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RESEARCH PAPER

Role of Prophylactic Fresh Frozen Plasma in Critically ill Neonate to Prevent Bleeding in Disseminated Intravascular Coagulation: A Randomized Controlled Trial

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Abstract

Background: Disseminated intravascular coagulation (DIC) has a high prevalence in critically ill neonates. In suspicion of DIC based on abnormal coagulation parameter is a common trigger to transfuse fresh frozen plasma (FFP), even in absence of bleeding. In past years, use of FFP has increased and has expanded to include prophylactic use in neonates especially in neonatal intensive care units (NICUs) as it contains several coagulation factors. Several studies suggest that, prophylactic use of FFP has no role to prevent bleeding in disseminated intravascular coagulation (DIC), but carries increase risk of transfusion related mortality and morbidity.

Objective: To assess the effectiveness of prophylactic use of FFP in critically ill neonate to prevent bleeding in DIC.

Methods: This randomized, open-label, blinded end-point study was conducted in Bangladesh Institute of Child Health and Dhaka Shishu (Children) Hospital from July, 2019 to June, 2021. Term, critically ill neonates who had underlying disease, suspected to develop DIC were conveniently selected. Later, they were randomly allocated using software in intervention group, who received 10 ml/kg of FFP along with standard management and control group, who received only standard management. Coagulation parameters were checked before and 24 hour after intervention in both groups. Outcome was occurrence of bleeding as a indicator of DIC.

Results: The mean age was 8.55 ± 3.5 days in intervention and 8.92 ± 6.1 days in control group. Male patients were predominant. There was no significant difference in baseline characteristics between two groups. The difference of mean ± SD of coagulation parameters between two groups were nonsignificant before intervention. Even after FFP transfusion, DIC developed among 40.1% neonates in intervention and without FFP transfusion among 48.9% neonates in control group without any significant difference (*P*-value >0.05).

Conclusion: Study result found no role of prophylactic use of FFP in critically ill neonate to prevent bleeding in DIC.

Key words: Prophylactic FFP, Critically ill, Term neonate, Coagulopathy, DIC, Randomized controlled trial.

Introduction

Disseminated intravascular coagulation (DIC) is acute, sub-acute, or chronic thrombohemorrhagic disorder characterized by the excessive activation of coagulation and the formation of thrombi in the microvasculature of the body.[1] It is characterized by the systemic activation of blood coagulation, which generates intravascular thrombin and fibrin, resulting in the thrombosis of small to medium sized vessel and ultimately organ dysfunction and severe bleeding.[2]

It can be divided into overt and non-overt type. Non-overt type is said when hemostatic system is both stressed and compensated and often remain unrecognized. Over DIC, a term used when hemostatic system is stressed, decompensated and associated with clinical consequences.[3]

In neonate, DIC is an acquired coagulopathy and secondary effect caused by various underlying diseases.[4] Neonates are more vulnerable to DIC than adult population.[5]

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The prevalence of coagulopathy, as detected by prolonged coagulation tests in critically ill patients is high.[6] There is currently no evidence-based studies that show at which level of the Prothrombin time (PT) or activated partial prothrombin time (APTT) a neonate is at an increased risk of bleeding. Coagulation time in neonate is longer than adult and not necessarily related to increase risk of bleeding. However, study found that found that, FFP failed to correct prolonged coagulation tests in neonates 70% of the time.[7]

In neonates, additional complexity is added by developmental haemostasis, whereby the immature hemostatic systems yields different normal ranges in standard tests during early life.[8]

FFP is a blood product produced by centrifugation of donated whole blood. It contains adequate levels of all soluble coagulation factors like >70% fibrinogen, albumin, natural anticoagulants (protein C, protein S, antithrombin, tissue factor pathway inhibitor) and added anticoagulants.[9] It is more available than individual clotting factor. FFP is used in neonates with abnormal clotting studies, with the assumption that correcting the clotting studies into the normal range will reduce the risk of, or stop ongoing bleeding.[10] Several studies concluded that though after transfusion of FFP in a standard dose, values of PT & APTT decreased, but it failed to bring them in normal range.[7,11] On the other hand, some studies found significant rise of Fibrinogen value, whether, other concluded as no significant rise of fibrinogen value.[12,13] It remained controversial the effect of FFP on these coagulation markers. However, Motta et al. said that, no altered laboratory test is significantly associated with bleeding as they have poor predictive value.[12]

The cornerstone of management of non-overt DIC is the treatment of underlying condition triggering the coagulopathy, which will lead to a spontaneous resolution of DIC.[3] But much of management of DIC continues to center around the use of Fresh frozen Plasma (FFP). The reason for increased usage of this is unclear but seems likely to continue.[14]

Indications of FFP transfusion in neonate is unclear.[14] One proposed use of FFP in neonates was to prevent intracranial hemorrhage.[15] However, a large randomized trial of FFP use in premature neonates showed that FFP failed to reduce the risk of intracranial hemorrhage.[16] FFP once used as a volume expander but, again randomized controlled trial failed to show any benefit.[17] The serious Hazard of Transfusion (SHOT) Haemovigilance scheme has also highlighted that there is a relatively higher risk of adverse events for transfused child than adults.[18,19]

Baer et al[10] and Puetz et al[14] found the rate of FFP transfusion was 6% and 12% of infants admitted to and Motta et al[12] found 8% of neonates have admitted to NICU received one or more transfusion, where 63% received prophylactically without any benefit on outcome. Raban and Harrison[13] stated, 25% FFP used as prophylactically with huge extra expenses to patients without any clinical benefit.

There is limited data found from Bangladesh about transfusion practice in critically ill neonates. By minimizing this inappropriate use of FFP, neonatal mortality, morbidity and extra expenses could be lessened that would be beneficiary for a country like Bangladesh with limited resources. There is limited studies done in Bangladesh in this regard. So, randomized controlled trial has been done to assess the effectiveness of prophylactic FFP to prevent bleeding in critically ill term neonates.

Materials and Methods

This was a prospective randomized open-label blinded endpoint study (PROBE design) conducted at neonatal unit of Bangladesh Institute of Child Health (BICH) and Dhaka Shishu (Children) Hospital which is an autonomous tertiary level children hospital comprising 650 beds of various sub specialty, SCABU, NICU and CICU. The study was done from July 2019 to June 2021 (24 months). Sick neonates admitted in neonatal unit of Dhaka Shishu (Children) Hospital during study period were the study population.

Sample size was calculated using this formula. where,

$$n = \frac{P_1(100-P_1) + P_2(100-P_2)}{(P_1-P_2)} \times (Z_\alpha + Z_\beta)^2$$

Target sample was 108 in each group. Inclusion criteria was term, critically ill neonate with suspicion of coagulopathy from investigations (According to international society for thrombosis and hemostasis

diagnostic scoring system for DIC- total score less than 5)[2] 1. Platelets level – less than 100,000/ cu mm, 2. Prothrombin time (PT)- more than upper limit[20,21], 3. Fibrinogen level- < 200 mg/dl, 4. D-dimer- >0.5 mg/L, 5. Activated partial thromboplastin time (APTT)- more than upper limit according to age[20,21]. Normal values are derived from Andrew et al.[21] Neonate who already have any sort of bleeding, or with shock, or any major congenital anomaly or syndromic baby, or Platelet count less than 30,000/ cumm, or, already been transfused with either FFP before collection of 1st sample or any other blood product before collection of 2nd sample were excluded. To prevent the bias on effect of multiple dose of FFP or other blood product on coagulation markers, we strictly observed the effect of single unit of FFP. Critically ill neonates were included by convenient sampling. Proper history were taken through a preformed structured interview and all data were collected using a preformed data collection check list. All the study patients got 1 dose of vitamin K (2mg/0.2 ml) injection intramuscularly as a routine practice, if not found documented. Patient was randomly assigned to intervention and control group to receive or not to receive a single dose of 10 ml/kg FFP respectively by unrestricted method that is simple random allocation by using computer software IBM SPSS Statistic 22. After enrollment initially, coagulation parameters (Platelets, PT, APTT, Fibrinogen, D-dimer) were sent in both groups. Intervention group received single transfusion of FFP 10 ml/Kg. Besides, both the groups received standard management depending on underlying disease. Coagulation parameters were repeated after 24 hours in both groups. Platelet count (PC) were measured by automated haematology analyzer mythic 22 using mythic 22 reagents from Orphée Switzerland. PT, APTT, Fibrinogen were measured by fully automated Sysmex® CA-500 Series System coagulation analyzer using Thromborel® S reagent from SIEMENS, Dade®Actin® FSL reagent, Dade® Thrombin reagent respectively. D-dimer was measured by GP-Getein-1100 Immunofluorescence analyzer using D-dimer fast test kit from Getein. They were regularly followed up for developing any DIC manifestation in the form of petechiae, purpura, ecchymosis, GI hemorrhage, pulmonary hemorrhage, intraventricular hemorrhage (by Cranial USG based on suspicion on sign-symptoms) till discharge or death. Whenever bleeding developed blood transfusion were done according to standard protocol

Statistical analysis

All the data were entered, processed and analyzed by using IBM SPSS Statistics 22 version for windows software. Quantitative data were expressed as mean ± SD and qualitative data as number (Frequency). To compare quantitative or numerical variable between two groups unpaired t-test were performed. To compare quantitative or numerical variable in each group before and after intervention, paired t-test were performed. To compare qualitative / categorical value between two groups, the Chi-square (χ^2) test and where applicable Fisher-exact test was used. For all statistical test *P*-value of less than 0.05 was considered as statistically significant.

Results

Total 216 term, critically ill neonates were enrolled but finally 200 completed this study. Among them, 102 were in intervention and 98 were in control group. Some drop out was there, as some got more than one dose of FFP or other blood product, some died before taking 2nd sample and some took discharge on risk bond.

Figure 1 shows disease distribution between two groups. In intervention group- Sepsis, Perinatal asphyxia, Perinatal asphyxia with sepsis, Sepsis with NEC, Perinatal asphyxia with MAS, Perinatal asphyxia with MAS with Sepsis is 35, 27, 25, 9, 5, 1 in number and in control group- 24, 30, 20, 15, 9, 0 in number respectively without any significant difference (*P* >0.05).

Table I shows, Mean ± SD age of intervention group was 8.55 ± 3.5 days, whereas for control group was 8.92 ± 6.1 days. Among male, 47.1% were in intervention group, 52.9% were in control group and among female 59.7% were in intervention group, 40.3% were in control group without any significant difference (Table-I).

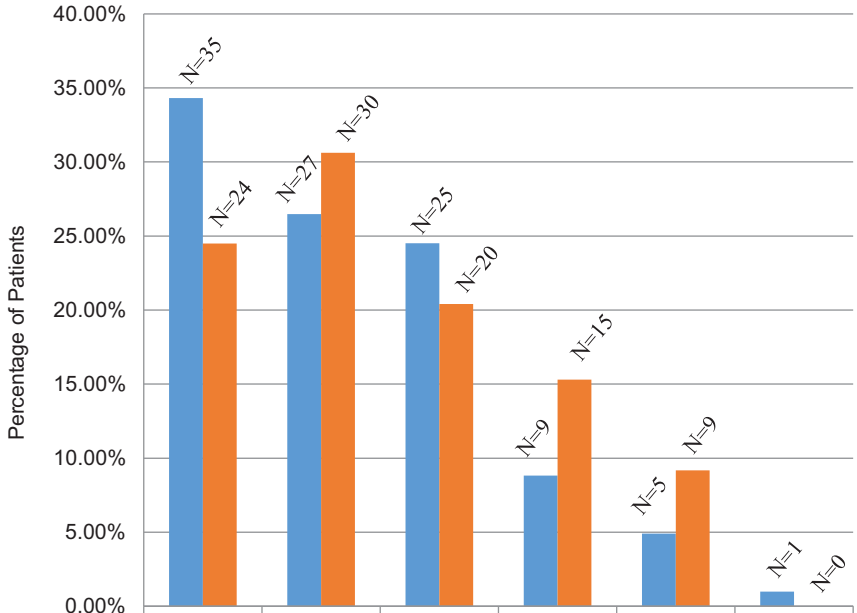

Figure 1: Graphical Presentation of Disease distribution between two groups

Table I: Comparison of demographic variables between two groups (n=200)

Demographic value	Intervention group (n=102) No. (%)	Control group (n=98) No. (%)	*P*-value
Age (in days)	8.55 ± 3.5	8.92 ± 6.1	0.596^{ns}
Gender			
Male	65 (47.1)	73 (52.9)	0.100^{ns}
Female	37 (59.7)	25 (40.3)	
Weight (In gram)	2674 ± 0.32	2695 ± 0.28	0.634^{ns}
Gestational age			
37 to 40 weeks	82 (80.39)	85 (86.73)	0.227^{ns}
41 to 42 weeks	20 (19.61)	13 (13.27)	

Table II shows home delivery was noted in 19.6% cases in intervention and 26.5% cases in control group (Table II).

In intervention group, 41 neonates were delivered by normal vaginal delivery, 59 by caesarean section and 2 by assisted vaginal delivery without any significant difference (*P*>0.05). In control group, 46 neonates were delivered by normal vaginal delivery and 52 by caesarean section without any significant difference (*P*>0.05).

Table-III shows, DIC in the form of bleeding developed in 40.1% cases in intervention and 48.9% cases in control group without any statistical significant difference (*P*>0.05).

Table-IV shows, before intervention, mean ± SD of these coagulation parameters between two groups were statistically nonsignificant (*P* >0.05). After intervention, fibrinogen value raised significantly (*P*<0.05) (Table-III).

Table II: Antenatal and natal characteristics and there comparison between two groups

Variable	Intervention group (n=102) No. (%)	Control group (n=98) No. (%)	*P*-value
Parity			
Primi para	50 (49.0)	53 (54.1)	0.474^{ns}
Multiparous	52 (51.0)	45 (45.9)	
Maternal Illness during pregnancy	57 (55.9)	47 (48.0)	0.262^{ns}
Diabetes	31 (54.3)	28 (59.5)	0.595^{ns}
Hypertension	10 (18.1)	3 (6.4)	0.134^{ns}
Diabetes and Hypertension	14 (24.1)	13 (27.7)	0.720^{ns}
Antepartum Haemorrhage	0 (0.0)	3 (6.4)	0.089^{ns}
Oligohydramnios	2 (3.5)	0 (0.0)	0.500^{ns}
Delivery Place			
Home	20 (19.6)	26 (26.5)	0.245^{ns}
Institutional	82 (80.4)	72 (73.5)	
Mode of delivery			
Normal vaginal delivery	41 (40.2)	46 (46.9)	0.266^{ns}
Cesarean section	59 (57.8)	52 (53.1)	
Assisted vaginal delivery	2 (2.0)	0 (0.0)	

Table III: Comparison of occurrence of DIC between two groups

Variable	Intervention group No. (%)	Control group No. (%)	*P*-value
Bleeding occurred	41 (40.1)	48 (48.9)	0.211^{ns}
Bleeding not occured	61 (59.9)	50 (51.1)	

Table IV: Comparison of coagulation parameters between two groups before and after 24 hour of intervention

Variable	Intervention group (n=102) Mean ± SD	Control group (n=98) Mean ± SD	*P*-value
Before intervention			
Platelet(/cumm)	76799.01 ± 19202.0	77448.98 ± 18338.1	0.807^{ns}
PT (s)	22.04 ± 8.1	20.44 ± 5.5	0.108^{ns}
APTT (s)	83.86 ± 20.2	84.65 ± 13.1	0.742^{ns}
Fibrinogen (mg/dl)	226.07 ± 57.3	240.17 ± 74.5	0.134^{ns}
D-dimer (mg/L)	4.68 ± 4.3	4.08 ± 3.9	0.306^{ns}
24 hour after intervention			
Platelet (/cumm)	74096.08 ± 15940.0	72357.14 ± 18678.0	0.479^{ns}
PT (s)	17.39 ± 5.7	18.24 ± 5.9	0.281^{ns}
APTT (s)	72.65 ± 18.9	76.20 ± 11.6	0.104^{ns}
Fibrinogen (mg/dl)	329.74 ± 134.7	295.43 ± 89.0	0.036*
D-dimer (mg/L)	4.14 ± 4.0	3.67 ± 3.5	0.174^{ns}

Table V shows, In Intervention group, fibrinogen values raised significantly ($P < 0.05$) after intervention. Table VI shows there was also no significant mean differences in Platelets PT, APTT, Fibrinogen, D-dimer in 24 hours apart in control group ($P>0.05$) by standard management.

Most of the cases DIC in the form of bleeding developed by 5±2.5 days irrespective of groups. Bleeding manifestation was dominated by petechiae, purpura followed by GI hemorrhage and pulmonary hemorrhage.

Table V: Comparison of coagulation parameters in intervention group before and after intervention

Variable	Before intervention Mean ± SD	After intervention Mean ± SD	*P*-value
Intervention group			
Platelet (/cu mm)	76799.01 ± 19202.0	74096.08 ± 15940.0	0.170^{ns}
PT (s)	22.04 ± 8.1	17.39 ± 5.7	0.108^{ns}
APTT (s)	83.86 ± 20.2	72.65 ± 18.9	0.167^{ns}
Fibrinogen (mg/dl)	226.07 ± 57.3	329.74 ± 134.7	0.001**
D-dimer (mg/L)	4.68 ± 4.3	4.41 ± 4.0	0.162^{ns}

Table VI: Comparison of coagulation parameters in control group at 24 hours apart.

Variable	At enrollment Mean ± SD	24 hours after enrollmentMean ± SD	*P*-value
Platelet (/cu mm)	77448.98 ± 18338.1	72357.14 ± 18678.0	0.251^{ns}
PT (s)	20.44 ± 5.5	18.24 ± 5.9	0.153^{ns}
APTT (s)	84.65 ± 13.1	76.20 ± 11.6	0.113^{ns}
Fibrinogen (mg/dl)	240.17 ± 74.5	295.43 ± 89.0	0.061^{ns}
D-dimer (mg/L)	4.08 ± 3.9	3.67 ± 3.5	0.160^{ns}

Discussion

In this study, coagulation parameters in both groups were indicating DIC. In Intervention group, after infusion of FFP, only Fibrinogen level significantly increased. Platelets level remained low; PT, APTT, D-dimer value although decreased, but fail to come within normal range. On The other hand in control group, 24 hour after standard management, Platelets value remained low. PT, APTT, D-dimer value also decreased, but still higher from normal range. Fibrinogen level raised insignificantly. DIC developed 40.1% cases in Intervention group even after FFP transfusion in comparison to Control group, where 48.9% neonates had DIC without any statistically significant difference.

Regarding Platelet, Dogra et al[22] reported a much lower pre transfused Platelet level. In this study, all the neonates had thrombocytopenia. However, thrombocytopenia is common in sick neonates, affecting 20%-35% of those admitted to NICU. Approximately, 75% of those neonates have mild to moderate thrombocytopenia (50,000- 150,000/cu mm).[23] Go et al[24] did not find low platelet as a risk factor of bleeding in neonatal settings.

In this study, mean±SD of PT and APTT was above normal range even after FFP transfusion in intervention group and 24 hours apart in control group. This finding is similar to other studies.[7,17,18] Our findings is similar to Motta et al.,[12] who stated that, no laboratory tests were associated with bleeding. Tripodi et al[25] stated that, these tests have poor predictive value as do not account for physiologically lower concentration of protein C and Antithrombin III in neonates, therefore, do not reflect the actual balance between pro coagulant and anticoagulants. FFP dose of 10 ml/ kg should raise most coagulation factors by 10 U/dl.[14] If a coagulation factor level before transfusion of FFP were below 40 U/dl (40%), then the infusion of 10 ml/kg of FFP would not be predicted to correct a prolong PT/ APTT. This may explain the poor response to FFP. However, this much low factor in a no bleeding patient is rare, and more goes with bleeding or congenital factor deficient patient, where specific coagulation factor would work better. However, complete correction was not the objective of this study and many other studies reported that higher doses of FFP is not a current practice.[6,19] and may hamper compliance to study protocol.

After FFP transfusion, mean±SD of fibrinogen level significantly increased in intervention group. This is similar to findings of Motta et al[12] Standard preparation FFP contains 400-900 mg/unit of fibrinogen.[26] However, Raban and Harrison[13] conducted a 5 year retrospective study where a wide range of neonates from different gestational age at different age point were included and found no significant increase of

fibrinogen after FFP transfusion. Fibrinogen level was within normal range in both groups at enrollment. As an acute phase reactant, it increases, though consumption process of DIC is going on. Tripodi et al[25] observed, increase fibrinogen marker in postnatal period.

Incidence of DIC after FFP is similar to findings of Mendicini et al[26], who conducted a controlled trial on preterm and found no benefit of prophylactic use of FFP to prevent DIC in form of bleeding. However, Dogra et al[22] found a higher rate (61.5%) of bleeding and Motta et al[12] found a lower number (36.5%) of bleeding among FFP transfused patient compare to this present study. A systematic review by Osborn and Evans[27] in Cochrane database included 4 studies showed that no significant differences in any grade of intraventricular hemorrhage or mortality rate. Elbourne and NNI trial group[16] is the largest of these 4 studies which found no benefit of FFP to prevent periventricular hemorrhage in preterm neonates. However, prophylactic FFP to prevent intracranial hemorrhage in preterm neonates still not recommended.[28]

Conclusion

Study result found no role of prophylactic use of FFP in critically ill neonate to prevent bleeding in DIC. This is not a double-blind placebo controlled trial. However, manufacturing a completely matched placebo was considered not feasible for this noncommercial, academic study. Corn trypsin inhibitor was not used during collection of blood to prevent accidental contact activation of coagulation. As, it is not a routine practice here and we have performed all coagulation studies from a single sample. Acquired coagulopathy is common in critically ill neonates. Timely intervention with standard management and care can prevent the underlying consumption process of DIC. Inappropriate transfusions have significant morbidity rate and mortality. Evidenced based practice of neonatal transfusion of restrictive strategy may prevent it. However, a multicenter randomized controlled trial on term neonates including other markers of DIC is needed to improve current knowledge.

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