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Evidence for using first-linecoagulationfactor concentrates for trauma-induced coagulopathy

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Fibrinogen limits coagulopathy and massive bleeding, has less transfusion requirements and thereby decreases the risk of multi-organ failure in trauma patients.

What stops the bleeding?

Haemostatic therapy aims to stop the bleeding, but is it a concentration of coagulation factors, mainly assessed by international normalised ratio (INR) readings that works, or is it fibrinogen/fibrin, which are the precondition for stable clot formation? We conducted a study in patients with polytrauma and those with isolated brain injury (Tauber et al. 2011) to find out what the most predominant pathology was (**Figure 1**). The red bars refer to polytrauma patients. There is significant increase in the frequency of low fibrinogen, low fibrinpolymerization and consequently low clot firmness, in 20-30%, while a significant and prolonged INR of about 1.5 was found in only about 14%. Clot firmness and fibrin polymerization were independently associated with mortality and also with blood loss as measured by early transfusion requirements. In addition patients had tremendously increased molecular markers of thrombin generation, regardless of the INR readings. It's not the main interest to increase it more by substituting plasma, because very huge thrombin levels do not benefit trauma patients. It may cause endothelial injury and also activate other receptors and inflammation and so on.

Further results confirm these findings, e.g. in a study that included more than 4,000 patients, with injury severity scores (ISS) considerably lower than in our patient population, fibrinogen deficiency occurred frequently and fibrinogen levels < 1.5g/L were associated with increased mortality (McQuilten et al. 2017). Hagemo et al.'s study investigating 1,133 patients in a multicentre trial, found that increased mortality was associated with fibrinogen levels < 2.29 g/L, which is barely below normal (Hagemo et al. 2014). The INR was not independently associated with mortality.

Coagulation factor substitutes

Plasma

Plasma refers to 6-8% protein solution and 92-94% water. It was introduced in clinical practice mainly for volume substitution but later to treat coagulation disorders. It contains all procoagulants and also anticoagulants. It's easy to use, is considered safe regarding thrombosis, and relatively low-cost. However, plasma transfusion is time-consuming and requires planning.

The concentration of coagulation factors and especially fibrinogen are rather low in plasma and vary depending on the individual donor and the type of processing. Plasma efficacy can be questioned and partial requirements correction is not possible. It may also induce transfusion-associated circulatory overload (TACO), transfusion-associated lung injury (TRALI), transfusion-associated immunomodulation (TRIM), multi-organ failure (MOF), immunosuppression, lung injury.

Fibrinogen concentrate

There are several concentrates on the market:

1. Fibrinogen concentrate
2. FXIII concentrate
3. PCC (FII, VII, IX, X)
4. vWF concentrate
5. rVIIa, PCCa
6. FVIII, IX, X, XI concentrate

No factor V concentrate is available.

Concentrates are immediately ready to use, contain defined and high concentration of the factor, no volume expansion is needed,

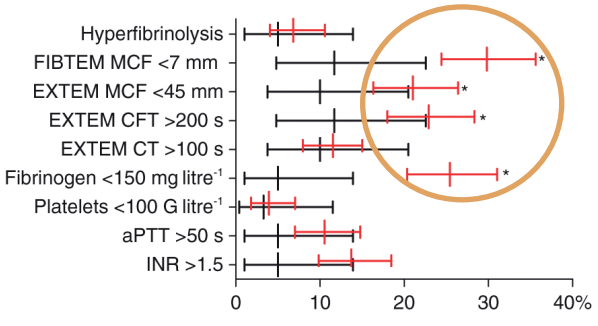

Figure 1

Source: Tauber et al. (2011)

so there will be an effective rise in concentration, making targeted therapy possible. There will be no TACO, TRALI or TRIM and the concentrates are virus-inactivated.

The main problem is cost; they are more expensive than plasma. Some may be concerned about the risk of thromboembolism, and this may occur if thrombin formation is increased by use of PCC and activated PCC and rFVIIa. It is not a problem with fibrinogen, which is also called antithrombin I, as fibrinogen and fibrin are able to capture free-flowing thrombin, and thrombin is the one that initiates thrombosis. Authors of reviews and meta-analyses also criticise the fact that currently there are only a few high-quality studies in trauma patients showing a benefit with coagulation factor concentrates.

The European guideline (Rossaint et al. 2016) recommends the use of standard coagulation tests and/or viscoelastic tests (level of evidence 1C). Viscoelastic testing gives a timely and more comprehensive picture. The guideline recommends use of plasma together with RBC at least 1:2 or use of fibrinogen concentrate with RBC and PCC and factor XIII in selected cases.

Evidence for fibrinogen concentrate

The most frequently cited studies using coagulation factor concentrates in trauma patients are summarised in Table 1. All show promising results: lower mortality than predicted, lower transfusion requirements, and lower multi-organ failure. Fibrinogen was maintained within a normal range even if much fibrinogen had been administered. There were fewer transfusions of red blood cells (RBCs) and platelets. In the study by Wafaisade and colleagues (2013), early mortality was also reduced. These patients received fibrinogen and also had massive transfusions of plasma.

Meta-analyses on plasma efficacy in bleeding patients have concluded that there is no clear benefit for blood loss, transfusion and mortality (Stanworth et al. 2004; Casbard et al. 2004; Yang et al. 2012; Kozek-Langenecker et al. 2011; Desborough et al. 2015). However, there are several reports in trauma patients showing improved survival with early aggressive transfusion without any blood measurements. Administration of 1:1 ratios is recommended, but there are studies that found that mortality did not change and coagulopathy was not corrected (Table 2). Before massive transfusion of plasma, reported mortality in many centres was about 50 percent. Now the rate is between 21% and 35% (Table 3). This mortality is considerably higher than studies using a targeted correction of coagulopathy and using coagulation factor concentrates, especially fibrinogen concentrate.

RETIC trial comparing plasma and coagulation factor concentrates

Our study group conducted the first randomised controlled trial comparing the effect of a plasma-based strategy to the use of coagulation factor concentrate in severe trauma (Innerhofer 2017). The study was

Table 1. Are CFCs useful in trauma patients?

Author	Design	n/ISS	Products	Main result
Schöchl 2010	Retrospective	131 38 ± 15	FC (128) PCC (98) FFP (12)	Mortality lower than predicted
Schöchl 2011	Retrospective	681 35 ± 11	CFC n=80 FFP n=601	Fewer RBC and PC with CFC
Nienaber 2011	Retrospective matched pair	311 44 (38,50)	CFC n=18 FFP n=293	Fewer RBC, lower MOF with CFC
Schlimp 2013	Retrospective	157 29 (23,41)	FC n=85 FC+PCC n=63 FC+PCC+FFP n=9	Fibrinogen maintained, within normal range at 24h ICU
Innerhofer 2013	Observational	144 37 (29,50)	CFC n=66 CFC +FFP n=78	Fewer RBC and PC with CFC alone, lower MOF
Wafaisade 2013	Retrospective matched pair	588 37 ± 13	FC 294 no FC 294	Reduced 6h mortality and MOF with FC

CFC coagulation factor concentrate FC fibrinogen concentrate FFP fresh frozen plasma MOF multi-organ failure PCC prothrombin complex concentrate RBC red blood cells

Table 2. Massive transfusion: Fixed ratio RBC: FFP: PC

Pro 1:1		Indifferent		Con	
Study	Type	Study	Type	Study	Type
Hirshberg et al. 2003	Mathematical model	Rangarajan et al. 2011	Retrospective	Scalea et al. 2008	Prospective
Maegele et al. 2008	Retrospective	Dirks et al. 2010	Retrospective	Nienaber et al. 2011	Matched pair analysis
Gonzalez et al. 2007	Retrospective	Magnotti et al. 2011	Registry - selection bias!	Johnson et al. 2010	Prospective
Duchesne et al. 2009	Retrospective	Snyder et al. 2009	Retrospective - selection bias!	Edens et al. 2010	Prospective
Teixeira et al. 2009	Retrospective	Holcomb et al. 2015	Only early death (secondary endpoint)	Kashuk et al. 2008	Prospective
Mitra et al. 2010	Retrospective			Rourke et al. 2012	Prospective
Peiniger et al. 2011	Retrospective			Chambers et al. 2011	Before/after
Holcomb et al. 2013	Prospective			Kahn et al. 2014	Prospective

Table 3. Mortality in trauma - 1:1:1(2) vs POCT-directed individualised therapy

Country	Author	Mortality	ISS
USA	Holcomb 2013	21.4-25.0%	25-26
USA	Nascimento 2013	24%	35 ± 13
USA	Holcomb 2015	24.3%	25
USA	Gonzalez 2016	27%	33 (25;43)
UK	Khan 2014	35%	34 (25;41)
Austria	Tauber 2011	12.8%	35 (25;50)
Austria	Innerhofer 2013	7.6%	37 (29;50)
Austria	Schöchl 2011	7.5-10%	35.5 ± 10.5
Austria	Innerhofer 2017	7.4%	34 (26;43)

terminated early following interim analysis after inclusion of 100 patients, because predefined stopping was met, showing disadvantages with use of plasma. Correction of coagulopathy was feasible in 96% of patients in the CFC group; only 2 patients had treatment failure and also received plasma (Table 4).

In the plasma group more than 50% of patients had no stop of bleeding and no correction of coagulation. These patients received additionally fibrinogen concentrate, some also PCC and factor XIII. Transfusion requirements were increased and patients received more frequently platelet concentrates. Importantly, the rate of massive transfusion at comparable ISS was increased tremendously.

Our primary endpoint was difference in MOF. However, to answer this question, we would have needed to include at least 200 patients. Therefore the difference of 16% between groups with a higher rate of MOF in the plasma group was not significant. However, ISS and brain injury are confounders, which should be considered when analysing the likelihood of MOF. These confounders were used for stratification and considered in regression analysis. Results showed a significant increased risk of MOF with plasma (OR 3·13 [1·19–8·88], p=0·025) even in this limited population of 94 patients.

What stops the bleeding–the concentration or the clot?

In the RETIC study the blue boxes refer to the CFC group that mainly received fibrinogen concentrate. The yellow boxes refer to the plasma group (Figure 2). Prothrombin is indexed as a percentage of normal, and at baseline they are comparable. After administration of plasma this improved, but decreased further in the CFC group. The patients in the plasma group received more RBC and platelets concentrates and, despite this, had a dramatic drop in platelet count. Also the haemoglobin levels were lower than in the CFC group that received fewer RBCS and platelets. Therefore improved INR or prothrombin time does not limit blood loss. What about fibrinogen and clot firmness? Fibrinogen increased to its normal levels immediately with the factor-based concept, but changed little and marginally and remained below normal in the plasma group. Consequently clot strength improved rapidly with CFC but remained unchanged or decreased in the plasma group. ■

Table 4. RETIC trial main findings

	CFC (n=50)	FFP (n=44)	OR	*P* value
Treatment failure (n)	2 (4%)	23 (52.3%)	25.34	<0.001
RBC/24h	4 (2.7)	6 (4,11)		.028
PC yes	20%	47.7%	3.599	.008
MT%	12%	29.5%	3.038	.042
MOF%	50%	65.9%		.1457

Logistic regression adjusted for confounders ISS/TBI
Significantly increased risk for MOF with FFP OR 3.1264 (CI 1.1906 - 9.8756), P = .0250

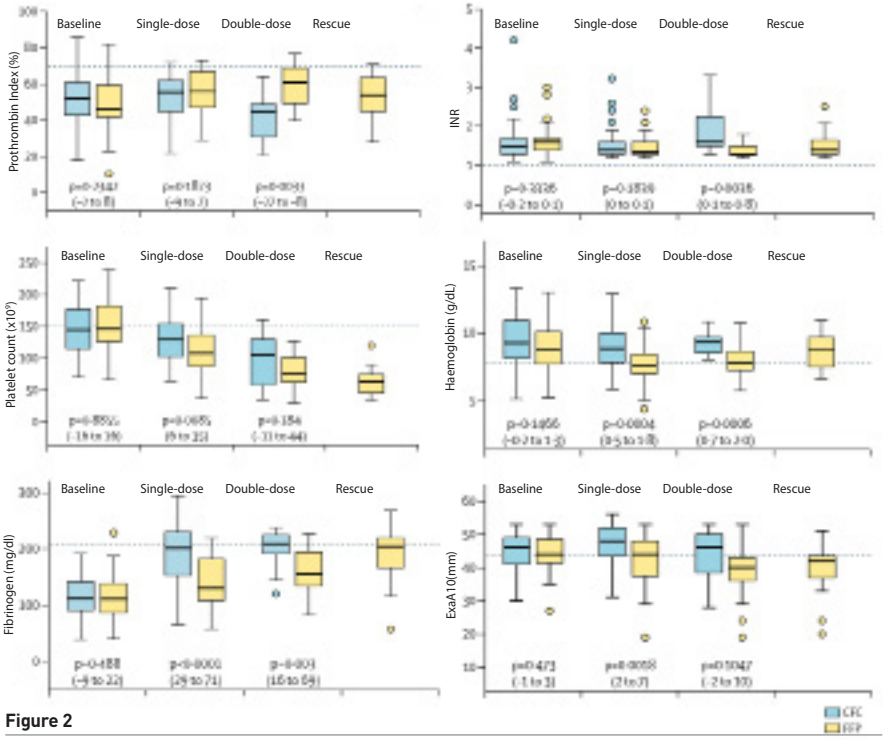

Figure 2

Abbreviations

ISS injury severity score
MOF multi-organ failure
TACO transfusion-associated circulatory overload
TRALI transfusion-associated lung injury
TRIM transfusion-associated immunomodulation

References

For full references, please email editorial@icu-management.org or visit https://iii.hm/o24

Conclusion/ Key points

- Early and effective fibrinogen supplementation is really important to limit blood loss and minimise risk of MOF
- Fibrinogen improves clot strength and also exhibits a platelet-saving effect. This is very important because platelets are one of the transfusion components that are sometimes dangerous and have many side effects
- Fibrinogen limits coagulopathy and massive bleeding and has less transfusion requirements especially massive transfusion and thereby it also decreases the risk of MOF
- An effective rise of fibrinogen concentration is not feasible with plasma
- The lower, better INR after plasma does not reduce the bleeding, therefore we should not focus on the INR
- Fibrinogen is of interest, should be monitored and should be supplemented early