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Evaluation of efficacy of twice-weekly prophylactic treatment with BeneFIX® (recombinant factor IX) followed by once weekly in children with severe hemophilia B: Six-year data from a local registry

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Abstract:

CONTEXT: Bleeding in severe hemophilia B is minimized by factor IX (FIX) replacement either as once- or twice-weekly prophylaxis. Recent trials have focused greater interest on once-weekly prophylaxis using standard recombinant FIX (rFIX) or enhanced half-life rFIX. Limited data are available on optimal prophylaxis regimens of FIX replacements for patients with hemophilia B.

AIMS: This study aimed to evaluate the efficacy of once-weekly prophylaxis compared with twice-weekly prophylaxis with BeneFIX (rFIX) in children with severe hemophilia B.

SETTINGS AND DESIGN: This study is a retrospective, two-period study from January 2012 to December 2017.

SUBJECTS AND METHODS: The study assessed the efficacy of 3-year twice-weekly prophylaxis with BeneFIX (rFIX) in patients with severe hemophilia B followed by 3-year once-weekly prophylaxis, then comparing once weekly versus twice weekly at a given period. The primary efficacy endpoint was the annualized bleeding rate (ABR) and the secondary endpoint included Functional Independence Score for patients with Hemophilia (FISH) scoring.

RESULTS: There was no statistically significant difference in the bleeding per year and the joint bleeding per year between once- and twice-weekly prophylactic treatment regimens ($P > 0.05$). There was no statistically significant difference in ABR between once- and twice-weekly prophylaxis, 11.9 and 9.1 bleeds per year, respectively ($P > 0.05$). In addition, there was no statistically significant difference in the hospitalization and school absence between once- and twice-weekly prophylactic treatment regimens ($P > 0.05$). There was no statistically significant difference in FISH score between once- and twice-weekly protocol ($P > 0.05$), but factor consumption was significantly higher in the twice-weekly protocol compared with once-weekly protocol ($P < 0.001$).

CONCLUSIONS: Once-weekly prophylaxis was effective and tolerated prophylaxis for most patients included in this study. Once-weekly prophylaxis is an effective alternative to twice-weekly prophylaxis, and both the regimens reduce ABR in children with severe hemophilia B.

Keywords:

Hemophilia B, prophylaxis with BeneFIX, recombinant factor IX

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Introduction

Haemophilia B is a rare, X-linked congenital bleeding disorder that occurs in about 1 in 25,000-30,000 newborns. Caused by a partial or total deficiency of coagulation factor IX (FIX), hemophilia B is less common than hemophilia A (deficiency of factor VIII), accounting for approximately 15%–20% of the total hemophilia population.[1]

The severity of hemophilia B is typically classified according to the levels of coagulation FIX activity in the blood. Severely affected patients have <1% of normal factor levels, patients with moderate disease have 1%–5%, and patients with mild disease have >5%–40%.[1] Patients with severe disease constitute approximately 30% of the hemophilia B patient population,[2] it characterized by frequent spontaneous bleeding and joint hemarthrosis.[3]

Hemophilia B is currently managed using FIX replacement therapy, using either plasma-derived FIX or recombinant (rFIX) therapies. Treatment may be administered in an episodic/on-demand manner to treat bleeding episodes, prior to surgical interventions, or using a prophylactic regimen, whereby FIX is administered on a regular basis to prevent or reduce bleeds. Prophylaxis is associated with improved patient outcomes, including reduced joint damage (the major long-term complication of hemophilia)[4] and improved quality of life.[5]

However, there are a number of barriers to adherence to prophylaxis regimens including the burden of frequent injections.[6]

Subjects and Methods

Study design and settings

This study is a retrospective, two-period study conducted in Hemophilia Center, Children Welfare Teaching Hospital, Medical City, Baghdad, by reviewing the records of patients with severe hemophilia B through the period from January 1, 2012, to December 31, 2017.

We studied the efficacy and safety of 3 years once-weekly prophylaxis with standard rFIX (BeneFix) in patients with hemophilia B compared with 3-year twice-weekly prophylaxis.

Study population

Twenty-five male patients <14 years of age with severe Hemophilia B were enrolled, received treatment, and completed the study. They were on twice-weekly prophylaxis with rFIX from January 1, 2012, to of December 31, 2014, and then, they were switched to once-weekly prophylaxis from January 1, 2015, to December 31, of 2017.

Inclusion criteria

1. Patients with severe hemophilia B, (FIX <1%), who were received twice-weekly prophylaxis for 3 years then reverted to once-weekly prophylaxis for another 3 years
2. Patients <14 years age
3. Patients who receive treatment as prophylaxis exclusively in our center.

Exclusion criteria

1. Patients with severe hemophilia B who had received prophylaxis for <3 years for both twice and once weekly
2. Hemophilia B with inhibitors
3. Patients >14 years age
4. Patients who were referred to other center according to their caregivers' request.

Assessment of patients' records

In January 2012, There were 25 patients with severe hemophilia B (<14years age) registered in Hemophilia Center, Children Welfare Teaching Hospital, and they were receiving twice-weekly prophylaxis, 23 patients had FIX <1% and two patients had FIX level 1% but had severe phenotype.

All of them were on twice-weekly prophylaxis with standard rFIX (BeneFix) using 15–25 I.U/Kg/dose, from 2012 to 2014 (we followed intermediate-dose protocol (Dutch protocol) in our prophylaxis, which stated to use FIX 15–25 I.U/kg per dose twice weekly).[7]

However in January 2015, there was a shortage of rFIX, prophylaxis was not stopped but continued prophylaxis with rFX (15–25 I.U/kg/dose) but once weekly.

In 2016, rFIX became available, but these 25 patients were continued on once-weekly prophylactic treatment in spite of availability of factor replacement because we observed good response to once-weekly protocol (clinically by observing ABR, joints bleeding and assessment of activity by Functional Independence Score for patients with Hemophilia [FISH] scoring).

Efficacy endpoints

1. The primary efficacy endpoint was the annualized bleeding rate (ABR), defined as the number of bleeding events per year and calculated as the number of bleeding events/(days on treatment/365.25)[8]
2. Secondary endpoint included FISH scoring (FISH), which has been developed as a measure of disability in patients with hemophilia. It is intended to measure what the person with disability actually does, and not what he ought to be able to do, or might be able to do if circumstances were different. It can be used to evaluate the change in functional independence over time, or after a therapeutic intervention.

The time needed to complete the score is 12–15 min, any trained therapist or clinician can administer the FISH, and each activity should be scored only after observing the subject performing the task, and not based on their subjective ability. For some of the tasks, the required action may be simulated in the clinic and not actually performed. Each activity is graded from 1 to 4 according to the amount of assistance required to perform the activity. The maximum possible score is 32.[9]

Results

This study reviewed the data of 25 male patients with severe hemophilia B (firstly treated with twice-weekly prophylactic treatment with rFIX for 3 years and then treated with once-weekly prophylactic treatment for 3 years also).

The mean age of patients was 9.0 ± 2.4 years ranging from 7 to 14 years, mean weight was 29.7 ± 9.1 kg, 23 patients (92%) had FIX level <1%, and two patients (8%) in spite of having FIX level 1%, but they had severe phenotype (severe presentation), 76% of the patients had a positive family history of hemophilia B.

There was statistically no significant difference in the bleeding per year and the joint bleeding per year between once and twice-weekly prophylactic treatment regimens ($P > 0.05$).

The study shows no statistically significant difference in ABR between once- and twice-weekly prophylaxis ($P > 0.05$), 11.9 and 9.1 bleeds per year, respectively. In addition, there was no statistically significant difference in the hospitalization and school absence between once- and twice-weekly prophylactic treatment regimens ($P > 0.05$).

There was no statistically significant difference in FISH score between once- and twice-weekly protocol ($P > 0.05$) (as shown in Table 1 and figure 1).

However, factor consumption was significantly higher in the twice-weekly protocol compared with once-weekly protocol ($P < 0.001$), as shown in Table 1.

Bleeding per year is defined as the number of bleeding events per year, while ABR is defined as the number of bleeding events/(days on treatment/365.25) ($P < 0.05$).

There was a direct significant correlation between factor consumption with age of hemophilic patients in both once- and twice-weekly prophylactic treatment regimens. Furthermore, there was a direct correlation between factor consumption and each of bleeding per year and joint bleeding per year at twice-weekly prophylaxis.

A significant inverse correlation was observed between factor consumption of once-weekly hemophilic B patients and school absence ($P = 0.03$).

There was a significant negative correlation between factor consumption of hemophilic B patients at twice-weekly prophylactic treatment and FISH score ($P = 0.008$), a decrease in FISH score was associated with an increase in twice-weekly factor consumption. All these findings are shown in Table 2.

No significant correlations were observed between FISH score of patients on once-weekly prophylaxis with joint bleeding per year, ABR, and factor consumption. The weight of hemophilic B patients on twice-weekly prophylaxis was significantly inversely correlated with FISH score ($P = 0.008$).

There was a significant inverse correlation between FISH score of hemophilic B patients and each of bleeding per year, ABR, and joint bleeding per year. Similarly, a significant inverse correlation was observed between FISH score of hemophilic B patients and each of hospitalization and school absence of patients for twice-weekly prophylaxis.

The FISH score was significantly inversely related with factor consumption among hemophilic B patients on twice-weekly prophylaxis ($P = 0.008$). All these findings are shown in Table 3.

Discussion

Many studies were done about once-weekly prophylaxis in hemophilia B with rFIX but using high dose, 100 I.U/Kg/dose. This study is the only study of using low-dose FIX (15–25 I.U/kg/dose) once weekly. hence, we want to clarify that our study discussion was with studies about once-weekly prophylaxis with FIX but not regarding the dose.

Prophylactic treatment of hemophilia B by coagulation FIX either once weekly or twice weekly aimed to prevent bleeding and other complications like joint damage of hemophilia B patients.[3] Some authors revealed discrepancies in this therapy regarding dosing and frequency of dosing which lead to differences in clinical practices and obstacles in use of this therapy in some cases.[10,11]

The present study showed no statistically significant difference in annual bleeding per year and joint bleeding per year between children with hemophilia B on twice-weekly prophylaxis and children with hemophilia B on once-weekly prophylaxis using small dose (15–25 I.U/kg/dose). This finding is consistent with the results of Rendo *et al*.'s[12]

Table 1: Distribution of clinical data according to frequency of prophylactic treatment dose

Variables	Once weekly	Twice weekly	*P*
Bleeding per year, mean±SD	3.2±2.8	3.6±2.2	0.5* (NS)
ABR, mean±SD	11.9±6.5	9.1±5.0	0.1* (NS)
Joint bleeding/year, mean±SEM	1.8±0.4	2.1±0.3	0.3* (NS)
Hospitalization, mean±SEM	0.72±0.16	0.64±0.24	0.2* (NS)
School absence, mean±SEM	1.9±0.4	2.1±0.9	0.1* (NS)
Factor consumption, mean±SD	28,493±8,749	56,986±17,498	<0.001* (S)
FISH score, mean±SD	31.3±2.1	31.0±1.7	0.6* (NS)
Total	25 (100.0)	25 (100.0)	

*Independent sample *t*-test. Bleeding per year defined as number of bleeding events per year while, ABR, defined as the number of bleeding events/(days on treatment/365.25) ($p<0.05$). NS=Not significant, S=Significant, SD=Standard deviation, SEM=Stander error mean, FISH=Functional Independence Score for Patients with Hemophilia, ABR=Annualized bleeding rate

Table 2: Pearson correlation between factor consumption and hemophilia B patients' characteristics

Variables	Factor consumption			
	Once weekly		Twice weekly	
	r	*P*	*r*	*P*
Age	0.782	<0.001 (S)	0.782	<0.001 (S)
Bleeding/year	0.048	0.822	0.412	0.041 (S)
ABR	0.110	0.599	0.387	0.056
Joint bleeding/year	0.303	0.141	0.458	0.021 (S)
Hospitalization	−0.350	0.087	0.068	0.747
School absence	−0.426	0.034 (S)	0.067	0.750
FISH score	−0.376	0.064	−0.515	0.008 (S)

r=Correlation coefficient, S=Significant, FISH=Functional Independence Score for Patients with Hemophilia, ABR=Annualized bleeding rate

Table 3: Pearson correlation between Functional Independence Score for Patients with Hemophilia score and hemophilia B patients' characteristics

Variables	FISH score			
	Once weekly		Twice weekly	
	r	*P*	*r*	*P*
Age	0.004	0.984	−0.322	0.116
Weight	−0.376	0.064	−0.515	0.008 (S)
Bleeding/years	−0.173	0.408	−0.743	<0.001 (S)
ABR	−0.247	0.233	−0.449	0.024 (S)
Joint bleeding years	−0.312	0.129	−0.527	0.007 (S)
Hospitalization	0.183	0.381	−0.653	<0.001 (S)
School absence	0.232	0.264	−0.645	<0.001 (S)
Factor consumption	−0.376	0.064	−0.515	0.008 (S)

FISH=Functional Independence Score for Patients with Hemophilia, S=Significant, ABR=Annualized bleeding rate

study in the USA which reported that once-weekly prophylaxis (100:I.U/kg/dose) of patients with hemophilia B represented safe and effective alternative for twice-weekly prophylaxis with no difference in bleeding episodes in addition to fact that the hemophilia patients and their caregivers were more convinced in once-weekly regimen.

We found that there were no significant differences between twice-weekly prophylaxis and once-weekly

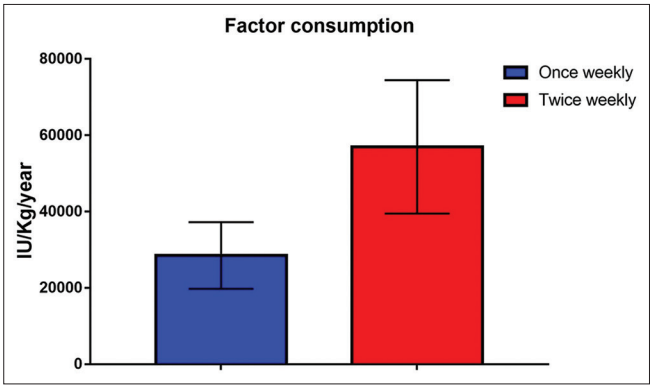

Figure 1: Assessment of total factor consumption (I.U) between once and twice-weekly protocols

hemophilia B prophylaxis regarding patient' hospitalization and school absence.

Similarly, Rocino *et al*.[13] study documented that prophylaxis treatment of hemophilia B patients in different frequencies is important in reduction of bleeding events and improving the quality of life by decreasing the hospitalization rates and school absents. Santagostino study in Italy[14] recommended the use of once weekly or once every 2 weeks rFIX for children prepared for surgical intervention like surgical circumcision.

The current study revealed that hemophilia B patients on twice-weekly prophylaxis significantly consumed rFIX more than hemophilia patients on once-weekly prophylaxis ($P < 0.001$). This finding coincides with results of Djambas Khayat[15] study in Lebanon which reported that once-weekly prophylaxis of hemophilia B patients with once-weekly dose of 100 IU/Kg rFIX has high cost-effectiveness than twice weekly of rFIX in dose of 50 IU/kg and more safe and adherent to patients and their caregivers.[16]

In addition, calculation of indirect costs related to treatment on demand such as hospitalizations, disability, and absenteeism, all affect the cost-effectiveness analysis. However, poor financial ability represented the main

obstacle to prophylaxis in hemophilia, specifically in developing countries.[17]

Poon and Lee[18] study in Canada suggested a reduction of rFIX dose to increase its feasibility in developing countries. Consistent with our findings, Iorio *et al*.'s[19] study in the USA found after comparing weekly dose of rFIX with frequent rFIX doses that weekly injection of rFIX is characterized by similar bleeding rates and safety but with low factor consumption as compared to conventional frequent rFIX dosing.

In the present study, the FISH score was not significantly different between hemophilia B patients on once-weekly prophylaxis and hemophilia B patients on twice-weekly prophylaxis. Similarly, Gouider *et al*.[20] study in Tunisia found a better FISH score for hemophilia B patients on prophylaxis than patients on demand treatment and found no statistically significant difference in FISH score between hemophilia B patients on prophylaxis according to rFIX doses' frequency (once, twice, or thrice weekly). Inconsistently, Huang *et al*.'s[21] study in China found that prophylaxis of hemophilic patients by an intermediate dose of rFIX had high FISH score than prophylaxis by low dose of rFIX. This inconsistency from our findings is related to dose and not frequency of dose as our study confirmed.

The current study found that the age of patients was significantly positively correlated to factor consumption in both once-weekly and twice-weekly hemophilia b. >B patients ($P < 0.001$). A study conducted in multiple European countries by Dolan *et al*.[22] documented that increased age of hemophilia B patients will increase the risk of bleeding events and other complications that needed more consumption of prophylaxis treatment. The school absence of hemophilia B patients was negatively correlated with once-weekly factor consumption ($P = 0.03$).

This finding is in agreement with the results of Thornburg and Duncan[6] study in the USA which stated that poor adherence of hemophilic patients to prophylaxis treatment leads to a high absence of patients from school.

The current study showed a significant positive correlation between twice-weekly factor consumption of hemophilia B patients and each of bleeding and joint bleeding per year. This finding is similar to reports of Castaman[23] study in Italy which stated that long-acting single weekly dose of prophylactic treatment for hemophilia B patients is associated with low consumption of factor and less bleeding events.

The FISH score of hemophilia B patients in the current study was negatively correlated with twice-weekly factor consumption ($P = 0.008$). This is similar to the results of Ferreira *et al*.[24] study in Brazil which found that FISH score of hemophilia B patients was correlated to prophylactic factor consumption.

In the present study, FISH score of hemophilic B patients was negatively correlated with their weight ($P = 0.008$). Similarly, Fischer *et al*.[25] study in India revealed that the FISH score was depending on the weight of hemophilic B patients as the obesity increased pressure on joints. Our study showed also a significant negative correlation between FISH score of twice weekly hemophilic B patients and each of bleeding per year, ABR and joint bleeding per year.

A study conducted in nine developing countries by Poonnoose *et al*.[26] found that FISH score of hemophilic B patients was worsening after the increased rate of bleeding per year and annualized joint bleeding rate.

The hospitalization and absence of hemophilic B patients on twice-weekly prophylaxis from school were also negatively correlated with FISH score. These findings are consistent with the results of Šalek *et al*.[27] study in Croatia which stated that hemophilic B patients with low FISH score were predominantly had low quality of life with high absenteeism from school and high hospitalization rates.

Conclusion

Once-weekly prophylaxis was effective and tolerated prophylaxis for most patients included in this study. Once-weekly prophylaxis is an effective alternative to twice-weekly prophylaxis, and both regimens reduce ABR in children with severe hemophilia B.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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