COUNCIL OF EUROPE
COMMITTEE OF MINISTERS

RECOMMENDATION No. R (86) 6

OF THE COMMITTEE OF MINISTERS TO MEMBER STATES

ON GUIDELINES FOR THE PREPARATION, QUALITY CONTROL AND USE OF FRESH FROZEN PLASMA (FFP)

(Adopted by the Committee of Ministers on 13 March 1986 at the 394th meeting of the Ministers' Deputies)

The Committee of Ministers, under the terms of Article 15.*b* of the Statute of the Council of Europe,

Considering that the aim of the Council of Europe is to achieve a greater unity between its members for the purpose of facilitating their economic and social progress;

Considering that this aim may be pursued, *inter alia*, by the adoption of common rules in the health field;

Recalling the ethical and clinical principles of blood transfusion and immunohaematology, in particular the need to promote the optimal use of blood and blood products, and to achieve national self-sufficiency in the production of coagulation factor products from voluntary, non-remunerated donors;

Recalling, in particular, its Recommendation No. R (80) 5 concerning blood products for the treatment of haemophiliacs and its Recommendations Nos. R (81) 14, R (83) 8 and R (84) 6 on preventing the transmission of infectious diseases by blood transfusion;

Considering that there is a general shortage of Factor VIII, which is needed for the treatment of haemophiliacs;

Considering that the use of FFP as a blood volume expander not only wastes Factor VIIIc, but also carries a risk of transmitting infectious diseases;

Considering that albumin solutions are equally effective in the expansion of blood volume and do not transmit infectious diseases,

Recommends that the governments of member states take all necessary measures and steps to ensure that the preparation, quality control and use of fresh frozen plasma are carried out in accordance with the guidelines set out in the appendix to this recommendation.

Definition of fresh frozen plasma (FFP)

FFP is a constituent of blood needed to reconstitute the clotting properties of the patient's blood (by virtue of the properties of the various coagulation proteins) and very occasionally to restore the plasma volume of the patient. There is no particular problem in preserving the intrinsic properties of albumin, but it is more difficult to preserve those of the coagulation proteins, in particular Factor VIII ; great care must be taken both during collection (particular attention being paid to the time it takes) and during freezing.

1. **Preparation of FFP**

1.1. *Plasma collection*

FFP may be prepared either from units of whole blood or from material collected by (manual or automatic) plasmapheresis. It is important that the volume of solution used to collect and store the blood should be the same as is normally used for collecting blood, so that the ratio of solution to collected blood is always between about 1:6 and 1:9. This constraint has to be complied with, especially in the case of machine collection, in order to prevent the plasma from becoming too dilute. In order to avoid any tendency to clotting, which would use up a greater or lesser proportion of the coagulation factors, attention should be paid to the following :

— Collection must be perfect, so that the blood flows at the maximum rate allowed by the bore of the needle (at least 16/10 mm). The needle should be properly inserted in the vein at the first attempt, and the flow of blood should be rapid from the start and remain constant until the operation is complete. It is recommended that the total time taken to collect the blood be not more than 10 minutes (at an approximate rate of 40-45 ml/minute).

— The blood and the anti-coagulant/preservative solution should be thoroughly mixed, if possible by shaking combining rotary and rocking motion. Shaking is particularly important at the end of the collection process when donor blood comes into contact with an anti-coagulant that has already been highly diluted in the blood previously collected.

— No donor blood (blood not mixed with the preservative anti-coagulant solution) should remain in contact with blood that has already been mixed : the collection tube should be drained and filled with mixed blood, either by expulsion into the bag or by suction into a sterile vacuum tube.

No blood that has not been collected under these conditions should be used to prepare FFP.

1.2. *Centrifugation and decantation*

Centrifugation should be carried out in such a way as to remove as many platelets as possible (so as to prevent these cellular bodies from initiating clotting). Centrifugation at 5-7°C for 20 minutes at 3 000 g or for 15 minutes at 4 000 g is sufficient to obtain high-quality FFP without damaging the erythrocytes. In the case of plasmapheresis, especially manual, but also machine plasmapheresis (non-filtering), a second centrifugation is necessary if not all the platelets have been removed. It is recommended that, in any event, the residual number of platelets be less than 20-25 x 10^9/l.

Decantation is carried out in the same way as in the preparation of other blood components, in a closed system under pressure, protected from contamination.

1.3. *Freezing*

This should be done as soon as possible after collection, and at any rate within six hours (with one hour tolerance).

The complete freezing process should be as short as possible. Experience has shown that it sometimes takes several hours in an atmosphere at −30°C. The time must be reduced to less than two hours, and if possible to one hour, by the following means :

— spreading the plasma in a thin layer (bags laid flat and not arranged vertically) ;

— freezing in a liquid environment (alcohol at −35°C) or at very low temperature (dry ice, liquid nitrogen cryostat) .

1.4. *Storage*

The aim is to preserve the coagulation factors for a reasonable storage time (up to one year): refrigeration units should be fitted with a recording thermometer with an audible alarm and should maintain a uniformly low temperature within.

Experience has shown that the most labile coagulation factors can be preserved. If the FFP is expected to be stored at sub-zero temperatures for a year, it is recommended that it be kept at a temperature of −30°C or below. Given the cost of efficient refrigerated storage units (maintaining temperatures of −30 or −35°C), a storage temperature of only −25°C to −30°C is permissible if the FFP is to be kept at sub-zero temperatures for no more than six months. It has in fact been shown that at this temperature and over this period of time the loss of activity of Factor VIIIc is negligible.[1] The refrigeration units need to be divided into compartments so as to prevent loss of negative kilo-calories when they are opened, which would cause the ambient temperature to fluctuate. If a refrigeration unit fails and the temperature of the stored products rises to −18°C or above, they should no longer be considered as FFP. Throughout storage in the frozen state, each bag should be placed in a protective cardboard or plastic box to prevent the bags from sticking to one another and splitting during handling.

1.5. *Thawing*

The formation of cryoprecipitates (containing Factor VIIIc, fibrinogen and fibronectin) should be avoided during thawing, for it would reduce the expected clotting properties of the product to a greater or lesser extent when the temperature reaches about zero to 4°C. The way to avoid it is to thaw the product quickly in a thermostatically controlled bath (35°-37°C) with continuous malaxation of the bag throughout the operation.

The FFP should be administered as soon as possible after thawing, and in any event within two hours. During this time it should be preserved at a temperature not exceeding 10°C and should not be refrozen.

2. Quality control of FFP

2.1. *Routine tests*

These tests should be carried out on all blood collected, according to national regulations.

Routine weighing of the bag containing FFP: the weight must be written on the label or be within 10% of the weight pre-printed on the label.

2.2. *Tests on samples of the finished product*

These are carried out every two months on a pool of six units that have been kept for less than a month, and a pool of six units nearing the end of their shelf life.

The most important things to check for in each sample are:

— the absence of flocculates after thawing at 37°C;

— the absence of splits or leaks in the plastic bag;

— the Factor VIIIc content which, in a mixture of six sample units, should not be less than 0,7 IU/ml.

It is important that the procedure for measuring Factor VIIIc should be regularly checked by the laboratory in order to remove the hazards of sample control.

3. Use of FFP

3.1. *Precautions to be taken before injection*

FFP containing anti-A or anti-B haemolysins, or FFP which has not been checked for these should be given only to patients with the same ABO group, or at least to patients having no A or B antigens matching the haemolysins (the rule being that the compatibility is the opposite of that of the red blood cells). In order to avoid any risk of

1. At storage temperatures of −18°C to −25°C, FFP may be kept for no more than three months.

allo-immunisation against antigen D of the Rhesus system, it is necessary, especially in patients at risk (girls, women of child-bearing age, persons who have undergone several transfusions), to administer infusions in which patient and donor have the same characteristics with regard to this antigen.

3.2. *Usual indications for the use of FFP*

FFP is indicated for treating :

— complex deficiencies of coagulation factors, such as consumption coagulopathy, coagulopathy due to severe hepatic failure, and massive transfusions ;

— rare isolated deficiencies of Factors V, VII, X, XI or XIII or AT III and deficiencies of C1 esterase inhibitor when specific factors are not available ;

— all haemorrhages due to clotting disorders, whether as yet unidentified by specific tests or because a specific factor is unavailable ; in the latter case, FFP is to be considered as a temporary substitute for the specific factor.

3.3. *FFP as a blood volume expander*

FFP produces excellent results when used to restore blood volume, but the results would be just as good in the absence of coagulation factors, and it is precisely in order to preserve these that all the above-mentioned expensive precautions are taken.

In view of the general shortage of Factor VIII, which is needed for the treatment of haemophilia, it seems regrettable that the Factor VIII in FFP should be administered to patients who do not need it.

It should also be pointed out that FFP can transmit viral diseases (hepatitis B, other forms of hepatitis and AIDS), whilst albumin solutions, which are just as effective for blood volume expansion, do not.

The use of FFP instead of albumin as a blood volume expander therefore has two major drawbacks : it carries a risk of transmission of infectious diseases and it wastes Factor VIIIc.

Unfortunately, these considerations are all too often overlooked, and FFP is being used increasingly widely for blood volume expansion, when it ought to be saved for the indications listed above. Accordingly, despite the risk of transmission of the same diseases as mentioned in connection with FFP, plasma which does not contain cryo-proteins should, whenever possible, be used instead.