Congenital Fibrinogen Deficiency in India and Role of Human Fibrinogen Concentrate

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Abstract
Congenital fibrinogen deficiency is an inherited disorder due to genetic mutations with diverse presentations arising from reduced fibrinogen levels (hypofibrinogenemia), absence of fibrinogen in circulation (afibrinogenemia), abnormal functioning (dysfibrinogenemia) or both reduced levels and abnormal functioning (hypodysfibrinogenemia) of fibrinogen. The decreased fibrinogen concentration in congenital fibrinogen deficiency necessitates fibrinogen replacement therapy with fresh frozen plasma, cryoprecipitate, or human fibrinogen concentrate. However, the use of fresh frozen plasma and cryoprecipitate is limited owing to their longer transfusion time, requirement of high doses, volume overload, risk of viral transmission, and other safety concerns. The availability of human fibrinogen concentrate has made it the preferred replacement alternative due to its reduced risk of viral transmission, smaller infusion volume, and accurate dosing. The hemostatic efficacy and safety of human fibrinogen concentrate in congenital fibrinogen deficiency is well established in the literature. We review the prevalence of congenital fibrinogen deficiency in India and the current role of human fibrinogen concentrate in its management.

Introduction
The deficiency of fibrinogen can be inherited (congenital) or acquired. Congenital fibrinogen deficiency (CFD), a rare inherited bleeding disorder, is characterized by decreased fibrinogen levels, absence of fibrinogen in circulation, or abnormal functioning of fibrinogen. The CFD can be associated with dysfunctional fibrinogen and defective synthesis and stability [1–3]. The CFD comprises 2 classes of plasma fibrinogen defects: type I, a quantitative deficiency with afibrinogenemia or hypofibrinogenemia, with absent or low plasma fibrinogen antigen levels, and type II, a qualitative defect of dysfibrinogenemia (low levels of fibrinogen with reduced activity) [1–4]. In addition to bleeding events, spontaneous thrombotic complications are seen in CFD [1]. Acquired fibrinogen...
deficiency involves decreased fibrinogen production or increased fibrinolysis, which could occur due to several conditions such as disseminated intravascular coagulation surgery, trauma, and placental abruption [5].

**Congenital Fibrinogen Deficiency**

We review the available literature about the molecule fibrinogen, the extent of CFD, and available treatment modalities and evaluate the advantages and disadvantages of plasma-derived human fibrinogen concentrate (HFC). CFD is a bleeding disorder with a prevalence rate of ∼8% among the rare bleeding disorders with an estimated prevalence of 1 in a million [1–3]. Prevalence data from India are sparse with only a few case reports [6–16]. Sumitha et al. [17] described the molecular basis of CFD in 27 patients, and Shetty et al. [18] reported fibrinogen deficiencies in 12.1% of the 321 rare clotting factor deficiency cohort. There is significant underdiagnosis in India when compared to the estimated global prevalence of CFD, which may be due to limited awareness and lack of diagnostic facilities in the country. Table 1 enlists the characteristics of CFDs [1–4].

**Fibrinogen Molecule**

**Structure and Normal Functions**

Fibrinogen is a soluble glycoprotein (340 kDa) synthesized in hepatocytes, which plays an important role in hemostasis through platelet aggregation and fibrin clot for-
Human Fibrinogen: Congenital Fibrinogen Deficiency

The plasma circulation concentration is 1.5–4 g/L, with an elimination half-life of 3–5 days [19]. Structurally, it has 2 identical subunits with each subunit containing 3 polypeptide chains (fibrinogen A [FGA], FGB, and FGG; Fig. 1). The mutation in any of the 3 genes that encode these polypeptide chains of fibrinogen (Aα, Bβ, and γ) may lead to reduced synthesis [21].

Fibrinogen is the precursor to fibrin, which binds to the aggregated platelets and thrombin, promoting coagulation (Fig. 2) [5, 19–21]. The hepatocytes synthesize fibrinogen, and thrombin cleaves the fibrinopeptides Aα and Bβ forming fibrin monomers. Polymerization of these monomers leads to fibrin protofibrils, and a structural fibrin network is formed within the clot at the tissue injury site [22, 24].

**Fibrinogen Assay**

There are many assays measuring fibrinogen levels in plasma, although most laboratories use the Clauss method [25]. Methods available are Clauss assay, TEG/ROTEM, immunological assay, gravimetric assay, and PT-derived fibrinogen assay [26]. Clauss assay gives estimation of the quantity of fibrinogen, and in a suspected case of dysfibrinogenemia, immunoassay has to be done [25, 26].

**Fibrinogen Supplementation Guidelines**

The normal plasma fibrinogen levels range between 1.5 and 4 g/L. While lower plasma concentrations may lead to bleeding, higher levels are associated with coronary artery diseases [27, 28]. Traditionally, a fibrinogen level of ≤1.0 g/L has been considered as a replacement threshold. However, this therapeutic threshold differs from country to country [24, 29]. The European Network of Rare Bleeding Disorders (EN-RDB) recommends fibrinogen levels of 1.0 g/L as a prophylactic target in view of protection from spontaneous bleeds with fibrinogen levels at 0.7 g/L and complete protection from bleeding events at >1.0 g/L [30]. A fibrinogen level of <0.8–1 g/L is recommended as the threshold to start treatment by the Italian Society of Transfusion Medicine and Immunohaematology [31]. Trigger levels of fibrinogen at <1.5–2 g/L are recommended by several other guidelines [32–34].
Disease severity, the urgency of treatment, and location of bleeding are some of the therapeutic indications in CFD. The primary choice of replacement therapy is HFC while cryoprecipitate and FFP may be other options [2]. The use of FFP is limited due to its larger volume requirements, transfusion-related acute lung injury, inconsistency in the available factor content, and transfusion-transmitted infection risks. Although cryoprecipitate may overcome the fluid overload issues, lack of availability, inconsistent dosing, and transfusion-transmitted infection remain a concern [35–37]. The solvent/detergent, pasteurization, and nanofiltration viral inactivation steps nullify the risk of lipid- and nonlipid-enveloped viral infections in HFC. The specific dose delivery and smaller infusion volumes make HFC the preferred replacement choice [1, 38].

The World Federation of Hemophilia (WFH) recommends the use of viral-inactivated plasma-derived or recombinant fibrinogen concentrates over cryoprecipitate for managing bleeding disorders [39]. The use of cryoprecipitate or FFP as an alternative replacement therapy is advised only in emergencies when HFC is not available [1]. Table 2 compares the pros and cons of available therapeutic options [35, 36, 39–43].

The treatment of CFD can be conventional (episodic or on demand) where HFC is administered as soon as possible after a bleeding episode or as prophylaxis. The prophylaxis can be either primary – giving HFC from an early age to prevent bleeding – or secondary – after bleeding to prevent recurrence (every 7–14 days) [44].

### Treatment Options in CFD

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<th>Table 2. Characteristics of FFP, cryoprecipitate, and HFC</th>
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FFP, fresh frozen plasma; HFC, human fibrinogen concentrate; RCT, randomized controlled trials.
Role of HFC in CFD

The efficacy and safety of HFC in CFD has been established in several studies. An HFC dose of 50 mg/kg is required to increase fibrinogen concentration of 1 g and depends on the surgery or injury type [45]. First licensed in 1963, HFC is an approved standard treatment for acute bleeds and is used as a prophylactic treatment for CFD in several countries including the UK, the USA, Canada, Australia, and many European countries [46].

Table 3. Summary of studies with HFC use in CFD treatment

<table>
<thead>
<tr>
<th>Study</th>
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<th>Details of the study</th>
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| Lissitchkov et al. [51] (FORMA-02 study) | 25 afibrinogenemia | Prospective interventional study HFC was administered for on-demand treatment of bleeding (n = 24; 89 episodes) or surgical prophylaxis (n = 9; 12 surgeries) | Hemostatic efficacy for on-demand treatment of bleeding
Investigator-assessed: excellent – 78.7%; good – 18%; moderate – 1.1; missing – 2.2% IDMEAC-assessed: excellent – 91%; good – 7.9%; moderate – 1.1% Treatment success (rating of excellent or good) Investigator – 96.6%; IDMEAC – 98.9% Hemostatic efficacy for surgical prophylaxis – intraoperative and postoperative Treatment success (rating of excellent or good) Investigator – 100%; IDMEAC – 100% | TEAEs – 43 (n = 15) 3 AEs in 3 patients were considered possibly related to treatment; including a moderate case of thrombosis No deaths, severe allergic or hypersensitivity reactions, or clinical evidence of neutralizing antifibrinogen antibodies were reported |
| Lasky et al. [52] | 22 patients (afibrinogenemia [n = 13], hypofibrinogenemia [n = 6], and dysfibrinogenemia [n = 3]) | Multicenter, noninterventional, retrospective cohort study with a 12-month prospective observational follow-up period | HFC was effective in treating ≥97.0% of bleeding events and effective for perioperative hemostasis in ≥97.5% of minor and major surgeries In patients receiving HFC for routine prophylaxis, the median ABRs were 1.4 and 1.3 for the retrospective and prospective periods, respectively | One treatment-related AE of thrombosis of the right cephalic vein No serious AEs related to HFC or deaths were reported |
| Négrier et al. [53] | 14 afibrinogenemia (prophylaxis: n = 9; treatment on-demand: n = 5) | Noninterventional, prospective, noncomparative, multicenter study of HFC for CFD in real-life medical practice in France | Prophylaxis (n = 9) Treatment success: 99.5% (365 of 367 infusions) Treatment on-demand (n = 5) Excellent – 56.25% (27/48 infusions) Good – 43.75% (27/48 infusions) | AEs: pallor, chills, cough, vomiting, headache, urticarial, and erythematous rash Serious AEs: anaphylactic shock and subclavian venous thrombosis |
| Djambas Khayat et al. [54] | 16 (afibrinogenemia [n = 15], hypofibrinogenemia with dysfibrinogenemia [n = 1]) | Open-label, phase 2–3 trial in patients ≥6 years. 32 bleeding episodes were treated in 9 patients, and 15 patients underwent 38 surgical/invasive procedures | All patients achieved appropriate hemostasis. Treatment was successful in all bleeds (95% CI: 0.89–1.00) and procedures (95% CI: 0.91–1.00). Most (94%) bleeds were controlled with a single HFC infusion (median 0.050 g/kg) | Distal venous thrombosis in 2 patients |
| Kreuz et al. [56] | 12 (afibrinogenemia [n = 8], hypofibrinogenemia [n = 3], dysfibrinogenemia with hypofibrinogenemia [n = 1]) | Open, multicenter, noncontrolled retrospective study HFC was used to stop bleeding (26 events), as prophylaxis for surgery (11 events), or for routine prophylaxis to prevent bleeding (4 events) | Physician-reported clinical efficacy – “very good,” except one “moderately good” event of pylorotomy | One patient reported an anaphylactic reaction (hypotension, cyanosis, and abdominal and back pain) |

ABR, annualized bleeding rate; CFD, congenital fibrinogen deficiency; IDMEAC, Independent Data Monitoring and Endpoint Adjudication Committee; HFC, human fibrinogen concentrate.
Experimental studies have indicated that HFC restore the functions of fibrinogen and improve fibrin structure and may reverse dilutional coagulopathy [47, 48] (Table 3).

HFC Preparation and Viral Inactivation Methods

The available plasma-derived HFC includes RiaSTAP® (CSL Behring, Germany), Fibryga® (Octapharma, Wien, Austria), and Fibrogen-I™ (Intas Pharmaceuticals Limited, Ahmedabad, India). RiaSTAP® is manufactured from pooled plasma cryoprecipitate into a glycine precipitate, which is then purified by multiple precipitation/adsorption steps. The half-life of RiaSTAP® is ∼78 h [49]. The median in vivo recovery of 1.7 mg/dL (range 1.30–2.73 mg/dL) indicates that a dose of 70 mg/kg will increase fibrinogen plasma concentration by ∼120 mg/dL [49].

In India, Fibrogen-I™, a plasma-derived HFC, manufactured by Intas Pharmaceuticals Limited is approved by the regulatory agency. Pooled blood plasma is used for the manufacturing of Fibrogen-I™ and is screened for mandatory infectious diseases. The plasma is processed only after being declared nonreactive for hepatitis B surface antigen, hepatitis C virus, and human immunodeficiency virus-I and -II antibodies and negative for human immunodeficiency virus-I and -2, hepatitis C virus, and hepatitis B virus by nucleic acid testing. The manufacturing procedure incorporates 2 dedicated orthogonal viral clearance steps such as solvent detergent and dried heat treatment. Multiple chromatography steps are incorporated for assurance of product safety [50].

Available Evidence on HFC Replacement in CFD

FORMA-02 is a recently published large intervention study in CFD where the hemostatic efficacy of HFC was evaluated in 25 afibrinogenemia patients. In this prospective, multicenter, open-label, uncontrolled phase 3 study, HFC was used for on-demand treatment of bleeding or as surgical prophylaxis [51]. Of 25 patients, 24 received HFC for the treatment of ≥1 bleeding episode (total 89 episodes), 9 as surgical prophylaxis (total 12 surgeries), 8 for bleeding and surgery, and 1 for surgery only. A total of 100 HFC infusions were required for 89 bleeding episodes and 31 infusions for 12 surgeries. The mean dose (mg/kg) of HFC for minor bleeds (91 infusions for 87 episodes) was 62.20 ± 11.31, major bleeds (9 infusions for 2 episodes) 209.49 ± 90.94, surgical prophylaxis (31 infusions for 12 events) 104.49 ± 54.86, and maintenance (20 infusions for 12 events) 20.13 ± 7.49 [51].

The hemostatic efficacy was excellent for 78.7% of bleeding episodes based on investigator assessment (treatment success [excellent or good]: 96.6% [0.920–0.988]) and 91% based on assessment from an independent data monitoring and endpoint adjudication committee (IDMEAC, treatment success: 98.9% [0.954–0.999]) [51]. Overall, the authors concluded that HFC was efficacious in the largest prospective study for on-demand treatment of bleeding and for surgical prophylaxis in CFD [51].

Lasky et al. [52] reported the effectiveness of HFC with treating ≥97% of the bleeding events and perioperative hemostasis in ≥98.5% minor or major surgeries. The bleeding events in patients receiving HFC for routine prophylaxis were infrequent with median annualized bleeding rates of 1.4 and 1.3 for retrospective and prospective periods of the study, respectively. Négrier and colleagues [53] reported the real-life safety data of HFC that most (99.5%) infusions received by 9 patients under prophylaxis were successful. The efficacy was rated “excellent” in 56.25% (27/48) and “good” in the remaining 43.75% (21/48) infusions for the 5 patients treated on demand. In a study by Djambas Khayat et al. [54], 32 bleeding episodes were reported in 9 patients, of which majority (94%, 30/32) of the episodes required a single HFC dose. The physicians’ global assessment rating was “excellent” or “good” – treatment success – in all patients. The perioperative hemostatic efficacy evaluated in 15 patients who underwent 38 surgical/invasive procedures was considered “excellent” and considered successful [54]. A systematic review of 50 case reports by Bornikova and colleagues [55] indicated that fibrinogen replacement therapy effectively prevented or treated bleeding and was associated with recovery or bleeding in most patients. In a study by Kreuz et al. [56], HFC was used to stop bleeding (26 events), as prophylaxis for surgery (11 events), or for routine prophylaxis to prevent bleeding (4 events). The physician-reported clinical efficacy was “very good” in all events, except one “moderately good” event of pylorotomy [56].

Safety of HFC in CFD

Allergic or anaphylactic type reactions, nausea, vomiting, chills, pyrexia, cough, and thromboembolic episodes are the most common AEs with HFC [50]. In the FOR-
MA-02 study, a single thrombotic event was reported in a patient, while allergic or hypersensitivity reactions were not observed [51]. Pallor, chills, cough, vomiting, headache, urticarial, erythematous rash [53], thrombosis [52], and anaphylactic reactions (hypotension, cyanosis, and abdominal and back pain) [53, 56] have been reported.

**Summary**

Fibrinogen replacement is the only available treatment modality in CFD. Although FFP and cryoprecipitates are used, plasma-derived or recombinant fibrinogen is the preferred option. Availability of HFC with its efficient viral inactivation steps and exact dose delivery makes it the favored option. However, many patients in India may be undiagnosed, and improved awareness among treating physicians with access to better diagnostic facilities would be the determinant in recognizing the need to offer HFC for patients with CFD.

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