Utilization of Fresh Frozen Plasma and Cryoprecipitate in Factor VIII and Factor IX Deficient Hemophilia Patient

ABSTRACT

Hemophilia is one of the most common cause of inherited bleeding disorder resulting from deficiency of coagulation factor VIII or factor IX. Ideally replacement should be done with factor concentrate. Due to economic constraints associated with its procurement, bleeding episodes are regularly dealt with Fresh Frozen Plasma (FFP) or cryoprecipitate in low resource countries.

This study was carried out with the objective to compare utilization profile and clinical characteristics of haemophilia patients receiving FFP and cryoprecipitate for replacing clotting factor deficiency.

This cross-sectional comparative study was conducted in day care unit of the Dept. of Transfusion Medicine of Bangabandhu Sheikh Mujib Medical University, Shahbag, Dhaka, Bangladesh, between 2 groups of haemophilia patient receiving either cryoprecipitate or FFP for treatment.

Out of total 100 hemophilic patients, 50 were treated with cryoprecipitate and 50 with FFP. In FFP group, majority of patients (48 % in cryoprecipitate group and 36% in FFP group) were in the age of more than 5 to10 years followed by 11 to 15 years age (24% versus 30%) with mean SD of age in cryoprecipitate group and FFP group being 11.78±5.61 and 13.42±6.12 years, respectively. 33 (66.0%) had history of bleeding following trauma followed by 32 (64.0%) with history of spontaneous bleeding among patients of cryoprecipitate group as cause of swelling/bleeding and in FFP group, 23 (46.0%) had history of spontaneous bleeding followed by 23 (34.0%) with history of bleeding following trauma. Regarding type of bleeding, oral bleeding was most common, followed by soft tissue bleeding in both group (40.0% versus 38.0%). Presence of ecchymosis in both groups was statistically significant. The difference in type of haemophilia between two groups was statistically significant ($p<0.001$) with prevalence of haemophilia A about 88%.

Life expectancy of haemophilia patient is increasing dramatically day by day with successful and effective treatment with the appropriate plasma component. Cryoprecipitate is better than FFP as there is less chanceof volume overload minimizing leucocyte induced non-haemolytic febrile transfusion reaction and rapid correction of coagulation factor.

Keywords: FFP, Cryoprecipitate, Haemophilia, low-resource.

INTRODUCTION

Hemophilia is an X-linked genetic disorder resulting from the recessive X-chromosomal inheritance pattern, affecting mostly male whereas their female relatives being heterozygous for the mutation, often referred to as carriers of haemophilia. It has two types, haemophilia A (classic hemophilia) and B (Christmas disease) caused by deficiency of factor VIIIand factor IX respectively. It affects approximately 400,000 people worldwide with an estimated prevalence of 1 in 5000 male live births in case of hemophilia A, and 1 in 30,000 live birth in case of haemophilia B.[1] There is no precise estimation of prevalence in our county despite likely extensive infliction of this geographical area with this disorder due to preference towards rituals of consanguineous marriage. The clinical manifestations of hemophilia A and B are almost indistinguishable and presents in mild, moderate and severe category. Spontaneous internal bleeding and excessive bleeding following trauma or surgery are the typical findings. Repeated bleeding into the muscle and joints leading to chronic crippling hemarthropathy, neurologic damage, damage to other organ systems, and death ensues if not treated very early or prophylactically.[2]

Bleeding episodes in this life-threatening coagulopathy should be treated early by raising the factor VIII level through intravenous infusion of factor VIII concentrate which has been the game changer in care of haemophilia patients dramatically improving the quality of life and life expectancy. The work of Dr. Edwin Cohn known as Cohn Fraction in developing fractionation of plasma with variation of temperature and concentrations of saline and alcohol led to the development of fairly crude plasma concentrates of human factor VIII in a number of centres. But the discovery by Dr. Judith Pool in 1965 that slow thawing of plasma to around 4°C led to appearance of brown sediment that has greater Factor VIII activity within the fibrinogen “sludge” which was slow to re-dissolve termed “cryoprecipitate” has revolutionized the treatment of haemophilia and although the preparation time is lengthy, today it remains the only treatment option in some countries.[3] Within a decade, lyophilized coagulation factor concentrates made an appearance. These offered considerable advantages: they could be stored in a domestic refrigerator at 4°C, and permitted the administration of a large and assayed quantity of coagulation factor rapidly and in a small volume. The availability of such products facilitated home treatment, allowing patients for the first time to treat themselves athome, work, school, or even whilst on holiday abroad freeing them from the physical and psychological shackles of haemophilia.[4] However, concentrates may not be readily available in developing countries leaving cryoprecipitate and fresh frozen plasma (FFP) as the only alternatives for treatment or prevention of bleeding in patients with hemophilia. Even if hospitals maintain an inventory of concentrates, owing to the high cost it is not a feasible option for a greater number of patients who choose plasma component instead for replacement of factor deficiency. FFP, despite being least indicated as well as effective among the treatment options, it is often the most available option in resource-poor area over cryoprecipitate which requires more time, relatively high cost and multiple donor. Single donation of FFP is approximately 200-240 ml wherever single unit of cryoprecipitate is only about 15-20ml. So managing severe haemophilia patient with cryoprecipitate is better than FFP. FFP is much more susceptible to produce anti leucocyte antibody which causes Non Haemolytic Febrile Transfusion

Reaction (NHFTR) following repeated transfusion. Transfusion of FFP may lead to volume over load followed by severe hazards and death.

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METHODOLOGY

This cross sectional study was done in the day care unit of the department of Transfusion Medicine, Bangabandhu Sheikh MujibMedical University from 1st January 2021 to 31st December 2021. Total 100 haemophilia patients attending day care unit were included in this study via non probability (purposive) sampling method according to inclusion and exclusion criteria. Within six to eight hours of whole blood collection from volunteer donor after meticulous assessment, meeting our blood bank's standard operative procedure, plasma was separated and frozen at -18°C or colder for getting fresh frozen plasma (FFP). Cryoprecipitate is a cold-insoluble fraction of plasma proteins contained in FFP. It is prepared by slowly thawing FFP at a temperature between 1-6°C over night until the plasma develops a slushy consistency. Then, centrifuged at 4000 RVPM (revolution per minute) for five minutes. The supernatant is separated from the plasma and refrozen within one hour and stored at -18°C or colder for upto 12 months. It is a low-volume blood component of approximately 15-20 ml per unit.

RESULTS:

Table I: Age distribution of haemophilia patients (n-100) between groups

Age (in year)	Groups		p value*
	Cryoprecipitate (n=50) %	FFP (n=50) %	
0-5	04 (8.0)	03 (6.0)	
>5-10	24 (48.0)	18 (36.0)	
>10-15	12 (24.0)	15 (30.0)	
>15-20	05 (10.0)	08 (16.0)	
>20-25	03 (6.0)	05 (10.0)	
>25	02 (4.0)	01 (2.0)	
Total	50 (100.0)	50 (100.0)	
Mean ± SD	11.78±5.61	13.42±6.12	0.165

*t test was done to measure the level of significance.

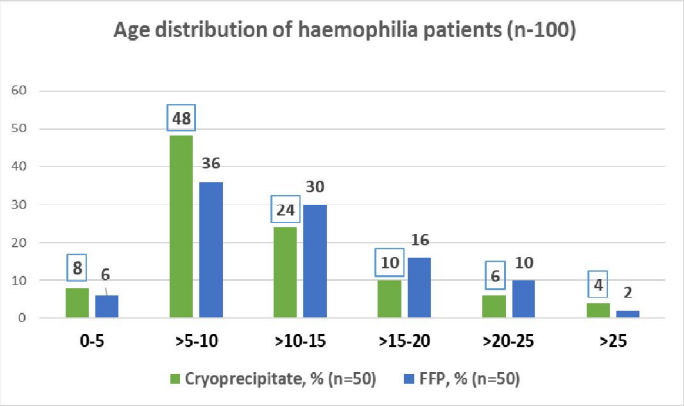

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Figure 1: **Age distribution of haemophilia patients (n-100) between groups**

Table I and figure 1 shows that among the patients in cryoprecipitate group nearly half (48.0%) are in the age of 5 to 10 years, followed by 24.0% in the 11 to 15 years age. Four patients were in the less than 5 years age and 5, 3, 2 patients in each of 15 to 20, 20 to 25 and more than 25 years group respectively. Among the patients in FFP 36% were in the age of 5 to10 years and 30% in the 11 to 15 years age. Followed by 16.0% in the 16 to 20 years, 10% were in the 20 to 25 and only one in more than 25 years. Three patients were in the less than 5 years age. Mean ± SD of age in cryoprecipitate group and FFP group was 11.78 ± 5.61 and 13.42±6.12 years respectively showing no statistically significant difference in age between the groups (p>0.05)

Table-II: Pattern of bleeding between cryoprecipitate and FFP group

Bleeding	**Groups**		**p value***
Causeofbleeding/ swelling	**Cryoprecipitate** (n=50) %	**FFP** (n=50) %	
Spontaneous	32 (64.0)	23 (46.0)	0.071
Following trauma	33 (66.0)	17 (34.0)	0.002*
Surgery	14 (28.0)	16 (32.0)	0.663
Tooth extraction	18 (36.0)	13 (26.0)	0.487
Site of swelling/bleeding			
Skin	8 (16.0)	12 (24.0)	0.373
Soft tissue	16 (32.0)	17 (34.0)	0.832

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Oral	20 (40.0)	19(38.0)	0.838
Wound	12 (24.0)	10 (20.0)	0.639
Bruises	17 (34.0)	9 (18.0)	0.068
Type of bleeding			
Echymosis	14(28.0)	05 (10.0)	0.022*
Hematoma	10 (20.0)	11(22.0)	0.806

Chi-square test was done tomeasure the level of significance.

Fisher's Exact test was done to measure the level of significance.

Table II shows the distribution of bleeding between groups. Among the 50 patients of cryoprecipitate group, 32 (64.0%) had history of spontaneous bleeding and 33 (66.0%) had history of bleeding following trauma, 14 (28.0%) had history of bleeding after surgery and 18 (36.0%) had history of bleeding after tooth extraction. Among the 50 patients of FFP group,23 (46.0%) had history of spontaneous bleeding and 17 (34.0%) had history of bleeding following trauma, 16 (32%) had history of bleeding after surgery and 13 (26.0%) had history of bleeding after tooth extraction. Among the patients of cryoprecipitate Group, 8 (16.0%) history of skin bleeding and same 16 (32.0%) had history of soft tissue bleeding/swelling, 20 (40.0%) had history of oral bleeding and 17 (34.0%) had history of bruises and 12 (24.0%) had wound bleeding. Among the patients of FFP group 12 (24.0%) had history of skin bleeding and same 17 (34.0%) had history of soft tissue bleeding/swelling, 19 (38.0%) had history of oral bleeding and 9 (18.0%) had history of bruises and 10 (20.0%) had wound bleeding. Among the patients of cryoprecipitate group, 14 (28.0%) had history of ecchymosis and 10 (20.0 %) had history of hematoma. Among the patients of FFP group, 5 (10%) had history of ecchymosis and 11 (22%) had history of hematoma. There is statistically significant difference in bleeding following trauma between the groups (p>0.05). There is statistically significant difference in type of bleeding between the groups (p>0.05).

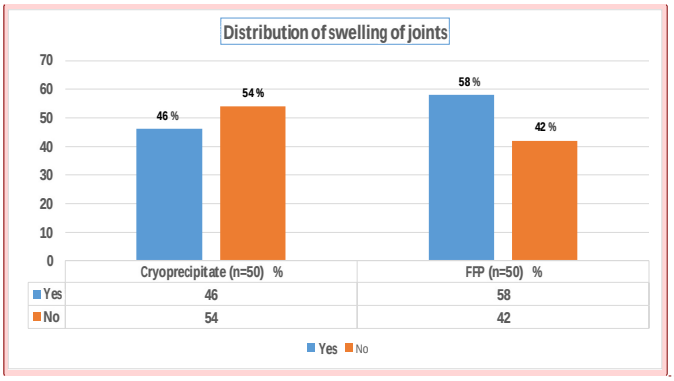

Figure 2: Distribution of swelling of joint between groups

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Chi-square test was done to measure the level of significance.

Figure 2 above depicts the distribution of swelling of joints between groups. Among the 50 patients of cryoprecipitate group, 23 (48.0 %) had swelling of joints and 27 (54.0%) had noswelling of joints. Among the 50 patients of FFP group, 29 (58.0%) had swelling of joints and 21 (42.0 %) had no swelling of joints.There is no statistically significant difference in swelling of joints between the groups (p>0.05).

Figure 3: Distribution of haemophilia A and B

Simple percentage analysis was done in figure 3 which shows that 88 % patients presented with haemophilia A, whereas only 12 % presented with haemophilia B giving a ratio of approximately 7:1.

Table-III: Distribution of the types of Hemophilia between groups

Types of Haemophilia	Groups		p value*
	Cryoprecipitate (n=50) %	FFP (n=50) %	
Haemophilia A	50 (100.0)	38 (76.0)	<0.001
Haemophilia B	0 (0.00)	12 (24.0)	
Total	50 (100.0)	50 (100.0)	

Chi-square test was done to measure the level of significance.

Table-III shows there is statistically significant difference in type of Hemophilia between the groups ($p<0.05$).

DISCUSSION

In the past haemophilia has been called 'the Royal Disease' due to several family tree of European royal family being afflicted with this hereditary disease including Queen Victoria herself. Hemophiliac male used to die inyoung age then.[5] Due to its fatal bleeding nature, transfusion medicine is closely linked to this disease as in the early nineties only treatment was blood transfusion. With diagnostic advances and development of safe and effective treatment, affected individuals can nowlook forward to a normallife expectancy if they can receive comprehensive care. Total one hundred hemophilia patients were included in thepresent study with fifty patient in each group according to the type of plasma product they received. Fifty were treated with cryoprecipitate and fifty were treated with FFP. Majority of patients (48 % in cryoprecipitate group and 36% in FFP group) were in the age of more than 5 to10 years followed by 11 to 15 years age (24% versus 30%). 2 and 1 patient were in more than 25 age group respectively. Mean SD of age in cryoprecipitate Group and FFP Group was 11.78±5.61 and 13.42±6.12 years respectively. There is no statistically significant difference in age between the groups ($p>0.05$) (Table 1). Chuansumrit et al. conductednational survey of patients with hemophilia and other congenital bleeding disorders in Thailand in the years 2000 to 2002. In their study out of 1450 patients with bleeding disorder, hemophilia comprised of 1,325 cases.[6] Most were pediatric patients of <15 years of age which are in close agreement to our findings. Kavakli etal. shows similar result in a study of 53 patients with haemophilia A withage range of 1-20 years and median age was 11 years and 12 patients with haemophilia B with an age range 34-20 years and median age was 10 years.[7]

Comment [JR5]: et al.

Patients with hemophilia experience a spectrum of bleeding manifestations, which usually, but not always, are in keeping with their baseline level of FVIII or FIX. Examples of bleeding include intracranial hemorrhage, deep muscle and joint hemorrhage, hematoma, retroperitoneal haemorrhage, bleeding following teeth extraction, post-surgical bleeding, easy bruising and mucosal bleeding with an increase predilection towards musculoskeletal hemorrhage leading to recurrent hemarthrosis and development of target joints.[8] In our study both group exhibited predominant cause of bleeding/swelling occurred following trauma. Among the 50 patients of cryoprecipitate group 33 (66.0%) had history of bleeding following trauma followed by 32 (64.0%) with history of spontaneous bleeding. Among the 50 patients of FFP group, 23 (46.0%) had history of spontaneous bleeding followed by 23 (34.0%) with history of bleeding following trauma. Regarding type of bleeding, oral bleeding was most common followed by soft tissue bleeding in both groups. Among the patients of cryoprecipitate group,10 (40.0%) had history of oral

bleeding with 16 (32.0%) with soft tissue bleeding. Among the patients of FFP group, 12 (34.3%) had history of soft tissue, 19 (38.0%) had history of oral bleeding. Presence of ecchymosis in both groups was statistically significant as among the patients of cryoprecipitate group,14 (28.0%) had history of ecchymosis and among the patients of FFP group,5 (10.0%) had history of ecchymosis. Presence of hematoma was not found statistically significant. There is statistically significant difference in bleeding owing to trauma between the groups ($p>0.05$) as well as type of bleeding between the groups ($p>0.05$) but no statistically significant difference in site of bleeding (Table 4).In a study by Moslehuddin et al. series found that 19.1% patients of haemophila A had spontaneous bleeding whereas 80.9% cases had bleeding following trauma and haemophilia B, 12.5% cases had spontaneous bleeding, 87.5% cases had bleeding following trauma which is in agreement with our result.[9] In a study by Kanjaksha et al. found that recurrent hematuria was present in 18 of 474 moderate and severe hemophiliacs.[10]

Among the 50 patients of cryoprecipitate group, swelling of joints were present in 23 (46.0%) and absent in 27 (54.0%). Among the 50 patients of FFP group, 29 (58.0 %) had swelling of joints whereas 21 (42.0%) did not have. There is no statistically significant difference in swelling of joints between the groups (0.05) (Table 3).

Prevalence of haemophilia A was found to be higher than haemophilia B in all studies till date with age-adjusted prevalence of about 12 case of haemophilia A and 3.7 case of haemophilia B per 100,000 males in a recent study conducted in United States[11] and hamophilia A affecting approximately about 80% to 85% of the total hemophilia population.[12]Similarly, in our study, total 100 haemophilia patient were studied and most of them were haemophilia A (88 %). Among the 50 patients in cryoprecipitate group 100.0% were hemophilia A indicating appropriate utilization of component. Among the 50 patients in FFP group 76.0% were hemophilia A and24.0% were hemophilia B[13]. The difference in type of hemophilia between the groups is statistically significant ($p<0.05$) (Table 4). Walker etal. found in his study that 81% patients had haemophilia A and 19% had haemophilia B which is also in concordance with the presentstudy.[14]

CONCLUSION

Longevity and quality of life of haemophilia patients are increasing dramatically day by day with successful and effective treatment with adequate plasma component. In the wake of lack of precise estimate of haemophilia population, our study shows that utilization profile as well as clinical characteristics of patient receiving both cryoprecipitate and Fresh Frozen Plasma (FFP) are almost similar. Therefore, guiding them towards more appropriate plasma component is of utmost importance. Cryoprecipitate is better than FFP owing to rapid correction of coagulation fraction leaving less chance of volume over load and minimizing recipient leucocyte mediated non-haemolytic febrile transfusion reaction. However, FFP is an easily available and affordable option. Consensus among clinician over which product to use in haemophilia should be established as the risk of increased donor exposure with delay in preparation with cryoprecipitate must be weighed against the risk of volume overload with the

use of FFP. Further extensive studies are required to identify challenges as well as ways to overcome and manage complications, establishing optimum care with the aid of hemophilia registry and government reimbursement in haemophilia treatment centres in resource-poor developing countries like ours.

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