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Analysing the Utility of Fresh Frozen Plasma in Neonatal Intensive Care Unit in a Rural Tertiary Care Hospital, South India

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Abstract: Transfusion of Fresh frozen plasma is relatively common in neonatal intensive care units. Most common indications for transfusion being neonatal sepsis, deranged coagulation profile or co existence of both these conditions. However a universal protocol for FFP transfusion in neonates is lacking, leading to injudicious administration of FFP to neonates in many hospitals and thus exposing them to untoward risks of transfusion. This is our attempt towards analyzing the use of FFP in our neonatal intensive care unit and our compliance with the established guidelines (AIIMS protocol for FFP transfusion in neonates). Data was collected retrospectively of all the neonates who received FFP transfusions in our hospital from January 2014 to December 2017 and relevant analysis was performed. Most of the neonatal transfusions (93%) at our hospital during the study period were compliant with AIIMS guidelines. Most common indication for transfusion was bleeding manifestations followed by sepsis and deranged coagulation profile. However on analysis of pre and post transfusion coagulation parameters in these babies, no statistically significant improvement was seen. FFP was often used in accordance with the published guidelines in our study. However evidence based uniform guidelines need to be established and implemented to increase the benefit and minimise the risk associated with transfusion, especially in newborns.
Keywords: Fresh frozen plasma, transfusion, neonate, sepsis, coagulation.

INTRODUCTION

Fresh frozen plasma (FFP) is a component of blood derived from a single whole blood unit or by plasmapheresis [1]. Transfusion of FFP is a common practice in the neonatal intensive care unit (NICU), especially among the critically ill neonates, pre term & extremely low birth weight infants. FFP is used in such patients with a hope to successfully treat neonatal sepsis, correct the coagulation parameters and most importantly to prevent complications which might hamper the further physical and neural development of these newborns. Various guidelines are available for FFP transfusion in neonates, namely British Hematological Society protocol, South African Transfusion guidelines, AIIMS protocol etc. One of the recent protocols is the updated "Guidelines for the administration of blood products: transfusion of Infants & neonates - 2004" published by British Committee for Standards in Haematology [2].

In a study conducted by Motta *et al*., it was reported that 60% of the neonatal FFP transfusions are non compliant with the published guidelines. Majority of the neonates (63%) received transfusion prophylactically without evidence of haemorrhage [4]. Unnecessary transfusions expose newborns to serious complications like TRALI, fluid overload and allergic reactions [3]. Therefore this is our attempt to analyse the utility of FFP in our NICU and its compliance with the established guidelines for FFP transfusions in neonates.

Aims and Objectives

- To document the indications for Fresh frozen plasma transfusion in neonates.
- Analysing the extent of compliance of these indications with 'AIIMS protocols for neonatal transfusions'
- Documenting the utility of FFP in pre term and low birth weight neonates.

MATERIALS AND METHODS

This is a retrospective study conducted at a rural tertiary care hospital for four years, from January 2014 to December 2017. Data was collected retrospectively for all infants who received FFP

transfusion in the study period. Following baseline data were collected: Gestational age, birth weight, age at transfusion, indications for transfusion, dose of FFP administered and clinical diagnosis. AIIMS protocol for FFP transfusion in neonates is followed at our hospital (Table-1). Data collection also included the type of hemorrhage as an indication for FFP transfusion. Hemorrhage was categorised into intraventricular hemorrhage, pulmonary hemorrhage and gastrointestinal bleeding.

Table-1: Indications for transfusing FFP according to AIIMS protocol [5]

1.	Disseminated intravascular coagulation (Sepsis)
2.	Vitamin K deficiency bleeding
3.	Inherited deficiencies of coagulation factors
4.	Other rare indications include patients with afibrinogenemia, von Willebrand factor deficiency, congenital antithrombin III deficiency, protein C deficiency and protein S deficiency
5.	Reconstitution of blood for exchange transfusion

Pre and post transfusion coagulation test findings were recorded in cases wherever it was available and statistical analysis performed. Further, compliance of FFP transfusions to the AIIMS protocol for neonatal transfusion was assessed.

RESULTS

During the study period, 60 neonates received FFP transfusion. Most of the neonates were born at term (37 cases) with normal birth weight (>2.5 kgs – 27 cases). The pre transfusion characteristics of the infants are described in Table-2.

Table-2: Pre transfusion characteristics of the infants transfused with FFP

Variables	**Results**
Gestational age (in weeks)	35.6 (30-40)
No. of infants <28 weeks (%)	0
No. of infants 28-34 weeks (%)	21 (35%)
No. of infants > 34 weeks (%)	39 (65%)
Birth weight	
Extremely low birth weight (<1.5 k g)	9
Low birth weight (1.5-2.5 kg)	27
Adequate (>2.5 kg)	24
Postnatal age at transfusion (days)	5 (1-24)
Dose of FFP (ml)	26 (7-47)
No. of infants presenting with haemorrhage	18
Types of haemorrhage	
Intraventricular hemorrhage	04
Pulmonary hemorrhage	08
Gastrointestinal hemorrhage	06

Most common indication for FFP transfusion in our hospital was bleeding, 18 of the 60 cases presented with hemorrhagic manifestation, most common form of bleeding being pulmonary hemorrhage (8 cases), followed by bleeding through nasogastric tube (6 cases) and intraventricular bleeding (4 cases) detected by ultrasound. The other common indications for FFP transfusion in neonates in our NICU was sepsis (12 cases) followed by sepsis associated with prolonged PT (11 cases) and prolonged prothrombin time (11 cases). Table 3 describes the indications for which FFP transfusions were administered.

Table-3: Indications for FFP transfusion in neonates

Indications	**No. of cases (60)**
Bleeding	18
Sepsis	12
Sepsis with prolonged PT	11
Vitamin K deficiency / prolonged PT	10
HIE/NEC	5
Others (hyperbilirubinemia, congenital pneumonia, hypoalbuminemia)	4

Nine cases (15%) of the 60 transfusions were not compliant with the "AIIMS protocol for neonatal transfusion" whereas the other 51 cases (85%) cases were in accordance with the guidelines. These non complaint cases included three cases of hypoxic ishchemic encephalopathy (HIE) & two cases of

necrotising enterocolitis (NEC). Though these conditions are not mentioned as indications for transfusion in "AIIMS protocol for neonatal transfusion", transfusions were administered in anticipation of impending neonatal sepsis. The other non compliant cases included those of hypoalbuminemia, hyperbilirubinemia and congenital pneumonia.

Coagulation profile - Pre and post FFP transfusion:

Prolonged bleeding time (21 cases) was the one of the indications for FFP transfusion in our study; most of the cases were associated with sepsis as well (11 cases). Unfortunately pre and post transfusion coagulation parameters were available only for 12 cases in our study, as post transfusion coagulation testing is not done routinely in our set up to avoid loss of blood which could further worsen the babies' condition. Comparison of the pre and post transfusion coagulation parameters is shown in Table-4.

Table-4: Comparison of coagulation parameters pre and post FFP transfusion in neonates

Test	Pre transfusion		Post transfusion		P value
	Mean	SD	Mean	SD	
PT (in secs)	32.38	20.48	22.12	13.5	0.16
INR	2.18	0.92	1.59	0.44	0.05
APTT (in secs)	94.56	50.38	51.51	15.89	0.0099

Though most of the cases showed decrease in Prothrombin time post FFP transfusion, statistically significant response to FFP transfusion was seen only for APTT. Comparison of pre and post FFP transfusion Prothrombin time (PT) values did not show statistical significance. Figure-1 shows the comparison of pre and post transfusion PT and APTT values of each case assessed.

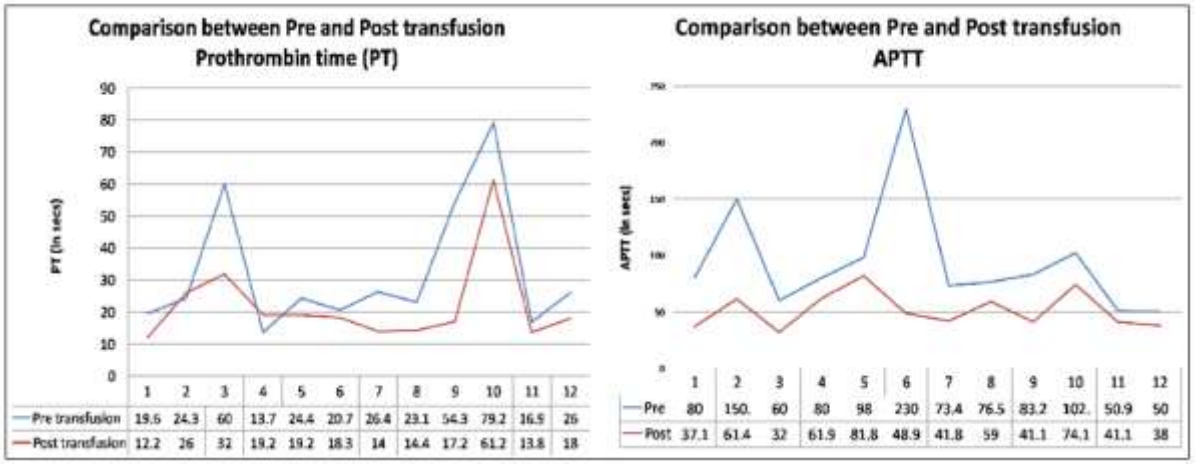

Fig-1: Comparison between coagulation parameters pre and post FFP transfusion

FFP transfusion in Low Birth Weight (LBW) neonates (Table-2)

In our study, we had 36 neonates whose weight was less than 2.5 kg at birth. Most common indication for FFP transfusion in these neonates was bleeding (11 cases) followed by sepsis with prolonged PT (7 cases). HIE or NEC was the indication in 3 babies. One of the neonates was transfused to treat hypoalbuminemia and another for hyperbilirubinemia. Both these conditions are not listed in the "AIIMS guidelines for FFP transfusion in newborns".

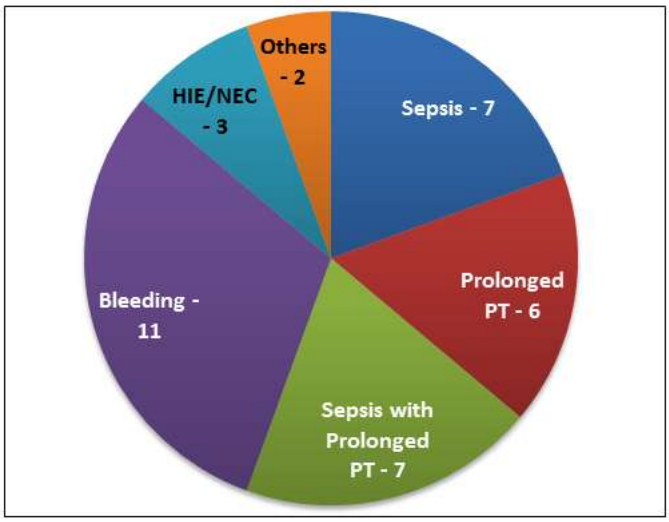

Fig-2: Indications for FFP transfusion in Low Birth Weight (LBW) neonates

FFP transfusion in pre term neonates

FFP transfusions are most often given to pre term babies, as they are at a higher risk of bleeding as well as contacting infections. In our study we had 21 pre term neonates, born before 37 weeks of gestational age. Most common indication for FFP transfusion in these neonates was bleeding (7 cases). Most of the babies (6 cases) suffered from both sepsis and had deranged coagulation parameters. In one case the baby was transfused for hypoalbuminemia and another case for congenital pneumonia (Figure-3).

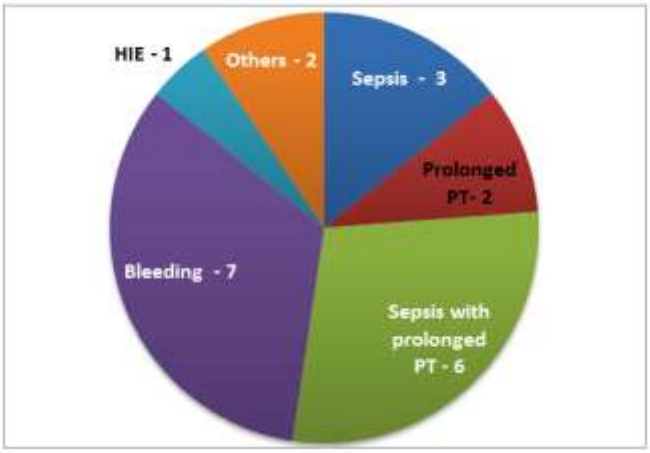

Fig-3: Indications for FFP transfusion in Preterm neonates

DISCUSSION

Transfusion of fresh frozen plasma is a common practice in neonatal intensive care units, especially in critically ill babies. Numerous guidelines are available for neonatal FFP transfusion. The most common indications for transfusion in neonates include sepsis and abnormalities of coagulation factors manifesting as bleeding [4]. In our study, 93% of the neonatal FFP transfusions were compliant with the "AIIMS protocol for neonatal transfusion". The non compliant cases included transfusion for hypoalbuminemia, congenital pneumonia and neonatal hyerbilirubinemia. Table-5 compares our study with those carried out by other authors.

In a study conducted by Akbar R et al at Rawalpindi, Pakistan, it was found that 79% of the FFP transfusions were given prophylactically to neonates with an intention to prevent bleeding [7]. The low rate of compliance in these studies is because the guidelines followed in their institutions do not include neonatal sepsis, whereas sepsis is one of the major indications for FFP transfusion and is included in AIIMS protocol, followed at our hospital. This indicates the need for a uniform universal protocol for FFP transfusion in neonates.

FFP is widely used as a source of immunoglobulins and complement in the treatment of neonatal sepsis. It increases motility of neutrophils to the site of infection by providing opsonins like

complement and fibronectin. In a study conducted by BA Aunas *et al*., it was shown that FFP is less effective than IV immunoglobulin for provision of components of humoral immunity in the management of neonatal sepsis [8]. However IVIG cannot be used in all centres due to financial constraints. Therefore FFP administration is still the management of choice in rural set ups like ours.

Table-5: Comparison with other studies – pre transfusion characteristics

Category	**Present Study**	**Motta M *et al*., [4]**	**Shukri Raban & MC Harrison [6]**
Gestational age	35 weeks	30 weeks	31 weeks
Common gestational age	> 34 weeks		28-34 weeks
Dose of FFP (ml)	26.2	16	15
Compliance with guidelines	93%	40%	75%
Common indication for FFP transfusion	Bleeding	Prophylactically with the intention of preventing haemorrhage	High risk of bleeding with coagulopathy
Haemorrhage	Pulmonary	Intraventricular	Pulmonary

In our study, including 60 neonates who received FFP transfusion, 18 cases presented with bleeding and 21 cases with prolonged Prothrombin time (PT). On monitoring the coagulation parameters post FFP transfusion, most of our patients showed mild improvement in PT, 2 hrs after transfusion. However there was no statistically significant improvement in PT, whereas there was statistically significant reduction in APTT in all patients. These findings were similar to the studies conducted by S. Hyatianen *et al.,* Abdel Wahab *et al.,* and CA Jhonson *et al.,* [9-11]. S Hyatianen *et al*., in their study measured thrombin antithrombin complex (TAT) and D dimer levels post transfusion in bleeding infants and found that there was no effect of FFP transfusion on these parameters [9]. Thrombin was down regulated only in a few cases, however levels of anticoagulants like Protein C and antithrombin increased post FFP transfusion. Therefore the effect of FFP on coagulation profile is neither predictable nor consistent.

Coagulation system in newborns is immature and undergoes profound development after birth. Under physiological conditions, there is no bleeding or thrombotic manifestation because of the balance between pro and anti thrombotic factors. However in certain conditions like prematurity and low birth weight, the neonates become susceptible to untoward consequences like intracranial hemorrhage, pulmonary hemorrhage and gastrointestinal bleeding [12]. In our study the most common indication for FFP administration in LBW (11 cases) and pre term neonates (7 cases) was bleeding.

One premature infant presented with intracerebral hemorrhage, 3 cases with pulmonary hemorrhage and 3 cases with GI bleed. A Cochrane metaanalysis of five clinical studies including the one carried out by Northern Neonatal Nursing Initiative Trial Group, concluded that routine administration of FFP to sick pre term infants in first 24 hrs of life did not show any benefit with respect to overall mortality or incidence of ICH in these newborns, similar findings were seen in a study conducted by G Hambleton *et al*., [12-14]. On these lines no neonate was administered FFP prophylactically to prevent bleeding in our study, unless there was a deranged coagulation status reflected by prolonged Prothrombin time (PT) and therefore an impending risk of bleeding.

Preterm infants are more susceptible to infections due to low immunoglobulin, complement and fibronectin levels due to lack of placental transfer. One of the common indications for FFP transfusion in pre term babies as well as low birth neonates in our study was sepsis. Hemorrhage is a frequent complication of sepsis, particularly in pre term neonates [15]. Therefore sepsis is most often associated with prolonged PT, as the procoagulant factors are rapidly consumed and FFP is administered to replenish these factors.

CONCLUSION

Majority of the FFP transfusions administered in our hospital where compliant with the AIIMS protocol followed here. However adopting and implementing evidence based guidelines for neonatal transfusions is much needed, to avoid the risks associated with transfusion in neonates. Coagulation profile in infants is different from that of adults, therefore standard inference intervals of coagulation tests for infants especially premature neonates need to be determined. Some authors have established reference ranges of coagulation parameters in neonates but these require further validation supporting their use in evidence based protocols for FFP transfusion [16, 17]. We should appreciate the limitations of coagulation screening in newborns, as in vitro abnormalities cannot be equated with in vivo failure of hemostasis and clinical coagulopathy. Thus FFP usage should be confined to therapeutic rather than prophylactic use, even in preterm & low birth weight neonates.

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