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Proposal to Change the UK Specification for Methylene Blue-Treated Cryoprecipitate

Rebecca Cardigan, 29th October 2008

Background

MB-FFP was introduced in the UK in 2002 for those born after January 1st 1996, and in 2004 plasma for manufacture of this component began to be sourced from North America as part of risk reduction strategies for vCJD. In 2005 the use of imported, MB treated FFP was extended to those under 16 years of age. The Department of Health have recommended that the use of imported, methylene blue treated plasma be extended to production of cryoprecipitate for recipients under the age of 16 based on advice from MSBTO. SACBC/JPAC approved MB treated cryoprecipitate as a new product some years ago based on validation data from SNBTS. The specification for coagulation factor content of MB treated cryoprecipitate is currently the same as for untreated: >75% units must contain >70IU FVIII and >140mg fibrinogen and there is no UK specification for the volume of this product. SNBTS have been producing MB cryoprecipitate since 2003, and NHSBT are in the process of rolling this product out.

Data from validation studies/routine quality monitoring

Data from SNBTS suggests that the current specification for FVIII content cannot be met consistently in routine production, and similar results have been obtained in recent operational validation studies in NHSBT (see table).

	NHSBT phase 0 data (n=20)	NHSBT phase 1 data (n=137)	SNBTS routine QM data (2003-2008, n=466)
Volume (ml)	60 (sd 4)	38 (24-42)	48 (29-131)
FVIII (IU/ml)	2.16 (sd 0.70)	2.31 (0.40-5.20)	
FVIII (IU/unit)	131 (sd 43)	87 (14-198)	79 (8-247)
% units >70IU	-	66	57
% units >50IU	-	82	82
Fibrinogen (g/l)	5.36 (sd 2.06)	6.70 (1.18-15.40)	
Fibrinogen (mg/Unit)	302 (sd 86)	252 (41-600)	219 (62-752)
% units >140mg	-	88	91

It is well documented that the MB treatment process results in a decrease in activity of various coagulation factors, most notably a 20-30% decrease in the activity of factor VIII, factor XI and fibrinogen (Zeiler *et al*, 1994;Riggert *et al*, 2001;Williamson *et al*, 2003;Garwood *et al*, 2003). We have investigated the effect of MB treatment of cryoprecipitate on clot formation using rotational thrombelastometry and shown that despite the loss of coagulation factor activity, clot strength is relatively unaltered (Cardigan et al,2008). The UK specification for factor VIII activity of MB treated FFP is lower than that of standard FFP (0.50 IU/ml as opposed to 0.70 IU/ml) to reflect the loss of FVIII that occurs during treatment. However, the specification for FVIII content of MB treated cryoprecipitate is the same as for untreated cryoprecipitate. This is not only inconsistent, but it means that the specification cannot be met consistently.

The way forward

Since the FVIII content of cryoprecipitate is a function of FVIII concentration and the volume of the unit, there would appear to be two options:

1) Increase the volume of cryoprecipitate so that the current specification of 70IU FVIII is met or;
2) Decrease the specification for FVIII content to 50IU/ml and keep the volume as it is. Data suggests this specification can be met.

It would seem sensible to decrease the specification for FVIII content in view of the fact that a) it is desirable to keep the volume of cryoprecipitate transfused as low as possible and b) the FVIII content

of cryoprecipitate is not clinically relevant since this product is not recommended for the treatment of haemophilia A and is mainly transfused to treat acquired hypofibrinogenaemia (BCSH Guidelines). My own personal (and well documented!) view is that FVIII content should be removed from the specification of cryoprecipitate all together, but that would require changes to the EU Directive and Blood, Safety and Quality Regulations.

Recommendation

That the specification for FVIII content of MB treated cryoprecipitate is changed from >75% units >70IU/unit to >75% units > 50IU/unit. The specification for fibrinogen content should remain unaltered at >140mg/unit.

References

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