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Development Of Inhibitors In Hemophilia A Patients Receiving Different Treatment Options

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ABSTRACT

Introduction: Hemophilia A is the most common inherited bleeding disorder in Pakistan. Apart from frequent bleeds and joint deformities, the formation of inhibitors is the major complication of hemophilia. Inhibitors are antibodies formed against the coagulation factor. The purpose of this study is to determine the incidence of inhibitor development in hemophilia A patient receiving different treatment modalities namely fresh frozen plasma (FFP)/cryoprecipitate, plasma derived FVIII concentrates and long-acting recombinant FVIII concentrates.

Aims &Objectives: To assess the development of inhibitors in hemophilia A patients receiving treatment modalities.

Place and Duration of Study: The study was conducted at Chughtai Institute of Pathology from November 2021 to November 2023.

Material &Methods:A total of 75 registeredpatientsof the Hemophilia Patient Welfare Society, Lahore and Sundas Foundation were initially screened for FVIII inhibitors .Those who were found negative for these inhibitors were included in the study and then divided into three equal groups of 25 patients each. One group received only FFP/cryoprecipitate for treatment, the other group received plasma derived FVIII concentrates and the last group received recombinant factor VIII concentrates. These patients were observed for two years i.eafter 15-20 exposures and following this period their inhibitors screening was done again to establish the effect of different treatment modalities on inhibitor development.The data collected was entered and analyzed by SPSS-21, a p-value of ≤0.05 was considered significant.

Results: Our study showed that only 3 patients out of 25, receiving FFP as treatment modality developed inhibitors. Whereas, none of the patients receiving plasma derived FVIII concentrates and recombinant factor VIII concentrates developed inhibitors. The P value calculated is 0.044 which is significant.

Conclusion: Plasma derived FVIII concentrates and recombinant FVIII concentrates are safer as compared to FFP/Cryoprecipitate and have lesser risk for inhibitor development.

Keywords: Hemophilia, Inhibitors, plasma derived factor concentrate, recombinant factor concentrates.

INTRODUCTION

Factor VIII (FVIII) and Factor IX (FIX)play an importantrole in the intrinsic pathway of coagulation cascade[1].These factors are crucial in formation of the hemostatic plug by fibrin. Absence of FVIII and FIX cause hemorrhagic disease known as hemophilia. Hemophilia A is an inherited X-linked recessive disorder caused by mutation in the FVIII gene leading to deficiency of FVIII[2]. The severity of the disease depends upon the FVIII levels present inthe plasma of the patient. In severe hemophilia the factor levels are less than 1% of the normal, in moderate hemophilia 1-5% of normal whereas in mild disease factor levels are between 5-40%[3].

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Hemophilia patients experience spontaneous and post traumatic bleeds usually in muscles and jointsbut life-threatening intracranial bleeds can also occur which greatly increase the mortality of the hemophiliacs[4]. Over the last few decades, the quality of life of hemophiliacs has improved drastically due to availability of factor replacement therapies but as these therapies are expensive,most patients cannot afford them[5].

The main aim of treatment is to maintain hemostasis and prevent and control active bleed through factor replacement. In resource constrained nations like Pakistan long term prophylaxis by FVIII is not possible thus on demand treatment is usually done. The different treatment modalities available include conventional plasma/cryoprecipitate transfusion, intravenous FVIII concentrates with extended half-life and FVIII resembling monoclonal antibodies[6]. Although the plasma derived and recombinant FVIII development of inhibitors whereas the role of environmental risk factors like surgery or infection and immunological responses at the time of factor administration remain as potential risk factor[8].

International data observed that inhibitors development occurs in around 30% of patients with severe disease and occurs within first 20 exposures to FVIII[9].

The aim of this study is to compare the incidence of inhibitor development in local hemophilia A patients who are receiving different treatment products including fresh frozen plasma (FFP)/ cryoprecipitate, plasma derived FVIII concentrates (Injection Koate DVI or InjectionKovaltry) and long-acting recombinant FVIII concentrates (Injection Eloctate).

MATERIAL AND METHODS

The study was conducted at Chughtai Institute of Pathology, Lahore after getting approval from the IRB Committee (CIP/IRB/1022). The duration of study was fromNovember 2021 to November, 2023.A total of 75 patients registered in Hemophilia Patient Welfare Society, Lahore and Sundas Foundation were assigned. It was a prospective analytical study in which 75 diagnosed patients of severe hemophilia A between the age of 2-12years were randomly included in the study after taking informed consent from their parents and guardians. All these patients were initially screened for Factor VIII inhibitors and only those who were negative for them were included in the study. Patients with known inhibitors or past history of inhibitors, those on bypassing agents, or with concomitant liver disease were excluded from the study.A detailed history of each patient regarding signs and symptoms, treatment and family were taken. The patients included in the study were then divided into three equal groups of 25 patients each. One group received only FFP/cryoprecipitate for treatment, the other group received plasma derived FVIII concentrates and the last group received recombinant factor VIII concentrates. These patients were observed for two years (after 15-20 exposures) and after two years their inhibitors screening was done again to establish the effect of different treatment modalities on inhibitor development.

The blood specimen for inhibitors screening was collected through venipuncture into a vial containing 3.2% trisodium citrate. The samples were transported to the lab without delay and centrifuged at 4000rpm for 10 minutes for preparation of platelet poor plasma. Then, activated partial thromboplastin time (APTT) method was used for inhibitor detection. A 50:50 fix of patient's plasma and normal pooled plasma was incubated for 2 hours at 37ºC and APTT was observed after 2 hours. APTT was checked manually as well as on Sysmex CS automated analyzer. Poor correctionof APTT in incubated mixture indicated presence of time dependent inhibitor whereas poor correction in mixture prepared after separate incubation of patient's plasma and normal plasma indicated immediate circulating inhibitors.

The data collected was entered andanalyzed by SPSS-21. Frequency and percentages were calculated for categorical values whereas mean and standard deviation were estimated for quantitative variables.Chi-square test was used to calculate the p value.

RESULTS

A total of 75 male hemophilia A patients were included in the study between 2-12 years of age. The mean age of these patients was 6.84 years (Fig-1). Out of these 75 patients only 5 (6.7%) had positive family history for inhibitors (Fig-2).

Our study showed that only 3 patients out of 25, receiving FFP as treatment modality developed inhibitors. Whereas, none of the patients receiving plasma derived FVIII concentrates and recombinant factor VIII concentrates developed inhibitors (Table-2) and family history data shows in (Table-1). The P value calculated is 0.044 which is less than 0.05, depicting that it is significant.

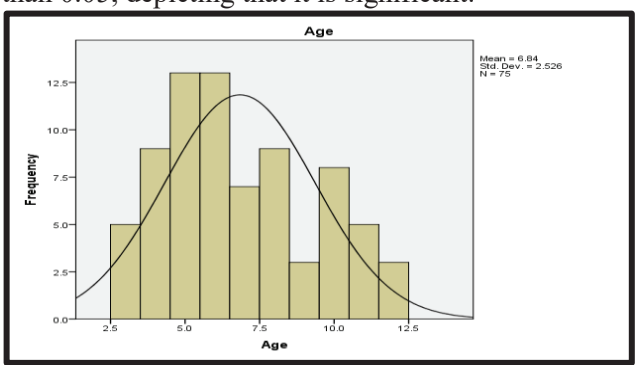

Fig-1: The age (years) of patients included in the study

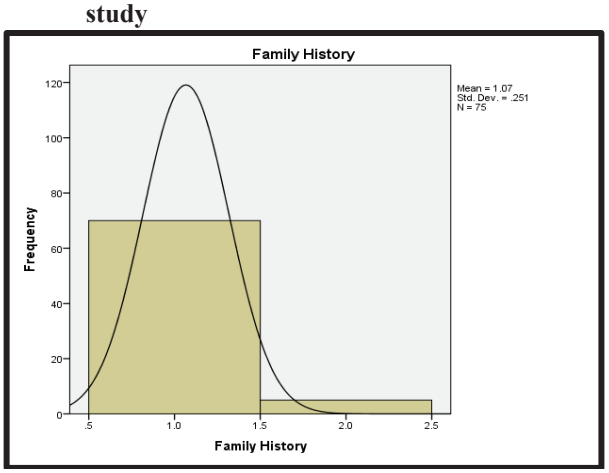

Fig-2: The family history of patient.

Validation		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Negative	70	93.3	93.3	93.3
	Positive	5	6.7	6.7	100.0
	Total	75	100.0	100.0	-

Table-1: Family History

Name of Drugs		Inhibitors		Total
		Negative	Positive	
Drug	Fresh Frozen Plasma (FFP)	22	3	25
	Plasma Derived FVIII Concentrates	25	0	25
	Recombinant FVIII Concentrates	25	0	25
Total		72	3	75

Table-2:Numberof Patients who developedFVIIIinhibitors

DISCUSSION

It has been found out that hemophilia A is the most common bleeding disorder in Pakistan where substandard diagnostic facilities along with inadequate factor replacement have worsened the disease complications[10]. The literature shows that children who regularly receive factor VIII replacement are at a lower risk of inhibitor development[11]. Furthermore, most inhibitors develop between 21 and 75 days after exposure to factor replacement therapy[12].These findings are similar to our finding were younger patients receiving factor replacement therapy did not develop inhibitors. According to Yesim et al around 30% of patients of severe hemophilia A develop inhibitors[13].However, we observed that the overall incidence of developing inhibitors in our population is lower as compared to the world. In India as well the incidence of inhibitor development is lower as a study showed that only 3.39% patients of Hemophilia A developed inhibitors[14]. This finding is quite similar to our findings were only 6.7% of patients developed inhibitors.

A study conducted in Europe found out that no inhibitors developed in patients using Kovaltry(plasma derived FVIII concentrates)[15]. Similarly, there was no inhibitor development in our study group using Kovaltry as treatment. Another study states that inhibitor development is not influenced by the type of factor VIII product used which could be either plasma derived factor or recombinant factor[16]. This finding matches with our finding as none of the patients using either plasma derived factor VIII or recombinant factor VIII developed inhibitors. However, another study found out that recombinant factor VIII has slightly higher risk of inhibitor development especially the second-generation full-length recombinant products[17].

With recent development in transfusion medicine, the use of FFP for inherited coagulopathies is on decline. FFPs are now recommended for liver disease, DIC, TTP and trauma management[18]. The use of FFP has a further disadvantage of causing blood borne infections such as HIV, HCV and HBV. A study conducted found 83.3% positive cases of HCV among hemophiliac in Tehran[19]. Therefore, the use of recombinant FVIII is preferred over FFP to mitigate the risk of transfusion transmitted infections. Another study conducted showed that the use of FFP/cryoprecipitate in severe hemophilia led to HCV infection which has very strong association with low levels of inhibitors[20]. In our study too FFP is associated with inhibitor development.

CONCLUSION

Despite the advancement in treatment of hemophilia, Inhibitors against FVIII remain one of the major hurdles in management of hemophilia A. In Pakistan the availability of factor concentrates either recombinant or plasma derived is scarce. Even if available the majority of the patients cannot afford them. Therefore, FFP transfusion remains the commonest treatment modality used in Pakistan. According to our study the chances of Inhibitors development is more in patients receiving FFP as compared to those receiving recombinant or plasma derived factor. Thus, we propose that hemophiliacs should avoid FFP transfusion and use the preferred factor 8 concentrates to avoid the development of inhibitors. For this there should be governmental policies that enable economical local production of factor concentrates thus ensuring safe and cost-effective treatment for the hemophiliacs.

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