Platelets, Trauma..., Hemorrhage: What should we do to help?

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Overview

- Platelet function and dysfunction
- Platelet Function Tests
- Platelet Function Testing on Antiplatelet Medication
- POC testing for neurosurgery
- Transfusion in TBI
- Desmopressin use in ICH
Patient Scenario

- 75 YO Male fell down the steps
- GCS 13
- Vitals Stable
- PMHx:
  - CAD with stent placement, PVD
- Meds:
  - Plavix and ASA
- CT Scan shows Intracerebral Hemorrhage
Patient Scenario

• Next steps?
• What antiplatelet medications?
• Do they need the medications?
• How do we assess medication effect?
• What do we do to maximize patient outcome?
• What literature is out there to support our approach?
Platelets

• Circulating anucleate disc shaped cell
• Responsible for initiating hemostatic mechanisms that repair injury to vascular endothelium
• 4 functions
  • Adherence
  • Activation & secretion
  • Aggregation
  • Interaction with coagulation factors
Platelets

- Endothelial break exposes collagen
- Stimulates platelets to adhere & secrete Thromboxane A2 & ADP into circulation
- This activates other platelets to also secrete
- Activated platelets bind to circulating fibrinogen
Platelet Function Tests

- Developed for bleeding disorders
- Increasingly used in basic research
  - Platelet physiology
  - Phenotype/ Genotype association
  - Drug development
  - Monitoring antiplatelet therapy
Platelet Function Tests

- Past 50 years golden era for PFT
- Understanding platelet targets for thrombotic inhibition led to wide arsenal of medications
- Assays developed to assess
  - Risk of thrombosis & hemorrhage
  - Monitor efficacy of drugs
  - Peri-procedural tool for prediction & management of hemorrhage in trauma patients
Platelet Function Tests
Duke Ivy Bleeding Time

- 1901 - Milian initially described
- 1910 - Duke first correlated platelet dysfunction
- 1941 - Ivy Refined the test
  - BP cuff to 40 mm Hg
  - 5 mm long & 1 mm deep incision on ventral forearm
Platelet Function Tests
Duke/Ivy

- 1961 – Mielke developed spring-loaded device with sterile blades
- Simple test
- No special equipment / lab
- Poorly reproducible
- Invasive
- Insensitive to mild platelet defects
- Time consuming
Platelet Function Tests
Light Transmission Aggregometry

- Light transmission through platelet rich plasma
- Non-physiological test: platelets isolated from other whole blood components
- As platelets aggregate to agonist, turbidity decreases & light transmission increases
- Modified technique: use pre-coated well plates to trigger aggregation upon addition of PRP. More rapid test, screening tool.
Whole Blood Aggregometry

- Performed on whole blood, small sample
- Based on change in electrical impedance resulting from platelet aggregation in response to classical agonists onto 2 electrodes immersed directly into saline diluted whole blood
- Delay between collection & test can influence result
Verify Now

- Developed to monitor anti-platelet therapy
- POC test Using Light aggregometry
- Fibrinogen coated polystyrene beads
- Agglutinate in whole blood in response to
  - Arachadonic acid (ASA cartridge)
  - ADP & Prostaglandin E1(P2/Y12)
  - Thrombin receptor activating peptide
    - (GIIbIIIa cartridge)
Verify Now

- Factors influencing assay:
  - Fibrinogen levels
  - HCT
  - Platelet count
  - Triglyceride levels
  - Time from sample to testing

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Platelet Function Analyzer (PFA-100/200)

- Cartridge based assay
- Small volume blood aspirated through aperture in membrane coated with platelet agonists
- “Closure time” is when aperture closes due to platelet plug
Platelet Function Analyzer (PFA-100/200)

- Easy to use, rapid, small volume (0.8ml)
- Minimal training
- Factors influencing test:
  - < 50,000 platelet count
  - < 25% Hematocrit
  - VWF level
- Limited in detecting mild platelet defects
TEG/Rotem

• Both tests exhibit relative insensitivity to various aspects of platelet function

• Not routinely recommended for platelet function testing
TEG-Platelet Mapping

- Arachadonic acid or ADP
- Whole blood

PlateletMapping™

There is a kit for monitoring the effect of platelet inhibiting drugs such as aspirin and clopidogrel.

- AA (if looking at aspirin) or ADP (if looking at clopidogrel) – Represents fibrin & platelets unaffected by platelet inhibiting drugs i.e. platelets that are still functioning.

- A (activated) – represents fibrin only clot i.e. no platelet aggregation

- K or KH – represents fibrin & thrombin-activated platelets i.e. maximum platelet aggregation

The traces run for a maximum of 20 minutes. Overlaying the traces causes the software to calculate and display % inhibition and % function.
Flow Cytometric Analysis of Platelet Function

- Laser based technology
- Analysis based on scatter of light produced as they cross light source
- Diluted anticoagulated whole blood incubated with variety of reagents
  - Antibodies
  - Dyes that bind to specific proteins, granules & lipid membranes
Multiplate Analyzer

- Multiple electrode aggregometry
- AA/ADP added
- Alteration in electrical impedance due to platelet aggregation is measured and quantified
PFT in Patients on Antiplatelet Medications

- Largest literature is with patients undergoing percutaneous coronary intervention (PCI)
- Class 1A evidence for dual antiplatelet therapy in PCI
- Individual variability in response seen
- ~ 40% pts. on antiplatelet meds may not have expected inhibitory effect!!!
PFT in Patients on Antiplatelet Medications

- Inadequate response to antiplatelet meds:
  - Drug interactions
    - Proton pump inhibitors
  - Genetic differences
  - Diabetes & other pre-existing conditions
  - Noncompliance
Non Compliance

When you don’t take your medication, you undermine healthcare provided by the United States of America...

...and the terrorists win!!

Heavy handed... but effective...
Platelet Reactivity

- High reactivity indicates NO therapeutic inhibition
- Low reactivity indicates Presence of therapeutic inhibition
- Verify Now
  - ARU (aspirin reaction units) < 549 = inhibited
  - PRU (Platelet reaction units) < 194 = inhibited
Interpretation of Verify Now - Aspirin

Post-Aspirin Ingestion

ARU: ASPIRIN REACTION UNITS

700
650
600
550
500
450
400
350

No evidence of aspirin-induced platelet dysfunction
Evidence of platelet dysfunction due to aspirin

NO DRUG EFFECT
DRUG EFFECT

Interpretation of Verify Now - Aspirin
High Platelet Reactivity

- Relationship between HPR & thrombotic events in PCI well established
- POPular study
  - 422 pts. assessed by Verify Now or AA LTA all cause death significant in HAPR at 1 year follow up
- ISAR-ASPI (Intracoronary PI & antithrombotic regimen)
  - 7,090 pts. HPR independent predictor of death

Breet et al J Thromb Haemost 2010;8(10):2140-2148
Mayer et al J Am Coll Cardiol 2014;64(9):863-871
High Platelet Reactivity

- Adapt DES 8,449 pts
  - VN > 550 inversely related to bleeding

- Aspirin Non-responsiveness & Clopidogrel Endpoint Trial (ASCET) 1,001 pts.

Stone et al Lancet 2013;382(9892) 614-23
Low Platelet Reactivity

- LPR key determinant of major bleeding & entry site complications in PCI pts.
- Adapt-DES registry LPR had more clinically relevant bleeding
- Cusset identified platelet inhibition as strongest predictor of bleeding when on Prasugrel

Stone et al Lancet 2013;382(9892) 614-23
Cusset et al JACC Cardiovasc Interv 2013; 6(8):854-63
GRAVITAS
Gauging Responsiveness with Verify Now Assay Impact on Thrombosis & Safety

- Blinded randomized controlled trial PCI pts.
- Stable angina or ACS
- HPR patients randomized to
  - additional loading dose of Clopidogrel (600 mg)
  - Increase MTC dose 150 mg or standard 75mg

- Among HPR pts. with drug-eluding stents high dose did not reduce incidence from death from CV causes, nonfatal MI or stent thrombosis
POC Testing in Neurosurgery

- 50 NS Pts.
- Severe TBI
- TEG PM utilized
- Decreased platelet function associated with increased mortality

Davis et al Neuro Crit Care 2013;18:201-8
POC Testing in Neurosurgery

- PFA-100 screened 58 pts. with subdural hematoma
- 38% had impaired platelet function
POC Testing in Neurosurgery

- PFA-100 screening tool in elective neurosurgery procedures
- 15/93 had abnormal findings

Karger et al ISRN Hematol; 2012;839242
POC Testing in Neurosurgery

- Multiplate analyzer used in 163 trauma pts.

- Decreased platelet function was significantly more frequent in non-survivors than survivors

Solomon et al Thromb Haemost 2010; 106:322-30
POC Testing in Neurosurgery

- Multiplate analyzer used in 22 pts. on antiplatelet medication
- Required urgent neurosurgical intervention
- Administration of desmopressin, TXA & platelet concentrate doubled platelet activity as measured by repeated analysis

Benyon et al J Clin Neurosci 2013; 20:1805-6
Benyon Clin Neurol Neurosurg 2013;115:2003-8
POC Testing in Neurosurgery

- 84 pts. With TBI
- Verify Now assay
- Demonstrated failure to normalize platelet function through platelet transfusion
- Associated with trend towards higher mortality

Bachelani et al. Surgery 2011; 150:836-43
Transfusion in TBI

- PRBC
- FFP
- Platelets

- A deficiency in any of these leads to worse clinical outcome
Transfusion in TBI

- TBI pts. Can develop platelet dysfunction even without antiplatelet therapy

- Mechanism unknown

Davis et al Neuro Crit care 2013; 18:201-8
Transfusion in TBI

- > 35% of adult population is on some form of antiplatelet medication
  

- TBI Pts. on antiplatelet therapy worse outcomes
  
  J Trauma 2008; 65:303-8
  J Trauma 2008; 65: 785-8
AAST Multicenter Trial (2016) – in press

- Prospective, observational trial

- Hypothesis: Patients on NOA have higher rates of ICH, ICH progression, and death compared to patients on traditional anticoagulant and antiplatelet agents

- 1,844 patients – 16 Trauma Centers including KMC

AAST Multicenter Trial (2016) – in press

- Overall mortality was 7%. No significant difference between groups. NOA’s did not have increased risk of death on multivariate analysis.

- Patients on aspirin had highest rate and risk of ICH

  - Kobayashi, Leslie et al. (2016) In press
Benefits of Platelet Transfusion? Dysfunction

- **Platelet Transfusion an Unnecessary Risk for Mild TBI**
  Washington et al J Trauma ACS 2011;71:358-63

- **Nishijima et al – No benefit in transfusion**
  J Trauma ACS 2012;72:1658-63

- **Worsened outcome seen**
Benefits of Platelet Transfusion?
Dysfunction

- **Improved outcome seen**
  Wong et al J Trauma 2008;65:1303-8

- **American Academy of Blood Bank Guidelines**
  - Insufficient evidence to recommend for or against platelet transfusion in TBI
Benefits of Platelet Transfusion?

Thrombocytopenia

- Studies showing ability to predict progression of hemorrhage in TBI
- Often due to DIC from severe TBI


- < 100,000 platelet count often used a “trigger” for transfusion
Thrombocytopenia < 100,000

- 9 fold increase in morbidity
  - “The impact of platelets on the progression of traumatic intracranial hemorrhage
    

- Increased likelihood of hemorrhage progression

    Allard et al J Trauma 2009;67:959-67
Risk: Benefit of Platelet Transfusion in TBI & Thrombocytopenia

- Retrospective analysis of TBI pts. with platelet count 50,000-100,000

- Did not result in any improvement in outcome at 6 months

- Suggests that 100,000 is TOO HIGH threshold for transfusion

Anglin et al. J Neurosurg 2013; 118: 676-86
Plavix & TBI

- 46 Plavix medicated trauma patients
- 28% had no measurable effect of platelet inhibition
- Platelet transfusion would unnecessarily increased transfusion related risks and waste product

Bansal et al J Trauma 2011;70:65-9
Recent Metaanalysis

- Failed to prove that transfusion of platelets to reverse antiplatelet effects in pts. with traumatic ICH was beneficial

Campbell et al. World Neurosurg 2010;74:279-85
PATCH: platelet transfusion in cerebral haemorrhage: study protocol for a multicentre, randomised, controlled trial

- The primary objective is whether platelet transfusion improves outcome in intracerebral haemorrhage patients who are on antiplatelet treatment.
- Patients randomised to receive platelet transfusion within six hours or standard care.
- The primary endpoint is functional health after three months.
- The main secondary endpoints are safety of platelet transfusion and the occurrence of haematoma growth.
What about Desmopressin??
Desmopressin exerts its haemostatic effect by:

1. Inducing synthesis of the von Willebrand factor (VWF) by endothelial cells

2. Stimulating release of the VWF from its storage sites in endothelial cells

3. Cleaving the large VWF multimers circulating in plasma into smaller multimers

4. Enhancing interaction between platelets and the VWF

5. Binding to VWF receptors on platelets
Desmopressin Improves Platelet Activity in Acute Intracerebral Hemorrhage

- Study Design: Prospective, single-center study

- Population: Patients with acute ICH confirmed with CT scan and known aspirin use or reduced platelet activity

- Intervention: DDAVP 0.4 mcg/kg IV over 30 minutes and other routine care

- Primary Endpoint: Change in the platelet function at T=1 hour after the start of DDAVP

- Secondary Endpoints
  - vWF antigen
  - Serum sodium
  - Hematoma volume

Desmopressin Improves Platelet Activity in Acute Intracerebral Hemorrhage

Author’s Conclusion

• DDAVP improved measures of platelet activity, vWF antigen, and decreased hematoma volume

• Given its safety, low cost DDAVP is an attractive pharmacological treatment for acute ICH

• Further larger randomized control trials are needed

Desmopressin Acetate in Intracranial Hemorrhage

- Study Design Prospective, single-center study
- Population Patients with acute ICH confirmed with CT scan and aspirin within 24 hours prior to admission
- Intervention DDAVP 24mcg IV over 30 minutes
- Primary Endpoint Platelet function half an hour after DDAVP administration
- Secondary Endpoints Platelet function 3 hours after DDAVP administration

Desmopressin Acetate in Intracranial Hemorrhage

- Author’s Conclusion:
  - DDAVP can improve platelet function after 30 minutes in ICH patients,
  - Coagulation status can be restored to normal between 30 minutes to 3 hours

The Effect of Platelet and Desmopressin Administration of Early Radiographic Progression of Traumatic Intracranial Hemorrhage

- Study Design 3-year retrospective analysis at a level I trauma center

- Population Adult trauma patients admitted with a diagnosis of traumatic ICH

- Intervention Platelets and DDAVP (0.3mcg/kg IV or 0.15mcg/kg IV in elderly patients) vs. No platelets and No DDAVP

- Primary Endpoint Hemorrhage progression defined as 25% increase in volume

- Secondary Endpoints
  - In hospital mortality
  - Length of stay

The Effect of Platelet and Desmopressin Administration of Early Radiographic Progression of Traumatic Intracranial Hemorrhage

- ICU and hospital length of stay were increased in the Platelet/DDAVP (+) group

- Patients in the Platelet/DDAVP (+) group had increased mortality \( (p=0.03) \) and more health services upon discharge
  - After controlling for baseline characteristics no difference in mortality

The Effect of Platelet and Desmopressin Administration of Early Radiographic Progression of Traumatic Intracranial Hemorrhage

- Platelets and DDAVP administration are not associated with statistically significant decreased early radiographic hemorrhagic progression.
- It is not known whether long-term neurological function is improved by platelet and DDAVP administration.

Cost of Desmopressin

- A 100kg patient receiving 0.4 mcg/kg = 40 mcg

- $168.34
DDAVP Summary

• Current literature is not conclusive of recommendations for management and reversal of patients with ICH on antiplatelet therapy
• DDAVP can be considered in patients who have taken anti-platelet therapy and have severe ICH
• New Guidelines for Reversal of Antithrombotics in Intracranial Hemorrhage recommend consideration of DDAVP in patients with ICH
What Have We Learned Today?

- Numerous platelet function tests
- 35% of population on antiplatelet therapy
- 40% of those taking antiplatelet therapy are non-responders
- 28% of TBI patients have platelet dysfunction not due to antiplatelet therapy
- Dysfunctional and deficient #’s (?) of platelets likely to show progression of traumatic hemorrhage
What Have We Learned Today?

- The decision to transfuse platelets in traumatic ICH has no strong evidenced based literature to support it.
- The decision to use Desmopressin also has no strong evidence for use in traumatic ICH.
Clear as Mud