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GUIDELINES

Guidelines for the use of fresh frozen plasma

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SUMMARY. Fresh frozen plasma should only be used to treat bleeding episodes or prepare patients for surgery in certain defined situations.

Definite indications for the use of FFP

1 Replacement of single coagulation factor deficiencies, where a specific or combined factor concentrate is unavailable.
2 Immediate reversal of warfarin effect.
3 Acute disseminated intravascular coagulation (DIC).
4 Thrombotic thrombocytopenic purpura (TTP).

Conditional uses: FFP only indicated in the presence of bleeding and disturbed coagulation

1 Massive transfusion.
2 Liver disease.
3 Cardiopulmonary bypass surgery.
4 Special paediatric indications.

No justification for the use of FFP

1 Hypovolaemia.
2 Plasma exchange procedures.
3 'Formula' replacement.
4 Nutritional support.
5 Treatment of immunodeficiency states.

Key words: clinical use, fresh frozen plasma, guidelines.

INTRODUCTION

Studies of the use of fresh frozen plasma (FFP) have shown that it is often misused (NIH Consensus Conference, 1985; Snyder *et al.*, 1986). This is largely due to the misconceptions regarding its haemostatic effectiveness and inadequate knowledge of the situations in which its use is inappropriate.

In the U.K., the number of units of FFP transfused during the past 15 years has increased greater than 10-fold. Although FFP has been used in an increasingly wide range of clinical situations, in many instances there is no rational basis for its administration.

The purpose of these guidelines is to specify the circumstances in which FFP is the treatment of choice, and those in which its use cannot be justified.

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PROPERTIES OF FFP

FFP is prepared from anticoagulated whole blood by separating and freezing the plasma to a core temperature of −30°C or below, within 6 h of blood collection. FFP can be stored at this temperature for a maximum period of 12 months. The volume of a typical unit is approximately 200 ml (Department of Health, 1989).

Prior to use, FFP must be thawed according to the manufacturer's instructions detailed on the package. It is recommended that a second heat-sealed bag is used for added protection when thawing in a water bath. An alternative option for the future may include the use of a microwave oven to replace the standard 37°C water-bath. The thawed plasma should be administered with a minimum delay (i.e. not more than 2 h) to avoid loss of potency of the coagulation factors.

Under these conditions of processing, FFP will have high levels of all coagulation proteins including the

labile factors V and VIII. The guidelines of the Council of Europe specify that the minimum level of factor VIII in FFP is 0·7 iu/ml. A typical unit also includes:

Sodium 170 mmol/l
Potassium 4·0 mmol/l
Glucose 22 mmol/l
Citrate 20 mmol/l
Lactate 3·0 mmol/l
pH 7·2–7·4

The dosage of FFP depends upon the clinical situation and underlying disorder, but 12–15 ml/kg is a generally accepted starting dose. It is important to monitor the response, both clinically and with measurement of prothrombin time (PT), partial thromboplastin time (PTT) or specific factor assays.

FFP units are labelled with the donor ABO and Rh D group. ABO compatible FFP should be used but compatibility testing is not required. Group O FFP should only be given to group O recipients. On the other hand, group A or B FFP can be given to group O recipients. Because of its scarcity, group AB FFP should be reserved for group AB recipients and rarely for emergencies when the blood group of a patient is unknown.

The small amount of red cell stroma present in FFP is capable of inducing Rh immunization and can boost anti-D levels in subjects with pre-formed anti-D. It is therefore advisable to give Rh D compatible FFP to females of child-bearing age; when this is not possible, anti-D immunoglobulin should be given at a dose of 50 iu per unit of FFP transfused.

Adverse effects

1 Allergic reactions may occur. Urticaria has been reported in 1–3% of patients. The incidence of life-threatening anaphylactic reactions is unknown but has been reported to be as high as 1:20,000 transfusions (Bjerrum & Jersild, 1971).
2 Infectious complications. The risk of infection with human immunodeficiency virus (HIV), hepatitis B, hepatitis non-A non-B and parvovirus following transfusion of FFP is similar to that following the transfusion of whole blood. However, agents transmitted by cellular components are not transmitted by FFP (e.g. herpes viruses, malaria). There have been no reported cases of cytomegalovirus (CMV) transmission (Bowden & Sayers, 1990) or graft-versus-host disease following transfusion of FFP, and therefore irradiation of FFP or the provision of CMV-negative FFP is not required.
3 Haemolysis. If ABO incompatible plasma is infused, potent anti-A or anti-B, which may be present, can cause lysis of the recipient's red cells. Plasma infusion has also been associated with intravascular haemolysis in neonatal patients with necrotizing enterocolitis and associated T activation.
4 Fluid overload. Treatment of severe factor deficiencies is often limited by the patient's ability to tolerate the infused volume of plasma without developing fluid overload. Specific factor concentrates are preferred when available.
5 Very rarely, potent antibodies against the patient's granulocytes may be present in donor plasma. They can cause leucocyte aggregation in pulmonary vessels and acute pulmonary injury, a syndrome known as Transfusion Related Acute Lung Injury (TRALI) (Nordhagen *et al.*, 1986).
6 Recent reports have suggested that plasma infusion may cause immune suppression (Blumberg & Heal, 1988; Hermanek *et al*, 1989).

CLINICAL INDICATIONS FOR THE USE OF FFP

There are few well-documented and universally accepted indications for the use of FFP (NIH Consensus Conference, 1985; Braunstein & Oberman, 1984). They are limited to the treatment of bleeding episodes or preparation for surgery in patients with factor deficiencies where specific factor concentrates are unavailable. There are a number of clinical situations in which the use of FFP has been advocated but has not been shown to be of benefit.

DEFINITE INDICATIONS FOR THE USE OF FFP

Replacement of single factor deficiencies

More specific factor concentrates are becoming available for clinical use and FFP is only required when specific or combined factor concentrates are unavailable. The dose will depend upon the specific factor being replaced, as both the half-life and plasma concentration required for haemostasis vary for individual factors (Table 1). For dosage calculations, 1 ml of FFP contains approximately one unit of coagulation factor activity.

Although specific factor II and X concentrates are unavailable, replacement therapy with a concentrate of combined factors II, IX and X (Prothrombin Complex), not FFP, is recommended in deficiency states. Cryoprecipitate, which contains fibrinogen, fibronectin and factor VIII, should be used as the replacement therapy in patients with a deficiency of fibrinogen (factor I). There is rarely a need for replacement therapy in factor XII deficiency, as its

Table 1. Coagulation factors in plasma

Coagulation factor	Plasma concentration required for haemostasis	Half-life of transfused factor	Stability in plasma and whole blood (4°C storage)	Specific concentrate available
I (fibrinogen)	1 g/l	4–6 days	Stable	No†
II (prothrombin)	0·4 iu/ml	2–3 days	Stable	No†
V	0·1–0·15 iu/ml	12 h	Unstable*	No
VII	0·05–0·1 iu/ml	2–6 h	Stable	Yes
VIII	0·1–0·4 iu/ml	8–12 h	Unstable**	Yes
IX	0·1–0·4 iu/ml	18–24 h	Stable	Yes
X	0·1–0·15 iu/ml	2 days	Stable	No†
XI	0·3 iu/ml	3 days	Stable	Yes
XII	—	—	Stable	No†
XIII	0·01–0·05 iu/ml	6–10 days	Stable	Yes

* Fifty per cent remains at 14 days, ** 25% remains at 24 h; † see text for comment.
Adapted from AABB Blood Transfusion Therapy. *A Physician's Handbook*, 3rd edn, 1989.

Table 2. Recommendations for reversal of oral anticoagulant treatment (BCSH, 1990)

A *Life threatening haemorrhage*
Immediately give 5 mg vitamin K by slow intravenous infusion and a concentrate of factor II, IX, X with factor VII concentrate (if available)
The dose of concentrate should be calculated based on 50 iu factor IX/kg body weight
If no concentrate is available, fresh frozen plasma should be infused (about 1 l for an adult), but this may not be as effective

B *Less severe haemorrhage such as haematuria and epistaxis*
Withhold warfarin for 1 or more days and consider giving vitamin K, 0·5–2·0 mg i.v.

C *INR of >4·5 without haemorrhage*
Withdraw warfarin for 1 or 2 days; then review

D *Unexpected bleeding at therapeutic levels*
Investigate possibility of underlying cause such as unsuspected renal or alimentary tract disease

clinical complications, if any, are those of thrombosis (Ratnoff and Saito, 1979).

Deficiency of von Willebrand factor (vWf) should not be corrected with FFP, as alternative therapy is available. This includes 1-desamino-8-D-arginine vasopressin (DDAVP), and some intermediate purity factor VIII concentrates. Specific vWF concentrates have now been developed so that cryoprecipitate should rarely be needed in this condition.

Immediate reversal of warfarin effect

Patients taking oral anticoagulant therapy have a deficiency of functionally active vitamin K-dependent proteins (i.e. the procoagulant factors II, VII, IX, X and anticoagulant factors, proteins C and S). This functional deficiency can be reversed by the parenteral administration of vitamin K; 4–6 h should be allowed for adequate clinical response in the average patient. Recommendations for the reversal of anticoagulant therapy are outlined in Table 2. In patients who are grossly overdosed and who have developed serious life-threatening bleeding episodes, immediate reversal of anticoagulant therapy is required. The recommended approach is to use a concentrate of factors II, IX and X (PCC) with factor VII concentrate (if available). If these are not available, then FFP should be infused. It must be noted though, that the use of

PCC and factor VII concentrate for reversal of anticoagulation or liver disease has not been approved by the Licensing Authority and can therefore only be undertaken by a doctor at his own responsibility. Clinical trials which address the safety and efficacy of the use of factor concentrates in these specific clinical situations are currently in progress. If it is necessary to treat patients with minor bleeding episodes, such as epistaxis or extensive skin bruising, FFP infusions of between 2 and 6 units will partially correct the anticoagulant effect.

Vitamin K deficiency

Haemorrhagic disease of the new-born, and conditions which may impair vitamin K absorption, such as biliary duct obstruction, are associated with a coagulation abnormality similar to that described with oral anticoagulant therapy. If bleeding results, a similar treatment regimen should be employed.

Acute disseminated intravascular coagulation (DIC)

Disseminated intravascular coagulation (DIC), which can be associated with shock, trauma and sepsis, results in variable deficiencies of factors V and VIII, fibrinogen, fibronectin and platelets due to activation of the coagulation and fibrinolytic systems. The spectrum of presentation is wide, ranging from a compensated state with abnormalities of coagulation demonstrable only in the laboratory, to a fulminant form with major bleeding and thrombotic complications.

The treatment of all patients must first be directed at the cause of the DIC. There is no evidence that any supportive or replacement therapy is of benefit unless it is possible to correct the underlying condition (Mount & King, 1979).

Replacement therapy is indicated in acute DIC, where there is haemorrhage and abnormality of coagulation. The infusion of FFP, cryoprecipitate and platelet concentrates forms the basis of initial therapy. The response should be closely monitored by repeated laboratory tests and clinical assessment, and further replacement judged by both.

In chronic DIC, or in the absence of haemorrhage, there is no indication to give component therapy in an attempt to normalize laboratory results.

Thrombotic thrombocytopenic purpura (TTP)

FFP is the accepted form of treatment for TTP, often in conjunction with plasma exchange (Machin, 1984). At least 3 l/day are generally given.

Inherited deficiencies of inhibitors of coagulation

FFP has been used as a source of antithrombin III (AT III), protein C and protein S in patients with inherited deficiencies of these inhibitors who are undergoing surgery or who require heparin for treatment of spontaneous thrombosis. AT III preparations are now widely available and have been used in the management of patients with inherited deficiencies. Protein C and protein S preparations are becoming available. Several clinical studies are in progress to determine the efficacy of AT III preparations as a prophylactic and therapeutic agent in the management of acquired AT III deficiency, especially shock and DIC (Vinazzer, 1987). These specific preparations will obviate the need for FFP.

C1 esterase inhibitor deficiency

FFP infusion can be used to treat patients with C1 esterase inhibitor deficiency who develop severe angio-oedema. However, specific preparations of C1 esterase inhibitor are becoming increasingly available.

CONDITIONAL USES: FFP IS ONLY INDICATED IN THE PRESENCE OF BLEEDING AND DISTURBED COAGULATION

Massive transfusion

'Massive transfusion' is defined as the replacement of the patient's total blood volume with stored blood in less than 24 h. The occurrence of clotting disorders in patients who receive large volume transfusions is more closely associated with the duration of volume deficit than with the volume of blood transfused (Harke & Rahman, 1980). Early adequate resuscitation from shock is therefore the most important factor in preventing the development of coagulopathy in massively transfused patients. 'Dilution' of clotting factors with stored blood is not commonly the cause of haemostatic disturbance. More important causes include the consumption of platelets and clotting factors and the possible development of DIC in patients who are hypotensive, septic or have pre-existing liver disease (BCSH, 1988; Hewitt & Machin, 1990).

There is no evidence that prophylactic replacement regimens with FFP or platelet concentrates, which have often been advocated, either prevent the onset of abnormal bleeding or reduce transfusion requirements (Mannucci *et al.*, 1982).

To prevent the indiscriminate use of blood compo-

nents in patients receiving massive transfusion, early laboratory assessment is needed to determine the precise nature of any disorders of coagulation which may be present. These patients may develop microvascular bleeding with oozing from the mucosae, raw wounds and puncture sites as a result of thrombocytopenia (platelet count $< 50 \times 10^9$/l) when one-and-a-half to twice their blood volume has been replaced (Ciavarella *et al.*, 1987). Initial treatment to control bleeding should therefore be with platelet concentrates. Plasma fibrinogen, PT and PTT should be monitored as a guide to additional replacement therapy. If the fibrinogen level is less than 0·8 g/l, then cryoprecipitate is indicated. If either the PT or PTT is prolonged to more than one-and-a-half times the control value, but the fibrinogen level is greater than 0·8 g/l, then significant deficiency of factors V and VIII is likely to be present and FFP is recommended. The volume of FFP that will usually promote coagulation in an adult is at least four units (Braunstein & Oberman, 1984).

Liver disease

A variety of abnormalities of coagulation are seen in patients with liver disease. Bleeding, however seldom, occurs as the result of a haemostatic defect alone, but usually has a precipitating cause, such as surgery, including liver biopsy, or the rupture of oesophageal varices. In practice, FFP is indicated either if bleeding has taken place, or may confidently be expected because surgery is proposed (Mannucci *et al.*, 1976; Spector *et al.*, 1966). However, because of the large volumes of FFP required by patients who already have an expanded plasma volume, due to ascites and oedema and the short biological half-life of some of the factors, complete correlation is virtually never possible. If a FFP infusion of 6–8 units fails to control bleeding or provide adequate correction of the prothrombin time to allow essential surgery, a trial infusion of PCC may be considered.

Studies in patients with liver disease have shown sufficient correction of coagulation after the infusion of factor VII-rich PCC to permit the performance of liver biopsies without haemorrhagic complications (Green *et al.*, 1975). However, better haemostatic control was achieved with the use of a combination of FFP and PCC than with FFP alone (Mannucci *et al.*, 1976). Nevertheless, PCCs contain variable amounts of activated coagulation factors (IIa, IXa, Xa and VIIa) and their widespread use has not become the accepted practice because of the risk of inducing thromboemolic disease or DIC. In advanced liver disease, in which there is impaired hepatic clearance of activated clotting factors and reduced antithrombin III levels, the risk will be greater. Factor concentrates should therefore only be used after carefully balancing these risks against the expected haemostatic advantages.

There is no agreement as to the levels of coagulation factors which are 'safe' for patients with liver disease, prior to surgery or intervention. A PT of 1·6–1·8 times the control value is probably realistic. Platelet concentrates may be needed to correct the thrombocytopenia and platelet function defects which are often also present.

Cardiopulmonary bypass surgery

The majority of patients undergoing cardiopulmonary bypass surgery do not have major coagulation abnormalities (McCarthy *et al.*, 1988). On the other hand, there are changes in the haemostatic mechanism during cardiopulmonary bypass. In most studies non-surgical bleeding has been attributed to platelet dysfunction rather than to a deficiency of plasma coagulation factors (Woodman & Harker, 1990). Normally the platelet dysfunction reverses within 1 h after completion of bypass. However, bleeding due to a persistent functional platelet defect may sometimes occur.

In the presence of microvascular bleeding, or postoperative bleeding that is not surgically correctable, the initial management should be with platelet concentrates. FFP should only be used in those patients in whom bleeding is associated with proven abnormalities of coagulation other than residual heparin effect. Such patients have usually been massively transfused and may have developed consumptive coagulopathy. The routine perioperative use of FFP for cardiopulmonary bypass surgery exposes the patient to unnecessary risk and provides no known benefit (Trimble *et al.*, 1964).

The wider use of pharmacological agents to reduce non-surgical perioperative bleeding is just beginning. From the data available aprotinin therapy offers the potential for a major reduction in perioperative blood loss and transfusion requirements in cardiac surgery, and probably in other surgery as well (Hunt, 1991). Further studies are needed to understand the mechanism of action of aprotinin in this situation and to determine its most appropriate dose.

Special paediatric indications

In paediatric patients with severe sepsis, including sepsis in the new-born, therapy with FFP and cryoprecipitate has been advocated. FFP is often clinically

indicated for the supportive treatment of DIC which may be a complication in these patients. However, even in the absence of DIC, the use of FFP has been advocated as it provides not only clotting factors but also a source of complement, fibronectin and protease inhibitors which may be deficient in these infants. No evidence confirming the efficacy of this use of FFP is yet available. Note, however, that in neonates with necrotizing enterocolitis and associated erythrocyte T-antigen activation, infusion of plasma may cause intravascular haemolysis.

Paediatric FFP, containing smaller volumes than the standard FFP for adults, is available from most transfusion centres.

NO JUSTIFICATION FOR THE USE OF FFP

Hypovolaemia

There is no place for FFP in the management of hypovolaemia. Crystalloids, synthetic colloids or 4·5% human albumin solution are safer, cheaper and more readily available.

Plasma exchange procedures

Intensive plasma exchange using coagulation factor-free replacement fluids results in progressive reduction in plasma coagulation factors and platelets. Despite marked abnormalities of coagulation, haemorrhagic episodes are rare and when present, are usually due to thrombocytopenia (Keller *et al.*, 1979). FFP therapy should only be used to correct the coagulation abnormality when abnormal bleeding occurs. Immunoglobulins, complement (Keller & Urbaniak, 1978) and fibronectin (Norfolk *et al.*, 1985) are also depleted by intensive plasma exchange. As there is no evidence that this leads to infections or immune deficiencies, however, replacement with FFP is not indicated.

'Formula' replacement

There is no indication for the use of FFP according to predetermined replacement schedules (e.g. 1 unit of FFP following each 4–6 units of blood). Such a policy cannot be justified as it exposes the patient to unnecessary risk, and is of no proven benefit.

Nutritional support and protein losing states

There is no justification for the administration of FFP for nutritional purposes, for chronic cases of cirrhosis with ascites and nephrosis, for cases of protein-losing enteropathy or for chronic thoracic duct drainage.

Treatment of immunodeficiency states

In the past, FFP has been used as a source of immunoglobulins in the treatment of inherited immunodeficiency states. Purified intravenous immunoglobulin is now available and has replaced the need for FFP in these patients.

CONTROL OF ISSUE AND TRANSFUSION

As with blood and other blood components, transfusion of FFP should be fully documented in the patient's notes. This documentation requires a signed medical order for the precribed units of FFP. The persons administering each unit must sign the plasma issue slip and fluid chart to confirm that they have identified that the unit and patient are matched. An entry should also be made on the patient's notes stating clearly the reasons for prescribing FFP.

CONCLUSIONS

Education programmes which outline the benefits and complications of blood component therapy have achieved a reduction in both the amount of FFP transfused and the number of patients transfused for inappropriate reasons (Barnette *et al.*, 1990). Hospital transfusion committees should examine the current use of FFP and other blood components and a programme of education should be implemented to promote the appropriate use of blood and blood components.

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ADDENDUM

The advice contained in these guidelines is believed to represent the state-of-the-art at the time of going to press. It is policy to revise the guidelines as new developments occur. However, it may not be possible to do this at the time of such changes and the guidelines should always be used with due regard to current acceptable practice.

Comments are invited to assist the review process. All correspondence regarding the guidelines should be addressed to: *BCSH Secretary, British Society for Haematology, 2 Carlton House Terrace, London SW1Y 5AF, U.K.*