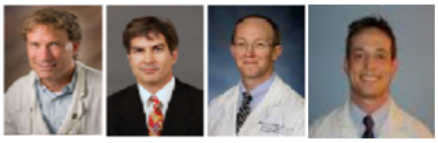
critical care perspectives in emergency medicine



Anticoagulation Reversal in ICH

Key Article

Kuramatsu JB, et al. Reversal of oral anticoagulation in patients with acute intracerebral hemorrhage. Crit Care. 2019; 23:206.

Background

- ICH accounts for approximately 15% of strokes
- Mortality can reach upwards of 50% at 1-year following ICH; many are left with significant functional deficits and dependency
- Overall incidence of ICH is increasing
- Oral anticoagulation (OAC) associated ICH is also increasing in frequency
    - Patients with OAC-ICH tend to have larger ICH volumes, more frequent IVH, and have a greater frequency of hematoma expansion
    - Patients have an even worse prognosis that those not taking an OAC

Vitamin-K Antagonists

- Though there is an increase in bleeding complications when INR is > 4, ICH can occur at any INR level
- *Kuramatsu JB, et al. JAMA. 2015; 313:824-36.*
    - VKA-associated ICH cohort of 1,176 patients across 19 centers in Germany
    - Mean INR level was 2.8 (interquartile range 2.3 to 3.5)
    - Results demonstrated that an INR target < 1.3 was necessary to reduce the risk of hematoma expansion (27% vs. 45% for INR > 1.3)
    - Association was stronger the earlier achieved (expansion 20% if INR < 1.3 achieved in 4 hours vs. 42% for > 4 hours)
- Treatment – Vitamin K, PCC, FFP?
    - *Sarode R, et al. Circulation. 2013;128:1234-43.*
        - Randomized phase IIIb, multicenter, open-label, non-inferiority trial
        - 202 patients with VKA-associated ICH
        - Coagulation more rapidly reversed with Vit K + 4-factor PCC in a staggered dosing regiment compared to FFP
            - INR 2-4; 25 U/kg, max 2500 units
            - INR 4-6; 35 U/kg, max 3500 units
            - INR > 6; 50 U/kg, max 5000 units
        - INR < 1.3 achieved by PCC + Vit K 62.2% vs. 9.6% with FFP
    - *Steiner T, et al. Lancet Neurol. 2016;15:566-73.*
        - Randomized controlled trial
        - VKA-associated ICH and INRs > 2 on admission

        - Compared 4-factor PCC + Vit K to FFP + Vit K
        - A larger portion of PCC-treated patients reached target INR < 1.2 after 3 hours than FFP-treated patients (67% vs. 9%)
        - At 24 hrs, those treated with FFP had a greater increase in ICH volume and 5x risk for hematoma expansion
    - *Scott R, et al. J Emerg Med. 2018;54:861-866.*
        - Evaluated fixed-dose 4-factor PCC for emergent reversal of warfarin in ICH patients
        - Resulted in standardized dosing, improved time to administration, and decreased cost
    - At Maryland, UMMC has moved to fixed-dose strategy for all warfarin-associated critical bleeding
        - ICH OR INR > 6 OR > 100 kg = 2000 units of 4-factor PCC

- **Recommendations for VKA-associated ICH**
    - **Target complete reversal to INR < 1.3 as soon as possible**
    - **Administer Vitamin K – 10 mg administered via slow IV infusion**
    - **4-factor PCCs recommended over FFP**
    - **Consider fixed-dosing strategy for 4-factor PCCs over weight-based/INR dosing strategy**

Direct Oral Anticoagulants

- Factor Xa-inhibitors (apixaban, rivaroxaban, edoxaban) and direct thrombin-inhibitor (dabigatran)
- Similar pharmacokinetic properties; elimination half-life ranges from 6 to 17 hours
- Oral anticoagulant activity cannot be timely or validly excluded by routine diagnostic test – conventional coagulation assays do not provide sufficient sensitivity or specificity;
- No data is available to define a threshold below which one can exclude a DOAC effect.
    - Thrombin time, PT, and aPTT could provide a rough estimate
    - If available, consider dilute thrombin time or ecarin clotting time
- Timing of last dose is important – activated charcoal can be considered if within 4 hours of ingestion
- Currently no evidence regarding effectiveness of reversal agents on hematoma expansion rates or clinical endpoints in DOAC-associated ICH

- *Ciraparantag*
    - Designed to reverse anticoagulant effect of heparinoids, direct thrombin, and factor-Xa inhibitors
    - Only phase II trials at present
    - Rapid onset of activity, single dose, long duration of effect
    - Not currently FDA approved

- *Idarucizumab for Dabigatran-associated ICH*

- FDA approved in 2015
- A humanized monoclonal antibody fragment that is a non-competitive inhibitor and binds to dabigatran with high affinity
- Renally excreted
- Administered in 2 IV boluses within 15 min
- *Pollack CV, et al. N Engl J Med. 2017;377:431-41.*
    - REVERSE-AD trial
    - 503 patients divided into uncontrolled hemorrhage and those needing urgent procedure
    - Nearly 100% maximum percentage reversal within 4 hours of administration
    - 98 patients with ICH
        - Repeat imaging not mandated so could not comment on hematoma expansion rates
    - Thrombotic rate for patients with ICH was 6%
    - Findings of this trial suggest that idarucizumab provides rapid, sufficient, and sustained reversal of anticoagulation for patients taking dabigatran

- *Andexanet alfa for Factor-Xa-inhibitor-associated ICH*
    - FDA approved in 2018
    - Acts as a human decoy receptor binding to the active site of factor-Xa inhibitors with high affinity without catalytic activity
    - Theoretically restores factor-Xa activity and attenuates anticoagulation effect
    - *Siegal DM, et al. N Engl J Med. 2015;373:2413-24.*
        - Phase 3 trial in healthy, older volunteers comparing different dosing regimens
        - Results demonstrated over 90% of anti-Xa activity was reduced
        - Significant rebound effect after end of infusion
    - Phase 4 study ongoing
    - Many concerns have been raised regarding this drug
        - Hemostatic rebound
        - Need for continuous infusion
        - Reported prothrombotic complications (up to 10% in some studies)
        - Significant cost!
        - Data on hematoma expansion rates and clinical outcomes in ICH patients not available

- *PCC for Factor-Xa-inhibitor-associated ICH*
    - PCCs may have the potential to reverse anticoagulation induced by factor-Xa inhibitors
    - Most of the current data evaluates 4-factor PCCs, 3-factor PCCs, and FEIBA (activated PCC) for rivaroxaban or edoxaban
    - Direct comparisons between 4-factor PCCs and FEIBA are not available
    - *Zahir H, et al. Circulation. 2015; 131:82-90.*

        - Largest randomized trial
        - 110 healthy patients treated with edoxaban (single dose)
        - Compared dosing regimens of 4-factor PCC
        - A dose of 50 U/kg influenced bleeding endpoints
    - Thrombotic rate appears low (approx. 4%)
    - Available data suggests that 4-factor PCC at 50 U/kg be considered for factor-Xa-inhibitor-associated ICH

- *Other Agents*
    - *Tranexamic Acid*
        - Clinical data on associations of TXA in OAC-associated ICH not available
        - Current trial examining effect of TXA on DOAC-associated ICH enrolling patients
        - No recommendation can be made
    - Recombinant FVIIa
        - Not currently recommended

- **Recommendations for DOAC-associated ICH**
    - **Consider charcoal if last intake < 4 hours**
    - **Consider idarucizumab in two divided doses 15 min apart for dabigatran-associated ICH**
    - **Consider 4-factor PCC or activated PCC at 50 U/kg for factor-Xa-associated ICH**
    - **More data needed on andexanet alfa**