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A Prospective Crossover Triple-Blind Controlled Trial on the Safety and Efficacy of Iranian Recombinant FVIII (Safacto®) Versus Plasma Derived FVIII; A Pilot Study

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ABSTRACT

Background: Considering the increasing number of patients with hemophilia and infrastructure requirements for a comprehensive approach, development of a recombinant factor has become a milestone.
The objective of this study was to assess the safety, efficacy and non inferiority of Safacto (Recombinant factor VIII) compared with plasma-derived factor in the treatment of hemophilia A.
Methods: 10 patients with severe hemophilia A were enrolled in this study. Each patient was treated by a 40-50 IU/kg infusion of either plasma derived or recombinant factor VIII after initiation of each of 4 consecutive hemarthrosis episodes in a triple-blind prospective crossover permuted block randomizing method. Clinical efficacy scale score and in vivo recovery of factor VIII was assessed in each of the treated bleeding episodes. Any adverse event was also recorded.
Results: The mean±SD level of factor VIII in the plasma versus recombinant groups was 111.5±39 and 115±39, respectively without any significant difference. Response scaling method which assessed pain and range of motion revealed equalized scores along with in vivo recovery, hence treatment success rate was comparable in both groups. One non-recurring, mild skin rash reaction occurred simultaneous with the administration of plasma derived factor.
Conclusion: Safacto (r-FVIII) is safe and effective and non-inferior to plasma derived factor VIII in the treatment of hemophilia A related bleeding events.

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Introduction

Hemophilia A is an X-linked bleeding disorder that results from insufficiency of factor VIII (FVIII) coagulant activity [1-4]. Patients with severe disease (FVIII levels <1%) may present with spontaneous bleeding and lack of appropriate treatment leads to life threatening bleeding [1-5].

Factor replacement is the main strategy in the treatment of hemophilia. Currently, the affordable treatment products include plasma derived factor which is originally isolated from pooled human plasma, and FVIII concentrates whom are produced via techniques that employ genetic engineering [1-3]. Various trials revealed comparable efficacy and safety of both products. Synthesis of coagulation factors ensure safe therapy for patients with hemophilia and protect them against blood borne infections [3-5].

In spite of challenges regarding the immunogenicity of recombinant FVIII and great progress in production and viral inactivation methods, the safety of recombinant coagulation factor is much higher compared with plasma derived counterparts [5-9]. The available products are categorized into four generations of recombinant FVIII that are shown in table 1.

Table 1: Available products categorized into four generations of recombinant FVIII

	1st Generation	2nd Generation	3th Generation	4th Generation
Recombinant technology	+	+	+	+
Chemical virus inactivation		+	+	+
Final product Free from human or animal protein		+	+	+
Cell culture Free from human or animal protein			+	+
Purification with a synthetic ligand				+
Nanofiltration				+

Parallel with the mentioned classifications few products were manufactured with deletion of the B domain which caused reduced immunogenicity [9-17]. The CANAL trial revealed that FVIII products have a similar propensity to produce FVIII inhibitors as plasma derived [9,10].

Management of haemophilia is a major challenge, especially in developing countries, from various aspects such as shortage of product, the cost, and problems with health-related infrastructures [4,11]. Iran as a middle eastern country with about 2767 US dollars per capita gross national product has higher than expected factor consumption index which is more than 2 unit/capita based on the 2011 annual global survey of the World Federation of Hemophilia (WFH) [5]. Since 2014, the treatment strategy of hemophilia in Iran is shifting toward prophylaxis which will impress factor demand. In order to solve the aforementioned issues and exert comprehensive care, Iranian scientists have manufactured SafactoÒ, B domain deleted, albumin free FVIII product in which the cell line culture was Chinese hamester's ovary (CHO) purified with a synthetic ligand whose pharmacological characteristics were registered in the food and drug organization of Iran in 2012 [14-18]. We hypothesize that manufacturing Iranian recombinant factor will have a profound impact on reducing governmental expenditure considering that 99% of hemophilia care disbursement in Iran has been factor supply expenditure [4]. We aimed to compare the efficacy, safety, and non inferiority of recombinant factor versus plasma derived factor.

Patients and Methods

This triple-blind prospective crossover randomized permuted blocking pilot study was conducted in two comprehensive care centers in Iran (Mofid children's Hospital, Tehran, and Ali Asghar Hospital, Zahedan). Investigators and analysts were unaware of the treatment arms in order to prevent any bias in this study. Potential subjects who had the inclusion criteria were identified from the Haemophilia Reference Centre database and were invited to participate. This study was approved by the ethical review committee of shahid Beheshti Medical University and the health ministry in agreement with declaration of Helsinki and Good Clinical Practice. Parent(s)/patient(s), of all study subjects gave informed written consent at the time of study entry. The trial was registered on the Iranian Registry of Clinical Trials (IRCT) web site with registration number 2014082018870N1.

Previously treated patients aged more than one year with severe hemophilia A with a history of experiencing more than 50 exposure days whose clinical biochemistry results were within the normal range were eligible for enrolment.

The exclusion criteria were history of inhibitors (neutralizing antibodies), hypersensitivity associated with any FVIII concentrate or intravenous immunoglobulin, or being affected by another bleeding disorder.

In order to assign allocation concealment appropriately, the corresponding manager of the trial firstly assigned identification numbers to participants then encoded them confidentially. The batches were encoded to A and B, concealed in an opaque sealed envelope not to be revealed until study termination. Randomization was done suing the random permuted block design with blocks with a length of four.

After enrollment, all of the eligible patients were assigned to receive on demand infusion, at dose of 40-50 mg/kg factor VIII for 4 consecutive times randomly (2 times for each kind of product either plasma derived or recombinant).

Each infusion of FVIII was monitored for significant changes in vital signs, other adverse signs or symptoms, and clinical response to treatment. The dose of factor administration was rounded to cost benefit vial, and estimated dosage was fixed for every patient.

Simultaneous with the first FVIII administration, plasma FVIII levels were drawn pre-infusion, and 15 minutes post-infusion and measured in the participating reference laboratory of the Iranian Blood Transfusion Organization.

Efficacy of recombinant factor in our trial was evaluated firstly by hemostatic recovery and by the quantitative self-assessment scaling method, which will be described in detail.

Following the infusion, the actual to expected FVIII recovery ratio at 15 minutes post infusion was calculated, based on the expectation that 1 IU FVIII U/kg body weight would raise plasma FVIII activity by 2%. Hence, a ratio of actual to predicted FVIII recovery>0.66 was considered within the normal limits [19]. Hematological parameters and inhibitor screening were assayed before and one month after termination of study.

Patients were instructed to stay in hospital for 3 hours and could be discharged if symptom free, and were informed of possible adverse reactions.

A clinical efficacy scaling system was designed based upon the patient's self-assessment of pain relief and improved joint mobility. The patients were instructed to give a score of 0 to 2 after assessing the mentioned items every 3 hours for 24 hours. Treatment efficacy was considered as reaching a minimum score of three

in the first three hours and no need for any further factor infusions thereafter due to pain relief in first eight hours.

Citrated plasma and serum were stored at -70°C and shipped in batches from the participating treatment centers to the reference laboratory. FVIII activity was measured at IBTO center by a one-stage, activated partial thromboplastin time based assay using substrate plasma deficient in FVIII. Citrated plasma was assayed for the presence of inhibitors using a modification of the Bethesda and Nijmegen method. Inhibitor titers were quantitated in the reference laboratory [20].

Data were analyzed using SPSS software, version 18. Quantitative data were expressed as mean, median and standard deviation. T, Mann-Whitney, Roc curve and Pearson's tests were used as appropriated.

Results

Ten patients with mean age of 5.5 year (range: 4-43years) were enrolled. At the end of the trial the drug batches were decoded: A was (Pd FVIII) and B was recombinant (rFVIII).

The mean±SD plasma level of FVIII activity was 111.5±39 U/dl in plasma derived FVIII and 115±39 U/dl in the recombinant FVIII (P=0.753). The mean±SD of actual to predicted recovery for plasma derived FVIII was 1.8±0.35 (0.54-1.75) and 1.1±0.31 for recombinant FVIII (0.66-1.75) (P=0.583). In spite of the mentioned results we used receiver operating characteristic ROC curve in order to determine a cut-off value for our clinical test. The area under the ROC curve, as an important measure of the accuracy of the clinical test was 0.475. The patients' efficacy scaling score of product A and B were comparable with each other: the pain relief score was 10.4±1.8 (4-12) for plasma derived FVIII, 11±1 (7-12) for recombinant FVIII (P=0.142). Joint mobility scores were 10.5 ±2 (4-12) and 11±1 (9-12) for plasma derived FVIII and recombinant FVIII, respectively (P=0.820).

One nonrecurring acute adverse reaction post infusion was detected after plasma derived administration which was manifested by paresthesia.

Equalized scores achieved in coordination with in vivo results revealed comparable efficacy and safety of recombinant factor versus plasma derived FVIII.

Discussion

Unquestionably the principal benefit of r-FVIII for subjects with hemophilia A is access to a source of clotting factor that is not dependent on the availability of human plasma which could be a potential transmissible of blood borne diseases [1-17]. Aforementioned biogeneric recombinant (Safacto®) and plasma derived products' safety and efficacy are completely comparable which is fully correlated with previous studies between the two products.

To the best our knowledge, this study is the first triple blinded prospective crossover clinical trial pilot study, with strongest study design according to the consolidated statement of reporting trials (CONSORT) [18-21].

In addition, most of the similar trials' methodologies are open label clinical trials, in which the researcher knows the full details of the treatment and so does the patient, hence potentially are more vulnerable to bias [18-24].

Evaluation of efficacy is one of our endpoints composed of components such as cessation of bleeding, pain relief, improvement of joint mobility and eventually hemostatic recovery. Clinical efficacy assessment score was based on pain relief and joint mobility, which revealed comparable results in both products. Actual to predicted FVIII recovery which was used as a laboratory efficacy index in our study which was desirable in almost all patients. The ratio of actual to predicted rFVIII recovery was less than 0.66 on 3 occasions.

Bray et al. conducted an open label trial on efficacy and safety of recombinant factor FVIII in untreated patients. Efficacy was evaluated by pharmacokinetics. Mean±SD of recovery to expected ratio was 1.0±0.4, comparable with our results which was 1.0±0.3. Two acute adverse reaction events were occurred. Efficacy and safety of recombinant FVIII was acceptable in their study [19]. Blanchette et al. designed a multicenter, open-label, prospective cohort study to assess pharmacokinetics, efficacy and safety of a plasma-free recombinant FVIII concentrate (ADVATE Ò) in 53 children less than 6 years of age with 50 days of prior FVIII exposure. 90% of the episodes were managed with one or two infusions and their response was rated excellent/good in 93.8% of episodes with a qualitative scoring method for a period of eight hours. Our study and the response scoring method was quantitative with extended observation time up to 24 hours [18].

In another long-term, multicenter study performed by Lusher et al. the safety, efficacy and rate of inhibitor formation of rFVIII B domain deleted (KogenateÒ) treating (PUPs) as a sole therapy was assessed. They used recovery and the subjective assessments using a five-point scale [23].

Apparently structural similarities such as prolonged assessment time and measuring recovery ratio between the mentioned study and ours is evident emphasizing on the importance of quantitative subjective scales.

Although it is difficult to overlook the small number of participants in this pilot study, the rigorous study design and the appropriate data analysis could compensate. On the other hand, since we studied previously treated patients, we were unable to evaluate the product's immunogenicity; the most challenging aspect of hemophilia treatment as this was the main reason for designing the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) currently under way. Due to small scale of this pilot study and lack of the power to recommend changes in clinical practice larger multicentre studies before launching the product to the market would be necessary.

Declaration of Conflicting Interests

This research was conducted upon the request of Food and Drug organization of ministry of Health and Medical Education of Iran. The research was financially supported by SAMEN Darou pharmaceutical company which were involved neither in the collection, interpretation, and analysis of the data nor in decision to write and submit of the report.

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