Iranian Journal of Pharmaceutical Research (2016), 15 (2): 635-640
Received: September 2014
Accepted: January 2015

Original Article

Long Term Follow up Study on a Large Group of Patients with Congenital Factor XIII Deficiency Treated Prophylactically with Fibrogammin P®

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Abstract

Factor XIII deficiency (FXIIID) is an extremely rare hemorrhagic disorder with a prevalence of 1/3-5 million. Management of disease is performed by fresh frozen plasma (FFP), Cryoprecipitate (CP) or FXIII concentrate (Fibrogammin P®). Our objective was to assess safety and effectiveness of Fibrogammin P® in patients with FXIIID. For this purpose we designed this long-term follow up study on a large group of patients with FXIIID.

This prospective study was conducted on 213 patients with FXIIID since 2009 to 2013. Administrated dose for Fibrogammin P® according to clinical situations of patients ranged from 10 to 26 IU/kg every 4-6 weeks. All patients in 6-month intervals were checked for human immunodeficiency virus (HIV), hepatitis A, B and C viruses (HAV, HBV, HCV).

Twelve percent of participants had at least one ICH episode until 2008 but after administration of Fibrogammin P® did not have any major bleeding or episode of ICH, except in one patient. We also had 7 females with recurrent miscarriage that were managed successfully with a dose of 10 to 26 IU/kg every 4-6 weeks. This dose also was quite successful in management of major and minor surgery. None of the participants showed allergic reaction during treatment. A total of 7155450 IU of Fibrogammin P® were infused but nobody was positive for HIV, HAV, HBV, and HCV. We found that Fibrogammin P® is a safe and effective therapeutic choice in management of FXIIID.

Keywords: Factor XIII deficiency; Fibrogammin P®; Safety; Effectiveness.

Introduction

Coagulation factor XIII (FXIII) is a fibrin-stabilizing transglutaminase consisting of catalytic A subunits (FXIII-A) and carrier B subunits (FXIII-B). FXIII strengthens fibrin clot mechanically by cross-linking fibrin chains and also protects newly formed fibrin from the activated fibrinolytic system by binding α_2-plasmin inhibitor to the fibrin meshwork. Congenital FXIIID is a rare but severe and

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potentially life-threatening autosomal recessive bleeding disorder with a prevalence of one in 3–5 million people and affects people from all races and ethnics (1-3). The prevalence of the FXIIID in Iran, with about 473 patients, is 12-fold higher than the global frequency (1, 2). There is often a history of consanguinity within certain families of FXIII deficient patients. The disorder is associated with severe hemorrhage, spontaneous central nervous system (CNS) bleeding, spontaneous miscarriage, delayed wound healing and umbilical bleeding which presents a few days after birth. Patients with severe innate FXIIID usually present with plasma FXIII levels less than 1% and severe hemorrhagic episodes (3, 5). Due to the risk of ICH and other severe bleeding episodes, most patients receive regular prophylaxis replacement therapy. Due to the risk of blood born diseases, FFP and CP are less satisfactory for on-demand treatment or prophylaxis and FXIII concentrate is recommended whenever available (2-5). Half-life of FXIII is the longest among coagulation factors and it has been suggested that serum factor levels around 2-5% are sufficient to prevent spontaneous bleeding and to avoid the risk of early fetal loss (1-3).

FXIII replacement by Fibrogammin P®, a highly purified pasteurized (at 60 ˚C for 10 h) FXIII concentrate which derived from HIV-negative, pooled human plasma screened for common viruses, is used to treat hemorrhage, to prevent perioperative bleeding during elective operating procedures, or prophylactically to prevent recurrent bleeding (6-8). High rate of consanguineous marriage in Sistan and Baluchestan Province of Iran leads to increased prevalence of disorders which inherited in autosomal recessive pattern (1). It seems that the province has the largest population of patients with severe FXIIID around the world and these patients are available for long-term follow-up and there is no published evidence on the safety and efficacy of Fibrogammin P®. Of course this disease is also seen in other provinces such as Fars, and a total number of 8 patients are already registered in this province. Fibrogammin has been available since 2009 in Iran. The aim of this prospective study was to evaluate the tolerance, efficacy and safety of Fibrogammin P® (CSL-Behring, Marburg, Germany) for the management of patients with severe inherited FXIIID in Iran.

Experimental

Study design

For investigation of safety and effectiveness of Fibrogammin P®, we designed this prospective study, based on long term follow up of a large group of FXIIID patients receiving this product. The key elements in performing the study included determination of characteristics of study population at baseline, then assessment of clinical presentations among patients in each referral and finally assessment of safety and efficacy of prophylaxis treatment.

Characteristics of study population

This prospective study was conducted on 213 patients with severe FXIIID. Patients gave their written consent and the study was approved by the medical ethics committee of Zahedan and Shiraz Universities of Medical Sciences. Demographic data and previous medical history of all patients including age, gender, family history of bleeding disorders, and bleeding events was obtained from their medical files or by interview. Recorded database of patients with congenital FXIIID who were regularly referred to the referral hospitals and received Fibrogammin P® prophylactically since 2009 to 2013 was prospectively captured. Patients who had incomplete medical history, blood viral infection, and patients received prophylactic FFP or CP during the study were excluded.

Screening and diagnosis of FXIIID

Diagnosis of the disease was based on clot solubility test, family history and clinical presentations. Once a case referred to our hemophilia centers with hemorrhagic complications or a new born baby with positive family history of any bleeding disorder or hereditary coagulation factor deficiencies and accompanied by normal results of screening clotting tests, their samples underwent FXIII screening test (9).

Table 1. Frequency of clinical presentations in the studied population before administration of Fibrogammin P® (in each gender and in total patients).

Clinical presentation	Female (n)%	Male (n)%	Total (n)%
Umbilical bleeding	(88) 80%	(90) 87%	(178) 84%
Deep soft tissue Hematoma	(52) 47%	(56) 54%	(108) 51%
Prolonged wound Bleeding	(29) 26%	(32) 31%	(61) 29%
Intracranial bleeding	(10) 9%	(15) 15%	(25) 12%
Gum bleeding	(22) 20%	(16) 15%	(18)18%
Ecchymosis	(19)17%	(17)16.5%	(36) 17%
Epistaxis	(21)19%	(17) 16.5%	(38) 18%
Delayed post dental extraction bleeding	(10) 9%	(9) 9%	(19) 9%
Miscarriage	(7) 6%	-	(7) 3%
Post circumcision bleeding	-	(6) 6%	(6) 3%
Hemarthrose	(5) 5%	(3) 3%	(8) 4%
Post-surgical bleeding	(2) 2%	(4) 4%	(6) 3%
Prolonged menstrual bleeding	(1) 1%	-	(1) 0.5%
Subcutaneous bleeding	(2) 2%	(1) 1%	(3) 1.5%

Assessment of clinical bleeding episodes

After diagnosis of severe FXIIID, patients underwent prophylaxis or on-demand treatment in special conditions such as CNS bleeding, pregnancy, surgery and dental procedures. Administrated dose for Fibrogammin P® was based on clinical situation of patients. Administrated dose, duration of treatment, bleeding episodes, usage of parallel therapeutic agents and adverse events in the previous five years was recorded for each patient. Bleeding episodes of each patient at the baseline, and after each referral to receive prophylactic treatment during the 5 years of follow up were recorded. In our assessment epistaxis was defined as positive only when occurred spontaneously, from both nostrils, and did not stop with compression, lasted more than 10 min or medical intervention was inevitable. Post-surgery or circumcision hemorrhage was defined as positive when happened without trauma.

Due to high rate of bleeding episodes in severely deficient patients and the risk of CNS bleeding leading to death, there is no control group. Therefore historical records of bleeding episodes were used to compare bleeding frequencies prior to and during Fibrogammin P® prophylaxis.

Assessment of safety and efficacy of prophylaxis treatment

An adverse event was defined as any unexpected or critical symptom, sign, or laboratory finding temporally associated with Fibrogammin P® infusion regardless of causal relationship. A serious adverse event was defined as any untoward medical occurrence that resulted in life threatening and prolonged existing hospital care, or that resulted in significant disability or patients' death. Adverse events documented for this study were those that occurred within five years of Fibrogammin P® administration. Patients were also regularly (every 6 months) checked up for viral diseases including, HIV, HBV, HAV and HCV.

Data analysis was done by SPSS v. 17 (SPSS Inc., Chicago, IL, USA). We used mean and range for indicating the age of patients and percentage for showing the frequency of descriptive variables such as gender and clinical manifestations.

Results

Characteristics of subjects

The study involved 213 patients with severe FXIIID including 103 (48.4%) males and 110 (51.6%) females, which received Fibrogammin

Table 2. Comparison of the major clinical presentations in the studied population, before and after administration of Fibrogammin P®.

	Before administration of Fibrogammin P®	**After administration of Fibrogammin P®**
General manifestations	Major bleeding events such as umbilical bleeding (84%), hematoma (51%), ICH (12%), and miscarriage (6%of females) were detected among patients	No major bleeding event was observed except hematoma which was detected in few cases. Mainly minor bleedings such as epistaxis and gum bleeding were observed
ICH	At least one ICH episode was observed in 12% of patients	No episode of ICH or other major bleeding events was occurred, except in one who experienced ICH despite prophylaxis (14)
Recurrent miscarriage	Seven females had experienced recurrent miscarriages	No fetal loss was observed and patients had successful pregnancies

P® at least once during 5 years of study. The mean age of patients was 18.5 years (range, 1 year to 44 years). A positive family history was found in 74 patients (about 35%) with FXIIID. One patient had factor VII deficiency simultaneously with FXIII deficiency.

Clinical manifestations

ICH was the primary bleeding episode leading to detection of FXIIID in about 12% of patients (15 males and 10 females). The most frequent symptom among our patients was umbilical cord bleeding (84%). All the bleeding events of the studied population which was detected at baseline are indicated in table 1. Prospective study on these patients revealed that some clinical manifestations such as epistaxis and deep soft tissue hematoma occurred several times in most patients and they experienced these phenomena more than once. However intracranial bleeding occurred just once in the majority of patients which experienced this complication. ICH was the main cause of hospitalization and the first fatal presentation among our FXIII deficient patients. The areas involved were occipital, frontal and parietal. The mean age of ICH was 3.5 years old (minimum 7 months and maximum 42 years). We also had mental retardation and dysphasia in three patients.

Safety and efficacy outcomes

During the five years of study, the average administrated dose of Fibrogammin P® for prophylaxis treatment was 10 to 26 IU/kg every 4 – 6 weeks. Moreover on-demand therapy with required dose in 25 patients in special situations such as major bleeding episodes, surgery and delivery was another treatment regimen. The main manifestations of the study population, before and after administration of Fibrogammin P® are compared in Table 2.

None of the participants showed allergic reaction attributable to Fibrogammin P® infusion during treatment period.A total of 7155450 IU of Fibrogammin P® were infused during the time of study but our regular follow-up and periodic serological evaluations of HIV, HAV, HBV and HCV showed negative results for all patients.

Discussion

Current replacement therapy of FXIIID is limited to CP, FFP and FXIII concentrate (1, 2). This prospective study reporting a long time follow-up among patients with severe FXIIID, receiving FXIII replacement therapy with Fibrogammin P®, a highly purified virus inactivated plasma derived FXIII concentrate. Fibrogammin P® appears to carry low and negligible risk of viral transmission, unlike other unprocessed products containing FXIII (6-8). Published evidence on the safety or efficacy of Fibrogammin P® therapy mainly includes case reports, retrospective surveys or small series (6-8, 10, 11). In a retrospective study by Lusher *et al*. on seven subjects with congenital FXIIID receiving only Fibrogammin P® in a period of one year, it was revealed that the frequency of spontaneous bleeding events was significantly lower during prophylaxis with Fibrogammin P®

than prior of this regimen (p=0.01) (6). Another study reported by Dreyfus *et al*. on 19 severely FXIII deficient patients also resulted in a good or excellent efficacy of Fibrogammin P® in 95% of cases in duration of 12 months follow up. They also introduced Fibrogammin P® as a safe product (7). Although the same findings were obtained in our study, but it must be considered that we enrolled a large number of patients and followed them for a long period (5 years), which may lead to more reliable and accurate results. However in such studies, missing the subjects during the long time of follow up due to lack of cooperation, inappropriate referral intervals or even death of the patients, is a major limitation. Previously we had assessed safety of human blood products in rare bleeding disorders (RBDs) in a long period study and found that FFP and CP were safe in treatment of RBDs (12). This study was conducted pursuant to the previous study on a large group of patients with RBDs. FXIII deficient patients are the biggest group of patients with RBDs in southeast of Iran and comprise 78.6 % of all patients with RBDs (12). This large group of patients had a wide spectrum of clinical presentations. Like previous studies umbilical cord bleeding was the most common clinical presentation (5, 13). ICH was other common clinical manifestation which led to high rate of morbidity and mortality (14, 15). Among study patients with ICH, a positive history of death was observed in 72 percent (18 individuals). The most common cause of death among these individuals was CNS bleeding (61 %). Out of 11 deaths, 8 cases were because of FXIIID. The remaining three patients were suspected to FXIIID. These individuals were not diagnosed as FXIIID because they did not refer to physician for diagnosis of their disorder, but based of clinical presentations which stated by their parents and also because of positive family history and CNS bleeding was suspected to FXIIID. This high rate of morbidity and mortality in patients with FXIIID makes CNS bleeding our main concern. These patients were managed successfully by a dose of 10-26 IU/Kg of Fibrogammin P®. This dose was completely successful in the management of these patients, and prevented occurrence of ICH in all patients except in one. This patient was received up to 26 IU/Kg of Fibrogammin P® but even this relatively high dose was not sufficient for prevention of recurrent ICH. Genetic risk factors are important causes of therapeutic response. We previously assessed the relationship between genetic risk factors and occurrence of ICH (15). We found a strong relationship between TAFI Thr325Ile polymorphism and risk of ICH. In that study we had a patient with inappropriate therapeutic response to prophylaxis treatment which was homozygote for TAFI Thr325Ile polymorphism (15). We also managed our patients with miscarriage by Fibrogammin P® in a dose of 10-26 IU/Kg. Out of seven patients with miscarriage; one had experienced this phenomenon 11 times but after administration of Fibrogammin P® in a dose of 20 IU/Kg had experienced a successful delivery.

Allergic reaction was other complication of human plasma derived products but no allergic reaction was observed during or after infusion of Fibrogammin P®, and the concentrate was well tolerated without untoward side-effects. We previously assessed occurrence of allergic reaction in patients with FXIIID treated prophylactically with FFP and CP, and did not observe any allergic reaction (12). It seems that allergic reaction is not a usual complication among the recipients of plasma derivative components. Our present study also confirmed it and we did not observe any allergic reaction in patients received Fibrogammin P® as plasma derived concentrate.

Moreover during time of study our patients were checked up at regular intervals of six months for HIV, HCV, HAV and HBV. Lack of transfusion-related viral infection after administration of 7155450 IU of Fibrogammin P® shows the safety of plasma-derived FXIII concentrate in management of FXIIID. These results are in accordance with those of previous small series in other countries such as USA and France (6-8, 10, 16). A short term study by Diane Nugent *et al* on 41 patients with congenital FXIIID confirms our data. They found Fibrogammin as an effective therapeutic choice in management of congenital FXIIID. They also did not find any viral transmitted disease among their patients (16). Like our study, Diane Nugent *et al* found Fibrogammin an effective therapeutic choice in

management of major bleeding episodes, surgery and delivery (16).

The result of this study revealed that Fibrogammin P® is a safe and also an effective therapeutic choice in management of severe FXIIID.

References

(1) Dorgalaleh A, Naderi M, Hosseini MS, Alizadeh S, Hosseini S, Tabibian S, and Esghi P. Factor XIII deficiency in Iran: a comprehensive review of the literature. Semin Thromb Hemost. 2015 Apr; 41(3): 323-9.

(2) Naderi M, Alizadeh S, Tabibian S, Hosseini S, Varmaghani B, Shamsizadeh M and Dorgalaleh A. Effect of Social Factors on the Highest Global Incidence of Congenital Factor XIII Deficiency in Southeast of Iran. Arch Iran Med. 2015 May;18(5):331.

(3) Dorgalaleh A, Naderi M and Shamsizadeh M. Morbidity and mortality in a large number of Iranian patients with severe congenital factor XIII deficiency. Ann Hematol. 2016 Feb;95(3):451-5.

(4) Dorgalaleh A, Farshi Y, Alizadeh S, Naderi M, Tabibian S, Kazemi A and Hosseini S. Challenges in implementation of ISTH diagnostic algorithm for diagnosis and classification of factor XIII deficiency in Iran. J Thromb Haemost. 2015;13(9):1735-6.

(5) Dorgalaleh A, Tabibian S, Hosseini MS, Farshi Y, Roshanzamir F, Naderi M, Kazemi A, Zaker F and Noroozi Aghideh A. Diagnosis of Factor XIII Deficiency. Hematology. 2015(just-accepted):1-28.

(6) Naderi M, Reykande SE, Dorgalaleh A, Alizadeh S, Tabibian S, Einollahi N and Miri Moghddam E. Establishment of a prenatal diagnosis schedule as part of a prophylaxis program of factor XIII deficiency in the southeast of Iran. Blood Coagul Fibrinolysis. 2016;27(1):97-100.

(7) Lusher J, Pipe S, Alexander S and Nugent D. Prophylactic therapy with Fibrogammin® P is associated with a decreased incidence of bleeding episodes: a retrospective study. Haemophilia. (2010) 16: 316-21.

(8) Dreyfus M, Barrois D, Borg JY, Claeyssens S, Torchet MF, Arnuti B and Pautard B. Successful long-term replacement therapy with FXIII concentrate (Fibrogammin® P) for severe congenital factor XIII deficiency: a prospective multicentre study. Thromb Haemost. (2011) 9: 1264-266.

(9) Meyer M, Ostrowski S, Windeløv N and Johansson P. Fibrinogen concentrates for bleeding trauma patients: what is the evidence?. Vox Sang. (2011) 101: 185-90.

(10) Naderi M, Dorgalaleh A, Alizadeh S, Tabibian S, Hosseini S, Shamsizadeh M and Bamedi T. Clinical manifestations and management of life-threatening bleeding in the largest group of patients with severe factor XIII deficiency. Inter J Hemato. 2014;100(5):443-9.

(11) Sullivan AP, MacDonald J and Sheppard C. Long-Term Outcomes Of a Small Cohort At a Single Canadian Centre Of Severe Subunit A FXIII Deficient Patients (F13A1: c. 691-1G> A) Treated Prophylactically With Fibrogammin P. Blood. (2013) 122: 2360.

(12) Odame JE, Chan AK, Wu JK and Breakey VR. Factor XIII deficiency management: a review of the literature. Blood Coagul Fibrinolysis. (2014) 25: 199-205.

(13) Naderi M, Eshghi P, Saneei Moghaddam E. Alizadeh Sh, Dorgalaleh A, Younesi MR and Kashani Khateb Z. Safety of human blood products in rare bleeding disorders in southeast of Iran. Haemophilia. (2013): e90–2.

(14) Eshghi P, Abolghasemi H, Sanei-Moghaddam E, Anwar R, Jazebi M, Amid A and Ala FA. Factor XIII deficiency in south-east Iran. Haemophilia. (2004) 10: 470-72.

(15) Naderi M, Alizadeh S, Kazemi A, Tabibian S, Zaker F, Bamedi T and Dorgalaleh A. Central nervous system bleeding in pediatric patients with factor XIII deficiency: A study on 23 new cases. Hematology. 2015;20 (2):112-8.

(16) Naderi M, Dorgalaleh A, Alizadeh S, Kashani Khatib Z, Tabibian S, Kazemi A, Dargahi H and Bamedi T. Polymorphism of thrombin-activatable fibrinolysis inhibitor and risk of intracranial haemorrhage in factor XIII deficiency. Haemophilia. (2014) 20: e89-e92.

(17) Nugent D. Corifact/Fibrogammin(R) P in the prophylactic treatment of hereditary factor XIII deficiency: results of a prospective, multicenter, open-label study. Thromb Res. (2012) 130: S12-4.

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