Managing the Anticoagulated TBI Patient

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HARBORVIEW MEDICAL CENTER / UW

Anticoagulation and TBI

- ATRIAL FIBRILLATION – roughly 1% of the pop
  approx. 3 million Americans
- DVT / PE - approx 900,000/year
- In 2010 – 29.7 Million Prescriptions for Clopidogrel

SPONTANEOUS ICH

- Anticoagulation increases the rate of ICH 7-10X
- Mortality 42.3 – 67%
- Driven by hematoma expansion
Hematoma Expansion
- REMEMBER! Your CT scan is just a snapshot in time
- What started out looking like:

Hematoma Expansion
- REMEMBER! Your CT scan is just a snapshot in time
- What started out looking like: Can quickly turn into:

Hematoma Expansion
- 218 ICH patients analyzed
- 73% of all ICH patients had some hematoma growth
  - For every 10% growth in hematoma size:
    - 5% increase in mortality
    - 16% more likely to increase one point on mRS
REVERSAL of ANTICOAGULATION

- 50% of warfarin associated ICH die within first 30 – 90 days.
- Limiting Hematoma Expansion is likely key to outcome.
- Anticoagulation Reversal is a TIME DEPENDENT EMERGENCY!!!

Initial CT / CTA

REVERSAL of ANTICOAGULATION

- 50% of warfarin associated ICH die within first 30 – 90 days.
- Limiting Hematoma Expansion is likely key to outcome.
- Anticoagulation Reversal is a TIME DEPENDENT EMERGENCY!!!

Initial CT / CTA 12 hours later

REVERSAL of ANTICOAGULATION

- Mortality 53.6% at 30 days

<table>
<thead>
<tr>
<th>MORTALITY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconscious at Admission</td>
<td>96%</td>
</tr>
<tr>
<td>Became unconscious before warfarin reversal started</td>
<td>80%</td>
</tr>
<tr>
<td>No Reversal Except Stopping Warfarin</td>
<td>75%</td>
</tr>
<tr>
<td>Active Reversal Started While Still Conscious</td>
<td>28%</td>
</tr>
</tbody>
</table>
Antithrombotics and TBI

- Grandhi et al – Warfarin associated with mortality of 28% in TBI vs 12.8%
- Pieracci et al – Therapeutic warfarin associated with OR = 4.48 for mortality in TBI
- Nishijima et al – both clopidogrel and warfarin associated with worse 6 month E-GOS and 6 month mortality after TBI

Delayed Intracranial Hemorrhage in patients on antithrombotics
Peck et al – 2011

- 362 mild TBI patients on warfarin or antiplatelet med with repeat CT at 6 hours after initial negative head CT
  - Warfarin – 68% of patients
  - Clopidogrel – 24%
  - Other – 7%
  - Combination – 6%

- Average INR of patients on warfarin = 2.5

<table>
<thead>
<tr>
<th>Case</th>
<th>Grade</th>
<th>Mechanism</th>
<th>Warfarin</th>
<th>Clopidogrel</th>
<th>Other</th>
<th>Combined</th>
<th>CT Finding</th>
<th>Symptom</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>01</td>
<td>Low</td>
<td>Headache</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Headache</td>
<td>No</td>
<td>Discharged</td>
</tr>
<tr>
<td>02</td>
<td>Low</td>
<td>Headache</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Headache</td>
<td>No</td>
<td>Discharged</td>
</tr>
<tr>
<td>03</td>
<td>Low</td>
<td>Headache</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Headache</td>
<td>No</td>
<td>Discharged</td>
</tr>
<tr>
<td>04</td>
<td>Low</td>
<td>Headache</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Headache</td>
<td>No</td>
<td>Discharged</td>
</tr>
<tr>
<td>05</td>
<td>Low</td>
<td>Headache</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Headache</td>
<td>No</td>
<td>Discharged</td>
</tr>
<tr>
<td>06</td>
<td>Low</td>
<td>Headache</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Headache</td>
<td>No</td>
<td>Discharged</td>
</tr>
</tbody>
</table>
TBI-Hemorrhage Progression

Hemorrhagic Contusion

Post Craniectomy

**REVERSAL of ANTICOAGULATION**

1. **VITAMIN K**
   - Important to give to reverse warfarin
   - 10–20 mg IV (slowly)
   - May not start working for 12–24 hours!

2. **Fresh Frozen Plasma**
   - Contains all clotting factors
   - 4 Units probably minimum dose
   - recheck INR one hour later.
   - Obtaining, thawing, and administering may cause significant delay in reversal.

**REVERSAL of ANTICOAGULATION**


- 45 patients with warfarin associated ICH given FFP
- Median Time from Door-to-Normal-INR = **30 hours**!!!

- Fresh Frozen Plasma associated with significant delays and pulmonary edema when used alone.
Prothrombin Complex Concentrate (PCC)

Two Types:

4 Factor PCC (Beriplex, Octaplex, Cofact, Proplex)
- Contains Factors II, VII, IX, X
- FDA Approved in USA

3 Factor PCC (Bebulin, Profilnine)
- No Factor VII
- Available in USA

<table>
<thead>
<tr>
<th>Prothrombin Complex Concentrate</th>
<th>Dose HMC Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INR&lt; 2 20 IU/kg $3,778</td>
</tr>
<tr>
<td></td>
<td>INR 2-4 30 IU/kg $5,379</td>
</tr>
<tr>
<td></td>
<td>INR &gt; 4 50 IU/kg $8,583</td>
</tr>
<tr>
<td>4-Factor (K-Centra)</td>
<td></td>
</tr>
<tr>
<td>INR &lt; 2 25 IU/kg $5,977</td>
<td></td>
</tr>
<tr>
<td>INR 2-4 35 IU/kg $8,102</td>
<td></td>
</tr>
<tr>
<td>INR &gt; 4 50 IU/kg $11,290</td>
<td></td>
</tr>
</tbody>
</table>

Prothrombin Complex Concentrate (PCC)


181 patients with INR>2 needing urgent surgical or invasive procedure.

RCT: 4F-PCC vs FFP

<table>
<thead>
<tr>
<th>INR</th>
<th>4F – PCC</th>
<th>FFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 4</td>
<td>25 IU/kg</td>
<td>10 ml/kg</td>
</tr>
<tr>
<td>4 – 6</td>
<td>35 IU/kg</td>
<td>12 ml/kg</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>50 IU/kg</td>
<td>25 ml/kg</td>
</tr>
</tbody>
</table>
Prothrombin Complex Concentrate (PCC)

PRIMARY OUTCOMES:
1.) Hemostasis – Effective or Not (blood loss > predicted by 30% or 50 mL).
2.) Reduction of INR to < 1.3 by 30 min post infusion

Secondary Outcomes:
- Time to INR < 1.3 from start of infusion
- PRBC transfusion to 24 h post surgery
- Proportion of pts receiving PRBC
- Plasma levels of coagulation factors, Protein C & S.

<table>
<thead>
<tr>
<th></th>
<th>4F - PCC</th>
<th>Plasma</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Hemostasis</td>
<td>78 (90%)</td>
<td>61 (75%)</td>
<td>0.0447</td>
</tr>
<tr>
<td>Rapid INR Reduction</td>
<td>48 (55%)</td>
<td>8 (10%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
HMC WARFARIN REVERSAL

1.) Vitamin K 10 mg IV over 30 min STAT

2.) K-Centra (4 factor PCC) – DO NOT WAIT FOR FFP
   For INR 2-3.9, infuse 25 U/kg over 10 min, Max 2500 Units
   For INR 4-6.0, 35 U/kg, Max 3500 Units
   For INR> 6.0, 50 U/kg, Max 5000 Units

3.) Recheck INR at 1hr, 6hr, 24hr after PCC administered, and consider 2 U of FFP.
ANTIPLATELET MEDS and TBI

Univ of Cincinnati – Fortuna et al – 2008

416 pts with hemorrhagic TBI
40% with preinjury use of clopidogrel/ASA/Warfarin

<table>
<thead>
<tr>
<th>Clopidogrel</th>
<th>Aspirin</th>
<th>Warfarin</th>
<th>Preop</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>57</td>
<td>89</td>
<td>18</td>
<td>29</td>
</tr>
<tr>
<td>Age (mean)</td>
<td>75.1 ± 27</td>
<td>71.5 ± 12</td>
<td>60.1 ± 17</td>
<td>56.1 ± 17</td>
</tr>
<tr>
<td>MO (SD)</td>
<td>83.8 ± 5.8</td>
<td>51.8 ± 5.1</td>
<td>142.3 ± 14</td>
<td>141.5 ± 11</td>
</tr>
<tr>
<td>GCS (mean)</td>
<td>10.5 ± 1.3</td>
<td>12.0 ± 1.6</td>
<td>13.5 ± 1.8</td>
<td>12.2 ± 0.9</td>
</tr>
<tr>
<td>LMR (mean)</td>
<td>7.6 ± 1.6</td>
<td>7.6 ± 1.8</td>
<td>7.1 ± 1.3</td>
<td>38.6 ± 12</td>
</tr>
<tr>
<td>Mortality</td>
<td>4%</td>
<td>3%</td>
<td>12%</td>
<td>54%</td>
</tr>
</tbody>
</table>

Study found no association between C/A/W use and mortality.

-40% of C/A/W patients received PLATELET transfusion – but sicker patients received platelets.

-Mortality significantly higher in pts receiving Platelets (30% vs. 16%, P=0.01)
ANTIPLATELET MEDS and TBI
Univ of Cincinnati – Fortuna et al – 2008

META-ANALYSIS (ASPIRIN DATA):

<table>
<thead>
<tr>
<th>Study Author</th>
<th>(+) Aspirin</th>
<th>(-) Antiplatelet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortuna et al.</td>
<td>13% 71.9</td>
<td>20% 66.4</td>
</tr>
<tr>
<td>Ivascu et al.</td>
<td>23% 77</td>
<td>9.5% 76</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>3.3% 67.3</td>
<td>1.1% 65.5</td>
</tr>
<tr>
<td>Mina et al.</td>
<td>47% 74</td>
<td>8.1% 75</td>
</tr>
</tbody>
</table>

POOLED OR = 2.435 (95% CI: 0.637 – 9.3)
## META-ANALYSIS (CLOPIDOGREL DATA):

### Study Author

<table>
<thead>
<tr>
<th>Study Author</th>
<th>(+) Clopidogrel</th>
<th>(-) Antiplatlet</th>
<th>Mortality</th>
<th>Avg Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortuna et al.</td>
<td>6%</td>
<td>75.1</td>
<td>20%</td>
<td>66.4</td>
</tr>
<tr>
<td>Ivascu et al.</td>
<td>17.6%</td>
<td>77</td>
<td>9.5%</td>
<td>76</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>14.3%</td>
<td>71.5</td>
<td>1.1%</td>
<td>65.5</td>
</tr>
<tr>
<td>Jones et al.</td>
<td>9.9%</td>
<td>73</td>
<td>9.9%</td>
<td>73</td>
</tr>
</tbody>
</table>

### POOLED OR = 1.554 (95% CI: 0.32 – 7.54)

## Clopidogrel and TBI

Joseph et al. – 2014

142 TBI patients (71 on Clopidogrel)

- Pts matched for age, sex, GCS, type and size of ICH, Platelet Tx, ISS, h-AIS
- 61% of patients received platelet transfusion

**PATIENTS on CLOPIDOGREL were MORE LIKELY to:**

1. **DEMONSTRATE ICH EXPANSION ON RHCT**  
   (65% v 18%; p = .01)

2. **RECEIVE NEUROSURGICAL INTERVENTION**  
   (7% v 1.5%; p = .04)
Clopidogrel and TBI
Joseph et al – 2014
142 TBI patients (71 on Clopidogrel)

BUT NO DIFFERENCE IN:
- Hospital LOS
- ICU LOS
- Ventilator Days
- Discharge GCS
- Mortality

Platelet Transfusions

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Approximate Risk per Platelet Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile reaction</td>
<td>1/14</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1/50</td>
</tr>
<tr>
<td>Bacterial sepsis</td>
<td>1/75,000</td>
</tr>
<tr>
<td>TRALI*</td>
<td>1/138,000</td>
</tr>
<tr>
<td>HBV infection</td>
<td>1/2,652,580</td>
</tr>
<tr>
<td>HCV infection</td>
<td>1/3,315,729</td>
</tr>
<tr>
<td>HIV infection</td>
<td>0 (95% CI, 0 to 1/1,461,888)</td>
</tr>
</tbody>
</table>

Platelet Transfusion for ICH
Ducruet et al - 2010

66 patients with ICH while on ASA or Clopidogrel
35/66 received platelet tx

Primary Outcome – Rate of Significant Hematoma Expansion (> 25%)
Platelet Transfusion for ICH

Ducruet et al - 2010

RESULTS:
- No Difference WRT hematoma growth (16.1% vs 17.7%, p=0.87)
- No Difference WRT discharge MRS
- No Difference WRT mortality

Should we be routinely transfusing platelets in TBI patients on ASA/Clopidogrel?

Platelet Transfusion in TBI

Washington et al - 2011

1,101 hospitalized TBI patients with GCS ≥ 13
321 with traumatic intracerebral hemorrhage
113 on antiplatelet meds - 44 (+) Plt Tx / 64 (-) Plt Tx

Transfused group more likely to be:
- On Clopidogrel (52 vs 20%)
- Higher Marshall Score
- Higher ICH volumes
Investigators looked at rates of:

1. Neurologic Decline
   - Increase in monitoring due to decline in MS or focal deficit (ICU)
   - Intervention due to decline in mental status (crani, ICP Monitor, EVD)
   - Development of a focal neurologic deficit

2. Medical Decline
   - Increase in monitoring due to cardiac, pulmonary, or renal decline.
   - (e.g. AKI, pulmonary embolism, CHF exacerbation, etc.)

<table>
<thead>
<tr>
<th>Antplatelet Outcomes</th>
<th>Yes (N = 44)</th>
<th>No (N = 64)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological decline</td>
<td>0</td>
<td>2 (3)</td>
<td>0.51*</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>2 (5)</td>
<td>0</td>
<td>0.16*</td>
</tr>
<tr>
<td>Medical decline</td>
<td>6 (14)</td>
<td>2 (3)</td>
<td>0.06*</td>
</tr>
<tr>
<td>Cardiac event</td>
<td>8 (18)</td>
<td>8 (12)</td>
<td>0.41*</td>
</tr>
<tr>
<td>Respiratory event</td>
<td>4 (9)</td>
<td>2 (3)</td>
<td>0.22*</td>
</tr>
<tr>
<td>Glasgow outcome</td>
<td>2 (5)</td>
<td>0</td>
<td>0.16*</td>
</tr>
<tr>
<td>1</td>
<td>2 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>5 (11)</td>
<td>3 (5)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>7 (16)</td>
<td>11 (17)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>30 (68)</td>
<td>50 (78)</td>
<td>0</td>
</tr>
<tr>
<td>HCT progression</td>
<td>5/41 (12)</td>
<td>4/58 (7)</td>
<td>0.48*</td>
</tr>
</tbody>
</table>
Platelet Transfusion in TBI
Washington et al – 2011

Any Transfusion

<table>
<thead>
<tr>
<th>Any Transfusion Outcomes</th>
<th>Yes (N = 65)</th>
<th>No (N = 256)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Neurological decline</td>
<td>1 (2)</td>
<td>3 (1)</td>
<td>1*</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>3 (5)</td>
<td>1 (0.4)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Medical decline</td>
<td>13 (20)</td>
<td>3 (2)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Cardiac event</td>
<td>13 (20)</td>
<td>11 (16)</td>
<td>&lt;0.0001*</td>
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<td>8 (12)</td>
<td>4 (2)</td>
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</tr>
<tr>
<td>Glasgow outcome</td>
<td></td>
<td></td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>1</td>
<td>4 (6)</td>
<td>0.255 (0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (9)</td>
<td>6.255 (2)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>13 (20)</td>
<td>20.255 (8)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>42 (65)</td>
<td>229.255 (90)</td>
<td></td>
</tr>
<tr>
<td>HCT progression</td>
<td>8.62 (13)</td>
<td>11.234 (5)</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

DESMOPRESSIN

- Alternative for reversing platelet dysfunction caused by ASA
- DOSE: 0.3 micrograms/kg IV

DESMOPRESSIN

- Interacts with type 2 vasopressin receptors of endothelium inducing release of vWF and FVIII
- Several Advantages over Platelet Transfusion
  - No risk of infection
  - Rapid
23 patients with CKD also taking ASA / Clopidogrel / or other antiplatelet
- All scheduled for emergent invasive procedures (CVL for HD, percutaneous nephrostomy, angiography)
- 0.3 microgram/kg DDAVP given
- Clotting parameters measured before and 1 hour after DDAVP
  PT, aPTT, CEPI-CT

Collagen Epinephrine – Closure Time significantly shortened:
252.7 seconds → 144.5 sec (p<0.001)
Reference range = 82-182 sec
DESMOPRESSIN

Naidech et al – 2014

CEPI-CT reduced:
from 192 to 124 sec
(p=0.01)

vWF increased in ALL patients.

MEAN [Na+] change = 0.6 MEQ/L

NEW ORAL ANTICOAGULANTS

NEW ORAL ANTICOAGULANTS
NEW ORAL ANTICOAGULANTS

- Limited evidence on reversal strategies
- Pts are not factor deficient so Vitamin K is not indicated
- Studies using PCC / FVIIa / FFP have mostly involved mouse models.
- Several authors recommend 4-Factor PCC (50µg/kg)
- Adjunctive therapy includes:
  - Activated charcoal – if last dose within 2-6h
  - Hemodialysis (Dabigatran Only)
Idarucizumab for Dabigatran Reversal

Interim analysis – 90 patients on Dabigatran

Group A – Life threatening bleeding requiring reversal
Group B – Requiring surgery or invasive procedure within 8h

Patients received 5 grams of Idarucizumab
Serial clotting and pharmacokinetic tests performed
Conclusions

1.) Rapid reversal of warfarin (INR>2) with 4-factor PCC is recommended in the setting of TBI with an abnormal CT scan.

Conclusions

2.) Patients on anticoagulation after head trauma with a normal head CT are unlikely to experience late hemorrhage.

Conclusions

3.) The appropriate reversal strategy for TBI patients on antiplatelet agents has not been defined. Desmopressin is an attractive agent that has the potential to supplant platelet transfusion in this setting.
Conclusions

4.) The best strategy for reversal of NOACs has not been defined but 4-factor PCC is a reasonable first line agent. Agent-specific reversal drugs are currently in the pipeline.

References

1.) Chugh SS et al – Worldwide Epidemiology of Atrial Fibrillation – Circulation 2014; 129: 837-847