Desmopressin (DDAVP) for Intracranial Hemorrhage

A Review of Recent Literature

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Objectives

• Review previous trials evaluating the implications of antiplatelet therapy in patients with traumatic brain injury and intracranial hemorrhage

• Explain the theoretical mechanism of DDAVP in the treatment of intracranial hemorrhage

• Discuss recent DDAVP literature to guide recommendations in an intracranial hemorrhage patient case
Case

72 year old male with CAD is brought to the ED after a fall. He is alert and oriented with a benign neurological exam. The non-contrast CT reveals a subdural hematoma. His medications include aspirin and clopidogrel. His platelets are 176 x 10^9/L.
Would you consider giving DDAVP to this patient?

A. Yes
B. No
C. Maybe
Epidemiology

• ICH can be spontaneous or occur from TBI
• Risk factors for spontaneous ICH include:
  • Hypertension
  • Age
  • Anticoagulation
• ICH causes 15% of strokes annually
• ICH is the deadliest, most disabling, and least treatable form of stroke
  • 30-day mortality rate of 35 - 52%

ICH = Intracranial hemorrhage
TBI = Traumatic brain injury

Do aspirin and antiplatelets lead to worse outcomes in patients with ICH?

- Decrease mortality?
- Increase mortality?
<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Criteria</th>
<th>Antiplatelet Therapy</th>
<th>Number of Subjects</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roquer et al. 2003</td>
<td>Spontaneous ICH</td>
<td>Aspirin, clopidogrel, ticlopidine, dipyridamole</td>
<td>47</td>
<td>Mortality</td>
</tr>
<tr>
<td>Ohm et al. 2005</td>
<td>Posttraumatic ICH</td>
<td>Aspirin, clopidogrel</td>
<td>90</td>
<td>Mortality</td>
</tr>
<tr>
<td>Jones et al. 2006</td>
<td>All TBI, age &gt; 50 years old</td>
<td>Clopidogrel</td>
<td>43</td>
<td>Cranial surgery and rebleeds</td>
</tr>
<tr>
<td>Sansing et al. 2008</td>
<td>Spontaneous ICH</td>
<td>Aspirin, clopidogrel, ticlopidine, dipyridamole</td>
<td>70</td>
<td>Hemorrhage expansion, surgical evacuation, mortality or functional status</td>
</tr>
<tr>
<td>Fortuna et al. 2008</td>
<td>TBI, age &gt; 50 years old</td>
<td>Aspirin, clopidogrel</td>
<td>166</td>
<td>Mortality</td>
</tr>
<tr>
<td>Bonville et al. 2011</td>
<td>All TBI</td>
<td>Aspirin, clopidogrel</td>
<td>271</td>
<td>Mortality and length of hospital stay</td>
</tr>
</tbody>
</table>

Patients taking aspirin and/or antiplatelets with ICH have increased mortality

A. True
B. False
Where does DDAVP come into play?
Mechanism of Action – Platelet Aggregation

vWF = Von Willebrand Factor

Platelet

Platelet

vWF

vWF

Desmopressin Overview

Mechanism of Action
- Analogue of vasopressin
- Binds to V2 receptors in the renal collecting ducts → increasing water reabsorption

Pharmacokinetics
- Onset: 30 min
- Duration: ~3 hrs
- Excretion: Renal
- Elimination ½ life: 1 – 3 hrs

Side Effects
- Anaphylaxis
- Hypervolemic
- ↓ urine output
- Hyponatremia

Desmopressin. Micromedex [Internet database].
Mechanism of Action – DDAVP

DDAVP increases platelet adhesion by which of the following mechanisms?

A. Increases fibrinogen
B. Increases vWF
C. Decreases fibrinogen
D. Decreases vWF
Desmopressin Improves Platelet Activity in Acute Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Prospective, single-center study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Patients with acute ICH confirmed with CT scan and known aspirin use or reduced platelet activity</td>
</tr>
<tr>
<td>Intervention</td>
<td>DDAVP 0.4 mcg/kg IV over 30 minutes and other routine care</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Change in the platelet function at T=1 hour after the start of DDAVP</td>
</tr>
</tbody>
</table>
| Secondary Endpoints  | -vWF antigen   
                       -Serum sodium   
                       -Hematoma volume |
Exclusion Criteria

- INR $\geq$ 1.7
- History of von Willebrand disease
- Pregnancy
- Known hypersensitivity to DDAVP
- Active cardiovascular disease or unstable angina
- Hyponatremia
- DVT or PE

INR = International normalized ratio
DVT = Deep vein thrombosis
PE = Pulmonary embolism

### Baseline Demographics

- **Study enrolled 14 patients**

<p>| | |</p>
<table>
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Mean age</strong></td>
<td>66.8 ± 14.6</td>
</tr>
<tr>
<td><strong>Race - White</strong></td>
<td>85%</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>57%</td>
</tr>
<tr>
<td><strong>History of HTN</strong></td>
<td>93%</td>
</tr>
<tr>
<td><strong>History of Diabetes</strong></td>
<td>36%</td>
</tr>
</tbody>
</table>
Results – Platelet Aggregation

Platelet Aggregation (in seconds)

Baseline: 192, p = 0.01
1 hour after DDAVP administration: 124

Results – Secondary Endpoints

- vWF antigen increased from 242±96% to 289±103%
- The mean change in serum sodium was 0.6 mEq/L
- Of 7 patients who received DDAVP within 12 hours of ICH symptoms the median change in hematoma was -0.5mL (-1.4 to 8.4 mL)
  - Two had hematoma growth

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

Study Critique

Strengths

- Pilot study
- Appropriate inclusion and exclusion criteria

Weaknesses

- Small sample size
- Routine care not defined
- No follow-up platelet activity
- Clinical applicability

Desmopressin Acetate in Intracranial Hemorrhage

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<th><strong>Study Design</strong></th>
<th>Prospective, single-center study</th>
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</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Patients with acute ICH confirmed with CT scan and aspirin within 24 hours prior to admission</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>DDAVP 24mcg IV over 30 minutes</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Platelet function half an hour after DDAVP administration</td>
</tr>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td>Platelet function 3 hours after DDAVP administration</td>
</tr>
</tbody>
</table>
Exclusion Criteria

- Intake of other anticoagulants or platelet aggregation inhibitors
- Known coagulation disorder
- Alcoholism
- Hypercoagulable tendency
- Renal failure
- Hypothermia
- Multiple traumas
Results

<table>
<thead>
<tr>
<th>Time After DDAVP Administration</th>
<th>Platelet Aggregation (in seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>ASA once in 24 hours</td>
</tr>
<tr>
<td></td>
<td>122.7</td>
</tr>
<tr>
<td>30 minutes after DDAVP</td>
<td>86.3</td>
</tr>
<tr>
<td>3 hours after DDAVP</td>
<td>99.5</td>
</tr>
</tbody>
</table>

Study Critique

Strengths

• Pilot study

Weaknesses

• Small sample size
• Unknown platelet administration
• Clinical applicability

Author’s Conclusion: DDAVP can improve platelet function after 30 minutes in ICH patients, and coagulative 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

<table>
<thead>
<tr>
<th>Study Design</th>
<th>3-year retrospective analysis at a level I trauma center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adult trauma patients admitted with a diagnosis of traumatic ICH</td>
</tr>
<tr>
<td>Intervention</td>
<td>Platelets and DDAVP (0.3mcg/kg IV or 0.15mcg/kg IV in elderly patients) vs. No platelets and No DDAVP</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Hemorrhage progression defined as 25% increase in volume</td>
</tr>
</tbody>
</table>
| Secondary Endpoints  | - In hospital mortality  
                       | - Length of stay |
Inclusion and Exclusion Criteria

• Inclusion Criteria:
  • Criteria for platelets and DDAVP 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
  • Severe polytrauma
  • No repeat CT scan
  • Received only platelets or only DDAVP
### Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Platelet/DDAVP (+) (n = 126)</th>
<th>Platelet/DDAVP (-) (n = 282)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>63 (49 – 77)</td>
<td>45 (29 – 62)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Admit GCS</strong></td>
<td>14 (11 – 15)</td>
<td>14 (14 – 15)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Admit SBP (mmHG)</strong></td>
<td>152 (136 – 167)</td>
<td>140 (128-154)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>52 (41.3)</td>
<td>44 (15.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>CVA</strong></td>
<td>7 (5.6)</td>
<td>0 (0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>20 (15.9)</td>
<td>15 (5.3)</td>
<td>0.0004</td>
</tr>
<tr>
<td><strong>Initial Hemorrhage (cm^3)</strong></td>
<td>5.9 (3.9 – 7.9)</td>
<td>3.1 (1.4 – 4.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Aspirin</strong></td>
<td>28 (22.2)</td>
<td>13 (4.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Clopidogrel</strong></td>
<td>10 (7.9)</td>
<td>3 (1.1)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

GCS = Glasgow coma scale  
SBP = Systolic blood pressure  
CVA = Cerebrovascular accident  

*Raw value and percentage  
**Median (interquartile range)  

Results – Hemorrhage Progression

Platelet/DDAVP (+) 43.7%  Platelet/DDAVP (-) 34.2%

$p = 0.07$

Results – Secondary Outcomes

- 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

Author’s Conclusion

• Platelets and DDAVP administration is 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
Study Critique

Strengths

• Larger study population
• Cohort received platelets and DDAVP
• Captured baseline characteristics
• Clinical outcome

Weaknesses

• Retrospective study
• Provider biases
• All patients were not receiving antiplatelets
Guideline Recommendations

Intracranial Hemorrhage

Receiving antiplatelets

Undergoing neurosurgical procedure
- DDAVP 0.4 mcg/kg IV
- 6 units of platelets

Not undergoing neurosurgical procedure
- DDAVP 0.4 mcg/kg IV

Cost of Desmopressin

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

$168.34
Patient Case

72 year old male with a PMH of CAD and HTN is brought to the ED after a fall. His neuro exam is worsening, and his GCS is 9. The non-contrast CT reveals a subdural hematoma. His home medications include ASA, clopidogrel, and amlodipine. The patient will undergo surgery.

Labs:

- Platelets: 176 x 10⁹/L
- Hemoglobin: 8.8 g/dL
What is your recommendation for use of DDAVP and platelets in this patient?

A. DDAVP 0.4 mcg/kg intranasally
B. DDAVP 0.4 mcg/kg IV and platelets
C. DDAVP 0.4 mcg/kg IV
D. I would not recommend DDAVP in this patient
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