NAC Statement on Fibrinogen Concentrate

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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
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 CONCENTRATE DOSING

Fibrinogen replacement 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), frozen plasma (FP), and cryoprecipitate are currently used to treat acquired hypofibrinogenemia, while fibrinogen concentrate is licensed for treatment of congenital hypofibrinogenemia.

Fibrinogen content of the above mentioned products is as follows (1-4):

- 1 vial FC = 0.9 – 1.3 g fibrinogen
- 1000 mL FP = 2.94 +/- 0.63 g fibrinogen (1 SD)
- 1 unit cryoprecipitate = 0.285 +/- 0.088 g fibrinogen (1 SD) or no more than 5g of fibrinogen per pool of 10 units (D. Devine (dana.devine@blood.ca), email communication December 14 2019).

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 2.0g/L (5). In a massively bleeding or preoperative patient with acquired hypofibrinogenemia, fibrinogen should be replaced when the level is less than 1.5g/L (6-8).

The following fibrinogen replacement options with suggested doses may be used in hypofibrinogenemic adult patients:

- FC: 2-4g
- FP: 3-4 units (10-15 mL/kg)
- Cryoprecipitate: 10 units (1 unit/10 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 (9-11) of acquired hypofibrinogenemia in neonatal or pediatric populations, fibrinogen concentrate dosing has ranged between 30-60 mg/kg.

SECTION 2.0: FC PRODUCTS IN CANADA

There are two FC products currently available in Canada: RiaSTAP (CSL Behring) and FIBRYGA (Octapharma) (3,4). Both are licensed for congenital hypofibrinogenemia. The use of fibrinogen concentrate in acquired hypofibrinogenemia is currently off-label, but is supported in bleeding cardiovascular patients by a recent high-quality randomized trial (12).

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* (13).

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 (3,4).

At this time, there is no evidence of superiority of one fibrinogen replacement over the others in terms of clinical efficacy. 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.

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