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Original article

Comparative evaluation of the safety and efficacy of recombinant FVIII in severe hemophilia A patients

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Key Words
Hemophilia A, Recombinant Factor VIII, Safacto, Xyntha.

Abstract

Objective: This study compared the safety and efficacy of Safacto® versus xyntha® in patients with severe hemophilia A.

Methods: Thirty-three male patients with severe hemophilia A were randomly divided into two groups. Seventeen patients received Safacto® and 16 patients received Xyntha® for four consecutive times. The dosage of FVIII was 40-50 IU/kg for each injection. Plasma level of FVIII activity was evaluated before every injection, 15 minutes after the injection and one month after the start of the trial. The rate of factor VIII activity, pain and joint motion were also assessed before and after the treatment.

Results: Plasma level of FVIII clotting activity in Safacto® and Xyntha® were 1.96±0.5 IU/dl and 1.63±0.5 IU/dl and increased to 88.84±25.2 IU/dl and 100.09±17.8 IU/dl, respectively (P<0.001). Pain score and range of motion improvement were 9.3±0.9 and 8.7±0.1 in Safacto® (P=0.17); and 9.4±0.8 and 8.8±0.3 in Xyntha® (P=0.35), respectively. No allergic or other unfavorable reactions was observed with either of the preparations.

Conclusion: This study showed that Safacto® has a favorable efficacy and safety profile.

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1. Introduction

Factor VIII (FVIII) deficiency or hemophilia A is caused by the absence of FVIII which is a clotting protein [1]. Hemophilia A is an X-linked recessive trait genetic disorder with a prevalence of 1 in 5000 live births in males that leads to spontaneous bleeding in muscles, joints and digestive tract .

FVIII or antihemophilic factor is a large plasma glycoprotein that is encoded by the F8 gene and mainly synthesized by multiple tissues such as liver, kidney and lymphatic tissues. Hemophilia is classified as mild, moderate and severe. In the severe form, the serum level of FVIII is below 0.01 IU/ml. In moderate and mild forms, the serum level of FVIII is 0.01-0.05 IU/ml and 0.05-0.40 IU/ml, respectively [2]. In patients with severe hemophilia, frequent spontaneous bleeding occurs that may reach as high as 30 times a year. The patients may experience intracranial or retroperitoneal bleeding. In patients with moderate form, hemarthroses are the major findings. Bleeding in soft tissue after minor trauma also occurs. In the mild form, patients experience only bleeding disturbances after major injuries, trauma or surgery.

Treatment of hemophilia is based on increased activity of defective factor in the blood. Different products such as human plasma-derived lyophilized FVIII, recombinant FVIII, desmopressin, and anti-fibrinolytic and local hemostatic drugs have been used for the treatment of hemophilia.

In Iran, about 7000 patients are living with hemophilia [2]. A significant number of these patients need plasma-derived or recombinant coagulation factors [3]. The cost of plasma- derived coagulation factors is a substantial burden on Iran's health care sector [2]. Based on personal communications with Iran Blood Transfusion Organization, mean per capita for FVIII in patients with hemophilia A is 3.5 IU in Iran, which is greater than the global mean. To decrease the treatment costs and supply standard medical care to the patients, Iranian health organizations seek alternative options like recombinant coagulation factors. The Iranian government highly subsidizes imported recombinant coagulation factors but the availability of these products depends on existing financial resources. Concerning these issues, local production of the recombinant coagulation factors is the most practical option [2]. Safacto® is a B-domain-deleted and albumin-free FVIII product. Cell line culture of Safacto® isChinesehamster'sovary(CHO)purifiedwithasyntheticligand[4].Safacto®,as a local recombinant FVIII product, has been compared with a plasma-derived FVIII in a crossover study in which acceptable results and good outcomes in the patients were observed [5].

The purpose of this study was to compare the safety and efficacy of the Iranian recombinant FVIII (Safacto®) versus recombinant FVIII (Xyntha®) in patients with severe hemophilia A.

2. Materials and Methods

Ethics Committee of the Baqiyatallah University of Medical Sciences (Tehran, Iran) approved the study protocol. The study was performed in agreement with the declaration of Helsinki and good clinical practice. All subjects were informed about the study and a written consent was obtained from the patients at the time of study entry. This study was also registered in the Iranian Registry of Clinical Trials (IRCT) (registration number: IRCT2014101218870N2). This trial was designed as triple-blind and parallel.

The inclusion criteria of the study were (1) patients with severe hemophilia A; (2) without inhibitors against factor VIII; (3) receiving factor VIII for more than 50 days; (4) having blood tests within the normal reference ranges; and (5) having acute or subacute hemarthroses. Exclusion criteria of this study were (1) patients with the history of factor VIII inhibitors; (2) patients with the history of other coagulation disorders except for hemophilia; (3) patients with the history of hepatitis; (4) patients with renal or liver failure; (5) HIV-positive patients; and (6) patients with any infection; allergy or severe adverse effect diagnosed by the physician.

Thirty-three male patients with severe hemophilia A were randomly divided into two groups. In group A (17 patients), patients received Safacto® (Saman Daroo 8 Pharmaceutical Company, Tehran, Iran), and in group B (16 patients) patients received Xyntha® (Pfizer Inc, New York, NY, USA) for four consecutive times. The dosage of FVIII was 50 IU/kg for each injection. The dosage was constant for each patient. Vital signs, adverse effects, every symptom and clinical response after drug administration were monitored. The efficacy and safety of these two recombinant FVIIIs were compared. Plasma level of FVIII activity was evaluated before every injection, 15 minutes after the injection and one month after the start of the trial. The rate of factor VIII activity, pain and joints motion were assessed before and after the treatment as response criteria. Any adverse effect was recorded. Kavakli global response scoring system [6] was used to evaluate pain and joints motion at 1, 3, 8, 12, 16 and 24 hours after drug administration.

Complete blood count and biochemistry profile were assessed before and after the trial. Chromogenic assay and Nijmegen inhibitory assay methods were used to evaluate plasma level of FVIII activity by the Iran Blood Transfusion Organization (IBTO) [2]. Patients stayed in the hospital for three hours and discharged if they were symptom-free. Patients were already informed about potential adverse drug reactions.

Statistical analysis was performed using SPSS software (SPSS Version 16, IBM Corp., New York, NY, USA). Data were analyzed using a t-test for data with normal distribution, and Mann-Whitney U test for data without normal distribution. Independent categorical data were compared using Chi-square and Fishers' exact tests, and dependent categorical data were compared using the McNemar test. P-value of <0.05 was considered as statistically significant. Data were expressed as Mean±SD.

3. Results

Thirty-three male patients with severe hemophilia A were enrolled in this study. No patient was excluded from the

study. Mean age of the patients were 19.44±17.00 and 16.47±17.0 in Safacto® and Xyntha® groups, respectively. Mean body weight of the patients were 52.50±56.50 and 43.47±50.00 in Safacto® and Xyntha® groups, respectively. No significant difference was observed between Safacto® and Xyntha® groups with respect to weight and age of the patients (P=0.24, P=0.44). Total drug dosage in Safacto® and Xyntha® groups were 2603.3±2750.0 IU and 2050.0±2250.0 IU, respectively (Table1). Plasma level of FVIII clotting activity in Safacto® and Xyntha® groups were 1.96±0.5 IU/dl and1.63±0.5 IU/dl and increased to 88.84±25.2 IU/dl and 100.09±17.8 IU/dl, respectively. This increase was significant in both groups (P<0.001). There was no significant difference between Safacto® and Xyntha® groups before and after the trial (P>0.31) (Table 2).

The mean±SD value of total pain score and range of motion improvement were 9.3±0.9 and 8.7±0.1 with Safacto® (P=0.17); and 9.4±0.8 and 8.8±0.3 with Xyntha® (P=0.35), respectively. Joint Range of Motion and Pain scores after injection in each group at different time points are summarized in Tables 3 and 4.

4. Discussion

All patients participated in this study because of occurrence of bleeding. In the Safacto® group, 16 patients had spontaneous bleeding and one had traumatic bleeding. In the Xyntha® group, all patients experienced spontaneous bleeding. Both recombinant FVIII products were used in our study as on-demand treatment. In our study, no adverse effect was observed and the patients well tolerated both drugs.

Local recombinant coagulation factors have been produced by some Iranian pharmaceutical companies. Both Iranian recombinant FVII (Aryoseven®) and FVIII (Safacto®) have been used in the patients with coagulation disorders. In 2015, Eshghi and others compared the safety and efficacy of the Safacto® with plasma- derivedFVIII[7].Safacto® increasedthelevelofFVIIIserumactivitymorethantheplasma- derivedproduct[8].However,thedifferencewasnotsignificant.BothSafacto® andplasma- derived FVIII were safe and efficient in the treatment of hemophilia A [8]. After drug therapy, the plasma level of FVIII activity in Safacto® and plasma-derived FVIII groups were 115 IU/dl and 111 IU/dl, respectively [9].

Toogeh et al. evaluated the safety of the Iranian recombinant activated FVII (Aryoseven®) in patients with bleeding [10]. They stated that careful dosing of Aryoseven® is needed to reduce potential side effects of this drug. Only 5.9% of the patients reported any side effects, though no long-term follow-up was performed by the investigators. In a study by Faranoush and others (2016), the safety and efficacy of Aryoseven® and NovoSeven® were compared in patients with hereditary FVII deficiency. In their study, clinical efficacy of Aryoseven® and NovoSeven® were found to be the same using the Kavakli Global Response Scoring System.Inthementionedstudy,FVIIlevelbeforeandafterthetreatmentinAryoseven® and NovoSeven® groups were 100 IU/dl and 88 IU/dl; 800 IU/dl and 800 IU/dl, respectively. From 31 patients in the Aryoseven® group, only three experienced nausea, rash and headache. In the NovoSeven® group, only one patient had a headache [11].

Comparison of plasma-derived and recombinant FVIII pharmacokinetics has been performed by Morfini et al. [12]. Higher in vivo recovery was reported for recombinant FVIII while elimination decay curves of both products were the same. Alpha constant and half-life of recombinant FVIII was smaller and longer compared to plasma-derived FVIII, respectively [12].

In the guideline of the committee for medicinal products for human use (2011) about the use of recombinant FVIII in hemophilia patients, the most frequent complication in patients was the production of inhibitory antibodies against the drug [13]. In 2007, Chalmers and others evaluated 384 patients for the effect of first exposure on the production of inhibitor in children. In their study, neonatal exposure to FVIII was not associated with a higher incidence of inhibitors [14]. In a retrospective cohort study, Gouw et al. (2007) showed that incidence of inhibitors in patients with severe hemophilia A was not dependent on the type of product. They did not find a significant difference between serum-derived FVIII and recombinant one in the incidence of inhibitors [15].

Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) was performed by Peyvandi et al.A total of 303 patients were screened for inhibitors. Seventy-six patients developed inhibitors and fifty of them had high-titer inhibitors (more than 5 BU). The authors reported that patients treated with plasma-derived FVIII had a lower incidence of inhibitors in comparison to the recombinant group [16].

Lee in 2002 used three recombinant FVIII (Kogenate, Recombinate, and rVIII-SQ) for the management of hemophilia A. All three products had good efficacy and safety after a single injection with a dosage between 20 and 30 IU/kg. The half-life of the three products was reported to be 14-15 hours [17]. The dosage of recombinant FVIII in our study was 40-50 IU/kg; we did not measure half-life and it was a limitation of our study. In 2003, Lusher and others evaluated safety and efficacy of B-domain-deleted recombinant factor VIII (ReFacto®) in 218 hemophilic patients. The drug was rated with excellent efficacy [18]. Ragni in 2017 assessed the safety and efficacy of recombinant FVIII as prophylaxis, when administered once weekly or three times weekly. In their study, 40 IU/Kg of recombinant FVIII was administered to the patients. The main outcome in the patients was low spontaneous or traumatic bleeding in both prophylaxis protocols. There was no difference in coagulation levels, the range of motion and quality of life in all the patients [19].

Saxena and colleagues in 2016 evaluated the efficacy and safety of Kovaltry® in hemophilia patients. Sixty-two patients received 20-50 IU/kg of recombinant FVIII twice or three times weekly. Both protocols were effective to maintain hemostasis during surgery and stopped bleeding in the patients [20].

Nolan and others (2016) evaluated the safety and efficacy of recombinant factor VIII Fc fusion protein in patients with hemophilia [12]. Long-term use of this recombinant FVIII maintained the low average bleeding rate and increased intervals of prophylactic injections [21].

Efficacy of pegylated full-length recombinant FVIII for the prophylactic and on-demand management of patients with severe hemophilia A was assessed by Konkle and

creased intervals of prophylactic injections [21].
Efficacy of pegylated full-length recombinant FVIII for the prophylactic and on-demand management of patients with severe hemophilia A was assessed by Konkle and others (2015) [22]. Annualized bleeding rate in on-demand use was higher than the prophylaxis regimen. The authors reported effectiveness and safety of the recombinant FVIII with twice-weekly infusions [22].
Recombinant factor VIII Fc fusion protein was used in children with severe hemophilia [15]. The drug was used as prophylaxis for 71 patients with a dose of ≤80 IU/Kg. Patients well tolerated two weekly infusions with low bleeding rate [23]. It is worth mentioning that small population size with low bleeds incidence was another limitation of our study.

5. Conclusions

Overall, both recombinant factors administered on-demand in this study had no significant side effects in patients with severe hemophilia. Our study did not show a significant difference in efficacy and safety between Safacto® and Xyntha® . A significant increase in serum level of FVIII activity without noticeable side effect was observed during the study.
Improvement in joint range of motion, a decrease of pain and control of bleeding were predominant findings in both Safacto® and Xyntha® groups. No allergic reaction was observed in patients with hemophilia A after Safacto® administration. The results of this study showed that Safacto® has favorable safety and efficacy. Future studies exploring the immunogenicity of Safacto® are warranted.

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Conflict of interest

The authors declare that there is no conflict of interests.

Table 1 Age, body weight and total drug dosage in both groups

Parameters	Safacto®				Xyntha®				P-Value
	Mean	Median	IQR	SD	Mean	Median	IQR	SD	
Age	19.44	10.22	18	17.00	16.47	6.78	12	17.00	0.187
Weight	52.50	23.97	34	56.50	43.47	16.76	34	50.00	0.446
TDD	2603.33	1238.73	2000	2750.00	2050.00	808.88	1200	2250.00	0.247

IQR: Interquartile range TDD: Total Drug Dosage

Table 2 Plasma FVIII level in two groups

Group	Baseline level of FVIII			Level of FVIII, 15 minutes PI			P-Value	Mean Difference	Between Group P-Value
	Mean	Median	IQR	Mean	Median	IQR			
Safacto®	1.96	2.00	0.5	88.84	98.00	25.2	<0.001	86.88	0.316
Xyntha®	1.63	1.00	0.5	100.09	116.00	17.8	<0.001	98.46	

IQR: Interquartile range

Table 3 Joint range of motion after treatment in two groups

Time	Safacto®		Xyntha®		P-Value
	Mean	SD	Mean	SD	
Time of Injection	1.2	0.4	1.1	0.3	0.096
3 hrs. PI	1.3	0.5	1.2	0.4	0.052
8 hrs. PI	1.5	0.6	1.5	0.5	0.051
12 hrs. PI	1.4	0.9	1.5	0.8	0.909
16 hrs. PI	1.5	0.9	1.4	0.9	0.257
24 hrs. PI	1.6	0.8	1.5	0.9	0.086
Total Score	1.41	0.51	1.39	0.45	0.351

PI: Post Injection

Table 4 Pain after treatment in two groups

Time	Safacto®		Xyntha®		P-Value
	Mean	SD	Mean	SD	
Time of Injection	1.3	0.5	1.3	0.4	0.096
3 hrs. PI	1.4	0.5	1.4	0.5	0.051
8 hrs. PI	1.7	0.5	1.5	0.5	0.051
12 hrs. PI	1.6	0.8	1.7	0.7	0.909
16 hrs. PI	1.6	0.8	1.4	0.9	0.257
24 hrs. PI	1.5	0.9	1.3	0.9	0.086
Total Score	1.53	0.49	1.44	0.48	0.171

PI: Post Injection

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