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Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials

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Summary

Randomized controlled trials of good quality are a recognized means to robustly assess the efficacy of interventions in clinical practice. A systematic identification and appraisal of all randomized trials involving fresh frozen plasma (FFP) has been undertaken in parallel to the drafting of the updated British Committee for Standards in Haematology guidelines on the use of FFP. A total of 57 trials met the criteria for inclusion in the review. Most clinical uses of FFP, currently recommended by practice guidelines, are not supported by evidence from randomized trials. In particular, there is little evidence for the effectiveness of the prophylactic use of FFP. Many published trials on the use of FFP have enrolled small numbers of patients, and provided inadequate information on the ability of the trial to detect meaningful differences in outcomes between the two patient groups. Other concerns about the design of the trials include the dose of FFP used, and the potential for bias. No studies have taken adequate account of the extent to which adverse effects might negate the clinical benefits of treatment with FFP. There is a need to consider how best to develop new trials to determine the efficacy of FFP in different clinical scenarios to provide the evidence base to support national guidelines for transfusion practice. Trials of modified FFP (e.g. pathogen inactivated) are of questionable value when there is little evidence that the standard product is an effective treatment.

Keywords: fresh frozen plasma, FFP, randomized controlled trial, blood transfusion, systematic review.

Fresh frozen plasma (FFP) is human donor plasma either recovered from a single whole blood donation or obtained by plasmaphaeresis. Its specification (e.g. Guidelines for the Blood Transfusion Services in the UK, 2002) requires that it is frozen within a specific time period after collection from a donor and stored at a defined temperature, typically −30°C. After thawing, although diluted with citrate anticoagulant, FFP contains near normal levels of many plasma proteins, including procoagulant and inhibitory components of the coagulation cascades, acute phase proteins, immunoglobulins and albumin. Clinical use of FFP has grown steadily over the last two decades in many countries (Wallace, 2003). In England, the usage of FFP (adult dose units) is currently about 300 000 units each year.

This level of usage is surprising as there are doubts about the effectiveness of plasma transfusion and it has well recognized complications (Cohen, 1987; McClelland, 1992; Dzik, 1999; Kleinman *et al*, 2003; Serious Hazards of Transfusion, 2003). As randomized controlled trials (RCTs) are the most robust way to assess the effectiveness of an intervention, we have undertaken a systematic review to identify and analyse all RCTs examining the clinical effectiveness of FFP.

Methods

Searching

Randomized controlled trials in which the intervention was transfusion of FFP were identified from MEDLINE (1966–2002), EMBASE (1980–2002) and the Cochrane Library (2002, issue 4). Sensitive RCT search strategies based on those devised by Dickersin and Lefebrve (Robinson & Dickersin, 2002) were

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used on MEDLINE and EMBASE, combined with text and index terms to capture the topic of interest. In the Cochrane Library, only topic-specific index search terms were employed. The reference lists of the identified RCTs and relevant narrative reviews were checked for additional trials. Full details of the search strategies are available from the authors.

Inclusion/exclusion

Citations and abstracts were screened for relevance to the subject of the use of fresh plasma or FFP by one reviewer. Full publications of accepted studies were assessed against formal inclusion/exclusion criteria by two reviewers working independently. The criteria for inclusion of full reports (not abstracts) were:

- there must have been at least two groups in the study;
- allocation to these groups must have been either by formal randomization or by a quasi-random method (e.g. alternation);
- one of the arms of the trial must include FFP or fresh plasma as an intervention;
- results on a relevant clinical or laboratory outcome must be presented.

Studies of plasma exchange and replacement fluid strategies that did not use FFP as the major replacement fluid (at least 50% of replacement volume) were excluded, as it was felt that this intervention did not clearly address the issue of FFP effectiveness.

Data abstraction and quality assessment

The details extracted were: country of origin, clinical setting, study population, hospital patient population, trial structure, study quality using a the Cochrane Collaboration framework, nature and duration of intervention and control groups, outcomes assessed and conclusions reported by the authors. The main evaluation of methodological quality of the included studies assessed the generation of random sequence, concealment of treatment allocation schedule and blinding of outcome assessment. Of all outcomes assessed in a trial, the main or primary clinical outcomes were separately recorded, if defined.

Analysis

The primary purpose of this study was achieved by describing the numbers and features of the studies identified in relation to groupings of clinical indications, particularly those conditions or procedures in which published guidelines suggest FFP might be of value. Analysis of the data abstracted from the included trials formed the basis for the conclusions reached. Quantifiable analysis (meta-analysis) was not a stated main aim for this study (see *Discussion*). Particular attention was paid within each grouping of clinical indications to the nature of the comparisons made in the trials, for which we differentiated:

1 Studies of interventions comparing FFP with no FFP/plasma.
2 Studies of interventions comparing FFP with a non-blood product (e.g. solutions of colloids and/or crystalloids).
3 Studies of interventions comparing FFP with a different blood product.
4 Studies comparing different formulations of FFP, e.g. solvent-detergent and methylene-blue treated (Pamphilon, 2000).

Studies in the final category were included in this review (but not shown in the Table I), as, although not directly evaluating effectiveness of FFP (e.g. by comparison with no FFP), there is now a UK national policy [British Committee for Standards in Haematology (BCSH), 2004a] to use these products in younger patients. Such trials could potentially therefore identify negative outcomes associated with the use of modified products (see *Discussion*).

Results

Number of trials

The search strategy identified approximately 500 citations in MEDLINE. Comparable topic-specific search terms in the Cochrane Library, and search strategies in EMBASE identified similar numbers of citations. Reference lists in narrative reviews and in a recent systematic review were cross-checked to identify other citations (Shehata *et al*, 2002). The majority of these identified citations from all three databases were easily excluded at the level of title or abstract on the basis of no relevance or lack of study randomization. A total of 57 publications of RCTs were eligible for inclusion in this review. Information about these trials is provided in Table I, and their quality is summarized below and in Table II. Trials comparing standard FFP with pathogen-inactivated FFP formulations were not included in Table I (except thrombotic thrombocytopenic purpura, TTP). *The main findings for individual or groups of identified trials have been placed in italics in the text.*

The trials are described in the following sections according to clinical groupings adapted from the BCSH Guidelines on the use of FFP, cryoprecipitate and cryosupernatant (BCSH, 1992, 2004a). The summary of these trials are given in Tables I and II.

Liver disease

Severe liver disease may be associated with a clinical bleeding tendency. FFP is recommended (BCSH, 1992, 2004a) for both prevention and treatment of bleeding (Kurtz, 1995). Six trials evaluating FFP administration in patients with liver disease were identified [one (Beck *et al*, 2000) has been included in the later, more representative section]. Most commonly, these

Table I. Summary details for trials evaluating the effectiveness of FFP.

Study	Intervention details (numbers randomized)	Comparator details (numbers randomized)	Clinical group	Main (clinical) outcome as reported in abstract/summary
Liver/cardiovascular/warfarin treatment/DIC/massive transfusion				
Gazzard *et al* (1975)	FFP 300 ml/ 6 h (600 ml if prothrombin time ratio >7), cross-over trial ($n = 10$)	No FFP (unless prothrombin time ratio >7); cross-over trial ($n = 10$)	Liver disease – paracetamol overdose	No significant benefit on bleeding morbidity or mortality
Mannucci *et al* (1976)	FFP 12 ml/kg ($n = 10$)	Clotting factor (prothrombin complex) concentrates ($n = 11$)	Chronic liver disease, prior to biopsy	No differences in clinical outcomes; tendency to improved correction of coagulation data with concentrates
Sampliner *et al* (1975)	FFP as component therapy with red cells and platelets ($n = 17$)	Fresh blood (and/or packed red cells) ($n = 16$) (and 17); three-arm trial	Liver disease with gastrointestinal bleeding	No differences in clinical outcomes between components and fresh blood
Boldt *et al* (1989)	FFP 2 units (mean 430 ml) ($n = 20$)	No FFP ($n = 20$)	Coronary artery bypass grafting	No positive effect of FFP on blood loss or transfusion requirements
Boldt *et al* (1990)	Plasma (autologous, platelet poor) 10 ml/kg ($n = 15$)	No plasmaphaeresis ($n = 15$); three-arm trial (with platelet rich plasma, $n = 15$)	Coronary artery bypass grafting	Possible reduction in blood loss/ transfusion requirements
Boldt *et al* (1993)	Plasma (autologous, platelet poor) 10 ml/kg ($n = 12$)	No plasmaphaeresis ($n = 12$); three-arm trial (with platelet rich plasma, $n = 12$)	Coronary artery bypass grafting	No significant effect on blood loss (outcomes of platelet function)
Menges *et al* (1996)	Plasma (autologous, platelet poor) 10 ml/kg ($n = 20$)	No plasmaphaeresis ($n = 20$); three-arm trial (with platelet rich plasma, $n = 20$)	Coronary artery bypass grafting	No significant effect of plasma on blood loss; possible reduction in transfusion requirements
Trimble *et al* (1964)	FFP 2 units adults, 1 unit child ($n = 21$)	No FFP ($n = 32$)	Cardiac surgery with bypass in adults and children	No significant differences in blood loss
Consten *et al* (1996)	FFP 3 units ($n = 24$)	Gelofusin 750 ml ($n = 26$)	Coronary artery bypass grafting	No significant differences in blood loss or transfusion requirements
Kasper *et al* (2001)	FFP (autologous) 15 ml/kg (average 1161 ml) ($n = 30$)	Hetastarch 15 ml/kg (average 1123 ml) ($n = 30$)	Coronary artery bypass grafting	No significant reduction in blood loss or transfusion requirements
Von Sommoggy *et al* (1990)	FFP (average 600 ml) with human albumin ($n = 13$)	Hydroxy-ethyl-starch (average 1450 ml) ($n = 11$)	Infrarenal aortofemoral grafting	No significant differences in blood loss or transfusion requirements
Wilhelmi *et al* (2001)	FFP 4 units (1000 ml) ($n = 60$)	Hydroxy-ethyl-starch 1000 ml ($n = 60$)	Coronary artery bypass grafting (primary)	No significant differences in blood loss or transfusion requirements
Oliver *et al* (2003)	FFP 1 unit (priming solution) ($n = 28$)	albumin 5% 200 ml (priming solution) ($n = 28$)	Open heart surgery for children <10 kg	No overall differences in blood loss, possible transfusion requirements greater in children receiving FFP
Martinowitz *et al* (1990)	Fresh plasma from one unit of blood, autologous, cross-over trial ($n = 20$)	Fresh packed cells (platelets/red cells, autologous) 1 unit; cross-over trial	Cardiac surgery with bypass	No differences in blood loss or transfusion requirements (outcomes platelet function)
Boulis *et al* (1999)	FFP infusion 60–100 ml/h; mean volume 2800 ml ($n = 13$)	Clotting factors concentrate with plasma infusion; weight-adjusted dose ($n = 8$)	Warfarin related haemorrhage (intracranial)	No significant differences in neurological outcomes; differences in correction of coagulation testing

Table I. *continued*

Study	Intervention details (numbers randomized)	Comparator details (numbers randomized)	Clinical group	Main (clinical) outcome as reported in abstract/summary
Gross *et al* (1982)	FFP (with platelets) 15 ml/kg (12 hourly) ($n = 11$)	No FFP ($n = 11$); three-arm trial (exchange transfusion, $n = 11$)	Neonates with criteria for DIC	No significant differences in survival, or resolution of DIC
Reed *et al* (1986)	FFP 2 units (440 ml) every 12 units of blood ($n = 22$)	Platelets 6 units every 12 units of blood ($n = 19$)	Massive transfusion	No differences in clinical bleeding outcomes (microvascular bleeding)
HUS/TTP				
Loirat *et al* (1988)	FFP 10 ml/kg/d for 7 d ($n = 39$)	No FFP ($n = 40$)	HUS	No differences in mortality; some differences in renal function but not at longer follow-up
Rizzoni *et al* (1988)	FFP 10 ml/kg/d ($n = 17$)	No FFP ($n = 15$)	HUS	No differences in mortality and measures of renal function
Rock *et al* (1991)	Plasma exchange with FFP 1·5 (initially) x plasma volume ($n = 51$)	FFP infusion 30 (initially) to 15 ml/kg ($n = 51$)	TTP (primary)	Improvement in response rate/survival for plasma exchange
Zeigler *et al* (2001)	Plasma exchange with FFP 60 ml/kg ($n = 13$)	Plasma exchange with cryoprecipitate poor plasma 60 ml/kg ($n = 16$)	TTP	No significant differences in early response rate/mortality
Henon (1991)	Plasma exchange with FFP 15 ml/kg (in albumin 45 ml/kg) ($n = 19$)	FFP infusion 15 ml/kg ($n = 19$)	TTP (primary and secondary)	Improvement in response rate/survival for plasma exchange
Röthele *et al* (2000)	Plasma exchange with FFP 50 ml/kg ($n = 20$)	Plasma exchange with cryosupernatant plasma 50 ml/kg ($n = 15$)	TTP and/or HUS	Preliminary data
Horowitz and Pehta (1998)	Plasma exchange with FFP dose not mentioned ($n = 10$)	Plasma exchange with FFP (solvent-detergent); dose not mentioned ($n = 16$)	TTP (primary and secondary)	No significant differences in response rates/survival
Neonatal				
Beverley *et al* (1985)	FFP 10 ml/kg for 2 d ($n = 38$)	No FFP ($n = 37$)	Prevention IVH	Possible beneficial effect in prevention of IVH
Hambleton and Appleyard (1973)	FFP 10 ml/kg for 2 d ($n = 33$)	No FFP ($n = 33$)	Prevention IVH	No evidence of beneficial effect in prevention of IVH
Mendicini *et al* (1971)	Plasma (with other supportive care) 3 ml/kg ($n = 40$)	No plasma ($n = 40$)	Prevention IVH	Higher (not significant) incidence of IVH in plasma arm
NNNI Trial Group (1996a,b)	FFP 20 ml/kg (10 ml/kg from day 2) ($n = 257$)	Gelofusin ($n = 261$) or dextrose-saline ($n = 258$); three-arm trial	Prevention IVH/disability	No significant differences using clinical outcomes of death/disability
Acunas *et al* (1994)	FFP 15 ml/kg ($n = 34$)	No plasma control ($n = 30$); three-arm trial (immunoglobulins, $n = 33$)	Neonatal sepsis	No evidence of benefit for FFP (laboratory measures of immunity)
Ekblad *et al* (1991, 1992)	FFP 10 ml/kg for 3 d ($n = 20$)	No FFP ($n = 20$); four study groups	Renal function in preterm infants	No significant differences using renal measures for outcomes

Table I. *continued*

Study	Intervention details (numbers randomized)	Comparator details (numbers randomized)	Clinical group	Main (clinical) outcome as reported in abstract/summary
Gottuso *et al* (1976)	FFP 15 ml/kg ($n = 26$)	No FFP ($n = 33$); three-way trial (with exchange $n = 53$)	Respiratory distress syndrome/ haemorrhages	Effects on mortality rates: possible benefit for exchange transfusion
Black *et al* (1985)	Partial plasma exchange with FFP ($n = 43$)	No exchange ($n = 50$)	Polycythaemic infants, neurological sequelae	Possible benefit for infants who had plasma exchange
Emery *et al* (1992)	FFP 15 ml/kg ($n = 20$)	Albumin solutions (5% or 20%) ($n = 20, 20$); three-arm trial	Hypotension	No significant benefit in blood pressure levels for FFP group
Deorari *et al* (1995)	Partial plasma exchange with FFP ($n = 15$)	Partial exchange with saline ($n = 15$)	Neonates polycythaemia	No significant differences using clinical and laboratory outcomes
Krishnan and Rahim (1997)	Partial plasma exchange with plasma ($n = 23$)	Partial exchange with saline ($n = 24$)	Neonates polycythaemia	No significant differences using clinical and laboratory outcomes
Supapannachart *et al* (1999)	Partial plasma exchange with FFP ($n = 11$)	Partial exchange with haemaccel ($n = 15$)	Neonates polycythaemia	No significant differences in decreases of haematocrit
Other clinical conditions				
Alexander *et al* (1979)	FFP 200 ml/m^2/d ($n = 11$)	Plasmanate (plasma protein derivative) 200 ml/m^2/d ($n = 9$)	Burns (children and adults)	No evidence of differences in infection (immunology outcomes)
Bocanegra *et al* (1978)	Plasma Supplementation (high volume) ($n = 192$)	Plasma supplementation (low volume) ($n = 193$)	Burns (children)	No significant differences in mortality
Boughton *et al* (1984)	FFP average 6·4 l/patient/48 h ($n = 5$)	Plasma protein fraction (fibronectin) average 6·9 l/patient 48 h ($n = 5$)	Burns (adults and children)	No significant differences in mortality (measures fibronectin)
Liu *et al* (1994)	Autologous plasma saver and infusion 10 ml/kg ($n = 8$)	No FFP ($n = 8$)	Hysterectomy	No clinical outcomes (outcomes using thromboelastography)
Johnson *et al* (1985)	Plasma exchange with FFP (2–2·5 l) + albumin ($n = 8$)	No plasma exchange ($n = 9$)	Glomerulonephritis (subtype)	Laboratory outcomes of renal pathology
Leese *et al* (1987)	FFP 2 units for 3 d (total 400 ml/d) ($n = 99$)	Albumin solution 400 ml/d ($n = 99$)	Acute pancreatitis	No significant differences in clinical outcomes/mortality
Leese *et al* (1991)	FFP 8 units/d for 3 d ($n = 36$)	Albumin solution 2000 ml/d ($n = 36$)	Acute severe pancreatitis	No significant differences in clinical outcomes/mortality
Carlon *et al* (1979)	FFP 7 ml/kg ($n =$ not reported; three arm trial: total 15 randomized)	Crystalloids: saline; 7 ml/kg (three-arm trial, albumin)	Lung disease	No clinical outcomes reported (outcomes of oxygen transport)
Raphael (1987)	Plasma exchange with FFP ($n = 52$)	Exchange with albumin ($n = 57$) (control group $n = 111$)	Guillain–Barre syndrome	Improvement in muscle strength with plasma exchange, but no evidence of benefit for FFP
Boyd *et al* (1996)	FFP 2 units ($n = 19$; numbers from authors)	Conjugated oestragens 50 mg ($n = 20$)	Renal disease and transplantation	No clinical outcomes reported (outcomes of coagulation testing)
Menges *et al* (1992)	Plasma (platelet poor, autologous) with blood ($n = 16$)	Allogeneic red cells ($n = 12$); three-arm study (autologous blood, $n = 14$)	Orthopaedic hip surgery	No differences in blood loss/ transfusion requirements

FFP, fresh frozen plasma; DIC, disseminated intravascular coagulation; HUS, haemolytic uraemic syndrome; TTP, thrombotic thrombocytopenic purpura; IVH, intra-ventricular haemorrhage. Information is provided on details of the intervention, comparator group, numbers randomized (or if not clearly reported, numbers analysed), clinical setting, and clinical outcome as summarized in the study. Trials comparing two formulations of FFP (i.e. pathogen inactivated) have not been included (see text).

Table II. Summary of quality criteria for all trials.

Clinical area	No. of RCTs identified	No. of trials with method of randomization described	No. of trials with method of allocation concealment described	No. of trials with blinding described	Mean size per arm (no. of patients)*
FFP vs. No FFP					
Liver	1	1	0	0	10
Cardiovascular	5	1	0	2	18
DIC (neonates)	1	1	0	0	11
HUS	2	2	2	0	28
Neonatal medicine	7	5	0	0	35
Other clinical conditions	2	0	0	0	8
FFP vs. alternative colloid					
Cardiovascular	5	3	1	2	31
Neonatal medicine	5	2	1	1	78
Other clinical conditions	5	4	1	0	45
FFP vs. alternative/blood/plasma product					
Liver	4	3	0	2	19
Cardiovascular	3	1	0	0	28
Warfarin-treated	2	1	0	1	22
DIC/massive transfusion	2	1	0	1	20
TTP	5	3	0	0	23
Burns	3	2	0	0	69
Other groups	5	2	1	1	29

RCTs, randomized controlled trials; DIC, disseminated intravascular coagulation; HUS, haemolytic uraemic syndrome; TTP, thrombotic thrombocytopenic purpura.

*Numbers for cross-over studies counted as applying in both arms.

trials evaluated prophylactic FFP administration to correct a coagulopathy and reduce a perceived risk of bleeding (Gazzard *et al*, 1975; Mannucci *et al*, 1976; Williamson *et al*, 1999; Lerner *et al*, 2000).

The clinical effectiveness of FFP in comparison with a control group given no FFP was addressed in one trial including 20 patients with liver disease due to paracetamol overdosage (Gazzard *et al*, 1975). *No effects on bleeding morbidity and mortality were observed as a result of treatment with FFP*. However, the small size of the study and the cross-over design were not optimal to detect any differences in clinical outcomes between the two groups. No trials comparing FFP with a non-blood or colloid product were identified.

Three trials in patients with liver disease compared the relative effectiveness of alternative formulations of FFP, specifically 'pathogen-reduced' products, which contain reduced levels of coagulation factors (Leebeek *et al*, 1999; Doyle *et al*, 2003). Beck *et al* (2000) enrolled patients with different causes of coagulopathy, in addition to liver disease, such as disseminated intravascular coagulation (DIC; see later section). Lerner *et al* (2000) also enrolled patients with warfarin overdosage. A total of 73 patients with liver disease were enrolled in the three trials (Williamson *et al*, 1999; Beck *et al*, 2000; Lerner *et al*, 2000). In none of the trials was there evidence that the studies had been specifically designed to test equivalence or non-inferiority between the groups of randomized patients and been powered accordingly. *No significant differences in bleeding events or transfusion requirements were reported in these three trials between the arms of the studies*.

One further trial compared FFP with infusions of clotting factor concentrates in a small number of patients with abnormal coagulation tests (Mannucci *et al*, 1976). Sampliner *et al* (1975) compared blood component therapy that included FFP with fresh blood and therefore did not test the effectiveness or relative effectiveness of FFP in isolation. *No significant differences in bleeding events or transfusion requirements were described in the two trials*.

The details of the doses of FFP in the intervention and comparator group varied among the included trials (varying from 6 to 15 ml/kg). All studies except one (Sampliner *et al*, 1975) reported on methods of randomization but allocation concealment was mentioned in only one study (Williamson *et al*, 1999); blinding was described in two trials (Williamson *et al*, 1999; Lerner *et al*, 2000). Multiple outcome measures for the five trials were described, that were both clinical (e.g. bleeding data) and laboratory based (e.g. coagulation testing). Only one of the trials reported a main outcome (correction of prothrombin time; Lerner *et al*, 2000), but it was not clear whether the trial was adequately powered to detect an effect on this outcome.

Cardiac and vascular surgery

Cardiopulmonary bypass (CPB) is associated with a multifactorial bleeding tendency (Bevan, 1999). FFP has been given

at the end of CPB (irrespective of coagulation results) with the aim of reducing subsequent postoperative blood losses and transfusion requirements (referred to in the publications as prophylactic use). Indications for additional transfusions of (therapeutic) FFP postoperatively include persistent bleeding with abnormal coagulation tests that is not due to residual heparin (BCSH, 1992, 2004a). Thirteen randomized trials of FFP in cardiac or vascular surgery were identified.

The clinical effectiveness of prophylactic FFP in comparison with a control group given no FFP was addressed in five trials. In three of these trials (which were also designed as three-arm studies), plasma was collected by plasmaphaeresis (Boldt *et al*, 1990, 1993; Menges *et al*, 1992); in the other two trials FFP was transfused (Trimble *et al*, 1964; Boldt *et al*, 1989). The combined number of participants in all trial arms in these five trials was 234, with a range of 12–21 in the intervention arm. *One trial ($n = 15$ in each arm) suggested a possible benefit for plasma (Boldt et al, 1990), but no significant differences in blood loss were reported in the other trials.*

Five trials compared prophylactic FFP with an artificial colloid solution (e.g. gelofusin, hetastarch or albumin). The latter products may have effects on *in vivo* coagulation, although these changes are generally not considered clinically relevant provided dosage does not exceed the limits recommended by the manufacturers (De Jonge & Levi, 2001). Although these studies were primarily aimed at evaluating the prophylactic use of FFP given at the end of CPB surgery, additional doses of FFP were permitted postoperatively for excessive bleeding or abnormal coagulation results in three of the included trials, possibly diluting the treatment effect (Kasper *et al*, 2001; Wilhelmi *et al*, 2001; Oliver *et al*, 2003). *No significant differences in blood loss were reported in these trials.* One of these studies evaluated FFP usage in small children, as part of the priming volume prior to initiating CPB. *Although blood losses were not different, the findings suggested that transfusion requirements might be greater in children receiving FFP* (Oliver *et al*, 2003). Therefore, in the 10 studies comparing FFP to either no FFP or non-plasma product, use of FFP after CPB did not appear to have a consistent significant effect on blood loss or transfusion requirements.

Two further identified trials were designed to compare the effectiveness of different types of 'pathogen-reduced' plasma (Haubelt *et al*, 2002; Noddeland *et al*, 2002). These studies enrolled patients undergoing CPB for plasma transfusion after they had developed bleeding with deranged coagulation tests (Haubelt *et al*, 2002; Noddeland *et al*, 2002). *No significant differences in blood loss were reported between the study arms in these trials*. The final identified (cross-over) trial compared fresh plasma and fresh packed red cells, and *reported no differences in blood loss* (Martinowitz *et al*, 1990).

The dose of FFP varied among all identified studies, from 2 adult units (approximately 6–7 ml/kg) up to 15 ml/kg (Kasper *et al*, 2001). The total number of patients randomized in the trial arms of all studies ranged from 12 to 60 in the intervention arm and 11 to 60 in the control arm. Methods of random allocation and concealment were not described in seven trials, and where stated, blinding to clinicians and/or participants was clearly reported in only four trials (Trimble *et al*, 1964; Boldt *et al*, 1993; Consten *et al*, 1996; Oliver *et al*, 2003). Multiple outcomes were evaluated in all trials. Clinical outcomes included data on blood loss and laboratory-based outcomes included transfusion requirements and coagulation tests, but only one trial reported a clear primary outcome (postoperative blood loss; Kasper *et al*, 2001). Information on sample size requirements was provided in three studies (Kasper *et al*, 2001; Haubelt *et al*, 2002; Oliver *et al*, 2003). No studies explicitly clarified whether the lack of a difference was reflected by insufficient power in the trial.

Reversal of warfarin treatment effect

Guidelines (BCSH, 1992, 2004a; Makris & Watson, 2001) recommend the use of FFP to treat warfarin overdosage only where there is severe bleeding or prothrombin complex concentrates (PCCs) are unavailable (Makris *et al*, 1997). In total, three relevant trials for this group were identified. No trials involving direct comparisons of FFP with a control group receiving no FFP were identified.

One identified randomized trial compared FFP with additional clotting factor concentrates to correct laboratory tests of coagulation abnormality in patients with warfarin-related intracranial haemorrhage (Boulis *et al*, 1999). This trial did not describe the method of random allocation and concealment, and was unblinded, with a very small number of enrolled pateints. *Although there was possibly a more rapid rate of coagulation correction with concentrate, no differences in clinical neurological outcomes were found*, although it is doubtful whether the trial was adequately powered to detect an effect on this outcome.

Two studies were identified which compared conventional FFP with a different 'pathogen-reduced' formulation of FFP (Lerner *et al*, 2000; Hambleton *et al*, 2002). Lerner *et al* (2000) studied 22 patients with warfarin overdosage (as well as liver disease) and compared conventional FFP with solvent-detergent-treated plasma (this study is included in the *Liver disease*). Hambleton *et al* (2002), in a single-blinded cross-over trial, compared the effects of photochemically treated FFP with standard FFP on the kinetics of coagulation assays in healthy subjects who received warfarin for 4 d prior to infusion (Hambleton *et al*, 2002). *For both studies, no significant differences in clinical or laboratory outcomes were noted between the two groups.*

FFP usage in disseminated DIC and massive transfusion

In total, three relevant trials for this clinical group were identified. One identified study addressed the effectiveness of FFP in DIC in a group of neonates, using defined criteria for a diagnosis of DIC (Gross *et al*, 1982). In this small three-way controlled trial, neonates were randomly allocated to therapy

with either additional exchange transfusion (using whole blood) or to FFP (and platelet) infusions or to a control group (with no plasma). *There were no differences in rates of improvement for coagulation tests or in survival.* However, the size of the trial was small (the combined number was 33 across three arms).

One study was identified that compared FFP with a pathogen-inactivated formulation of FFP in a clinically heterogeneous group of 35 patients with DIC (criteria for diagnosis not defined), dilution coagulopathy, or trauma (Beck *et al*, 2000). Outcome measures in this trial were laboratory based. *No significant differences in the levels of different markers of coagulation factors were reported* (Beck *et al*, 2000). An additional RCT comparing FFP with platelet transfusion in patients receiving massive transfusion was identified (Reed *et al*, 1986). However, this trial was aimed at evaluating the effectiveness of transfused platelets (in which there were significant amounts of plasma) rather than the efficacy of plasma. *No differences were reported in this study for clinical measures of bleeding* (Reed *et al*, 1986).

Of the three identified trials, two described methods of random allocation (Gross *et al*, 1982; Beck *et al*, 2000), and one incorporated blinding to clinicians and patients (Reed *et al*, 1986). No clear primary outcomes were defined in any of the three studies.

Haemolytic uraemic syndrome (HUS) and TTP

Two randomized trials in HUS were identified comparing FFP infusions and no plasma (Loirat *et al*, 1988; Rizzoni *et al*, 1988). The larger trial had allocated 79 patients between both arms (Loirat *et al*, 1988), the other trial 32 patients (Rizzoni *et al*, 1988). Both trials reported methods of allocation and allocation concealment, and were designed to address the effectiveness of the product. *Both trials failed to identify any benefit of FFP infusions with respect to mortality or (longer term) renal outcome measures*. Whether the sizes of the trials were sufficient to define significant differences will be discussed later.

Daily plasma exchange using FFP is the recommended treatment of TTP (BCSH, 1992, 2003, 2004a). Identified randomized trials in TTP have focused on the role of plasma infusion *versus* plasma exchange or comparisons of plasma exchange using different types of plasma, rather than comparisons of plasma (infusion or exchange) with no plasma. In the pivotal RCT conducted by the Canadian Apheresis Study Group (Rock *et al*, 1991), therapeutic plasma exchange with FFP was compared with infusion of FFP in 102 patients (51 in each arm). This trial reported information on sample size requirements (50 patients would be required in each group to demonstrate a 20% difference in response outcomes). The analysis of the trial was complicated by the number of patients crossing over to the (plasma-exchange) arm *but significantly improved rates of response and survival were reported for the exchange arm* (Rock *et al*, 1991).

Four other smaller controlled trials for TTP that evaluated FFP administration were identified. The total volume of plasma infused in the infusion arm compared with the exchange arm may be important, and this was comparable between the two arms in the French multicentre trial (Henon, 1991) but reduced compared with the exchange arm in the Canadian study (Rock *et al*, 1991). FFP was compared with cryosupernatant as the replacement fluid in one small, randomized trial and *no differences in outcome were reported* (Zeigler *et al*, 2001); further results to those reported by Röthele *et al* (2000) are awaited.

Overall, methods of random allocation were described in four of the five trials of TTP. Further details of methodological quality for these trials are summarized in Table II.

FFP usage in neonatal medicine

Twelve identified RCTs assessed the role of FFP in neonates across different clinical settings [excluding the study by Gross *et al* (1982) mentioned above]. Although not included in current national guidelines (BCSH, 1992, 2004a,b), FFP may still be transfused to neonates as a volume expander or for unspecified immunological effects (Emery *et al*, 1992; Acunas *et al*, 1994). *Neither of these two identified studies reported evidence of benefit for FFP*. FFP or plasma was used in four identified trials to evaluate the treatment of polycythaemia by (partial) exchange transfusion (Black *et al*, 1985; Deorari *et al*, 1995; Krishnan & Rahim, 1997; Supapannachart *et al*, 1999). For the three trials comparing different replacement fluids for plasma exchange, one of which was FFP/plasma, *no significant differences were reported*.

In the largest identified trial in this group, the Northern Neonatal Nursing Initiative (NNNI) Trial Group randomized 776 neonates and compared FFP with volume expanders (gelofusin or dextrose-saline) in the prevention of intra-ventricular haemorrhage (NNNI Trial Group, 1996a,b). This was a large, high-quality trial with allocation concealment and blinded outcome assessors to monitor clinically relevant long-term developmental outcomes, and it provided information about the sample sizes required to provide adequate power to detect clinically important differences between the groups of patients. This well-designed study provided better quality evidence for *a lack of effect for prophylactic use of FFP in this group*. The three other identified trials of prophylaxis in this clinical setting reported variable effects on rates of intra-ventricular haemorrhage, but the individual studies enrolled much smaller numbers of neonates (Mendicini *et al*, 1971; Hambleton & Appleyard, 1973; Beverley *et al*, 1985).

Information about aspects of methodological quality for these trials is summarized in Table II.

FFP usage in other conditions

Fifteen randomized trials of FFP usage in a range of other clinical conditions were identified.

Acute pancreatitis. In two trials by the same group, 275 patients were randomized to receive FFP or a colloid solution (Leese *et al*, 1987, 1991). Random allocation was by sealed envelopes. This study, like the NNNI trial, was designed to evaluate the effectiveness of FFP in a large group of patients, and also provided information about numbers required to adequately power the study (Leese *et al*, 1987). *No differences in a range of clinical and laboratory outcome measures were reported.*

Burns. Three identified trials enrolled patients with severe burns. FFP was used with the aim of reducing infection (Bocanegra *et al*, 1978; Alexander *et al*, 1979; Boughton *et al*, 1984). These trials addressed comparisons between different plasma-related fractions, and overall *reported no differences between the groups.*

Guillain–Barre syndrome (GBS). In the largest study identified in this section, 220 patients with GBS were allocated to FFP or alternative fluids as replacement for aphaeresis (Raphael, 1987; Raphael *et al*, 2004). However, the method of allocation actually meant that only 52 patients were randomized to receive FFP. *A beneficial effect of FFP as replacement was not substantiated.*

Plasma was used in two other small, identified RCTs as the main replacement fluid for therapeutic aphaeresis procedures in clinical conditions other than TTP and GBS (Johnson *et al*, 1985; Keller *et al*, 2000; refer to tables for further details). Additionally, seven further trials involving FFP were identified, across a range of clinical settings. Four of these seven studies in different patient groups (Carlon *et al*, 1979; Menges *et al*, 1992; Liu *et al*, 1994; Boyd *et al*, 1996) enrolled small numbers of participants (intervention arm numbers ranged from 8 to 19). The other three identified trials compared different types or formulations of FFP/plasma (Vittecoq *et al*, 1992; Simonsen & Sørensen, 1999; Palfi *et al*, 2001). Information about the results and methodological quality of these trials is summarized in Tables I and II.

Discussion

Although clinical use of FFP has grown steadily, concerns about the appropriate use and the clinical effectiveness of this blood component have been voiced for many years (Cohen, 1987; McClelland, 1992). Guidelines with recommendations for usage continue to be published, for example, by the BCSH (1992, 2004a), the College of American Pathologists (1994), the American Association of Blood Banks (Triulzi, 2002) and for children (Roseff *et al*, 2002). However, clinical practice is characterized by considerable variation in the use of FFP (Sanguis Study Group, 1994). Local audits of FFP use in different hospitals in the UK suggest that only around 60% of transfusions were compliant with recommendations in guidelines and in many cases the doses given were below those recommended (Jones *et al*, 1998; Eagleton *et al*, 2000; Stainsby & Burrowes-King, 2002).

In this review, 57 RCTs reporting on transfusion of FFP as an intervention were identified. RCTs were selected as the form of clinical study best designed to address the issue of efficacy. Although it may appear that this represents a substantial RCT evidence base to help guide clinicians in deciding on the most appropriate use of FFP, this is placed in doubt by the characteristics of many of the identified trials. Three areas of concern are the nature of the intervention, the sample size and the quality of the trials.

Quality of the RCT evidence: the nature of the comparison in the trials

Seven of the 24 identified trials involving patients with liver disease, cardiac/vascular disease, warfarin treatment, DIC or massive transfusion, were comparisons between different types of FFP, i.e. pathogen-inactivated forms. The value of such comparisons presupposes that the clinical effectiveness of one of the intervention arms used within a study has already been demonstrated. However, there were few controlled RCTs identified in this review comparing FFP with no treatment. This may reflect the difficulties in designing such trials in sick patients. It is important to undertake well-designed studies of new types of FFP (e.g. pathogen-inactivated plasma) from a number of points, including safety in addition to efficacy. However, trials comparing variants of conventional FFP should not be confused with those aimed at determining the effectiveness of the conventional treatment in a trial compared with no treatment (or a placebo).

New or modified variants of FFP would have little clinical value unless there is evidence that either the standard FFP product is clinically an effective treatment or there is reason to consider the possibility that the modified product may have effectiveness or harm that the standard product does not have (e.g. pathogen inactivation). Solvent/detergent pooled plasma is known to have lower levels of anticoagulants than untreated FFP, and there are case reports suggesting an association with thrombosis in patients with TTP receiving plasma exchange with this product that had not been raised with standard FFP (Yarranton *et al*, 2003). Transfusion of pathogen-inactivated FFP has also been associated with a greater overall demand for plasma in one retrospective study (Atance *et al*, 2001), and although the reasons for this are unclear, it may reflect perceived differing degrees of effectiveness, for example, lower levels of fibrinogen or other procoagulants (Williamson *et al*, 2003).

Quality of the RCT evidence: the nature of the intervention

There is increasing awareness of the need to consider how FFP is used and the optimal dose for FFP administration as an intervention. For example, it has been suggested that early use of FFP may be more effective in massive transfusion (Hirshberg *et al*, 2003). Current guidelines for usage (BCSH, 1992, 2004a) also generally specify a dose of 15 ml/kg. Smaller doses

may be ineffective in correcting laboratory measures of coagulation in patients with bleeding related to a coagulopathy and could underlie the apparent lack of effectiveness in some trials. The doses of FFP used in the intervention arm for acquired disorders of haemostasis in the randomized trials included in this study (Table I) varied from 6 to over 15 ml/kg [higher doses were given in Boulis *et al* (1999)]. One avenue of future clinical research might be to explore different trigger levels and doses of FFP for different severities of bleeding or coagulation disturbance.

Quality of the RCT evidence: the size of the trials

The ability to answer questions about effectiveness of interventions in trials is less dependent on the actual number of trials identified than on the combined size of those trials, the frequency of outcomes expected in the study populations and the size of the differences expected. In the RCTs identified, the number of patients was frequently small, often less than 30 subjects per arm. With regard to trials comparing FFP and no FFP, the number of patients in the treatment arm ranged from 10 to 22 for patients with liver disease, DIC, massive transfusion, or those undergoing cardiac surgery (Table II). These are clinical conditions where the use of FFP is recommended in national guidelines. In some trials, the numbers of included patients were not reported (Carlon *et al*, 1979; Boyd *et al*, 1996). The high numbers of small studies may not only exaggerate the amount of evidence available, but could also compromise the quality as randomization is less likely to achieve equivalence of baseline characteristics.

It is likely that few of the identified trials had sufficient power to document a significant difference between the treatment and control arms, and failure to observe a difference may not exclude an actual difference in practice. The results from two trials in HUS might initially suggest that this is a clinical area where the combined RCT evidence could be more helpful in providing evidence for no benefit of FFP. However, neither report clearly explored whether the lack of a difference reflected insufficient power in the trial. It is possible that the small size of individual studies means that statistical combination of the results could lead to a hypothesis of benefit or harm that is not apparent in a statistically significant manner at the individual study level. However, even taking the total number of patients in trials of cardiac disease for such a meta-analysis, the findings have not been sufficient to allow conclusions to be drawn about effectiveness (Casbard *et al*, 2004).

Trial design: blinding and concealment of allocation (Table II)

It is recognized that bias can operate at different levels within RCTs, including selection, intervention and outcome assessment, and we have extracted and summarized information about these measures of methodological quality in Table II. Methods of allocation concealment were not described in the majority of trials, although there is evidence to suggest that this is critical to the validity of trial results (Schulz *et al*, 1995). Only a few studies clearly reported blinding of clinicians or participants to allocation. Closer reading of the methods section in other trials suggested that many were probably unblinded. The importance of blinding in transfusion studies that use outcome measures requiring subjective judgements, such as bleeding severity, has been well described (Heddle *et al*, 2003), but few studies in this review had explicitly stated that individuals assessing outcomes were blinded (NNNI Trial Group, 1996a,b). Other important areas of methodological quality include attrition bias (avoided by analysis using the intention-to-treat principle) and publication bias. Neither issue was examined in detail in this paper; it is hoped that initiatives to improve the quality of trial design and the identification of ongoing and unpublished studies or protocols in registers will start to address these points.

The outcomes and use of FFP for prophylaxis or treatment of bleeding

Although the outcome measures in many trials covered clinical endpoints, in a small number of RCTs no clinically relevant outcomes were defined (Liu *et al*, 1994; Deorari *et al*, 1995; Boyd *et al*, 1996; Beck *et al*, 2000). As highlighted in the text, for those clinical outcomes reported in identified trials comparing FFP with no FFP or with potentially 'active' controls (e.g. colloids), there was no overall evidence of any consistent beneficial effect. The trials identified in this review have evaluated either prophylactic or therapeutic indications for FFP, although some studies do not include explicit definitions of these terms. Many of the identified trials in groups such as cardiac, neonatal and other clinical conditions, including those of higher quality, were assessing a prophylactic transfusion strategy.

A prophylactic policy aimed at preventing bleeding complications could involve transfusing a large number of patients, many of whom might not bleed even if prophylactic FFP were not given (Dzik, 1999). Studies of prophylaxis must therefore also include an estimate of the adverse outcomes as well as an estimate of the proportion of patients for whom a significant bleeding problem may be prevented. One of the RCTs in this review specifically addressed a side effect (transfusion-related acute lung injury) (Palfi *et al*, 2001). However, the RCT may not be the most appropriate form of trial design to identify and analyse rare events. Data on the incidence of adverse effects should be collected from other sources such as treatment registers, which can be designed to include much larger numbers of patients and so give more useful estimates of the incidence of these events in day-to-day clinical practice.

Current guidelines for clinical administration of FFP emphasize therapeutic usage, for example, in the presence of bleeding, rather than the correction of isolated abnormal laboratory results (BCSH, 1992, 2004a; College of American

Pathologists, 1994; Eagleton *et al*, 2000). However, on the basis of the randomized trials identified in this review (with the exception of TTP), the evidence base that the therapeutic use of FFP is effective appears poorly supported.

Conclusions

The findings of this systematic review are that, for most clinical situations, the RCT evidence base for the clinical use of FFP is limited. Lack of such evidence does not mean the intervention is ineffective, but that there is insufficient RCT evidence to support or to refute the efficacy of the intervention. To a degree, the strongest RCT evidence seems to indicate that the prophylactic use of FFP is not significantly or consistently effective across a range of different selected clinical settings. The review has also highlighted concerns about other aspects of the intervention and how FFP was used (e.g. dose), and the methodological quality of the published assessments of the effectiveness of treatment with FFP, including the number of patients included in the trials, and the power of the trials to document differences.

This study of the RCT evidence base provides some guidance for future trials and insight into difficult trial design issues. Such studies need to take account of the extent to which adverse effects might negate the clinical benefits of treatment with FFP. For any indication in which conventional FFP is effective, comparisons of effectiveness of a modified product should thoroughly address the relative risk of adverse effects. Definitive RCTs should consider whether the aim of the study is to document equivalence or difference, and should be appropriately powered and consistently reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Begg *et al*, 1996).

This review focused exclusively on evidence from RCTs of the use of FFP. Much of the evidence utilized for making clinical decisions on the relative merits of different interventions and for writing clinical guidelines is taken from observational data, and it remains uncertain to what degree this is valid to guide clinical transfusion practice (Pocock & Elbourne, 2000). Observational data may well be applicable in the context of treatment sized effects that are expected or shown to be large (Barton, 2000). The retrospective study of FFP in liver disease (McVay & Toy, 1990) is frequently cited despite the fact that it contains no control group data. Controlled but non-randomized data could be valid for some clinical areas, for example, the management of warfarin overdosage (Makris *et al*, 1997). Finally, clinicians' anecdotal experience may be an important factor in defining their use of a given intervention (Sackett *et al*, 1996). Authors of guidelines may therefore need to be more discriminating in deciding what level evidence is appropriate to determine practice. Evidence from high quality studies reporting negative findings should also be fully reflected in guidelines (NNNI Trial Group, 1996a).

In summary, there has been a general enthusiasm for FFP usage for many years, possibly because at an intuitive level it seems to be an appropriate product to replace or supplement different constituents of plasma in patients. This intervention has, over time, become more accepted in practice, and has not been subjected to the clinical research scrutiny that should be required to demonstrate effectiveness. This also means it may be more difficult to assess the effectiveness of newer, modified FFP products (e.g. pathogen inactivated).

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