Fortbildung für die Anwender/innen von Blutprodukten

Donnerstag, 18. Oktober 2018
12.00 bis 17.30 Uhr im Stade de Suisse Wankdorf Bern

Neue Wirkungsmechanismen von Transfusionsplasma

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Service et Laboratoire centrale d'Hématologie
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Trauma patient

Injury ————> Healing

Legend
ACT, acute trauma coagulopathy
Acute Traumatic Coagulopathy

Injury + soluble thrombomodulin → Coagulopathy

- thrombin
- systemic APC:
  - anticoagulation
  - hyperfibrinolysis

Curr Opin Crit Care 2007;13:680
Protein C (PC) and infection

Patients who fail to recover physiologic plasma values of protein C have an increased propensity to nosocomial lung infection.

*Legend:*
OR, odds ratio
VAP, ventilator-associated pneumonia

*Ann Surg 2012;255:379*
Loss of the endothelial surface layer (ESL)
- induces neutrophil adhesion to endothelial cells,
- facilitates neutrophil extravasation
- increases the intensity of inflammatory tissue injury
Glycocalyx : **Syndecan-1**

Circulating levels of **syndecan-1** are a marker of glycocalyx loss.

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**Physiology** 2011;26:334

**Nature Rev Urol** 2012;9:196
Syndecan-1 in trauma patients

Syndecan-1 levels at admission

Histone complexed DNA

- high (● filled circles, black lines)
- low (○ white circles, dotted lines)

Injury severity score

Ann Surg 2011;254:194
Syndecan-1 in trauma patients

Soluble Thrombomodulin

Protein C

Syndecan-1 levels at admission

high (● filled circles, black lines)
low (○ white circles, dotted lines)
Syndecan-1 in trauma patients

High syndecan-1 levels at admission are associated with:

- Inflammation
- Protein C depletion
- Increased fibrinolysis
- Increased mortality

\[
\begin{align*}
\text{Acute Traumatic Coagulopathy}
\end{align*}
\]

in trauma patients
Rats

**Hemorrhagic shock**
(mean arterial BP 30 mmHg, 90 minutes)

**Resuscitation with**
either lactated Ringer’s (LR) solution
or fresh frozen plasma
(mean arterial BP 80 mmHg)

Compared with **shams** or **shock alone**
Resuscitation volume

Volume required to maintain MAP at 80 mmHg during resuscitation

**Plasma**

- Set point
- Shed blood
- Plasma infused

**Lactated Ringer’s**

- Set point
- Shed blood
- LR infused

29.5 ± 2.8 mL/kg/h  
73.9 ± 10.0 mL/kg/h

Anesth Analg 2011;112:1289
Glycocalyx in mesenteric venules

Anesth Analg 2011;112:1289
Syndecan-1 in the lungs

A Sham
B Negative Control
C Shock
D Lactated Ringers
E Plasma

Anesth Analg 2011;112:1289
Syndecan-1 in the lungs

![Graph showing fluorescence intensity (RFUs) for Sham, Shock, LR, and Plasma groups.]

Anesth Analg 2011;112:1289
Lung histopathology

Table 1. Lung Histopathologic Injury Score

<table>
<thead>
<tr>
<th>Group</th>
<th>Alveolar thickness</th>
<th>Capillary congestion</th>
<th>Cellularity</th>
<th>Overall score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>0.3 ± 0.19</td>
<td>0.2 ± 0.19</td>
<td>0.1 ± 0.09</td>
<td>0.20 ± 0.01 a</td>
</tr>
<tr>
<td>Shock</td>
<td>1.5 ± 0.45</td>
<td>1.7 ± 0.52</td>
<td>1.4 ± 0.48</td>
<td>1.63 ± 0.26 b</td>
</tr>
<tr>
<td>LR</td>
<td>2.3 ± 0.64</td>
<td>1.9 ± 0.33</td>
<td>1.8 ± 0.34</td>
<td>2.00 ± 0.25 b</td>
</tr>
<tr>
<td>Plasma</td>
<td>0.4 ± 0.18</td>
<td>0.9 ± 0.33</td>
<td>0.7 ± 0.38</td>
<td>0.67 ± 0.17 c</td>
</tr>
</tbody>
</table>

Anesth Analg 2011;112:1289
Hemorrhagic shock degrades the endothelial glycocalyx

Lactated Ringer’s solution resuscitation resulted in
- fewer signs of repair
- lower syndecan-1 levels
- greater lung injury

compared to plasma resuscitation

Plasma appears to have the ability to restore the endothelial glycocalyx and preserve syndecan-1 after hemorrhagic shock
Mice

Hemorrhagic shock
(mean arterial BP 35 mmHg, 90 minutes)

Resuscitation over 15 minutes with either lactated Ringer’s (LR) solution or fresh frozen plasma

Compared with shams or shock alone
Shedding of syndecan-1

![Bar graph showing syndecan-1 concentration levels for different treatments: Sham, HS, HS+LR, HS+FFP. The graph indicates significantly lower concentrations for HS compared to Sham, and a trend towards lower concentrations for HS+LR and HS+FFP compared to HS. The p-values are marked as <0.01 for comparisons between Sham and HS, and <0.05 for comparisons between HS and HS+FFP.](image)
Pulmonary syndecan-1
Neutrophil infiltration in the lung
Pulmonary permeability

Extravasation of Alexafluor 680 into the lung

Shock 2013;40:195
FFP resuscitation

inhibited endothelial cell inflammation and hyperpermeability and
restored pulmonary syndecan-1 expression

Modulation of pulmonary syndecan-1 expression may contribute to the beneficial effects of FFP
Adiponectin, which is produced in adipocytes and is present in significant amounts in plasma, has diverse functions including:
- anti-diabetic
- anti-atherogenic
- anti-inflammatory
- inhibition of cytokine-induced endothelial cell hyperpermeability

Plasma adiponectin levels are significantly reduced in severely injured patients in haemorrhagic shock and partially restored by FFP based resuscitation.
Adiponectin?

Mice

Hemorrhagic shock
(mean arterial BP 35 mmHg, 90 minutes)

Resuscitation over 20 minutes with
- mouse fresh frozen plasma (mFFP)
- Adiponectin (Adpn) immunodepleted mFFP
- Adpn-depleted mFFP + recombinant Adpn

Compared with shams or shock alone
Depletion of adiponectin abrogates FFP's ability to inhibit hemorrhagic shock-induced pulmonary microvascular permeability in mice.

**Legend**

Adpn, adiponectin; EBD, Evan’s blue dye; HS, haemorrhagic shock.
These findings suggest that adiponectin is an important component in FFP resuscitation contributing to the beneficial effects on vascular barrier function after haemorrhagic shock.
The dietary or intravenous application of glycine has been demonstrated to prevent inflammatory complications in several experimental models, such as:
- ischemia/reperfusion
- transplantation
- shock
- endotoxemia
- diabetes
Glycine?

Rats

Hemorrhagic shock
(mean arterial BP 30-35 mmHg, 60 minutes)

Resuscitation with transfusion of
- 60% of shed blood (over 5 min) and
- lactated Ringer’s (LR) solution (over 1 h)

Prior to resuscitation, rats were randomly assigned to
- Control (saline)
- Glycine (11-90 mg/kg)
Glycine : Survival

![Graph showing the relationship between glycine (mg/kg) and survival percentage.](image.png)

**Survival**

- 0%: 2/10, 2/9
- 25%: 3/6
- 50%: 7/9
- 75%: 6/8

**Glycine (mg/kg)**

- 0
- 25
- 50
- 75
- 100

Shock 1999;12:54
Glycine : Lung histopathology

Sham

Shock

Shock + Glycine

Shock 1999;12:54
Glycine : TNF-α production

![Graph showing TNF-α production vs LPS concentration]
It is concluded that glycine reduces organ injury and mortality caused by haemorrhagic shock by preventing free radical production and TNF-α formation.
Our results show that glycine, histidine and cysteine can inhibit NF-κB activation [...] and IL-6 production in HCAECs, suggesting that these amino acids may exhibit anti-inflammatory effects during endothelial inflammation.
FFP & survival: experimental data

Rats

Hemorrhagic shock
(mean arterial BP <25 mmHg, 30 minutes)

Resuscitation with
either saline (NS)
or fresh frozen plasma
(mean arterial BP >30 mmHg, 15 minutes)
FFP & survival: experimental data

J Trauma Acute Care Surg 2015;79:897
FFP & survival: experimental data
Early FFP resuscitation: clinical data

PROMMTT Study
Prospective, Observational, Multicenter Major Trauma Transfusion Study

619 patients, severe injury, massive bleeding
3-6 blood product transfusions within 2.5 hours of admission

Adjusted Odds Ratios (95% Confidence Intervals) Associating In-hospital Mortality with Early Plasma and Platelet Transfusion Status at Entry to the Analysis Cohort*

<table>
<thead>
<tr>
<th>Plasma &amp; Platelets at Entry</th>
<th>6 Hour Mortality</th>
<th>24 Hour Mortality</th>
<th>30 Day Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one unit plasma</td>
<td>0.37 (0.19 – 0.73) p=0.004</td>
<td>0.47 (0.27 – 0.84) p=0.01</td>
<td>0.44 (0.27 – 0.73) p=0.002</td>
</tr>
</tbody>
</table>

* A total of 619 patients entered this analysis cohort having received 3–6 units of blood products (including RBCs) within 2.5 hours of admission. Odds ratios are adjusted for the cumulative sum of unit blood products transfused at entry, injury severity score, entry time interval, age, bleeding sites (head, chest and limb) and center differences as a random intercept in the multi-level logistic models25.
Prehospital Resuscitation

Trauma patients at risk for hemorrhagic shock

- at least one episode of hypotension (systolic BP <90 mm Hg) and tachycardia (defined as a heart rate >108 beats per minute)

or

- any severe hypotension (systolic blood pressure <70 mm Hg), either before the arrival of air medical transport or any time before arrival at the trauma center

1:1 randomization

Administration of 2 units of thawed plasma, [either group AB or group A with a low anti-B antibody titer (<1:100)], which was initiated in the prehospital setting by the air transport

versus

Standard care resuscitation
Prehospital Resuscitation

Survival

![Graph showing survival rates over hours since randomization.](Graph.png)

<table>
<thead>
<tr>
<th>Hours since Randomization</th>
<th>Plasma</th>
<th>Standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>48</td>
<td>90</td>
<td>80</td>
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<tr>
<td>96</td>
<td>80</td>
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<tr>
<td>144</td>
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<td>192</td>
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<td>240</td>
<td>50</td>
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</tr>
<tr>
<td>288</td>
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<td>30</td>
</tr>
<tr>
<td>336</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>384</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>432</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
</tr>
<tr>
<td>Standard care</td>
</tr>
</tbody>
</table>

Early plasma-based resuscitation appears to increase survival in trauma patients with massive bleeding.

Plasma-based resuscitation appears to preserve endothelial glycocalyx and reduce inflammation.

It is not known which plasma components are responsible for this possible beneficial effect.