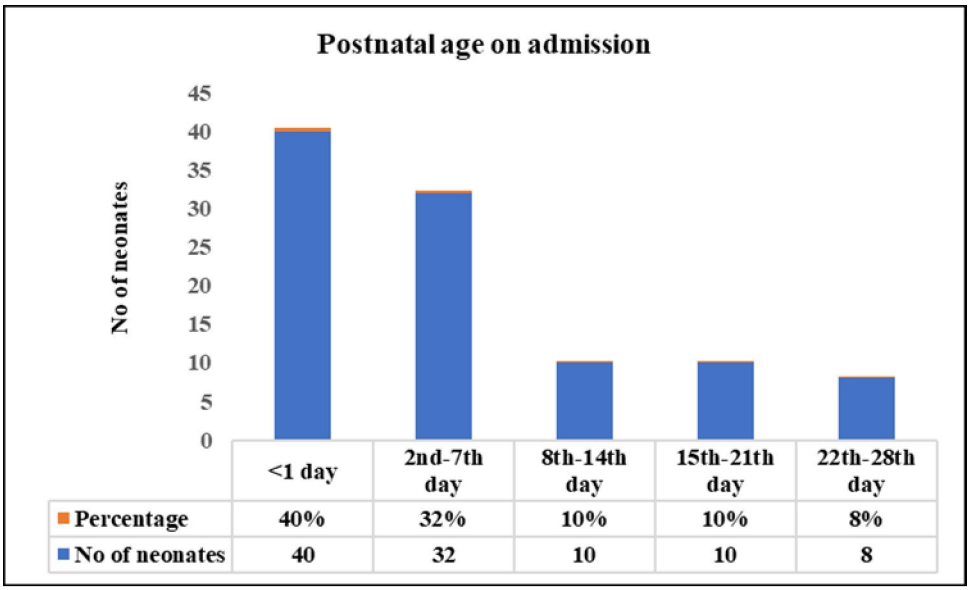


In the study population (n=100), 64% (n=64) were male and 36% (n=36%) were females.

Table 10: Distribution of the age of the neonate at the time of admission

Age of the neonate on admission	No of neonates	Percentage of neonates
<1 day	40	40%
2nd - 7th day	32	32%
8th - 14th day	10	10%
15th - 21th day	10	10%
22th - 28th day	8	8%

Fig. 3: Distribution of the postnatal age of the neonate at the time of admission

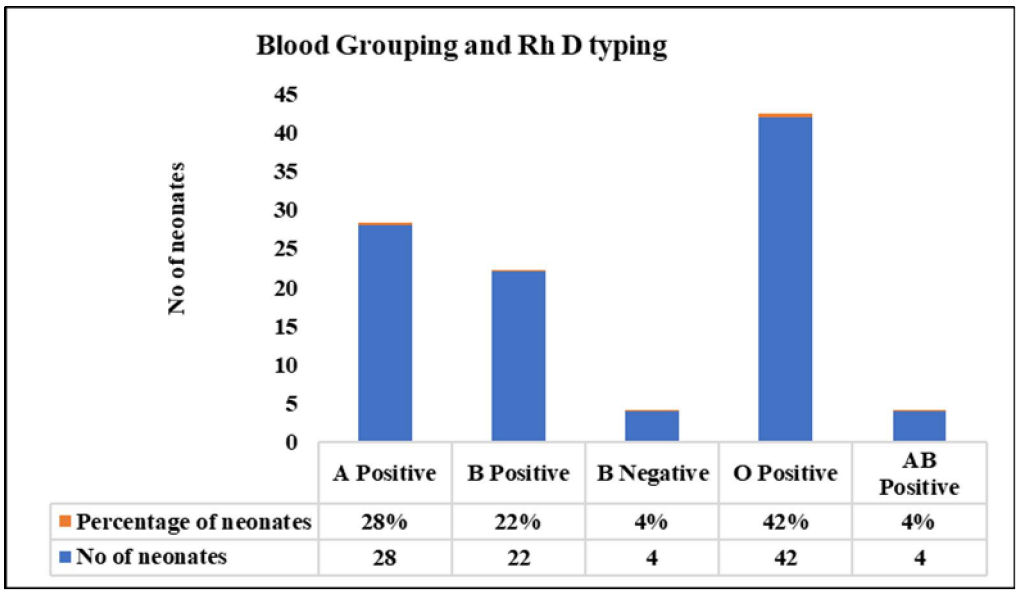


In the study population (n = 100), 40% (n=40) of the neonates were admitted within 24 hours of delivery, 32% (n=32) were admitted on 1st week [2nd to 7th day], 10% (n=10) were admitted on 2nd week, 10% (n=10) were admitted on 3rd week and remaining 8% (n=8) were admitted on 4th week of postnatal age of the neonate.

Table 11: Distribution of Blood grouping and Rh D typing among neonates

Blood grouping and Rh D typing	No of neonates	Percentage of neonates
A Positive	28	28%
B Positive	22	22%
B Negative	4	4%
O Positive	42	42%
AB Positive	4	4%

Fig. 4: Distribution of blood grouping and Rh D typing among neonates

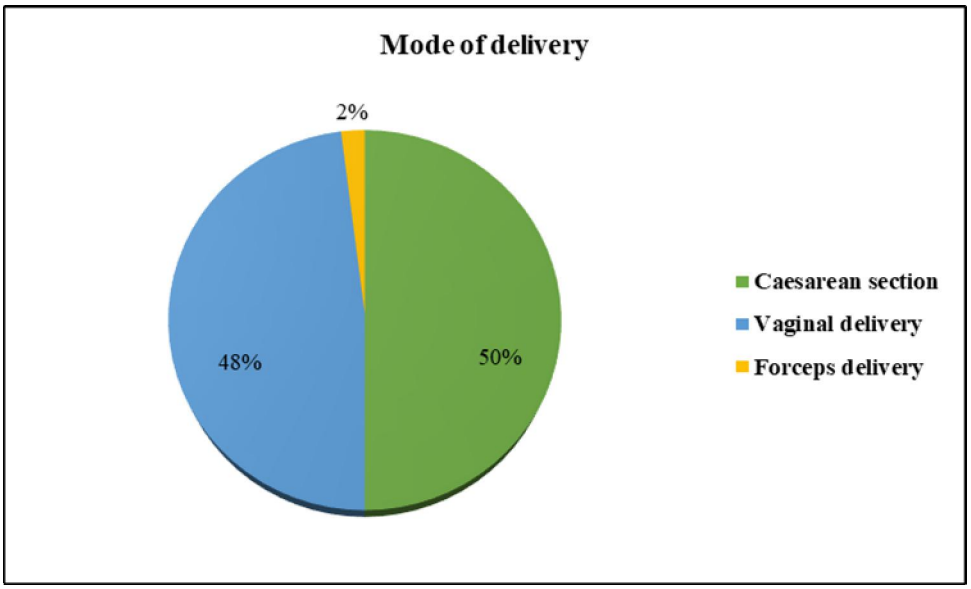


Distribution of Blood grouping and Rh typing among neonates showed 28% (n=28) were A Positive, 22% (n=22) were B Positive, 4% (n=4) were B Negative, 42% (n=42) were O Positive and 4% (n=4) were AB positive.

Table 12: Distribution of mode of delivery among neonates

Mode of delivery	No of neonates	Percentage of neonates
Caesarean section	50	50%
Vaginal delivery	48	48%
Forceps delivery	2	2%

Fig. 5: Distribution of mode of delivery among neonates

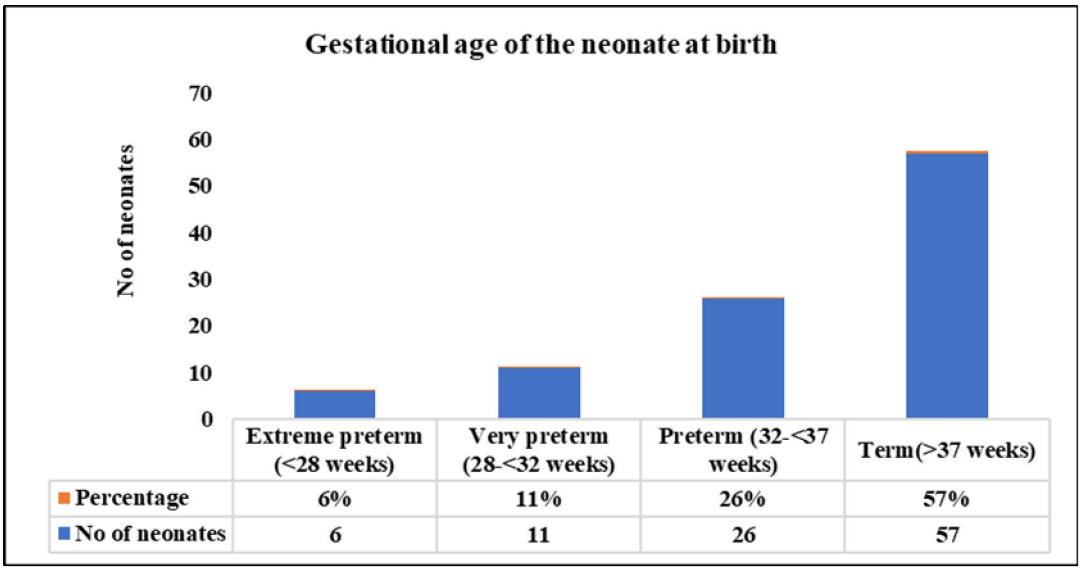


In the study population (n=100), 50% (n=50) of the neonates were delivered through caesarean section, 48% (n=48) were by vaginal delivery and 2% (n=2) by forceps delivery.

Table 13: Distribution of gestational age at birth among neonates

Gestational age of the neonate	No of neonates	Percentage of neonates
Extreme preterm (<28 weeks)	6	6%
Very preterm (28 - <32 weeks)	11	11%
Preterm (32 - <37 weeks)	26	26%
Term (>37 weeks)	57	57%

Fig. 6: Distribution of gestational age at birth among neonates

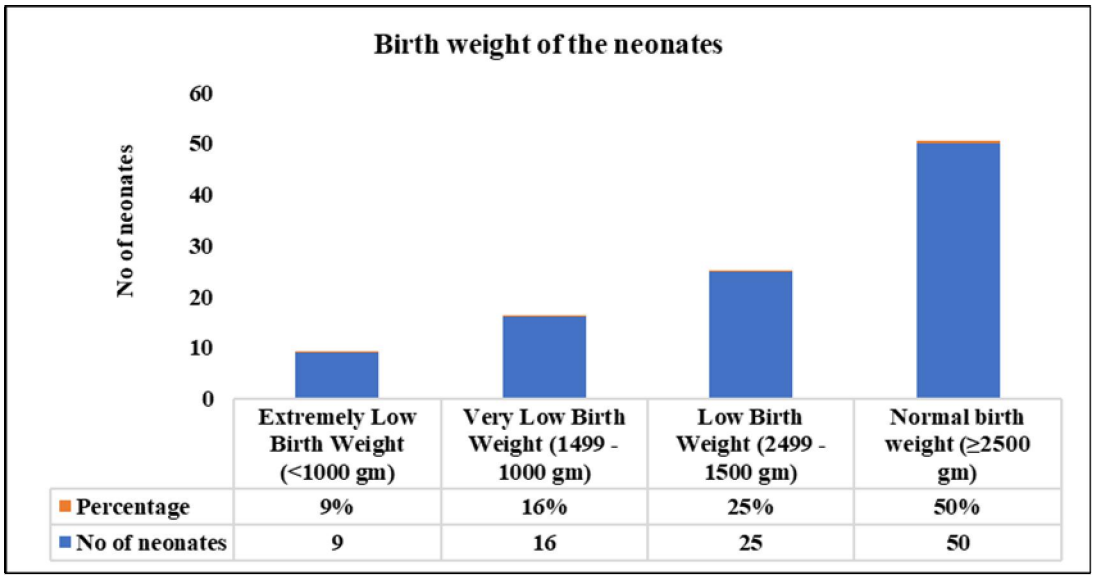


In the study population (N=100), 57% of the neonates were Term, 43% were preterm. In preterm neonates (n=43), 26% were born between 32 weeks to 37 weeks, 11% were very preterm (28 to less than 32 weeks) and 6% were extreme preterm (less than 28 weeks).

Table 14: Distribution of birth weight among neonates

Birth Weight	No of neonates	Percentage of neonates
Extremely Low Birth Weight (<1000 gm)	9	9%
Very Low Birth Weight (1499 - 1000 gm)	16	16%
Low Birth Weight (2499 - 1500 gm)	25	25%
Normal birth weight (≥2500 gm)	50	50%

Fig. 7: Distribution of birth weight among neonates

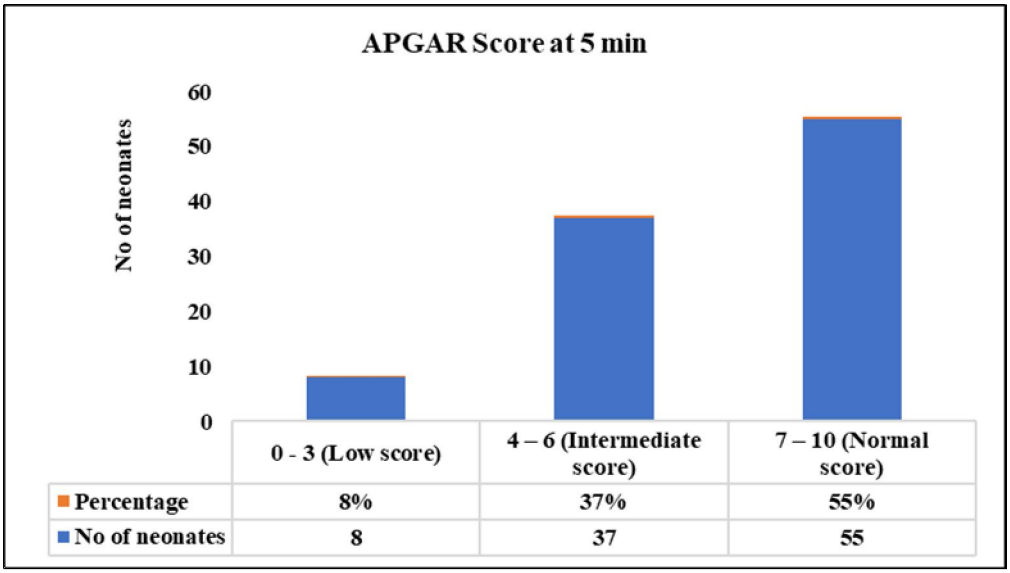


In the study population (n=100), 50% of the neonates born with normal weight, 25% were low birth weight, 16% were very low birth weight and 9% were extremely low birth weight.

Table 15: Distribution of APGAR score at 5 minutes of neonates

APGAR Score at 5 min	No of neonates	Percentage of neonates
0 - 3 (Low score)	8	8%
4 – 6 (Intermediate score)	37	37%
7 – 10 (Normal score)	55	55%

Fig. 8: Distribution of APGAR score at 5 minutes of neonates

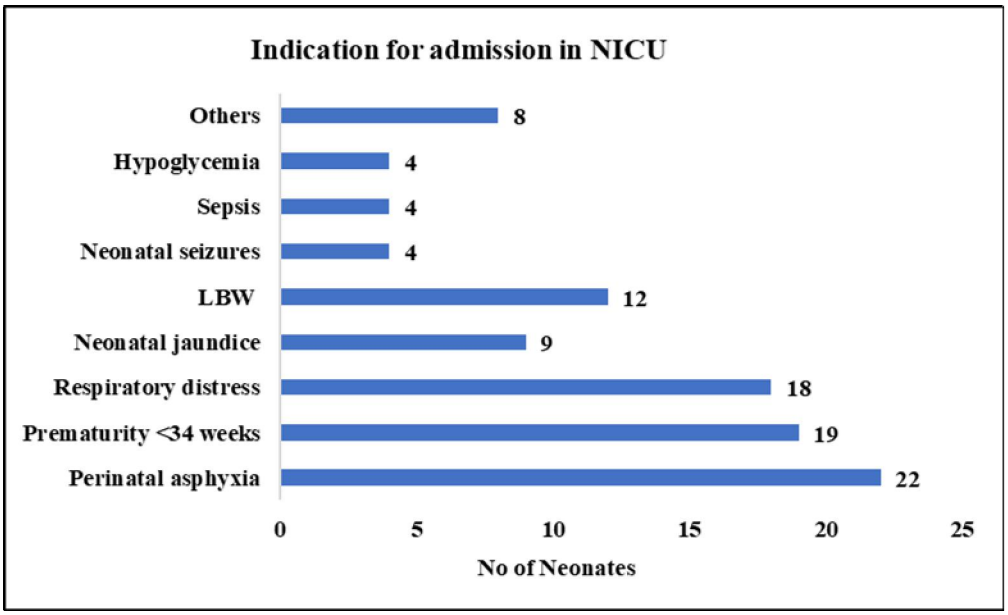


In the study population (n=100), 55% of the neonates were with normal (7-10) score, 37% with intermediate (4-6) score and 8% of the neonates were with low (0-3) APGAR score.

Table 16: Indication for admission in NICU among neonates

Indication for admission in NICU	No of neonates	Percentage of neonates
Perinatal asphyxia	22	22%
Prematurity <34 weeks	19	19%
Respiratory distress	18	18%
Neonatal jaundice	9	9%
LBW	12	12%
Neonatal seizures	4	4%
Sepsis	4	4%
Hypoglycemia	4	4%
Others	8	8%

Fig. 9: Indication for admission in NICU among neonates

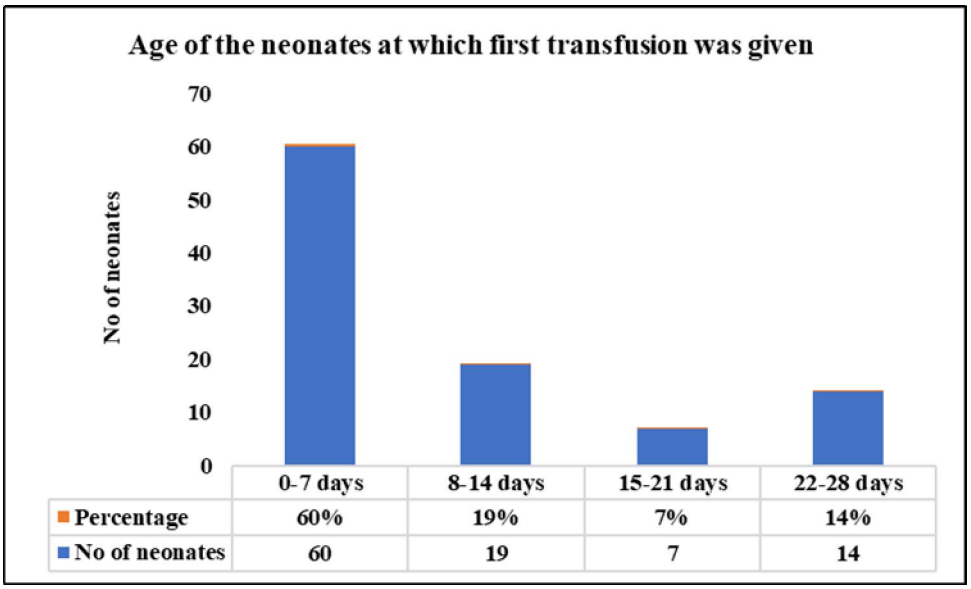


In the study population (n=100), the major cause for NICU admissions were perinatal asphyxia (22%), Prematurity <34 weeks (19%), Respiratory distress (18%) and Low birth weight <1800 gm (12%). The various were Neonatal jaundice, seizure, sepsis, hypoglycaemia.

Table 17: Distribution of age of the neonates (in days) at which first transfusion was given

Age of the neonate at which first transfusion was given	Mean ± SD (in days)	Percentage (%)
0 - 7 days	4 ± 2	60
8 - 14 days	11 ± 2	19
15 - 21 days	16 ± 1	7
22 - 28 days	24 ± 2	14

Fig. 10: Distribution of age of the neonates (in days) at which first transfusion was given

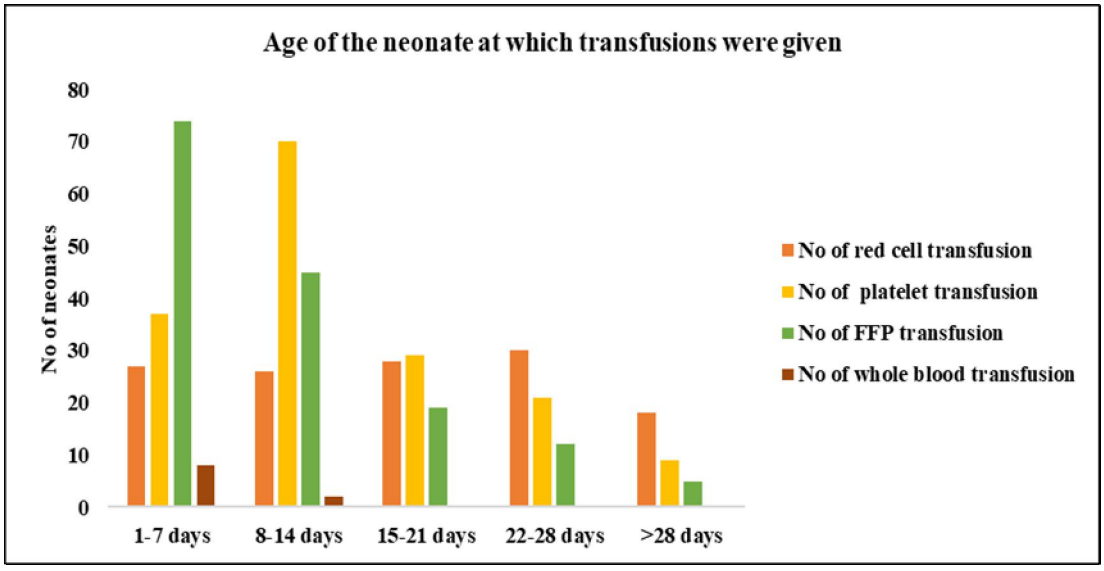


In the study population (n=100), 60% of the neonates received transfusion during the first week of life. 19% in the second week, 7% in the third week and 14% in the fourth week of life. The minimum and maximum age at which first transfusion was given were day 1 and day 28.

Table 18: Distribution of age of the neonates (in days) at which blood components were given

Age of the neonate at which components were given	No of red cell transfusion	No of platelet transfusion	No of FFP transfusion	No of whole blood transfusion	Total No of transfusion
1 - 7 days	27	37	74	8	146
8 - 14 days	26	70	45	2	143
15 - 21 days	28	29	19	0	76
22 - 28 days	30	21	12	0	63
>28 days	18	9	5	0	32

Fig. 11: Distribution of postnatal age (in days) of the neonates at which red cells, platelets, FFP transfusions and whole blood were given

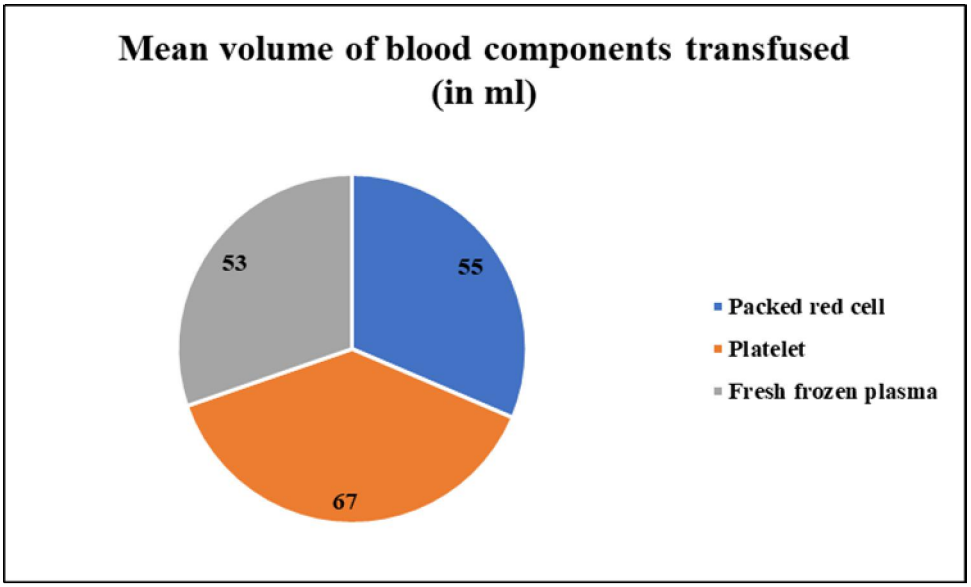


On analysis, most of the neonates had transfusions in the first and second week of life. In the first week of life, FFP was the major component utilized. In the second week, platelets usage predominant over the other components. Whole blood usage is seen only in the first two weeks.

Table 19: Distribution of the volume (ml) of blood transfused among neonates

Components	Mean ± SD (in ml)	Minimum (in ml)	Maximum (in ml)
Packed red cell	55 ± 41	9	235
Platelet	67 ± 59	10	297
Fresh frozen plasma	53 ± 52	6	231

Fig. 12: Distribution of the volume (ml) of blood transfused among neonates

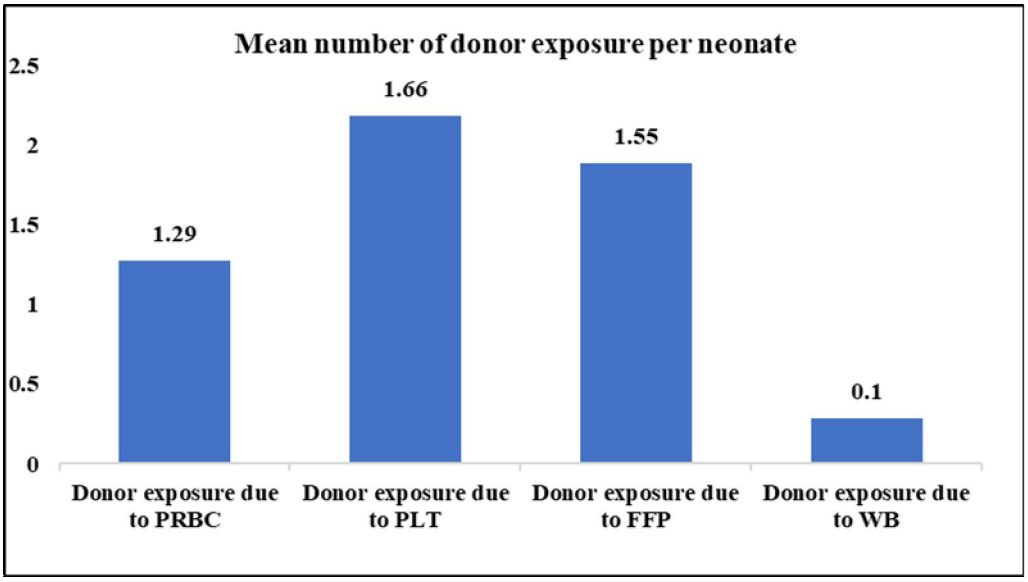


In the study population, the mean volume of packed red cells, platelets and FFP transfusions per neonates were 55ml, 67 ml and 53 ml respectively. The minimum and maximum volume of PRBC transfusions were 9ml and 235ml respectively. The minimum and maximum volume of platelets transfusions were 10ml and 297ml respectively. The minimum and maximum volume of FFP transfusions were 6ml and 231ml respectively.

Table 20: Distribution of mean number of donor exposure per neonate

Number of donor exposure	Mean ± SD	Minimum	Maximum
Total No. of donor exposure	4.6 ± 4.2	1	20
Donor exposure due to PRBC	1.29 ± 1.3	1	5
Donor exposure due to PLT	1.66 ± 2.2	1	10
Donor exposure due to FFP	1.55 ± 1.9	1	8
Donor exposure due to WB	0.1 ± 0.3	1	2

Fig. 13: Distribution of mean number of donor exposure per neonate



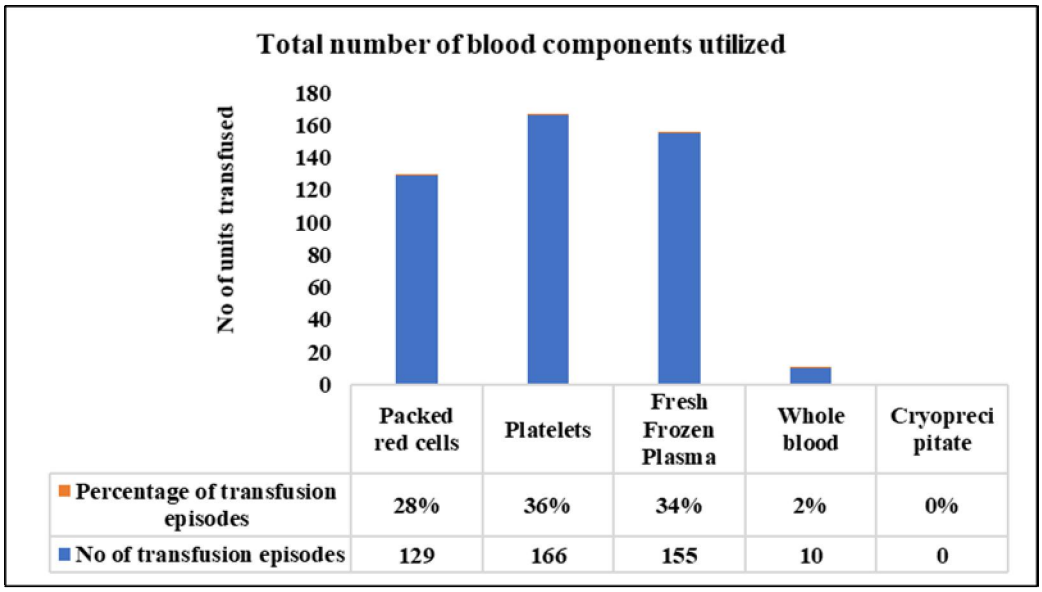
In the study population (n=100), the mean number of donor exposure per neonate was 4.6 ± 4.2. Mean number of donor exposure due to platelet transfusion was higher (1.66 ± 2.2), followed by FFP (1.55 ± 1.9), PRBC (1.29 ± 1.3) and whole blood (0.1 ± 0.3). The minimum and maximum number of donor exposed were 1 and 20 respectively.

II. APPROPRIATENESS OF BLOOD AND COMPONENT TRANSFUSION IN NEONATES

Table 21: Total blood components utilized in neonates

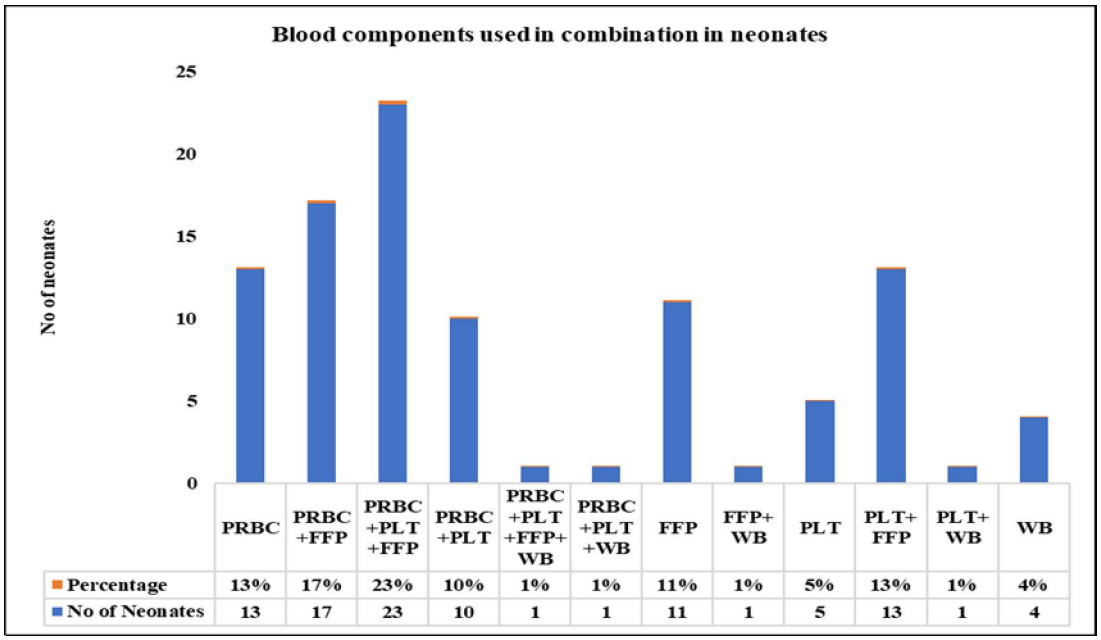
Component	No of neonates	No of transfusion episodes	Percentage of transfusion episodes
Packed red cells	66	129	28%
Platelet	53	166	36%
Fresh Frozen Plasma	66	155	34%
Whole Blood	8	10	2%
Cryoprecipitate	0	0	0%

Fig. 14: Total blood components utilized in neonates



In the study population (n=100), a total 460 transfusions were given. Of the 460 transfusions, 166 (36%) were platelet transfusions, followed by 155 (34%) FFP transfusions, 129(28%) red cell transfusions and 10 (2%) whole blood transfusions. Cryoprecipitate and single donor platelets were not used in the study population.

Fig. 15: Number of neonates for whom various blood components were used in combination

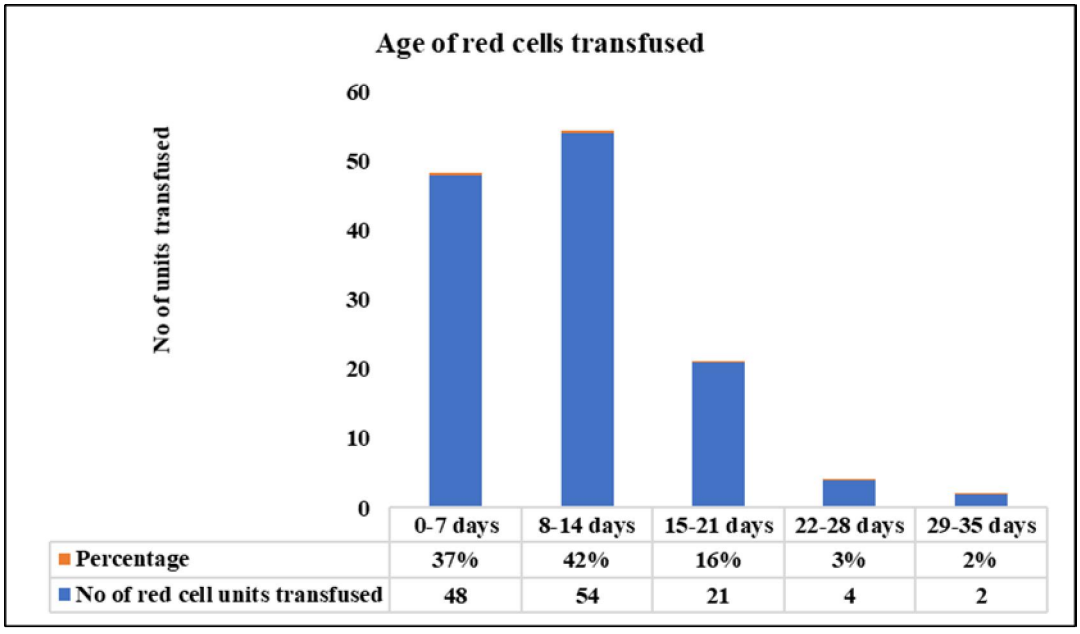


In the study population (n=100), packed red cells with platelets and FFP (23%) was the commonly used combination of blood components in neonates. The other commonly used combinations were packed red cells with FFP, packed red cells with platelets and platelets with FFP.

Table 22: Distribution of age of red cell units transfused to neonates

Age of red cells transfused	Mean ± SD (in days)
0 - 7 days	5 ± 2
8 - 14 days	10 ± 2
15 - 21 days	18 ± 2
22 - 28 days	24 ± 1
29 - 35 days	29 ± 0

Fig. 16: Distribution of age of red cell units transfused to neonates

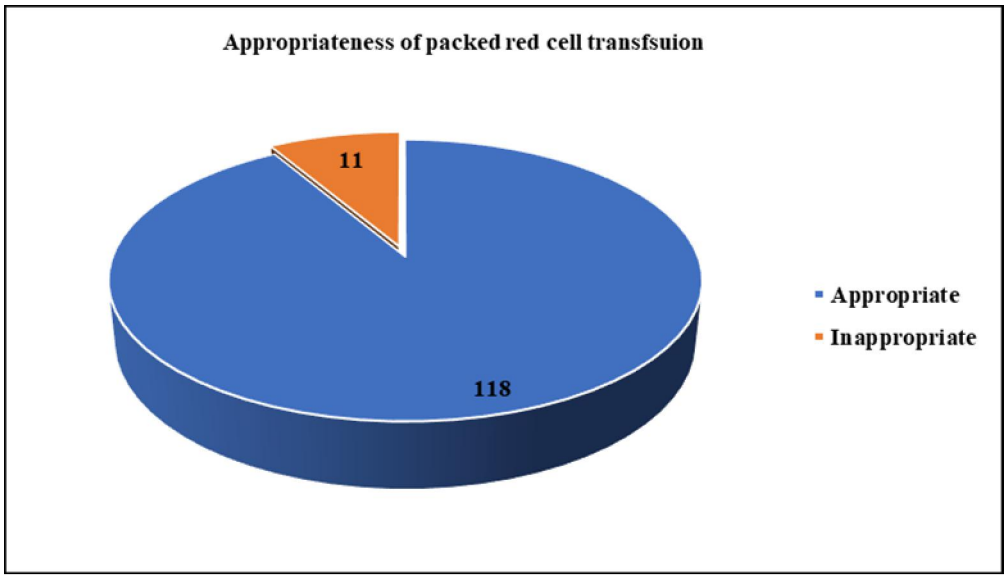


In the study population (n=100), most of the red blood cell transfusions belonged to first week (37%) and second (42%) week of storage. The mean age of red cells transfused in first and second week were 5 days old and 10 days old blood respectively. The minimum and maximum storage age of red cells units used were 1st and 29th day respectively.

Table 23: Distribution of red cell appropriateness among neonates

Appropriateness of red cell transfusion	No of transfusion episode	Percentage
Appropriate	118 out of 129	91%
Inappropriate	11 out of 129	9%

Fig. 17: Distribution of red cell appropriateness among neonates



Out of 129 packed red cell transfusions,91% (n=118) of the transfusions were appropriate and 9% (n=11) were inappropriate. Out of 118 appropriate PRBC transfusion, 53% (n=63) were compliant with NNF guidelines, 47% (n=55) were compliant with other guidelines.

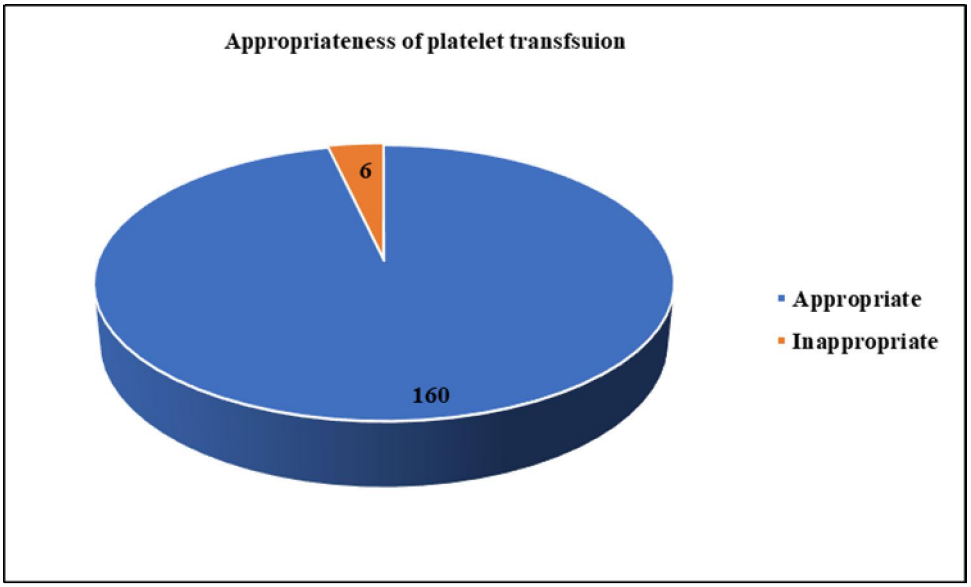
Table 24: Indications for packed red cell transfusion

Indications compliant with NNF guidelines	**No of transfusion**
PCV <18%, Symptomatic at room air	5
PCV <18%, on mechanical ventilation	6
PCV <20%, heart rate >180/min for 24 hours	1
PCV <20%, on supplementary oxygen requirement	7
PCV <25%, FiO2 <0.35	1
PCV <25%, on mechanical ventilation (MAP - <8cm of water)	11
PCV <30%, on mechanical ventilation (MAP - >8cm of water)	29
PCV <40%, early neonatal anaemia	3
Indications compliant with other guidelines (AABB)	**No of transfusion**
HCT <30%, with significant tachycardia (heart rate >180 beats/minute for 24 hours)	12
HCT <30%, on mechanical ventilation with mean airway pressure <6 cm of water	5
HCT <30%, on oxygen by nasal cannula	9
HCT <35%, on mechanical ventilation with mean airway pressure >6-8 cm of water	25
HCT <35%, on >35% oxygen hood	4
Inappropriate indications for packed red cell transfusion	**No of transfusion**
PCV >45%, without any symptoms	3
PCV >40%, without any symptoms	2
PCV >30%, without any symptoms	3
FiO2 ≥40% without laboratory assessment of haematocrit	3

Table 25: Distribution of platelet appropriateness among neonates

Appropriateness of platelet transfusion	No of transfusion episode	Percentage
Appropriate	160 out of 166	96%
Inappropriate	6 out of 166	4%

Fig. 18: Distribution of platelet appropriateness among neonates



Out of 166 platelet transfusions, 96% (n=160) of the transfusions were appropriate and 4% (n=6) were inappropriate. Out of 160 appropriate platelet transfusions, 97% (n=155) were compliant with NNF guidelines, 3% (n=5) were compliant with other guidelines.

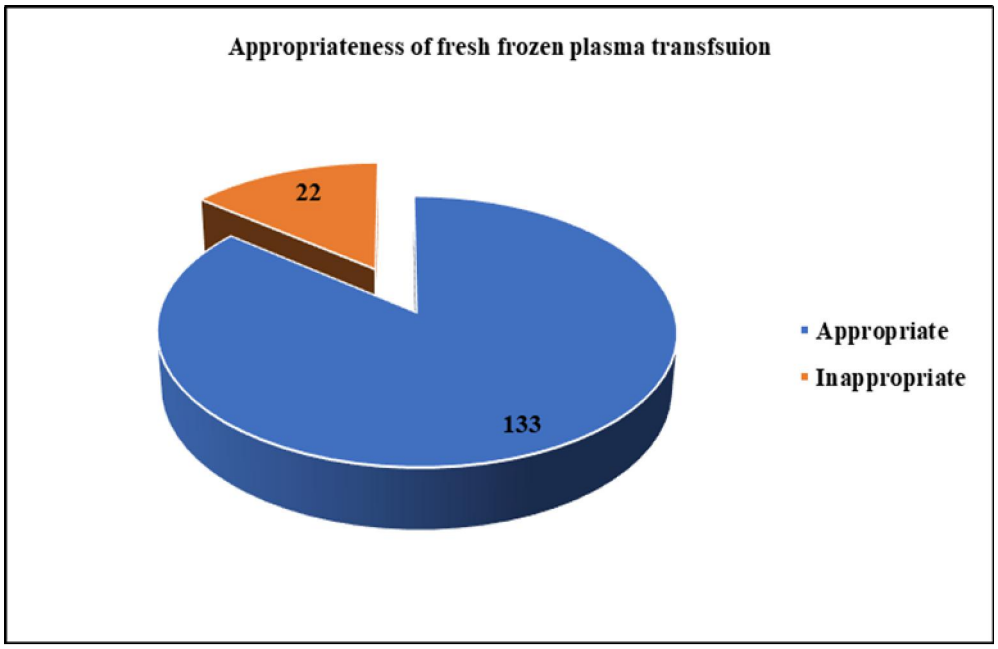
Table 26: Indications for platelet transfusion

Indications compliant with NNF guidelines	**No of transfusion**
Platelet count <30 × 10^9/L, with bleeding	41
Platelet count <30 × 10^9/L, without bleeding	81
Platelet count 30 to 49 × 10^9/L, with bleeding	3
Platelet count 30 to 49 × 10^9/L, neonates who were unstable	10
Platelet count 30 to 49 × 10^9/L, with associated coagulopathy	10
Platelet count 30 to 49 × 10^9/L, neonate with postnatal age <1 week	3
Platelet count 30 to 49 × 10^9/L, surgery or invasive procedure done	3
Platelet count 50 to 99 × 10^9/L, surgery or invasive procedure done	2
Indications compliant with other guidelines (BCSH, Expert opinion)	**No of transfusion**
Platelet count 32000/µL to 35000/µL, sepsis	3
Platelet count >50000/µL, major surgery done	2
Inappropriate indications	**No of transfusion**
Platelet count 61000/µL to 78000/µL, without bleeding	6

Table 27: Distribution of FFP appropriateness among neonates

Appropriateness of FFP transfusion	No of transfusion episodes	Percentage
Appropriate	133 out of 155	86%
Inappropriate	22 out of 155	14%

Fig. 19: Distribution of FFP appropriateness among neonates



Out of 155 FFP transfusions, 86% (n=133) of the transfusions were appropriate and 14% (n=22) were inappropriate. Out of 133 appropriate FFP transfusions, 38% (n=51) were compliant with NNF guidelines, 62% (n=82) were compliant with other guidelines.

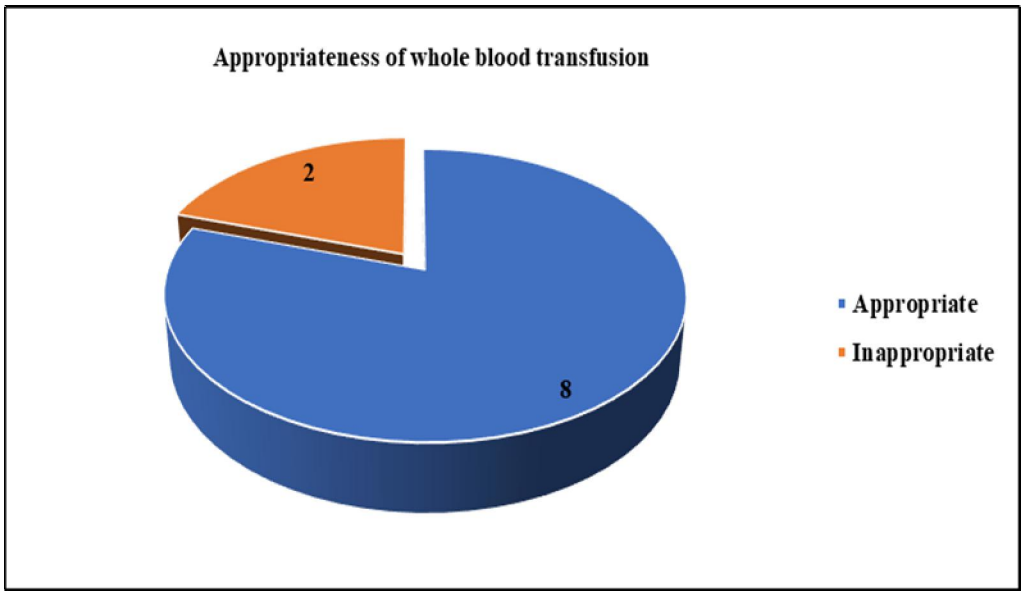
Table 28: Indications for FFP transfusion

Indications compliant with NNF guidelines	**No of transfusion**
Severe clotting deficiency (including DIC) with bleeding	47
Severe clotting deficiency in a neonate undergoing invasive procedure	3
Vitamin K deficiency with bleeding	1
Indications compliant with other guidelines (BCSH, Expert opinion)	**No of transfusion**
Sepsis with bleeding	25
High risk group (preterm and or intubated)	39
HIE on therapeutic hypothermia with bleeding	16
Shock	2
Inappropriate indications	**No of transfusion**
INR <1.5 without bleeding	8
Single episode of Nasogastric bleed in a term neonate	7
Metabolic abnormalities (hypernatremia, hyponatremia, hypokalaemia)	5
Coagulopathy without laboratory parameters done	2

Table 29: Distribution of whole blood appropriateness among neonates

Appropriateness of whole blood transfusion	No of transfusion episodes	Percentage
Compliant with NNF guidelines	9 out of 10	90%
Inappropriate	1 out of 10	10%

Fig. 20: Distribution of whole blood appropriateness among neonates



Out of 10 whole blood transfusions, 90% (n=9) of the transfusions were appropriate and 10% (n=1) were inappropriate. 9 appropriate whole blood transfusions were compliant with NNF guidelines.

Table 30: Indications for whole blood transfusion

Indication compliant with NNF guidelines	**No of transfusion**
Exchange transfusion	9
Inappropriate indications	**No of transfusion**
Both haemoglobin and platelets reduced	1

III. RELATIONSHIP BETWEEN NEONATAL PARAMETERS WITH TRANSFUSION REQUIREMENTS OF BLOOD COMPONENTS

Table 31: Relationship between gestational age of the neonate with transfusion requirements of blood components

Gestational Age Wise Component Usage	Red cell transfusion Mean ± SD	Platelet transfusion Mean ± SD	FFP transfusion Mean ± SD	Whole Blood transfusion Mean ± SD	Total no of transfusion Mean ± SD
Extreme preterm (<28 weeks)	2.16 ± 1.47	0.33 ± 0.81	1.00 ± 1.09	0.00 ± 0.00	3.50 ± 1.76
Very preterm (28 - <32 weeks)	2.45 ± 1.43	1.54 ± 1.91	1.72 ± 2.24	0.00 ± 0.00	5.72 ± 4.81
Preterm (32 - <37 weeks)	1.65 ± 1.52	3.07 ± 3.00	1.42 ± 1.81	0.77 ± 0.27	6.23 ± 5.03
Term (>37 weeks)	0.80 ± 0.97	1.17 ± 1.72	1.63 ± 2.01	0.14 ± 0.44	3.75 ± 3.68
P value	**0.00**	**0.01**	0.855	0.557	0.059

On analysis, the red cell requirement increases as the gestational age decrease. Platelet requirement is high in the preterm (32 - <37 weeks). No statistical difference in FFP usage as increase in gestational age. Preterm (32 - <37 weeks) were the most frequently transfused group.

Table 32: Relationship between birth weight of the neonate with transfusion requirements of blood components

Birth Weight Wise Component Usage	Red cell transfusion Mean ± SD	Platelet transfusion Mean ± SD	FFP transfusion Mean ± SD	Whole Blood transfusion Mean ± SD	Total no of transfusion Mean ± SD
Extremely Low Birth Weight (<1000 gm)	2.00 ± 1.32	0.89 ± 1.45	1.11 ± 1.05	0.00 ± 0.00	4.00 ± 1.87
Very Low Birth Weight (1499 - 1000 gm)	2.37 ± 1.50	2.37 ± 2.70	1.81 ± 2.34	0.63 ± 0.25	6.62 ± 5.94
Low Birth Weight (2499 - 1500 gm)	1.32 ± 1.18	1.88 ± 2.38	1.64 ± 2.07	0.00 ± 0.00	4.84 ± 3.55
Normal birth weight (≥2500 gm)	0.80 ± 1.12	1.46 ± 2.15	1.50 ± 1.86	0.18 ± 0.48	3.94 ± 4.08
P value	**0.00**	0.357	0.842	0.157	0.161

On analysis, the red cell requirement increases as the birth weight decrease. Platelet requirement also increases as a decrease in birth weight. But not statistically significant. No statistical difference in FFP usage as increase in gestational age. Very Low Birth Weight (1499 - 1000 gm) were the most frequently transfused group.

Table 33: Relationship between APGAR SCORE (5 min) of the neonate with transfusion requirements of blood components

APGAR Score at 5 min wise component usage	Red cell transfusion Mean ± SD	Platelet transfusion Mean ± SD	FFP transfusion Mean ± SD	Whole Blood transfusion Mean ± SD	Total no of transfusion Mean ± SD
0 – 3 (Low score)	2.12 ± 0.178	2.12 ± 3.27	2.87 ± 3.13	0.00 ± 0.00	7.12 ± 7.41
4 – 6 (Intermediate score)	1.16 ± 1.01	1.32 ± 1.93	1.62 ± 1.67	0.27 ± 0.16	4.13 ± 3.38
7 – 10 (Normal score)	1.25 ± 1.44	1.81 ± 2.32	1.30 ± 1.83	0.16 ± 0.46	4.54 ± 4.11
P value	0.178	0.497	0.096	0.149	0.192

On analysis, no significant difference in transfusion requirement across APGAR score at 5 min group. However, FFP transfusion was high in low APGAR score group.

IV. AGE OF RED CELLS AND LENGTH OF STAY (LOS)

Table 34: Difference in mean LOS in patients receiving RBCs of various storage ages

Variable **Age of red cells**	**Length of stay** **(in days)** **Mean ± SD**	**P value**
Neonates transfused with RBC units with <7 days storage (n=21)	17.00 ± 20.41	0.973 (>0.05)
Neonates transfused with RBC units with >7 days storage (n=26/79)	17.19 ± 18.51	
Neonates transfused with RBC units with <14 days storage (n=48)	18.81 ± 21.12	0.858 (>0.05)
Neonates transfused with RBC units with >14 days storage (n=6/52)	17.16 ± 21.48	

In the study population (n=100), it was observed that the mean length of stay of neonates receiving red blood cells stored for greater than 7 days and 14 days was not significantly longer than those receiving red blood cells stored less than 7 days and 14 days.

DISCUSSION

DISCUSSION

I. NEONATE DETAILS

1. Sex of the neonate

In our study, 64% (n=64) were male and 36% (n=36) were female. Similarly, in Rahim et al[22] study 71.96% were male and 28.04% were female, in Ogunlesi et al[5] study 71.4% (n=80) were male and 28.6% (n=32) were female.

2. Age of the neonate on admission

In our study, the minimum and maximum age of the neonate on admission were 2 hours and 27 days respectively. But in Ayede et al[24] study the age of the neonate was between 2 to 34 days. In our study, 72% (n=72) of the neonates were admitted in NICU in the first postnatal week. Of the 72%, 40% got admitted within 24 hours of delivery. Similarly, in Ogunlesi et al[5] study 81.2% (n=98) got admitted in NICU in the first postnatal week. But only 11.6% (n=13) were admitted within 24 hours of delivery.

3. Blood grouping and Rh typing of the neonate:

In our study, 42% belonged to O blood group, 28% belonged to A group, 26% belonged to B group and 4% to AB group. In Ayede et al[24] study, 43.9% were O group, 40% were A group, 13% B group and 2% were AB group.

4. Birthweight of the neonate

In our study, the mean birth weight of the neonate was 2199 gm with the minimum and maximum birth weight were 560 gm and 3655 gm respectively. 50% of the neonates were with normal birth weight (≥2500 gm), 25% were Low Birth weight neonates (2499 – 1500 gm), 16% were Very Low Birth weight (1499 – 1000 gm) and 9% were Extremely Low Birth weight (<1000 gm). In Ayede et al[24] study, the weight ranged from 800 gm to 3600 gm with the mean weight of 1640 gm. But in Ali et al[74] study, 0.8% of the neonates were ELBW, 5.4% were VLBW, 37.7% were LBW.

5. Gestational age of the neonate

In our study, the gestational age of the neonate ranged from 24 weeks to 42 weeks with the mean gestational age of 36 weeks. Similarly, in Boo et al[95] study, the mean gestational age was 33.6 weeks ranging from 24 to 41 weeks. 57% were term (>37 weeks), 26% were late preterm (32 - <37 weeks), 11% were very preterm (28 - <32 weeks) and 6% were extremely preterm (<28 weeks). Overall 57% were term and 43% were preterm neonates. In Boo et al[95] study, 22.7% of the neonates were extreme preterm, 25.5 were very preterm, 15.5% were late preterm and 36.4% were term neonates. In Ayede et al[24] study, 82% were preterm and 18% were term neonates.

6. Mode of delivery of the neonate

In our study, 50% were delivered by caesarean section, 48% by normal vaginal delivery and 2% by forceps delivery.

7. APGAR score at 5 min of the neonate:

In our study, APGAR score at 5 min ranged from score 2 to score 10 with the mean APGAR score of 6.5. 55% belonged to Normal score (7 – 10), 37% belonged to Intermediate score (4 -6) and 8% belonged to Low score (0 – 3).

8. Indication for admission in NICU

In our study, the indications for admission in NICU were perinatal asphyxia, prematurity, respiratory distress, neonatal jaundice, low birth weight, neonatal seizures, sepsis, hypoglycaemia and others (failure to thrive, lethargy, congenital malformation, hyperthermia and surgical interventions). In Rahim et al[22] study, the indications for admissions were prematurity, neonatal infection, neonatal jaundice and birth asphyxia. In Neogi et al,[11] the various reasons for admissions were respiratory distress, sepsis, low birth weight/prematurity, birth asphyxia, congenital malformation, jaundice and others.

9. Age of the neonate at which first transfusion was given

In our study population, 60% of the neonates received transfusion during the first week of life. 19% in the second week, 7% in the third week and 14% in the fourth week of life. The minimum and maximum age at which first transfusion was given were day 1 and day 28.

10. Age of the neonate at which transfusions were given

In our study, most of the neonates had transfusions in the first and second week of life. In the first week of life, FFP was the major component utilized. In the second week, platelets usage predominant over the other components. Whole blood usage is seen only in the first two weeks. Packed red cell requirement was same in all weeks.

II. APPROPRIATENESS OF BLOOD COMPONENT UTILIZATION

In the present study, 460 transfusions were given to 100 neonates. In Ogunlesi et al[5] study, 251 transfusions were given to 112 neonates. In Boo et al[95] study, 223 transfusions were given to 110 neonates. In Kaur et al[64] study, 557 transfusions were given to 280 neonates.

In the present study, 28% (n=129) received packed red cell, 36% (n=166) received random donor platelet, 34% (n=155) received fresh frozen plasma and 2% received whole blood. Cryoprecipitate and single donor platelets were not used in the study. Cellular products were not leukoreduced

or irradiated in the study. In Kaur et al[64] study, 54.7% received platelets and 24.5% received packed red cells. In Giridharan et al[6] study, 53% received platelets, 35% received packed red cells, 10% received FFP and 2% received cryoprecipitate. In Ogunlesi et al[5] study, 66.1% received packed red cells and 8% received plasma. In Ramanathan et al[41] study, 54.5% received platelets. In Bowen et al[31] study, 88.9% received packed red cells and 23.9% received platelets.

In the present study, 66 neonates received 129 packed red cells, 53 neonates received 166 platelets, 66 neonates received 155 FFP and 8 neonates received whole blood. In Kasat et al[26] study, 111 neonates received 559 packed red cells. In Altuntas et al[52] study, 80 neonates received 225 FFP. In Essabar et al[49] study, 60 neonates received 77 packed red cells. In Raban et al[53] study, 113 neonates received 142 FFP.

In the present study, packed red cells with platelets and FFP (23%) was the commonly used combination of blood components in neonates. The other commonly used combinations were packed red cells with FFP, packed red cells with platelets and platelets with FFP.

In the present study, the mean donor exposure was 4.6 which ranged from single donor exposure to 20 donor exposures. In Donowitz et al[83] study, the mean donor exposure was 6.9 which ranged from single donor exposure to 25 donor exposures. In Wang-Rodriguez et al[88] study, the mean donor

exposure was 1.6 ± 0.8. In Cook et al[85] study, the mean donor exposure in Group I was 8.2 (1 -25) and in Group II was 2.2 (1 – 9). The strategies to reduce donor exposure in neonates are delayed clamping or milking of the umbilical cord at preterm, drawing the initial blood tests from cord/placental blood from VLBW neonates, limiting phlebotomy losses of VLBW neonates, aliquoting the blood components into Pedi packs or using sterile connecting device and using till its expiration date, selected use of erythropoiesis stimulating agents to prevent transfusions, using platelet mass (number of platelets per microliter of blood and average platelet size) rather than platelet count in platelet transfusion services, permitting the platelet count to fall to <20000/μL in stable neonates and <50000/μL in unstable neonates, not performing routine coagulation test screening on every VLBW neonate.[89]

1. Appropriateness of red blood cell transfusions:

In the present study, out of 129 red cell transfusions, 91% (n=118) were appropriate and 9% (n=11) were inappropriate. Out of 118 red cell transfusions, 63 (53%) were compliant with NNF guidelines and 55 (47%) were compliant with other guidelines such as AABB and expert opinion. The reasons for inappropriate use of packed red cells in the present study were PCV 31% to >45%, without any symptoms and FiO2 ≥40% without laboratory assessment of haematocrit. In Wade et al[16] study, 77% packed red cell transfusions were appropriate. In Baer et al[23] study, 70% of packed red cell transfusions were appropriate.

The mean volume of red cell transfusion was 55 ml with the range of 9 ml to 235 ml. The mean donor exposure due to red cell transfusion was 1.29 with the range of single donor exposure to 5 donor exposures. In the present study, the mean haemoglobin before transfusion was 9.2 g/dL. In Kaur et al[64] study, Essabar et al[49] study and Portugal et al[2] study, the mean haemoglobin before transfusion was 8.2 g/dL, 8.59 g/dL and 9.0 g/dL respectively.

In the present study, most of the red blood cell transfusions belonged to second (42%) and first week (37%) of storage. The mean age of red cells transfused in first and second week were 5 days old and 10 days old blood respectively. The minimum and maximum storage of red cells units used in the present were day 1 and day 29 blood respectively.

2. Appropriateness of platelet transfusions

In the present study, out of 166 platelet transfusions, 96% (n=160) were appropriate and 4% (n=6) were inappropriate. Out of 118 platelet transfusions, 155 (97%) were compliant with NNF guidelines and 5 (3%) were compliant with expert opinion. The reasons for inappropriate use of platelets in the present study was transfusing at a platelet count 61000 to 78000, without bleeding. In Wade et al[16] study, 75% of platelet transfusions were appropriate. In Baer et al[23] study, 69% of platelet transfusions were appropriate.

The mean volume of platelet transfusion was 67 ml with the range of 10 ml to 297 ml. The mean donor exposure due to platelet transfusion was 1.66 with the range of single donor exposure to 10 donor exposures. In the present study, the mean platelet count before transfusion was 24973/µL. In Kaur et al[64] study and Ramanathan et al[41] study, the mean platelet count before transfusion was 35453/µL and 43118/µL respectively.

3. Appropriateness of fresh frozen plasma transfusions

In the present study, out of 155 FFP transfusions, 86% (n=133) were appropriate and 14% (n=22) were inappropriate. Out of 133 appropriate FFP transfusions, 38% (n=51) were compliant with NNF guidelines, 62% (n=82) were compliant with other guidelines such as BCSH and Expert opinion. The reasons for inappropriate use of FFP in the present study were INR <1.5 without bleeding, single episode of nasogastric bleed in a term neonate, metabolic abnormalities (hypernatremia, hyponatremia, hypokalaemia) and coagulopathy without laboratory parameters done. In Wade et al[16] study, 100% inappropriate FFP transfusions. In Raban et al[53] study, 75% of FFP transfused were appropriate. In Baer et al[23] study, 65% of FFP transfusions were appropriate.

The mean volume of FFP transfusion was 53 ml with the range of 6 ml to 231 ml. The mean donor exposure due to FFP transfusion was 1.55 with the range of single donor exposure to 8 donor exposures.

4. Appropriateness of whole blood transfusions

In the present study, out of 10 whole blood transfusions, 90% (n=9) of the transfusions were appropriate and 10% (n=1) were inappropriate. 9 appropriate whole blood transfusions were compliant with NNF guidelines. In one case, whole blood was used to treat combined anaemia and thrombocytopenia. Platelets are inactivated at 2-6˚C storage of whole blood. So, whole blood usage for this transfusion is inappropriate.

The mean donor exposure due to whole blood transfusion was 0.1 with the range of single donor exposure to 2 donor exposures. The age of the whole blood units transfused ranged from day 1 storage to day 5 storage with the mean storage age of whole blood was 2.9 days. In the present study, all exchange transfusions were double volume exchange transfusions.

III. RELATIONSHIP BETWEEN NEONATAL PARAMETERS WITH TRANSFUSION REQUIREMENTS

1. Relationship between gestational age of the neonate with transfusion requirements

In the present study, a significant linear association is present between gestational age of the neonate and red cell transfusion except for extreme preterm (<28 weeks). The survival rate of extreme preterm was low and also most of the extreme preterm neonates were also extremely low birth weight

neonates. When gestational age increases there is a decrease in the red cell requirement. This linear association is because preterm neonates enter extrauterine life with low iron stores and a small circulating volume of RBCs. Very preterm (28 - <32 weeks) had received more of red cell transfusion. Similarly, in Bowen et al[31] study and Freitas et al[32] study, there is an increase in red blood cell transfusion in neonates <32 weeks' gestation.

In our study, a significant linear association is present between gestational age and the platelet requirement. As gestational age increase platelet requirement also increases. But in term neonates' platelet requirement is low because term neonates born with normal adult platelet count values. Preterm neonates born with low platelet count. In our study, platelet requirement is high in preterm (32 - <37 weeks). Similarly, in Bowen et al[31] study platelet requirement is high in neonates ≥32 weeks of gestation. But in Ramanathan et al[41] study, there was no significant relationship between gestational age and neonatal thrombocytopenia and platelet transfusion. In the present study, no statistical difference in FFP usage as increase in gestational age. Association between gestational age and whole blood requirement could not make out because very preterm and extreme preterm neonates have not received whole blood.

2. Relationship between birth weight of the neonate with transfusion requirements

In the present study, a significant linear association was present between birth weight and transfusion requirement except extremely low birth weight neonates. The survival rate of ELBW neonates was low. In the present study, VLBW neonates received transfusion more frequently. Similarly, in Strauss[33] in an international forum stated that transfusions were greatly influenced by birth weight. 88% of ELBW neonates are transfused with blood. Platelet requirement also increases as a decrease in birth weight. But there is no statistical significance. In Ramanathan et al[41] study also VLBW neonates received more platelet transfusions. No statistical difference in FFP usage across the birth weight group of the neonates. Association between birth weight and whole blood requirement could not make out because very preterm and extreme preterm neonates have not received whole blood.

3. Relationship between APGAR SCORE (5 min) of the neonate with transfusion requirements

In the present study, no association between APGAR score at 5 min and transfusion requirement. FFP requirement increases as a decrease in APGAR score. But there is no statistical significance. In most cases, Low APGAR score was due to perinatal asphyxia. Coagulation derangement is

common in perinatal asphyxia. So, FFP usage is more common in the Low APGAR score group.

IV. AGE OF RED CELLS AND LENGTH OF STAY (LOS)

Prolonged storage of RBCs leads to morphological changes that could have a deleterious impact on microvascular perfusion and thus oxygen delivery. These changes include changes to the cell shape and membrane, an increase in adhesiveness, a decline in flexibility and reductions in capillary flow. Further, older blood is associated with the release of free iron that may predispose to vascular dysfunction, thrombosis and nosocomial infections. The storage medium could be deleterious by generating superoxides and inflammatory mediators that could result in oxidative damage.[13,62,90]

Various studies have shown that prolonged RBC storage is associated with increased rates of infection, organ failure, death and increased length of stay.[91] So, neonates are usually transfused with fresh RBCs because of the storage lesion associated with older RBCs. However, it is still unclear whether the high mortality and morbidity were the direct result of transfusions, with the sickest neonates receiving more transfusions and predictably having worse outcomes.[49]

But recent literatures are saying that there is no difference in outcome when transfusing with fresh or old units of red blood cells for small volume top up transfusion.[13,14] Fresh (<5 days old) RBCs are required in case of large

volume transfusion such as exchange transfusion, during cardiac surgery and ECMO.[14]

In the present day, the association between age of red cells transfused and length of stay was assessed. Based on Cochrane review,[93] AABB[3] standards and ARIPI trial,[91] <7 days and <14 days were considered fresh RBCs in the present study because of the lack of uniform definitions of fresh or old RBC storage. In the study population (n=100), it was observed that the mean length of stay of neonates receiving red blood cells stored for greater than 7 days and 14 days was not significantly longer than those receiving red blood cells stored less than 7 days and 14 days. Similarly, Alexander et al[13] study, AABB[3] and Cochrane review,[93] the length of stay was not influenced by the storage age of red cells. But in Hassan et al[10] study and Karam et al[94] study, LOS was influenced by the storage age of red cells and found to prolonged when using >14 days old blood.

Table 34: Master Chart for appropriateness of blood component utilization

Study	Present study	Kaur et al[64]	Giridharan et al[6]	Ogunlesi et al[5]	Cook et al[85]	Kasat et al[26]	Altuntas et al[52]	Ramanathan et al[41]	Essabar et al[49]	Boo et al[95]	Wade et al[16]	Portugal et al[2]	Bowen et al[31]	Wang-Rodriguez et al[88]	Raban et al[53]	Donowitz et al[83]	Baer et al[23]
Total no of transfusion	460 transfusions in 100 neonates	557 transfusions in 280 neonates	-	251 transfusions in 112 neonates	-	-	-	-	-	223 transfusions in 110 neonates	-	-	-	-	-	-	-
No of components transfused	66 neonates – 129 PRBC, 53 neonates – 166, 66 neonates – 155 FFP, 8 neonates – 10 WB	-	-	-	-	111 neonates – 559 PRBC	80 neonates – 225 FFP	-	60 neonates – 77 PRBC	-	-	-	-	-	113 neonates – 142 FFP	-	-
Percentage of components utilized	36 % platelets, 34% FFP, 28% PRBC, 2% WB	54.7% Platelets, 24.5% PRBC	53% Platelets, 35% PRBC, 10% FFP, 2% Cryo	66.1% PRBC, 8% Plasma	-	-	-	54.5% Platelets, 83.6% FFP	-	-	-	-	88.9% - PRBC, 23.9% - Platelets	-	-	-	-
Mean pre-transfusion HB	9.2 g/dL	8.2 g/dL	-	-	-	-	-	-	8.59 g/dL	-	-	9.0 g/dL	-	-	-	-	-
Mean pre-transfusion platelet	24973/µL	35458/µL	-	-	-	-	-	43118/µL	-	-	-	-	-	-	-	-	-
RBC appropriate transfusion	91%	-	-	-	-	-	-	-	-	-	77%	-	-	-	-	-	70%
Platelet appropriate transfusion	96%	-	-	-	-	-	-	-	-	-	75%	-	-	-	-	-	69%
FFP appropriate transfusion	86%	-	-	-	-	-	-	-	-	-	0%	-	-	-	75 %	-	65%
Whole blood	2%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Study	Present study	Kaur et al[64]	Giridharan et al[6]	Ogunlesi et al[5]	Cook et al[85]	Kasat et al[26]	Altuntas et al[52]	Ramanathan et al[41]	Essabar et al[49]	Boo et al[95]	Wade et al[16]	Portugal et al[2]	Bowen et al[31]	Wang-Rodriguez et al[88]	Raban et al[53]	Donowitz et al[83]	Baer et al[23]
appropriate transfusion																	
Mean donor exposure	4.6 ± 4.2 (1 – 20)	-	-	-	Group I – 8.2 (1 – 25), Group II – 2.2 (1 – 9)	-	-	-	-	-	-	-	-	1.6 ± 0.8	-	6.9 (1 – 25)	-

Table 35: Master chart for age of red cells and Length of Stay (LOS)

Study	Present study	Hassan et al[10]	Alexander et al[13]	AABB[3]	Cochrane[93]	Karam et al[94]
Storage age of red cells vs LOS	LOS not prolonged	LOS prolonged	LOS not prolonged	LOS not prolonged	LOS not prolonged	LOS prolonged

Table 36: Master chart for relationship between neonatal parameters with transfusion requirements of blood components

Study	Present study	Bowen et al[31]	Ramanathan et al[41]	Strauss in an international forum[33]	Freitas et al[32]
Gestational age of the neonate with transfusion requirements	Red cell requirement higher in <32 weeks and platelet requirement higher in >32 weeks	Red cell requirement higher in <32 weeks and platelet requirement higher in >32 weeks	No significant relation between gestational age and neonatal thrombocytopenia	-	Red cell requirement higher in <32 weeks
Birth weight of the neonate with transfusion requirements	VLBW <1500 gm neonates received more platelet transfusion	-	VLBW <1500 gm neonates received more platelet transfusion	Transfusions are greatly influenced by birth weight. 88% of ELBW neonates transfused with blood	-
APGAR SCORE (5 min) of the neonate with transfusion requirements	FFP usage was high in low APGAR score group. But not significant statistically	-	-	-	-

SUMMARY

SUMMARY

In our study,

I. On appropriate use of blood components

- Out of the 100 neonates, 64 were male and 36 were female.
- The minimum and maximum age of the neonate on admission were 2 hours and 27 days respectively. 72% (n=72) of the neonates were admitted in NICU in the first postnatal week. Of the 72%, 40% got admitted within 24 hours of delivery.
- The mean birth weight of the neonate was 2199 gm which from 560 gm to 3655 gm. 50% of the neonates were with normal birth weight (≥2500 gm), 25% were Low Birth weight neonates (2499 – 1500 gm), 16% were Very Low Birth weight (1499 – 1000 gm) and 9% were Extremely Low Birth weight (<1000 gm).
- The gestational age of the neonate ranged from 24 weeks to 42 weeks with the mean gestational age of 36 weeks. 57% were term (>37 weeks), 26% were late preterm (32 - <37 weeks), 11% were very preterm (28 - <32 weeks) and 6% were extremely preterm (<28 weeks). Overall 57% were term and 43% were preterm neonates.
- APGAR score at 5 min ranged from score 2 to score 10 with the mean APGAR score of 6.5. 55% belonged to Normal score (7 – 10), 37% belonged to Intermediate score (4 -6) and 8% belonged to Low score (0 – 3).

- The indications for admission in NICU were perinatal asphyxia, prematurity, respiratory distress, neonatal jaundice, low birth weight, neonatal seizures, sepsis, hypoglycaemia and others.
- 60% of the neonates received transfusion during the first week of life.
- 460 transfusions were given to 100 neonates.
- 28% (n=129) received packed red cell, 36% (n=166) received random donor platelet, 34% (n=155) received fresh frozen plasma and 2% received whole blood.
- 66 neonates received 129 packed red cells, 53 neonates received 166 platelets, 66 neonates received 155 FFP and 8 neonates received whole blood.
- Packed red cells with platelets and FFP (23%) was the commonly used combination of blood components in neonates.
- The mean donor exposure was 4.6 which ranged from single donor exposure to 20 donor exposures.
- Out of 129 red cell transfusions, 91% (n=118) were appropriate and 9% (n=11) were inappropriate. Out of 118 red cell transfusions, 63 (53%) were compliant with NNF guidelines and 55 (47%) were compliant with other guidelines such as AABB and expert opinion.
- The mean volume of red cell transfusion was 55 ml with the range of 9 ml to 235 ml.

- The mean donor exposure due to red cell transfusion was 1.29 with the range of single donor exposure to 5 donor exposures.
- The mean haemoglobin before transfusion was 9.2 g/dL.
- Most red blood cell transfusions belonged to second (42%) and first week (37%) of storage.
- Out of 166 platelet transfusions, 96% (n=160) were appropriate and 4% (n=6) were inappropriate. Out of 118 platelet transfusions, 155 (97%) were compliant with NNF guidelines and 5 (3%) were compliant with expert opinion.
- The mean volume of platelet transfusion was 67 ml with the range of 10 ml to 297 ml.
- The mean donor exposure due to platelet transfusion was 1.66 with the range of single donor exposure to 10 donor exposures.
- The mean platelet count before transfusion was 24973/µL.
- Out of 155 FFP transfusions, 86% (n=133) were appropriate and 14% (n=22) were inappropriate. Out of 133 appropriate FFP transfusions, 38% (n=51) were compliant with NNF guidelines, 62% (n=82) were compliant with other guidelines such as BCSH and Expert opinion.
- The mean volume of FFP transfusion was 53 ml with the range of 6 ml to 231 ml.
- The mean donor exposure due to FFP transfusion was 1.55 with the range of single donor exposure to 8 donor exposures.

- Out of 10 whole blood transfusions, 90% (n=9) of the transfusions were appropriate and 10% (n=1) were inappropriate. 9 appropriate whole blood transfusions were compliant with NNF guidelines.
- The mean donor exposure due to whole blood transfusion was 0.1 with the range of single donor exposure to 2 donor exposures.
- The age of the whole blood units transfused ranged from day 1 storage to day 5 storage with the mean storage age of whole blood was 2.9 days.
- All exchange transfusions were double volume exchange transfusions.

II. On relationship between neonatal parameters with transfusion requirements

- A significant linear association is present between gestational age of the neonate and red cell transfusion. Red cell requirement is inversely proportional to the gestational age of the neonate.
- Platelet requirement is high in ≥32 weeks of gestation.
- A significant linear association was present between birth weight and transfusion requirement. Platelet requirement is inversely proportional to the birth weight of the neonate.

III. Age of red cells and Length Of Stay (LOS)

- The mean length of stay of neonates receiving red blood cells stored for greater than 7 days and 14 days was not significantly longer than those receiving red blood cells stored less than 7 days and 14 days.

CONCLUSION

CONCLUSION

Neonatal physiology and transfusion requirement varies with maturity, age, weight and the presence of morbidities. So, while considering the necessity for transfusing blood components to neonates these parameters along with normal physiological adaptation after birth should be taken into consideration. On analysing the blood utilization practices among neonates in our study, appropriateness is on par with the current consensus of transfusion practice. But the current NNF guidelines need some revision of the available transfusion triggers. So, institution-based neonatal transfusion guidelines should be formulated with new concepts in the field, by the combined efforts from neonatologist and transfusion medicine specialist.

In our study, Gestational age and Birth weight of the neonate had a significant association with transfusion requirement. Very low birth weight premature neonates bear the brunt of multiple donor exposures due to frequent transfusions. This could be avoided by usage of Pedi-packs/aliquoting with the aid of SCD from a single donor, irrespective of the storage age of red cells, especially for small volume top-up transfusions.

Further, our study reiterates that there is no significant difference between LOS and storage age of red cells in neonates. This is contrary to the wider belief of using fresh blood for neonatal transfusions to avoid storage lesion induced effects in immature neonates. However, for larger volume

transfusions as in exchange transfusion, usage of fresh RBCs is recommended.

This study emphasizes the rational use of blood and its components and reduction of multiple donor exposure. In a developing country like India, due to the financial constraint, leukoreduction and irradiation should be practised at least for high-risk neonates.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. World Health Organization. Infant, Newborn. [Online]. 2017 [cited 2017 Sep 30]; Available from: URL:http://www.who.int/topics/infant_newborn/en/

2. Portugal CAA, de Paiva AP, Freire ES, et al. Transfusion practices in a neonatal intensive care unit in a city in Brazil. Rev Bras Hematol Hemother 2014;36(4):245-9.

3. Fung MK, Grossman BJ, Hillyer CD, Westhoff CM. Chapter 23 Neonatal and pediatric transfusion practice. AABB Technical Manual 18th Edition p571.

4. National Neonatology Forum India. Evidence based Clinical Practice Guidelines. [Online]. 2010 Oct [cited 2017 Sep 30]; Avaiable from: URL:www.nnfpublication.org

5. Ogunlesi TA, Ogunfowora OB. Pattern and determinants of blood transfusion in a Nigerian neonatal unit. Niger J Clin Pract 2011 Jul-Sep;14(3):354-8.

6. Giridharan J, Ramalingam GR. Study of blood component therapy in neonates. IJSR 2015 Mar;4(3):196-200.

7. O'Brien RT, Pearson HA. Physiologic anemia of the newborn infant. J Pediatr 1971 Jul;79(1):132-8.

8. Simon TL, McCullough J, Snyder E, Solheim BG, Strauss RG. Rossi's Principle of Transfusion Medicine. 5th ed. United Kingdom: John Wiley & Sons; 2016.

9. Carr R, Kelly AM, Willaimson LM. Neonatal thrombocytopenia and platelet transfusion – a UK perspective. Neonatology 2015;107:1-7.

10. Hassan N, Bush J, Foster A, et al. Complications associated with Red Blood Cell (RBC) Transfusions in the Very Low Birth Weight (VLBW) Infant. J Pediatr Neonatal Care 2015;2(3):00077.

11. Neogi SB, Malhotra S, Zodpey S, et al. Assessment of special care newborn units in India. J Health Popul Nutr 2011 Oct;29(5):500-9.

12. British Committee for Standards in Haematology. Guidelines on the transfusion of foetuses, neonates and older children. Available at: www.bcshguidelines.com. Accessed on June 15, 2016.

13. Alexander PE, Barty R, Fei Y, et al. Transfusion of fresher vs older red blood cells in hospitalized patients: a systematic review and meta-analysis. Blood 2016 Jan 8;127(4):400-10.

14. Smit Sibinga CT, Luban N. Neonatology and Blood Transfusion. Netherlands: Springer; 2005.

15. Liumbruno G, Bennardello F, Lattanzio A, et al. Recommendations for the transfusion of plasma and platelets. Blood Transfus 2009;7:132-150.

16. Wade M, Sharma R, Manglani M. Rational use of blood components – an audit. Indian J Hematol Blood Transfus 2009;25(2):66-9.

17. World Health Organization. Preterm birth. [Online]. 2017 [cited 2017 Sep 30]; Available from: URL:http://www.who.int/mediacentre/factsheets/fs363/en/s

18. American Congress of Obstetricians and Gynaecologists. Definition of Term pregnancy. [Online]. 2017 [cited 2017 Sep 30]; Available from: URL:http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Definition-of-Term-Pregnancy

19. World Health Organization. Newborns with low birth weight. [Online]. 2017 [cited 2017 Sep 30]; Available from: URL:http://www.who.int/whosis/whostat2006NewbornsLowBirthWeight.pdf

20. American Congress of Obstetricians and Gynaecologists. The APGAR score. [Online]. 2017 [cited 2017 Sep 30]; Available from: URL:https://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/The-Apgar-Score

21. Hillman N, Kallapur SG, Jobe A. Physiology of Transition from intrauterine to Extrauterine Life. Clin Perinatol 2012 Dec;39(4):769-83.

22. Rahim F, Jan A, Mohummad J, et al. Pattern and outcome of admissions to neonatal unit of Khyber teaching hospital, Peshawar. Pak J Med Sci 2007 Apr;23(2):249-53.

23. Baer VL, Lambert DK, Schmutz N, et al. Adherence to NICU transfusion guidelines: data from a multihospital healthcare system. J Perinatol 2008;28:492-7.

24. Ayede AI, Akingbola TS. Pattern, indications and review of complications of neonatal blood transfusion in Ibadan, Southwest Nigeria. Ann Ibd Pg Med 2011 Jun;9(1):30-6.

25. O'Riordan JM, Fitzgerald J, Smith OP, et al. Transfusion of blood components to infants under four months: review and guidelines. Ir Med J 2007 Jun;100 Suppl:1-21.

26. Kasat K, Hendricks-Muṅoz KD, Mally PV. Neonatal red blood cell transfusions: searching for better guidelines. Blood Transfus 2011;9:86-94.

27. Transfusing the neonates: Unique issues and Guidelines. [Online]. 2017 [cited 2017 Sep 30]; Available from: URL:http://www.bloodcenter.org/webres/file/vol08_no03.pdf

28. Hillyer CD, Strauss RG, Luban NLC. Handbook of Pediatric transfusion medicine. United States of America: Elsevier: 2004.

29. Hillyer CD, Silberstein LE, Ness PM, Anderson KC, Roback JD. Blood banking and transfusion medicine: Basic principles & practice. 2nd ed. United States of America: Churchill Livingstone Elsevier: 2007. p 510-22.

30. Pearson HA. Life-span of the fetal red blood cell. J Pediatr 1967 Feb;70(2):166-71.

31. Bowen JR, Patterson JA, Roberts CL, et al. Red cell and platelet transfusions in neonates: a population-based study. Arch Dis Child Fetal Neonatal Ed 2015;0:F1-F5.

32. Freitas BA, Franceschini SC. Factors associated with packed red blood cell transfusions in premature infants in an intensive care unit. Rev Bras Ter Intensiva 2012;24(3):224-9.

33. New HV, Stanworth SJ, Engelfriet CP, Reesink HW, McQuilten ZK, Savoia HF, Wood EM, Olyntho S, Trigo F, Wendel S, Lin Y, Hume H, Petäjä J, Krusius T, Villa S, Ghirardello S, Von Lindern J, Brand A, Hendrickson JE, Josephson CD, **Strauss RG**, Luban NLC and Paul W. Neonatal transfusions. Vox Sanguinis 2009;96:62–85.

34. Sisson TRC, Whalen L, Rochester AT. The blood volume of infants. J Pediatr:430-46.

35. Nexϕ E, Christensen NC, Olesen H. Volume of blood removed for analytical purposes during hospitalization of low-birthweight infants. Clin Chem 1981;27(5):759-61.

36. Roberts I, Murray NA. Neonatal thrombocytopenia: causes and management. Arch Dis Child Fetal Neonatal Ed 2003;88:F359-64.

37. Sesok-Pizzini DA, Friedman D. Neonatal and infant platelet transfusions. Immunohematology 2008;24(1):15-9.

38. Platelet transfusions in neonates: questions and answers [editorial]. Expert Rev Hematol 2010;3(1):7-9.

39. Weidmeier SE, Henry E, Sola-Visner MC, et al. Platelet reference ranges, defined using data from over 47000 patients in a multihospital healthcare system. J Perinatol 2009;29:130-6.

40. Sparger K, Deschmann E, Sola-Visner M. Platelet transfusions in the Neonatal Intensive Care Unit. Clin Perinatol 2015. http://dx.doi.org/10.1016/j.clp.2015.04.009

41. Ramanathan T, Maya Devi S, K.C. Usha. Factors associated with platelet transfusions in neonates admitted in intensive care unit in a tertiary care centre. IJCMR 2017;4(6):1351-5.

42. Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the full-term infant. Blood 1987 Jul;70:165-72.

43. Motta M, Del Vecchio A, Chirico G. Fresh Frozen Plasma administration in the Neonatal Intensive Care Unit Evidence-based guidelines. Clin Perinatol 2015. http://dx.doi.org/10.1016/j.clp.2015.04.013

44. Motta M, Del Vecchio A, Radicioni M. Clinical use of fresh-frozen plasma and cryoprecipitate in neonatal intensive care unit. J Matern Fetal Neonatal Med 2011;24 suppl:129-31.

45. Chalmers EA. Neonatal coagulation problems. Arch Dis Child Fetal Neonatal Ed 2004;89:F475-8.

46. Pisciotto PT. Neonatal plasma transfusions. Immunohematology 2008;24(1):20-6.

47. The investigation and management of neonatal haemostasis and thrombosis. Br J Haematol 2002;119:295-309.

48. Jain R, Jose B, Coshic P, et al. Blood and blood component therapy in neonates. Indian J Pediatr 2008 May;75:489-95.

49. Essabar L, Knouni H, Barkat A. Red blood cell transfusion in a neonatal tertiary care center: A Moroccan study. J Biosci Med (Irvine) 2016 Sep 30;4:54-60.

50. Poterjoy BS, Josephson CD. Platelets, Frozen Plasma and Cryoprecipitate: What is the clinical evidence for their use in the Neonatal Intensive Care Unit? Semin Perinatol 33:66-74.

51. National AIDS Control organisation. National blood policy. Ministry of Health & Family Welfare Government of India. New Delhi. 2007.

52. Altuntas N, Yenicesu I, Beken S, et al. Clinical use of fresh-frozen plasma in neonatal intensive care unit. Transfus Apher Sci 2012;47:91-4.

53. Raban MS, Harrison MC. Fresh Frozen Plasma use in a neonatal unit in South Africa. J Trop Pediatr 2015;61:266-71.

54. Mahapatra M, Choudhry VP. Blood transfusion in newborn. Indian J Pediatr 2003;70:909-14.

55. Ringer SA, Richardson DK, Sacher RA, et al. Variations in transfusion practice in neonatal intensive care. Pediatrics 1998 Feb;101:194-200.

56. Roseff SD, Luban NLC, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion. Transfusion 2002 Nov;42:1398-411.

57. World Health Organization. The clinical use of blood – Handbook.. [Online]. 2017 [cited 2017 Sep 30]; Available from: URL:http://www.who.int/bloodsafety/clinical_use/en/Handbook_EN.pdf

58. Zagol K, Lake DE, Vergales B, et al. Anemia, Apnea of Prematurity, and Blood Transfusions. J Pediatr 2012 Sep;161(3):417-21.

59. Kirpalani H, Whyte RK, Andersen C, et al. 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. J Pediatr 2006 Sep;149:301-7.e3.

60. Whyte RK, Kirpalani H, Asztalos EV, et al. Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. Pediatrics 2009;123:207-13.

61. Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. Pediatrics 2005 June;115(6):1685-91.

62. Nickel RS, Josephson CD. Neonatal transfusion medicine. Clin Perinatol 2015. http://dx.doi.org/10.1016/j.clp.2015.04.006

63. Saracco P, Vitale P, Scolfaro C, et al. The coagulopathy in sepsis: Significance and implications for treatment. Pediatr Rep 2011;3;e30.

64. Kaur A, Dhir SK, Kaur G, et al. Blood component therapy in neonates in a neonatal intensive care unit of northern India. Clin Epidemiol Glob Health 2015;3:538-42.

65. Bauman ME, Cheung P, Massicotte MP. Hemostasis and platelet dysfunction in asphyxiated neonates. J Pediatr 2011;158(2 Suppl 1):e35-9.

66. Forman KR, Diab Y, Wong ECC, et al. Coagulopathy in newborns with hypoxic ischemic encephalopathy (HIE) treated with therapeutic hypothermia: a retrospective case-control study. BMC Pediatr 2014;14:277.

67. Murthy S, Krishnamurthy V. Coagulation profile in perinatal asphyxia. Pediatr Rev: Int J Pediatr Res 2015;2(4):64-8.

68. British Committee for Standards in Haematology. (2004) Transfusion guideline for neonates and older children. British Journal of Haematology, 124, 433-453

69. Strauss RG. Transfusion therapy in neonates. AJDC 1991;145:904-11.

70. Benson JW, Bodden SJ, Tobin JO'H. Cytomegalovirus and blood transfusion in neonates. Arch Dis Child. 1979;54:538-41.

71. Kothari A, Ramachandran VG, Gupta P, et al. Seroprevalence of cytomegalovirus among voluntary blood donors in Delhi, India. J Health Popul Nutr 2002 Dec;20(4):348-51.

72. Litty CA. Neonatal red cell transfusions. Immunohematology 2008;24(1):10-4.

73. Strauss RG, Levy GJ, Sotelo-Avila C, et al. National survey of neonatal transfusion services: II. Blood component therapy. Pediatrics 1993 Mar;91(3):530-6.

74. Ali SR, Ahmed S, Lohana H. Disease patterns and outcomes of neonatal admissions at a secondary care hospital in Pakistan. Sultan Qaboos University Med J 2013 Aug:13(3):424-4.

75. Noto TA, Steib MD. Use of exchange transfusions in neonatology. Lab Med 1981 Oct;12(10):609-16.

76. Malla T, Poudyal P, Sathian B, et al. A prospective study on Exchange Transfusion in Neonatal Unconjugated Hyperbilirubinemia – in a Tertiary Care Hospital, Nepal. Kathmandu Univ Med J 2015;50(2):102-8.

77. Mishra S, Chawla D, Agarwal R. Effect of exchange transfusion on mortality in neonates with septicemia. Cochrane Database of Systematic Reviews 2016;(12). Art. No: CD012477.

78. Murray NA, Roberts IAG. Hemolytic diseases of the newborn. Arch Dis Child Fetal Neonatal Ed 2007;92:F83-8.

79. Liu EA, Mannio FL, Lane TA. Prospective, randomized trial of the safety and efficacy of a limited donor exposure transfusion program for premature neonates. J Pediatr 1994 Jul;125(1):92-6.

80. Sloan S. Technical issues in neonatal transfusions. Immunohematology 2008;24(1):4-9.

81. Blanchette VS, Hardie MJ, MacMurray SB, et al. Hyperkalemia after neonatal exchange transfusion; risk eliminated by washing red cell concentrates. J Pediatr 1984 Aug;105(2):321-4.

82. Hume H, Bard H. Small volume red blood cell transfusions for neonatal patients. Transfus Med Rev 1995 Jul;9(3):187-99.

83. Donowitz LG, Turner RB, Searcy MAM, et al. The high rate of blood donor exposure for critically ill neonates. Infect Control Hosp Epidemiol 1989;10(11):509-10.

84. Uezima CL, Barreto AM, Guinsburg R, et al. Reduction of exposure to blood donors in preterm infants submitted to red blood cell transfusions using pediatric satellite packs. Rev Paul Pediatr 2013;31(3):285-92.

85. Cook S, Gunter J, Wissel M. Effective use of a strategy using assigned red cell units to limit donor exposure for neonatal patients. Transfusion 1993;33(5):379-83.

86. Arora S, Marwaha N, Dhawan HK, et al. Dedicated donor unit transfusions reduces donor exposure in pediatric surgery patients. Asian J Transfus Sci 2017 Jul - Dec;11(2):124-30.

87. Lee DA, Slagle TA, Jackson TM, et al. Reducing blood donor exposures in low birth weight infants by the use of older, unwashed packed red blood cells. J Pediatr 1995 Feb;126(2):280-6.

88. Wang-Rodriguez J, Mannino FL, Liu E, et al. A novel strategy to limit blood donor exposure and blood waste in multiply transfused premature infants. Transfusion 1996;36:64-70.

89. Christensen RD, Carroll PD, Josephson CD. Evidence-based advances in transfusion practice in neonatal intensive care units. Neonatology 2014;106:245-53.

90. Aubron C, Nichol A, Cooper DJ, et al. Age of red blood cells and transfusion in critically ill patients. Annals of Intensive Care 2013;3:2.

91. Fergusson DA, Hebert P, Hogan DL, et al. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants: The ARIPI randomized trial. JAMA 2012 Oct 10;308(14);1443-51.

92. dos Santos AMN, Guinsburg R, de Almeida MFB, et al. Red Blood Cell transfusions are independently associated with intra-hospital mortality in Very Low Birth Weight preterm infants. J Pediatr 2011 Sep;159(3):371-6.e3.

93. Brunskill SJ, Wilkinson KL, Doree C, et al. Transfusion of fresher versus older red blood cells for all conditions. Cochrane Database of Sys Rev 2015;(5).

94. Karam O, Tucci M, Bateman ST, et al. Association between length of storage of red blood cell units and outcome of critically ill children: a prospective observational study. Critical Care 2010;14:R57.

95. Boo NY, Chan BH. Blood transfusion reactions in Malaysian newborn infants. Med J Malaysia 1998 Dec;53(4):358-64.

ANNEXURES

THE TAMIL NADU DR. MGR, MEDICAL UNIVERSITY, CHENNAI-600032
Institutional Ethics Committee

Proposal No: ECMGR0309053

Date: 19.09.2016

CERTIFICATE

This is to certify that the project **No. ECMGR0309053** entitled **"Evaluation of Blood Utilisation practices in Neonates."** submitted by **Dr K.C. Gayathiri, DEPARTMENT OF TRANSFUSION MEDICINE** has been approved by the Institutional Ethics Committee, at the meeting held on **15-07-2016,** under the following terms and conditions.

a. This approval is valid for three years or the duration of the project whichever is less from the date of the Certificate.

b. All procedures to be used on participants are professionally acceptable and standardized.

c. All adverse events during the course of study must be recorded and reported to the IEC within a period of seven days

d. Any change in the study procedure/site/investigator should be informed to the IEC.

e. A yearly progress report of the project has to be submitted to the IEC for review.

(Dr. S. Mini Jacob)
Member Secretary
Institutional Ethics Committee
The Tamil Nadu Dr MGR Medical University

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301A
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.K.C. Gayathiri
II Year Post Graduate in M.D. Immunohaemotology &
Blood Transfusion
The Tamil Nadu Dr.MGR Medical University
Chennai 600 032

Dear Dr.K.C. Gayathiri ,

The Institutional Ethics Committee has considered your request and approved your study titled **"EVALUATION OF BLOOD UTILIZATION PRACTICES IN NEONATES " NO. 29012017.**

The following members of Ethics Committee were present in the meeting hold on **03.01.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.A.Rajendran,MS, Prof. of Surgery,MMC,Ch-3	: Member
6.Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
7.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
8.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
9.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
10.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

PROFORMA

1. Name: .....
2. Age: .....days
3. Sex: .....
4. Ip.No: .....
5. Blood Group: .....
6. Birth Weight: .....gms (VLBW / ELBW / NORMAL)
7. Gestational Age: .....wks (Preterm / Term)
8. Mode of delivery of the neonate: .....
9. APGAR Score: 1min.....5min.....
10. Indication for Admission In NICU: .....
11. Diagnosis: .....
12. Indication for PRBC Transfusion: .....
13. Indication for PLATELET Transfusion: .....
14. Indication for FFP Transfusion: .....
15. Indication for WHOLE BLOOD Transfusion: .....
16. Age at which first transfusion was given: .....Days / 28
17. Age at which transfusions were given: .....
18. Number of Transfusions Given: .....
19. Transfused Blood Date of Collection: ……
20. Pre - transfusion Haematocrit: .....

21. Pre - Transfusion Platelet count: .....

22. Blood utilization

Blood utilization	ml
PRBC	
WB	
FFP	
Platelets	
Cryo	

23. Duration of Hospital Stay: .....Days

24. No of donor exposure:…….

URKUND

Urkund Analysis Result

Analysed Document: EVALUATION OF BLOOD UTILIZATION PRACTICES IN NEONATES.doc (D31139946)
Submitted: 10/9/2017 11:21:00 AM
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https://en.wikipedia.org/wiki/Transfuse

Instances where selected sources appear:

4

CERTIFICATE – II

This is to certify that this dissertation work titled **"EVALUATION OF BLOOD UTILIZATION PRACTICES IN NEONATES"** of the candidate **Dr. K. C. GAYATHIRI** with the registration number **201531001** for the award of **M.D.** in the branch of **XXI - IMMUNOHAEMATOLOGY & BLOOD TRANSFUSION.** I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **1** percentage of plagiarism in the dissertation.

Guide & Supervisor sign with Seal

PATIENT INFORMATION SHEET

EVALUATION OF BLOOD UTILIZATION PRACTICE IN NEONATES

A neonate experiences rapid change of physiology at birth and during initial few days of life. Blood forms one of the therapeutic modalities in neonatal care. This study is done to evaluate Blood usage pattern among neonates in Neonatal Intensive Care Unit (NICU).

PROCEDURE

Data will be collected from Case records, Blood request forms and Blood Bank records for analysis.

BENEFITS AND RISKS

There is no risk for patients enrolled in this study as their treatment protocols are not interfered with.

CONFIDENTIALITY

Your privacy will be protected in so for as permitted by law. Only your researcher and Ethical committee members will have access to the data collected during the study.

PARTICIPATION

Your participation in this study is voluntary and you are free to decide now or later whether to continue or discontinue from the study.

Name of the patient:

Parent/ Guardian Signature:

Date:

CONSENT

I confirm that I read and understood the information about the above research study dated _____ and I received chance to ask the questions.

My participation in this study is voluntary and I know that I am free to withdraw from the study at any time, without giving any reason and without affecting of my legal rights.

I agree to this access. I know that my identification will not be revealed in any details that is released to third persons or published.

I agree not to restrict or interfere with any data or results that are obtained from this study. I agree to participate in this research study for the above listed purpose.

Patient's Name : Date :

Parent's Name : Parent's Signature :

Patient IP Number :

Signature of the person

who obtains consent : Date :

பங்கேற்பாளர்கான தகவல் படிவம்

குழந்தைக்கு செலுத்தப்படும் இரத்தக்கூறுகள் மற்றும் அவற்றின் முறையான தன்மை கண்டறிதல்

பச்சிளம் குழந்தைகள் பிறந்த ஆரம்ப சில நாட்களில் உடலில் விரைவான மாற்றத்தை அனுபவிக்கிறது. குழந்தைக்கு செலுத்தப்படும் இரத்தக்கூறுகள் அந்த மாற்றங்களை எதிர் கொள்ள உதவுகிறது . இந்த ஆய்வு தீவிர சிகிச்சைப் பிரிவில் உள்ள பச்சிளம் குழந்தைகள் மத்தியில் இரத்த பயன்பாடு முறை மதிப்பீடு செய்ய செய்யப்படுகிறது.

குறிக்கோள்

குழந்தைக்கு செலுத்தப்படும் இரத்தக்கூறுகள் மற்றும் அவற்றின் முறையான தன்மை கண்டறிதல்.

செய்முறை

நோயாளிகளின் மருத்துவமனை குறிப்பேடுகள் இரத்தக்கூறுகள் வேண்டி விண்ணப்பங்கள் மற்றும் இரத்த வங்கியில் உள்ள குறிப்புகள் ஆகியவை பெறப்பட்டு ஆய்வுக்கு உட்படுத்தப்படும்.

பலன்களும் பாதிப்புகளும்

தீவிர சிகிச்சைப் பிரிவில் உள்ள பச்சிளம் குழந்தைகள் மத்தியில் இரத்த பயன்பாடு முறை மதிப்பீடு செய்ய பயன்ப்படுகிறது.இதன் மூலம் பச்சிளம் குழந்தைக்கு எந்தவித பாதிப்பும் ஏற்படாது.

இரகசிய பாதுகாப்பு

சட்டவரைமுறையின்படி தங்களின் சொந்த விசயங்கள் பாதுகாக்கப்படும் .தங்களின் ஆராய்ச்சியாளர் மட்டும் இந்த ஆராய்ச்சியின்போது கிடைக்கும் புள்ளி விவரங்ககளை பயன்பயன்படுத்த இயலும்.

பங்களிப்பு

இந்த ஆராய்ச்சியில் தங்களின் பங்களிப்பு தன்னார்வமானது.இந்த ஆராய்ச்சியில் தங்களின் பங்களிப்பினைத் தொடர்வதற்கும்.விடுபடுவதற்கும் எந்த நேரமும்தங்களுக்கு உரிமையுண்டு .

குழந்தையின் பெயர் :

குழந்தையின் பெற்றோர் கையொப்பம் :

தேதி :

ஒப்புதல் படிவம்

ஆய்வாளர் சொன்ன _____ நாளது செய்முறை ஆய்வு குறித்த தகவல்களை நான் படித்து அறிந்து புரிந்து கொண்டேன்,என இதன்மூலம் உறுதியளிக்கிறேன். இது குறித்து கேள்விகள் கேட்பதற்க்கும் எனக்கு வாய்ப்பு அளிக்கப்பட்டதையும் உறுதி செய்கிறேன்.

இந்த ஆய்வில் என் பங்கேற்பு முற்றிலும் என் விருப்பம் சார்ந்தது என்பதையும் அறிந்து கொண்டேன்.எந்த காரணமும் குறிப்பிடாமல் எனது சட்ட உரிமை பாதிக்கபடாதவண்ணம் இந்த ஆய்விலிருந்து எப்பொழுது வேண்டுமானலும் விலகிக்கொள்ள எனக்கு உரிமைஉண்டு என்பதையும் அறிந்து கொண்டேண்

இந்தசெயல்முறை ஆய்வுக்கு நான் ஒத்துழைப்பு நல்குகிறேன் என்று வாக்களிக்கிறேன். இந்த ஆய்வுத்தகவல்கள்,மூன்றாவது நபர்களுக்கோ அல்லது விளம்பரத்திற்காக வெளியிடப்படும் போதோ,எனது அடையாளம் அல்லது தனித்துவம் தெரிவிக்கப்படமாட்டாது என்பதையும் நான் அறிந்து கொண்டேன்.

இந்த ஆய்வின் மூலம் பெறப்படும் யாதொறுதகவல் அல்லது முடிவுகளைத் தடைசெய்யவோ அல்லதுகுறுக்கிடவோ மாட்டேன் என்று உறுதி அளிக்கிறேன் .மேற்கூறிய குறிக்கோளை அடைய எடுத்துக் கொள்ளும் இந்தசெய்முறை ஆய்வில் பங்கேற்க நான் முழுமனதுடன் சுயநினைவுடன் சம்மதிக்கிறேன்

நோயாளின் பெயர்

கையொப்பம் தேதி

ஒப்புதல் பெறுபவரின் கையொப்பம் தேதி