Platelet Dysfunction in Critical Care

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Disclosures

• None

• Definite discussion of off-label indications to treat bleeding and platelet dysfunction
Learning Objectives

After the presentation, the participant should be able to:

• Understand concepts of normal hemostasis
• Identify causes of platelet dysfunction
• Be familiar with tests of platelet function
• Be aware of treatment options for platelet dysfunction
Components of Normal Hemostasis

Vessel wall
Platelets
Coagulation enzymes
Fibrinolytic system
Inhibitors / natural anticoagulants
Normal Hemostasis

Primary Hemostasis:
1. Vasoconstriction (5-HT, TXA2)
2. Exposure of collagen, release of von Willebrand factor (vWF), and binding of platelets to collagen/vWF – Adhesion
3. Platelet activation and aggregation

Secondary Hemostasis:
4. Tissue Factor release and formation of thrombin and a stable fibrin clot
Platelets

- Anucleate cellular fragments
- Contain granules (over 300 substances)
  - **Alpha**: (adhesive proteins, procoagulants, anti-lytics, chemokines, growth promoting factors, anti-microbial enzymes)
  - **Dense**: (5-HT, ADP, ATP, Calcium)
- Thrombogenic phospholipids
- Many receptors (adhesion/activation/release)
- Change shape when activated
- Bind to endothelium and to each other
Could your patient have platelet dysfunction?

- Epistaxis, mucocutaneous bleeding
- IV site bleeding, petechiae, bruising
- Failure of surgical hemostasis

- Anti-platelet agents
  - ASA, clopidogrel, prasugrel, ticagrelor, IIb/IIIa inhibitors
- Cardiopulmonary bypass, ECMO
- Renal or liver failure
Causes of Platelet Dysfunction

• **Congenital**
  – Bernard Soulier
  – Glanzman’s
  – Storage pool disease
  – Gray Platelet syndrome
  – Von Willenbrand Disease
  – Platelet release disorders
  – ...and others

• **Acquired**
  – Uremia
  – Medication
    • NSAIDS (ASA, ibuprofen, etc)
    • Clopidogrel
  – Trauma
  – Cardiac Surgery
  – Liver failure
  – Myeloproliferative disorders
  – Myelodysplasia
Mechanisms of Platelet Dysfunction

- **Uremia**
  - Unknown
    - Defects in adhesion, aggregation and secretion
  - Anemia?
  - Uremic toxins?
  - Nitric Oxide?
  - *<Insert your theory here>*

- **Medication**
  - Irreversible receptor inhibition
    - ASA (COX-1 / Thromboxane A$_2$)
    - Clopidogrel/prasugrel (ADP/P2Y$_{12}$)
    - Abciximab (IIb/IIIa)
  - Reversible receptor inhibition
    - tirofiban, eptifibatide (IIb/IIIa)
    - ticagrelor
Mechanisms of Platelet Dysfunction

• **Trauma**
  - Hemodilution
  - Hypothermia
  - Acidosis
  - Anemia
  - **Hypofibrinogenemia**
  - Disseminated intravascular coagulation

• **Cardiopulmonary bypass**
  - Acquired storage pool disorder
    • Activation/release of platelet alpha granules
  - Decreased functional receptors
  - Medications
  - Fragmentation by CPB circuit
  - Hypofibrinogenemia
  - Hypothermia / acidosis
  - Large doses of heparin

Reversible
Evaluating platelet function

- History and physical exam
- Closure time (has replaced bleeding time)
- Platelet aggregation studies
- Flow cytometry
- Thromboelastography /ROTEM

- Be mindful of acidosis, hypothermia...
Closure time

- Replaced bleeding time
- Performed on whole blood
- A ‘global’ measure of hemostasis
- Mimics coagulation under ‘high shear’
- Evaluates clot formation using:
  - Collagen/ADP
  - Collagen/epinephrine
- NOT specific for platelet function
- No clear routine role in the ICU
Platelet aggregation

- Detailed evaluation of platelet function in response to specific agonists
- Best performed at steady state
- Requires ‘normalized’ platelet concentration
- No routine role in the ICU
Thromboelastography (TEG) & ROTEM

- Global assessments of hemostasis based on viscoelastic properties of whole blood
  - Time to clot, kinetics, clot strength, dissolution
- Point of care
- Used in trauma, cardiac surgery, hepatic surgery...but good data are still emerging
- Can inform transfusion decisions
- Can reduce unnecessary transfusions
TEG vs ROTEM
TEG and platelet # or function
Low Maximum amplitude

Probable causes → Common treatments:
• Low platelet count → platelet transfusion
• Low platelet function → platelet transfusion

Can be combined with TEG PlateletMapping® to evaluate the effect of specific antiplatelet agents
TEG / ROTEM

• Pros
  – Point of Care
  – Distinguishes platelet function from concentration

• Cons
  – Relative impact of TEG/ROTEM is not consistently understood...trials are ungoing
  – Interpretation
  – Machine calibration
  – Operator time
Incorporated into many centres (U.S. & Europe)

Associated with reductions in blood products transfused

Impact on patient outcomes is uncertain

Should be considered a research tool
TEG in cardiac surgery

- Transfusion Algorithm Cardiac Study

(Keyvan Karkouti et al. 2016)

- ROTEM + Plateletworks® algorithm in 7000 cardiac surgical patients vs. standard of care.
- Stepped-wedged cluster RCT
- 12 Canadian sites not using routine POC
- N = 7402 undergoing cardiac surgery and CPB
TEG in cardiac surgery

Outcomes:

Reduced RBC transfusion: \( RR \ 0.91; \ 95\%CI \ 0.85–0.98; \ P=0.02 \)

Reduced PLT transfusion: \( RR \ 0.77; \ 95\%CI \ 0.68–0.87; \ P<0.001 \)

Reduced major bleeding \( RR \ 0.83; \ 95\%CI \ 0.72–0.94; \ P=0.004 \)

No effect on other blood product transfusions, length of stay or major complications

Box plots of the adjusted predicted probability of red blood cell transfusion for patients at each hospital to quantify the case-mix.
TEG in cardiac surgery

Limitations

• Effect was highly variable on local practice and testing
• Data pertains only to intraoperative use
• Not general ICU patients
• Requires equipment and expertise

Treatment of platelet dysfunction

- Platelet transfusion
- DDVAP
- Tranexamic acid
- Fibrinogen
- Estrogen
- Correction of hypothermia/acidosis
Treatment of platelet dysfunction

• **Platelet transfusion**
  – 1 adult dose (5-6 donor equivalents)
  – Balance risks of bleeding with risk of transfusion

**Risk of bleeding:**
Spontaneous bleeding is generally low with platelets > 10 x 10⁹/L

**Risk of transfusion:**
Sepsis
TRALI
Thrombosis
Treatment of platelet dysfunction

• DDAVP (desmopressin)
  – Releases vWF from endothelium
  – Reduces ‘Bleeding Time’ in uremia and liver dysfunction
  – Effective treatment in Type A Von Willebrand disease, mild hemophilia, and mild platelet function defects
  – Dose: 0.3 mcg/kg up to 20 mcg. IV/SQ.
  – Contraindicated in unstable coronary syndromes
  – Careful re: hyponatremia with repeated doses
Treatment of platelet dysfunction

• **Cryoprecipitate** ...perhaps fibrinogen concentrates?

  – Cryoprecipitate = low volume blood product that primarily contains fibrinogen and factor VIII and vWF
  – Reykin (NEJM 1980) 10 units of cryoprecipitate infused in 6 uremic patients with bleeding

    • **Results**: Decreased/normalized bleeding times, control of clinical bleeding, and small/no increases in vWF
    • Temporary response
Treatment of platelet dysfunction

• What about fibrinogen concentrates?
  – Might be the ‘active’ ingredient??
  – Essential for Platelet-Platelet interactions (aggregation)
  – Shown to reduce bleeding in cardiac surgery/Cardio-pulmonary bypass

  – Meta-analysis of fibrinogen concentrate in bleeding (2013)
    • 6 RCTs (248 patients)
    • Reduced transfusion
    • No difference in bleeding
    • 12 ONGOING TRIALS
Rx: Uremic platelet dysfunction

- DDVAP (0.3 mcg/kg up to 20 mcg IV/SQ in adults)
- Dialysis
- Correction of anemia (? Up to 90-100 g/L)
- Estrogen: IV: 0.6 mg/kg per day x 4-5 days OR
  PO: 50 mg/kg per day x 4-5 days
- Cryoprecipitate or...perhaps fibrinogen concentrates?
- Tranexamic acid (PO or IV options exist)
Rx: Medication induced platelet dysfunction

Strategy depends on urgency and seriousness of bleed

- Consider: Platelet transfusion (ASA, clopidogrel/P2Y$_{12}$ inhibitors)

- Consider: Supportive care - if tirofiban/eptifibatide or NSAIDs
  - (reversible, short-acting IIb/IIIa inhibitors)

- Consider: Tranexamic acid, DDVAP, estrogen for short term control of mild bleeding
Rx: CPB induced platelet dysfunction

Platelet dysfunction is generally one component of a multifactorial coagulopathy.

- Platelet transfusion
- Tranexamic acid (intra-operatively)
- Fibrinogen (cryoprecipitate or fibrinogen concentrates)
- Correction of hypothermia and acidosis
  - Reversible causes of platelet dysfunction
- (Aprotinin will reduce bleeding but increase mortality)
- Consider intra-operative use of Point of Care devices to guide transfusion decisions
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