TREATMENT STRATEGIES FOR THE ENDOTHELIOPATHY OF TRAUMA

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Endotheliopathy of trauma: result of systemic endothelial injury caused by trauma and hemorrhage leading to disturbances in:

- Coagulation
- Inflammation
- Blood-organ endothelial barrier integrity
- Vasoregulation
SYNDECAN-1 (sdc-1)

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- **Glycocalyx projects from the cell surface and shields receptors from being exposed to proinflammatory mediators and adhesion ligands.**
SYNDECAN-1 (sdc-1)

- Disruption of the sdc-1 backbone by shedding of its ectodomain is thought to result in vascular hyperpermeability and breakdown of the endothelial barrier
Hypothesis:

- Hemorrhagic shock induces shedding of sdc-1 from the endothelium
- Sdc-1 shedding leads to vascular instability and organ injury
- FFP based resuscitation is protective by restoring the endothelial glycocalyx
Modulation of Syndecan-1 Shedding after Hemorrhagic Shock and Resuscitation

Ricky J. Haywood-Watson, John B. Holcomb, Ernest A. Gonzalez, Zhanglong Peng, Shibani Pati Pyong Woo Park, WeiWei Wang, Ana Maria Zaske, Tyler Menge, Rosemary A. Kozar

Survivors vs nonsurvivors

Prospective pilot study of 32 severely injured patients
A High Admission Syndecan-1 Level, A Marker of Endothelial Glycocalyx Degradation, Is Associated With Inflammation, Protein C Depletion, Fibrinolysis, and Increased Mortality in Trauma Patients

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**Prospective cohort study of 75 trauma patients**  
3 fold increase in mortality in patients with high circulating syndecan-1 levels
Cytokines that correlated with syndecan shedding
In vitro: endothelial cell permeability

HUVECs underwent hypoxia/reoxygenation and IL-1β then incubation in 5% LR or FFP
VE-cadherin immunoreactivity is enhanced by FFP in an in vitro model of endothelial injury.
Endothelial ultrastructure is restored by FFP

Atomic Force Microscope

A. Normoxic controls: no gap
B. LR: gap 6.5 ± 1.1 um
C. FFP gap: 2.4 ± 0.2 um
Cell surface syndecan is enhanced by FFP

A
Normoxia | HR | HR + LR
---|---|---
HR + Plasma | HR + IL-10
B

Relative Fluorescence Units (RFUs)

<table>
<thead>
<tr>
<th>Condition</th>
<th>RFUs</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoxia</td>
<td>350</td>
<td>a</td>
</tr>
<tr>
<td>HR</td>
<td>150</td>
<td>b</td>
</tr>
<tr>
<td>HR + LR</td>
<td>150</td>
<td>b</td>
</tr>
<tr>
<td>HR + Plasma</td>
<td>250</td>
<td>c</td>
</tr>
<tr>
<td>HR + IL-10</td>
<td>200</td>
<td>c</td>
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Proposed model of syndecan-1 interaction with inflammatory cytokines after shock and resuscitation with FFP
Plasma Restoration of Endothelial Glycocalyx in a Rodent Model of Hemorrhagic Shock

Anesth Analg 2011 112:1289
Pulmonary syndecan-1 is restored by plasma
Evaluation of resuscitation fluids on endothelial glycocalyx, venular blood flow, and coagulation function after hemorrhagic shock in rats

Luciana N. Torres, PhD, Jill L. Sondeen, PhD, Lisa Ji, MD, Michael A. Dubick, PhD, and Ivo Torres Filho, MD, PhD, San Antonio, Texas
Glycocalyx thickness

![Graph showing glycocalyx thickness post-resuscitation for different treatments: SHAM, HEM, LR, HEX, and FFP.](image)
FRESH FROZEN PLASMA LESSENS PULMONARY ENDOTHELIAL INFLAMMATION AND HYPERPERMEABILITY AFTER HEMORRHAGIC SHOCK AND IS ASSOCIATED WITH LOSS OF SYNDENCan 1


Effect of resuscitation fluids on MAP

![Graph showing the effect of resuscitation fluids on MAP. The graph compares Sham, HS, LR, and FFP treatments over time (BL, 0min, 5min, 10min, 15min).]
Pulmonary syndecan-1 is restored by FFP
Pulmonary inflammation is lessen by FFP
FFP is being used in the prehospital setting in some civilian trauma centers.

We have been examining the use of lyophilized plasma and comparing its effects to fresh frozen plasma.
Question

• When using a rodent model of hemorrhagic shock, should we be testing rodent plasma or human plasma?

• Tested mouse FFP, human FFP, and human LP
Early Changes in MAP After Resuscitation

![Graph showing changes in MAP after resuscitation with different treatments. The graph compares baseline to 15 minutes post-resuscitation with different fluids: sham, HS, LR, HFFP, HLP, MFFP. Each line represents a different fluid, with error bars indicating variability.]
Lung Injury: histopathology

No significant differences between groups
Lung permeability: Evan’s Blue dye extravasation

No significant differences between groups
Lung Edema: wet/dry weight ratio

No difference between groups
Lung Inflammation: Neutrophil staining

Mouse and human LP were similar but a significant increase in human FFP
Conclusion: Mouse vs human plasma

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- Lung inflammation was still reduced by human plasma compared to LR.
Conclusion: Mouse vs human plasma

- There is an adverse early effect of human plasma on systemic perfusion.
- This does not seem to translate into significant effects on end organ (lung) injury, permeability, or edema but does increase inflammation.
- Lung inflammation was still reduced by human plasma compared to LR.
- The protective effects of plasma may be slightly masked by using human plasma in animal experiments.
Still Lots to Do

- Determine the effect of syndecan-1 silencing
- Determine the effect of endothelial specific syndecan-1: syndecan-1 is found on both endothelial and epithelial cells
- What are the mechanisms by which syndecan-1 is shed after hemorrhagic shock
What is the effect of syndecan-1 silencing??

Syndecan-1 null mice have a worse survival compared to WT.

Preliminary data in KO mice demonstrate that FFP loses its protective effects in the small intestine.
Examine endothelial specific sdc-1

VE cadherin-tTA/TRE
Mechanisms: Determine the effect of HS on sdc-1 sheddases and sheddase inhibitors

Pro-TNFα → TACE → Active TNFα

ADAM-17

Plasma ADAM17 (ng/ml)

<table>
<thead>
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<th>Condition</th>
<th>Plasma ADAM17 (ng/ml)</th>
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</thead>
<tbody>
<tr>
<td>Sham</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>Shock</td>
<td>4.6 ± 1.3</td>
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Summary

- HS adversely affects endothelial integrity
- Leads to hyperpermeability and organ damage
- Associated with syndecan-1 shedding
- Plasma reconstitutes the syndecan-1 ectodomain. This may represent one mechanism by which plasma restores the endothiopathy of trauma
Targeting the injured endothelium may represent a future area of research

- Certain fractions of FFP
- Inhibitors of sheddases: TIMP3
- Slit-2