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Treatment of trauma-induced coagulopathy with factor concentrates versus treatment with fresh frozen plasma

RETIC study

Presents results of the RETIC study that compared treatment of trauma-induced coagulopathy using coagulation factor concentrates or fresh frozen plasma.

Background

Trauma-induced coagulopathy (TIC) represents a clinical picture resulting from severity of injury, hypoperfusion, blood loss, consumption, dilution and platelet dysfunction. Activation of the protein C system seems to mediate increased fibrinolytic attack. Despite the complex pathophysiology, the clinical picture is quite uniform: low fibrin formation and consequently low clot firmness occur predominantly and are the outcome-related pathologies. In addition, plasmatic test results are more or less impaired, albeit thrombin generation is maintained in the early phase of trauma, and hyperfibrinolysis can be expected in the very severely injured patient.

During the past 10 years coagulation management has gained great importance. Several studies have shown that early and aggressive fresh frozen plasma (FFP) is better than late plasma administration in terms of survival. In addition the evidence that use of coagulation factor concentrates (CF) is an effective alternative has grown. However, only a few study data are available for use of CF and thus both treatments are still recommended by guidelines. The European guideline’s recommendation for initial coagulation resuscitation is for either fresh frozen plasma: red blood cell (FFP:RBC) at least 1:2 (evidence grade 1B) or fibrinogen concentrate and RBC (1C) (Rossaint et al. 2016).

RETIC trial

The Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC) study focused on treatment of coagulation in major trauma. It was a single-centre, parallel-group, open-label, randomised trial that aimed to compare the efficacy of FFP or CF in reversing TIC, as well as the arising transfusion requirements and development of multiple organ failure (MOF).

The study was terminated early due to institutional review board-mandated, predefined stopping rules; in the plasma arm there was an undesirable harmful effect of massive transfusion. The study received no outside funding. The results are published in Lancet Haematology (Innerhofer et al. 2017).

The hypothesis of the study was that the use of CF is superior to FFP for correction of TIC and that this should reduce bleeding and transfusion requirements, and consequently MOF.

The overall primary clinical endpoint was difference in MOF (calculated sample size n=200). The interim analysis was preplanned after 100 included patients.

The main secondary endpoints of the study were:

- transfusion requirements, massive transfusion
- frequency of treatment failure (rescue rate)
- laboratory parameters
- time until reversal of coagulopathy
- other clinical outcome parameters
- post hoc subgroup analysis, analysis adjusted for stratification factors (Injury Severity Score [ISS])

The inclusion criteria for the study were male and female patients ≥ 18–≤ 80 years who had experienced major trauma (ISS >15), who had clinical signs of ongoing bleeding, or who were at risk for significant haemorrhage assessed and judged by the emergency department (ED) team in charge of the patient, and who had the presence of coagulopathy defined by rotational thromboelastometry (ROTEM) —FibTEM assay (10-min value of fibrinogen polymerisation [FibA10] <9 mm) and/or prolonged initia-
tion of coagulation in the extrinsically activated ROTEM (ExTEM) assay (coagulation time of ExTEM assay [ExCT] >90 s).

Patients were excluded from the study if they had sustained a lethal injury, received cardiopulmonary resuscitation at the scene, had an isolated brain injury, burn injury, avalanche injury, had received FFP or coagulation factor concentrates before ED admission, were admitted to ED more than 6 hours after the trauma, or had known use of oral anticoagulants, or platelet aggregation inhibitors within 5 days before injury or a known history of severe allergic reaction to plasma products.

Adult trauma patients with severe injury were screened by one of the study team and a ROTEM was performed (Figure 1) (see p. IX). If ROTEM was pathological the patient was included. Using closed envelopes the patient was allocated to one of the two groups, a blood sample for detailed coagulation analysis was drawn and all patients received a tranexamic acid bolus. Patients in the plasma group received FFP at a single dose of 15ml/kg, the dose recommended by the European guidelines published in 2010 (the protocol was created in 2011) (Rossaint et al. 2010). As plasma is not a single substance but contains factors for thrombin formation, fibrinogen and also FXIII, we needed to consider this in the CF arm to avoid bias. Patients in the CF group received fibrinogen 50 mg/kg, if indicated also prothrombin complex concentrate (PCC) 20 IE/kg and FXIII 20 IE/kg was administered in patients needing double-dose fibrinogen (repeat).

After study drug administration, ROTEM was checked again and the bleeding situation was assessed. Successful therapy was defined as normalised ROTEM and absence of diffuse or massive bleeding. Patients who showed insuf-
Massive transfusion RBC ≥ 10 U/24 h (% per group)

**Figure 5. RBC**

CF vs FFP: MT 12% vs 29.5%

- **p=0.042; OR 3.038 (CI 0.0951–10.873)**
- **Log. Regression/ISS/TBI p=0.0169; OR 4.2421 (CI 1.3630–14.0935)**

**NNH (FFP) = 5.7**

- **Figure 6. Platelets**

*Table 2. Study drugs*

<table>
<thead>
<tr>
<th>Drug</th>
<th>CF (n=50)</th>
<th>FFP (n=44)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP U</td>
<td>2</td>
<td>14</td>
<td>N/A</td>
</tr>
<tr>
<td>FFP g</td>
<td>50 (100%)</td>
<td>23 (52.3%)</td>
<td>N/A</td>
</tr>
<tr>
<td>PCC IU</td>
<td>8 (16%)</td>
<td>2 (4.5%)</td>
<td>0.09</td>
</tr>
<tr>
<td>FXIII n</td>
<td>27 (54%)</td>
<td>11 (25%)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

**Table 2. Study drugs**

- **CF** coagulation factor concentrate
- **FC** fibrinogen concentrate
- **FFP** fresh frozen plasma
- **PCC** prothrombin complex concentrate
- **FXIII** coagulation factor XIII concentrate

**Additional rescue therapy.** The odds for receiving rescue were significantly higher for FFP patients and the calculated number needed to treat (NNT) was remarkably low for CF. On average 100 out of 207 patients receiving initial CF treatment will show reversal of TIC, which would have not occurred with initial FFP treatment. **Figure 5** shows RBC transfusion.

The odds for receiving massive transfusion were three-fold higher with plasma. If ISS and brain injury were considered as influencing factors, the odds were four-fold higher with plasma therapy. The calculated NNT was 5.7, meaning that on average 10 out of 57 patients treated initially with FFP need massive transfusion (MT), which would not have occurred with initial CF treatment. We also found a significant difference in numbers of RBC used during the first 24 h.

Patients of the plasma group more frequently needed transfusion of platelet concentrates (PC) (**Figure 6**).

**Table 2** summarises the dosages of study drugs used in the first 24 hours; important is the finding that patients in the plasma group needed FC after double dose FFP in comparable amounts as did patients receiving FC first-line, meaning nothing had been saved with late fibrinogen concentrate administration. PCC was seldom needed in the CF group; FXIIIc was frequently administered and also needed in the plasma group.

**Figure 7** shows the response of ROTEM parameters according to therapy, blue is CF, yellow is plasma. EXCT shortened in both groups, shortest values were reached with CF; Exalpa, EFA10 and FibrA10 increased with CF, but remained unchanged or even decreased with plasma.

**Baseline CF 50, FFP 44**
- Single dose CF 50, FFP 44
- Double dose CF 12, FFP 32
- Rescue FFP 20 (3 patients received rescue at later treatment loops)

**Figure 8** (see p. XII) shows levels of FXIII, Hb and platelet count during the first treatment loop.
However, if the influencing factors ISS and brain injury were considered, which were also used for stratification at randomisation, there was an increased risk for MOF with plasma therapy. Patients in the plasma group developed MOF at significantly lower ISS than patients of the CF group (Figure 9).

**Conflict of interest**

The RETIC study received no funding. Petra Innerhofer has received personal fees from Baxter, Bayer, CSL Behring, Fresenius and LFB, and non-financial support from Tem International outside the study.

**Key Points**

- Early and effective fibrinogen supplementation important
- Targeted CF-based therapy superior to FFP
- Correction of TIC in 96% with CF, less than 50% with FFP
- Remarkably low NNT with CF (mainly fibrinogen concentrate)
- First-line FFP
  - persisting hypofibrinogenaemia
  - low clot firmness
  - prolonged coagulopathic bleeding
  - increased transfusion of RBC and PC/24 hours
  - increased rate of massive transfusion
  - increased risk of MOF
  - results with continued FFP and without rescue?
- In-hospital mortality rather low with 7.4%

**Abbreviations**

- CF: coagulation factor concentrate
- ED: emergency department
- FC: fibrinogen concentrate
- FFP: fresh frozen plasma
- FXIII: coagulation factor XIII concentrate
- Hb: haemoglobin
- ISS: injury severity score
- MT: massive transfusion
- NNT: number needed to treat
- PC: platelet concentrate
- PCC: prothrombin complex concentrate
- RBC: red blood cells
- RESIST: rotational thromboelastometry
- TIC: trauma-induced coagulopathy

**References**


