NAC Statement on Fibrinogen Concentrate Use in Acquired Hypofibrinogenemia

NAC STATEMENT ON FIBRINOGEN CONCENTRATE SUBCOMMITTEE

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LIST OF ABBREVIATIONS

NAC	National Advisory Committee for Blood and Blood Products
FC	Fibrinogen concentrate

SUMMARY OF REVISIONS

Revision Date	Detail
January 2021	Revision of document title from "NAC Statement on Fibrinogen Concentrate" to "NAC Statement on Fibrinogen Concentrate Use in Acquired Hypofibrinogenemia"
	Update of fibrinogen concentration in cryoprecipitate and plasma, with new references
	Clarification inserted that plasma should not solely be used for fibrinogen replacement.
	Added language re: licensure of FIBRYGA for acquired hypofibrinogenemia
	Inserted suggested timeframe for fibrinogen level reassessment following fibrinogen replacement therapy
February 2020	Added discussion on RiaSTAP and FIBRYGA as two brands of fibrinogen concentrate now available from CBS
	Added reference for the FIBRES study
	Added statement on fibrinogen concentrate having a favorable safety profile over cryoprecipitate or frozen plasma for fibrinogen replacement
July 2018	Addition of dosing recommendations for pediatric patients
	Clarified suggested fibrinogen replacement threshold for obstetrical patients

SECTION 1.0: FIBRINOGEN REPLACEMENT PRODUCTS IN CANADA

Fibrinogen replacement in the setting of acquired hypofibrinogenemia plays an important role in management of massive bleeding post cardiac surgery, trauma and obstetrical hemorrhage among others. However, there continues to be a lack of evidence firmly guiding fibrinogen replacement product choice as well as ongoing uncertainties as to the optimal target and dose. Fibrinogen concentrate (FC), plasma (including both frozen plasma (FP) and fresh frozen plasma (FFP)), and cryoprecipitate are currently used to treat acquired hypofibrinogenemia.

There are two FC products currently available in Canada: RiaSTAP (CSL Behring) and FIBRYGA (Octapharma) (1,2). Both are licensed for treatment of acute bleeding episodes and perioperative prophylaxis in adult and pediatric patients with congenital afibrinogenemia and hypofibrinogenemia. FIBRYGA is also licensed as a complementary therapy during the management of uncontrolled severe bleeding in patients with acquired fibrinogen deficiency during surgical interventions (2). The use of fibrinogen concentrates in acquired hypofibrinogenemia is supported by studies, including a high-quality randomized trial in bleeding patients undergoing cardiovascular surgery (3).

According to data provided by the manufacturers, in addition to fibrinogen, fibrinogen concentrates contain trace amounts of the other substances, such as FXIII and fibronectin. These substances are not listed as active ingredients in the product monograph and the concentrations in the final product may vary. As such, their clinical relevance, if any, is unknown. Furthermore, both fibrinogen concentrates appear to have similar efficacy in improving clot firmness in a dilutional hypofibrinogenemia model *in vitro* (4).

The major difference between these products is related to the product storage: FIBRYGA is stored at room temperature for up to 36 months whereas RiaSTAP is stored in a refrigerator for up to 60 months (1,2).

Plasma is indicated for replacement of multiple clotting factor deficiencies and should not be used solely for fibrinogen replacement. FP and FFP are considered equivalent in terms of clinical effectiveness. The additional risks of plasma transfusion include transfusion associated circulatory overload (TACO), transfusion related acute lung injury (TRALI) and allergic reactions.

Cryoprecipitate is prepared from slowly thawed FP and is indicated for replacement of fibrinogen in patients with congenital and acquired fibrinogen deficiency (quantitative or qualitative) in the setting of bleeding or an increased risk of bleeding (ex. impending major surgery).

Currently, there is no evidence of superiority of one fibrinogen replacement source over the others in terms of clinical effectiveness. However, fibrinogen concentrate is pathogen inactivated and has a preferred safety profile in terms of transmissible disease risk as compared to frozen plasma and cryoprecipitate. Furthermore, fibrinogen concentrate offers many

logistical advantages, including a more precise fibrinogen dose, simpler preparation (without need for thawing and with capability for bedside reconstitution), and efficiency of administration.

SECTION 2.0: FIBRINOGEN CONCENTRATE DOSING

Fibrinogen content of the above-mentioned products is as follows (1,2,5-7):

- FC = 0.9 – 1.3 g per vial
- FFP (thawed) = 2.79 +/- 0.50 g/L
- FP (thawed) = 2.94 +/- 0.63 g/L
- Cryoprecipitate = 0.366 +/- 0.115 g per unit

Optimal dosing of the above-mentioned products is affected by:

- The inter-donor variability of fibrinogen content in blood components
- Each unique patient clinical situation, including size, amount and rate of bleeding, baseline fibrinogen level, liver synthetic function and underlying diagnosis.

In a bleeding obstetrical patient with acquired hypofibrinogenemia, fibrinogen replacement is indicated when fibrinogen level is less than 2.0 g/L (8,9). In a massively bleeding or preoperative patient with acquired hypofibrinogenemia, fibrinogen should be replaced when the level is less than 1.5 g/L (10-12).

Options for fibrinogen replacement in adult patients with acquired hypofibrinogenemia include the following:

- FC: 2-4 g
- Cryoprecipitate: 10 units (1 unit/10 kg)
- FP or FFP: 3-4 units (10-15 mL/kg)

In neonates and pediatric patients, it is recommended to consult with the product monograph and a specialist with expertise in managing pediatric/neonatal coagulopathy prior to administration of fibrinogen concentrates. In published studies (13-14) of acquired hypofibrinogenemia in neonatal or pediatric populations, fibrinogen concentrate dosing has ranged between 30-60 mg/kg.

Following administration of a fibrinogen replacement therapy, repeat bloodwork should be completed within 60 minutes to assess the degree of fibrinogen increment. The expected increment is approximately 0.5-1.0 g/L (3,7,14).

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