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Original Article

On-Demand versus Prophylactic Therapy with Factor VIII Concentrate in Patients with Hemophilia A: Differences in Efficacy and Quality of Life: A Multicenter Study

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Abstract

Background: Hemophilia A and B are inherited bleeding disorders in factors VIII and IX. **Objectives:** The study was to compare between on-demand and prophylactic treatment by factor VIII (FVIII) concentrate of hemophilic patients in Kirkuk, Sulaymaniyah, and Erbil hemophilia centers. **Materials and Methods:** The study included 45 patients with moderate and severe hemophilia treated with FVIII concentrate in three Iraqi centers (Kirkuk Oncology Center [*n*: 15], Hiwa Hospital in Sulaimaniya [*n*: 18], and Nanakali Hospital in Erbil city [*n*: 12]) and compared two different protocols in prophylactic therapy with FVIII concentrate in 2016 and on-demand treatment with FVIII concentrate in 2018 on the same patients. Comparisons included the number of vials used in two procedures and patient visits to our centers. **Results:** The survey found that hemophilia patients at Kirkuk Oncology Center are older than those in Sulaimaniya and Erbil. The average number of vials of FVIII concentrate used to treat hemophilia on prophylaxis was 73.58/year and 6.13/month, which was substantially less than in on demand ($P < 0.001$). The study found that the average number of FVIII concentrate vials used in on-demand hemophilia therapy at Hiwa Hospital was 79.4 vail/year and 6.62 vail/month, compared to 119.7 vail/year and 9.97 vail/month in prophylaxis ($P < 0.001$). The study also found that the average number of vials used in hemophilia therapy at Kirkuk Oncology Center and Nanakali Hospital in Erbil was lower than in other hospitals ($P < 0.001$). The study demonstrated that all patients in the on-demand hemophilia treatment program were dissatisfied, but their views improved after treatment with FVIII concentrate in prophylaxis protocol. **Conclusions:** We find that prophylactic administration of FVIII concentrate to hemophilia patients is superior than on-demand administration. We urge that future studies improve our results with larger patient groups and clinics in all governorates of Iraq.

Keywords: Factor VIII, hemophilia, Kirkuk, on demand, prophylaxis

Introduction

Hemophilia A and B are inherited bleeding disorders that are connected to the X chromosome and are caused by mutations in the genes that code for factor VIII (FVIII) and factor IX, respectively.[1] Both types of hemophilia are characterized by an inability to produce enough blood clotting FVIII. About 80%–85% of all cases of hemophilia are caused by the hemophilia A gene.[2-4] This, in turn, causes a decrease in the blood's ability to coagulate, which in turn results in an increased risk of delayed bleeding, which in turn results in serious and perhaps life-threatening health problems. Researchers suggest that homozygosity and lionization may be to blame for its increased prevalence in males as opposed to females.[1,5] The condition is observed more frequently in males than in females. The concentration of clotting factors in the blood is what determines the severity of the problem, which can range from severe (factor level of 1 IU/dL) to moderate (factor level of 1–5 IU/dL) to mild (factor level of >5 IU/dL) depending on the patient's specific situation. Almost half of all occurrences of hemophilia

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are found in patients who have been given a diagnosis of severe hemophilia.[2,6,7] The joints (hemarthrosis), muscles, especially deep compartments (iliopsoas, calf, and forearm), and mucous membranes in the mouth, gums, nose, and genitourinary tract are the most common serious sites of bleeding in hemophilia. Other common sites include the mucous membranes in the mouth, nose, and genitourinary tract. However, the most dangerous areas for bleeding to occur are in the gastrointestinal tract, the neck and throat, or the cerebral space. The amount of time between bleeding episodes varies according to the location: joints (70%–80%), muscle (10%–20%), various locations (severe bleeding; 5%–10%), and the central nervous system (5%).[2] The muscle accounts for 10%–20% of all bleeding, whereas other locations account for 5%–10%. Joints are responsible for 70%–80% of all bleeding. The severity of hemophilia, hemophilic arthropathy, and related immobility can all contribute to an elevated risk of mineral density in patients who have hemophilia as compared with the general population. It's possible that this is what caused the elevated risk. As a result, the World Federation of Hemophilia advises participating in consistent physical activity.[8] Treatment of hemophilia has undergone considerable evolution over the past 70 years due to epic progress and innovation in coagulation factor replacement and improved clinical services extending life expectancy from the early teens to 75+ years.[9,10] In the 1960s, there were relatively crude plasma preparations like cryoprecipitate. In the 1980s, there were highly purified recombinant concentrates, and now there are new agents with a longer duration of action that could make treatment a lot easier for patients.[11,12] Even though new therapies have the potential to make the clinical experience of patients and their families much better, the benefits of this may not be fully understood by other stakeholders if they don't have the right tools to measure how well they work. It's important for everyone in the hemophilia community—patients, providers, and payers—to have the same idea of what value means when looking at and comparing different parts of hemophilia care.[13,14] There is evidence that prophylaxis, which involves taking factor replacement drugs, is a big part of lowering the number of bleeds that happen each year and keeping joints from getting hurt. This is different from treatment on an as-needed basis, where the treatment is only given when it is needed. Even though about 400,000 people around the world have hemophilia, only 25% of them get the right treatment.[2] Only about 15% of people with hemophilia who are younger than 18 are getting prophylaxis at the moment, and only about 7% of people with hemophilia who are older than 18 are getting prophylaxis.[4] The number of people with hemophilia who are registered in China is very low. Even though the number of people in China who get prophylaxis has been going up recently, the percentage of those people is still very low. Inadequate treatment for hemophilia can lead to joint damage, which can eventually cause more pain, less physical activity, the need for a synovectomy, or prolonged bleeding from an injury, surgery, or severe bruising.[9,10] The study was designated to compare between on-demand and prophylactic treatment by FVIII concentrate of hemophilic patients in Kirkuk, Sulaymaniyah, and Erbil hemophilia centers

Materials and Methods

Study population

All patients with moderate and severe hemophilia (*n*: 45) (FVIII) in Iraq (Kirkuk Oncology Center [*n*: 15], Hiwa Hospital in Sulaimaniya [*n*: 18], and Nanakali Hospital in Erbil city [*n*: 12]).

We used data from the three centers where on-demand prophylaxis as the standard treatment has been the standard treatment for moderate and severe hemophilia. This allowed us to avoid the selection bias that can occur when patients are placed into a particular treatment strategy because of the hemorrhage patterns they experience. Selection bias refers to the presence of factors that can lead to incorrect conclusions. Additionally, the commonalities in the institutional framework of the three centers had a role in their selection (social services, healthcare organization, labor-market structure, etc.). This was crucial, especially considering that we covered the utilization of resources in fields other than health care.

Primary prophylaxis was the definition of prophylactic treatment, which meant regular injections of factor concentrate at least once weekly for hemophilia B patients and at least twice weekly for hemophilia A patients. On-demand treatment was characterized as receiving injections when bleeding occurred, but it also included scheduled intervals of secondary prophylaxis.

Patients diagnosed with hepatitis C and HIV/AIDS were not excluded from the study since, according to our experience, the treatment of hemophilia in and of itself does not change. There does not appear to be any discernible difference in the risk of getting these diseases between the two approaches.

Instead, the risk of infection has been linked to the particular brand of factor concentrate as well as the production window for the concentrate during which it was made. Since the introduction of heat inactivation of FVIII concentrates in 1983, there has not been a single case of a patient becoming infected with HIV since 1985.[2]

Patient and treatment data

Through a backward analysis of clinical records, we were able to compile comprehensive annual statistics on resource utilization within the healthcare industry for the years 2016 and 2018. A new computerized data input form was designed specifically for the project in order to

Table 1: Mean of age of patients with hemophilia

Center	No.	Age (years)							*P*-value
		Mean	SD	Minimum	Q1	Median	Q3	Maximum	
Hiwa Hospital	18	12.78	4.81	7.0	8.75	12.0	16.5	22.0	0.001
Kirkuk Oncology Center	15	23.87	12.86	8.0	15.0	17.0	33.0	55.0	
Nanakali Hospital	12	12.42	3.50	7.0	8.75	13.50	15.50	17.0	

cut down on the number of possible error sources and ensure that the data were generated in a manner that was consistent across all of the centers. All of the collaborating centers' Ethics committees gave their blessing to the study before it was conducted.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of our Directorate. It was carried out with patients' verbal and analytical approval before a sample was taken. The study protocol and subject information, and consent form were reviewed and approved by a local ethics committee according to document number 1077 (including the number and the date on March 11, 2016) to get this approval.

Results

The study showed that hemophilia patients admitted to Kirkuk Oncology Center have a high mean age than patients in Hiwa Hospital in Sulaimaniya and Nanakali Hospital in Erbil [Table 1].

The study showed that all patients enrolled were males [Table 2].

In this study, all patients in Nanakali Hospital were with severe hemophilia compared with 26.67% of Kirkuk Center and 0% of patients in Hiwa Hospital [Table 3].

The study showed that the mean number of vials of FVIII concentrate used in the treatment of hemophilia on prophylaxes was (73.58 vail/year and 6.13 vail/month), which was much less than in on-demand program (97.0 vail/year and 8.08 vail/month) ($P < 0.01$) [Table 4].

The study showed that the mean number of FVIII concentrate vials used in the treatment of hemophilia in the prophylaxis program in Hiwa Hospital was (79.4 vail/year and 6.62 vail/month) which was much lower than in on-demand program in the same center in Hiwa Hospital (119.7 vail/year and 9.97 vail/month) ($P < 0.01$). The study also showed that the mean number of vials used in the treatment of hemophilia in the prophylaxis program in Kirkuk Oncology Center and Nanakali Hospital in Erbil were much lower than in the on-demand program in same these ($P < 0.01$) [Table 5].

The study showed no difference between the two programs regarding the number of visits of patients to total centers by enrolled patients [Table 6], and the study showed no difference between the two programs regarding the number of visits of patients to patients enrolled patients who admitted to Kirkuk Oncology Center, Hiwa Hospital in Sulaimaniya, and Nanakali Hospital in Erbil city separately [Table 7].

Table 2: Sex of patients with hemophilia

Sex	Hiwa Hospital	Kirkuk Oncology Center	Nanakali Hospital
Male	18	15	12
	100	100	100
Female	0	0	0
	0	0	0
Total	18	15	12
	100	100	100

Table 3: Distribution of patients according to the severity of hemophilia

Severity of hemophilia	Hiwa Hospital	Kirkuk Oncology Center	Nanakali Hospital
Moderate	18	11	6
	100	73.33	50
Severe	0	4	6
	0.00	26.67	50.00
Total	18	15	12
	100	100	100

P-value: 0.006

The study showed that all patients, when under the on-demand program for the treatment of hemophilia, had bad or poor satisfaction, but their opinion had been changed to good and very good satisfaction after treatment FVIII concentrates in prophylaxes protocol [Table 8].

Discussion

Progress in hemophilia treatment has led to significant gains in survival, from median life expectancies of ~8–11 years in the early 1900s to 75+ years now, which is approaching that of the general male population.[12] This is even more remarkable considering some major setbacks, most notably the contamination of donor plasma with HIV and hepatitis viruses, which led to high infection and mortality rates in recipients of pooled plasma products from the 1970s to 1990s. The traumatic experience of plasma-borne infection changed the focus from efficacy to safety of therapy and led to the development of plasma-free recombinant factor concentrates. In the three decades

Table 4: Comparison between patients treated on demand and patients under prophylaxis treatment regarding the number of vials

Treatment advantages		No.	Mean	SD.	Minimum	Median	*P*-value
No. of factor VIII concentrate vial/year	Prophylaxis treatment	45	73.58	54.85	10.0	55.0	0.003
	Treated on demand	45	97.0	47.01	27.0	94.0	
No. of factor VIII concentrate vial/ month	Prophylaxis treatment	45	6.13	4.57	0.833	4.58	0.004
	Treated on demand	45	8.08	3.91	2.25	7.83	

Table 5: Comparison between patients within the studied center who were treated on demand and patients under prophylaxis treatment regarding the number of vials

Variable		Center	No.	Mean	SD.	*P*-value
No. of factor VIII concentrate vial/year	Hiwa Hospital	Prophylaxis treatment	18	79.4	56.2	0.001
		Treated on demand	18	119.7	49.3	
	Kirkuk Oncology Center	Prophylaxis treatment	15	84.2	62.7	0.045
		Treated on demand	15	90.8	46.8	
	Nanakali Hospital	Prophylaxis treatment	12	51.6	37.7	0.003
		Treated on demand	12	70.67	25.46	
No. of factor VIII concentrate vial/month	Hiwa Hospital	Prophylaxis treatment	18	6.62	4.68	0.004
		Treated on demand	18	9.97	4.108	
	Kirkuk Oncology Center	Prophylaxis treatment	15	7.02	5.22	0.042
		Treated on demand	15	7.57	3.90	
	Nanakali Hospital	Prophylaxis treatment	12	4.299	3.140	0.41
		Treated on demand	12	5.889	2.122	

P value: < 0.001.

Table 6: Comparison between patients treated on demand and patients under prophylaxis treatment regarding the number of visits per time

Treatment advantages		No.	Mean	SD.	*P*-value
No. of visits/year	Prophylaxis treatment	45	11.73	8.81	0.21
	Treated on demand	44	11.27	5.23	
No. of visits/month	Prophylaxis treatment	45	0.97	0.73	0.27
	Treated on demand	45	0.97	0.73	

P value: < 0.001.

Table 7: Comparison between patients within the studied center who were treated on demand and patients under prophylaxis treatment regarding visits per time

Variable		Center	No.	Mean	SD.	P-value
No. of visits/ year	Hiwa Hospital	Prophylaxis treatment	18	11.94	8.87	0.61
		Treated on demand	18	13.94	6.42	
	Kirkuk Oncology Center	Prophylaxis treatment	15	12.07	11.24	0.69
		Treated on demand	15	7.600	2.501	
	Nanakali Hospital	Prophylaxis treatment	12	11.00	5.24	0.72
		Treated on demand	12	11.909	2.300	

P value: < 0.001.

since this tragedy, scientific and technological advances have now led to safe and innovative therapy with real potential to improve the clinical experience and outcomes for those with hemophilia.[13] Along with the changing landscape of hemophilia healthcare, quality of life and the ability to lead a normal life have become priorities for patient care. In addition, increased life expectancy has led to a growing need for the management of previously

Table 8: Comparison between patients treated on demand and patients under prophylaxis treatment regarding their satisfaction with treatment protocol

Patients' satisfaction	Treated on demand		Prophylaxis treatment	
	No.	%	No.	%
Very good	0	0	17	37.78
Good	0	0	28	62.22
Poor	31	68.89	0	0
Very poor	14	31.11	0	0
Total	45	100	45	100

P value: < 0.001.

unseen comorbidities associated with aging. Evaluation of treatments and other areas of hemophilia comprehensive care cannot be limited to singular efficacy or safety measures but must also incorporate a multitude of both direct and indirect effects of treatment.[14] Porter supports this notion, highlighting that patient-centered outcomes "encompass the whole cycle of care," including both clinical status and functional outcomes, as described in this paper.[15,16] The study showed that the mean number of FVIII concentrate vials used in the treatment of hemophilia in a prophylaxis program was (73.58 vail/year and 6.13 vail/month), which was much lower than in an on-demand program (97.0 vail/year and 6.13 vail/month). It may be because people who received FVIII concentrate on demand are, in fact, taking hemophilia treatment when the body needs that treatment, unlike people or patients who receive prophylaxis FVIII concentrate treatment who are characterized by taking treatment continuously. It is expected that there will be significant differences between the two protocols, as the number of FVIII concentrate vials used to treat patients in 2016 (on demand) was more than the number of vials used for the same patients in 2018 (prophylaxis), so we found that people in forced to receive treatment when needed may consume more treatment bottles than with the other, and it is clear that consuming less bottles of treatment avoids patients significant complications while taking hemophilia treatment and also avoids a few visits to specialized centers for the treatment of hemophilia. Also, patients who received treatment on demand consumed less vials than those on prophylaxis, the three in Kirkuk Governorate, Erbil Governorate, and Sulaymaniyah Governorate. In line with our findings, other research has shown that administering FVIII concentrate to patients on a prophylaxis basis is preferable to doing so as part of a preventative treatment protocol for a variety of treatment outcomes, including the detection of subtle early signs of joint damage.[17-21] Additionally, Trakymiene *et al.*[21] reported a considerably superior outcome in primary prophylaxis compared to on-demand therapy in children aged 4–17 years (*P* 0.001); other researchers found no significant difference between the two treatment methods.[15,16] The reasons for the differences may be related to the type of treatment used to treat hemophilia in those people, as well as the ages taken in previous studies, as well as the duration of the treatment, and the type of outcomes used to compare the types of treatments.

Conclusions

Therefore, we conclude that the administration of FVIII concentrates on hemophilia patients in prophylaxis protocol is better than on-demand protocol and recommend that researchers after us enhance the results of our study with larger groups of patients and in centers that include all governorates of Iraq, especially that hemophilia centers in Iraq's provinces is almost few.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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