ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Fibrinogen Concentrates

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H&O What are some of the blood disorders that can currently be treated with fibrinogen concentrates?

Human fibrinogen concentrates have been commercially available for decades as substitution therapy in congenital fibrinogen deficiency. Recent data suggest that fibrinogen plays a critical role in achieving and maintaining hemostasis; in particular, they appear to show benefit in cases where early intervention is important, such as with patients suffering from acquired fibrinogen deficiency during massive bleeding.

Congenital fibrinogen deficiency is rare, with an estimated prevalence of approximately 1 in 1,000,000 people. The disease affects, genetically, either the quantity (hypofibrinogenemia, characterized by fibrinogen levels lower than 1.5 g/L, and afibrinogenemia, characterized by the complete deficiency of fibrinogen) or the quality of the circulating fibrinogen (dysfibrinogenemia) or both (hypodysfibrinogenemia).

Acquired hypofibrinogenemia can result from reduced fibrinogen production, as seen in liver failure, or from increased fibrinolysis. Fibrinolysis may be primary, occurring in the absence of a generalized activation of coagulation, or secondary to disseminated intravascular coagulation. Causes of primary fibrinolysis (and fibrinogenolysis) include the therapeutic administration of thrombolytic agents (eg, colloid plasma expanders, dextran, or gelatins), certain malignancies, and liver failure. Any cause of disseminated intravascular coagulation may result in secondary fibrinolysis, although certain conditions are associated with disproportionate degrees of fibrinolysis, including brain trauma, placental abruption, cardiac surgery, aortic aneurysm rupture, and acute promyelocytic leukemia.

H&O How does a physician diagnose and treat these disorders? What are the treatment options?

Depending on the patient's country of residence, therapeutic substitution with fibrinogen is based on products derived from human plasma, including fresh-frozen plasma, cryoprecipitate, or virally-inactivated concentrates of fibrinogen. No fibrinogen products manufactured by recombinant cell technology are yet available on the market; however, the Dutch Pharming Group N.V. has started the development of a recombinant human fibrinogen.

Fibrinogen concentrate is the treatment of choice because it is safer than cryoprecipitate or fresh-frozen plasma. When fresh-frozen plasma is used as a source of fibrinogen, large volumes may be required to ensure an adequate increase in plasma fibrinogen, which could lead to hypervolemia. A pool of cryoprecipitate is based on plasma from 5 or 6 donors, and most often the product is not subjected to virus inactivation/elimination, whereas fibrinogen concentrate contains highly purified and concentrated human fibrinogen and is subjected to a viral inactivation procedure.

Currently, 4 fibrinogen concentrates are available on the market. CSL Behring has produced a plasma-derived pasteurized human fibrinogen concentrate (Haemocomplettan P/HS in Europe and RiaSTAP in the United States), which is the only available human fibrinogen concentrate; this agent is licensed and distributed in some countries for the management of hemorrhagic diathesis in congenital hypofibrinogenemia, dysfibrinogenemia, and afibrinogenemia, as well as acquired hypofibrinogenemia resulting from disorders of synthesis, increased intravascular consumption, and hyperfibrinolysis. Moreover, there are locally manufactured fibrinogen concentrates: Fibrinogen HT in Japan (Yoshitomi, Inc.), FibroRAAS in China (Shanghai RAAS Blood Products Co.), and Clottagen in France (LFB).

In addition to fibrinogen substitution in congenital fibrinogen deficiency, antifibrinolytic agents may be given, particularly in order to treat mucosal bleeding or prevent bleeding that follows procedures such as dental extraction. Fibrin glue is useful to treat superficial wounds or for after dental extractions. Estrogen-progestin preparations are useful in cases of menorrhagia.

H&O Are there any unmet needs with fibrinogen concentrates? What do we know of their efficacy and safety?

Contraindications for the administration of pasteurized fibrinogen concentrate include overt thromboembolism and myocardial infarction, except for use in life-threatening bleeds. During disseminated intravascular coagulation, the use of fibrinogen concentrate has been suggested to be potentially hazardous due to the risk of accelerated fibrin formation.

However, although there are only limited numbers of studies on the clinical safety of pasteurized fibrinogen concentrate, the treatment has been reported to be effective and generally well-tolerated.

Congenital Fibrinogen Deficiency

Kreuz and colleagues evaluated the clinical efficacy of 151 infusions of pasteurized fibrinogen concentrate administered to 12 patients with hypofibrinogenemia, afibrinogenemia, and/or dysfibrinogenemia.[1] In 86 of the cases, the infusions were given prophylactically. All infusions were reported as being well-tolerated except for 1 case where a patient developed an anaphylactic reaction and 1 case where another patient developed deep vein thrombosis and nonfatal pulmonary embolism; the hemostatic efficacy was judged as very good except for 1 surgical procedure where the efficacy was noted as moderate (Table 1).

A multinational, prospective, open-label, uncontrolled study of patients with afibrinogenemia 6 years or older was conducted in the United States and Italy in order to assess the pharmacokinetic profile, clot integrity, and safety of Haemocomplettan P/HS fibrinogen concentrate.[2] Combined pharmacokinetic and safety data indicated that the plasma levels of fibrinogen achieved when fibrinogen concentrate is infused at a dose of 70 mg/kg are sufficient to restore hemostasis with a good safety profile (Table 1).

FibrinogeneT1 preparation (FGT1, LFB) has been evaluated in an open, prospective, multicenter study to assess the pharmacokinetic and pharmacodynamic profiles in 5 adult patients with congenital afibrinogenemia.[3] Overall, FGT1 was well-tolerated and behaved like the natural functional fibrinogen; its pharmacokinetic properties are in line with those expected from a fibrinogen concentrate (Table 1). The efficacy and safety of this new triple-secured fibrinogen concentrate has also been evaluated in a multicenter, noncontrolled, phase II study[4] that assessed the treatment of postpartum hemorrhage and suggested the efficacy of FGT1 to control postpartum hemorrhage in cases of first-line treatment failures. These results are to be confirmed by larger controlled trials.

Acquired Fibrinogen Deficiency

Laboratory, animal, and clinical studies have consistently shown that pasteurized fibrinogen concentrate significantly raises the levels of fibrinogen and improves clot firmness. Fibrinogen substitution has been reported to reduce bleeding and postoperative transfusion requirements and to protect against postpartum bleeding at levels greater than 2 g/L.[5-7] Low frequency of serious events and no local reactions were recorded during the observation period.

H&O Are there any ongoing investigations on how to better use fibrinogen concentrates?

Most of the current knowledge on the function, mode of action, and clinical potential of fibrinogen concentrate is based on laboratory studies, a few animal studies, retrospective studies, and clinical reports. Therefore, more controlled clinical studies would be desirable and are in progress. Optimizing the clinical use of fibrinogen concentrate requires more studies that address various dose regimens and monitoring. Also, it is important to focus on the thrombotic risk in patients affected by afibrinogenemia.

The increasing need for fibrinogen preparations has prompted some companies to improve existing preparations or to develop new ones. FGT1, containing 1.5 g of fibrinogen, has been announced for marketing authorization by the LFB; the manufacturing process includes 3 specific biologic safety steps for the inactivation/removal of a wide range of viruses of diverse physicochemical characteristics.

Moreover, the Dutch Pharming Group N.V. has initiated the development of a recombinant human fibrinogen (rhFIB), which is currently in phase II studies. The commercialization of this or other fibrinogen recombinants would be an important achievement for safety reasons because the manufacturing of recombinant molecules does not rely on plasma supply. However, because

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Table 1. Combined Pharmacokinetic and Safety Data of Fibrinogen Concentrate Infusion Doses

	Kreuz et al[8]	Negrier et al[3]	Manco-Johnson et al[2]
Type of study	Retrospective open-label	Open, prospective, multicenter	Multinational, prospective, open-label, uncontrolled
Type of patient	Afibrinogenemia or severe hypofibrogenemia, 22–33 years old	Afibrinogenemia, 18–65 years old	Afibrinogenemia, >6 years old
N of patients	6	5	15
Type of product	Lyophilized plasma-derived human fibrinogen concentrate, pasteurized	FibrinogeneT1	Lyophilized plasma-derived human fibrinogen concentrate, pasteurized
Manufacturer	Aventis Behring	LFB	CSL Behring
Dosage	69–71 mg/kg	0.06 g/kg	70 mg/kg
Fibrinogen activity level	1.45 g/L	1.39 g/L	1.3 g/L
Peak	After 40 min	After 1 hour	After 1 hour
Median half life	3–5.3 days	3.4 days	77.1 hours
Duration of observation	240 hours	336 hours	312 hours
Adverse events	Moderate	–	4 mild

fibrinogen concentrates are already unaffordable in many countries, recombinant products will probably be even more inaccessible. It is hoped that new recombinant technologies will increase the availability and markedly reduce the cost of fibrinogen concentrates in the future.

H&O What advancements do you hope to see in the future?

The first major advance would be the development of better assays to diagnose these disorders and to characterize the bleeding and thrombotic phenotypes of patients suffering from fibrinogen deficiencies. This development would be extremely useful for choosing the appropriate treatment and avoiding unnecessary exposure to blood-derived products. Concerning the choice of fibrinogen substitute, fibrinogen concentrates are presently the best option. However, in many countries, only fresh-frozen plasma or cryoprecipitates are available, which is problematic because the viral inactivation process is not as efficient for these products as it is for fibrinogen concentrates, and they can induce a volume overload. New fibrinogen preparations, including recombinant fibrinogen, are under development. These products are expected to be safer than current preparations in use; however, for cost reasons, it is unlikely that recombinant products will be available to all patients.

Additionally, we need more basic research on the thrombogenicity of fibrinogen products in patients with either afibrino/hypofibrinogenemia or dysfibrinogenemia.

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