Background

The Red Duke Trauma Institute frequently evaluates patients receiving anticoagulant or prescription antiplatelet (ACAP) therapy at the time of injury. Because there are reports of delayed intracranial hemorrhage (ICH) after blunt trauma in such patients, we have developed a clinical practice policy for the evaluation and treatment of patients receiving ACAP therapy in the setting of blunt trauma with both normal and abnormal screening CT scans.

Introduction:

Traumatic brain injury or intracranial hemorrhage is a major source of morbidity and mortality in the trauma patient. Patients receiving pre-injury anticoagulants and antiplatelet therapy are especially susceptible to poor neurological outcome due to the risk of injury progression. Immediate reversal of such agents is crucial to limiting progression of devastating neurological outcomes.

The Neurocritical Care Society, in conjunction with the Society of Critical Care Medicine, organized an international, multi-institutional committee with expertise in neurocritical care, neurology, neurosurgery, stroke, hematology, hemato-pathology, emergency medicine, pharmacy, nursing, and guideline development to evaluate the literature and develop an evidence-based practice guideline. Utilizing the GRADE methodology, the committee developed recommendations for reversal of vitamin K antagonists, direct factor Xa antagonists, direct thrombin inhibitors, unfractionated heparin, low-molecular weight heparin, heparinoids, pentasaccharides, thrombolytics, and antiplatelet agents in the setting of intracranial hemorrhage.

A current literature search did not yield any new or contradicting data and hence this guideline should be adopted to use in our population until further data is available.

Perhaps the most notable portion of the guideline pertains to the use of platelets in the setting of TBI in patients on anti-platelet agents. There is no evidence that platelet transfusion is indicated in patients receiving anti-platelets agents who present with traumatic brain injury or intracranial hemorrhage. Platelet transfusion is only indicated if instrumentation (such as bolt placement) or neurosurgical intervention is planned.

As for patients on anticoagulation who present with mild head trauma and no evidence of bleeding on initial CT scan, the question is raised regarding the need for repeat imaging and observation to detect delayed hemorrhage. Multiple studies have shown that patients on warfarin with a negative initial head CT had very low rates of delayed intracranial hemorrhage (ranged from 0.6-6%) with clinically significant bleeds requiring intervention ranging from 0.1-1.1%. This data provides the confidence to discharge patients home from the ER with low mechanisms of injury who are completely neurologically normal.
with no associated injuries. Emerging data suggests that there is no increased rate of delayed ICH in patients on DOACs compared to warfarin.

Summary of guidelines:

Patients on warfarin or DOACs may be **discharged home after an observation period of 6 hours (from time of injury)** if ALL of the following criteria are met:

- no findings of intracranial bleeding on initial head CT
- no signs of neurologic deterioration during 6 hour observation period
- INR < 3.5 in warfarin-therapy patients
- patient has no other injuries that warrant admission

Patients will be **observed in the hospital for 23hrs** and a repeat head CT obtained in 6 hours if ANY of the following criteria are met:

- findings of intracranial bleeding on head CT (consult Neurosurgery)
- neurologic deterioration during 6 hour observation (obtain repeat CT Head)
- INR ≥ 3.5 in warfarin-therapy patients
- inability to obtain neurologic exam despite normal baseline head CT

Reversal of Specific Agents in Patients with TBI

**Vitamin K Antagonists (Warfarin) Reversal**

- Patients with cerebral venous thrombosis with concomitant intraparenchymal hemorrhage should not receive reversal agents due to the increased risk of hematoma expansion related to venous hypertension. (Conditional recommendation, very low-quality evidence).
  - This must be discussed with neurosurgery staff
- Administer vitamin K (10mg IV) to ensure durable reversal (Strong recommendation, moderate quality evidence)
- Administer 3 factor or 4 factor PCC over FFP for INR target <1.4 (Strong recommendation, moderate quality evidence). Dosing based on weight and INR level

<table>
<thead>
<tr>
<th>INR</th>
<th>Dose</th>
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<tbody>
<tr>
<td>&lt;4</td>
<td>25 units/kg</td>
</tr>
<tr>
<td>4-6</td>
<td>35 units/kg</td>
</tr>
<tr>
<td>≥6</td>
<td>50 units/kg</td>
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</tbody>
</table>

- Check INR 15-60 minutes after PCC administration and then serially every 6hrs
  - Treat accordingly. Repeat PCC dosing has increased risk of thrombotic complications
  - Further correction with FFP is recommended
- Administration of rFVIIa is not recommended
- If PCC is not available, reversal with vitamin K and FFP (10-15cc/kg) is recommended

**Direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) Reversal**

- Reversal should be guided clinically and not by lab values
- Hemodialysis does not reverse the effect of oral direct factor Xa inhibitors because these drugs are highly protein bound.
- Administer activated charcoal (50 g) to patients who present within 2 h of ingestion of an oral direct factor Xa inhibitor. (Conditional recommendation, very low-quality evidence)
• Administer a 4-factor PCC (35 U/kg) if intracranial hemorrhage occurred within 3–5 terminal half-lives of drug exposure or in the context of liver failure. (Conditional recommendation, low-quality evidence)
• Administration of rFVII is not recommended due to risk of thrombotic events

Direct thrombin inhibitors (Dabigatran, argatroban, bivalirudin) Reversal
• Reversal should be guided clinically and not by lab values
• Administer activated charcoal (50 g) to patients who present within 2 h of ingestion of an oral direct factor Xa inhibitor. (Conditional recommendation, very low-quality evidence)
• Administer idarucizumab (5g IV in two divided doses) within a period of 3-5 half-lives or in the setting of renal impairment
• If idarucizumab is not available, consider hemodialysis
• In the setting of ongoing clinically significant bleeding, idarucizumab can be re-administered
• Administration of rFVII or FFP is not recommended
• Reversal of IV direct thrombin inhibitors is not necessary due to their short half-lives. Consider PCC in case of life-threatening hemorrhage

Unfractionated heparin Reversal
• Full dose heparin should be reversed in the setting of new onset intracranial hemorrhage while prophylactic heparin does not require reversal (unless aPTT is significantly elevated)
• Administer Protamine sulfate at 1mg for every 100 units of heparin received in the last 2-3hrs (max dose 50mg)

Low-molecular weight heparin (enoxaparin) Reversal
• Administer protamine in the setting of new intracranial hemorrhage in a patient receiving therapeutic LMWH
  o If enoxaparin was given within 8hrs, give 1mg of protamine for every 1mg of enoxaparin (max dose 50mg)
  o If enoxaparin was given within 8-12hrs, give 0.5mg of protamine for every 1mg of enoxaparin (max dose 50mg)
• Patients receiving prophylactic enoxaparin do not require reversal
• Use of PCC or FFP is not recommended

Pentasaccharides (fondaparinux) Reversal
• No clear evidence exists regarding the reversal of pentasaccharides in humans
• Consider activated PCC or rFVIIa
• Protamine is not recommended

Thrombolytics (tPA) Reversal
• Administer cryoprecipitate (10 units initially then re-dose to fibrinogen level >150)
• If cryoprecipitate is not available or contraindicated, antifibrinolytics (tranexamic acid or aminocaproic acid) may be used

Antiplatelet agents (ASA, clopidogrel, prasugrel, Ticagrelor) Reversal
• Platelet transfusion in the setting of intracranial hemorrhage not requiring neurosurgical intervention is NOT recommended.
• Patients undergoing a neurosurgical intervention should receive platelet transfusion if they were taking ASA or ADP inhibitors
  o Patients on NSAIDs or GP IIb/IIIa inhibitors do not require transfusion even if having a neurosurgical intervention
• Consider a single dose of DDAVP (0.4 mcg/kg)
### Appendix A: DOACs and delayed ICH

<table>
<thead>
<tr>
<th>Search</th>
<th>Database</th>
<th>Search Term</th>
<th>Limits</th>
<th>Total Yield: # of Articles</th>
<th># Excluded Articles</th>
<th># Included Articles</th>
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<tbody>
<tr>
<td>1</td>
<td>PubMed</td>
<td>phenytoin AND levetiracetam AND traumatic brain injury</td>
<td>Clinical Trial</td>
<td>3</td>
<td>1 (outcome long-term seizures)</td>
<td>1 Prospective observational, 1 RCT</td>
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<td>2</td>
<td>PubMed</td>
<td>phenytoin AND levetiracetam AND traumatic brain injury</td>
<td>Randomized Controlled Trial</td>
<td>2</td>
<td>0</td>
<td>1 Prospective observational, 1 RCT (both duplicates)</td>
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<td>3</td>
<td>PubMed</td>
<td>phenytoin AND levetiracetam AND traumatic brain injury</td>
<td>Systematic Review</td>
<td>7</td>
<td>1 (retrospective study); 1 (non-trauma)</td>
<td>6</td>
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<td>Total</td>
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**Exclude Multiples 2**

Included Papers 7 (1 RCTs, 1 Observational, 5 SRs)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Type of Study</th>
<th>N</th>
<th>Age</th>
<th>Population</th>
<th>Study Characteristics</th>
<th>Conclusion</th>
<th>DOAC Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Battle et al. 2017</td>
<td>Single center retrospective ’05-06</td>
<td>110</td>
<td>65+</td>
<td>Fall on anticoagulants</td>
<td>All with repeat head CT in 6hrs 21 patients on DOAC</td>
<td>- 2 had small SDH (1.8%) of no clinical consequence (1 on Plavix, 1 on dabigatran)</td>
<td>1/21 delayed ICH</td>
</tr>
<tr>
<td>Bauman et al. 2017</td>
<td>Prospective observational study ’13-14</td>
<td>1180</td>
<td>18+</td>
<td>Fall on anticoagulants or antiplatelet</td>
<td>All repeat head CT in 12hrs 69% ASA, 19% coumadin 17% Plavix, 3% rivaroxaban 11% combo</td>
<td>- 7 patients developed delayed ICH (0.51%). 1/7 on DOAC - No change in clinical management or surgical intervention - 5/7 patients were greater than 90</td>
<td>1/82 delayed ICH</td>
</tr>
<tr>
<td>Ricarddi et al. 2017</td>
<td>Single institution prospective observational ’15-16</td>
<td>225</td>
<td>18+</td>
<td>100% ground level fall</td>
<td>118 on coumadin 107 on DOACs Observed for 24hrs. Only scanned for symptoms</td>
<td>- 12 patients on coumadin with ICH (10.15%) - 3 patients on DOACs with ICH (2.8%)</td>
<td>3/107 delayed ICH</td>
</tr>
<tr>
<td>Barmparas et al 2017</td>
<td>Multicenter retrospective review ’14-17</td>
<td>249</td>
<td>18+</td>
<td>80% ground level fall</td>
<td>82% had repeat CT in 24hrs 47% rivaroxaban, 41.4% apixaban, 11.6% dabigatran, 4.8% also on antiplatelet</td>
<td>- 3 patients developed ICH (1.2%) - 1 patient with ICH received TPA - none required surgical intervention</td>
<td>2/249 delayed ICH</td>
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<tr>
<td>Cirpriano et al 2018</td>
<td>Single center prospective observational study ’16-17</td>
<td>183</td>
<td>18+</td>
<td>91.3% ground level fall</td>
<td>85 patients on DOAC (41.3%)</td>
<td>- 3 patients experienced delayed ICH (1.7%). 1 died from complication</td>
<td>2/81 delayed ICH</td>
</tr>
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</table>

DOAC = direct oral anticoagulant, ICH = intracerebral hemorrhage
References:


