Injury, Int. J. Care Injured 44 (2013) 209–216

Contents lists available at SciVerse ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma

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ARTICLE INFO

Article history:
Accepted 29 August 2012

Keywords:
Coagulation
Blood transfusion
Thrombelastometry
Trauma
Fresh frozen plasma
Fibrinogen concentrate
Prothrombin complex concentrate

ABSTRACT

Background: FFP and coagulation factor concentrates are used to correct trauma-induced coagulopathy (TIC). However, data on coagulation profiles investigating effects of therapy are scarce.
Methods: This is an analysis of 144 patients with major blunt trauma ((ISS) $\geq$ 15), who were enrolled in a prospective cohort study investigating characteristics and treatment of TIC. Patients who received fibrinogen concentrate and/or prothrombin complex concentrate alone (CF Group) were compared with those additionally receiving FFP transfusions (FFP Group).
Results: Sixty-six patients exclusively received CF, while 78 patients additionally received FFP. Overall, patients were comparable regarding age, gender and ISS (CF Group, ISS 37 (29, 50); FFP Group ISS 38 (33, 55), $p = 0.28$). Patients treated with CF alone showed sufficient haemostasis and received significantly fewer units of red blood cells (RBC) and platelets than did those also receiving FFP [(RBC 2(0, 4) U vs. 9 (5, 12) U; platelets 0 (0, 0) U vs. 1 (0, 2) U, $p < 0.001$)]. In addition, fewer patients in the CF Group developed multiorgan failure (MOF) (18.2% vs. 37.2%, $p = 0.01$) or sepsis (16.9% vs. 35.9%, $p = 0.014$) than in the FFP Group. Propensity score-matching ($n = 28$ pairs) used to reduce the impact of treatment selection confirmed that additional FFP administration showed no benefit in restoring haemostasis, but was associated with significantly higher transfusion rates for RBC and platelets.
Conclusion: The use of CF alone effectively corrected coagulopathy in patients with severe blunt trauma and concomitantly decreased exposure to allogeneic transfusion, which may translate into improved outcome.

Introduction

Development of coagulopathy occurs quickly in major trauma because of adrenergic stress, massive tissue factor liberalisation, blood loss and dilution through necessary fluid administration. Presence of acidosis and hypothermia aggravate coagulopathy and hypoperfusion might induce activation of the protein C system. The presence of trauma-induced coagulopathy (TIC) reflects severity of injury and independently increases mortality of trauma patients. Thus, immediate and effective correction of coagulopathy, acidosis and hypothermia, as well as damage control surgery are the primary goals of current management concepts.[1,2]

Most guidelines recommend transfusion of FFP as first line treatment,[3,4] while the Austrian Task Force on Coagulation Management (AGPG) of the Austrian Society of Anaesthesia, Reanimation and Intensive Care (OEGARI) favours the initial use of coagulation factor concentrates (CF) in major bleeding.[5] On the one hand, there is only scant evidence for the use of CF in acquired coagulopathy at this time and no large randomised study comparing CF and FFP has been conducted so far.[6] On the other hand, evidence to show that FFP can limit blood loss or prevent microvascular diffuse bleeding is also lacking.[7] However, available data, especially those referring to the use of fibrinogen concentrate, show quite a good benefit-risk profile for the use of CF.[8–11] The early and aggressive transfusion of FFP as compared to crystalloid resuscitation and late FFP transfusion has been shown to improve survival, but increased incidence of infection, sepsis, acute lung injury and multiorgan failure has also been reported.[12–19] The principal advantage of CF is that they are immediately available and contain defined and high concentrations of the factor(s) of

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http://dx.doi.org/10.1016/j.injury.2012.08.047

Table 1
Characteristics of trauma patients (full unmatched population).

	Coagulation factors only ($n=66$)	FFP and coagulation factors ($n=78$)	p-Value
Age (years)	35 (23, 53)	44 (34, 53)	0.055
Male gender (n)	54 (81.8)	57 (73.1)	0.238
Time until ED (min)	70 (60, 120)	75 (60, 116)	0.793
ISS (points)	37 (29, 50)	38 (33, 55)	0.277
GCS (points)	13 (7, 15)	13 (7, 15)	0.504
Pattern of injury			
Head (n)	45 (68.2)	36 (46.2)	0.007
Chest (n)	57 (86.4)	53 (67.9)	0.006
Abdominal (n)	36 (54.5)	51 (65.4)	0.234
Limbs (n)	40 (60.6)	61 (78.2)	0.042
SBP (mm Hg)	115 (100, 138)	100 (90, 120)	0.002
BE (mmol L^{-1})	−3.3 (−5.7, −1.6)	−4.3 (−7.6, −2.9)	0.012
Temperature (°C)	34.9 (34.3, 35.7)	34.5 (33.2, 35.5)	0.230
Colloids until ED (mL)	500 (0, 1000)	500 (0, 1000)	0.230
Crystalloids until ED (mL)	1000 (500, 1500)	1000 (500, 1625)	0.926

ISS, Injury Severity Score; SBP, systolic blood pressure; BE, base excess; Hb, haemoglobin.
Data are given as median (interquartile range) or numbers (%).
p-Values were calculated using non-parametric Mann–Whitney U-test for metric data and Fisher's exact test for categorical data.

interest, which can be administered without volume expansion and thus enable quick restoration of haemostasis. Besides quickly restoring clot strength and increasing thrombin formation the lack of volume expansion might explain why two retrospective studies observed markedly reduced transfusion rates for red blood cells (RBC) and platelets when patients were treated with fibrinogen and prothrombin complex concentrate (PCC) only.[20,21] However, in those studies only a few coagulation parameters were available to show the efficacy of various treatments, and differences in transfusion rates might have been influenced by differences in institutional transfusion triggers.

Our institution has long-term clinical experience in using CF in acquired bleeding guided by viscoelastic methods or for overdose of vitamin K antagonists. Although published data suggest that coagulation factor concentrates (CF) can be used exclusively, many physicians believe that at least additional FFP transfusions are necessary to effectively correct acquired coagulopathy.[10]

To test the hypothesis that targeted administration of CF alone sufficiently restores haemostasis we analysed data from patients included in the single-centre Diagnosis and Treatment of Trauma-induced Coagulopathy (DIA-TRE-TIC) study.[22] The response profile for coagulation parameters following administration of CF alone was compared to that observed after administration of CF combined with FFP. Secondary endpoints were transfusion rates for red cell and platelet transfusions and clinical outcome.

Methods

Patients

Details of patients included in the DIA-TRE-TIC Study are described elsewhere.[22] In brief, that prospective, single-centre cohort study was conducted to investigate the frequency and characteristics of trauma-induced coagulopathy (TIC) and to evaluate the change in coagulation parameters during routine treatment in the initial 24 h. The general inclusion criteria were age $\geq$18 years, admission to the Level I Trauma Centre at Innsbruck Medical University Hospital, Injury Severity Score, ISS $\geq$ 15 or isolated brain injury (Glasgow Coma Score (GCS) $\leq$ 14). The study protocol was approved by the Ethics Committee of Innsbruck Medical University. The need for written informed consent was waived, because study-related blood sampling was judged a

Table 2
Laboratory and haemodynamic parameters of trauma patients receiving coagulation factor concentrates alone (CF Group; $n=66$) or coagulation factor concentrates and fresh frozen plasma (FFP Group; $n=78$) (full unmatched population).

		ED	4 h	6 h	24 h
PT (%)	CF	74 (63, 87)*	63 (53, 73)*	63 (53, 75)*	70 (61, 80)*
	FFP	60 (49, 76)	70 (57, 81)	76 (68, 89)	75 (65, 88)
INR	CF	1.3 (1.2, 1.4)*	1.4 (1.3, 1.5)*	1.4 (1.3, 1.4)*	1.3 (1.2, 1.5)*
	FFP	1.4 (1.3, 1.6)	1.3 (1.2, 1.5)	1.2 (1.1, 1.3)	1.3 (1.1, 1.4)
aPTT (s)	CF	32 (29, 37)*	41 (34, 48)	42 (37, 46)*	46 (41, 52)*
	FFP	38 (33, 48)	41 (36, 54)	38 (34, 44)	41 (37, 46)
Fibrinogen (mg dL^{-1})	CF	195 (149, 231)*	176 (128, 222)*	192 (148, 247)*	341 (281, 436)
	FFP	154 (120, 210)	205 (150, 238)	232 (196, 259)	392 (308, 456)
Haemoglobin (g dL^{-1})	CF	11.4 (9.9, 12.4)*	9.3 (8.6, 10.7)	9.5 (8.3, 10.4)	8.8 (7.9, 10.0)
	FFP	9.4 (7.2, 10.9)	9.2 (8.5, 10.1)	9.1 (8.3, 10.1)	9.2 (8.4, 9.9)
Platelets (g L^{-1})	CF	139 (170, 199)*	140 (114, 164)*	137 (114, 157)*	120 (103, 140)*
	FFP	152 (119, 180)	82 (60, 118)	81 (60, 108)	73 (63, 102)
pH	CF	7.34 (7.29, 7.38)	7.36 (7.33, 7.40)	7.38 (7.31, 7.39)	7.40 (7.37, 7.44)*
	FFP	7.31 (7.26, 7.36)	7.37 (7.33, 7.43)	7.40 (7.36, 7.44)	7.42 (7.36, 7.46)
BE (mmol L^{-1})	CF	−3.3 (−5.7, −1.6)*	−3.5 (−4.6, −2.6)*	−3.9 (−4.4, .2.2)*	−0.2 (−2.1, 1.3)*
	FFP	−4.3 (−7.6, −2.9)	−2.4 (−4.6, −1.5)	−1.0 (−2.8, 1.6)	1.4 (−1.0, 3.1)

ED, Emergency department admission; PT, prothrombin time; aPTT, activated partial thrombin time, BE, base excess.
* $p<0.05$ Mann–Whitney U-test CF vs. FFP Group; data are given as median (interquartile range).

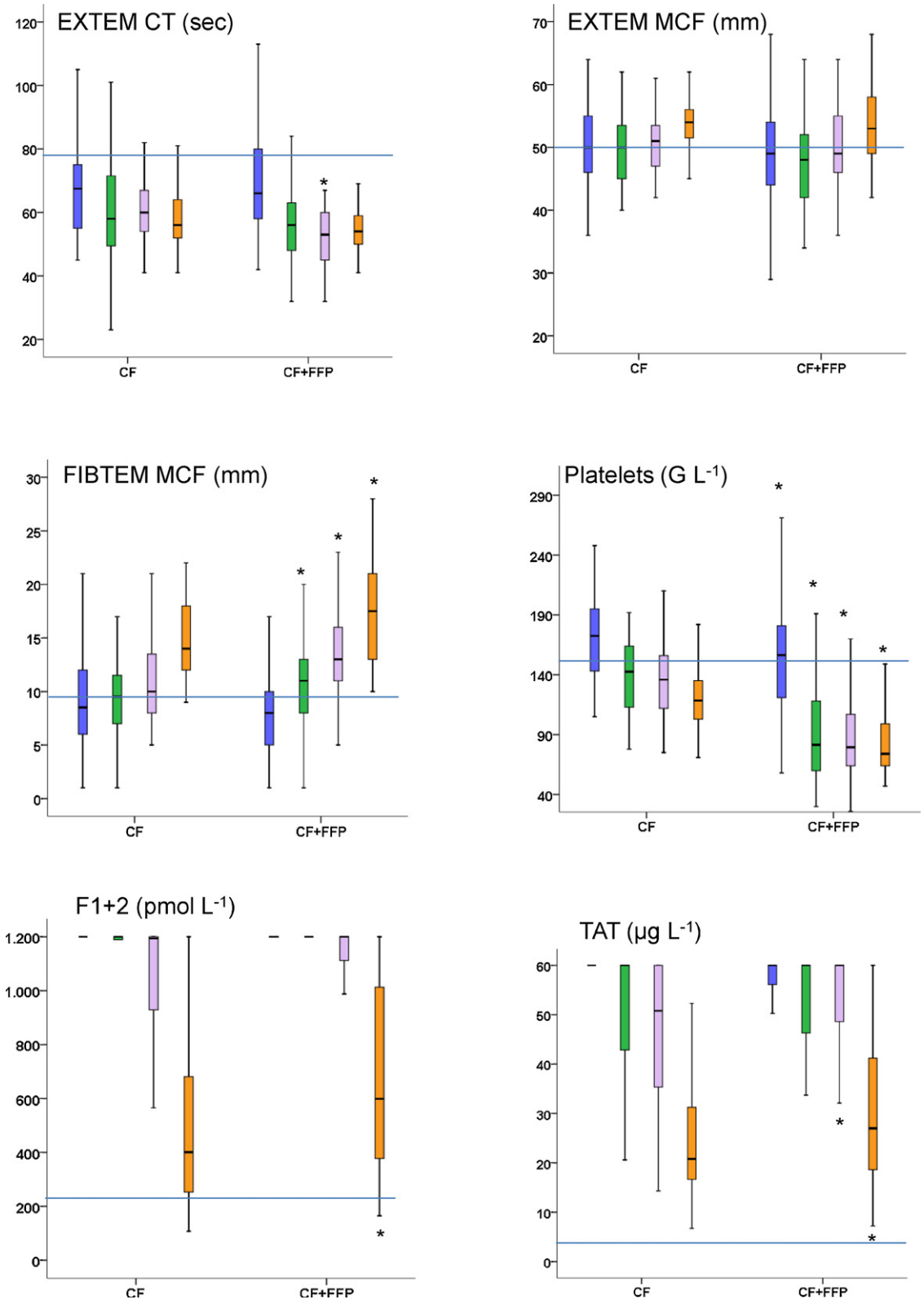

Fig. 1. Results of ROTEM® assays, platelet count and molecular markers of thrombin formation in patients with severe blunt trauma receiving exclusively coagulation factors for correction of coagulopathy (CF, $n = 66$), as compared to patients also receiving FFP (CF + FFP, $n = 78$). Measurements were performed at Emergency Department (ED) admission (blue), 4 (green), 6 (pink) and 24 h (orange) thereafter. Thresholds of upper and lower normal values, respectively, are indicated by solid lines. EXTEM, extrinsically activated ROTEM assay; CT, coagulation time (normal value < 78 s); MCF, maximum clot firmness (normal value ≥ 50 mm); FIBTEM MCF, strength of fibrinogen/fibrin polymerisation (normal value ≥ 9 mm). Platelets, platelet count (normal value > 150 g L^{-1}); F1 + 2, prothrombin fragments 1 + 2 (reference range 70–230 pmol L^{-1}); TAT, thrombin–antithrombin complex (reference range 1–4.1 µg L^{-1}). Friedmann ANOVA analysis showed that all parameters changed significantly over time; $^{*}p < 0.05$ comparison between groups at measurement points (Mann–Whitney *U*-test). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

Table 3
Transfusion and coagulation factor requirements during the first 24 h in trauma patients treated exclusively with coagulation factor concentrates (CF Group, $n = 66$) as compared to those additionally receiving fresh frozen plasma (FFP Group, $n = 78$).

	CF Group	FFP Group	p-Value
RBC (U)	2 (0, 4)	9 (5, 12)	<0.001
Patients transfused (n)	40 (60.6)	76 (97.4)	<0.001
FFP (U)	0(0, 0)	10 (5, 13)	<0.001
Patients transfused (n)	0 (0)	78 (100)	NT
PC (U)	0 (0, 0)	1 (0, 2)	<0.001
Patients transfused (n)	3 (4.5)	44 (56.4)	<0.001
Fibrinogen concentrate (g)	4 (2, 4)	4 (2, 7)	0.007
Patients treated (n)	66 (100)	70 (89.7)	0.1252
PCC (IE)	0 (0, 1000)	750 (0, 1800)	0.006
Patients treated (n)	23 (34.8)	40 (51.3)	0.064

RBC, red blood cell concentrate; FFP, fresh frozen plasma; PC, aphaeresis platelet concentrate; PCC, prothrombin complex concentrate (factors II, VII; IX, X); NT not tested.
Data are given as median (interquartile range) or numbers (%).
p-Values were calculated using non-parametric Mann–Whitney U-test for metric data and Fisher's exact test for categorical data.

minimal-risk intervention and all patients were treated according to clinical routine.

For the present analysis patients were selected from the DIA-TRE-TIC population on the basis of the following criteria: presence of multiple blunt injury, survival for at least 24 h, and need for haemostatic therapy. Patients with isolated brain injury or those who did not receive haemostatic therapy were excluded. Patients who had received fibrinogen concentrate and/or PCC only but no FFP were grouped post hoc as the CF Group. Patients who received CF and FFP were designated the FFP Group.

Data collection

The following data were collected prospectively: patient demographics, type and severity of injury (ISS), GCS, prehospital fluids, time elapsed between trauma and study hospital admission, vital signs. Type and numbers of transfused blood components, and dosage of coagulation factors, amounts of intravenous fluids administered, heart rate, blood pressure, pH value, base excess and the oxygenation index were registered at 4, 6, 24 h thereafter. The need for intensive care unit admission, 28-day ventilator-free days, diagnosis of sepsis and MOF, rate of thromboembolic events, intensive care unit and hospital length of stay, as well as 30-day mortality were recorded.

MOF was defined as the simultaneous failure of two or more organs. Organ failures were defined as a total of >2 points in single organ subcategories of the Sequential Organ Failure Assessment Score. Sepsis was defined according to the criteria suggested by the American College of Chest Physicians and the Society of Critical Care Medicine.

Table 4
Outcome parameters of the full unmatched trauma population treated exclusively with coagulation factor concentrates (CF Group, $n = 66$) as compared to those additionally receiving fresh frozen plasma (FFP Group, $n = 78$).

	CF Group ($n = 66$)	FFP Group ($n = 78$)	p-Value
paO_2/FiO_2 24 h	317 (250, 377)	241 (201, 325)	0.002
Ventilator-free days	18 (8, 25)	16 (4, 23)	0.139
Sepsis (n)	11 (16.9)	28 (35.9)	0.014
MOF (n)	12 (18.2)	29 (37.2)	0.015
ICU stay (days)	12 (6, 24)	14 (7, 30)	0.217
LOS (days)	24 (12, 35)	29 (16, 50)	0.074
30-day mortality (n)	5 (7.6)	6 (7.7)	0.979
Thromboembolism (n)	6 (10.0)	6 (7.7)	0.772

Data are given as median (interquartile range) or numbers (%).
ICU, intensive care unit; LOS, length of hospital stay; MOF, multiple-organ failure.
p-Values were calculated using non-parametric Mann–Whitney U-test for metric data and Fisher's exact test for categorical data.

Laboratory tests

The response profile for coagulation parameters during treatment was analysed by obtaining blood samples at emergency department (ED) admission and 4, 6, and 24 h thereafter.

Viscoelastic assays, standard plasmatic coagulation tests, blood cell count, prothrombin fragments 1 + 2 (F1 + 2), and thrombin–antithrombin complex (TAT) were measured using rotational thrombelastometry (ROTEM®, TEM International GmbH, formerly Pentapharm, Munich, Germany) and standard laboratory assays (Siemens Healthcare AG, Erlangen, Germany). The ROTEM parameters coagulation time (EXTEM® CT, reference range <78 s), maximum clot firmness (EXTEM® MCF, reference range ≥50 mm) and fibrin polymerisation (FIBTEM® MCF, reference range ≥9 mm) were recorded.

Transfusion of blood components and administration of coagulation factor concentrates

At our institution all used blood components are leucocyte-depleted, and quarantine FFP are available within 30–45 min. CF concentrates are used first for immediate treatment according to deficiency detected with ROTEM assays. Fibrinogen concentrate (Haemocomplettan P 1 g®, CSL Behring, Marburg, Germany) is used to correct low fibrinogen concentration and/or poor fibrin polymerisation (fibrinogen concentration < 150–200 mg dL^{-1} equals FIBTEM MCF < 7 mm) at dosages of 25–50 mg kg^{-1} body weight. Prothrombin complex concentrate (Beriplex P/N 500 IU® CSL Behring, Marburg, Germany) containing Factors II, VII, IX and X is used at dosages of 20–30 IU kg^{-1} body weight in cases showing delayed initial thrombin formation (PT < 50% or INR > 1.5 and/or EXTEM CT > 90 s). FFP are transfused according to the clinical experience of the anaesthesiologist in charge and plasmatic coagulation test results (INR > 1.5, aPTT > 50 s). Aphaeresis platelet concentrates are used in bleeding patients showing platelet counts <50–100 g L^{-1} and/or poor clot firmness (EXTEM MCF < 45 mm). Haemoglobin levels <8–9 g dL^{-1} are the usual trigger for administering RBC in actively bleeding trauma patients. At the time the study was conducted antifibrinolytics were not used prophylactically.

Statistical analysis

Due to skewed distribution of several metric variables investigated, continuous data are presented as median (interquartile range). Categorical data are presented as numbers and percentages. Univariate comparisons between the CF and FFP Groups were performed with a non-parametric Mann–Whitney U-test for metric data and Chi-square and Fisher's Exact test for categorical data. Changes in laboratory parameters over time were analysed using a non-parametric Friedman ANOVA. Propensity score-matching was used to reduce the impact of treatment selection in comparing treatment with CF alone and with additional FFP administration. Numerical variables revealing a p-value < 0.05 between the two groups at ED admission were entered into a logistic regression analysis with the use of CF alone vs. CF plus FFP as the dependent variables. This was performed to create a propensity score for each patient, representing the probability of receiving either CF alone or CF plus FFP as described by Blackstone and Austin.[23,24] The resulting propensity score was used to create a matched-pair patient subsample. As a prior analysis showed that coagulation variables were similar in

Table 5
Characteristics of the propensity score-matched population.

	CF Group ($n = 28$)	FFP Group ($n = 28$)	p-Value
Age (years)	45 (16, 54)	37 (23, 50)	0.421
Male gender (n)	22 (78.6)	22 (78.6)	1.000
ISS (points)	40 (±12)	40 (±17)	0.413
GCS (points)	8 (3, 14)	12 (7, 15)	0.018
Pattern of injury			
Head trauma (n)	20 (71.4)	13 (46.4)	0.039
Chest trauma (n)	16 (57.1)	19 (67.9)	0.146
Abdominal trauma (n)	16 (57.1)	18 (64.3)	1.000
Limb trauma (n)	20 (71.4)	23 (82.1)	0.754
MAP (mm Hg)	75 (67, 90)	78 (69, 88)	0.854
BE (mmol L^{-1})	−3.90 (−5.65, −1.48)	−4.0 (−5.9, −2.83)	0.269
paO_2/FiO_2	44 (38, 63)	50 (40, 75)	0.563
Temperature (°C)	35.0 (34.2, 35.8)	34.7 (33.4, 37.0)	0.345
Colloids until ED (mL)	500 (500, 1000)	500 (25, 1000)	0.580
Crystalloids until ED (mL)	1000 (625, 1500)	1000 (500, 1500)	0.896

ISS, Injury Severity Score; GCS, Glasgow Coma Score; MAP, mean arterial pressure; BE, base excess.
Data are given as median (interquartile range) or numbers (%).
p-Values were calculated using Wilcoxon and McNemar test for metric and categorical data.

multiple injured patients regardless of the presence or absence of head injury patients were not stratified for head injury. The balance of variables between the study groups in the matched sample was assessed using the Wilcoxon test for continuous measures and the McNemar test for categorical measures.

All statistical analyses were conducted using SPSS (Version 17.0; SPSS Inc; Chicago, IL, USA). p-Values < 0.05 were considered statistically significant.

Results

Full unmatched patient population

Data from 144 trauma patients were available for this analysis. Sixty-six patients were treated with CF alone, and 78 patients additionally received FFP. Patients were comparable regarding age, gender, ISS and time until admission to ED. Patients had received similar amounts of fluids before admission to ED (Table 1) and also during the first 24 h [crystalloids CF Group 5225 mL (3738, 6500) vs. FFP Group 5150 mL (3650, 6412), $p = 0.76$ and colloids CF Group (3500 mL (2375, 4738) vs. FFP Group 3500 mL (2000, 5000, $p = 0.90$)].

On admission patients in the FFP Group showed lower haemoglobin, platelet count, plasmatic test results and BE, while all ROTEM parameters were comparable, as were values of pH and molecular markers of thrombin formation (Table 2 and Fig. 1). During the first 24 h mean blood pressure and heart rate were comparable among groups except mean arterial pressure at admission [CF Group 85 mm Hg (71, 97), FFP Group 76 mm Hg (65, 87); $p < 0.05$]. Laboratory readings changed significantly over time in both groups (Friedman ANOVA all $p < 0.05$), with the exception of haemoglobin which remained unchanged in the FFP Group (Friedman ANOVA $p = 0.963$). In both groups molecular markers of thrombin formation were excessively high and treatment resulted in acceptable median values for plasmatic and viscoelastic tests already at 4 h. As compared to the CF Group numbers of platelets decreased more in the FFP Group and were significantly lower at 4, 6 and 24 h.

The 24 h cumulative transfusion and coagulation factor requirements are presented in Table 3. At 24 h 97.4% of patients in the FFP Group had received RBC and 56.4% had received platelet concentrates, while this was true for only 60.6% and 4.5% of patients receiving CF alone, respectively (24 h RBC and PC $p < 0.001$). At all study time points (ED-4 h, 4–6 h, 6–24 h) the median number of units of RBC and platelet concentrates was significantly higher in the FFP than in the CF Group, as were the numbers of transfused patients (data not shown). Dosages of fibrinogen concentrate and PCC were comparable between groups, except for the period ED-4 h. By that time patients in the FFP Group had received larger doses of fibrinogen concentrate [CF Group fibrinogen concentrate 2 g (0, 4), FFP Group 4 g (2, 6), $p < 0.05$] and more patients had also received larger doses of PCC [PCC 0 IU (0, 1275)] than had patients in the CF Group [PCC 0 IU (0, 0); $p < 0.05$].

Patients in the FFP group showed significantly lower calculated oxygenation indices at 24 h As compared to the FFP Group fewer patients in the CF Group developed sepsis or MOF, while 30-day mortality and prevalence of venous thromboembolism were similar in both groups. Patients receiving only CF showed higher numbers of ventilator-free days and a shorter length of ICU and hospital stay. However, these differences were not statistically significant (Table 4).

Propensity score-matched population

Propensity scores were used to create a matched-pair subsample, which resulted in formation of 28 pairs. Patient characteristics, admission laboratory and haemodynamic parameters were comparable between groups (Table 5). Because matching was performed without prior stratification for head injury more patients in the CF Group exhibited concomitant head trauma and also showed fewer GCS points. Patients in the CF and FFP Groups received similar amounts of crystalloids [(4950 mL (3425, 6500) vs. 4900 mL (4125, 6412), $p = 0.33$] and colloids [(3500 mL (2500, 4875) vs. 3800 (2125, 5375, $p = 0.79$)] for fluid replacement during the first 24 h.

Analysis of the response profile for coagulation parameters, haemoglobin and platelet count showed a few statistically significant differences between groups at 4 and 6 h (Table 6). At 24 h all parameters were similar regardless of whether patients had received FFP or not, except counts of platelets which were markedly lower in patients in the FFP Group than in those treated with CF alone ($p = 0.008$) (Table 6). The 24 h transfusion rates for RBC and platelets were significantly higher in patients also receiving FFP. As measured at time points, RBC numbers differed significantly except in the period 6–24 h after admission to ED (data not shown). At 24 h 92.9% of the patients in the FFP Group had received RBC and 42.9% had received platelet concentrates, while this was true for 67.9% and 3.6% of the patients receiving CF alone (24 h RBC $p = 0.039$; PC $p = 0.001$). No difference was observed for CF dosages (see Table 7).

Table 6
Laboratory parameters of propensity score-matched trauma patients receiving coagulation factor concentrates alone (CF; $n = 28$) or coagulation factor concentrates and fresh frozen plasma (FFP; $n = 28$).

		ED	4 h	6 h	24 h
EXTEM CT (s)	CF	70 (58, 79)	61 (52, 78)	61 (55, 70)	56 (52, 66)
	FFP	64 (57, 71)	56 (48, 67)	53 849, 58)	57 (52, 61)
EXTEM MCF (mm)	CF	50 (46, 53)	50 (45, 54)	52 (46, 55)	55 (52, 57)
	FFP	50 (46, 56)	49 (47, 55)	53 (47, 58)	53 (51, 59)
FIBTEM MCF (mm)	CF	7 (5, 9)	9 (6, 12)*	10 (8, 14)*	14 (12, 19)
	FFP	9 (6, 10)	12 (9, 14)	14 (11, 18)	17 (13, 22)
PT (%)	CF	66 (59, 78)	63 (48, 70)*	70 (53, 77)*	71 (59, 77)
	FFP	70 (59, 84)	73 (57, 87)	82 (71, 91)	73 (61, 79)
INR	CF	1.4 (1.3, 1.5)	1.4 (1.3, 1.6)	1.4 (1.2, 1.5)*	1.4 (1.2, 1.5)
	FFP	1.3 (1.2, 1.4)	1.3 (1.2, 1.5)	1.2 (1.1, 1.3)	1.3 (1.2, 1.4)
aPTT (s)	CF	35 (31, 28)	39 (34, 50)	42 (37, 47)*	46 (41, 49)
	FFP	34 (31, 40)	37 (34, 47)	36 (33, 41)	42 (36, 47)
Fibrinogen (mg dL^{-1})	CF	197 (150, 235)	201 (126, 230)	229 (170, 258)	377 (307, 496)
	FFP	191 (156, 219)	212 (162, 244)	235 (210, 278)	394 (311, 500)
TAT (μg L^{-1})	CF	60 (60, 60)	60 (47, 60)	59 (37, 60)	27 (16, 33)
	FFP	60 (56, 60)	51 (32, 60)	60 (54, 60)	27 (17, 42)
F1 + 2 (pmol L^{-1})	CF	1200 (1200, 1200)	1200 (1200, 1200)	1123 (922, 1200)	488 (294, 892)
	FFP	1200 (1200, 1200)	1200 (842, 1200)	1200 (966, 1200)	394 (271, 633)
Haemoglobin (g dL^{-1})	CF	10.6 (8.7, 11.9)	9.3 (8.4, 10.7)	10.0 (7.8, 11.7)	9.7 (8.4, 10.8)
	FFP	10.2 (9.4, 11.7)	9.3 (8.8, 10.1)	8.9 (8.4, 9.7)	9.3 (8.5, 9.7)
Platelets (g L^{-1})	CF	163 (134, 192)	138 (111, 167)*	133 (108, 156)*	115 (95, 130)*
	FFP	169 (137, 182)	107 (72, 132)	87 (69, 115)	71 (62, 92)
pH	CF	7.33 (7.25, 7.38)	7.35 (7.30, 7.39)*	7.35 (7.31, 7.41)	7.40 (7.37, 7.44)
	FFP	7.33 (7.28, 7.36)	7.38 (7.34, 7.45)	7.40 (7.37, 7.45)	7.41 (7.35, 7.47)
BE (mmol L^{-1})	CF	−3.9 (−5.7, −1.5)	−3.9 (−5.2, −2.7)*	−3.7 (−5.7, −2.5)	−1.1 (−3.0, 1.2)
	FFP	−4.0 (−5.9, −2.8)	−2.1 (−4.5, −0.1)	−0.6 (−2.5, 1.9)	1.3 (−1.5, 3.0)

ED, Emergency department admission; EXTEM, extrinsically activated ROTEM assay; CT, coagulation time; MCF, maximum clot firmness; FIBTEM MCF, fibrin polymerisation; TAT, thrombin–antithrombin complex; F1 + 2, prothrombin fragments 1 + 2; BE, base excess.
* $p < 0.05$ CF vs. FFP group (Wilcoxon test); data are median (interquartile range).

Oxygenation index was higher in patients in the CF Group 323 (228, 390) than in the FFP Group 286 (206, 345), but the difference was not significant. All other outcome parameters were similar between groups (data not shown).

Discussion

This study for the first time presents detailed data on the response profile for plasmatic and viscoelastic coagulation parameters during treatment of bleeding trauma patients using CF exclusively or combined with FFP. Results show that administration of CF alone effectively restored coagulation parameters, even during ongoing blood loss and fluid replacement using colloids and crystalloids. Importantly, the use of CF alone was associated with markedly reduced transfusion rates for RBC and platelets, and avoidance of RBC and platelet transfusion was feasible in significantly more patients than after FFP administration. Albeit patients in the FFP Group had received more RBC, haemoglobin did not change significantly and platelet counts decreased markedly despite platelet transfusions. Although patients received FFP at median dosages of more than 30 mL kg^{-1} 1 body weight, the overall benefit of additional FFP transfusion for restoring coagulation parameters was small and in the matched-pair analysis no benefit at all was detectable. These observations raise the question whether FFP are always necessary when CF are used.

It has been increasingly recognised that low fibrinogen concentrations, impaired fibrin polymerisation and consequently poor clot firmness characterise the acquired coagulopathy of surgical and trauma patients.[22,25,26] Furthermore, poor clot strength is associated with mortality and RBC transfusion requirement.[22,27,28] Thus, from a pathophysiological point of view the benefit of transfusing FFP as first line treatment seems questionable. FFP contains only low concentrations of the main protein of interest, namely fibrinogen. In fact, a recently published study shows that Fibrinogen supplementation during transfusion maintained but did not augment fibrinogen levels.[29] In addition, the volume-expanding effect of FFP unavoidably provokes thrombocytopenia, which weakens clot strength and aggravates anaemia, thereby increasing the need for RBC transfusion.[30,31] This

Table 7
Transfusion and coagulation factor requirements during the first 24 h in trauma patients treated exclusively with coagulation factor concentrates (CF Group, $n = 66$) as compared to those additionally receiving fresh frozen plasma (FFP Group, $n = 78$).

	CF Group	FFP Group	p-Value
RBC (U)	2 (0, 6)	7 (4, 11)	0.001
Patients transfused (n)	19 (67.9)	26 (92.9)	0.039
FFP (U)	0 (0, 0)	8 (5, 10)	NT
Patients transfused (n)	0 (0)	78 (100)	NT
PC (U)	0 (0, 0)	0 (0, 1)	0.003
Patients transfused (n)	1 (3.6)	12 (42.9)	0.001
Fibrinogen concentrate (g)	4 (2, 4)	4 (2, 6)	0.550
Patients treated (n)	28 (100)	27 (96.4)	1.000
PCC (IE)	0 (0, 1200)	0 (0, 1200)	0.943
Patients treated (n)	13 (46.4)	11 (39.3)	0.774

RBC, red blood cell concentrate; FFP, fresh frozen plasma; PC, aphaeresis platelet concentrate; PCC, prothrombin complex concentrate (factors II, VII; IX, X); NT not tested.
Data are given as median (interquartile range) or numbers (%).
p-Values were calculated using Wilcoxon and McNemar test.

assumption is confirmed by the present data on the propensity score-matched population, showing markedly decreased platelet numbers despite platelet transfusion, unchanged haemoglobin values during RBC transfusion and identical fibrinogen concentrations regardless of whether patients had received FFP or not. All but one of these patients had also received fibrinogen concentrate at a median dose of 57 mg kg^{-1} body weight. We thus hypothesise that the measured fibrinogen concentrations resulted mainly from administration of fibrinogen concentrate and that values below 150 mg dl^{-1} would have been seen for exclusively FFP transfusions. At our institution no fixed transfusion algorithms are used, but the 24 h cumulative numbers of FFP and RBC show that blood components were used at about 1:1 ratios. Two other recent studies reported serial coagulation parameters in response to FFP therapy. Chambers and co-workers compared coagulation profiles in patients treated with laboratory-driven non-RBC transfusions as compared to those receiving FFP, RBC and platelets at ratios 1:1:1. The authors of that study found that the coagulation profiles of the two cohorts were indistinguishable. Despite increased administration of FFP and platelets patients became coagulopathic and fibrinogen below 100 mg dl^{-1} was almost always the initial abnormality.[32] Furthermore, the mean numbers of RBC transfusions were 11.2 U vs. 18.1 U ($p = 0.0135$) with the original and more aggressive protocol, respectively. When analysing the change in clotting times and clot strength during different transfusion regimens in 50 trauma patients Davenport found a marked variability in response to FFP. In that study a 1:1 FFP:RBC ratio had no additional benefit over ratios of 1:2–3:4 and may even have negative effects on haemostasis.[33]

Nevertheless, several data show improved survival with high FFP:RBC ratios in trauma patients. In fact, Brown et al.[34] reported decreased mortality in all trauma patients receiving high FFP:RBC ratios regardless of admission INR. The authors concluded that it is not necessary to determine whether INR is elevated or not before starting transfusion of high FFP:RBC ratios. Considering the above-cited results and ours it is conceivable that patients benefited from other aspects accompanying liberal FFP transfusion than from rapid reversal of coagulopathy. For example, early administration of FFP instead of huge amounts of crystalloids may more effectively correct hypovolaemia, hypoperfusion, acidosis and their consequences, as FFP refer to an 8.3% protein solution. The present data indicate that an exclusively CF treatment effectively corrected coagulopathy and maintained clot firmness. Furthermore, this strategy preserved a decline in platelet and red blood cell numbers throughout 24 h, although avoidance of RBC and platelet transfusion was feasible in 39% and 96% of patients, respectively. In the group of patients also receiving FFP only 3% received no RBC and 44% received no platelet transfusion. These results are in agreement with the findings of two retrospective studies using closed matched-pair analysis for comparison of trauma patients who were treated at different institutions and received either FFP only or CF only.[20,21] The transfusion-sparing effect of a CF-based concept seems important as this could reduce the risk of non-infectious side-effects of blood transfusions, like transfusion-related immunomodulation, transfusion related lung injury, circulatory overload, storage related negative effects of RBC in the microcirculation and lastly development of MOF.[35] Furthermore, the availability of blood components is not unlimited and especially platelet concentrates are costly too, as is the treatment of transfusion-related side-effects.

The present study found no influence of FFP on mortality, but some data indicate that FFP per se and/or the concomitantly increased RBC and platelet transfusions might increase susceptibility to sepsis and MOF. One of the above-cited studies also observed an increased incidence of MOF in patients treated with FFP only as compared to those receiving CF exclusively.[20] However, these preliminary data need to be confirmed in randomised trials. As CF effectively restore coagulation factor concentrations, they might increase the rate of thromboembolic events. Although in the present study population thromboembolic events occurred with a similar frequency in both groups, the sample size was probably too small to definitively answer this question.

Several study limitations need to be discussed. First, the study was observational and, thus, the choice of therapy was not controlled. Second, patients in the FFP Group could have had prolonged bleeding episodes and could have been sicker, albeit showing comparable ISS. However, propensity score-matched analysis minimising the influence of uncontrolled treatment selection showed identical results for transfusion requirements and a response profile for coagulation parameters comparable to that observed in the full unmatched population. We strongly assume that the increased need for RBC and platelet transfusions was a consequence of the volume-expanding effect of FFP transfusion. Nevertheless, we cannot exclude that the duration of active bleeding varied between patient groups, because bleeding scores were not registered. An argument against this possibility is the fact that in the FFP Group receiving more transfusions surrogate markers of hypoperfusion, pH, BE and haemodynamics were restored in a similar manner as or even better than in patients receiving CF only. The question may be asked why several patients needed haemostatic therapy but no RBC transfusion. This is not unexpected because trauma patients are commonly young and rarely exhibit pre-existent anaemia or thrombocytopenia, but frequently show borderline fibrinogen concentrations. Thus, fibrinogen deficiency manifests early, but transfusion triggers for red cells or platelets are commonly reached late in these patients.[36]

In conclusion, this study demonstrates that severe blunt trauma patients can be effectively managed by individualised and targeted administration of CF alone. Fibrinogen concentrate was used predominately because poor fibrin polymerisation occurred most frequently during blood loss and fluid administration. Only about 30% of these patients additionally needed PCC for correction of delayed initial thrombin formation. Markers of thrombin formation were excessively high in all patients already at admission and remained elevated regardless of whether patients received FFP or not. Our data further indicate that a CF-based concept enables minimisation of patient exposure to allogeneic blood transfusions, which might be beneficial in terms of morbidity of trauma patients. This will be evaluated as endpoint in a larger randomised trial.

Conflict of interest

Petra Innerhofer has received educational grants or honoraria for consulting and lecturing, expenses for travel and hotel accommodations and partial support for conducting studies (without any exertion of influence on her study design, statistics or manuscript preparation) from the following companies: Abbott GmbH (Vienna, Austria), Baxter GmbH (Vienna, Austria), B. Braun Melsungen GmbH (Melsungen, Germany), CSL Behring GmbH (Marburg, Germany), Fresenius Kabi GmbH (Graz, Austria), Novo Nordisk A/S (Bagsvaerd, Denmark), Octapharma AG (Vienna, Austria) and TEM Innovations GmbH (formerly Pentapharm GmbH) (Munich, Germany).

Markus Mittermayr has received honoraria for lecturing, expenses for travel and hotel accommodations and partial support for conducting studies (without any exertion of influence on his study design, statistics or manuscript preparation) from the following companies: B. Braun Melsungen GmbH (Melsungen, Germany), CSL Behring GmbH (Marburg, Germany), Fresenius Kabi GmbH (Graz, Austria), and TEM Innovations GmbH (formerly Pentapharm GmbH) (Munich, Germany).

Dietmar Fries has received funding, study grants as well as honoraria for lectures and consulting from the following companies and institutiones: Astra Zeneca, Baxter, BBraun, Biotest, CSL Behring, Delta Select, Dade Behring, Deutsche Bundeswehr, Fresenius, Glaxo, Haemoscope, Hemogem, Lilly, LFB, Mitsubishi Pharma, NovoNordisk, Pentapharm, US Army – Department of Defense/Coalition Warefare Program. Dietmar Fries signed a consulting contract with LFB, which ended in July 2011 and holds several US patent applications for: The use of fibrinogen and recombinant fibrinogen in trauma haemorrhage; the use of fibrinogen and recombinant fibrinogen in thrombocytopenia and the use of rFVIIa for intraarterial embolisation.

All other co-authors have no conflict of interest.

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