Antiplatelet-related intracerebral hemorrhage: Does Desmopressin Actually Improve Platelet Function?

Sharmin Amjad, PharmD
PGY-2 Emergency Medicine Pharmacy Resident
Department of Pharmacy, University Health System, San Antonio, TX
Division of Pharmacotherapy, The University of Texas at Austin College of Pharmacy
Pharmacotherapy Education and Research Center
UT Health San Antonio
November 17, 2017

Learning Objectives:

1. Describe intracerebral hemorrhage (ICH) and associated morbidity and mortality
2. Explain risk factors associated with hematoma expansion including antiplatelet use
3. With respect to desmopressin, evaluate current literature in reversal of antiplatelet-related platelet dysfunction
Assessment Questions:

1. True or False: Survivors of ICH are often left with severe disability, with less than 40% of patients regaining functional independence.

2. What are the 2015 AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage recommendations for blood pressure management in patients presenting with SBP between 150 - 220 mmHg?
   a. Lower SBP to 140 mmHg
   b. Lower SBP to 120 mmHg
   c. Do not lower blood pressure in this case
   d. Maintain blood pressure greater than 190 mmHg

3. True or False: Desmopressin reduces vWF and tissue plasminogen activator, thereby improving hemostasis.

***To obtain CE credit for attending this program please sign in. Attendees will be emailed a link to an electronic CE Evaluation Form. CE credit will be awarded upon completion of the electronic form. If you do not receive an email within 72 hours, please contact the CE Administrator at ana.franco-martinez@uhs-sa.com***

Speaker Disclosure: Sharmin Amjad has indicated she has no relevant financial relationships to disclose relative to the content of her presentation
I. Hemorrhage of blood vessels within the brain 1-3
   A. Second most common cause of stroke after ischemia
      1. Accounts for 10-15% of all stroke cases
      2. Annual incidence of 16 to 33 cases per 100,000 with 1 year mortality rates approaching 50%
      3. Survivors often left with severe disability, with less than 40% of patients regaining functional independence

II. Etiology
   A. Primary causes
      1. Hypertensive vasculopathy (~50% of cases)
         a. Risk of recurrent hypertensive ICH < 2% per year with well-controlled hypertension
      2. Cerebral amyloid angiopathy (CAA) (~35% of cases)
         a. Risk of CAA-associated ICH 10-20% per year
   B. Secondary causes
      1. Underlying vascular malformations
      2. Coagulation disorders
      3. Use of anticoagulants and thrombolytic agents
      4. Hemorrhage into a preexisting infarct
      5. Brain tumor
      6. Drug abuse
   C. Risk factors 4-5
      1. Chronic hypertension (present in 50-70% of patients who develop ICH)
      2. Advanced age
         a. Twenty fold increase in incidence of ICH for each decade of life after age 50
      3. High alcohol intake
      4. African American ethnicity
      5. Antiplatelet or antithrombotic therapy

III. Pathogenesis of brain injury 6-7
   A. Accumulated volume of extravasated blood → sudden rise in intracranial pressure (ICP)
   B. Further neurological worsening caused by hematoma expansion, edema, and resultant secondary brain injury
   C. Secondary injury from inflammation can compromise the surrounding brain parenchyma
IV. Diagnosis
   A. Clinical Presentation
      1. Acute and rapidly developing neurologic deficits
      2. Severe headache, decreased levels of arousal, nausea and vomiting = signs of ↑ ICP
      3. Elevated systolic blood pressure (SBP)
      4. Photophobia
      5. Neck stiffness
      6. Loss of consciousness
   B. Radiographic Findings
      1. Non-contrast head CT scan is highly sensitive and specific
         a. Hematoma location, size, and intraventricular extension
         b. Presence of hydrocephalus can be quickly and reliably assessed on CT alone

V. Outcomes 14-16
   A. Morbidity
      1. ICH survivors are often left with disability
         a. Between 12 and 39% of patients achieve functional independence
      2. Modified Rankin Scale (mRS) (See Appendix A)
         a. Measures degree of disability or dependence in people who have suffered a stroke or other cause of neurologic disability
         b. Utilized in clinical trials as a measure of functional status
         c. Scores range from 0 to 6
            (1) 0 defined as no symptoms at all
            (2) 6 defined as death
      3. FUNC Score: Prediction of 90-day functional outcome in primary ICH
         (See Appendix B)
B. Mortality
1. Ranges from 23 – 58% at 6 months after spontaneous ICH
   a. One-half of these deaths occur within the first 48 hours
   b. Extension into all 4 ventricles increases mortality rate to 60 – 91%
2. Predictors of mortality
   a. Initial location and volume of the hematoma
   b. Low Glasgow Coma Scale (GCS) score
   c. Hematoma expansion
   d. Intraventricular extension/number of ventricles containing blood
   e. Early neurologic deterioration
3. Antithrombotic and antiplatelet therapy
   a. Portend larger initial hematoma volumes and increased likelihood of hematoma expansion
      (1) Leads to poor prognosis
4. ICH Score
   a. Reliable grading scale to predict ICH mortality

<table>
<thead>
<tr>
<th>Component</th>
<th>ICH Score Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS score</td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>2</td>
</tr>
<tr>
<td>5–12</td>
<td>1</td>
</tr>
<tr>
<td>13–15</td>
<td>0</td>
</tr>
<tr>
<td>ICH volume (cm³)</td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>0</td>
</tr>
<tr>
<td>NH</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Intraventricular origin of ICH</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Age (year)</td>
<td></td>
</tr>
<tr>
<td>≥ 80</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 80</td>
<td>0</td>
</tr>
<tr>
<td>Total ICH Score</td>
<td>0–6</td>
</tr>
</tbody>
</table>

Figure 2. ICH Score

Hematoma Expansion

1. Enlargement of cerebral hematoma volume from baseline assessment
   A. Associated with neurologic deterioration and worsening outcomes
      1. One third of patients with hypertensive ICH have hemorrhagic enlargement of > 33 % from baseline at 24 hours
II. Predictors of hematoma expansion

A. Time from ICH onset to CT
   1. Majority (26%) of significant hematoma growth happening between baseline and 1-hour CT scans compared to 12% between 1-hour and 20-hour CT scans

B. Computed tomography angiography (CTA) “spot sign” (See Appendix C)

C. Hypertension
   1. 46-76% of patients presenting with ICH have elevated blood pressure (BP)
   2. ↑ BP causes greater tearing of blood vessels, allowing for greater blood flow through these vessels → predisposes to hematoma expansion

Clinical Questions: Will rapid lowering of blood pressure improve patient outcomes in acute ICH? What blood pressure should we be targeting in patients presenting with acute ICH? How low is too low?

### Table 1. Blood Pressure Management: Literature Review and Guideline Recommendations

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Outcome</th>
<th>Take Home Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTERACT (2008)</td>
<td>Intensive: SBP &lt; 140 mmHg x 7 days vs. Guideline: SBP &lt; 180 mmHg</td>
<td>Proportional change in growth of hematoma during first 24 hours after randomization</td>
</tr>
</tbody>
</table>
### ATACH (2010)

| 3 levels of treatment goals in a step-wise fashion: 1) 170 – 200 mm Hg 2) 140 – 170 mm Hg 3) 110 – 140 mm Hg | Treatment feasibility, neurologic deterioration within 24 hours, and serious adverse events within 72 hours | Incidence of neurologic deterioration and severe adverse reactions < prespecified thresholds |

### INTERACT II (2013)

| Intensive-treatment: intravenous antihypertensive agent given to target SBP < 140 mmHg within 1 hour of randomization vs. Standard-treatment: management initiated when SBP ≥ 180 mm Hg | Death or major disability defined as a score of 3 to 6 on the mRS at 90 days | No association with the rates of death or serious adverse events No clear effect on reducing the growth of the hematoma Of those receiving intensive treatment, 52% had death or major disability (modified Rankin of 3 to 6) vs 55.6% of those receiving guideline-based treatment (p = 0.06) Ordinal analysis showed a significant favorable shift in the distribution of scores on the mRS with the intensive treatment group (p = 0.04) |

### 2015 AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage

- For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindications to acute lowering of BP, **acute lowering of SBP to 140 mm Hg is safe** (Class I; Level of Evidence A) and can be effective for improved functional outcome (Class IIa; Level of Evidence B). (Revised from the previous guideline)

- For ICH patients presenting with SBP > 220 mm Hg, it may be reasonable to consider **aggressive reduction of BP** with a continuous intravenous infusion and frequent BP monitoring (Class IIb; Level of Evidence C). (New recommendation)

### ATACH-2 (2016)

| Intravenous nicardipine for Intensive-treatment: SBP target 110 – 139 mm Hg vs. Standard-treatment: SBP target 140 – 179 mm Hg | Proportion of patients with mRS score 4 to 6 at 3 months | No significant differences in the mRS score at 3 months and in the percentage of patients with expansion of hematoma Secondary outcomes: ↑ renal adverse events at 7 days with intensive treatment group (9.0% vs 4.0%; p = 0.002) |

### Clinical Question: Does the use of antiplatelet agents (APAs) impact hematoma expansion?

**D. Coagulopathy**

1. Anti-thrombotic agents
2. New oral anticoagulants (NOACs) have an estimated pooled incidence of hemorrhagic stroke of 0.4%
a. > 50% relative reduction in ICH rate from the 0.9% observed with warfarin

3. APAs

   a. Japanese study reviewing 251 patients with ICH
      (1) Initial hematoma volume in those patients taking APAs was ↓ than that of patients not taking APAs
      (2) Patients taking APAs had statistically significant ↑ risk of acute hematoma expansion and surgical evacuation of the hematoma

   b. Creutzfeldt evaluated 368 patients with spontaneous ICH
      (1) Use of APAs prior to admission was associated with an ↑ risk of mortality

   c. Caso looked prospectively at patients with a first ICH who had been taking APAs for at least 7 days
      (1) Use of APAs was not associated with ↑ mortality or disability

   d. Considerable variability in the results of the studies looking at the impact of APAs on outcomes in patients who present with ICH

---

### Platelets and Hemostasis

I. Hemostasis: process of blood clot formation
   A. Primary hemostasis
      1. Platelet adhesion via von Willebrand factor and aggregation via fibrinogen at the site of endothelial injury, providing immediate seal
   B. Secondary hemostasis
      1. Involves sequential activation of a series of proenzymes (nonactivated coagulation factors) to enzymes (activated coagulation factors) → generating fibrin → further clot formation

II. Role of platelets

![Figure 4. Primary hemostasis](image)
III. APAs and ICH
   A. Use for primary and secondary stroke prevention
   B. Aging population and in incidence of atrial fibrillation
   C. May have risk of hematoma expansion, poor functional outcome and death
      1. Hematoma Expansion
         a. Initial hematoma volume remains the strongest predictor of 30-day mortality and functional outcome, along with hematoma location
         b. Holds potential for being the only modifiable predictor of outcome

IV. Platelet Function Assays (PFA) *(See Appendix D)*
   A. In recent years, the assessment of platelet (dys)function has become increasingly necessary in a variety of clinical settings:
      1. Identification of patients with bleeding disorders
      2. Monitoring response to antiplatelet treatment
      3. Evaluation of perioperative hemostasis
      4. Transfusion medicine

V. Platelet Transfusion
   A. Platelet Transfusion
      1. Preparation: repeated centrifugation of whole blood to make a concentrated form of platelets
      2. Contents: >5.5x10^10 platelets suspended in roughly 50 mL of plasma
      3. Indications: thrombocytopenia, hemorrhage
      4. Storage: room temperature
      5. Stable for 5 days; circulating platelets have short half life
      6. Dose: “six pack” – should raise platelets by 25-50 x 10^9/L within 1 hour of transfusion (250-350 mL)

**Clinical Question:** Does platelet transfusion reduce death or dependence compared to standard care in patients with spontaneous ICH on antiplatelet medications?

<table>
<thead>
<tr>
<th>Table 2. Platelet Transfusion for spontaneous ICH</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Baharoglu et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral hemorrhage associated with antiplatelet therapy (PATCH): a randomized, open-label, phase 3 trial</em></td>
</tr>
</tbody>
</table>

**Design**
- Multicenter, open-label, randomized trial
- Standard care or standard care with platelet transfusion

<table>
<thead>
<tr>
<th>Patient population</th>
<th><strong>Inclusion Criteria:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antiplatelet therapy for at least 7 days preceding ICH</td>
</tr>
<tr>
<td></td>
<td>Cyclooxygenase (COX) inhibitors (Aspirin)</td>
</tr>
<tr>
<td></td>
<td>Adenosine Diphosphate (ADP) Receptor Inhibitor (Clopidogrel)</td>
</tr>
<tr>
<td></td>
<td>Adenosine Reuptake Inhibitor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Exclusion Criteria:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Subdural or epidural hemorrhage on brain imaging</td>
</tr>
<tr>
<td>Underlying aneurysm or arteriovenous malformation</td>
</tr>
<tr>
<td>Planned surgical evacuation of ICH within 24 hours of admission</td>
</tr>
<tr>
<td>Known use of vitamin K antagonist <em>(Unless</em></td>
</tr>
</tbody>
</table>
(Dipyridamole)  
- Pre-ICH mRS 0 – 1  
- INR ≤ 1.3)  
- History of coagulopathy  
- Known thrombocytopenia

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Platelet transfusion (n = 97)</th>
<th>Standard care (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GCS score: 5 – 12: 19 (20%)</td>
<td>GCS score: 5 – 12: 11 (12%)</td>
</tr>
<tr>
<td></td>
<td>GCS score: 3-4: 1 (1%)</td>
<td>GCS score: 3-4: 0</td>
</tr>
<tr>
<td></td>
<td>ICH Volume &gt; 30 mL: 32 (34%)</td>
<td>ICH Volume &gt; 30 mL: 19 (21%)</td>
</tr>
<tr>
<td></td>
<td>Intraventricular extension: 12 (13%)</td>
<td>Intraventricular extension: 20 (22%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Primary: shift towards death or difference in functional outcome at 3 months after randomization rated on mRS  
| Secondary:  
|   - Survival (mRS 1 – 5) at 3 months  
|   - Poor outcome defined as mRS 4 – 6  
|   - Median absolute ICH growth in mL after 24 hours on brain imaging  
|   - Safety: complications of platelet transfusion (transfusion reactions, and/or thrombotic complications)  
|   - Serious adverse events – complications of ICH (enlargement, intraventricular extension, hydrocephalus, edema, or brain herniation), epileptic seizures |

**Results**

- No significant difference in the rate of re-hemorrhage between the two groups (15% in the platelet transfusion group vs. 14% in the standard of care)  
- Primary outcome: ↑ death/dependence in patients receiving platelet transfusion  
- Secondary outcomes: mRS 4-6 at 3 months 72% in platelet transfusion group vs. 52% in the standard of care group

**Authors’ Conclusion**  
Platelet transfusion seems inferior to standard care for people taking anti-platelet therapy before ICH. Platelet transfusion cannot be recommended for this indication in clinical practice.

**Reviewer’s Critique**

**Strengths**

- First randomized trial to investigate the role of platelet transfusion in this population  
- Multicenter, international study  
- Primary outcome was clear and patient centered  
- Follow-up was complete; no patients were lost at 90 days

**Limitations**

- Patients and clinical providers were not blinded to treatment allocation (this likely favors the platelet transfusion arm)  
- Relatively small study  
- Majority of patients were on aspirin as their APA; results may not be generalizable to other antiplatelet medications  
- Variations in baseline characteristics

**Take Home Points**

- No clear support for the notion of routinely using platelet transfusions in ICH associated with antiplatelet use  
- Practice adopted based on physiologic grounds  
- PATCH does not speak to what to do among ICH patients who need a surgical procedure

---

**Clinical Question:** What is the utility of desmopressin in ICH-reversal secondary to antiplatelet use?
Desmopressin Review

I. Desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP)
   A. Synthetic analog of the antidiuretic hormone vasopressin
   B. ↑ plasma levels of factor VIII and von Willebrand factor (vWF)
      1. Produces little or no vasoconstriction
      2. No ↑ in blood pressure
      3. No contraction of the uterus or gastrointestinal tract

II. Historical Context
   A. 1977: desmopressin used for the first time in patients with mild hemophilia A and von Willebrand’s disease (VWD) for prevention and treatment of bleeding
   B. Clinical use expanded to bleeding disorders not involving a deficiency or dysfunction of factor VIII or vWF
      1. Congenital and acquired defects of platelet function
      2. Abnormalities of hemostasis associated with chronic kidney and liver diseases

III. Mechanism
   A. Synthetic analogue of vasopressin that binds to the V2 receptor in the collecting ducts of the kidney, thereby increasing water reabsorption
   B. Effect on hemostasis in ICH
      1. Proposed mechanism is to increase blood factor VIII
      2. ↑ vWF and tissue plasminogen activator
      3. ↓ activated partial thromboplastin time
      4. Improve hemostasis
      5. ↓ postoperative blood loss

IV. Pharmacokinetics
   A. Onset: 30 min
   B. Duration: ~ 3 hours
   C. Excretion: renal
   D. Elimination ½ life: 1-3 hours

V. Clinical uses
   A. Central diabetes insipidus
   B. Hemophilia A
   C. VWD type I
   D. Off label use for prevention of surgical bleeding in patients with uremia and uremic bleeding associated with acute or chronic renal failure
## Table 3.
Naidech AM, et al. Desmopressin Improves Platelet Activity in Acute Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospective, single-center study (n = 14)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Population:</strong> Patients with acute ICH confirmed with CT scan and known aspirin use or reduced platelet activity on VerifyNow-ASA</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention:</strong> Desmopressin 0.4 mcg/kg IV over 30 min and other routine care</td>
<td></td>
</tr>
<tr>
<td><strong>Primary Endpoint:</strong> Change in the platelet function at T=1 hour after the start of desmopressin</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Endpoints:</strong> vWF antigen, serum sodium, hematoma volume, mRS at 28 days and 3 months</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Baseline Demographics:</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age: 66.8 ± 14.6 years</td>
<td></td>
</tr>
<tr>
<td>White: 85%</td>
<td></td>
</tr>
<tr>
<td>Men: 57%</td>
<td></td>
</tr>
<tr>
<td>History of Hypertension: 93%</td>
<td></td>
</tr>
<tr>
<td>History of Diabetes: 36%</td>
<td></td>
</tr>
</tbody>
</table>

## Results

**Primary endpoint:**
- The Platelet Function Analyzer-epinephrine decreased from 192 ± 18 to 124 ± 15 seconds (P=0.01)

**Secondary endpoints:**
- vWF antigen ↑ from 242 ± 96% to 289 ± 103% activity (p=0.004)
- Mean change in sodium was 0.6 mEq/L from baseline to follow-up at 12 to 24 hours
- Of seven patients who received desmopressin within 12 hours of ICH symptoms, the median change in hematoma was -0.5 mL (-1.4 mL to 8.4 mL)
- Two patients had hematoma growth

**Authors’ Conclusion:**
- Desmopressin improved measures of platelet activity, increased vWF antigen, and ↓ hematoma volume
- Given its safety and low cost, desmopressin is an attractive pharmacological treatment for acute ICH
- Further larger randomized control trials are needed

## Reviewer’s Critique

**Strengths**
- Pilot study
- No major adverse effects reported

**Weaknesses**
- Small sample size
- Routine care not defined
- No follow-up platelet activity
- Questionable clinical applicability (used monotherapy)
- No comparator arm
- One patient had hypotension and another had fever
### Table 4.
Kapapa T, et al. Desmopressin Acetate in Intracranial Hemorrhage

**Design**

- Prospective, single-center study

<table>
<thead>
<tr>
<th>Population:</th>
<th>Patients with acute ICH confirmed with CT scan and aspirin within 24 hours prior to admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Desmopressin 24mcg IV over 30 minutes</td>
</tr>
<tr>
<td>Primary Endpoint:</td>
<td>Platelet function 30 min after desmopressin administration</td>
</tr>
<tr>
<td>Secondary Endpoint:</td>
<td>Platelet function 3 hours after desmopressin administration</td>
</tr>
</tbody>
</table>
| Exclusion Criteria: | - Other anticoagulants or platelet aggregation inhibitors  
- Known coagulation disorder  
- Alcoholism  
- Hypercoagulable tendency  
- Renal failure  
- Hypothermia  
- Multiple traumas |

**Results**

Platelet function was analyzed in 10 patients:
- Received single ($N = 4$) or multiple ($N = 6$) doses of acetylsalicylic acid  
- 3 patients (control group)

Mean membrane occlusion time:
- Aspirin once in 24 hours (122.7 seconds) vs aspirin regularly (126.6 seconds)  
- 30 mins after desmopressin administration: aspirin once in 24 hours (86.3 seconds) vs aspirin regularly (73.83 seconds)  
- 3 hours after desmopressin administration: aspirin once in 24 hours (99.5 seconds) vs aspirin regularly (86.3 seconds)

Author’s conclusion: Desmopressin can improve platelet function after 30 minutes in ICH patients following aspirin intake, and coagulative status can be restored to normal between 30 minutes to 3 hours

**Reviewer’s Critique**

**Strengths**
- Pilot study  
- Included TBI and spontaneous ICH  
- Used objective measures (platelet function assay) to guide therapy  
- Aspirin dose and time could not be determined (applicable to practice)  
- Raised a question of whether or not to re-dose desmopressin

**Weaknesses**
- Use standard 24mcg dose but recommend weight-stratifying dosing  
- No mention of ICH volume, GCS, neurologic deficits at baseline  
- Small sample size with 3 patients as cohorts  
- No mention of adjunct therapy (platelet transfusion)  
- Only included patients with aspirin use, not other APA  
- Enrollment dependent on possibility to perform laboratory test
Table 5.
Kim YD, et al. The Effect of Platelet and Desmopressin Administration on Early Radiographic Progression of Traumatic Intracranial Hemorrhage 34

<table>
<thead>
<tr>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year retrospective analysis at a level 1 trauma center</td>
</tr>
</tbody>
</table>

| Population: | Adult trauma patients admitted with a diagnosis of traumatic ICH |
| Intervention: | Platelets and desmopressin (0.3 mcg/kg IV or 0.15 mcg/kg IV in elderly patients) vs. no platelets and no desmopressin |
| Primary Endpoint: | Hemorrhage progression defined as 25% increase in volume |
| Secondary Endpoint: | In hospital mortality |
| | Insertion of intracranial pressure monitor |
| | Surgical intervention |
| | Complications |
| | Duration of mechanical ventilation |
| | ICU and hospital length of stay |
| | Disposition and capacity at discharge |

| Inclusion criteria: | Criteria for platelets and desmopressin included one or more of the following: |
| | History of pre-injury antiplatelet use |
| | Platelets <100,000/mm³ |
| | In need of emergent operation |
| | At the discretion of neurosurgery and trauma attending |

| Exclusion criteria: | • Nontraumatic ICH |
| | • Penetrating mechanism |
| | • Emergent craniotomy at time of admission |
| | • Traumatic full arrest |
| | • Severe polytrauma |
| | • No repeat CT scan |
| | • Received only platelets or only desmopressin |

<table>
<thead>
<tr>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hemorrhage progression: platelet/desmopressin (+) (43.7%), Platelet/desmopressin (-) (34.2%)</td>
</tr>
<tr>
<td>• Secondary outcomes: ICU and hospital length of stay were ↑ in the platelet/desmopressin (+) group</td>
</tr>
<tr>
<td>• Patients in the platelet/desmopressin (+) group had increased mortality (p=0.03) and more health services upon discharge, after controlling for baseline characteristics, no difference in mortality</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author’s conclusion:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Platelets and desmopressin administration is not associated with statistically significant decreased early radiographic hemorrhagic progression</td>
</tr>
<tr>
<td>• It is not known whether long-term neurological function is improved by platelet and desmopressin administration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reviewer’s Critique</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strengths</strong></td>
</tr>
<tr>
<td>• Studied traumatic ICH</td>
</tr>
<tr>
<td>• Weight-stratified desmopressin dose based on risk of adverse effects</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Weaknesses</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decision to administer platelets and desmopressin was at the discretion of the attending</td>
</tr>
<tr>
<td>• Aspirin and clopidogrel captured only, possible that patients were taking other APA</td>
</tr>
<tr>
<td>• Hemorrhage progression on CT may have resulted in difference in management</td>
</tr>
<tr>
<td>• Post-discharge and long-term clinical outcomes not assessed</td>
</tr>
</tbody>
</table>
Conclusion & Recommendations

I. Summary
1. ICH accounts for 10-50% of all cases
2. Survivors often left with severe disability, with less than 40% of patients regaining functional independence
3. Predictors of mortality, specifically hematoma expansion, is associated with neurologic deterioration and worsening outcomes
4. Elevated blood pressure is linked to hematoma expansion
5. Goal SBP range in ICH patients can be between 160 – 180 mmHg
6. Antiplatelet use has not been confirmed to cause hematoma expansion
7. Platelet transfusion is not recommended in this setting
8. Potential for desmopressin to reduce ICH volume and thus delay progression to neurological defects

II. Unanswered questions and opportunities for investigation
1. Within which time frame is desmopressin considered efficacious after the incidence of an ICH?
2. What are adverse effects of using desmopressin in this patient population?
3. What is the utility of administering desmopressin along with platelets vs platelets alone vs desmopressin alone?
4. What is the correct dose and administering technique?
5. Are there better/different outcomes in patients who are taken for surgical procedures vs those who are not?

III. Recommendations
A. Additional room for research and stronger data, but due to minimal side effects, may be an option to reduce hematoma volume in antiplatelet-related ICH
   1. Specifically in patients who present with low ICH scores
   2. Consider repeating doses if needed due to short half-life of desmopressin
   3. Administration of platelets in this patient population not beneficial as seen in the PATCH trial
   4. Role of desmopressin and platelets as dual therapy may benefit patients going for surgical procedure
   5. Overall, reducing any chance of hematoma expansion, without major adverse events, can lead to improved functional outcomes in ICH patients


Appendix A: Modified Rankin Scale (mRS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Appendix B: FUNC Score
Appendix C. CTA “spot sign”

Appendix D: Platelet Function Assays

<table>
<thead>
<tr>
<th>Test</th>
<th>Abnormal (&quot;positive&quot;)</th>
<th>Normal (&quot;negative&quot;)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Function Assay (PFA-100)</td>
<td>&gt; 180 seconds = abnormal</td>
<td>63-180 seconds</td>
<td>Nonspecific test for platelet function, use when history of APA therapy unknown</td>
</tr>
<tr>
<td></td>
<td>&gt; 200 seconds = aspirin effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 300 = GPIIb/IIIa inhibitor effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet Function Assay ASPIRIN (VerifyNow Aspirin Assay)</td>
<td>&lt; 550 ARU</td>
<td>≥550 ARU</td>
<td>Specific test for platelet inhibition due to aspirin</td>
</tr>
<tr>
<td>Platelet Function Assay PLAVIX (VerifyNow P2Y12 Assay)</td>
<td>&lt; 194 PRU</td>
<td>194 – 419 PRU</td>
<td>Specific test for platelet inhibition due to P2Y12 inhibitors (clopidogrel)</td>
</tr>
</tbody>
</table>

ARU = Aspirin reaction units; PRU = P2Y12 reaction units