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ORIGINAL ARTICLE

Fresh Frozen Plasma and Platelet Transfusion Practices in Neonatal Intensive Care Unit of a Tertiary Care Hospital

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Abstract Blood transfusion is an indispensable part of modern medical and surgical practices. More than 35% of critically ill patients receive transfusion of blood components during their intensive care unit stay. The aim of study is to obtain an information regarding the relationship of platelet concentrate (PC) and fresh frozen plasma (FFP) transfusion on clinical outcome of neonates admitted in neonatal ICU (NICU). This prospective cohort study was conducted from 1st November 2011 to 30th April 2013. The clinical history, blood component details and laboratory parameters were evaluated with clinical outcome. The neonates requiring PC and FFP transfusion were followed up in blood bank for laboratory parameters. Clinical parameters were noted from case file. During the study period, 291 neonates were admitted in NICU. 2 neonates had congenital malformations and thus, were excluded from the study. Of the remaining 289 neonates, 49 neonates received transfusion of platelets and/or FFP. The combined mean donor exposure for all components was found to be 1.48. The mean volume of PC and FFP transfused was 20 ml and 30 ml respectively. The mean pre- and post-transfusion platelet count was 34,000 µl and 42,000 µl respectively. The mean pre- and post-transfusion INR was 2.37 and 1.53 respectively. There was a significant increase in platelet count and decrease in INR in transfused neonates. However, no clinical benefit of PC and FFP transfusion seen on bleeding. Transfusion of PC and FFP has significant effect on laboratory parameters as compared to clinical parameter.

Keywords Fresh frozen plasma · Platelet concentrate · Intra-ventricular hemorrhage · Neonatal intensive care unit · Gestational age · Very low birth weight

Introduction

Blood transfusion is an indispensable part of modern medical and surgical practices. More than 35% of critically ill patients receive transfusion of blood components during their intensive care unit (ICU) stay [1]. Neonates are the most fragile and unstable patient population in any of the hospital and treating neonatologists should be aware of the prevailing transfusion strategies for managing neonatal anemia as giving or withholding transfusions in them may bear potential adverse outcomes [2]. Therefore, the decision to transfuse a critically ill neonate is complex and may be influenced by factors such as maturity, medications, disease severity and specific diagnoses.

The optimal role of platelet transfusions, the second most commonly transfused blood component in neonates, remains controversial. Thrombocytopenia affects 20–35% of patients admitted to NICUs, and up to 70% of neonates

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born with birth-weight of < 1000 g [3]. Most platelet transfusions in neonates are performed therapeutically for platelet count < 50,000 µl in the presence of active bleeding [4]. Prophylactic platelet transfusions are still controversial. However, the platelet count at which the risk of bleeding justifies a transfusion has not been established in neonates and neither the severity of thrombocytopenia correlates well with the risk of haemorrhage nor platelet transfusions reduces this risk. Intra-ventricular haemorrhage (IVH), occurs in approximately 40% of preterm neonates during first 72 h after birth. Although prophylactic platelet transfusions has not shown to reduce the incidence of IVH, the severity of thrombocytopenia appears to be independent of the risk of IVH (> Grade 2) [4, 5]. Hence, the use of platelets in this situation and the appropriate platelet dose remains controversial.

Spontaneous bleeding and thrombosis are rare in term healthy neonates because the procoagulant and anticoagulant systems are usually in equilibrium with each other. However, the reserve capacity for both systems is limited. Therefore, serious bleeding may occur in sick premature infants during the first week of life. In older children and adults, coagulopathy is often defined as a PT or aPTT greater than 1.5 times the mid-point of normal range, but this is more difficult to apply in neonates, especially in very preterm neonates given that the ranges may be uncertain and broad [4].

The indications for transfusions of fresh frozen plasma (FFP) in neonates are also unclear. Common indications for plasma transfusion include reconstitution of whole blood for exchange transfusion and active bleeding in disseminated intravascular coagulation (DIC). The use of prophylactic plasma transfusions to prevent intracranial hemorrhage (ICH) in preterm neonates is again controversial [4]. Infusions of FFP in neonates is effective in reducing blood loss associated with extracorporeal membrane oxygenation (ECMO) or cardio-pulmonary bypass and to treat active bleeding due to DIC, liver failure or Vitamin K deficiency [6]. However, routine use of FFP in sick preterm neonates for volume expansion, to treat coagulopathy in the absence of bleeding, or for partial exchange transfusion does not decrease morbidity or mortality [7].

There is relative paucity of data especially from India about the prevalent transfusion practice in this high-risk group of neonates. Neither the importance of a specific transfusion threshold nor the clinical characteristics that influence transfusion practice have been documented clearly in literature. This study aims to obtain information regarding the relationship of platelet concentrate (PC) and fresh frozen plasma (FFP) transfusion on clinical outcome in neonates admitted in neonatal intensive care units.

Materials and Method (Fig. 1)

After the approval from the Institute Ethics Committee, we conducted a prospective cohort study in collaboration with the Department of Pediatrics for over a period of 18 months (1st November 2011 to 30th April 2013) to characterize the actual neonatal transfusion practices and the transfusion triggers for such neonates admitted to NICU. All neonates admitted to NICU, were considered for enrollment, taking due consideration to the inclusion and exclusion criteria. Babies with gestational age (GA) at birth ≥ 26 completed weeks; birth weight ≥ 700 g and duration of stay in NICU for > 6 h were included in the study after getting the written informed consents from their respective mother and/or father while babies with major congenital malformations were excluded. The subjects requiring transfusion of blood component were then followed up in the Blood bank for various laboratory parameters. Clinical parameters and clinical outcome were noted from case files. All neonates receiving blood component transfusions were assessed for general clinical parameters viz. GA at birth, birth weight and APGAR score at 1 min and 5 min.

Platelets Transfusion

The requisition for platelet transfusion were assessed for component type i.e. whether platelet concentrate (PC), platelet rich plasma or single donor platelets. The transfusion trigger was kept at 10,000 µl. In addition, indication for transfusion was also assessed i.e. thrombocytopenia, bleeding or any other indication. The requisition was assessed for component details i.e. volume of the component required, age of the component unit at the time of issue and blood group (ABO and Rh only). Pre-transfusion and post-transfusion platelet count and total number of donor exposure for each patient were also noted.

FFP Transfusion

The requisition for FFP/plasma transfusion was assessed for component type i.e. whether FFP or plasma. The indication of transfusion was noted i.e. bleeding, DIC or other indications. Component details i.e. volume of FFP/plasma, age and blood group were assessed. Pre-transfusion and post-transfusion prothrombin time (PT)/International normalised ratio (INR) and total number of donor exposures were also noted.

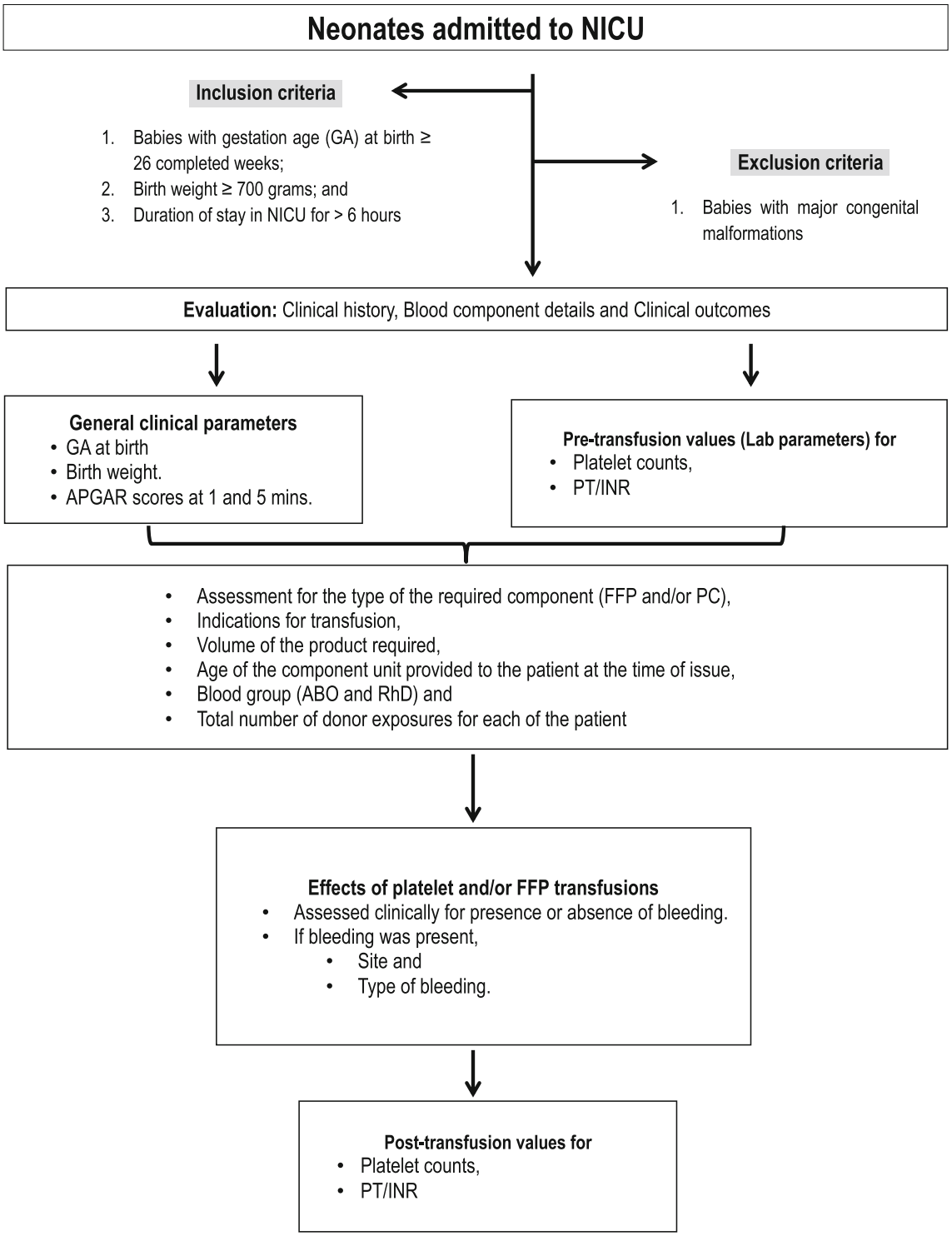

Fig. 1 Study design

Clinical Effect

Effect of platelet and/or FFP transfusions were assessed clinically for presence or absence of bleeding. If bleeding is present, then the site and type of bleeding were noted. Transfusion associated adverse reactions were noted, as well. Outcome of admission was assessed as discharged, referred to other hospital or death.

Statistical Analysis

The various laboratory and clinical parameters were analysed and correlated statistically for transfusions. For all quantitative variables, mean, median and standard deviation were calculated. Means were compared using paired or unpaired Student's *t* test for the two groups, i.e., transfused patients and non-transfused patients, and pre-transfusion and post-transfusion: laboratory and clinical parameters. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared using Chi square test. Statistical tests were performed at a significance level of p B 0.05. The statistical analysis was done by SPSS [IBM, Ver. 19] and Microsoft Excel, 2010.

Results

Of the total 291 neonates admitted in NICU, 2 neonates had congenital malformations and thus, were excluded from the study. Of the remaining 289 neonates, 49 neonates received transfusion of platelets and/or FFP. These neonates received a total of 58 platelet transfusions and 15 FFP transfusions. The combined mean donor exposure for all components was found to be 1.48 with individual mean donor exposure rates for PC being 1.3 and for FFP being 1.2. Seven neonates received both platelet and FFP transfusion.

The mean GA of these neonates was 33.8 ± 3.07 weeks (Range 27–41 weeks). The mean birth weight of these neonates was 1310 ± 513.2 g (Range 750–3100 g) (Table 1). Neonates with birth weight < 1500 g were 30 (61%), who received total 44 (60%) transfusions while those with birth weight > 1500 g were 19 (38.7%), who received total 29 (39.7%) transfusions. Neonates with GA < 37 weeks were 41 (83.6%), who received total 60 (82%) transfusions and those with GA > 37 weeks were 8 (16%), who received total 13 (17.8%) transfusions (Table 2).

Platelet Transfusion

Main indications for platelet transfusion to neonates were thrombocytopenia, sepsis, bleeding and DIC (Table 3).

Volume and Age of Transfused Platelet Unit

Volume A total of 1290 ml of platelets was administered to 42 neonates. The mean volume of platelets transfused was 20 ± 6.43 ml (Range 15–50 ml).

Age of unit The mean age of platelet unit was 2 ± 0.9 days (Range 1–5 days).

Platelet Counts

Forty-two neonates received 58 platelet transfusions out of which 20 were O Rh D Positive, 14 were A Rh D Positive, 14 were B Rh D Positive, 3 were B Rh D Negative, 6 were AB Rh D Positive, and 1 was AB Rh D Negative. The average pre-transfusion platelet count was 34,000 ± 17,579.5 µl (Range 10,000–86,000 µl).

The average post transfusion platelet was 42,000 ± 37,407.6 µl (12,000–200,000 µl).

The difference between means of post-transfusion and pre-transfusion platelet count was significant ($p < 0.001$).

Division of neonates according to platelet count.

Six neonates had pre-transfusion platelet count < 20,000 µl, 31 had platelet count between 20,000 and 50,000 µl, and 5 neonates had pre-transfusion platelet count > 50,000 µl. Post-transfusion, 4 neonates had platelet count < 20,000 µl, 17 infants had platelet count between 20,000 and 50,000 µl and 21 had platelet count > 50,000 µl (Fig. 2a).

Table 1 Demographic details of the study population

Parameters	Transfused (platelets and FFP)	Non transfused
No. of patients	49	228
Birth weight (in g)	1310 ± 513	1300 ± 320
Gestational age (in weeks)	33.8 ± 3.0	26 ± 5
APGAR		
1 min	2–9	2–9
5 min	5–9	5–9
Platelet count		
Pre-transfusion	10,000–86,000 µl	–
Post transfusion	12,000–200,000 µl	–
INR		
Pre-transfusion	1.19–2.96	–
Post transfusion	1.00–2.43	–
Mortality	29	85

Table 2 Distribution of neonates according to (a) gestational age, (b) birth weight

(a) Gestational age (weeks)	No. of neonates
< 28	01
28–31	12
32–36	28
> 37	8
(b) Birth weight (g)	
< 1000	04
1000–1499	26
1500–2499	17
> 2500	02

Table 3 Indications for (a) platelet transfusion, (b) FFP transfusion

Indication	No. of neonates
(a) Platelet transfusion	
Thrombocytopenia	21
Sepsis	12
DIC	4
Bleeding	5
(b) FFP transfusion	
DIC	6
Sepsis	5
Bleeding	1
NNJ	1

FFP Transfusion

Main indications for FFP transfusion to neonates were DIC, sepsis, bleeding and NNJ as shown in Table 3.

Volume and Age of Transfused FFP

Volume: A total of 425 ml FFP was transfused to 13 neonates. The mean volume of FFP transfused was 30 ± 7.23 ml (Range 20–50 ml).

Age of unit: The mean age of FFP unit was 3.8 ± 1.7 months (Range 2–7 months).

13 neonates received 15 FFP transfusions out of which 4 were O Rh D Positive, 3 were A Rh D Positive, 2 were B Rh D Positive, 1 was B Rh D Negative, and 4 were AB Rh D Positive. The pre-transfusion mean INR was 2.37 ± 0.48 (Range 1.19–2.96). The post-transfusion mean INR was 1.53 ± 0.46 (1.00–2.43). Thus, after FFP transfusion change in INR was significant ($p < 0.001$).

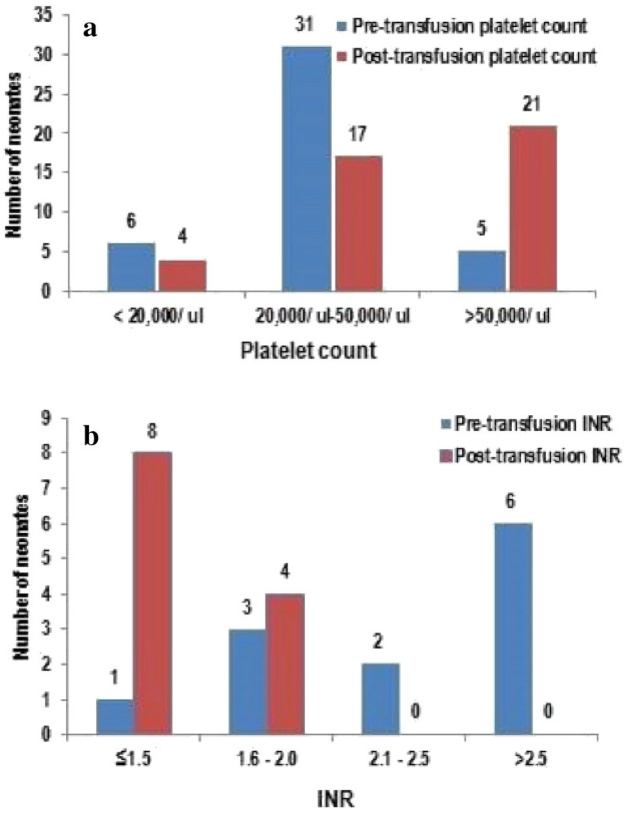

Fig. 2 Effects of neonatal transfusion of components on laboratory parameters. **a** On platelet; **b** on PT/INR

The categorical distribution of neonates w.r.t. INR is shown in Fig. 2b. Out of 13 patients who had deranged coagulogram, bleeding was present in 8 neonates and all these 8 neonates died. Out of these 8 neonates, 3 had INR between 1.6 and 2.0, 1 had INR between 2.1 and 2.5 and 4 had INR more than 2.5.

There were 7 neonates who received both platelets ($N = 9$ units) and FFP ($N = 9$ units) transfusions among which neonatal sepsis was the transfusion indication for 6 neonates and bleeding was the transfusion indication for only 1 neonate.

Bleeding

Out of 49 transfused infants, bleeding was present in 20 infants (32.7%). Of these 20 infants, 7 (35%) were having ET tube bleed, 8 infants (40%) were having oro-mucosal bleed, 4 (20%) were having GIT bleed and 1(5%) was having ICH.

Birth Weight w.r.t. Number of Transfusions

No significant correlation was seen between birth weight and number of transfusions ($p > 0.05$).

GA w.r.t. Number of Transfusions

We didn't find any significant correlation between GA and number of transfusions ($p > 0.05$).

Mortality w.r.t. Number of Transfusions

There was not much difference in the mean no. of transfusions among those who died and survived. Hence, we didn't find any correlation between number of transfusions and mortality ($p > 0.05$). There were no specific transfusion related reasons of death in the neonates.

Outcome

Out of 49 transfused neonates, 18 neonates (36.73%) were discharged, 2 neonates (4.08%) were referred to higher center and 29 neonates (59.19%) died. There was no significant association ($p > 0.05$) of neonatal mortality and/or neonatal discharges with blood component transfusion.

Discussion

Out of the 289 neonates admitted to the NICU, 49 (16.9%) neonates were transfused with platelets and FFP. These neonates received total of 58 platelets and 15 FFP transfusions. Of the transfused neonates, 83.6% were born preterm and 61.2% were having VLBW (< 1500 g).

Platelet Transfusion

Severe thrombocytopenia (platelet count less than 50,000 µl) remains a common occurrence in NICU population, developing in 12.4% of all our admissions and 6% of admissions in study by Murray et al. [8]. Incidence of severe thrombocytopenia was double in our patient population due to admission of more sick neonates in NICU. Thrombocytopenia has become a common management problem to every practicing neonatal pediatrician.

In our study 73.8% thrombocytopenic neonates who received platelet transfusion had platelet count between 20,000 and 50,000 µl, 14.4% had < 20,000 µl and 11.9% had platelet count > 50,000 µl. Hence, most of the platelet transfusions were done when platelet count was between 20,000 and 50,000 µl. Sparger et al. [9] also found that most (65.2%) of platelet transfusions were given for pre-platelet count of at least 50,000 µl. In UK NICUs, prophylactic platelet transfusions were given to neonates at platelet count $< 20 \times 10^9$ L, to stable preterm infants if platelet count $< 30 \times 10^9$ L and to all infants with a birth weight < 1000 g if the platelets are $< 50 \times 10^9$ L during the first week of life [10, 11]. Whereas studies done by U.S. and Canadian neonatologists revealed that most of platelet transfusions were given to non-bleeding neonates with platelet counts between 50,000 and 100,000 µl, particularly in the first week of life [12]. Hence, there is a wide practice differences in regard to platelet transfusion thresholds in different clinical scenarios, some hospitals follow liberal transfusion threshold whereas others restrictive threshold.

Stanworth et al. [10] found that approximately 25% of thrombocytopenic neonates had platelet counts < 60,000 µl, and 9% of them experienced clinically significant bleeding (most commonly intracranial). But von Lindern et al. compared the bleeding outcome between restrictive transfusion threshold and liberal transfusion threshold in NICU patients but they found no significant difference between the two [5]. In our study, out of 14.5% (42/289) neonates who received platelet transfusions, bleeding was present in 40.4% (17/42) of thrombocytopenic neonates. Out of these 17 thrombocytopenic neonates, 13 neonates died. Nine of them had their platelet count less than 30,000 µl, 2 had platelet count between 30,000 and 50,000 µl and two had platelet count more than 50,000 µl. The mean Tx_{Pre} platelet count of the bleeding thrombocytopenic neonates was 30,000 µl and a Tx_{Pre} platelet count of 30,000 µl may be opined as a transfusion trigger for neonates. But we found that there was no effect of platelet transfusion on bleeding. The reason may be that those neonates were having severe systemic illness. Kenton et al. found that 62% of infants with active bleeding treated with platelet transfusions had a resolution of bleeding; however, no obvious benefit of platelet transfusions was noted in thrombocytopenic infants with multi-systemic inflammatory diseases. They proposed that the reason for that may be presence of various bioactive substances like pro-inflammatory cytokines that can further exacerbate the multi-system inflammatory diseases [13].

However, the clinical diagnoses and associated complications must not be over-looked while deciding for blood component transfusions or with-holding the same. Our study demonstrated that severity of complications and on-going bleeding are the principal determinates of patient outcome. Improved outcome in such patients can be achieved with improved therapy for both underlying conditions and the resulting complications, i.e. by combining platelet transfusion with therapy to cure sepsis and stimulate platelet production. Murray et al. [8] also demonstrated that severity of complications and ongoing bleeding determine patient outcome.

FFP Transfusion

The use of prophylactic plasma transfusions to prevent ICH in preterm neonates is still not-recommended [14].

Moreover, there are reports showing no benefits for routine administration of FFP to prevent peri-ventricular hemorrhage in preterm neonates [14, 15]. We found that 13 neonates received FFP transfusions. Our study demonstrated that rate of FFP transfusion was 4.4% (13/289) among admitted patients and 26.5% (13/49) among transfused patients. As compared to our study, Motta et al. [16] found higher rate (8%) of FFP transfusion among admitted patients whereas Altuntas et al. [17] reported a lower rate (2%) of FFP transfusion. The reason for such difference may be that various centers follow variable transfusion guidelines (restrictive or liberal) for FFP transfusion.

Out of 13 neonates, who received FFP for deranged coagulogram, bleeding was present in 61.5% (8/13) neonates and mortality was seen in all of them. Whereas Motta et al. has lower number of bleeding (36.8%) among FFP transfused neonates as compared to our study. The authors had also found that coagulation tests did not predict subsequent clinical hemorrhage [16].

In our study, mean INR of neonates who were bleeding was 2.1 and mean INR of neonates who were not bleeding was 2.5. This demonstrates that INR of 2.1 is a trigger threshold for unstable neonates and INR $>$ 2.5 is a trigger threshold for stable patients. Stanworth et al. [18] found that the median INR before FFP transfusion to neonates for bleeding was 1.6 and for those with non-bleeding was 1.7.

Gestational Age w.r.t Number of Transfusions

In our study, total 41 neonates were preterm out of 49 transfused neonates who received total 60 transfusions. But the median number of transfusions per neonate was only 1.4. Hence, we didn't find correlation between gestational age and number of transfusions. We also didn't find any correlation between birth weight and number of transfusions. Whereas, Murray et al. found that total of 60 platelet transfusions were given to 25 preterm out of 44 preterm neonates. The median number of transfusions were 2 [8].

Mortality w.r.t. Transfusion

We didn't find any statistically significant correlation between mortality and no. of transfusion events in contrary to the result reported by Sparger et al. [9] who concluded that transfused neonates receiving platelet transfusions have a greater risk for death than non-transfused neonates. Co-morbid conditions of these neonates may be the cause of the bias associated with such outcome. Kenton et al. [13] also found that transfusion in multi-systemic inflammatory patients was associated with greater morbidity without the benefit of lower mortality.

Limitations

Sample size of our study was less. Patients were not followed-up, therefore, the long-term complications of transfusion therapies administered to these neonates may have been missed.

Conclusion

Based on observations of this study, we conclude that no clinical benefit of platelet and FFP transfusion seen on bleeding. Hence, severity of complication and ongoing bleeding determine patient outcome. Every NICU facility must formulate and approve neonatal transfusion guidelines in the light of the current clinical practices which help limiting unnecessary transfusion practices that are not beneficial and may carry certain unavoidable risks. The transfusion associated benefits and risks in humans and more importantly in neonates always remain in limbo. Evidence-based objective criteria for safe neonatal transfusion practices are to be quickly formulated and the current clinical neonatal practitioners are to be enlightened of the same so as to prevent any ill-effects which may arise out of such injudicious transfusions.

Authors Contribution KD, GK wrote the manuscript, KD collected and analysed the data, SB, DC revised the article critically for important intellectual content, DC also took care of the patients. All authors have read and approved the manuscript being submitted, and agree to its submission to this journal.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

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