Original article

Fresh frozen plasma transfusion usage and appropriateness in neonatology

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ABSTRACT

Background: It is essential that blood and its components should be used appropriately. There are only a few clear indications for transfusing Fresh frozen Plasma (FFP).The British Society of Hematology recommends FFP usage either when the patient is actively bleeding or in patients who are at high bleeding risk and have coagulation profile abnormality with PT (prothrombin time) or aPTT (activated partial thromboplastin time) values significantly above the normal ranges for age and gestation concurrent to invasive procedures, it is also recommended that prophylactic FFP should not be transfused to "non-bleeding" children who have minor prolongation of PT/aPTT, even prior to surgery, but it may be considered for surgery to critical sites. This study was conducted to determine the usage and estimate appropriateness of FFP transfusion in neonatology.

Subjects and methods: This was a descriptive cross sectional study included all neonates who received FFP from July to Sep 2018. We recorded their demographics, indication for FFP transfusion, hemoglobin, white cell count, platelet count, pretransfusion and post transfusion PT/APTT/INR (international normalized ratio). Neonates whose mothers were on anticoagulants were excluded from the study. Statistical Analysis was done using SPSS 24.

Results: Ages ranged from 1 to 28 days. Male: female 1.6:1. 55% FFP were transfused to bleeding neonates while 45% were transfused either for deranged coagulation tests or as pre-procedural prophylaxis.

Conclusion: Prophylactic FFP use is very common. Developing awareness among physicians can improve adherence to recommended indications. Studies that would evaluate restrictive vs. liberal FFP use are needed.

Keywords:
Fresh frozen plasma, neonates

INTRODUCTION

It is essential that blood and its various components be used appropriately. The prescribing clinician should have a sound and valid reason for doing so.[1] Haemorrhage is an important cause of morbidity and mortality in extremely preterm infants but it is rare in neonates, older infants and adolescents, fresh frozen plasma (FFP), platelet concentrates, cryoprecipitate and other plasma derived or recombinant products are used to treat these patients.[2] Use of red cell transfusions have fallen in last two decades but FFP transfusions have remained unchanged or increased[3,4] There are only a few clear indications for transfusing FFP , there is a growing consensus that most of the time FFP is used inappropriately.[5,6] There are alternative and safer forms of treatment available which can be used instead of plasma.[1]

Retrospective studies suggest that bleeding risk is low following invasive procedure with less than 1% requiring intervention or blood transfusion.[7] Currently FFP is used to treat coagulopathy resulting from deficiency of multiple coagulation factors including Disseminated Intravascular Coagulation, warfarin reversal, liver disease, massive transfusion and as replacement for coagulation factors, the suggested indications are comparable worldwide including Pakistan. [8-10]

The British Society Hematology recommendation for FFP usage is either when the patient is actively bleeding or in those patients who are at high bleeding risk, have coagulation profile abnormality with Prothrombin time (PT) or activated partial thromboplastin time (aPTT) values significantly above the normal ranges for age and gestation concurrent to invasive procedures it is further recommended that prophylactic FFP "should not" be administered to "non-bleeding" children who have minor prolongation of PT/aPTT, even prior to surgery, but transfusion

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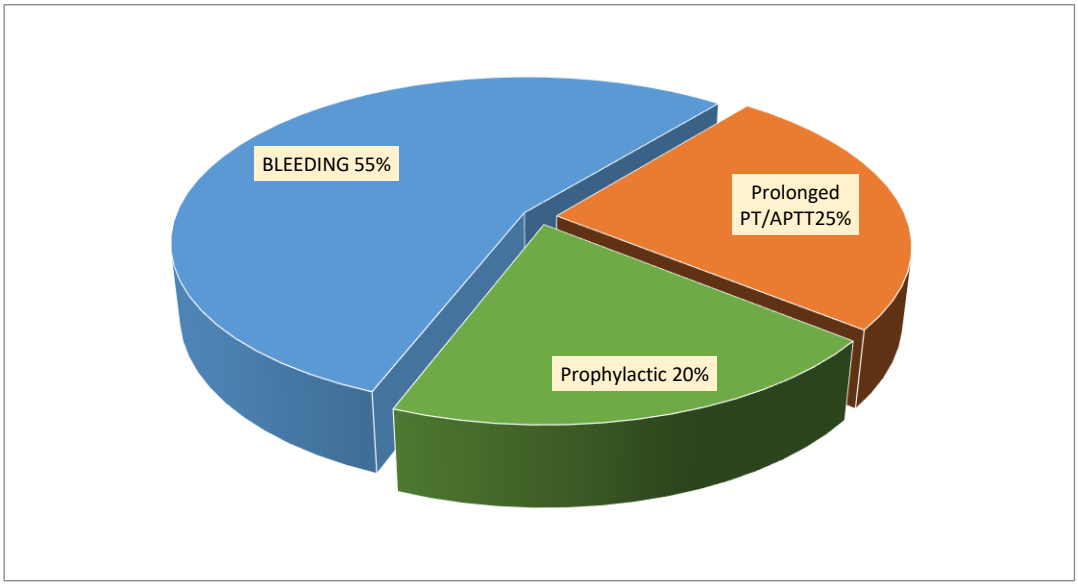

Figure 1. Indications for FFP transfusion

may be considered for surgery to critical sites. These guidelines also advise that plasma should not be used for volume replacement or for prevention of bleeding e.g. Intra Ventricular Hemorrhage in neonate.[11]

Evidence guiding FFP use in neonates is very weak, only a few multicentre studies are available.[12] This study was undertaken to determine usage and estimate appropriateness of FFP transfusion in neonatology setting in our hospital. Thus initiating the process of auditing blood products which could help in developing strategies to avoid wastage of blood products.

PATIENTS AND METHODS

All neonates who received FFP from July to Sep 2018 were included in the study we recorded their diagnosis, indication for FFP transfusion, hematology parameters like hemoglobin, white cell count, platelet count as well as, pretransfusion and post-transfusion PT/APTT/INR. Neonates whose mothers were on anticoagulants were excluded from the study. Statistical analysis was done using SPSS 24.

RESULTS

In a period of 3 months, 120 neonates received FFP transfusions. Ages of patients ranged from 1 to 28 days with mean of 8 days. Male:female being74:46(1.6:1). The diagnosis of these patients were sepsis, asphyxia neonatorum, jaundice neonatorum, necrotizing enterocolitis, hemorrhagic disease of newborn, heart block and admissions for various surgical procedures. The indications for transfusing FFP are given in Figure 1. 70% of the neonates had Hb <12gm/dl, mean Hb being 11.2 gm/dl and ranged from 2.8 to 20gm/dl. Total white cell count ranged from 1.6 $x10^3$/µL to 30 x 10^3 /µL with mean being 6.9 $x10^3$/µL. Platelet count ranged from 3x 10^3/µL to 512 $x10^3$/µL with mean count of 123 x 10^3/µL, only 28% had platelet count within normal range. 33 (27.5 %) patients received platelet transfusions in addition to FFPs and 35 (30%) patients received packed cell transfusions in addition to FFPs

FFP were transfused to 66 (55%) presenting with bleeding and to 54 (45%) non bleeding patients out of these 30 (25%) were transfused because of deranged coagulation profile with mean pre transfusion INR of 3.3. Another 24 (20%) were transfused as preprocedural prophylaxis for various surgeries and had mean pretransfusion INR of 1.1.

Both pre and post transfusion INR values were available in 62 patients. Both values were missing in 16 either because of clotting of sample or inability to draw blood. One of two values was missing in remaining cases. Pre transfusion INR <1.5 was present in 42 (35%), between 1.5-3.0 in 27 (22%) and was >3.0 in 36 (33%) neonates. Post transfusion INR <1.5 in 63 (53%) and 1.5-3.0 in 15 (13%) & > 3.0 in 10 (08%). Relationship between FFP transfusion and INR response of 62 cases is shown in Figure 2. Higher the pretransfusion INR the greater was post transfusion INR improvement (Table 1).

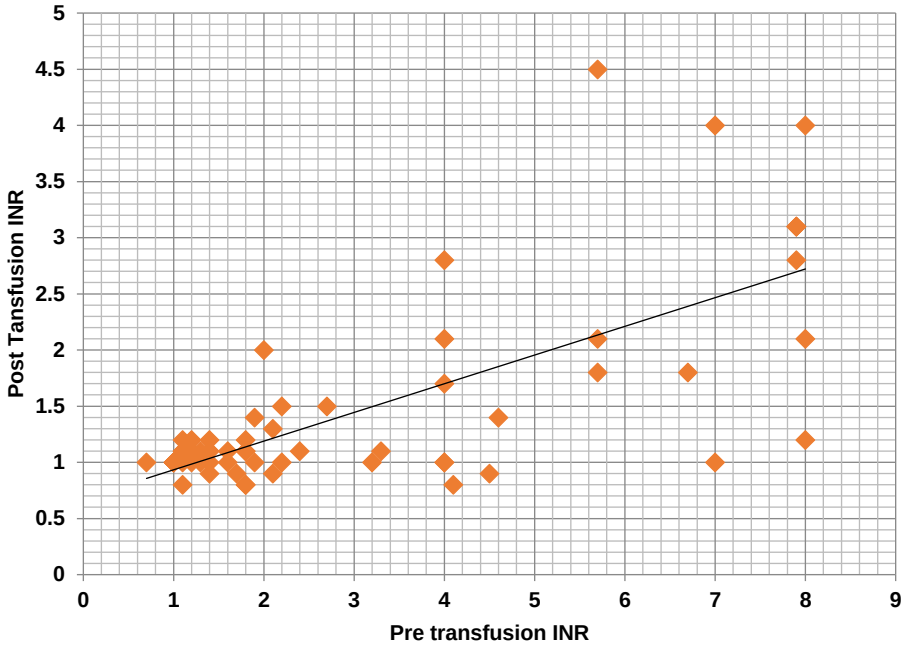

Figure 2. INR improvement following FFP transfusion

DISCUSSION

The use of red cell transfusions has reduced in the past two decades in contrast to the use of FFP transfusions that has remained unchanged or has increased.[3,4] Physicians use conventional screening tests of coagulation to guide their clinical decisions regarding transfusing FFP, PT/ aPTT values typically above 1.5 times the control. PT and aPTT values depend on laboratory quality controls and reagents. There are various reasons for their prolongation that are not associated with risk of bleeding.[13] When INR value starts to exceed >1.5 value, factor levels drops to <30%, which for most treating physicians become a threshold for deranged hemostasis.[14]

Despite the lack of consensus regarding the prophylactic use, 30-50% FFP are transfused to non-bleeding patients.[15-17] A United Kingdom national audit of neonatal plasma transfusions reported 50% prophylactic transfusions to non-bleeding neonates.[4] Using FFP to correct multiple coagulation factors deficiencies in bleeding patients is supported by numerous international guidelines[18,19] but, the efficacy of using prophylactic FFP in patients who are not bleeding is not certain.[3] Motta et al[12] reported that only 37% NICU patients who were transfused were actively bleeding while 63% received prophylactic FFP transfusions. Logistic regression analysis of their data revealed that PT, aPTT, platelet count & fibrinogen levels were not associated independently with bleeding. In our study 45 % neonates received prophylactic FFP transfusions while 55% were transfused FFP as they were actively bleeding. Inappropriate FFP transfusions were reported by Kakar et al[20] reported in 60.3% which reduced to 26.6% after educational campaigns of clinicians.

Numerous studies have shown a reduction in INR following FFP transfusion but not complete normalization.[7,21-23] An INR elevation up to 1.5 cannot be corrected, even with higher FFP doses.[24,25] When INR is >1.5, a relationship between dose and target INR is found.[21,25] Prophylactic FFP transfusions to patients with mildly deranged coagulation screening tests (INR <1.5) without any bleeding, need further scrutiny. Reduction in INR was observed with pretransfusion INR (>3.0) values.[26] Holland et al[7] also concluded that in cases with INR <2.0-2.5 transfusing FFP did not result in correction of INR. In present study similar relationship between FFP transfusion and pre and post transfusion INR was noted in our results (Figure 2). While analyzing pre and post transfusion values of 62/120 neonates we observed that 25 (40%) cases had pretransfusion INR <1.5 while in 14 (22.5%) INR was between 1.5-2.5 and it was over 2.5 in 23

Table 1. Mean INR improvement with FFP transfusion

INR	Mean INR pre transfusion	Mean INR post transfusion	Post FFP transfusion INR improvement
<1.5	1.1913	1.0348	0.1565
1.5—2.5	1.9750	1.1813	0.7937
>2.5	5.7870	2.1043	3.6827

(36.8%) cases. FFP transfusion resulted in marked reduction of INR in cases with higher pretransfusion INR (>2.5) (Figure 2).

Using FFP as pre procedural prophylaxis is very common despite presence of little evidence favouring this practice. Numerous studies have shown that skilled physicians can perform invasive procedures even in patients with hemostatic disorders without use of FFP.[27,28].In our study we observed use of FFP as pre procedural prophylaxis with 15 out of 40 (37.5%) patients having INR <1.5.

According to Biu et al[29] the risk- benefit ratio for liberal use of FFP may be unfavourable. Plasma use in neonates may be associated with multiple risks eg allergic / febrile reactions, Transfusion associated circulatory overload, Transfusion related acute lung injury. FFP transfusion should be done only in presence of clear indications. Association between plasma transfusion and venous thrombosis in neonatal and pediatric patients may be because of platelet-derived microparticles and clotting factors in plasma.[30].Rate of venous thrombosis was 10 times more frequent in neonates and children who received plasma than cases not receiving FFP transfusion[4].

Decisions to transfuse FFP are made on the basis of adult reference ranges used to define coagulopathy despite the fact that neonatal reference ranges are different from adult reference ranges. In newborns clotting factors are synthesized in the liver & do not cross placenta, hemoastsis is different from adults.[31] Levels of contact factors as well as vitamin K dependent clotting factors are 50% of the adult levels at birth. [32,33] Thrombin generation is 30-50% of adult values[34].It is observed that even when Thrombin Time(TT), PT, aPTT are prolonged in neonates they may not bleed this can be explained by the compensatory balances. The fibrinolytic system is down regulated, plasminogen level is 50% of adult value also there is an associated increase in inhibitors of plasminogen activator.[35] therefore reference ranges which are age specific are required for proper interpretation of test results.[36,37] Validated bleeding prediction is also needed to standardize actual bleeding in neonates. Correlating increased values with actual risk of bleeding is needed, so far none has been established. Randomized controlled trials are needed to explore prophylactic plasma use in neonates who have abnormal coagulation tests or are at high bleeding risk.[38] Newer methods to asses global haemostasis like thromboelastography and rotational ThromboelastoMetry and thrombin generation tests can better determine the cause of bleeding and predict bleeding risk as well and outcome after haemostatic therapies, such as FFP transfusion in cardiac and liver surgery patients.[39] Close collaboration between transfusion medicine specialists and pediatricians- neonatologists is needed.[40]

Large prospective clinical trials should be done to determine whether or not tests of global haemostasis are better than coagulation screening tests being used routinely in guiding blood component therapy.

CONCLUSION

Inappropriate use of FFP transfusions remains high. The commonest reason for inappropriate FFP use is the belief that the prolongation of PT or aPTT is predictive of bleeding, and transfusing FFP would cause normalization of these tests and prevent bleeding. In the present analysis, we found 45% of FFP transfusions given to non-bleeding neonates either for deranged coagulation screen or as pre-procedural prophylaxis. Prophylactic FFP transfusions on the basis of only mildly elevated conventional tests in non-bleeding patients is not justified. However at a higher pre transfusion INR, the post transfusion INR improvement was marked. It was our intent to shed light on this common practice hoping that this would contribute to appropriate FFP use and also reduce burden of transfusion transmitted infections. Studies that would evaluate restrictive *vs.* liberal FFP use are needed.

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