Anticoagulant reversal in ICH

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Outline

- Warfarin Reversal
- Dabigatran Reversal
- Factor Xa Inhibitor Reversal (including Rivaroxaban and Apixaban)
- Antiplatelet Reversal
Introduction

- Goal of anticoagulation reversal: Lower the risk of ICH expansion
- Vitamin K antagonist

- Vitamin K is required for carboxylation of factors II, VII, IX, and X

- Warfarin therefore prevents the synthesis of biologically active factors
Warfarin (Coumadin)

- Patients **do not have enough** of Factors II, VII, IX, and X. We just need to give them back.
- Intravenous vitamin K lets them make their own!
- It has some effect as early as 4-6 hours, but full effect can take 24 hours.
- Until then, we need to deliver the 4 clotting factors!

Watson HG et al, Br J Haem 2008
Donated blood is split into:
- PRBCS (packed red blood cells)
- Platelets
- Plasma
  - Plasma is then “Fresh Frozen”
  - It contains ALL the coagulation factors!!!
    - (Including the 4 that are missing in warfarin patients)
  - Costs $200-$400 for 4 units
PCC (Prothrombin Complex Concentrate)

- The major one available in the US is “Kcentra”
- A concentrate of the 4 coagulation factors (Factor II, VII, IX, X, plus protein C, S, and some heparin)
- No type/screening necessary
- Infuse in <20 minutes
- RAPID INR correction
- Can cost $2000-$5000
PCC vs. FFP for ICH

- There have been a few randomized trials of PCC.
- In the INCH trial, 54 patients with warfarin-ICH were randomized to PCC vs. FFP.
- PCC showed faster INR reversal, less ICH expansion, and a nonsignificant trend towards lower mortality.

PCC Dosing

- Standard dosing is based on weight and INR

<table>
<thead>
<tr>
<th>Pre-treatment INR</th>
<th>2−&lt;4</th>
<th>4−6</th>
<th>&gt;6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose* of Kcentra (units† of Factor IX) / kg body weight</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Maximum dose‡ (units of Factor IX)</td>
<td>Not to exceed 2500</td>
<td>Not to exceed 3500</td>
<td>Not to exceed 5000</td>
</tr>
</tbody>
</table>

- However, many hospitals use an initial fixed dose (1000-1500 units)
  - Easy to calculate, more rapid delivery, often lower cost, and is effective for many patients.

Fuh L et al, J Thromb Thrombolysis 2019
Warfarin reversal

- For ICH with elevated INR (over 2.0):
- Treat with IV Vitamin K and PCC if available.
- If PCC is not available:
  - IV vitamin K and FFP.
Question
Direct Oral Anticoagulants

- Factor IIa Inhibitor: Dabigatran

- Factor Xa Inhibitors: Rivaroxaban, Apixaban, Edoxaban

- How to reverse these?
Time can be a reversal agent!

- Half life in healthy subjects:
  - Rivaroxaban: 5-9 hours
  - Dabigatran: 7-9 hours
  - Apixaban: 12 hours
  - Edoxaban: 10-14 hours
  - Warfarin: 40 hours

- N.B. These times are longer with older age, renal insufficiency
Dabigatran (Pradaxa) reversal

- Idarucizumab (Praxbind)
  - Monoclonal antibody – binds dabigatran
  - 2 IV boluses, given 15 minutes apart

- Some use PCC for this purpose
  - PCC contains Factor II
  - Goal is to give “extra” Factor II

Dabigatran reversal

- Single arm trial (no comparison arm)
- Reversal is rapid, and lasts at least 24 hours.
- Cost: Approx. $3500

- 90-day mortality: 19%
- 90-day thrombo-embolism: 6.8%

Pollack C et al, NEJM 2017
Dabigatran reversal

- Time as a reversal agent
  - Can the patient wait?
- Idarucizumab is a specific reversal agent
- PCC is often used off label as a nonspecific reversal agent
  - (no clinical trials of this)
Question
Factor Xa inhibitor reversal

- How to check if the patient is “anticoagulated?”
  - Laboratory test: Anti-Xa level (not widely available quickly)
  - PT/PTT can be false negative up to 44% of the time

Purrucker et al, Stroke 2017
Rivaroxaban/Apixaban reversal

- Andexanet (Annexa)
  - Monoclonal antibody – binds Factor Xa inhibitors (Rivaroxaban, Apixaban, Edoxaban). It binds low molecular weight heparins (enoxaparin) as well.
  - IV bolus then 2 hour infusion

- Some use PCC for this purpose
  - PCC contains Factor X
  - Goal is to give “extra” Factor X
Andexanet – Rivaroxaban/apixaban reversal

Randomized trial in healthy volunteers

Siegal DM et al, NEJM 2015
Andexanet

- Single arm trial (no comparison arm)
- Reversal is rapid:
  - Complete during 2 hour infusion
  - Then, between 4-5 hours, anti-Fxa activity rises (still below baseline).
  - Cost: Between $26,000-$58,000
- 90-day mortality: 14%
- 90-day thrombo-embolism: 10%

Connolly, SJ et al, NEJM 2019
Question
Guidelines:

- **Neurocritical Care Society (NCS):**
  - Give 4F-PCC (50U/kg) or FEIBA if ICH occurred within 3-5 half lives of drug

- **ENLS (Emergency Neurologic Life Support, from NCS):**
  - Andexanet as first line agent, PCC as second line

- **American Heart Association:**
  - FEIBA, other PCCs, or rFVIIa might be considered

- **American College of Chest Physicians:**
  - Use specific reversal agents where available, rather than nonspecific agents.

Antiplatelet agents

- Most common agents in the US are aspirin and clopidogrel (Plavix).
- These are platelet inhibitors. They circulate and BLOCK platelet activity
  - Patients still have plenty of platelets in their bodies!
- Can platelet transfusion help?
  - Goal: Give extra platelets, hopefully override these drugs.
  - Does this work? Or are we just giving extra platelets to be blocked?
Antiplatelet agents

- PATCH trial: Randomized 190 ICH patients to platelet transfusion or not.
- Platelet transfusion led to significantly WORSE outcome!

Conclusion: Do not transfuse platelets

Is there anything to reverse in antiplatelet-ICH?

- It may be that there is no currently effective way to “reverse” antiplatelets.

- Some authors check platelet activity – this is not easy to do at many hospitals.
  - Consider platelet activation assays or TEG to guide therapy if available.

- Observational study:
  - GWTG analysis of 82,000 ICH patients, examining whether antiplatelet use was associated with outcome
    - Those on single antiplatelet - no difference in outcome compared to those on no antiplatelet.
    - Those on dual antiplatelet regimens, however, had worse outcomes.
    - Conclusion: Perhaps only those on dual antiplatelet regimens "need" reversal.

Khan NI al, Stroke 2017
Conclusions

- **Warfarin reversal**
  - IV vitamin K plus PCC

- **Dabigatran reversal**
  - Idarucizumab – specific agent
  - PCC – nonspecific agent

- **Factor Xa inhibitor reversal**
  - Andexanet – specific agent
  - PCC – nonspecific agent

- **Antiplatelet reversal**
  - No current clear “reversal” agent
Question
Thank You