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Focus on fresh frozen plasma – facilitating optimal management of bleeding through collaboration between clinicians and transfusion specialists on component specifications

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Summary

Background > A symposium on plasma for direct clinical use was held in September 2015 by the European directorate for the quality of medicines and healthcare (EDQM) in order to consider changes to the Council of Europe guide to the preparation, use and quality assurance of blood components monographs on plasma components.
Methods > The programme reviewed use of plasma in various settings, novel components, adverse reactions, manufacturing and quality monitoring issues.
Results > The main requirement identified was that plasma should be made available to support early transfusion in the trauma/massive haemorrhage setting. Further guidance on component manufacturing and reviewing of quality monitoring requirements will also be addressed.
Conclusion > A working group has been established to review component monographs and other advice in the guide relating to plasma components, with the aim of providing optimal components to support clinical management of patients requiring plasma.

Introduction

The primary indication for fresh frozen plasma (FFP) is to correct a deficit in coagulation factors in the patient, particularly when the deficit is accompanied by bleeding.
Clinical guidelines for the therapeutic use of fresh frozen plasma (FFP) defining indications for FFP transfusion, and for management of massive haemorrhage in which FFP transfusion is critical, have provided guidance for some years [1–4]. Traditionally, these have stated that "formula" replacement of plasma and platelets in the management of bleeding should not be used, but instead FFP transfusion should be guided by results of coagulation tests. Recent publications, however, have emphasised that early transfusion of plasma in acute trauma is associated with improved survival, and new recommendations on the speed of delivery of FFP in the acute trauma setting have emerged [5,6].

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FFP is "fresh frozen" because unless it is frozen within a reasonable timescale after collection, the coagulation factor activity will deteriorate. The FFP needs to be thawed out in controlled conditions before administration which will normally take approximately 20 minutes. In urgent situations, this can cause significant delay in treatment. Emergency departments and prehospital care providers are increasingly demanding access to appropriate doses of FFP in a form they can use immediately, i.e. not frozen.

Regarding the "dose" of FFP, it might seem logical to replace ongoing blood loss of whole blood with the same product (i.e. whole blood). The majority of blood services, however, no longer have whole blood available as they prefer to make the most of this donated gift by manufacturing blood components which can be stored in the most optimal conditions and which can be targeted to recipients who need each. Recent evidence suggests that even if whole blood is not available, use of plasma and platelets in a ratio approaching that in whole blood is beneficial [7].

The Council of Europe guide to the preparation, use and quality assurance of blood components is now in its 18th edition [8]. This publication, hereafter named the "Guide", is widely used throughout Europe and has also been adopted by other countries outside Europe, providing harmonised guidance for blood services on all aspects of provision of blood components including blood component specifications. The Guide is updated regularly (initially annually, now biannually) by a Expert working group operating under the aegis of the Council of Europe european committee (partial agreement) on blood transfusion (CD-P-TS) and each new edition is subject to wide public consultation before its publication.

The specifications for clinical use plasma components in the Guide state that they should be used as soon as possible after thawing. These specifications have not been revisited for some years, and consultation reveals that they are no longer aligned with current practice in many clinical establishments who now ask for plasma to be immediately available.

In order to review and update specifications where necessary, a symposium entitled "plasma for direct clinical use" was held in Strasbourg on 22–23 September 2015, organised by the European directorate for the quality of medicines and healthcare (EDQM) within the Council of Europe. The aim of the symposium was to address comments and requests for change arising from the consultation process by reviewing all aspects of FFP with a view to considering amendments to the Guide: examining use of FFP in European countries, defining what clinicians required from FFP and how as blood services we could fulfil these requirements, and also considering quality monitoring aspects so that we could ensure that components fully meet the needs of clinicians. This report summarises the information presented, points raised during discussion and plans for revision of the Guide with respect to plasma components.

Survey of use of components

There are four plasma components currently listed in the Guide: FFP, FFP pathogen reduced, cryoprecipitate and cryoprecipitate-depleted plasma. Prior to the symposium, a survey was conducted of use of plasma components amongst the CD-P-TS member countries. Twenty-four responses were received from 19 out of the 35 countries surveyed. All responders use FFP; 9/19 countries manufacture cryoprecipitate and five use cryoprecipitate-depleted plasma. Only one country uses non-frozen fresh plasma, two extended post-thaw shelf life plasma (7–14 day shelf life) and two lyophilised plasma (military use only). Two thirds leucodeplete plasma and a majority have processes for limiting the risk of transfusion transmitted infections (either pathogen reduction or quarantine). There was a marked variation in handling of plasma around freezing with differences in storage temperatures and time pre-freeze, while frozen and post-freeze. Although most countries performed quality monitoring of components as listed in the Guide, there was no clear information about whether these are useful and relevant. Conclusions from this exercise were that evidence-based guidance is needed on which components are clinically effective (and should therefore be listed in the Guide), best practice in manufacture and handling, and determination of most appropriate quality monitoring tests.

Clinical use of plasma; what do clinicians need?

The scientific committee were keen to begin with information from clinicians about clinical use of plasma, to gain an understanding of what factors were important in determining efficacy of plasma components and how these could be built into the review of specifications.

The overriding message coming over was that what clinicians value most about FFP is ready availability in the acute trauma/massive haemorrhage setting. As previously highlighted, there is evidence from randomised controlled trials that early transfusion of FFP reduces bleeding and mortality [5]. Some blood services have achieved ready availability by use of extended thawed plasma, others by use of liquid (never-frozen) plasma. One consequence of provision of liquid or extended thaw plasma is increased wastage if the component is not required – the longer the shelf life of the component the lower the wastage rate. Concerns about reduced coagulation factor levels and potential reduced efficacy was not borne out in one study in which use of extended shelf life liquid plasma was not seen to be associated with any difference in mortality [9].

The use of visco elastic tests at the bedside rather than laboratory-based classic coagulation tests during management of massive haemorrhage is increasing and these seem to provide a more immediate and accurate measurement of coagulation status. If there is clinical evidence of effect, then routine