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AryoSeven RT (Coagulation factor VIIa, recombinant) safety and efficacy study among congenial factor VII deficient patients in Iraq

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Abstract:

BACKGROUND: Recombinant activated factor VII (FVII) is a product onetime evolved to stop bleeding occurring in hemophilia A and B patients with inhibitor, congenital FVII deficiency, Glanzmann disease, and in life-threatening bleeding.

AIM: The aim was to evaluate the safety and efficacy of the coagulation factor VIIa, recombinant (AryoSeven RT) among congenital FVII deficiency patients at different centers in Iraq.

METHODOLOGY: This is a prospective, observational, noninterventional study done at 5 medical centers in Iraq and it included 22 patients with FVII deficiency (congenital form) older than 14 years of age. Patients are recorded and followed for 6 months and they are subjected to AryoSeven RT depending on each patient individually. There were 3 main visits and 3 unscheduled visits for each patient during the study. Effectiveness evaluation was performed 6 h after each intervention. Adverse drug reactions related to the administration of AryoSeven RT were reported for each patient during each visit.

RESULTS: A total of 22 participants were enrolled, classified into 18 (82%) were female and 4 (18%) were male. The mean age was 27.5 ± 14.0 years. Among 91 bleeding events, AryoSeven RT efficacy was effective in 89 events, excellent in 1 event, and partially effective in also 1 event. There was a reduction of PT from baseline (57.3 ± 15.2 s) to (13.9 ± 6.2 s) after 1st dose of AryoSeven RT and more reduction after 2nd dose of therapy (13.4 ± 4.4 s) and these were statistically significant ($P = 0.001$). Regarding FVII activity, there was a significant increase from baseline (8.4% ± 8.0%) to (95.8% ± 46.6%) after 1st dose and (131.8% ± 40.1%) after 2nd dose of AryoSeven RT with $P = 0.001$ for both. No major adverse events were reported except for headache in one participant (4.5%), and injection site reactions in three participants (13.6%).)

CONCLUSION: AryoSeven RT is safe and effective clinically and by laboratory data in stopping bleeding in patients older than 14 years with inherited FVII deficiency.

Keywords:

Activated Factor VIIa, AryoSeven RT, factor VII deficiency, hemophilia, Iraq

Introduction

Factor VII (FVII) is a plasma Vitamin K-dependent factor synthesis by the liver. It is the unique clotting factor involving 1%–3% of free circulating form of (FVIIa), even in the absence of activation.[1] The complex of activating r F VIIa to tissue factor results in the activation of both factor IX into factor IXa and factor X into factor Xa, causing conversion initially prothrombin into thrombin. Factor 2 (Thrombin) results in the platelets activation and both factors V and VIII at the site of vessel injury leading

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to the hemostatic plug formation through converting fibrinogen into fibrin. The minimum amounts of FVIIa are required to trigger hemostasis.[2-6]

Congenital F VII deficiency is an autosomal recessive disease. It is a rare inherited bleeding disorders, and it is a chameleon disease because of the lack of a direct correlation between FVII plasma level and bleeding episodes.[7] It is described by a broad variation of clinical manifestations ranging from asymptomatic or mild conditions to severe life-threatening hemorrhage including gastrointestinal (GI) and central nervous system (CNS).[8,9] The most common clinical manifestations are mild (mucocutaneous) bleeds (as in platelet disorders) and 10%–15% appear as potentially life-threatening bleeding (as CNS and GI bleeding, or hemarthrosis).[1,10] In cases of "platelet-like" FVII deficiency, is presented as menorrhagia in (69% of females), epistaxis (60%), easy skin bruising (36%), and bleeding in the gum (34%).[7]

Recombinant-activated FVII is a clotting factor agent basically developed for the treatment of bleeding episode in patients with inhibitor in hemophilia A and B and life-threatening bleeding.[3,11-13]

AryoSeven RT (Eptacog alfa) is the first biosimilar or biogeneric of the original drug with the name NovoSeven. It is a product of AryoGen Pharmed with trade name called AryoSeven RT. This biosimilar medicine is a glycoprotein created by recombinant technology in the Baby Hamster Kidney cell line and is highly purified to accept as an injectable drug.[14] It has the active ingredient eptacog alfa (activated), which belonged to a class of drugs named blood coagulation factors that are involved in blood hemostasis. It is materially analog to the human plasma-derived FVIIa.[2]

It is used to manage bleeding and prevent hemorrhage through surgical operations in the following: Hereditary hemophilia A or B with inhibitors (poor response to FVIII or IX), Acquired hemophilia, Congenital FVII deficiency, and Glanzmann's thrombasthenia refractoriness to platelets transfusions.[15,16]

AryoSeven RT is marketed in 4 different doses of 1 mg, 2 mg, 5 mg, and 8 mg (50 KIU, 100 KIU, 250 KIU, and 400 KIU, respectively). The solvent vial contains solution with a clear and colorless. The reconstituted solution is a colorless. The powder must be reconstituted with the supplied solvent and injected within 2–5 min.[2]

The recommended dose of AryoSeven RT for a bleeding disorder in congenital hemophilia A or B with inhibitors or expected to have a high anamnestic reaction is 90 μg/kg intravenously every 2–3 h until hemostasis is established or the doctor may recommend a single high dose in some cases. The dose, duration, and interval, of therapy may be adjusted depend on the severity of bleeding. In the case of bleeding event and surgical interventions in the patient with inherited FVII deficiency, the recommended dose is 15–30 μg/kg was given every 4–6 h until hemostasis is established. While in the patients with acquired hemophilia and Glanzmann's thrombasthenia, the dose in these bleeding episodes is 90 μg/kg given every 2–3 h until hemostasis is completed (and at least three doses needed in Glanzmann's thrombasthenia should be administered to ensure effective hemostasis).[2]

Efficacy and safety profile is the most important concern of a hemostatic drug like rFVIIa. The aim of this study was to estimate the safety and efficacy of AryoSeven RT among congenital FVII deficiency patients at different centers in Iraq.

Methodology

Study design and setting

It is a prospective, noninterventional, observational, study carried out at 5 medical centers in Iraq:

1 The National Center for Hematology/Mustansiriyah University
2 Child Welfare Hospital-Medical City Teaching Hospital
3 Basra Center for Hereditary Blood Diseases
4 Karbala Hereditary Blood Disease Center
5 Babylon hereditary blood disease center.

The study was performed over a period of 6 months extending from June 1, 2021, to December 31, 2021. By the study definition, there did not need a control group and only required the effects of the drug and no comparison was made.

Study participants

The current study was done on 22 patients with hereditary FVII deficiency over 14 years old. Patients enrolled were followed for 6 months for efficacy and adverse drug reactions. Written informed consent was obtained from all patients.

Inclusion and exclusion criteria

The participant was eligible for this study, and they were assessed according to the following criteria:

1. Inclusion criteria:
   a. Isolated congenital FVII deficiency
   b. Patients aged ≥14 years.
2. Exclusion criteria:
   a. Hypersensitivity reaction to bovine proteins
   b. Patients treated with an investigational medicinal product within 30 days before this trial
   c. With malignancy or a history of malignancy

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d. Pregnancy
e. Patient had a history of corticosteroids consumption (within 7 days of study enrollment)
f. Pregnant women or within 12 weeks' postpartum and/or lactating during the study
g. Thromboembolic or vaso-occlusive disease in the past 90 days as cerebrovascular accident, infarction of myocardium, and embolism anywhere
h. Concomitant drugs used as desmopressin, inhibitors drugs to platelets, and fibrinolysis
i. Major surgery within 28 days before investigation
j. Anticoagulant therapy within 7 days of study.

Study treatment

AryoSeven RT was given to treat the participants with congenital FVII deficiency with the usual dose is 15–30 μg/kg every 4–6 h until coagulation is performed. The administered doses given depended on each patient individually. Patients were evaluated clinically 2 h, 6 h, and then 24 h and 48 h posttherapy.

Visits and data collection

There were 3 main visits and 3 unscheduled visits for each patient during the study. A designed notebook was used for collecting the data. Participants' demographic data, habitual history, medical history, and baseline laboratory findings were taken. Follow-up physical and clinical assessments were done during each next visit in addition to the administration of the different doses of AryoSeven RT according to each patient case. Moreover, laboratory tests were taken post-AryoSeven RT administration. Finally, an assessment of adverse effects in addition to the proper intervention in case of the presence of any.

The data collection included: participant's demographic (age, gender, and weight), habitual history (smoking, alcohol consumption, and drug abuse), and medical history (cardiovascular, cerebrovascular, neurologic, hepatic, hematologic, musculoskeletal, malignancy/tumor, thromboembolic, vaso-occlusive, and other background diseases). Baseline laboratory findings (prothrombin time [PT], international normalized ratio [INR], activated partial thromboplastin time [aPTT], FVII activity (%), white blood cell (WBC) with differential count, red blood cell (RBC), PLt, renal and liver function tests, laboratory data post administration 1st, 2nd and 3rd doses of AryoSeven RT (PT/INR, aPTT, FVII activity [%]) and adverse events were recorded.

Study endpoints

Safety assessment

Adverse drug reactions related to the AryoSeven RT administration were reported for each patient in each visit according to the following definitions:

Adverse event

Any complaint reported by the patient:

Assessment of side effects

The action was taken to control any side effects as follows:

a. No intervention: No treatment has been required to control the adverse event
b. Medication: If the patient has received any therapy to govern the abnormal event
c. Withdrawal from trial: This option should choice if the patient is withdrawn from the study because of an adverse event
d. Permanent/temporary dose reduction: The dose of this therapy given to the patient is reduced transiently or permanently
e. Permanent/Temporary drug discontinuation: The patient does not receive any medication transiently (e.g., for a few hours or a visit) or permanently because of an adverse event.

Efficacy assessment

Effectiveness evaluation in attack of bleeding event is performed 6 h after any intervention, as in the following marks:

a. Excellent: Single dose resulting in stooping of bleeding attack and associated symptoms; urgent (within a few hours) pain relief; hidden of the swelling and back to normal mobility of the joint. Also, bleeding cessation may be assessed by imaging study if required
b. Effective: Two or more doses are required to get the similar results as above
c. Partially effective: Two or more doses are required, with disappeared of the symptoms slowly and limb and joint mobility is partially improved
d. Ineffective therapy: There did not alter
e. Not evaluable: Assessments were not available at that time.

Ethical considerations

Written consent was gained from the participants or the caregivers before the initiation of collection data, throughout the study, the information's should be confidentiality and maintained of all data to participants. This study was endorsed by the Institutional Review Board Committee at the National Centre of Hematology/Mustansiriyah University.

Statistical analysis

The Statistical Package for Social Sciences (SPSS, The statistical package for social science, Chicago, Illinois, United States) was done for the analysis of data. To illustrate categorical variables, number, and percentage. And also to express continuous variables, mean and standard deviation. Paired *t*-test was presented to identify the difference between means of continuous variables. A $P \leq 0.05$ is considered statistically significant.

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Results

Table 1 presents the participants' demographic data, habitual history, and medical history.

A total of 22 participants were included, classified as 18 (82%) females and 4 (18%) males. The mean age was 27.5 ± 14.0 years. The average weight was 59.0 ± 16.5 kg. All of the participants were nonsmokers 22 (100%), nonalcohol users 22 (100%), and nonsubstance abusers 22 (100%). None of the 22 participants had any past medical history.

Figure 1 shows the type of bleeding with FVII deficiency. Hemarthrosis represented 46% of all types, menorrhagia 35%, epistaxis 7%, hematuria 6%, gum bleeding, ecchymosis, and bleeding per rectum, are presented in each 2%.

Table 2 presents the baseline laboratory findings. The following values for each test were reported as PT (57.3 ± 15.2) s, INR (4.4 ± 1.1), aPTT (30.6 ± 1.1) s, FVII Activity (8.4 ± 8.0) %, WBC (6.64 ± 2.03) × 103/mm^3, RBC (4.34 ± 0.64) million/µL/cu mm, PLt (366 ± 117) × 109/L, neutrophil (58.1 ± 6.9) %, lymphocyte (38.7 ± 1.8) %, serum creatinine (0.3 ± 0.2) mg/dL, serum glutamic-pyruvic transaminase (16.8 ± 9.1) units/l, serum glutamic-oxaloacetic transaminase (19.6 ± 7.9) units/l, total bilirubin level (3.34 ± 6.9) mg/dl, and direct bilirubin (0.7 ± 0.1) mg/dl.

Table 3 presents the clinical efficacy and improvement of AryoSeven RT in bleeding episodes. There were 91 events of total bleeding attacks in the 22 patients over 6 months. Hemarthrosis was found in 42 events. Forty-one of hemarthrosis showed an effective response, where 2 doses were needed in 35 events and 3 doses in 2 events and 4 doses in 1 event. One patient showed partial efficacy, where 3 doses for 3 days were needed, symptoms subsided slowly and joint mobility was partially improved. Regarding the efficacy of AryoSeven RT in 32 events of menorrhagia in female patients, AryoSeven RT was effective in 32 events. Two doses for 2 days were needed in 22 events beside hormonal therapy with contraceptive pills, 2 of them were on continuous contraceptive therapy, with iron supplementation. Mean that .Two doses of AryoSeven for 2 days were needed in 22 events of menorrhagia beside hormonal therapy including contraceptive pills were given monthly,

Table 1: Participant specifications

Participant's demographic data	Mean ± SD	
Age (years), mean±SD	27.5±14.0	
Weight (kg), mean±SD	59.0±16.5	
Male, *n* (%)	4 (18)	
Female, *n* (%)	18 (82)	
Participant's habitual history	**No, *n* (%)**	**Yes, *n* (%)**
Smoking	22 (100)	0
Alcohol consumption	22 (100)	0
Substance abuse	22 (100)	0
Participant's medical history	***n* (%)**	
Cardiovascular disease	0	
Cerebrovascular disease	0	
Neurologic disease	0	
Hepatic impairment	0	
Hematologic disease	0	
Musculoskeletal disease	0	
Malignancy/Tumor	0	
Thrombo-embolic disease	0	
Vaso-occlusive disease	0	
Other background disease (s)	0	

SD=Standard deviation

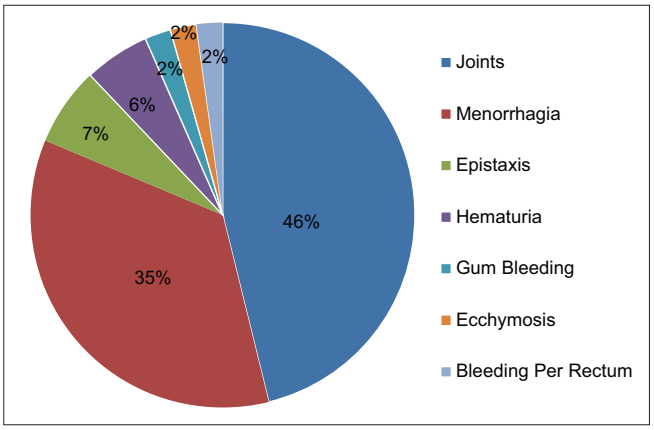

Figure 1: Bleeding site in patients with inherited factor VII deficiency

Table 2: Baseline laboratory findings

Test	Mean±SD	Test	Mean±SD
PT (s)	57.3±15.2	Neutrophil (%)	58.1±6.9
INR	4.4±1.1	Lymphocyte (%)	38.7±1.8
aPTT (s)	30.6±1.1	Creatinine level (mg/dL)	0.3±0.0.19
FVII activity (%)	8.4±8.0	ALT (SGPT) (units per liter)	16.8±9.1
WBC (×10^3/mm^3)	6.64±2.03	AST (SGOT) (units per liter)	19.6±7.9
RBC (million/µL/cu mm)	4.34±0.64	Total bilirubin (mg/dL)	3.34±6.9
PLt (×10^9/L)	366±117	Direct bilifrubin level (mg/dL)	0.6±0.2

PLt=Platelet, PT=Prothrombin time, INR=International normalized ratio, aPTT=Activated partial thromboplastin time, FVII=Factor VII, WBC=White blood cell, RBC=Red blood cell, SGOT=Serum glutamic-oxaloacetic transaminase, SGPT=Serum glutamic-pyruvic transaminase, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase

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except 2 patients on continuous therapy with iron supplementation. Furthermore, 5 events were treated with 3 doses for 2 days and 5 events were treated with 3 doses for 3 days. Regarding AryoSeven RT effectiveness in treating 6 events of epistaxis, it was noticed that excellent effectiveness in one event where only 1 dose was required to stop the bleeding, and it was effective in 5 events where 2 doses were needed for treating the events. In all 5 events of hematuria, AryoSeven RT was effective, where 3 doses were needed for treating the events. Moreover, AryoSeven RT was effective in treating 2 events of gum bleeding where 2 doses were needed for treating the events, 2 events of ecchymosis where also 2 doses were needed for treating the events, and 2 events of bleeding per rectum where 3 doses for 2 days were needed for treating the events, consulted the gastroenterologist who did a colonoscopy after receiving AryoSeven RT dose as prophylaxis before this interventional procedure.

Table 4 presents the efficacy of AryoSeven RT. There was a statistically significant decrease PT from baseline (57.3 ± 15.2 s) to (13.9 ± 6.2 s) after 1st dose of AryoSeven RT (P = 0.001). Similarly, there was a reduction of PT from baseline to (13.4 ± 4.4 s) after 2nd dose of AryoSeven RT and also statistically significant (P = 0.001).

Regarding FVII activity, there was a significant increase of FVII activity baseline (8.4 ± 8.0%) to (95.8 ± 46.6%) FVII activity after 1st dose of AryoSeven RT and from FVII activity baseline to FVII activity (131.8 ± 40.1%) after 2nd dose with P = 0.001 for both.

Table 5 presents the adverse events of AryoSeven RT. No major adverse events were reported except headache developed in one participant (4.5%), and injection site reactions in three participants (13.6%).

Discussion

Efficacy and safety profile are the most important concern of a hemostatic drug like FVIIa. In this study, we evaluated the safety and efficacy of AryoSeven RT among 22 participants with congenital FVII deficiency at various centers in Iraq.

In this study, AryoSeven RT proved to be effective and it showed clinical improvements in all the patients. Among 91 bleeding events, AryoSeven RT efficacy was effective in 89 events, excellent in 1 event, and partially effective in also 1 event.

Regarding the laboratory results, there was a statistically significant improvement related to the bleeding disorders where baseline PT dropped from 57.3 ± 15.2 s to 13.9 ± 6.2 s after 1st dose AryoSeven RT and to 13.4 ± 4.4 s

Table 3: Clinical efficacy and improvement of AryoSeven RT in bleeding episodes

Bleeding attacks (n=91)	Baseline, n (%)	Excellent	Effective	Partially effective	Ineffective	Not evaluable
Hemarthrosis	42 (46)		41[a]	1[b]		
Menorrhagia	32 (35)		32[c]			
Epistaxis	6 (7)	1[d]	5[e]			
Hematuria	5 (6)		5[f]			
Gum bleeding	2 (2)		2[g]			
Ecchymosis	2 (2)		2[h]			
Bleeding per rectum	2 (2)		2[i]			

[a]2 doses were needed in 35 events and 3 doses in 2 events and 4 doses in 1 event, [b]3 doses for 3 days were needed, symptoms and mobility of joint partially improved, [c]2 doses for 2 days were needed in 22 events beside hormonal therapy with contraceptive pills, 2 of them were on continuous contraceptive therapy, with iron supplementation. Also, 5 events were treated with 3 doses for 2 days and 5 events were treated with 3 doses for 3 days, [d]Only 1 dose is required to stop the bleeding, [e]2 doses were needed for treating the events, [f]3 doses were needed for treating the events, [g]2 doses were needed for treating the events, [h]2 doses were needed for treating the events, i3 doses for 2 days were needed for treating the events, consulted the gastroenterologist who did a colonoscopy after receiving AryoSeven RT dose as prophylaxis before this interventional procedure. RT=Recombinant therapy

Table 4: Efficacy of AryoSeven RT

	Mean±SD	P	
		Baseline and post 1st dose	Baseline and post 2nd dose
PT (s)			
Base value	57.3±15.2	0.001*	0.001*
After 1st dose of therapy	13.9±6.2		
After 2nd dose of therapy	13.4±4.4		
FVII activity (%)			
Base value	8.4±8.0	0.001*	0.001*
After 1st dose of therapy	95.8±46.6		
After 2nd dose of therapy	131.8±40.1		

*P<0.05 which is significant statistically. FVII=Factor VII, SD=Standard deviation, PT=Prothrombin time, RT=Recombinant therapy

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Table 5: Adverse events

Adverse event	Preferred Term	*n* (%)	Intervention	
			No, *n* (%)	Yes, *n* (%)
Blood and lymphatic system disorders	Disseminated intravascular coagulation	0	0	0
Gastro intestinal disorder	Nausea	0	0	0
	Vomiting	0	0	0
General disorders and local reaction	Fever	0	0	0
	Therapeutic response decreased	0	0	0
	Reaction to site of injection	0	0	0
Immune system disorders	Hypersensitivity	0	0	0
Neurological disorder	Headache	1 (4.5)	0	0
Dermatological disorder	Skin rash	0	0	0
	Urticaria	0	0	0
	Pruritus	0	0	0
	Flushing	0	0	0
	Angioedema	0	0	0
	Reactions to site of injection	3 (13.6)	0	0
Vascular disorders	DVT	0	0	0
	Injection site thrombosis	0	0	0
	Thrombosis in portal vein	0	0	0
	Thrombosis in renal artery	0	0	0
	Thrombosis in renal vein	0	0	0
	Thrombophlebitis	0	0	0
	Thrombosis in peripheral arteries	0	0	0
Vascular disorders	Peripheral ischemia	0	0	0
	Peripheral ischemia	0	0	0
	Pulmonary embolism	0	0	0
	Cerebral ischemia	0	0	0
	TIA	0	0	0
	Cerebral artery occlusion	0	0	0
	Myocardial infarction	0	0	0
	Angina pectoris	0	0	0
	Purpura	0	0	0
Investigations	ALT increased	0	0	0
	Blood alkaline phosphatase increased	0	0	0
	Serum lactate dehydrogenase increased	0	0	0
Cardiovascular	Fibrin D dimer increased	0	0	0
	Edema	0	0	0
	Hypertension	0	0	0
	Hypotension	0	0	0
	Bradycardia	0	0	0

DVT=Deep vein thrombosis, ALT=Alanine aminotransferase, TIA=Transient ischemic attack

after 2nd dose AryoSeven RT. Regarding FVII activity, the improvement was shown in the statistically significant increase in baseline FVII activity, from 8.4% ± 8.0% to 95.8% ± 46.6% after 1st dose AryoSeven RT and to 131.8% ± 40.1% after 2nd dose AryoSeven RT.

Regarding the safety profile of AryoSeven RT, it proved to be safe since only 4 participants out of 22 reported adverse events and they were not serious events: headache in one participant 1 (4.5%) and pain at the site of injection in three participants 3 (13.6%).

Comparable to our study is a randomized, double-blind, multicenter study carried out in 8 hemophilia care centers in Iran in 2015 by Faranoush *et al*., where they compared AryoSeven efficacy and biosimilarity to that of NovoSeven in treating inherited FVII deficiency. The main objective was comparing FVII: Coagulation activity (FVII: C), 20 min after the administration of AryoSeven (rFVIIa) therapy, it was done in two groups of patients. A total of 66 patients were enrolled in the trial and they were randomized between two treatment groups (Group A with AryoSeven as the intervention group, and Group B with NovoSeven as the control group). Those patients received 1 single dose of rFVIIa (AryoSeven in Group A and NovoSeven in Group B) 30 mg/kg, intravenously, once weekly for 4 consecutive weeks as a prophylaxis regimen. Patients

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visited the center 6 times as follow: Visit 1 as screening, visits 2–5 as prophylaxis therapy given, and 1 visit 6 is considered as follow-up. The increment levels of FVII: C compared between these 2 groups showed no difference in levels of FVII: C 20 min after each 2-5 visits. Minor adverse effects were recorded as headache, nausea) and they were similar in both groups of patients (Group A in: 4 [11.4%] and Group B: in 3 [9.7%]). This Iranian study concluded that AryoSeven is the same as NovoSeven therapy, in addition, the clinical efficacy and safety. However, in our study, we used on-demand therapy, not prophylaxis therapy.[17]

Our study can be evaluated in light of its strengths and limitations. One of its strengths is that it is the first one carried out in Iraq. Furthermore, it is a study that covered different centers from different parts of Iraq. Nevertheless, there are some limitations where the sample size was small, there was a gender bias where females were more than males, and it was used for only one indication which is congenital FVII deficiency. In addition to that, there was a difficulty in monitoring patients through laboratory investigations: PT and FVII level activity after doses of AryoSeven RT in most centers either due to unavailable tests at night, poor veins, or refusal of some patients to frequent testing.

Conclusion

AryoSeven RT in the current study was proven to be effective for the patients, they were used as NovoSeven. AryoSeven RT is safe and effective clinically and by laboratory finding including PT and FVII level in stopping bleeding after 2–6 doses within 24–48 h. The adverse events were to those noticed with NovoSeven. Overall Efficacy Assessment: It is as effective as NovoSeven. Overall Safety Assessment: it is as safe as NovoSeven.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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