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

Eshghi P1, Abolghasemi H1, Malek F*,1, Naderi M3, Panahi Y2, Habibpanah B4, Fatohlahzadeh E4, Gorji F1

1. Pediatric Congenital Hematologic Disorders Research Center, Mofid Children’s Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Baqiyatallah University of Medical Sciences, Tehran, Iran
3. Zahedan University of Medical Sciences, Zahedan, Iran
4. Comprehensive Care Center for Children with Hemophilia, Mofid Children’s Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article History:
Received: 12.01.2015
Accepted: 06.07.2015

Keywords:
Hemophilia A
Plasma derived factor VIII
Recombinant factor
Safacto

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.

*Corresponding author: Malek F,
Email: fmalek7721@gmail.com

Please cite this article as: Eshghi P, Abolghasemi H, Malek F, Naderi M, Panahi Y, Habibpanah B, Fatohlahzadeh E, Gorji F. A Prospective Crossover Triple-Blind Controlled Trial on the Safety and Efficacy of Iranian Recombinant FVIII (Safacto®) Versus Plasma Derived FVIII; A Pilot Study. IJBC 2015; 7(4): 171-174.

Introduction

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

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. 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.

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. The available products are categorized into four generations of recombinant FVIII that are shown in table 1.
Parallel with the mentioned classifications few products were manufactured with deletion of the B domain which caused reduced immunogenicity. The CANAL trial revealed that FVIII products have a similar propensity to produce FVIII inhibitors as plasma derived.

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. 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). 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 hamster's ovary (CHO) purified with a synthetic ligand whose pharmacological characteristics were registered in the food and drug organization of Iran in 2012. 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. 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) 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 using 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. 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 19.

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 years (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 manifestated 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 1-37. 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) 16-21.

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,
herein 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,
and 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 (Kogenate®)
treating (PUPs) as a sole therapy was assessed. They
used recovery and the subjective assessments using a
five-point scale 21.

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)
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 (Kogenate®)
treating (PUPs) as a sole therapy was assessed. They
used recovery and the subjective assessments using a
five-point scale 21.

Apparent 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)
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.

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.
Acknowledgments
We are grateful to the staff of comprehensive care center for children with hemophilia, in Mofoò Children’s Hospital, Tehran, and Ali Asghar’s Children’s Hospital in Zahedan for their valuable contributions to this investigation.

References