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].
FFP is "fresh frozen" because unless it is frozen within a reason-
able 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 pre-
hospital 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 compo-
ments 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 coun-
tries outside Europe, providing harmonised guidance for blood services on all aspects of provision of blood components includ-
ing blood component specifications. The Guide is updated regu-
larly (initially annually, now biannually) by a Expert working group operating under the aegis of the Council of Europe euro-

pean 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 Euro-

pean 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 require-
ments, 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 con-
ducted 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 cryopre-
cipitate-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 vari-
ation 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 moni-
toring 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 guid-
ance 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 appro-
priate 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 under-
standing 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 trans-
fusion 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 labora-
tory-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
monitoring may be unnecessary – if clinical improvement is not seen then whole blood tests such as ROTEM or thromboelastography may be able to guide therapy.

There is no clear consensus on what active ingredient(s) FFP must contain in order to be effective. Haemostasis is likely to be adequate if coagulation factors are greater than 30% [10]. There is some evidence in animal models that clotting factor VIII (FVIII) is less important than fibrinogen in reducing bleeding [11]. More recently, it has been postulated that vascular endothelial damage plays a role in coagulopathy of trauma and adiponectin and other factors contained in plasma may help to restore this [12, 13].

The case for transfusion of FFP as prophylaxis prior to invasive procedures is less clear. Coagulation tests do not appear to predict the risk of bleeding in this situation and administration of prophylactic plasma in these circumstances is in most instances not indicated [10,14].

ABO identical FFP is considered the ideal to prevent problems from minor mismatches. RhD compatibility does not appear to be a problem but it was felt that criteria for maximum red cell content should be developed to ensure prevention of immunisation [15]. Adverse events due to FFP transfusion appear to be rare but more standardisation of haemovigilance definitions would enable better comparison between countries and plasma types [16].

**Manufacturing of FFP**

There is good evidence that elements of the process of manufacturing FFP, particularly storage temperature and time pre-freeze and rate of freezing, can affect the coagulation factor activity of the component [17]. Levels of FVIII and protein S are reduced most. Clear guidelines on the manufacturing process are therefore required to ensure the maximal effectiveness of FFP.

**Quality monitoring**

Quality monitoring tests are routinely performed on a proportion of blood components produced, and requirements for this are set out within the specification in the Guide. Routine quality monitoring has two main functions – it provides an indication that the manufacturing process is in control and being applied as validated, but also provides assurance that the component meets specification and is likely to be clinically effective [18]. The EU directive requires measurement of FVIII, total protein and residual cellular content for FFP; fibrinogen and FVIII for cryoprecipitate [19]. Fibrinogen is the most important factor clinically in cryoprecipitate, however measurement of FVIII in FFP is arguably not – shortage of FVIII is not the main indication for transfusion of FFP. However, as FVIII is one of the most labile factors and affected by any problems with manufacturing, there is an argument for retaining it as a monitoring test. Total protein estimation is only relevant if plasma is to be provided for fractionation according to specifications laid down in the European pharmacopoeia monograph “Human plasma for fractionation 0853”.

**Discussion**

A series of questions were posed at the outset of the symposium and the final discussion session centred on these.

**When is plasma required and at what dose?**

It was agreed that this depended on whether the indication was for treatment of haemorrhage or for prophylaxis. In massive bleeding, the current standard is now to give plasma as soon as possible in the urgent situation in a 1:1:1 ratio with red cells and platelets. For prophylactic use, there appears to be no evidence of efficacy – FFP might have some role but this remains unclear.

**What do clinicians need from plasma components? – is this the same for all indications?**

The ideal coagulation factor content of plasma is not clear and it is possible that different types of plasma may be more appropriate for different clinical indications. There are two monographs in the Guide for FFP with different specifications for FVIII content (FFP and FFP pathogen reduced) but these are used interchangeably clinically. There is also emerging interest in other factors that are contained in plasma which may act to stabilise endothelial integrity such as adiponectin.

It was noted that there is a resurgence of interest from some clinicians in a return to whole blood in the trauma setting, although this provides logistical problems for blood establishments. There should be ongoing dialogue between blood establishments and clinicians about providing optimal components, whether that is whole blood or immediately accessible (liquid) plasma. If liquid plasma is provided, storage time should be defined.

There was a question whether fibrinogen concentrate was a suitable alternative to FFP; however, some felt that FFP was a better product in the trauma setting and there appears to be two schools of thought on this with little underpinning evidence.

**What components achieve these requirements best and which should be listed in the COE Guide?**

Ready availability of liquid plasma was considered the key. It was agreed to consider both frozen thawed and non frozen plasma. Additional monographs for pooled plasma and cryoprecipitate were suggested although some felt that we should not include too many different products.

**What parameters should be sought for evidence of efficacy?**

Clinical endpoints (i.e. stopping bleeding) are preferable to surrogate markers such as laboratory endpoints.

**Are more clinical studies required?**

Clinical studies are expensive and they do not always provide a definitive answer. A large number of trials with high numbers of
trauma patients have already been completed – it is important to clearly define the research question and make sure that any cost of running a trial would be balanced by a clear outcome.

What laboratory testing is required to ensure that components are fit for purpose?
There was much discussion about whether measurement of FVIII is an appropriate test to indicate process consistency; there was not much support for dropping this requirement in the absence of a viable alternative measure. It was agreed that there should be consideration of whether other factors are important in addition. Process consistency can also be ensured by adherence to GMP requirements, validation, etc. The main question is what proportion of components should comply with the specifications. It was reported that 0.3–0.4 IU/mL FVIII still generates thrombin and this correlates with observations in haemophiliacs.

Are regulatory changes necessary to make sure that requirements are achieved consistently?
Total protein content is irrelevant for clinical use components and could be removed.

Conclusion and next steps
The symposium provided an extremely useful forum for collaboration between clinicians and transfusion specialists in working towards provision of the most appropriate plasma components to meet need. It is clear that in order to support clinicians in management of massive haemorrhage, revision of the Guide plasma monographs is required. A working group has therefore been formed to review evidence and consider:
- change to current monographs;
- extension of post-thaw storage;
- new monograph:
  - liquid plasma (non-frozen);
- review of quality monitoring requirements;
- clarification of manufacturing steps.

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