Haemophilia
The Official Journal of the World Federation of Hemophilia,
European Association for Haemophilia and Allied Disorders and
the Hemostasis & Thrombosis Research Society

Haemophilia (2015), **21**, 481–489 DOI: 10.1111/hae.12655

ORIGINAL ARTICLE *Rare bleeding disorders*

Factor XI replacement for inherited factor XI deficiency in routine clinical practice: results of the HEMOLEVEN prospective 3-year postmarketing study

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Summary. Factor XI (FXI)-deficient patients may develop excessive bleeding after trauma or surgery. Replacement therapy should be considered in high-risk situations, especially when FXI levels are below 20 IU dL^{-1}. HEMOLEVEN is a human plasma-derived factor XI concentrate available in France since 1992, but there are few data regarding its use by physicians. This prospective study assessed the use, efficacy and safety of HEMOLEVEN in common clinical practice. HEMOLEVEN was evaluated in FXI-deficient patients in 13 French centres in a 3-year postmarketing study. Forty-four patients (30 females, 14 males) received 67 treatments. The median age was 37 years (8 months–91 years). Basal FXI levels were <1 to 51 IU dL^{-1} (median: 5.5); 29 patients were severely FXI-deficient (<20 IU dL^{-1}). FXI was administered prophylactically before 43 surgical procedures, 10 invasive procedures, 8 vaginal deliveries, or as curative treatment for six bleeds. The efficacy was assessed as excellent/good in 63, moderate in two and undetermined in two treatments. Seven patients experienced seven adverse effects, including two rated as serious: one sudden massive pulmonary embolism with fatal outcome and one case of inhibitor to FXI. HEMOLEVEN is effective for bleeding prevention in FXI deficiency. However, considering the benefit/risk ratio observed in relation to dosage in this study; firstly, it should be used sparingly due to its potential prothrombotic effect; secondly, new prescription procedures should be defined to adapt the dosage, especially in patients with intrinsic and/or acquired risk factors for thrombosis.

Keywords: factor XI, factor XI concentrate, factor XI deficiency

Introduction

Factor XI (FXI) deficiency is a rare autosomal coagulation disorder with an estimated prevalence of 1 in 1 000 000 individuals [1]. It is the second most commonly reported rare bleeding disorder according to the current global survey of the World Federation of Haemophilia [2]. This disorder is observed in many parts of the world and the incidence of severe form is very population dependent. Unlike haemophilia, the clinical manifestations of this disorder are generally mild [1,3,4]. Most severely FXI-deficient patients (FXI activity below 20 IU dL^{-1}) are at a higher risk of bleeding, but some patients shows no manifestations. On the other hand, some individuals with partial deficiency may develop haemorrhagic symptoms after injury or surgery. The bleeding history, the associated haemorrhagic (or prothrombotic) risk factors and the severity of the scheduled procedure must be considered when evaluating the need for FXI correction

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Accepted after revision 26 January 2015

[4,5]. For many years, fresh frozen plasma (FFP) was the only replacement treatment. However, since FXI levels in FFP are low and variable, large amounts of plasma are often required which may lead to volume overload [6,7]. In addition, FFP may carry the risk of allergic reactions and the potential for exposure to blood-borne infectious agents. Therapeutic infusions of FXI concentrate are commonly used in some countries. Two human plasma-derived FXI concentrates are currently available: one with a marketing authorization since 1998 held by LFB Biomedicaments, LesUlis, France (HEMOLEVEN), and the other manufactured by BioProducts Laboratory, Elstree, UK and delivered under compassionate use. A postmarketing study was conducted in France on patients treated with HEMOLEVEN to document treatment practices.

Patients and methods

Study population

This study was a prospective, multicentre, observational, non-interventional study conducted from November 2006 to November 2009. Patients with inherited FXI deficiency of any gender, age or disease severity, previously treated or untreated with FFP or a FXI concentrate were eligible if replacement therapy was planned. The investigator reported the bleeding history and exact cumulative exposure days to FXI replacement (concentrate and/or FFP) as well as any inhibitor observed. Clinical and biological follow-up was conducted according to the routine procedures in each centre. The same patient could experience more than one therapeutic situation. The detailed daily replacement therapy and laboratory parameters as well as concomitant medications (i.e. antifibrinolytic drugs used at any time, heparin or other thrombo-prophylactic agents) were recorded.

Treatment

HEMOLEVEN is a highly purified human coagulation FXI (100 U mL^{-1}) prepared in France from donor plasma since 1992. Several reports on its use have been published [8–10]. The concentrate is manufactured using a filter adsorption step followed by chromatography on a cation-exchange resin [11]. Virus elimination/inactivation relies on a combination of solvent/detergent and nanofiltration (15 nm filter) procedures [12]. Human antithrombin (4 IU mL^{-1}), sodium heparin (4.5 IU mL^{-1}) and C1 esterase inhibitor (2.6 U mL^{-1}) are added as stabilizers and to protect against *in vitro* FXI activation during manufacturing. The dosage was determined by the treating physician based on the Summary of Product Characteristics (SmPC) that recommends therapeutic FXI levels of approximately 30–40% (0.3–0.4 IU mL^{-1} of plasma). Normal recovery is estimated at 2 U dL^{-1} per U kg^{-1} [9]; thus, for severe deficiency patients, this corresponds to a dose of about 15 U kg^{-1}. For lower recovery, the dose should not exceed 30 U kg^{-1} to prevent the risk of thrombosis [13,14]. In addition, injections more often than every 48 h are not necessary due to the long FXI half-life of 45.5 ± 7.9 h in plasma [9].

Efficacy assessment

The investigators rated the efficacy of HEMOLEVEN for overt bleeding or for prophylaxis in surgery, childbirth or invasive procedures as excellent (haemostasis similar to that expected for normal individuals), good (slightly excessive bleeding at the surgical incision), moderate (moderately excessive bleeding) or none (severe uncontrolled bleeding).

FXI:C incremental recovery (IR) was calculated based on the preinfusion plasma levels and the 0.5-h postinfusion level, in the absence of bleeding and not during pregnancy, as follows:

$$\text{IR (IU dL}^{-1}\text{)/(U kg}^{-1}\text{)} = \frac{\text{(Factor XI rise) (IU dL}^{-1}\text{)} \, x \, \text{Weight (kg)}}{\text{Factor XI dose (U)}}$$

Safety assessment

Safety was evaluated based on adverse events (AEs) suspected to be related to the study drug or not, occurring within 10 days of administration and corresponding to about five half-lives of the protein. In addition, all serious AEs (SAEs), regardless of their relationship with the study drug, were also reported. Death or life-threatening complications, congenital abnormality in the new-born, permanent or transient significant disability, hospitalization or prolongation of hospitalization, medically significant AEs (including inhibitor development) considered as SAEs. The investigator rated the relationship with the study product as "not related", "doubtful", "possible" or "probable".

Both the monitoring schedule and the frequency of inhibitor testing were determined by the treating physician. All these tests were performed by the local laboratories at each participating centre.

Statistical analysis

The results were analysed descriptively. Quantitative variables were expressed in terms of mean ± standard deviation (SD), median, minimum and maximum. Qualitative variables were summarized using frequency tables. The percentage of responses judged to be either excellent or good was presented. Where

useful, the confidence interval (CI) using the exact method and the *P*-value (*P*; considered significant when <0.05) were provided.

Ethics

This study was approved by the French Advisory Committee for the Treatment of Data for Health Research (CCTIRS) and the French Data Protection Committee (CNIL). This work was conducted in accordance with Good Clinical Practice Guidelines (ICH E6) with strictly controlled data collection procedures. Written informed consent was obtained from each participating patient.

Results

Population characteristics and HEMOLEVEN use

Our study enrolled a total of 44 patients. The baseline characteristics of the study population are shown in Table 1. The median age was 37.5 years and nine patients were over 65 years old. There was a female predominance (68%). The median body weight was 67 kg (range: 9–97) and six of 36 patients had a body mass index (BMI) of 30 kg m^{-2} or more. FXI activity ranged from <1 to 51 IU dL^{-1} (median: 5.5) and 29 (66%) patients had severe FXI deficiency (<20 IU dL^{-1}).

Thirty-one (70.5%) patients had a history of haemorrhage with an equal proportion between those with FXI levels higher or lower than 20 IU dL^{-1}. About 30% of patients in each category had required at least one red blood cell transfusion. One patient had a history of allergic reaction to FFP.

This 3-year study documented 67 different clinical situations in the 44 patients treated with HEMOLEVEN in the 13 participating French centres. Patients received HEMOLEVEN for surgical procedures including caesarean sections (43), invasive procedures (10), vaginal deliveries (8) or bleeding episodes (6). Most procedures (29 of 43, 67.4%) were performed in severe FXI-deficient patients. The total dose per patient ranged from 93 IU (one infusion in an infant) to 22 700 IU administered as 22 infusions in a 36-year-old patient with a retroperitoneal haematoma (15 infusions) related to a pancreatic cyst removed 3 months later (7 infusions). The dosing for each clinical situation is given in Table 2. Overall, the median infusion dose per episode was 18.0 U kg^{-1} (mean 18.7) and the median number of infusions per episode was 1.0 (mean 2.1). One single dose was sufficient in 37 of 67 (55.2%) episodes. Fifteen episodes including one vaginal delivery involved six obese patients, and were treated at a median infusion dose of 20.9 U kg^{-1} (range: 10.4–31.3). Of the 143 infusions administered, 55 (38.5%) were given at a dose ≤15 U kg^{-1}, 49 (34.3%) from 16 to 20 U kg^{-1}, 30 (21.0%) from 21 to 30 U kg^{-1}. In nine instances, an infusion above 30 U kg^{-1} (up to 38.7 U kg^{-1}) was used because the full content of vial was infused, or the exact content of the vial was unidentified. The concomitant treatments during surgery included 40 mg per day enoxaparin in 10 procedures (23.3%) and tranexamic acid in 11 procedures either in association with FXI (eight procedures, 18.6%) or later (three procedures, 7.0%).

The surgeries and treatments in 31 patients with basal FXI levels below (n = 22) or equal or above (n = 9) 20 IU dL^{-1} are shown in Table 3 and Table 4 respectively. The mean preoperative bolus dose for 29 surgeries in severe patients was 21.3 U kg^{-1} (median: 20.5, range: 9.3–34.0). As expected, dosing was lower in patients with basal FXI levels >20 IU dL^{-1} (mean: 16.9 U kg^{-1}, median: 16.6 U kg^{-1}, range:

Table 1. Patient characteristics at baseline (n=44).

Variable	Value	
Age (years)	Mean (SD)	43.3 (22.6)
	Median (min–max)	37.5 (8 months-91)
Gender		
Male	*n* (%)	14 (32)
Female	*n* (%)	30 (68)
BMI (kg m^{-2}) (n = 36)	Mean (SD)	25.0 (5.1)
	Median (min–max)	24.3 (14–40)
FXI activity levels (IU dL^{-1})	Median (min–max)	5.5 (<1–51)
FXI activity levels [*n* (%)]	<5 IU dL^{-1}	20 (46)
	5–20 IU dL^{-1}	9 (20)
	21–30 IU dL^{-1}	5 (11)
	31–40 IU dL^{-1}	8 (18)
	>40 IU dL^{-1}	2 (5)
Circumstances of diagnosis [*n* (%)]	Known family history of FXI deficiency	8 (18)
	Fortuitously during haemostasis work-up	22 (50)
	Secondary to excessive bleeding	12 (27)
	Unknown	2 (5)
Patients with bleeding history	*n* (%)	31 (70.5)
Patients requiring at least one red blood cell transfusion during life	*n* (%)	13 (29.5)

Table 2. Use of HEMOLEVEN in our cohort of FXI-deficient patients.

Factor XI concentrate usage (n: episodes; N: patients)	Infusion dose (U kg^{-1})	Number of infusions	Total dose (U kg^{-1})	Time between infusions if >1 infusion (h) (number of infusions)
Haemorrhages* (n = 6, N = 6)	17.5 [10.8–22.0]	2.5 [1–15]	45.5 [10.8–254.2]	48 [43–96] (21 infusions)
Surgery (including caesarean section) (n = 43, N = 31)	16.9 [9.3–34.0]	2.0 [1–7]	28.9 [9.6–148.4]	48 [5–192] (50 infusions)
Invasive procedures† (n = 10, N = 8)	19.6 [10.4–25.8]	1.0 [1–2]	19.6 [10.4–50.0]	47 [47–47] (1 infusion)
Vaginal deliveries (n = 8, N = 7)	19.5 [13.1–38.7]	1.0 [1–3]	31.1 [13.1–76.5]	24 [5–48] (4 infusions)
Vaginal/caesarean deliveries combined‡ (n = 13, N = 12)	18.8 [11.6–38.7]	1.0 [1–3]	32.1 [13.1–76.5]	36 [5–77] (8 infusions)
All (n = 67, N = 44)	18.0 [9.3–38.7]	1.0 [1–15]	26.4 [9.6–254.2]	48 [5–192] (76 infusion)

Results are expressed as median values with range in parentheses. *N* represents the number of patients and n represents the number of episodes.
*Bleeding symptoms reported during or after procedures without haemostatic cover [port-a-cath installation (1), caesarean section (1), postdelivery haemorrhage (1)] and spontaneous or trauma-induced bleeding [gastrointestinal tract haemorrhage (1), retroperitoneal haematoma (1), posttrauma elbow haemarthrosis (1)].
†Oesogastroscopy + colonoscopy (1), colonoscopy (1), bone marrow biopsy (2), drain mobilization (2), knee arthroscopy (1), ventriculography (1), epidural catheter ablation (1), knee infiltration (1).
‡13 separate childbirths including five caesarean section and eight vaginal deliveries.

9.6–32.3 U kg^{-1}). Three quarters of the preoperative infusions were performed within 3 h before the procedure. For other infusions, postponement of the procedure up to 14 h after infusion was often due to technical reasons in case of caesarean sections. One 81-year-old patient (UPN 35-02) was treated 13 h before surgery to reduce the thrombosis risk for total hip prosthesis. In 22 of 43 procedures, subsequent postoperative doses (mean: 16.0 U kg^{-1}, median: 14.4 U kg^{-1}, range: 9.3–29.7 U kg^{-1}) were administered every 48 h (range: 5.0–191.5 h) to maintain haemostasis.

Individual pre- and postinfusion levels were determined for 11 surgeries in seven patients with severe FXI deficiency. In this setting, a dose ranging from 12.9 to 33.1 U kg^{-1} (median: 18.5) increased plasma levels between 26 and 62 IU dL^{-1} (median: 31). In seven surgeries in five patients with basal FXI:C levels >20 IU dL^{-1}, the peak levels were higher (62 IU dL^{-1}, range: 30–81), suggesting that the dose (median: 19.6 U kg^{-1}, range: 10.7–32.3) was not adjusted to reach recommended target levels.

Efficacy

Haemostatic efficacy was documented in 65 of 67 episodes and was excellent (58) or good (5) in 63 of 65 cases (96.9%, 95% CI: 89.3 to 99.6%). Efficacy was rated as moderate for the curative treatment of two serious bleeding episodes. The first was a digestive tract haemorrhage (haemoglobin 6.8 g dL^{-1} at admission) in an 81-year-old patient with FXI level <1 IU dL^{-1} who required transfusion and five injections at 14 IU kg^{-1}, and the second was a posttraumatic elbow haemarthrosis in a 7-year-old patient with FXI level of 3 IU dL^{-1} requiring four injections at 22 IU kg^{-1}. The outcome of all surgeries was excellent (93%) or good (7%) (95% CI: 73.5–100.0%). It is noteworthy that there were no excessive bleeds during the operation in six severe FXI-deficient patients who received the lowest preoperative doses (15 U kg^{-1} or less) for eight surgeries. However, reduced haemoglobin levels required transfusion on the third postoperative day due to a large haematoma of the operative scar in an 81-year-old patient who underwent a right total hip arthroplasty (UPN 35-02) after a single dose of 15 U kg^{-1}. RBC units were transfused during surgery on four other occasions due to significant haemoglobin decreases, either the day of the procedure (pancreatic cyst excision (UPN 04-01), hepatectomy (UPN 34-05) and aortic valve replacement (UPN 20-01) or the day after (left total hip arthroplasty, UPN 35-02) (Table 3). Response to HEMOLEVEN was not documented in two cases because of a concomitant confounding haemorrhagic factor: uterine atony following caesarean section (UPN 36-09) and postpartum haemorrhage leading to the use of concomitant other curative treatments (UPN 36-03).

FXI recovery could only be evaluated in 12 patients at baseline, as most patients did not have both pre- and postinfusion sampling. Median incremental recovery measured within 2 h post infusion was 2.0 IU dL^{-1} per U kg^{-1} (range: 0.7–2.2). The results were comparable between obese and non-obese patients (2.1 IU dL^{1} per U kg^{-1} vs. 1.9 IU dL^{-1} per U kg^{-1}).

Safety

The study follow-up varied between 4 days and 31 months and the median treatment exposure per patient was 2 days (range: 1–22 days). Seven AEs in seven of 44 patients (15.9%) were attributed to HEMOLEVEN. Five of these AEs, rated as mild or moderate, resolved promptly and spontaneously: vertigo, pain at the injection site, pain in extremity, D-dimer increase. No biological signs of DIC or clinical symptoms suggesting thrombosis were reported in the obstetrical context. A total of 12 pregnant women received replacement therapy prior to 13 live births and no detectable deleterious effects were observed in the neonates.

Table 3. Use of HEMOLEVEN during surgery (n = 29) in 22 FXI-deficient patients with a basal factor XI level <20 IU dL^{-1}.

Intervention	UPN	Gender, Age, Level (IU dL^{-1})	Number of doses		First infusion dose (U kg^{-1})	T0.5 h Postinf. levels	Efficacy rating	Side effects	RBC units (day of transfusion)	Tranexamic acid (days of treatment)
			Presurgery	Post surgery						
Orthopaedic surgery										
Total right hip prosthesis	35-02	M, 81 y., <1	1	0	15	26[†]	Excellent	High DD	Yes (D3)	No
Total left hip prosthesis	35-02	M, 82 y., <1	1	1	13	29	Excellent	No	Yes (D2, D13)	No
Osteotomy for hallus valgus	14-01	F, 47 y., <1	1	4	21		Excellent	No	No	No
Repair tendons left thumb	14-02	F, 59 y., <1	1	1	21		Excellent	No	No	No
Cardio surgery										
Atrial septal defect	23-01	F, 48 y., 5	1	0	15		Excellent	No	No	No
Atrial septal defect	34-01	F, 16 y., 5	1	6	28	62	Excellent	No	No	No
Aortic valve bioprosthesis	20-01	F, 78 y., 2	1	4	29	28	Excellent	No	Yes (D1)	Yes (D1)
Dental										
Extraction of 4 wisdom teeth*	21-01	F, 17 y., 8	1	1	17		Excellent	No	No	Yes (D-2:D10)
Tooth extraction*	14-06	F, 91 y., <1	1	0	25		Excellent	No	No	Yes (D2:D12)
Tooth extraction*	14-07	F, 54 y., 3	1	0	27		Excellent	No	No	Yes (D1:D10)
Obstetric, Gynaecological and abdominal surgery										
Caesarean*	38-02	F, 24 y., 6	2	0	16, 7		Excellent	High DD	No	No
Caesarean*	38-01	F,27 y., <1	1	0	19		Excellent	Vertigo	No	No
Caesarean*	34-02	F, 28 y., 6	1	2	19	41	Excellent	No	No	Yes (D1:D10)
Caesarean*	03-01	F, 32 y., <1	1	1	25		Excellent	No	No	No
Therapeutic abortion*	17-02	F, 35 y., 6	1	0	20		Excellent	No	No	Yes (D2:D3)
Hernioplasty	22-04	M, 50 y., 1	1	2	9		Excellent	Inhibitor	No	No
Excision of pancreatic cyst	04-01	M, 37 y., 4	1	6	19		Good	No	Yes (D1)	No
Abscess of abdominal wall	34-02	F, 26 y.,6	1	0	31		Excellent	No	No	No
Debridement pericicatricial abscess	34-02	F, 26 y., 6	1	0	21	45	Excellent	No	No	No
Neurosurgery										
Neurolysis of cubital & median nerves	34-03	M, 79 y., 3	1	0	14	28	Excellent	No	No	No
Neurolysis of pudendal nerve	38-03	M, 57 y., 2.5	1	0	22	48[†]	Excellent	Thrombosis	No	No
Subthalamic electrodes Implantation	14-03	M, 50 y., 10	1	0	34		Excellent	No	No	No
Tunnelled stimulator placement	14-03	M, 50 y., 10	1	3	34		Excellent	No	No	No
Ophthalmological and ENT surgery										

Table 3. (continued).

Intervention	UPN	Gender, Age, Level (IU dL^{-1})	Number of doses		First infusion dose (U kg^{-1})	T0.5 h Postinf. levels	Efficacy rating	Side effects	RBC units (day of transfusion)	Tranexamic acid (days of treatment)
			Presurgery	Post surgery						
Macular hole	17-01	F, 72 y., <1	1	0	13		Excellent	No	No	No
Strabismus	34-01	F, 14 y., 5	1	0	33	59	Excellent	No	No	No
Ectropion right eye	35-03	M, 83 y., 1.1	1	0	13	31	Excellent	No	No	No
Incision eyelid	35-03	M, 83 y., 1.1	1	1	13	28	Good	No	No	No
Tonsillectomy*	17-03	M, 4 y., <1	1	4	25		Excellent	No	No	Yes (D3:D10)
Vascular										
Stripping left great saphenous vein	14-02	F, 58 y, <1	1	1	23		Excellent	No	No	No

M, Male; F, Female; y., years; D1, Day of surgery; RBC, Red Blood Cells; DD, D-dimer.
*Surgery at a site with fibrinolytic activity.
†Blood sample drawn within 2 h post infusion.

Table 4. Use of HEMOLEVEN during surgery (n = 14) in nine FXI-deficient patients with a basal factor XI level >20 IU dL^{-1}.

Intervention	UPN	Gender, Age, Level (IU dL^{-1})	Number of doses		First infusion dose (U kg^{-1})	T0.5 h Postinf. levels	Efficacy rating	Side effects	RBC units (day of transfusion)	Tranexamic acid (days of treatment)
			Presurgery	Post surgery						
Cardio surgery										
Aortic valve replacement	34-05	M, 66 y., 22	1	1	23	62	Excellent	No	No	No
Dental										
Multiple wisdom tooth extraction*	23-02	M, 80 y., 29	1	0	10		Excellent	No	No	No
Obstetric, Gynaecological and abdominal surgery										
Hysterectomy*	36-08	F, 40 y., 37	1	1	20	56†	Excellent	No	No	Yes (D1:D10)
Laparotomy with pelvic surgery*	36-05	F, 61 y., 38	1	1	14	81	Good	No	No	No
Correction of annexal torsion on ovarian cyst by coelioscopy		F, 31 y., 38	1	0	13		Excellent	No	No	No
Caesarean*	36-09	F, 29 y., 41	1	0	32	77	NA	No	Yes (D1)	Yes (D1)
Liver biopsy	34-05	M, 65 y., 22	1	0	11	30	Excellent	No	No	No
Hepatectomy	34-05	M, 66 y., 22	1	3	22	68	Excellent	No	Yes (D1)	Yes (D1:D11)
ENT surgery										
Ethmoidectomy	22-03	F, 25 y., 31	1	1	20		Excellent	No	No	Yes (D1:D2)
Ethmoidectomy	22-03	F, 26 y., 31	1	1	20		Excellent	Site pain	No	No
Tympanoplasty	22-01	M, 60 y., 35	1	3	12	43†	Excellent	No	No	No
Tympanoplasty/ ossiculoplasty	22-01	M, 61 y., 35	1	1	10		Excellent	No	No	No
Urological										
Endoscopic urethrotomy*	23-02	M, 80 y., 29	1	0	12		Excellent	No		
Vascular										
Stripping of varices	35-01	F, 49 y., 35	1	0	17		Excellent	No	v	

M, Male; F, Female; y., years; D1, Day of surgery; RBC, Red Blood Cells.
*Surgery at a site with fibrinolytic activity.
†Blood sample drawn within 2 h post infusion.

Two of seven AEs fulfilled the criteria for SAEs. In the first case (UPN 38-03, Table 3), acute non-febrile respiratory distress associated with agitation appeared about 15 h after the HEMOLEVEN infusion and 7 h after a neurosurgical procedure, causing the death of the patient. Unfortunately, no autopsy was performed.

The most plausible explanation was massive pulmonary embolism according to the local investigator. An expert committee was not able to draw any firm conclusion regarding the pathophysiology of this event, i.e. thrombotic vs. non-thrombotic (fat embolism). This patient cumulated several thrombotic risk factors (obesity: 30 kg m^{-2}, elevated baseline factor VIII level (180 IU dL^{-1}), air travel and large fatty tissue around large pack of varicose veins), although no hereditary biological abnormality predisposing to thromboembolism was detected retrospectively using a preoperative frozen plasma. Considering these data, this SAE was rated as a possibly drug related. In the second case (UPN 22-04), an inhibitor to FXI was diagnosed 3 months after an inguinal hernia surgery. This patient was homozygous for a FXI null mutation (C118X in exon 5). The inhibitor was undetectable 1 year later, but an anamnestic response upper than 500 BU after a new administration for surgery was reported to the pharmacovigilance unit after the end of the study.

Discussion

We report here a large prospective series investigating routine use of a human plasma-derived FXI concentrate in FXI-deficient patients including numerous patients with severe defect. Only case reports with HEMOLEVEN or limited series with BPL concentrate have been published so far [15–19]. FXI concentrates are of special interest considering their reduced volume compared with FFP and their reduced risk of viral transmission or clinical intolerance [6,7]. We acknowledge the limitations of this observational study and in particular the lack of homogeneity in the use of HEMOLEVEN and its biological monitoring. Our major aim was to evaluate this concentrate in routine practice after more than 15 years of commercial availability for an orphan disease.

This work confirms previous data regarding the efficacy of HEMOLEVEN obtained from 31 French patients [9]. The recovery here was 2.0 IU dL^{-1} U kg^{-1}, which is in accordance with the SmPC. The circumstances of use varied either for preventing haemorrhages in invasive procedures, or more rarely for treating overt bleeding episodes. Expected haemostasis was obtained in 93% of the procedures. Of note, the two patients who achieved only a suboptimal response presented with particular clinical conditions: a GI haemorrhage whose management is not restricted to the use of HEMOLEVEN and a joint bleeding which is not a feature of FXI deficiency. Tranexamic acid was given on 11 occasions concurrently or apart from the FXI concentrate to control mucosal bleeding. There may have been possible unnecessary use of HEMOLEVEN in a significant fraction of our patients, especially in those who were non-severely deficient and had no past history of bleeding after surgical challenges. It is now well established that FXI concentrate infusions are not recommended for dental extractions, and tranexamic acid is the therapy of choice even in severe deficiency [20]. Here, pregnant women who had previously experienced postdelivery bleeding did not develop any haemorrhagic complication under HEMOLEVEN. Kadir *et al.* reported no significant modifications in FXI:C levels during pregnancy in eight FXI-deficient women [21]. However, prophylactic therapy for vaginal delivery might not be mandatory in FXI-deficient patients. Salomon *et al.* reported a low frequency of bleeding complications after delivery in severe deficient patients. Of the 62 women who underwent 139 vaginal and 13 caesarean deliveries, 43 (69%) did not develop any postpartum bleeding [22]. Perioperative haemostasis was achieved with doses as low as $\leq$15 U kg^{-1} either in severe or in non-severe patients, except in one elderly patient undergoing orthopaedic surgery. Therefore, considering the risk of coagulation overstimulation and thrombosis, our experience does not support the use of higher dosages. We postulate that physiological changes during surgery, for example, platelet activation, could also contribute to haemostasis. Replacement therapy in patients with severe FXI deficiency contributes to normal haemostasis by increasing the thrombin burst.

The coagulation activation following infusion of concentrates in FXI-deficient individuals has been reported using a series of markers: prothrombin fragment 1 + 2 (F1 + 2), thrombin-antithrombin complex (TAT) and fibrinopeptide A [16,23]. Delayed signs of secondary fibrinolysis (D-dimer and plasmin–antiplasmin complex elevations) were also observed [16]. FXI concentrates have been associated with increased risk of consumptive coagulopathy [8,13,14,16,23] or thromboembolic events [17]. The sudden presumed pulmonary embolism with fatal outcome immediately after surgery in one patient receiving a dose (21.6 U kg^{-1}) below the upper limit of 30 U kg^{-1} is a matter of concern and underscores the need to reassess the treatment recommendations and the benefit/risk ratio. Multiple environmental thromboembolic risk factors were present in this patient who probably presented an early pulmonary embolism. Unfortunately, in the absence of postmortem investigations, no formal conclusion about the cause of this fatal event can be drawn. Boehlen *et al.* reported recently a similar thrombotic complication following bariatric surgery in an obese patient (BMI 41.9 kg m^{-2}) who received 27 U kg^{-1} before intervention [25]. These cases were included in a recent update on the risk of thrombosis associated with the FXI concentrate published by Bolton-Maggs *et al.* [29]. In this review, a total of 12 thromboembolic events with HEMOLEVEN have

been reported to LFB from 2002. In the previous French series of 31 patients undergoing 33 procedures with the pure FXI concentrate and evaluated using a questionnaire sent to physicians in 1995, biological DIC was observed in three individuals (one of whom developed venous thrombosis and pulmonary embolism 10 days later) [9]. Of interest, these three patients who received HEMOLEVEN before 1994 were over 60 years old and the first infusion dose exceeded 40 U kg^{-1}. These events led to definition of 30 U kg^{-1} as the recommended upper safety limit. In our series, the dose administered was <30 U kg^{-1} in 94% of the infusions (134/143). Among 25 patients submitted to 45 haemorrhagic challenges, the BPL FXI concentrate induced serious AEs in three individuals as reported by Collins *et al.* in 1995: one death of myocardial infarction in a patient with a previous history of cardiovascular disease, a transient ischaemic heart episode and a delayed bilateral pulmonary embolism after a prolonged course of concentrate administration [17]. In this cohort, the dose was double in comparison with that used in our study suggesting a tendency to dose reduction over time. We did not see any thrombotic complication after hip replacement which is considered as a high-risk situation for thromboembolism. Santoro *et al.* described the successful use of repeated low doses (10–15 U kg^{-1}) of HEMOLEVEN, a first dose of 15 U kg^{-1} 12 h before and three doses of 10 U kg^{-1} every 3 days after hip arthroplasty without any complication [19]. In our study, thromboprophylaxis was used mainly in orthopaedic and abdominal surgery (10 procedures).

We report here a specific high-titre FXI inhibitor that developed after three consecutive infusions in a previously untreated patient. Without reintroduction, the inhibitor was undetectable and these patients should most likely be identified before major surgery. A similar complication was described previously in response to replacement therapy with FFP [24]. In contrast to the aforementioned study, the involved mutation is not described in association with inhibitor formation [26]. This complication is recognized in patients with stop codon mutations and this is another reason for avoiding FXI-containing therapies.

This longitudinal study has greatly improved our policy for the management of FXI-deficient patients in various therapeutic situations. Overall, considering the physiology of FXI [27] and the thrombosis risk associated with either high FXI levels in the normal population [28] or infusion of FXI concentrates in deficient individuals [13,16,17, 29], innovative uses of HEMOLEVEN need to be developed if the replacement therapy with FXI concentrate is essential. First, the traditional dose of 20–30 U kg^{-1} is probably excessive and 10–15 U kg^{-1} could suffice in most cases [10,19]. Second, the timing of injection should be reconsidered in light of the D-dimer kinetics and long half-life of FXI [19]. HEMOLEVEN must be used with caution in patients with significant risk factors for thromboembolism and activated states of coagulation [16,23,29]. Screening for early biological signs of DIC is strongly recommended, especially for surgical procedures and in high-risk patients such as obese or elderly patients, and pregnant women. For surgery, thromboprophylaxis must be given according to the local guidelines in both deficient and non-deficient individuals. HEMOLEVEN is a powerful tool for protecting against bleeding; however, the potential risk of thrombosis is a major issue that should not be neglected. Our data argue in favour of low doses to reach recommended FXI levels of 30–40 IU dL^{-1}. Based on the recent revised guidelines [29], the benefit/risk ratio of HEMOLEVEN could be improving. In summary, this FXI concentrate should be used sparingly. The potential haemostatic benefits of use must be weighted and management must be tailored to each individual patient.

Acknowledgements

CC, CH, FBr, JG, FBa and ER designed the study. FBa, ER, CBN, MT, PB, AF, JP, JY, and PC included patients, collected their own data and critically read the manuscript. FBa, JG and FBr analysed the results and wrote the manuscript.

Disclosures

ER has received support for attending scientific meetings and honoraria (speaker fees) from LFB. PB has received financial support from LFB for conference attendance and previous studies as investigator. JG has received support for attending scientific meetings and honoraria (speaker fees, consultant and advisory board) from Baxter, LFB, Bayer, NovoNordisk and Pfizer. CC, FBr and CH are employees of LFB. The other authors stated that they had no interests which might be perceived as posing a conflict or bias.

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