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Fibrinogen concentrate for bleeding in patients with congenital fibrinogen deficiency: Observational study of efficacy and safety for prophylaxis and treatment

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Abstract

Background: Congenital fibrinogen deficiency (CFD) is a rare bleeding disorder characterized by reduced levels (afibrinogenemia, hypofibrinogenemia) or dysfunctional fibrinogen (dysfibrinogenemia), for which fibrinogen supplementation is the mainstay treatment.

Objectives: To assess the efficacy and safety of human fibrinogen concentrate (FCH) in patients with CFD.

Methods: This was a multicenter, noninterventional, retrospective cohort study with a 12-month prospective follow-up period in the United States and Canada. Individuals with CFD who received FCH for the treatment of bleeding, perioperative hemostasis, or prophylaxis were included. Data were collected retrospectively from medical records and every 3 months during the prospective period. Hemostatic efficacy was rated by the investigators as effective or ineffective using a 4-point efficacy scale. Annualized bleeding rate (ABR) was summarized for patients who received FCH for routine prophylaxis.

Results: Twenty-two patients were enrolled. FCH treatment was rated effective in treating ≥97.0% of bleeding events, in the retrospective and prospective periods. FCH was effective for perioperative hemostasis in ≥97.5% of minor and major surgeries across both periods. In patients treated with FCH for routine prophylaxis, the median ABRs for the retrospective and prospective period were 1.4 and 1.3, respectively. One adverse event (AE), thrombosis of the right cephalic vein, was reported as related to FCH treatment and resolved with a short course of anticoagulant. No serious AEs related to FCH or deaths were reported.

Conclusions: In patients with CFD, FCH is a well-tolerated and effective treatment to achieve hemostasis during bleeding events and surgery and associated with infrequent bleeding events when used prophylactically.

KEYWORDS
afibrinogenemia, congenital hypofibrinogenemia, fibrinogen, hemorrhage, hemostasis, observational study

Essentials

- Fibrinogen concentrate (FCH) is indicated for treatment of congenital fibrinogen deficiency.
- FCH efficacy and safety were assessed in an observational retrospective and prospective study.
- FCH is effective for treating bleeding events during surgery and for prevention of bleeding.
- The safety profile of FCH was favorable and consistent with previous clinical studies.

1 | INTRODUCTION

Congenital fibrinogen deficiency (CFD) encompasses a group of rare hereditary coagulation disorders, characterized by bleeding symptoms resulting from reduced levels of plasma fibrinogen (afibrinogenemia and hypofibrinogenemia, defined by quantitative deficiency) and/or impaired function (dysfibrinogenemia and hypodysfibrinogenemia, defined by qualitative defects) due to mutations in the fibrinogen genes located on chromosome 4.[1-4]

Patients with afibrinogenemia have a complete absence of fibrinogen associated with umbilical cord bleeding and variable, often severe spontaneous bleeding and significant risk of intracranial hemorrhage.[2-4] Hypofibrinogenemic patients have fibrinogen levels of <1.5 g/L and usually remain asymptomatic, depending on fibrinogen level; however, they are vulnerable to bleeding after trauma or in the presence of a second hemostatic abnormality.[4-6] While fibrinogen levels are generally normal (≤1.5-3.5 g/L) in patients with dysfibrinogenemia, abnormal fibrinogen function can lead to both spontaneous bleeding and risk of thrombosis.[2,3,7] Hypodysfibrinogenemia, characterized by reduced levels of dysfunctional and antigenic fibrinogen, is often symptomatic, with mild to moderate bleeding events and is more likely to lead to thrombosis compared with dysfibrinogenemia.[4,8]

In individuals with CFD, individualized fibrinogen supplementation can be used to treat spontaneous or traumatic bleeding events and as prophylaxis, including perioperatively.[2,9-11] Fibrinogen replacement was traditionally performed with fresh frozen plasma (FFP) or cryoprecipitate; however, these treatments have been largely replaced by human fibrinogen concentrate (FCH).[1,12,13] FCH has the advantage of providing a standardized dose of human plasma-derived fibrinogen that can be administered in a small volume, reducing the risk of volume overload compared with FFP or cryoprecipitate, while also reducing the risk of transfusion-related acute lung injury versus FFP.[1,12,14,15] FCH is also associated with a lower risk of viral transmission, as it undergoes a viral inactivation process.[1,12,13] In patients with CFD, guidelines suggest that to maintain plasma levels of >1.0 g/L, administration of 50-100 mg/kg of FCH for severe bleeding/major surgery should be considered.[16] In addition, consideration should be given to long-term prophylaxis with FCH (with an aim to maintain plasma fibrinogen levels >0.5 g/L) in individuals with a personal or family history of severe bleeding, or with fibrinogen levels <0.1 g/L.[16]

Haemocomplettan P, also licensed as RiaSTAP (CSL Behring GmbH, Marburg, Germany) is an FCH indicated for the treatment of CFD.[17] Studies show that it is effective in both the treatment of bleeding episodes and as prophylaxis for surgical procedures.[18-20]

A prospective study to evaluate the efficacy of FCH in patients with CFD is challenging, due to the rarity of the patient population and heterogeneous but overall low incidence of bleeding in most patients, particularly those with hypofibrinogenemia or dysfibrinogenemia.[3,5,10] Therefore, an observational retrospective study with an additional prospective component was conducted to assess the efficacy of FCH for the treatment of acute bleeding events, perioperative hemostasis, and routine prophylaxis in patients with CFD.

2 | METHODS

2.1 | Study design

This was a multicenter, noninterventional, retrospective cohort study with a 12-month prospective observational follow-up period, conducted across 11 sites in the United States and Canada between May 7, 2015, and December 6, 2017. All patients enrolled in the retrospective cohort participated in the prospective period. Patients were treated at the discretion of the treating physician and according to the standard of care at the participating study site. The study was performed in accordance with the International Conference of Harmonization Good Clinical Practice guidelines and approved by the Institutional Review Boards of each participating center, and all patients provided written informed consent.

2.2 | Study population

Patients were eligible for the study if they had a diagnosis of CFD (afibrinogenemia, hypofibrinogenemia, or dysfibrinogenemia) and had received at least one dose of FCH (RiaSTAP or Haemocomplettan P), for the treatment of bleeding events, perioperative hemostasis, or routine prophylaxis. There were no exclusion criteria.

2.3 | Study objectives and assessments

2.3.1 | Study objectives

The primary objective of the study was to assess retrospectively the efficacy of FCH for the treatment of acute bleeding events, perioperative hemostasis, and routine prophylaxis in patients with CFD. Secondary objectives were retrospective and prospective safety assessments, and a prospective assessment of efficacy in patients treated with FCH.

2.3.2 | Assessments

Data (including demographics, medical/surgical history, concomitant medications, indication for FCH, clinical events/efficacy, and adverse events [AEs]), were collected retrospectively from medical records (corresponding with the first use of FCH). The capture of data was dependent on the investigator, and the questions in the electronic case report form were not compulsory; therefore, analyses were conducted on available data. During the prospective period, data on the treatment of bleeding events, perioperative hemostasis, routine prophylaxis, and AEs were collected by phone calls or site visits at months 3, 6, 9, and 12. The study documented the exposure to FCH, cryoprecipitate, or other hemostatic products. Efficacy and safety end points were assessed for patients who received FCH treatment (RiaSTAP or Haemocomplettan P). Data on exposure to FCH and efficacy were obtained from different pages of the medical records; hence, the data sets were sometimes incomplete and the number of exposures to FCH and bleeding events were occasionally inconsistent.

Bleeding type was categorized as gastrointestinal tract; musculoskeletal, other (including abdomen, vagina, nasal, placental, eye, retroperitoneal, scrotum, umbilical cord, plus instances of hematuria, hemoptysis, and renal colic), and unknown. Bleeding locations were also categorized into internal (nasal, oral, chest, stomach, and retroperitoneal), upper limb, lower limb, any other location, and unknown. Surgeries were considered minor/major based on clinical judgment.

2.3.3 | Efficacy assessments

Hemostatic efficacy was rated by the investigator using a 4-point efficacy scale, comprising excellent, good, poor, or none (Table 1). Treatment of a bleeding event or perioperative management were classified as effective if the efficacy rating was excellent or good; otherwise, it was classified as ineffective. Routine prophylaxis was defined as FCH treatment for at least 3 days and not starting immediately after a bleeding event; the median dose per infusion and length of treatment period were recorded, and the treatment schedule was not recorded. The number of bleeding events while undergoing prophylaxis was assessed and reported as the annualized bleeding rate (ABR; the coefficient between the number of treated bleeding events during the treatment period and the duration of treatment period in days). An ad hoc analysis of ABR was conducted with patients who were treated with FCH for bleeding events, on-demand only, during the prospective period.

TABLE 1 Rating of hemostatic efficacy, assessed by the investigator

	Definition	
Rating	**Bleeding events**	**Surgery[a]**
Excellent	• Immediate and complete restoration of hemostasis in the absence of other hemostatic intervention[b], as clinically assessed by the treating physician • And/or <10% decrease in hemoglobin vs baseline	• Hemostasis clinically not significantly different from normal (eg, hemostasis achievement comparable to that expected during similar surgery in a non–factor-deficient patient) in the absence of other hemostatic intervention[b]
Good	• Eventual complete restoration of hemostasis in the absence of other hemostatic intervention[b] • And/or <20% decrease in hemoglobin vs baseline	• Normal or mildly abnormal hemostasis (quantity and/or quality [eg, slight oozing, prolonged time to hemostasis with increased bleeding compared to a non–factor-deficient patient]) in the absence of other hemostatic intervention[b]
Poor	• Incomplete restoration of hemostasis and additional hemostatic intervention[b] required • And/or 20%-25% decrease in hemoglobin vs baseline	• Moderately abnormal hemostasis (quantity and/or quality [eg, moderate hemorrhage that is difficult to control]) and/or additional hemostatic intervention[b] required
None	• No restoration of hemostasis and alternative hemostatic intervention[b] required • And/or >25% decrease in hemoglobin vs baseline	• Severely abnormal hemostasis (quantity and/or quality [eg, severe hemorrhage that is difficult to control]) and/or additional hemostatic intervention[b] required

Note: The assessments considered the clinical condition of the patient, laboratory values, and any additional hemostatic treatments, when available.

[a]The surgical assessment ranged from the start of the surgical procedure until hemostasis was secured and wound healing adequate; ≤6 weeks after the procedure.

[b]For example, fresh frozen plasma, cryoprecipitate, recombinant activated factor VIIa.

2.3.4 | Safety assessments

Safety was assessed for both the retrospective and prospective periods by analyzing the occurrence of AEs, serious AEs (SAEs), and AEs of special interest (AESIs), which included thromboembolic events and hypersensitivity reactions. For the retrospective period, only AEs that were related to the use of FCH were recorded; for the prospective period, all AEs were collected. AEs with an unknown relationship to FCH treatment (based on the investigator's assessment) were classed as related; AEs with unknown severity were classed as severe.

2.4 | Statistical analyses

No formal statistical hypothesis testing was applied in this study; descriptive summary statistics were used throughout. The analyses conducted included only those patients for whom data were available; data were analyzed as recorded in the database (ie, observed cases). No imputation of missing values was performed. Continuous variables were summarized by number of nonmissing observations, mean (standard deviation [SD]), and median (interquartile range [IQR], range [minimum and maximum]). Categorical variables were summarized by number of nonmissing observations, frequency counts, and percentages. Statistical analyses were performed on both the enrolled population (all patients with written informed consent) and the safety population, which included all enrolled patients who received ≥1 dose of FCH.

3 | RESULTS

3.1 | Study population

A total of 23 patients were screened for inclusion, of whom 22 were enrolled in the study (one screened patient had never received FCH treatment). None of the patients were withdrawn from the study or lost to follow-up. All patients completed both the retrospective and prospective periods of the study. An overview of patient demographics and characteristics is presented in Table 2. The median (range) age was 34 (2-78) years; 59% of patients were female. Thirteen (59%) patients had a history of afibrinogenemia, six (27%) with hypofibrinogenemia and three (14%) with dysfibrinogenemia. The earliest known mean (SD) fibrinogen level was 0.3 (0.2) g/L in patients with afibrinogenemia, 0.6 (0.3) g/L in patients with hypofibrinogenemia, and 0.6 (0.2) g/L in patients with dysfibrinogenemia, although it should be noted that some values may not represent the baseline for patients already treated with FCH. The genotype was identified in five (38.5%) of the patients with afibrinogenemia (Table S1). Antithrombotic agents were prescribed at any time in six (27%) patients during the retrospective period and in two (9%) patients during the prospective period. Additional hemostatic agents were prescribed for seven (32%) patients during the retrospective period only. The median (IQR) ABR for the number of treated bleeds before FCH prophylaxis was 1.0 (0.0-2.0, Table 2).

TABLE 2 Patient demographics, disease characteristics, and medical history

	Enrolled population (N = 22)	
Age at enrollment, y		
Mean (SD)	34.0 (24.4)	
Median (range)	34 (2-78)	
Sex, n (%)		
Male enroll	9 (40.9)	
Female	13 (59.1)	
Race, n (%)		
White	21 (95.5)	
Asian	1 (4.5)	
CFD history, n (%)		
Afibrinogenemia	13 (59.1)	
Hypofibrinogenemia	6 (27.3)	
Dysfibrinogenemia	3 (13.6)	
Earliest known fibrinogen level, g/L[a]		
n	22	
Mean (SD)	0.5 (0.3)	
ABR for number of treated bleeds prior to FCH prophylaxis[b]		
n (%)	15 (68.2)	
Median (IQR)	1.0 (0.0-2.0)	
Mean (SD)	1.9 (3.0)	
	Safety population (N = 22)	
	Retrospective period	**Prospective period**
Any concomitant medication, n (%)	22 (100.0)	10 (45.5)
Analgesics	16 (72.7)	5 (22.7)
Anesthetics	12 (54.5)	0
Antibacterials for systemic use	12 (54.5)	6 (27.3)
Hemostatic agents[c]	7 (31.8)	0
Antihistamines for systemic use	13 (59.1)	3 (13.6)
Antithrombotic agents[d]	6 (27.3)	2 (9.1)

Abbreviations: ABR, annualized bleeding rate; CFD, congenital fibrinogen deficiency; FCH, human fibrinogen concentrate; IQR, interquartile range; SD, standard deviation.

[a]The earliest known fibrinogen level may have been before or after the date of congenital fibrinogen deficiency diagnosis; therefore, patients may have been receiving FCH treatment before this measurement. Fibrinogen level measured by Clauss assay.

[b]Ad hoc analysis; ABR calculated from treated bleeds within 366 days before the first routine prophylaxis treatment.

[c]Hemostatic agents included aminocaproic acid, phytomenadione, and thrombin.

[d]Antithrombotic agents included acetylsalicylic acid, alteplase, clopidogrel bisulphate, dabigatran, enoxaparin, fondaparinux, heparin, tinzaparin, and warfarin.

3.2 | FCH exposure during the retrospective period

3.2.1 | Bleeding events

Fifteen of the 22 patients enrolled in the study required treatment for 326 bleeding events; of these, 243 events in 13 patients were treated with FCH. Of these 243 events, 237 occurred in 11 patients with afibrinogenemia, five in one patient with hypofibrinogenemia and one in a patient with dysfibrinogenemia. The median (IQR) FCH dose per infusion was 3.0 (1.0-4.0) g. Hemostasis was achieved by a single FCH infusion in 146 of 160 (91%) treatments for acute bleeding events, for which data were available (Table S2).

3.2.2 | Perioperative hemostasis

Fourteen patients underwent surgical procedures, for which 89 perioperative treatments were administered. Of these, 13 patients with available exposure data received 82 treatments with FCH at a median (IQR) dose per infusion of 3.0 (IQR, 1.1-5.0) g. Hemostasis was achieved by a single FCH infusion in 23 of 23 (100%) treatments for perioperative hemostasis, for which data were available (Table S2).

3.2.3 | Routine prophylaxis

Fifteen patients received 119 periods of routine prophylaxis, all of whom received FCH treatment at a median (IQR) dose per infusion of 3.0 (1.5-5.0) g. Of the bleeding events that occurred during prophylaxis treatment for which data were available, 94 of 107 (88%) achieved hemostasis with a single FCH infusion, 8 of 107 (8%) with two infusions, and 5 of 107 (5%) with three infusions (Table S2).

3.3 | Efficacy of FCH during the retrospective period

3.3.1 | Bleeding events

There were 250 bleeding events treated with FCH, the majority of which (175/250 [70%]) were traumatic in nature (followed by spontaneous, 32/250 [13%], postsurgery, 6/250 [2%] and unknown, 37/250 [15%]). Heparin was administered concomitantly to FCH in eight (3%) bleeding events. For events where hemostatic efficacy assessments were recorded, efficacy was rated as effective in 224 of 231 (97%) acute bleeding events in 15 patients treated with FCH (Figure 1A). Where bleeding type was recorded, most events were musculoskeletal (195/226 [86%]) followed by gastrointestinal in 13 of 226 (6%). Hemostatic efficacy was rated as effective across all types of bleeds (Figure 2A). Most bleeding events for which location was recorded, occurred in the lower limb (122/226 [54%]), followed by upper limb (55/226 [24%]), and internal (29/226 [13%]). Hemostatic efficacy was consistent across the bleeding locations and was rated as effective in >93% of bleeding events where locations were reported.

3.3.2 | Perioperative hemostasis

Perioperative hemostatic efficacy was assessed for 40 surgical procedures (32 [80%] minor and 8 [20%] major) in 14 patients treated with FCH. The most common major surgery was lumpectomy; there was also one instance of open-heart surgery, knee replacement, hernia repair, nephrectomy, sentinel node biopsy, and arthroscopic fusion. The most common minor surgeries included dental procedures and arthroscopies. Heparin was administered concomitantly to FCH in 5 of 40 (13%) procedures. Overall, FCH was rated as effective in managing perioperative hemostasis in 39 of 40 (98%) surgical procedures, including 31 of 32 (97%) minor surgical procedures and 8 of 8 (100%) major surgical procedures (Figure 1B).

3.3.3 | Routine prophylaxis

Fifteen patients received periods of routine prophylaxis with FCH for a median (range) duration of 860 (7-6574) days (treatment schedule was not recorded). The median (IQR) ABR was 1.4 (0.0-2.4), calculated from 14 evaluable patients (one patient had one bleeding event with an incomplete start and stop date, whose data were not included in the ABR calculation; Table 3). Heparin was administered concomitantly to FCH in 14 of 119 (11.8%) of the bleeding events reported during routine prophylaxis treatment with FCH.

3.4 | Adverse events during the retrospective period

A total of nine AEs were reported in two (9%) patients during the retrospective period (Table 4). Six (67%) AEs were reported as mild, one (11%) as moderate, and two (22%) as severe. Seven (78%) AEs resulted in a temporary disruption to FCH treatment, but there were no permanent treatment withdrawals. There were no reports of hypersensitivity reactions associated with FCH treatment. One AESI, a thrombosis of the right cephalic vein, was reported in a pregnant patient with dysfibrinogenemia (aged 35 years), who was receiving prophylaxis with FCH. The patient underwent a cesarean section for placental insufficiency; in the postoperative period, 4 days after the last dose of FCH, the patient developed a minor thrombosis of the right cephalic vein. The event was considered by the investigator to be mild and related to FCH and resolved with a brief course of anticoagulant. No SAEs or deaths were reported during this study period.

3.5 | FCH exposure during the prospective period

3.5.1 | Bleeding events

Seven of the 22 (32%) patients experienced bleeding events. Exposure data were available for four patients with afibrinogenemia,

who experienced 11 bleeding events. All events were treated with FCH; the median (IQR) FCH dose per infusion was 3.3 (3.0-5.0) g. Where data were available, hemostasis was achieved by a single FCH infusion in 100% of the treatments for acute bleeding events (5/5) (Table S3).

3.5.2 | Perioperative hemostasis

Five patients had nine surgical procedures (all were minor), of which eight were treated with FCH. Exposure data were available for three patients, who received three perioperative FCH treatments. The median (IQR) FCH dose per infusion was 5.0 (2.0-10.0) g. Hemostasis was achieved by a single FCH infusion in 100% of the treatments for perioperative hemostasis (3/3) (Table S3).

3.5.3 | Routine prophylaxis

Six patients received 11 periods of routine prophylaxis with FCH at a median (IQR) dose of 3.0 (1.5-3.5) g (Table S3). Exposure data were available for a single bleeding event treated during prophylaxis; hemostasis was achieved by a single FCH infusion in this case.

3.6 | Efficacy of FCH during the prospective period

3.6.1 | Bleeding events

Seven of the 22 patients (32%) experienced bleeding events that required treatment during the prospective period. All were treated with FCH, and efficacy was rated as effective in all cases (19/19 [100%])

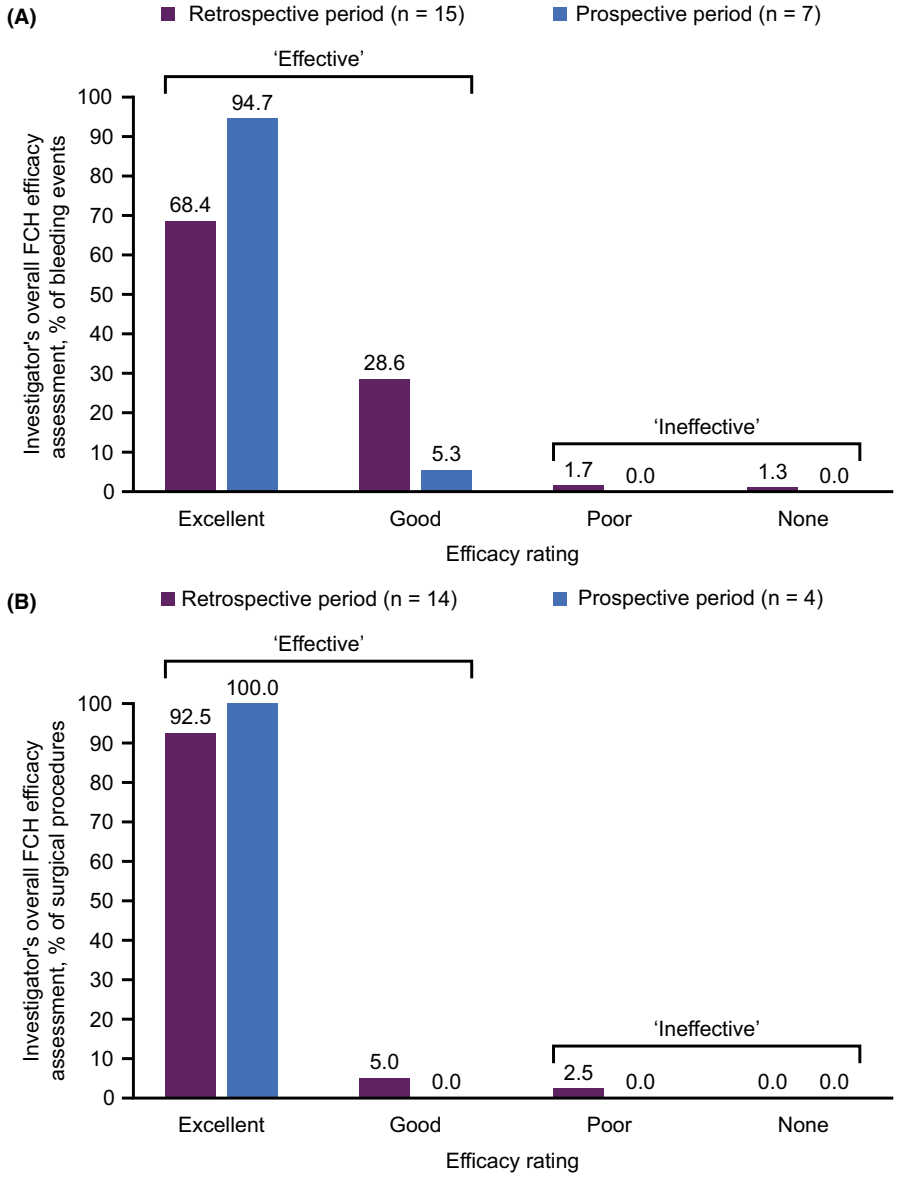

FIGURE 1 Efficacy assessments of (A) acute bleeding events and (B) perioperative hemostasis, in patients treated with FCH (safety population). *Effective* refers to an efficacy rating of excellent or good. *Ineffective* refers to an efficacy rating of poor or none. FCH, human fibrinogen concentrate

(Figure 1A); heparin was not concomitantly administered in any patient. Where data were available, bleeding events were mainly traumatic (11/14 [79%]), followed by spontaneous, (2/14 [14%]) and postoperative (1/14 [7%]). The bleeding events for which the type of bleed was recorded were musculoskeletal (17/18 [94%]) or gastrointestinal (1/18 [6%]). Hemostatic efficacy was effective across all types of bleed (100% of patients; Figure 2B). Where bleeding location was recorded, the majority of bleeding events occurred in the lower limb (10/17 [59%]), followed by upper limb (4/17 [24%]) and internal (1/17 [6%]). Hemostatic efficacy was 100% effective in all categories.

3.6.2 | Perioperative hemostasis

The perioperative hemostatic efficacy of FCH was rated as effective in all (8/8 [100%]) of the surgical procedures in four patients treated with FCH (Figure 1B). All surgical procedures were considered minor; the most common minor surgeries included urological surgeries and procedures. Heparin was not concomitantly administered in any case.

3.6.3 | Routine prophylaxis

Six patients (6/22 [27%]) received 11 periods of routine prophylaxis with FCH, with a median (range) duration of 227 (128-340) days (the treatment schedule was not recorded); the median (IQR) ABR was 1.3 (0.0-1.9). An ad hoc analysis of ABR was conducted with 16 of the enrolled patients who were treated with FCH for bleeding events, on-demand only. During the prospective period, 4 of 16 (25%) patients experienced bleeding events, with a median (IQR) ABR of 0.0 (0.0-0.5, Table 3).

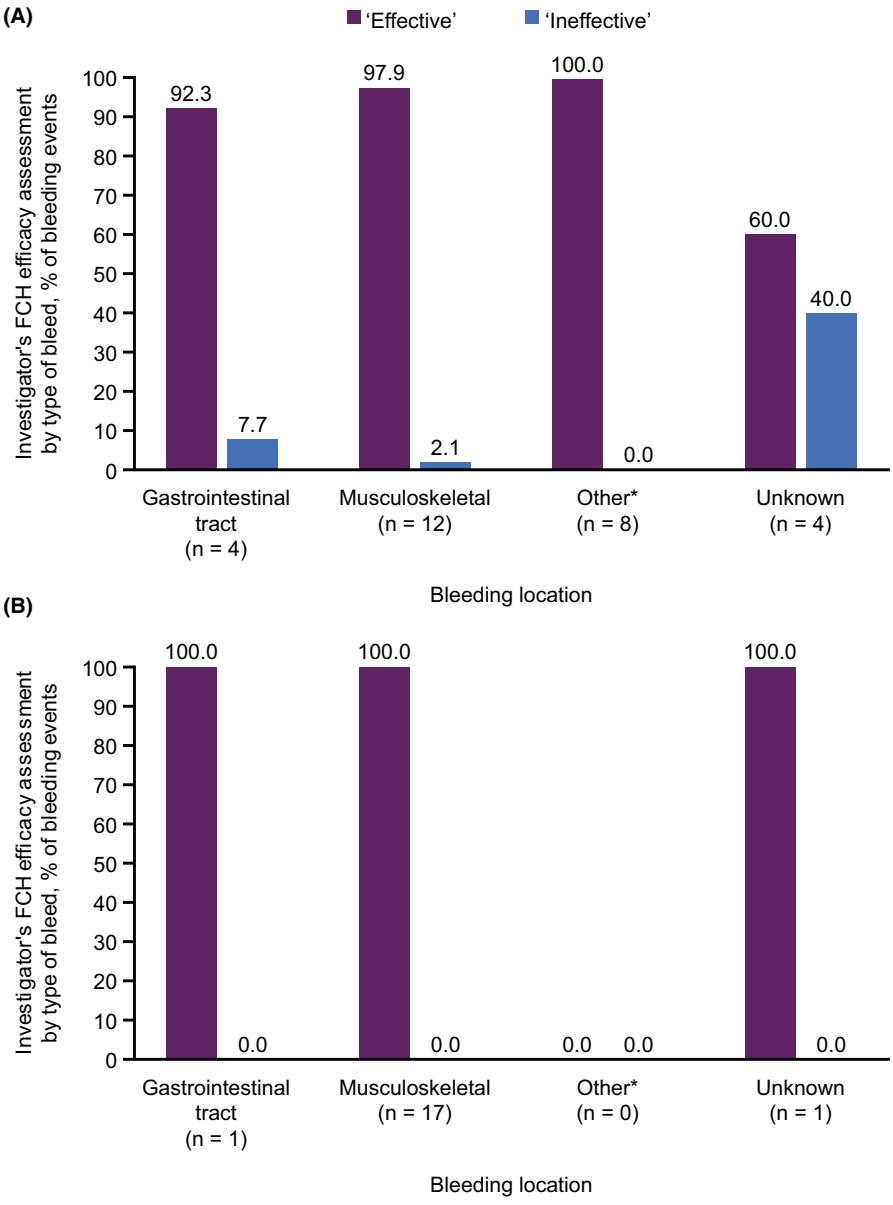

FIGURE 2 Efficacy assessments of acute bleeding events by type of bleed in the (A) retrospective period and (B) prospective period, in patients treated with FCH (safety population). *Effective* refers to efficacy rating of excellent or good. *Ineffective* refers to efficacy rating of poor or none. *Other types of bleed include bleeding events located in abdomen, hematuria, hemoptysis, renal colic, nasal, placental, eye, retroperitoneal, scrotum, umbilical cord, and vagina. FCH, human fibrinogen concentrate

TABLE 3 Summary of FCH treatment for routine prophylaxis and ABR analyses in the retrospective and prospective periods

FCH treatment for routine prophylaxis	Retrospective period, N = 22	Prospective period, N = 22
Period of routine prophylaxis in days, n (%)	15 (68.2)	6 (27.3)
Median (IQR)	860 (405-2315)	220 (132-324)
Range	7-6574	128-340
ABR for routine prophylaxis, n (%)[a]	14 (63.6)	6 (27.3)
Median (IQR)	1.4 (0.0-2.4)	1.3 (0.0-2.0)
Mean (SD)	5.7 (13.8)	1.2 (1.1)
Ad hoc analysis of FCH treatment for bleeding events on demand		
Patients included in ad hoc analysis of bleeding events on demand, n (%)	NA[b]	16 (72.7)
Patients who experienced bleeding events, n (%)		4 (25.0)
Total number of bleeds treated with FCH		12
ABR for bleeding events on-demand, n (%)		16 (72.7)
Median (IQR)		0.0 (0.0-0.5)
Mean (SD)		0.8 (1.6)

Abbreviations: ABR, annualized bleeding rate; FCH, human fibrinogen concentrate; IQR, interquartile range; SD, standard deviation.

[a]ABR calculated from 14 evaluable patients; one patient had one bleeding event with an incomplete start and stop date, whose data were not included in the ABR calculation.

[b]Not assessed in the retrospective period.

3.7 | Adverse events during the prospective period

A total of 56 AEs were reported during the prospective period, none of which were considered by the investigator to be related to FCH treatment. Nine (16%) AEs in two patients resulted in an FCH dose increase; there were no disruptions in or withdrawals from FCH treatment.

Two AESIs were reported (both reported by the investigator as unrelated to FCH treatment). The first was a pulmonary embolism in a 30-year-old patient with afibrinogenemia and a history of chronic thromboembolic pulmonary hypertension, three pulmonary embolisms, and three central-line–associated venous thromboses. The patient had been receiving prophylactic treatment with FCH and concomitant heparin, over a duration of 253 days. Five days after the last dose of FCH, hemoptysis occurred and was reported by the investigator as a severe SAE, not related to FCH; 8 days after receiving the last dose of FCH, the patient was diagnosed with a pulmonary embolism, reported as severe, nonserious, and in the opinion of the investigator, not related to FCH, given the patient's history.

The second AESI was a contact dermatitis of the earlobes in a 5-year-old patient with afibrinogenemia. The event was attributed to ear piercing and was reported as a mild nonserious AE. Three SAEs were reported, none considered by the investigator as related to FCH treatment; there were no deaths (Table 4).

4 | DISCUSSION

Congenital fibrinogen deficiency comprises a group of rare fibrinogen disorders for which data on the treatment modalities are scarce.[10] Therefore, our objective was to retrospectively and prospectively assess the efficacy of FCH treatment, and prospectively assess the safety of FCH treatment, in patients with CFD. In this observational study, we have shown that in patients with CFD, FCH is well tolerated and effective in treating bleeding events and achieving perioperative hemostasis and is associated with infrequent bleeding events when administered as prophylaxis.

In both the retrospective and prospective periods of the study, the hemostatic efficacy of FCH was rated as effective in ≥97% of acute bleeding events and in perioperative hemostasis, indicating that FCH treatment in patients with CFD has a clinically meaningful effect. This effect is consistent regardless of the type of CFD (afibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia, although the majority of patients had afibrinogenemia), or the nature or anatomic location of bleeding event. Similarly, it is important to note that while we do not have a true baseline fibrinogen level recorded in this study, FCH was effective and well tolerated in these clinical settings, regardless of fibrinogen level.

There are limited data on the use of FCH for bleeding prophylaxis.[11,21] In this study, the FCH dose and number of infusions, as well as the prophylaxis duration were recorded, and the ABR was summarized to evaluate the number of bleeding events while receiving prophylaxis.

The ABR following prophylactic FCH treatment was similar across both retrospective and prospective periods of the study, at fewer than two bleeding events per year (median ABRs for the retrospective and prospective periods were 1.4 and 1.3, respectively), indicating that our cohort of patients with CFD do not frequently bleed. However, previous studies have indicated that the annual incidence of bleeding in patients with CFD receiving prophylactic or on-demand treatment is highly variable and can range from <1 to >10 bleeding episodes per year.[10] Therefore, it may be beneficial for prophylactic treatment to be decided on an individual basis according to the bleeding phenotype or when encountering hemostatic challenges, such as invasive procedures.

Furthermore, an ad hoc analysis of data from patients treated with FCH on demand during the prospective period revealed a slightly lower median ABR compared with prophylactic treatment, at closer to zero bleeding events per year. In addition, the median ABRs calculated following prophylactic FCH treatment were slightly increased, compared with the median ABR recorded before FCH prophylaxis (approximately one bleeding event per year). Together, these findings suggest that patients with more frequent bleeding episodes or a more severe condition may be more likely to receive

TABLE 4 Summary of AEs in the retrospective and prospective periods (safety population)

	Retrospective period (N = 22)[a]		Prospective period (N = 22)	
	Number of patients	Number of AEs	Number of patients	Number of AEs
Any AE, n (%)	2 (9.1)	9	13 (59.1)	56
Relationship to FCH, reported by the investigator, n (%)				
Not related	0	0	13 (59.1)	56 (100.0)
Related	2 (9.1)	9 (100.0)	0	0
Severity of AEs, n (%)				
Mild	2 (9.1)	6 (66.7)	13 (59.1)	51 (91.1)
Moderate	1 (4.5)	1 (11.1)	2 (9.1)	2 (3.6)
Severe[b]	1 (4.5)	2 (22.2)	1 (4.5)	3 (5.4)
Action taken with FCH due to AEs, n (%)				
Dose increased	0	0	2 (9.1)	9 (16.1)
Dose not changed	0	0	6 (27.3)	33 (58.9)
Drug interrupted	1 (4.5)	7 (77.8)	0	0
Drug withdrawn	0	0	0	0
Not applicable	1 (4.5)	1 (11.1)	6 (27.3)	12 (21.4)
Unknown	1 (4.5)	1 (11.1)	1 (4.5)	2 (3.6)
Outcome of AE, n (%)				
Recovered/resolved	2 (9.1)	9 (100)	13 (59.1)	50 (89.3)
Not recovered/not resolved	0	0	3 (13.6)	3 (5.4)
AESI	1 (4.5)	1	2 (9.1)	2
Venous thrombus of limb	1 (4.5)	1	0	0
Pulmonary embolism	0	0	1 (4.5)	1
Contact dermatitis	0	0	1 (4.5)	1
SAEs, n (%)	0	0	2 (9.1)	3 (5.4)
Deaths, n (%)	0	0	0	0

Abbreviations: AE, adverse event; AESI, adverse event of special interest; FCH, human fibrinogen concentrate; SAE, serious adverse event.

[a]In the retrospective period, only AEs that were considered related to FCH treatment were reported.

[b]One AE with unknown severity was classed as severe.

FCH prophylaxis. Indeed, the approach of tailoring the prophylaxis treatment to the severity of the condition is supported by the literature and the guidelines.[2,5,16] However, data for bleeding events during prophylaxis in this study are limited, which make it difficult to draw conclusions when comparing pre- and postprophylaxis ABRs. Further studies that capture additional data on the treatment schedule (such as the patient's fibrinogen trough level) and more complete records for the bleeding events are needed to validate the efficacy of FCH for bleeding prophylaxis.

The FCH dose per infusion was generally consistent across the different clinical settings. The highest median (IQR) FCH dose per infusion was given for perioperative hemostasis in the prospective period (5.0 [2.0-10.0] g), while the lowest FCH dose per infusion was given for treatment of bleeding events during the retrospective period (3.0 [1.0-4.0] g). However, data were collected for a small number of patients, and data on patient weight were not routinely recorded, limiting any further analysis of these seemingly modest differences.

There were no deaths or permanent withdrawals of FCH treatment due to AEs recorded in this study. Thrombotic complications have been reported in patients with CFD, both related and unrelated to fibrinogen supplementation.[1,13,22] However, pharmacovigilance data suggest that this risk is low and that low-dose prophylactic fibrinogen is a well-tolerated and effective treatment option in patients with both CFD and thromboembolic complications.[22,23] Only two instances of thromboembolic events were reported in the present study: The first was in a patient with dysfibrinogenemia who underwent a cesarean section for placental insufficiency; in the postoperative period she developed a mild thrombosis of the cephalic vein, reported as related to FCH and successfully treated with a brief course of anticoagulant. The second thromboembolic event was a pulmonary embolism reported in a patient with afibrinogenemia who had a history of recurrent pulmonary embolisms; this event was considered unrelated to the use of FCH. To prevent thrombosis in patients with CFD, some clinicians administer heparin or low-molecular-weight heparin with FCH.[6] In this study, heparin was prescribed on isolated occasions (concomitantly with FCH and at any time during periods of prophylaxis), with no distinguishable pattern of use.

The results of this study are consistent with the published literature on the effectiveness and safety profile of FCH for the treatment of bleeding and perioperative hemostasis in patients with CFD[11,18,24]; this includes a recently published prospective study that reported that FCH was effective and had a favorable safety profile when used as treatment for both on-demand bleeding and surgical prophylaxis in patients with afibrinogenemia.[11] Our study broadens this insight by including patients with all types of congenital fibrinogen deficiency, and by investigating the efficacy of FCH for use as routine prophylaxis.

The strengths of this study, in comparison with several previous reports, are the inclusion of a large number of patients with CFD, given the low prevalence of this disorder, and the inclusion of prospective data, which may capture a more accurate record for the patient, compared with retrospective data collection.[1,18] However, the study has the following limitations. First, it is a noninterventional study, and the availability of the data and the data collected were dependent on the specific clinical practice of the individual investigators. In addition, the majority of the data were collected from historic clinical records, with some patients having extensive treatment histories. Therefore, it was not possible to collect all the relevant data, in some cases because certain data were unavailable and in other cases because of the magnitude of the clinical record. Finally, as only one bleeding event was recorded in the patients with dysfibrinogenemia, we cannot conclude that the findings relating to FCH efficacy and safety (which were mostly recorded in patients with afibrinogenemia and hypofibrinogenemia), apply to those patients with dysfibrinogenemia.

5 | CONCLUSIONS

This study demonstrates that FCH is an effective treatment to achieve hemostasis during bleeding events, allows effective control of perioperative hemostasis and is associated with infrequent bleeding events when used prophylactically, in patients with CFD. Furthermore, the safety profile of FCH in this study was favorable and consistent with previous clinical studies.

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RELATIONSHIP DISCLOSURE

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AUTHOR CONTRIBUTIONS

Concept or design: DD, DSS, AB. Acquisition of data: JL, JT, MW. Data analysis or interpretation: JT, JL, MW, DD, DSS, AB. All authors approved the final version of the manuscript before submission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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