

Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients

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Summary

This study assessed the effect on coagulation tests of fresh frozen plasma (FFP), given according to guidelines compared with higher doses in critically ill patients. Group 1 (10 patients) received 12.2 ml/kg and group 2 (12 patients) 33.5 ml/kg FFP. Prothrombin time, activated partial thromboplastin time and factors I–XII were measured before and after FFP infusion. Factor levels of 30 IU/dl (1 g/l for fibrinogen) were considered haemostatic. A retrospective review showed 10 of 22 (five in group 1 and five in group 2) patients had not required FFP. Of those that needed FFP, one of five in group 1 and seven of seven in group 2 had coagulation factor levels above the target post-FFP. Increments for group 1 *versus* 2 were: fibrinogen 0.4 vs. 1.0 g/l, FII 16 vs. 41*, FV 10 vs. 28*, FVII 11 vs. 38*, FVIII 10 vs. 17, FIX 8 vs. 28*, FX 15 vs. 37*, FXI 9 vs. 23 and FXII 30 vs. 44 IU/dl* (**P* < 0.01). *In vivo* recovery of coagulation factors was the same for both groups and the observed increments correlated with the dose of FFP. In conclusion, coagulation screens were poor predictors of coagulation factor levels and current guidelines on the use of FFP result in predictably small increments in coagulation factors in critically ill patients and should be reviewed.

Keywords: fresh frozen plasma, haemostasis, coagulation tests, coagulation factors.

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Data are limited on the use of fresh frozen plasma (FFP) in clinical practice. Guidelines from the American Society of Anesthesiologists Task Force on Blood Component Therapy suggest that, in patients with microvascular bleeding, FFP should be infused if the prothombin time (PT) or activated partial thromboplastin time (aPTT) is above 1.5 times normal. They state that a dose of FFP should be given to raise the coagulation factor levels above 30 IU/dl and recommend a dose of 10–15 ml/kg (American Society of Anesthesiologists Task Force on Blood Component Therapy, 1996). The Fresh-Frozen Plasma, Cryoprecipitate and Platelet Administration Practice Guidelines Development Task Force of the College of American Pathologists (1994) recommend a dose of 400–460 ml (about 6.5 ml/kg). Current UK guidelines give indications for the use of FFP but do not give dosing recommendations for replacement therapy during invasive procedures and many clinicians use a 'formula' approach and

prescribe 4 units (about 800 ml), 1 l or 15 ml/kg of FFP. This practice is an extrapolation of a recommendation to give about 1 l of FFP for the emergency reversal of warfarin (British Committee on Standards in Haematology, 1992, 1998). These approaches are not evidence-based as they are not supported by clinical studies of efficacy and do not take into account the degree of abnormality of the haemostatic defect, the likely coagulation factor deficiencies or the increase in specific coagulation factors that could be expected following infusion of this amount of FFP. If the hypothesis is correct that haemostasis is achieved at a specific coagulation factor level, then it follows that FFP replacement should be individualized so that enough is given to increase the patient's factor levels above this threshold. The amount required will depend on the baseline level of the coagulation factor and the predicted rise of that coagulation factor, calculated on the expected *in vivo* recovery.

In practice, FFP is often used to correct haemostatic abnormalities that have been identified on coagulation screening tests in patients who are either bleeding or about to undergo an invasive procedure. Patients who are being managed in intensive care units (ICU) have multiple risk factors for developing abnormal coagulation tests although there is a poor correlation between coagulation screen results and risk of bleeding during invasive procedures (Ewe, 1981; Eisenberg *et al*, 1982).

We compared whether a standard dose of 10–15 ml/kg, as recommended in current guidelines, or 30 ml/kg of FFP corrected individual coagulation factor deficiencies to an arbitrary chosen level of 30 IU/dl (or 1 g/l for fibrinogen) in patients on ICU who were bleeding or about to undergo an invasive procedure. The results suggested that 1 l or 12.5 ml/kg of FFP did not predictably correct laboratory abnormalities of coagulation whereas 30 ml/kg did.

Methods

Patients

The aim of the study was to assess whether FFP, given at recommended doses, corrected the laboratory parameters of haemostasis. Clinical end points were not assessed, as to do so, patient groups would have had to have been matched for clinical situation and haemostatic defect and been randomized. This would have entailed a more complicated study design and investigation of significantly more patients. A consecutive cohort of patients who received FFP on the ICU at the University Hospital of Wales was therefore investigated. Patients with either a PT or an aPTT ratio greater than 1.5 were given FFP, either to arrest bleeding or before invasive procedures, according to the routine protocols of the ICU. The first 10 consecutive patients were infused with FFP at a dose dictated by current guidelines. A further 12 consecutive patients were infused with FFP aiming for a dose of 30 ml/kg. The study was reviewed by the Bro Taf Local Research Ethics Committee. Blood was taken into sodium citrate 0.129 mmol/l before and between 1 and 2 h after the infusion of FFP, centrifuged at 2000 g within 1 h, tested for PT and aPTT and the remaining plasma stored in aliquots at -70°C . An aliquot of the infused FFP was also stored at -70°C . Stored plasma aliquots were tested on a CA6000 coagulometer (Sysmex, Milton Keynes, UK) for fibrinogen, factors II, V, VII, VIII, IX, XI and XII. An aliquot of infused FFP was assayed for each coagulation factor.

Analysis

The median and 90th percentile for each coagulation factor level pre- and post-FFP were calculated. The coagulation factor increments were calculated for each patient and the median and 90th percentile reported. The amount of coagulation factor infused was calculated from the measured coagulation

factor level in each unit of FFP and the volume of FFP given. The *in vivo* recovery is the measured rise in coagulation factor level divided by the amount of coagulation factor given per kilogram.

Statistical analysis was made using SSCP software and employed the Mann–Whitney *U*-test and Spearman rank correlation coefficient. *P*-values < 0.05 were considered significant.

An arbitrary decision was made to consider an individual coagulation factor level of 30 IU/dl, or in the case of fibrinogen 1 g/l, to be sufficient to allow an invasive procedure or arrest bleeding (any factor XII level was accepted as adequate for haemostasis). This is an extrapolation of clinical experience from patients with inherited individual coagulation factor deficiencies (Bloom, 1994) and follows studies performed on the reversal of warfarin (Makris *et al*, 1997). In addition, a previous study has shown that coagulation factor levels below 20 IU/dl, or 0.5 g/l for fibrinogen was predictive of diffuse microvascular bleeding but no data in this study was available on patients undergoing invasive procedures (Eisenberg *et al*, 1982).

Results

Patients

Group 1. The first 10 patients were infused with a dose of FFP according to current guidelines. The median dose of FFP infused was 1.0 l (range 0.5–1.5 l). The median volume of FFP given according to body weight was 12.2 ml/kg (range 5.6–22.1 ml/kg).

Group 2. The second group of 12 patients was infused with FFP with the aim of giving 30 ml/kg. The median volume of FFP infused was 2.5 l (range 1.25–4 l). The median volume of FFP given according to body weight was 33.5 ml/kg (range 18–51 ml/kg).

Coagulation screens and requirement for FFP assessed retrospectively

Retrospective analysis of the individual coagulation factor levels of patients (using the threshold of 30 IU/dl and 1 g/l for fibrinogen) showed that 10 of the 22 patients had not required FFP replacement (nine patients had no coagulation factor levels below 30 IU/dl and one patient had only a decreased level of factor XII). Of these 10 patients, five were in group 1 and five in group 2 and the range of their PT and aPTT showed significant overlap with those that, in retrospect, had required FFP (Table I). Thus in this cohort, coagulation screens poorly predicted the levels of coagulation factors.

Correction of coagulation abnormalities by FFP

The median PT, aPTT and coagulation factor levels are shown in Table II before and after the infusion of FFP. In

Table I. PT and aPTT ratios of patients during the study.

	All patients, median (range)	In retrospect FFP not required, median (range)	In retrospect FFP required, median (range)
PT ratio	1.8 (1.4–2.0)	1.6 (1.4–1.9)	2.2 (1.5–2.0)
aPTT ratio	1.8 (1.1–1.0)	1.4 (1.1–2.8)	2.2 (1.2–1.0)

The median and range of the ratio of PT and aPTT, expressed as patient time divided by the mid-point of the normal range, are shown. Patients who, after retrospective analysis of coagulation factor results, had not required FFP are shown separately from those that had.

group 1, only 1 of the five patients who had had decreased coagulation factor levels before FFP had all coagulation factor levels above 30 IU/dl following infusion of 12.2 ml/kg FFP. The lack of correction of the individual coagulation factor levels was due to relatively small coagulation factor increments. Factors V, VIII, IX and XI had increments of 10 IU/dl or less and the median increment in fibrinogen was 0.4 g/l (Table II).

In group 2, all seven of the patients who had had low coagulation factor levels before FFP had levels above 30 IU/dl post-FFP (33 ml/kg). The median increment for group 2 for the individual coagulation factors was between 17 and 44 IU/dl. The fibrinogen increased by a median of 1 g/l, although this was not significantly different from group 1. Before FFP infusion, the coagulation factor levels were not statistically different between groups 1 and 2 but after FFP, group 2 had significantly highly levels of factors II, VII, X, XI and XII (Table II). There was a significantly greater increment of factors II, V, VII, IX, X, XI and XII in group 2 patients compared with those in group 1.

In vivo recovery of coagulation factors

The median observed increment in coagulation factor levels was significantly greater for group 2 compared with group 1 for all coagulation factors except fibrinogen and factor VIII. This difference was due to the amount of coagulation factor infused, as shown by the *in vivo* recovery of coagulation factor (standardized for amount of factor infused and weight of patient), and is the same for both groups (Table III).

Discussion

This study assessed the effect of FFP on laboratory coagulation parameters in patients on the ICU and compared the effect of different doses of FFP. The results suggested that in many patients FFP was not indicated (based on coagulation factor levels), coagulation screening tests were poor predictors of significantly low coagulation factor levels, a standard regimen of 1 l or about 12.5 ml/kg of FFP lead to relatively small and, in most patients, inadequate increments in coagulation factor levels and that 30 ml/kg of FFP adequately corrected all individual coagulation factors.

The possibility that many patients are unnecessarily infused with FFP is important because blood product exposure is associated with significant adverse effects such as allergic reactions and volume overload and the potential risk of transmission of infectious agents, including variant Creutzfeldt-Jacob disease (Schreiber *et al*, 1996; Burthem & Roberts, 2003).

The levels of individual coagulation factors that were considered adequate for haemostasis in this study were extrapolated from the experience of managing patients with single inherited deficiencies of these factors. Patients with inherited deficiencies of factor VIII and factor IX are at risk of

Table II. PT, aPTT and coagulation factor levels before and after the infusion of FFP.

	Group 1			Group 2		
	Preinfusion	Postinfusion	Observed increment	Preinfusion	Postinfusion	Observed increment
PT (s)	22.8 (17–222)	19 (15–36)		24 (17–44)	16 (14–20)	
aPTT (s)	46.4 (30–223)	37 (30–158)		41 (28–198)	30** (24–45)	
FI (g/l)	2.7 (0.2–4.4)	3.4 (0.2–7.2)	0.4 (–1.5–2.9)	1.5 (0.4–4.5)	2.7 (1.7–4.1)	1.0 (–0.9–2.4)
FII (IU/dl)	36.5 (22–65)	56 (43–76)	16 (7–42)	35 (16–73)	83** (60–102)	41* (15–61)
FV (IU/dl)	36 (2–126)	58 (14–121)	10 (–4.7–37)	41 (10–99)	69 (39–119)	28* (–16–51)
FVII (IU/dl)	43 (6–99)	55 (17–114)	11 (4–32)	48 (16–91)	85** (54–127)	38* (–3–75)
FVIII (IU/dl)	146 (8–391)	159 (18–360)	10 (–49–46)	157 (58–535)	175 (120–313)	17 (–250–96)
FIX (IU/dl)	83 (29–165)	98 (41–167)	8 (–6–30)	73 (43–174)	114 (65–156)	28* (–35–53)
FX (IU/dl)	49 (28–133)	61 (50–94)	15 (–7.3–43)	53 (16–94)	88** (65–104)	37* (–5–65)
FXI (IU/dl)	38 (20–105)	48 (38–101)	9 (–4.3–32)	34 (15–58)	55** (41–80)	23* (6–37)
FXII (IU/dl)	39 (27–64)	57 (44–83)	30 (1–37)	30 (5–69)	73** (60–105)	44* (23–66)

The median and 10th and 90th percentiles for PT, apt and coagulation factor levels in groups 1 and 2 before and after FFP infusion and observed increments are shown. The coagulation factor levels were not statistically different between the two groups before the infusion.

*Observed increment in group 2 was significantly greater than group 1 (Mann–Whitney *U*-test, $P < 0.05$).

**Significant difference when comparing groups 1 and 2 post-transfusion (Mann–Whitney *U*-test, $P < 0.05$).

	Group 1 <i>In vivo</i> recovery, IU/dl/IU/kg infused	Group 2 <i>In vivo</i> recovery, IU/dl/IU/kg infused	Correlation between adjusted increment (IU/dl) and IU/kg infused, correlation coefficient (<i>P</i> -value)
FI (g/l)	NA	NA	0.21 (0.2)
FII (IU/dl)	1.2 (0.5–3.2)	0.94 (0.4–1.7)	0.73 (0.001)
FV (IU/dl)	1.1 (–1.0–2.5)	1.0 (–0.7–1.8)	0.61 (0.001)
FVII (IU/dl)	0.9 (0.3–1.5)	0.8 (–0.1–2.1)	0.66 (0.001)
FVIII (IU/dl)	0.7 (–1.3–2.0)	0.3 (–8–3.0)	0.4 (0.05)
FIX (IU/dl)	0.4 (–1.2–1.7)	0.7 (–1.1–1.7)	0.63 (0.001)
FX (IU/dl)	1.3 (–3.2–3.2)	0.9 (–0.2–1.4)	0.64 (0.001)
FXI (IU/dl)	0.8 (0.97–1.7)	0.8 (0.2–1.4)	0.69 (0.001)
FXII (IU/dl)	1.5 (0.2–2.6)	1.0 (0.6–1.8)	0.73 (0.001)

There is no significant difference between groups 1 and 2. Correlation of all observed increments with the amount of coagulation factor infused is shown (Spearman rank correlation coefficient).

bleeding from invasive procedures with levels below 30 IU/dl and require levels above 30 IU/dl to arrest bleeding (Bloom, 1994). Similar target levels of coagulation factors are commonly used when reversing warfarin in bleeding patients. In massively transfused patients, diffuse microvascular bleeding has been shown to be associated with a platelet count below $50 \times 10^9/l$, fibrinogen level below 0.5 g/l and other coagulation factor levels below 20 IU/dl (Ciavarella *et al*, 1987).

It is already recognized that coagulation screens are poor predictors of bleeding following invasive procedures (Ewe, 1981; Eisenberg *et al*, 1982). The data presented here showed that coagulation tests are poor predictors of whether critically ill patients have significantly decreased coagulation factor levels and may, in part, explain why they are poor predictors of bleeding during invasive procedures. Critically ill patients often have multiple decreased coagulation factors, which, taken together may prolong the aPTT and PT when individual coagulation factors are not necessarily decreased to a level that compromises haemostasis. It is not possible in routine practice to assay all coagulation factors and a more global assessment of haemostasis such as thromboelastography or thrombin generation potential may be useful.

This study aimed to assess the effect of FFP on the laboratory parameters of haemostasis in critically ill patients and did not aim to assess clinical haemostasis. If this had been the case, a much larger number of matched patients would have been required. There was a wide range of FFP given in the two groups. Group 1 reflected standard clinical practice where, commonly, 1 l of FFP is given irrespective of the weight of the patient. Although in group 2, the ICU clinicians aimed to give about 30 ml/kg, clinical issues such as volume overload were also considered. This is a weakness of the study but does not detract from the findings that standard recommended doses of FFP often do not correct coagulation factor levels.

The data presented here do not support current guidelines on FFP usage (British Committee on Standards in Haematology, 1992, 1998; Fresh-Frozen Plasma, Cryoprecipitate and Platelet Administration Practice Guidelines Development Task

Table III. The *in vivo* recovery of coagulation factor levels.

Force of the College of American Pathologists, 1994; American Society of Anesthesiologists Task Force on Blood Component Therapy, 1996), as a dose of 6.5 or 10–15 ml/kg is unlikely to raise the coagulation factor levels above 30 IU/dl and be sufficient to stop microvascular bleeding.

The low increments in coagulation factors observed in this study are in line with findings from studies on the reversal of warfarin, which showed that FFP given at a dose of about 12 ml/kg was only successful in raising factors II, VII, IX and X by between 9 and 14 IU/dl (Makris *et al*, 1997). A further study in liver disease has shown that infusion of 8 ml/kg FFP resulted in coagulation factor increments of about 10 IU/dl and fibrinogen increment of 0.25 g/l (Mannucci *et al*, 1976) whilst infusion of 8 ml/kg FFP or solvent/detergent treated FFP only raised the factors II, V, VII, IX, X and XI between 0.1 and 9.9 IU/dl (Lerner *et al*, 2000). Youssef *et al* (2003) have also shown that, in patients with chronic liver disease, an infusion of 2–4 units of FFP did not adequately correct the prothrombin time in 90% of patients and suggest that higher doses of FFP may be more effective.

The inadequate increase in coagulation factor levels noted in these studies is predictable in view of the consistent *in vivo* recoveries of coagulation factors demonstrated in the present study. The coagulation factor content of FFP may be variable from unit to unit as this product is standardized only for fibrinogen and factor VIII content. Our findings do not support recommendations to give a specific weight-related dose of FFP to all patients. An assessment should be made of the likely degree of haemostatic defect and replacement, tailored to the amount of FFP predicted to correct that defect. Consideration should be given to the strategy of using coagulation factor concentrates or other haemostatic agents, such as recombinant activated factor VII, to more rapidly and predictably correct coagulation factor deficiencies or haemostatic defects. Clinical trials are required to assess the role of these therapies.

The data presented here demonstrated that coagulation screens poorly predicted coagulation factor levels in critically

ill patients. Many patients did not need FFP, and in those that did, standard recommended doses were often inadequate to correct deficiencies of individual coagulation factors. Some patients are unnecessarily exposed to the risks of complications from blood products and where FFP is indicated, patients are exposed to the risks of blood products without adequate correction of coagulation.

Studies are required to assess other methods for measuring global haemostasis, such as thromboelastography or endogenous thrombin potential, and assessing replacement therapy in this clinical situation. Clinical studies with endpoints that assess bleeding are needed to inform clinicians on the need for, and efficacy of, coagulation factor replacement as well as the use of tests of haemostasis. Clinical trials of haemostatic agents other than FFP should be considered. Until more data are available, FFP replacement should be tailored for individual patients, depending on clinical and laboratory assessment of the likely haemostatic defect, and given in doses that can be expected to increase coagulation factor levels to a predetermined level. In selected patients coagulation factor levels may be useful in determining the need for, and adequacy of, FFP replacement.

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Note added in proof

Updated guidelines for the use of fresh frozen plasma have been posted by The British Committee for Standards in Haematology (2004) at <http://www.bcsghguidelines.com>

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