Crosstalk between the Inflammatory and Coagulation Cascades: A Potential Mechanism for Coagulopathy and Organ Failure in Hemorrhagic Shock

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Overview

- Significance
- Specific Aims
- Background
- Research Method and Design
- Conclusion
Significance

- Massive hemorrhage is a major cause of death after trauma.
- Death after hemorrhagic shock is due either to uncontrollable bleeding from coagulopathy, multiple organ failure or both.
Aims in Animal Studies

- Determine the effects of hemorrhagic shock with subsequent reperfusion on markers of inflammation and coagulation
- Determine if inhibiting the thrombin thrombomodulin PAR signaling complex and phosphatidylserine signaling leads to reduction in proinflammatory markers and organ injury and its effect of coagulation markers
Aims in Human Study

- Determine if molecular markers of coagulation and inflammation seen in our animal model are identifiable in human patient and if they correlate with clinical evidence of a hyperinflammatory response or coagulopathy in a temporal fashion
Hemorrhagic shock and resuscitation leads to a systemic ischemia reperfusion injury (IRI)

Severe trauma

Acidosis
Bleeding
Hypothermia

Consumption, hemodilution

Imbalance in inflammatory and coagulation cascade
Reactive oxygen species promote oxidative stress leading to cell necrosis or apoptosis

Thrombin is involved in the crosstalk between the inflammatory and coagulation cascade

- Injury and Bleeding
- Thrombin activation

Thrombin thrombomodulin complex binds to PAR

- Upregulation of adhesion molecules
- Upregulation of Protein C
- Upregulation of inflammatory cytokines

Boopholin
Phosphatidylserine (PS) is involved in the crosstalk between the inflammatory and coagulation cascade.

Hypoxia and ATP depletion

Translocation of PS to the outer cell membrane

- Procoagulant Mediator
- Upregulation of Inflammatory Markers
- Diannexin
Rat Hemorrhagic Shock Study

- Rats undergo 120 minutes of hemorrhagic shock and then are resuscitated with lactated ringers and shed blood.
- Experimental rats are given either boophilin or diannexin end the end of the shock period prior to resuscitation.
- Rats are sacrificed at 6 and 24 hours.
Analysis of Rat Specimens

- Blood samples:
  IL-6, IL-10, fibrinogen, Factor V and VII, Protein C

- Tissue samples (lung and liver):
  RNA and protein levels of IL-6, IL-10, Protein C, P selectin
Human Hemorrhagic Shock Study

- Trauma patients presenting to the ER with evidence of major injury and SBP<100 are enrolled
- Blood samples are collected over a 7 day period
- Clinical data including injury severity scores and outcomes are collected
Analysis of Human Specimens

- Blood samples
  - WBC, hemoglobin, platelets
  - PT, PTT, INR, fibrinogen
  - IL-6, IL-10
  - Protein C
  - P Selectin
Protease receptors and phosphatidylserine are involved in crosstalk between inflammatory and coagulation cascades, leading to hyperinflammatory state, organ injury and coagulopathic state, and derangements in clotting cascade.
Conclusion

- Inhibition of molecules involved in activation of both systems may lead to new strategies for resuscitating patients from hemorrhagic shock.

- This may also improve outcomes by not only preventing organ injury and dysfunction but also preventing the development of coagulopathy.