EMERGENCY MEDICINE CASES

EPISODE 37: ANTICOAGULANTS, TRANSFUSIONS & BLEEDING (PART 2) WITH DR. HIMMEL, DR. CALLUM & DR. PAVENSKI

Summary of New Oral Anticoagulants

Direct Thrombin (IIa) Inhibitor:
- Dabigitran (Pradax)

Factor Xa inhibitors:
- Rivaroxaban (Xarelto)
- Apixaben (Eliquis)

Advantages:
- Oral (vs. LMWH)
- No monitoring of INR
- Fast onset (within hours)
- Standard dose (no weight adjustment)
- Minimal drug/dietary interaction

Disadvantages:
- Expensive
- No antidote (i.e Vit K, PCC, plasma with warfarin)
- No means to determine compliance, anticoagulation effect
- Renal failure prolongs half life (with CrCl <15-30 newer anticoagulants are contraindicated –guidelines vary with each drug)

Compliance:
New oral anticoagulants have short half life (~12 hours), therefore, if miss 2-3 doses, treat as uncoagulated patient.

INR tends to be increased with Rivaroxaban/Apixaban, PTT tends to be increased with Dabigitran. Therefore, INR/PTT may give a clue to compliance.

Indications:
Atrial fibrillation; DVT/PE
**NOT mechanical heart valve

Newer Anticoagulants in DVT/PE:

Newer anticoagulants are equivalent in preventing recurrent DVT and/or PE when compared to warfarin with LMWH bridge[1,2].

Factors to consider when deciding to use a newer anticoagulant in DVT/PE:

- Renal failure (contraindication to new anticoagulants)
- Dehydration & acute renal failure increases half life of new anticoagulants (exp Dabigitran & Rivaroxiban)
- Liver impairment (new anticoagulants partailly hepatically cleared)
- Pregnancy (new anticoagulants contraindicated)
- Absoloute contraindication: mechanical heart valve

Starting Newer Anticoagulants in the ED for DVT

- Rivaroxaban (approval in Canada):
  - 15 mg po bid x 3 week
  - Then step down dose
- Apixaben:
  - 10 mg po bid x 7 days
  - Then step down dose
- Important to ***emphasize compliance***! These medications have a short half life, therefore, missing 2-3 doses could mean becoming uncoagulated and at higher risk of thromboembolism.

Managing Life Threatening Bleeds in the Anticoagulated Patient

Warfarin Reversal in Major Life Threatening Bleeds

Vitamin K: 10 mg IV over 30 minutes (starts to work in 2-3 hours, INR reversed within 24 hrs with adequate production of coagulation factors). Administer in 50 cc of Normal Saline over 30 min.

Plasma (FFP): 4-6 units typically required, large volume, need time for thawing, ABO compatibility, risks of transfusion – infection, TRALI, TACO, etc.)

Prothrombin Complex Concentrate (PCC, e.g. Octaplex, Beriplex – 4 factor PCC in Canada, with factors 2,7,9,10)

- Works almost immediately
- Factor 7 has short half life, so, PCC stops working effectively after 4-8hrs. Thus, ***vitamin K must be given with PCC.***
- Contraindicated in HIT, liver disease, recent thrombosis, MI, ischemic stroke, DIC
- Check INR immediately (within 15 min) and in 6 hrs

Dosing PCC

- Dosing may be INR or weight based. Check product monographs or institutional guidelines.
- Current Canadian recommendations:
  - INR<3: 1000 U PCC+Vit K
  - INR3-5: 2000 U PCC+Vit K
  - INR>5: 3000 U PCC+Vit K
- Dose may vary with extremes of weight
- Mix powder with provided solvent and administer as per manufacturer's monograph (slow push or minibag) or institutional guidelines.

What to do when there is a high clinical suspicion of intracranial bleed, with a suggestive history, and patient on warfarin while waiting coagulation studies and imaging?

In select scenarios where there is high likelihood of intracranial bleed based on history and physical exam, and delay to bloodwork/imaging, our experts have used 1000 units of PCC while waiting for these results.

What is the Risk of Thrombosis with PCC vs. Plasma?

Unclear. There may be a small increased risk of thrombosis in patients receiving PCC.

Use of Recombinant Factor VIIa (rFVIIa) in Bleeding Patients

No benefit from using rFVIIa in bleeding patients, and clear harm (increased risk of thromboembolic events) in prophylactic or therapeutic use. Might be beneficial in a bleeding hemophiliac patient who has developed inhibitors.

Reversing INR in Preparation for OR in Non-bleeding Patients

IV Vitamin K usually required as PO Vitamin K will take 1-2 days to work.

Bleeding with New Oral Anticoagulants

Bleeding Risk with Newer Anticoagulants

Dabigitran/Rivaroxaban: overall bleeding risk approximately equal to warfarin. Increased risk of GI bleed, but decreased risk of intracranial bleed.

Apixaban: less major and clinically significant non-major bleeding vs. warfarin in one study.

Reversal Strategies[3]

- Supportive management, hydration, local control.
- Ongoing life threatening bleed, PCC, APCC (FEIBA), rFVIIa may be considered. No human studies available..
- Case reports: PCC may be helpful if no alternative and patient declining: 40-50 units/kg. Then monitor 30 minutes. If no improvement and continued bleed, try FEIBA (50-80 units/kg). rFVIIa as last resort.
- Dabigitran:
  - Dialysis may be helpful: less drug bound to protein
  - No change in laboratory abnormalities with PCC (vs. change with Rivaroxaban)

Risk of Anaphylaxis with IV Vitamin K

Anaphylaxis risk with IV Vitamin K is approximately 3/10,000

Anaphylactoid reactions are more common. To prevent, give slowly. For example, to give 10mg of Vitamin K, put in 50cc of Normal Saline, and give at a rate < 1 mg/min (i.e. over 30 minutes is appropriate).

Managing Thrombocytopenia

DDx: ITP, TTP, bone marrow failure, myelodysplastic syndrome…

TTP: most life threatening condition. Diagnosis should be entertained in all patients with low plts and low Hb. If fragments or shistocytes on blood film and elevated LDH assume TTP. These patients need transfer to a facility where plasmapheresis is available. Consider starting FFP infusion while awaiting transfer. Once patient develops classic pentad, often too late.

When and How to Transfuse Platelets

Transfuse if platelet count < 10, as increased risk of spontaneous ICH. Consider transfusion if known coagulopathy, sepsis or high fever and platelet count < 20.

Transfuse ***1 pool*** of platelets (equivalent to 4 units of platelets in older terminology) over 1 hour.

Measure platelet count after transfusion (15-60 min post transfusion). Expect increase in platelet count of 20-40. Variability due to how brisk the bleed, how quickly platelets are consumed.

Group & Screen for Platelets

Platelets should ideally be ABO identical.

Very few RBCs in platelets, however, enough to cause alloimmunization. Therefore, Rh neg females with child bearing potential should receive Rh neg platelets. If such a patient receives Rh pos platelets, consider giving Rh immunoglobulin.

Risks of Platelet Transfusion

- Sepsis 1/10,000
- Death from sepsis 1/60,000
- TRALI/TACO (see part 1)

Thrombocytopenia in Patients Requiring Invasive Procedures

Dependent on skill level. General guidelines recommend platelet counts as follows for common ED procedures:

- Central line: plt count > 20-25
- LP: plt count >50-100
- Paracentesis/Thoracentesis >10

Thrombocytopenia and Platelet Transfusions in Special Circumstances:

- ITP: Life Threatening Bleed:
  - Corticosteroids, IVIG, platelets transfusions
  - 40-60% of patients with ITP will respond to platelets
- ITP: Non-bleeding Patients:
  - No platelet transfusion
- HIT/TTP:
  - Reserve platelet transfusions for life threatening bleeding, as increased thrombotic risk

Bleeding in Patients on Antiplatelet Agents

No prospective studies. In life threatening bleed, consider 1 pool of platelets. If worsening clinically or progression of bleed, consider 2nd pool of platelets.

DDAVP may counteract ASA and clopidogrel effect. No studies have evaluated effectiveness of this.

Tranexamic Acid

Effective in reducing bleeding in heavy menstrual bleeding,; consder in intracranial hemorrhage, oral bleeding, epistaxis and major trauma.

oral dosing: 1g tid x 4-5 days

In oral bleeding consider using 5% tranexamic acid dissolved in tap water and swishing in mouth for 2 minutes then spitting out. Repeat if necessary.

Thrombosis Risk with Tranexamic Acid

No increased risk of thrombosis in cardiac and non-cardiac surgery. CRASH-2[4] study – trend toward ***decreased*** thrombotic events if given within 3 hours.

IV dosing 1g over 10 min then 1 g over 8 h

References:

1. Prins et al. 2013. Thromb J: 11: 21.
2. Agnelli et al. 2013. NJEM: 369; 799-808.
3. Heidbuchel et al. 2013. Europace:15; 625-51.
4. CRASH-2 Investigators. 2010. Lancet: 376; 23-32.
5. Kuwashiro et al. 2011. Cerebrovascular Diseases: 31; 170-176.

Division of Emergency Medicine
UNIVERSITY OF TORONTO