Gerinnungsmanagement beim Polytrauma

Assoc. Prof. Dr. Dietmar Fries

Department for General and Surgical Critical Care Medicine

Medical University Innsbruck

Austria
Partners:
Tel Hashomer Medical University of Tel Aviv, Israel
US Army, Fort Sam Houton, Texas, USA
Dept. of Bioengineering, Univ. of San Diego, USA
Dept. for Anesthesia, Aarhus, Denmark
Dept. for Hematology, Kings College London, UK
Dept. for Trauma Surgery, Cologne Merheim Medical Center, Germany

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Public grants/support
Coagulopathy in Trauma Patients.
Brohi K et al. 2003, J. Trauma; 54(6):1127-30

mortality in %

ISS

normal
Coagulopathy
Trauma associated coagulopathy

1. Massive bleeding – consumption coagulopathy
2. Dilutional coagulopathy: - interaction: colloids – coagulation „fibrinpolymerisation disturbance“
3. Hypothermia
4. Acidosis
5. Hyperfibrinolysis
6. Anaemia
7. Electrolyte disturbances
Trauma associated coagulopathy

1. Massive bleeding – consumption coagulopathy

2. Dilutional coagulopathy: - interaction: colloids – coagulation „fibrinpolymerisation disturbance“

3. Hypothermia

4. Acidosis

5. Hyperfibrinolysis

6. Anaemia

7. Electrolyte disturbances
sequence of critical clotting factor concentrations:

1. Fibrinogen (FI)
2. Prothrombin (FII)?
3. Factor V
4. Factor VII
5. Platelets
Impact of fibrinogen levels on outcomes after acute injury in patients requiring a massive transfusion

Impact of fibrinogen levels on outcomes after acute injury in patients requiring a massive transfusion.

FIBTEM® provides early prediction of massive transfusion in trauma
Schöchl H et al. Critical Care 2011, 15:R265
Trauma associated coagulopathy

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2. Dilutional coagulopathy: - interaction: colloids – coagulation „fibrinpolymerisation disturbance“

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Side effects of fluid replacement therapy

- Dilution
- Coagulopathy
- Volume overload
- Pulmonary dysfunction
- (Abdominal compartment) syndrome
- Increase in blood pressure → increases blood loss
„The lethal triad of hypothermia, acidosis and coagulopathy...“
Trauma associated coagulopathy

1. Massive bleeding – consumption coagulopathy
2. Dilutional coagulopathy: - interaction: colloids – coagulation
   „fibrinpolymerisation disturbance“
3. Acidosis
4. Hypothermia
5. Hyperfibrinolysis
6. Anaemia
7. Electrolyte disturbances
Protein C activation due to shock, hypoperfusion and hypovolemia

- increased pT and apTT due to acidosis/increased BE
- acidosis/increased BE: high thrombomodulin and protein C activation
Tissue hypoperfusion (BD > 6) and trauma injury (ISS > 15) resulted in an activation of Protein C; Higher plasma levels of aPC are predictive of poor clinical outcomes.
Activated Protein C Drives the Hyperfibrinolysis of Acute Traumatic Coagulopathy

Ross A. Davenport, Ph.D., Maria Guerreiro, M.D., Daniel Frith, Ph.D., Claire Rourke, B.Sc., Sean Platton, B.Sc., Mitchell Cohen, M.D., Rupert Pearse, Ph.D., Chris Thiemermann, Ph.D., Karim Brohi, M.D.
Effects of Acidosis on Coagulation

plasmatic haemostasis:
- decrease in fibrinogen
- decreased thrombin generation
  *Martini W: J Trauma (2006) 61: 99*

platelets:
- thrombocytopenia
- thrombocytopathia
pH Neutralisation:

Not effective to correct acidosis related coagulopathy!

Despite effective treatments of acidosis, coagulopathy was not corrected in ICU patients\textsuperscript{1-2}

Trauma associated coagulopathy

1. Massive bleeding – consumption coagulopathy
2. Dilutional coagulopathy: - interaction: colloids – coagulation „fibrinpolymerisation disturbance“
3. Acidosis
4. Hypothermia
5. Hyperfibrinolysis
6. Anaemia
7. Electrolyte disturbances
hypothermia

plasmatic haemostasis

- decreased enzymatic activity

- Increase in fibrinolysis?
  - PAI 1 + a2-AP

platelets

- thrombocytopenia
  - thrombocytopathia
  - adhesion + aggregation
Severe chest trauma
... dynamics of haemostasis ...
Trauma associated coagulopathy

1. Massive bleeding – consumption coagulopathy
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7. Electrolyte disturbances
Trauma associated coagulopathy

1. Massive bleeding – consumption coagulopathy
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hyperfibrinolysis – when?

1. huge blood loss
2. liver (-transplant) surgery
3. cardiac/ -thoracic surgery
4. obstetrics
5. urologic surgery
6. severe trauma (ISS>25)
7. CPR
8. chest trauma
9. cranial trauma
10. DIC
11. ...
More than 20,000 patients were randomized to receive either tranexamic acid or placebo. 10,060 patients received 1g tranexamic acid, initially followed by an infusion of 1g over 8 hours. 10,067 received placebo.

<table>
<thead>
<tr>
<th>Any cause of death</th>
<th>Tranexamic acid (n=10 060)</th>
<th>Placebo (n=10 067)</th>
<th>RR (95% CI)</th>
<th>p value (two-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1463 (14.5%)</td>
<td>1613 (16.0%)</td>
<td>0.91 (0.85-0.97)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Bleeding</td>
<td>489 (4.9%)</td>
<td>574 (5.7%)</td>
<td>0.85 (0.76-0.96)</td>
<td>0.0077</td>
</tr>
<tr>
<td>Vascular occlusion*</td>
<td>33 (0.3%)</td>
<td>48 (0.5%)</td>
<td>0.69 (0.44-1.07)</td>
<td>0.096</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>209 (2.1%)</td>
<td>233 (2.3%)</td>
<td>0.90 (0.75-1.08)</td>
<td>0.25</td>
</tr>
<tr>
<td>Head injury</td>
<td>603 (6.0%)</td>
<td>621 (6.2%)</td>
<td>0.97 (0.87-1.08)</td>
<td>0.60</td>
</tr>
<tr>
<td>Other causes</td>
<td>129 (1.3%)</td>
<td>137 (1.4%)</td>
<td>0.94 (0.74-1.20)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Data are number (%), unless otherwise indicated. RR=relative risk. *Includes myocardial infarction, stroke, and pulmonary embolism.

Table 2: Death by cause
"all cause mortality by subgroup"
Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial

Death related to bleeding ....

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid group</th>
<th>Placebo group</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from delivery (h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>22/4844 (0.5%)</td>
<td>45/4726 (1.0%)</td>
<td>0.48 (0.29-0.79)</td>
</tr>
<tr>
<td>&gt;1-3</td>
<td>19/2672 (0.7%)</td>
<td>35/2682 (1.3%)</td>
<td>0.54 (0.31-0.95)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>41/2514 (1.6%)</td>
<td>47/2569 (1.8%)</td>
<td>0.89 (0.59-1.35)</td>
</tr>
<tr>
<td>p=0.135*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>37/7080 (0.5%)</td>
<td>58/7108 (0.8%)</td>
<td>0.64 (0.42-0.97)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>45/2951 (1.5%)</td>
<td>69/2873 (2.4%)</td>
<td>0.63 (0.44-0.92)</td>
</tr>
<tr>
<td>p=0.958*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cause of haemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine atony</td>
<td>37/6426 (0.6%)</td>
<td>58/6333 (0.9%)</td>
<td>0.63 (0.42-0.95)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>45/3606 (1.3%)</td>
<td>69/3652 (1.9%)</td>
<td>0.66 (0.45-0.96)</td>
</tr>
<tr>
<td>p=0.873*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>82/10 032 (0.8%)</td>
<td>127/9985 (1.3%)</td>
<td>0.64 (0.49-0.85)</td>
</tr>
<tr>
<td>Two-sided p=0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial

Time to treatment ....
Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients

Angèle Gayet-Ageron, David Prieto-Merino, Katharine Ker, Haleema Shakur, François-Xavier Ageron, Ian Roberts, for the Antifibrinolytic Trials Collaboration*

Figure 4: Reduction in effectiveness of tranexamic acid with increasing treatment delay
OR for NOT dying from bleeding
1. **Thromboembolic risk increased?** *Crash2, MATTERs, etc. (n.s.!!*)
2. **TXA = GABA antagonist:** seizures following CABG
3. **Renal failure/insufficiency:** higher risk to develop complications
4. **Cave:** Sepsis – DIC!
Trauma associated coagulopathy

1. Massive bleeding – consumption coagulopathy
2. Dilutional coagulopathy: - interaction: colloids – coagulation „fibrinpolymerisation disturbance“
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5. Hyperfibrinolysis
...

Massive Transfusion Packages (1:1:1)

Pro: additional volume effect
Con: side effects of FFP, time delay, prophylactic, transfusion, efficacy, ...

Individualised target controlled coagulation management and transfusion

Pro: no prophylactic transfusion, less side effects of transfusion related complications, efficacy
Con: additional demand of colloids/crystalloids, close POC monitoring, ...
<table>
<thead>
<tr>
<th></th>
<th>635 ml</th>
<th>Whole Blood</th>
<th>FFP – RBC – Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct</td>
<td></td>
<td>38-45</td>
<td>29</td>
</tr>
<tr>
<td>platelet</td>
<td></td>
<td>150-300</td>
<td>87</td>
</tr>
<tr>
<td>coagulation factors</td>
<td></td>
<td>100%</td>
<td>65%</td>
</tr>
<tr>
<td>fibrinogen</td>
<td></td>
<td>ca. 1,6 g</td>
<td>0,8 g</td>
</tr>
</tbody>
</table>

Hemostatic profile of reconstituted blood in a proposed 1:1:1 ratio

RBCs, Plasma and PC in a 1:1:1 ratio supports dilution!

Massive Transfusion Protocols:

1. fixed ratios (1:1:1)

2. first plasma – on top factor concentrates
Massive Transfusion Protocols:

1. fixed ratios (1:1:1)

2. first plasma – on top factor concentrates
Massive Transfusion: optimal ratio of RBC:FFP

**Pro 1:1**
- Hirshberg *et al.* *J Trauma* 2003; 54:454–63 *Math. model*
- Maegele M *et al.* *Vox Sanguis* 2008; *Retrospective*
- Gonzalez *et al.* *J Trauma* 2007; 62:112–9 *Retrospective*
- Duchenese J *et al.* *J Trauma* 2009; 67:33-37 *Retrospective*
- Teixeira P *et al.* *J Trauma* 2009; 66:693-697 *Retrospective*

**Indifferent**
- Dirks J *et al.* *Sand J Trauma* 2010; 18:65 *Retrospective*
- Davenport R *et al.* *J Trauma* 2011; 70:90-95 *Prospective*
- Magnotti L *et al.* *J Trauma* 2011; 70:97-102 trauma Registry – selection bias!
- ... 

**Con 1:1**
- Johnson J *et al.* *Arch Surg* 2010; 145:973-977. *Prospective*
- Edens JW *et al.* *J Trauma* 2010; 69:81-86. *Prospective*
- Watson *et al.* *J Trauma* 2009; 67:221-227. *Prospective*
- Kashuk *et al.* *J Trauma* 2008; 65:261–70. *Prospective*
- ...
“the non-survivors did not die because they got a lower FFP:PRBC ratio; they got a lower ratio because they died”

Snyder C: J Trauma 2009
Magnotti L et al. J Trauma 2011
Fibrinogen levels during trauma hemorrhage, response to replacement therapy and association with patient outcomes

Prospective cohort analysis - 517 trauma patients with massive transfusion protocols including TX of RBC/FFP in a fixed ratio

Results:

✓ low fibrinogen at admission  ➔ Mortality ↑

✓ Administration of Cryo (Fibrinogen)  ➔ Survival ↑

Fibrinogen levels during trauma hemorrhage, response to replacement therapy and association with patient outcomes

Thrombin Generation Parameters in Trauma following FFP Transfusion

Endogenous Thrombin Potential (nM/L)

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>4 U RBCs</th>
<th>8 U RBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1731</td>
<td>1448</td>
<td>1090</td>
</tr>
</tbody>
</table>

RBCs:FFP ratio = 1.5:1

Frith D et al. Shock 2015, 44:Suppl 2;1-2
Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma haemorrhage.

International prospective cohort study; blood sample was drawn immediately on arrival and after 4, 8 and 12 packed red blood cell (PRBC) transfusions in 160 patients.

Coagulopathy after ...

Effect of a fixed-ratio (1:1:1) transfusion protocol versus laboratory-results-guided transfusion in patients with severe trauma.

78 patients expected to need massive transfusion (≥ 10 RBC units in 24 h) assigned to either the fixed-ratio (1:1:1) transfusion protocol (n = 40) or to a laboratory-results-guided transfusion protocol (control; n = 38).

“The 1:1:1 protocol could be exposing patients to unnecessary blood transfusions and an increased risk of acute respiratory distress syndrome, sepsis and multiple organ dysfunction.”

Nascimento B et al. CMAJ. 2013 Sep 3;185(12):E583-9.
The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study: Comparative Effectiveness of a Time-varying Treatment with Competing Risks

➢ Higher plasma and platelet ratios early in resuscitation were associated with decreased mortality in patients transfused at least three units of blood products during the first 24 hours after admission.

➢ Among survivors at 24 hours, the subsequent risk of death by day 30 was not associated with plasma or platelet ratios.

Transfusion of Plasma, Platelets, and Red Blood Cells in a Ratio of 1:1:1 vs 1:1:2 Ratio and Mortality in Patients with Severe Trauma. The PROPPR Randomized Controlled Clinical Trial.

- No significant differences were detected in mortality at 24 hours or at 30 days
- More patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 hours.

<table>
<thead>
<tr>
<th>Country</th>
<th>Authors &amp; Journal</th>
<th>ISS</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Holcomb et al. JAMA 2015</td>
<td>25</td>
<td>24.26%</td>
</tr>
<tr>
<td>USA</td>
<td>Holcomb et al. JAMA 2013</td>
<td>25 - 26</td>
<td>21.4 – 25.0%</td>
</tr>
<tr>
<td>Austria</td>
<td>Innerhofer et al. Injury 2012</td>
<td>37 – 38</td>
<td>5.0 – 6.0 %</td>
</tr>
<tr>
<td>Austria</td>
<td>Schöchl et al. Crit Care 2011</td>
<td>35.2 - 35.5</td>
<td>7.5 – 10%</td>
</tr>
<tr>
<td>Austria</td>
<td>RETIC study Lancet Hematology 2017</td>
<td>34</td>
<td>7.4 %</td>
</tr>
</tbody>
</table>
### Fibrinogen Dose Calculator

#### Patient Information

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight</td>
<td>85</td>
<td>kg</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>25%</td>
<td>%</td>
</tr>
<tr>
<td>Plasma Volume</td>
<td>3485</td>
<td>ml</td>
</tr>
<tr>
<td>Blood Volume</td>
<td>4647</td>
<td>ml</td>
</tr>
</tbody>
</table>

#### Baseline & Target Fib Concentration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Fib Concentration</td>
<td>0.8</td>
<td>g/l</td>
</tr>
<tr>
<td>Target Fib Concentration</td>
<td>1.7</td>
<td>g/l</td>
</tr>
</tbody>
</table>

#### Concentration of Fibrinogen in Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Concentration</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP</td>
<td>2.3</td>
<td>g/l</td>
</tr>
<tr>
<td>Cryo</td>
<td>12</td>
<td>g/l</td>
</tr>
<tr>
<td>FibCon</td>
<td>20</td>
<td>g/l</td>
</tr>
</tbody>
</table>

#### Volume of Product per Unit

<table>
<thead>
<tr>
<th>Product</th>
<th>Volume per Unit</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP</td>
<td>250</td>
<td>ml</td>
</tr>
<tr>
<td>Cryo</td>
<td>12.5</td>
<td>ml</td>
</tr>
<tr>
<td>FibCon</td>
<td>50</td>
<td>ml</td>
</tr>
</tbody>
</table>

#### Dose Calculation

<table>
<thead>
<tr>
<th>Component</th>
<th>FFP</th>
<th>Cryo</th>
<th>FibCon</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>28</td>
<td>33</td>
<td>5</td>
<td>units</td>
</tr>
<tr>
<td>Volume</td>
<td>7000</td>
<td>412.5</td>
<td>250</td>
<td>ml</td>
</tr>
<tr>
<td>Resultant Fib Concentration</td>
<td>1.70</td>
<td>1.71</td>
<td>1.78</td>
<td>g/l</td>
</tr>
</tbody>
</table>
Formula driven protocols: not effective to reverse coagulopathy

... may result in a higher number of complications???
Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection.

Transfusion of FFP Gabe was associated with:

- **VAP** with (RR 5.42) and without shock (RR 1.97)
- **Septic shock with positive blood culture** (RR 3.35)
- **Non-specified septic shock** (RR 3.22)
- **RR for transfusion of FFP and all infections**: 2.99
Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FFP (n=44)</th>
<th>No FFP (n=71)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New bleeding episodes, n (%)</td>
<td>3 (6.8)</td>
<td>2 (2.8)</td>
<td>0.369</td>
</tr>
<tr>
<td>New onset of acute lung injury, n (%)</td>
<td>8 (18.2)</td>
<td>3 (4.2)</td>
<td>0.021</td>
</tr>
<tr>
<td>Hospital mortality, n (%)</td>
<td>11 (25.6)</td>
<td>20 (28.2)</td>
<td>0.763</td>
</tr>
<tr>
<td>Median (IQR) ICU length of stay, days</td>
<td>2.4 (1.7–6.8)</td>
<td>2 (0.9–3)</td>
<td>0.184</td>
</tr>
</tbody>
</table>

- No difference in new bleeding episodes
- New onset acute lung injury was more frequent in the transfused group (18% vs 4%, p=0.021)
- Risk-benefit ratio of FFP transfusion in critically ill medical patients with coagulopathy may not be favourable

Impact of plasma transfusion in trauma patients who do not require massive transfusion.

ARDS, acute respiratory distress syndrome; MOF, multiple organ failure


ARDS, acute respiratory distress syndrome; MOF, multiple organ failure
Each unit of FFP was independently associated with a 2.1% higher risk of MOF and a 2.5% higher risk of ARDS.
Massive Transfusion Protocols:

1. fixed ratios (1:1:1)

2. first plasma – on top factor concentrates
The exclusive use of coagulation factor concentrates enables reversal of coagulopathy and decreases transfusion rates in patients with major blunt trauma

Petra Innerhofer\textsuperscript{a}, Isabella Westermann\textsuperscript{a}, Helmuth Tauber\textsuperscript{a}, Robert Breitkopf\textsuperscript{a}, Dietmar Fries\textsuperscript{b}, Tobias Kastenberger\textsuperscript{c}, Rene El Attal\textsuperscript{c}, Alexander Strasak\textsuperscript{d}, Markus Mittermayr\textsuperscript{a,*}

144 patients multiple trauma
- 66 Pat. only CF: ISS 37 (29, 50)
- 78 Pat. CF+FFP: ISS 38 (33, 55)

Response Profil Coagulation tests
Transfusions, Outcome
Transfusion requirements full population

<table>
<thead>
<tr>
<th></th>
<th>CF Group</th>
<th>FFP Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC (U)</td>
<td>2 (0, 4)</td>
<td>9 (5, 12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FFP (U)</td>
<td>0 (0, 0)</td>
<td>10 (5, 13)</td>
<td>NT</td>
</tr>
<tr>
<td>PC (U)</td>
<td>0 (0, 0)</td>
<td>1 (0, 2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen concentrate(g)</td>
<td>4 (2, 4)</td>
<td>4 (2, 7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Patients treated (n)</td>
<td>66 (100)</td>
<td>70 (89.7)</td>
<td>0.1252</td>
</tr>
<tr>
<td>PCC (IE)</td>
<td>0 (0, 1000)</td>
<td>750 (0, 1800)</td>
<td>0.006</td>
</tr>
<tr>
<td>Patients treated (n)</td>
<td>23 (34.8)</td>
<td>40 (51.3)</td>
<td>0.064</td>
</tr>
</tbody>
</table>
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).

<table>
<thead>
<tr>
<th>Outcome Parameter</th>
<th>CF Group (n=66)</th>
<th>FFP Group (n=78)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>paO$_2$/FiO$_2$ 24h</td>
<td>317 (250, 377)</td>
<td>241 (201, 325)</td>
<td>0.002</td>
</tr>
<tr>
<td>Ventilator-free days</td>
<td>18 (8, 25)</td>
<td>16 (4, 23)</td>
<td>0.139</td>
</tr>
<tr>
<td>Sepsis (n)</td>
<td>11 (16.9)</td>
<td>28 (35.9)</td>
<td>0.014</td>
</tr>
<tr>
<td>MOF (n)</td>
<td>12 (18.2)</td>
<td>29 (37.2)</td>
<td>0.015</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>12 (6, 24)</td>
<td>14 (7, 30)</td>
<td>0.217</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>24 (12, 35)</td>
<td>29 (16, 50)</td>
<td>0.074</td>
</tr>
<tr>
<td>30-day mortality (n)</td>
<td>5 (7.6)</td>
<td>6 (7.7)</td>
<td>0.979</td>
</tr>
<tr>
<td>Thromboembolism (n)</td>
<td>6 (10.0)</td>
<td>6 (7.7)</td>
<td>0.772</td>
</tr>
</tbody>
</table>
Hypothesis/Study design

Prospective, randomized, single center, open labeled, parallel-group cross-over study.

Objective: incidence of MOF after treatment of TIC with FFP or coagulation factor concentrates.
adult trauma patients
ISS >15
bleeding/risk for hemorrhage

Screening
ROTEM

ROTEM pathological
FibA10 < 9 mm, ExCT > 90 sec

FFP 15ml/kg
GF - Fibrinogen 50mg/kg
- PCC 20IE/kg
- FXIII 20IE/KG

After each IMP:  ROTEM and bleeding score
Target:  FibA10 > 8 mm, ExCT < 78 s and normal or no bleeding
2 dosages of IMP without success: cross over
Treatment failure

cross over rate

FFP vs CF: 52.3 % vs 4% (p < 0.001)
Massive transfusion (≥ 10 RBCs in 24 h)

RBC ≥ 10 U/24h (% per group)
Bleeding Score

0 = no significant bleeding
1 = normal injury related bleeding (clotting visible)
2 = diffuse micro-vascular bleeding
3 = massive bleeding with need of >3 RBC per hour
BT analysis: Multiorgan failure

- FFP no cross
- FFP cross
- CF no cross

Legend:
- MOF
- no MOF
Standard regimes vs individualized approach
Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy

Gonzalez et al.; Annals of Surgery 2016;
Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy

RCT to compare goal directed therapy with MTP guided by conventional coagulation assays including 111 patients. Primary outcome was 28-day survival.

<table>
<thead>
<tr>
<th></th>
<th>CCA</th>
<th>TEG</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death no (%)</td>
<td>19 (40,4)</td>
<td>12 (18,7)</td>
<td>0,011</td>
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<tr>
<td>Time to death in hours</td>
<td>3,5 (2,2-8,3)</td>
<td>11,5 (4,9-211)</td>
<td>0,073</td>
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<tr>
<td>Death in the first 6 h no (%)</td>
<td>11 (23,4)</td>
<td>4 (6,2)</td>
<td>0,010</td>
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<tr>
<td>Death in the &gt; 6 no (%)</td>
<td>8 (17)</td>
<td>8 (12,5)</td>
<td>0,589</td>
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<tr>
<td>Haemorrhagic death no (%)</td>
<td>11 (23,4)</td>
<td>5 (7,8)</td>
<td>0,02</td>
</tr>
<tr>
<td>TBI death no (%)</td>
<td>6 (12,8)</td>
<td>4 (6,3)</td>
<td>0,321</td>
</tr>
<tr>
<td>Organ failure</td>
<td>2 (4,3)</td>
<td>3 (4,7)</td>
<td>1,0</td>
</tr>
</tbody>
</table>

Gonzalez et al.; Annals of Surgery 2016;
Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy

Gonzalez et al.; Annals of Surgery 2016;
critical blood loss - fibrinogen baseline concentrations

Singbartl K et al. Anest&Analg 2003

fibrinogen ≥ 150 mg/dL: 750 ml or 3.750 ml
A. 28- or 30-day mortality

... try to avoid (massive-) transfusion (-protocols) in your trauma patients!

dietmar.fries@i-med.ac.at