Pathogen inactivated fresh frozen plasma: solvent-detergent (SDFFP) and methylene blue (MBFFP)

Overview

SDFFP and MBFFP are the two main types of pathogen inactivated plasma under consideration for use by hospitals in UK at present. Both components show differences compared to standard quarantined FFP. These and other points are described below.

A summary comparison of SDFFP and MBFFP can be found in the table in the BCSH guidelines for the use of fresh frozen plasma, cryoprecipitate and cryosupernatant [1].

Department of Health and SaBTO guidance

In 2006 the DH issued a letter to hospitals about the use of imported plasma for children; available on the following link:

http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_4127673

This recommends the use of MBFFP for children, and SD plasma for plasma exchange in TTP.

No further instruction on the use of FFP has been issued by the DOH since the letter in 2006.

In July 2009, SaBTO recommended importation of plasma for all age groups, as follows:

- Use of UK-derived FFP should be ceased, and replaced by imported FFP for all recipients
- Source countries of plasma should show an estimated subclinical vCJD prevalence of at least 3 log below that of the UK (but in principle the lower the better)
- Use of pooled FFP is acceptable where a combination of sourcing and processing results in a 4-5 log decrease in relative risk compared with UK-derived FFP

This recommendation has not yet been approved by Ministers. SaBTO plans to contact the BCSH for advice on whether SDFFP is suitable for all patients if Ministerial approval is received.

In answer to the Question “In the event of a shortage of MBFFP for use in the under-16s, does SaBTO have a view on what alternative approach should be taken?”, SaBTO agreed with the vCJD Working Group that the recommendation should be SDFFP sourced from the US, preferably with a prion-reduction step once licensed.

vCJD risk

The plasma for the manufacture of MBFFP is sourced from Europe, from a country with a lower risk of vCJD than the UK. The only licensed SDFFP in the UK is currently sourced from both Europe and the USA. At the present time not all groups of SDFFP are manufactured from US plasma but by mid 2011 all SDFFP imported into the UK will be sourced from the USA. As SDFFP is a pooled product, the plasma must be sourced from the USA, or a prion reduction process included, to meet the SaBTO stipulation of 4-5 log reduction in vCJD risk.

Emerging pathogens

SDFFP is manufactured by pooling up to 1500 plasma donations whereas MBFFP is manufactured from single units. The donor exposure is therefore greater for SD FFP and this may increase risk of transmission of emerging pathogens.

Pathogen reduction

SDFFP and MBFFP have a similar profile with respect to pathogen reduction.

The Solvent Detergent process inactivates all enveloped viruses by disrupting the lipid envelope. The most important non-enveloped viruses are Parvovirus B19 and Hepatitis A virus, for which genome testing is done to prevent transmission. There have been no reported transmissions of HIV, HCV or HBV from SDFFP.

MB also inactivates most enveloped viruses but non-enveloped are more resistant. The risk of transmission of non-enveloped viruses is no greater than for standard FFP, and this is a rare event.

Other transfusion complications

TRALI has not been reported following transfusion of SDFFP – it is thought that the plasma pooling dilutes out the antibodies associated with the pathogenesis of TRALI.

To reduce the risk of TRALI from MBFFP, plasma is sourced from male donors. There have been no reports of TRALI following NHSBT MBFFP transfusion.

The risk of allergic reactions to MBFFP is the same as for standard FFP. The risk is likely to be reduced for SDFFP due to plasma pooling.

Coagulation factor content

SD plasma can be guaranteed to contain > 0.5 IU of all clotting factors since these can be tested in the pool. There is loss of approximately 15% fibrinogen, 20 – 30% Factor VIII, 15 – 20% Factor XI and 10 – 15% Factor XIII, with other factors < 5 % loss.

There is also loss of plasminogen (15 – 20%), alpha-2 antiplasmin (50%), Protein C (10%) and Protein S (30 – 40%) during the SD process, which is not seen in the MB process, these factors showing > 95% recovery. Loss of Protein S and alpha-2 antiplasmin could result in thrombotic complications or hyperfibrinolysis in certain clinical situations.

The MB treatment process results in a decrease in activity of various coagulation factors, most notably a 20-30% decrease in factor VIII and fibrinogen. The decrease in fibrinogen is observed when assayed using a functional (Clauss) assay, but not using antigenic assays, which suggests that MB treatment affects the biological activity of fibrinogen and not the concentration of fibrinogen protein per se. It has also been shown that MB treatment does not alter fibrinogen when assayed by clottable protein assay. Due to this product being sourced from a single donor there is a variability of coagulation factors per bag.

The specification for Factor VIII content is > 0.5 IU/mL for both SDFFP and MBFFP.

Use of PR plasma

There is wide experience of use of both SD and MB plasma in European countries. Finland, Norway and Ireland have used SD plasma exclusively for some years. France, Germany, Italy and the UK (for TTP patients) also use SD plasma. There is considerable experience with MB plasma in Spain, Belgium, France and Italy as well as the UK.

Several hospitals in the UK have taken the decision to switch to SDFFP for children and are in the process of implementing this change – the rest have been using MB FFP for children since its introduction.

Summary

NHSBT currently provides MBFFP for children following previously expressed preferences from users and DH guidance, but current feedback from hospitals suggests that this preference may be changing, for several reasons including cost.

Selection of plasma components on grounds of safety profile, should also acknowledge the observation that the safest transfusion is the inappropriate or unnecessary transfusion that was never given. There is abundant evidence, including from the recent National Comparative Audit of FFP [2] that FFP continues to be commonly used in adult and paediatric patient settings where many specialists would regard its transfusion as inappropriate e.g. prophylactically in non-bleeding patients with no or mild (or moderate) abnormalities of standard coagulation test (e.g. prothrombin time).

Compared to quarantined FFP, pathogen reduced plasmas offer advantages of additional security from transfusion transmitted infections, as well as other potential benefits, although coagulation factor content is significantly reduced.

There are differences between SDFFP and MBFFP in terms of increased consistency of product for SDFFP vs. decreased risk of transmission of emerging pathogens with MBFFP. The currently available SDFFP product, will be sourced solely from the USA by the summer of 2011 and will therefore then meet the SaBTO recommendation that source countries of a pooled product should show an estimated subclinical vCJD prevalence of 4-5 logs below that of the UK, although at present this is not the case for all ABO groups.

References

1. BCSH Transfusion Task Force. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. Brit J Haematol 126, 11-28 (2004)
2. Stanworth SJ, Grant-Casey J, Lowe D, Laffan M, New H, Murphy MF, Allard S. The use of fresh frozen plasma in England: high levels of inappropriate use in adults and children. Transfusion 2010 Aug 27