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

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Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Haemophilia is one of the most common causes 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 to compare the 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 the day care unit of the Department of Transfusion Medicine of Bangabandhu Sheikh Mujib Medical University between 2 groups of haemophilia patients receiving either cryoprecipitate or FFP for treatment. Out of the total 100 haemophilia patients, 50 were treated with cryoprecipitate and 50 with FFP. In FFP group, the majority of patients (48% in cryoprecipitate group and 36% in FFP group) were in the age group of more than 5 to 10 years followed by 11 to 15 years age (24% versus 30%) with a mean SD of age in

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cryoprecipitate group and FFP group being 11.78±5.61 and 13.42±6.12 years, respectively. About 33 (66.0%) had a history of bleeding following trauma and 32 (64.0%) had a history of spontaneous bleeding among the patients in cryoprecipitate group as a 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 the 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 the two groups was statistically significant (p<0.001) with a prevalence of haemophilia A of about 88%. The life expectancy of haemophilia patients 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 chance of volume overload minimizing leucocyte induced non-haemolytic febrile transfusion reaction and rapid correction of coagulation factor.

### 1. INTRODUCTION

Haemophilia is an X-linked genetic disorder resulting from the recessive X-chromosomal inheritance pattern, affecting mostly males, whereas their female relatives being heterozygous for the mutation are often referred to as carriers of haemophilia. It has mainly two types, haemophilia A (classic hemophilia) and B (Christmas disease) caused by deficiency of factor VIII and factor IX respectively. It affects approximately 400,000 people worldwide with an estimated prevalence of 1 in 5000 male live births in case of haemophilia A and 1 in 30,000 live birth in case of haemophilia B. There is also haemophilia C or factor XI deficiency which was not discussed in our study due to its very low prevalence [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 present in the mild, moderate and severe categories. Spontaneous internal bleeding and excessive bleeding following trauma or surgery are the typical findings. Repeated bleeding into the muscle and joints leads to chronic crippling haemarthropathy, 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 the 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 a variation of temperature and concentrations of saline and alcohol led to the development of fairly crude plasma concentrates of human factor VIII in some centres. But the discovery by Dr. Judith Pool in 1965 that slow thawing of plasma to around 4°C led to the 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 at home, 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 components instead for replacement of factor deficiency. FFP, despite being least indicated as well as effective among the treatment options, is often the most available option in resource-poor areas over cryoprecipitate which requires more time, relatively high cost, and multiple donors. A single donation of FFP is approximately 200-240 ml wherever a single unit of cryoprecipitate is only about 15-20 ml. So managing severe

**Keywords**: FFP; cryoprecipitate; haemophilia; low-resource.
haemophilia patients with cryoprecipitate is better than FFP. FFP is much more susceptible to produce anti leucocyte antibody which causes Non-Haemolytic Febrile Transfusion Reaction (NHFTTR) following repeated transfusion. Transfusion of FFP may lead to volume overload followed by severe hazards and death.

2. METHODOLOGY

This cross sectional study was done in the day care unit of the department of Transfusion Medicine, Bangabandhu Sheikh Mujib Medical 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.

2.1 Statistical Analysis

All the data were collected through an Excel sheet and statistical analysis was done by statistical software Statistical Package for Social Science (SPSS) version 24. All the data were expressed as numbers and percentages. Comparison of quantitative variables was done using unpaired Student’s t test. For comparing categorical data, Chi-square (x2) test was performed. Simple percentage analysis was also done. For all statistical test, p value <0.05 was considered as significant.

3. RESULTS

Table 1 and Fig. 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 2 shows the distribution of bleeding between groups. Among the 50 patients in 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 in 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. Regarding the site of bleeding, among the patients in cryoprecipitate group 8 (16.0%) gave history of skin bleeding and 16 (32.0%) had history of soft tissue bleeding/swelling whereas 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 in FFP group, 12 (24%) 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 in cryoprecipitate group, 14 (28.0%) had history of ecchymosis and 10 (20.0 %) had history of hematoma. Among the patients in FFP group, 5 (10%) had history of ecchymosis and 11 (22%) had history of hematoma. There is a statistically significant difference in bleeding following trauma between the groups (p<0.05).

Fig. 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 no swelling 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).
Table 1. Age distribution of haemophilia patients (n=100) between groups

<table>
<thead>
<tr>
<th>Age (in year)</th>
<th>Cryoprecipitate (n=50)</th>
<th>FFP (n=50)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>04 (8.0)</td>
<td>03 (6.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;5-10</td>
<td>24 (48.0)</td>
<td>18 (36.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;10-15</td>
<td>12 (24.0)</td>
<td>15 (30.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;15-20</td>
<td>05 (10.0)</td>
<td>08 (16.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;20-25</td>
<td>03 (6.0)</td>
<td>05 (10.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;25</td>
<td>02 (4.0)</td>
<td>01 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>50 (100.0)</td>
<td>50 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>11.78±5.61</td>
<td>13.42±6.12</td>
<td>0.165</td>
</tr>
</tbody>
</table>

Fig. 1. Age distribution of haemophilia patients (n=100) between groups

Table 2. Pattern of bleeding between cryoprecipitate and FFP group

<table>
<thead>
<tr>
<th>Cause of bleeding/swelling</th>
<th>Cryoprecipitate (n=50)</th>
<th>FFP (n=50)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>32 (64.0)</td>
<td>23 (46.0)</td>
<td>0.071</td>
</tr>
<tr>
<td>Following trauma</td>
<td>33 (66.0)</td>
<td>17 (34.0)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Surgery</td>
<td>14 (28.0)</td>
<td>16 (32.0)</td>
<td>0.663</td>
</tr>
<tr>
<td>Tooth extraction</td>
<td>18 (36.0)</td>
<td>13 (26.0)</td>
<td>0.487</td>
</tr>
<tr>
<td>Site of swelling/bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>8 (16.0)</td>
<td>12 (24.0)</td>
<td>0.373</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>16 (32.0)</td>
<td>17 (34.0)</td>
<td>0.832</td>
</tr>
<tr>
<td>Oral</td>
<td>20 (40.0)</td>
<td>19 (38.0)</td>
<td>0.838</td>
</tr>
<tr>
<td>Wound</td>
<td>12 (24.0)</td>
<td>10 (20.0)</td>
<td>0.639</td>
</tr>
<tr>
<td>Bruises</td>
<td>17 (34.0)</td>
<td>9 (18.0)</td>
<td>0.068</td>
</tr>
<tr>
<td>Type of bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echymosis</td>
<td>14 (28.0)</td>
<td>05 (10.0)</td>
<td>0.022*</td>
</tr>
<tr>
<td>Hematoma</td>
<td>10 (20.0)</td>
<td>11 (22.0)</td>
<td>0.806</td>
</tr>
</tbody>
</table>
**Fig. 2. Distribution of swelling of joint between groups**

**Fig. 3. Distribution of haemophilia A and B**

**Table 3. Distribution of the types of Hemophilia between groups**

<table>
<thead>
<tr>
<th>Types of Haemophilia</th>
<th>Groups</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cryoprecipitate (n=50)</td>
<td>FFP (n=50)</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>50 (100.0)</td>
<td>38 (76.0)</td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>0 (0.00)</td>
<td>12 (24.0)</td>
</tr>
<tr>
<td>Total</td>
<td>50 (100.0)</td>
<td>50 (100.0)</td>
</tr>
</tbody>
</table>
Simple percentage analysis was done in Fig. 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 3 shows there is statistically significant difference in type of Hemophilia between the groups (p<0.05).

4. DISCUSSION

In the past hemophilic male used to die in young age due to its fatal bleeding nature, transfusion medicine is closely linked to this disease, as in the early nineties only treatment was blood transfusion [5]. With diagnostic advances and development of safe and effective treatment, affected individuals can now look forward to a normal life expectancy if they can receive comprehensive care. Total one hundred hemophilia patients were included in the present 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 to 10 years followed by 11 to 15 years age (24% versus 30%). In more than 25 years age group, two patients were in FFP and only one in cryoprecipitate group. 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. conducted national 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 disorders, 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 et al. showed similar results in a study of 53 patients with haemophilia A in age range of 1-20 years and median age of 11 years and 12 patients with haemophilia B in age range of 34-20 years and median age of 10 years [7].

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 hemorrhage, 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 that bleeding/swelling predominantly occurred following trauma. Among the 50 patients in 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 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 found in majority followed by soft tissue bleeding in both groups. Among the patients in cryoprecipitate group, 10 (40.0%) had history of oral bleeding and 16 (32.0%) presented with soft tissue bleeding. Among the patients in FFP group, 12 (34.3%) had history of soft tissue and 19 (38.0%) had history of oral bleeding. Presence of ecchymosis in both group was statistically significant. Presence of hematoma was not found statistically significant, although it is believed to be the most common presentation in haemophilia. 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 was found in site of bleeding (Table 3). A similar study by Moslehuiddin et al. reported that 19.1% of patients of haemophilia A had spontaneous bleeding whereas 80.9% cases had bleeding following trauma and among haemophilia B, 12.5% cases had spontaneous bleeding and 87.5% cases had bleeding following trauma which are in agreement with our findings [9]. In a study by Kanjaksha et al. found that recurrent hematuria was present in 18 of 474 moderate and severe hemophilia [10].

Among the 50 patients in cryoprecipitate group, swelling of joints were present in 23 (46.0%) and absent in 27 (54.0%). Among the 50 patients in FFP group, 29 (58.0 %) had swelling of joints whereas 21 (42.0%) had no swelling. There is no statistically significant difference in swelling of joints between the groups (p>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 cases of haemophilia A and 3.7 cases of haemophilia B per 100,000 males in a recent study conducted in United States and haemophilia A affecting approximately about 80% to 85% of the total haemophilia population [11,12]. Similarly, in our
study, a total of 100 haemophilia patients 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 and 24.0% were hemophilia B. The difference in type of hemophilia between the groups is statistically significant (p<0.05) (Table 3). Walker et al. found in their study that 81% of patients had haemophilia A and 19% had haemophilia B which is also in concordance with the present study [13].

5. 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.

CONSENT

As per international standard or university standard, patients’ written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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