Current Thoughts on Anticoagulants and Regional Anesthesia

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Once the world was young...

- Smoking was cool.
- Families ate dinner together and it was safe to play outside after dark.
- Walter Cronkite brought you the evening news.
- Only two countries had nuclear weapons & there were only two anticoagulants to worry about:
  - Heparin
  - Coumadin
Goal: Reduce Perioperative Venous Thromboembolism

The stress response to surgery or trauma leads to increased secretion of:

- Cortisol
- ADH
- Renin
- Catecholamines
- Endorphins

Resulting in:

- Hyperglycemia
- Negative nitrogen balance
- Hypercoagulable state

Reduced postoperative mobility, hypercoagulability, and a variety of other variables increase the risk of postoperative venous thromboembolism (VTE).
VTE Risk Factors

- Trauma
- Surgery
- Immobility
- Cancer
- Venous compression
- Previous VTE
- Pregnancy

- Increasing age
- Acute medical illness
- Obesity
- Estrogen-containing oral contraceptives
- Inflammatory bowel disease
Qualifying Risk Groups

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor surgery in mobile patients</td>
<td>Most general, open gynecologic or urologic surgery patients</td>
<td>Hip or knee arthroplasty</td>
</tr>
<tr>
<td>Fully mobile medical patients</td>
<td>Sick medical patients on bed rest</td>
<td>Major trauma, spinal cord injury</td>
</tr>
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## Quantifying Risk for Thromboprophylaxis [TPP]

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Approximate Risk without TPP</th>
<th>Suggested TPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>&lt; 10%</td>
<td>No specific TPP recommendations, early aggressive ambulation</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>10-40%</td>
<td>LMW Heparin, low dose unfractionated heparin</td>
</tr>
<tr>
<td>High Risk</td>
<td>40-80%</td>
<td>LMW Heparin, fondaparinux, warfarin, and/or mechanical TPP</td>
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</tbody>
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Other Disease Related Considerations

- Patients with occlusive vascular disease may be taking anti-platelet drugs.
- Patient with recent myocardial events or acute thrombosis may be receiving fibrinolytic agents.
- Patients with a history of heparin induced thrombocytopenia could be receiving direct thrombin inhibitors.
Brief Review of Coagulation

- Blood Vessels
- Platelets
- Coagulation Cascade
- Limiting Coagulation
Primary Coagulation: Step 1

- Vessels constrict in response to injury
- Tissue Factor (TF) is exposed to blood
- TF + FVII
- fVIIa activates FX
- fXa generates thrombin
- Thrombin activates platelets

Primary Coagulation: Step 2 Platelets

- Activation
- Shape Change
- Mediator Release
- Aggregation
- Appearance of phospholipid binding sites
### Platelet Stored Mediators Released

<table>
<thead>
<tr>
<th>Physiologic Agonists</th>
<th>Alpha Granules</th>
<th>Dense Granules</th>
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<tbody>
<tr>
<td>Epinephrine</td>
<td>vWF</td>
<td>ATP</td>
</tr>
<tr>
<td>ADP</td>
<td>Fibrinogen</td>
<td>Serotonin</td>
</tr>
<tr>
<td>Thrombin</td>
<td>Fibronectin</td>
<td>Histamine</td>
</tr>
<tr>
<td></td>
<td>Thrombospondin</td>
<td>Calcium</td>
</tr>
<tr>
<td>PDGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FV, FXI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAI</td>
<td></td>
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</tbody>
</table>
Propagation of Coagulation: Key Role for Platelets

- Adhere to the sub-endothelium/vWF complex via glycoprotein Ib receptors.
- Provide sites for interaction and orientation of others pro-coagulants.
- Glycoprotein IIb/IIIa receptors link activated platelets & concentrate fibrinogen.
- Platelet derived FXIII cross-links fibrin monomers.
Finis: Fibrinogen Polymerization

RBCs: Red
Fibrin fibers: Blue
Platelet aggregates: Purple

Control of Coagulation & Limiting the Spread: Step 3

Intact endothelium releases:
- Nitric oxide
- Prostacyclin
- Ecto-ADPase
- Endothelium derived tissue factor pathway inhibitor
- Heparan sulfate (catalyses anti-thrombin)
Control of Coagulation: Limiting Downstream Activity

- Activated pro-coagulants are diluted downstream.
- Thrombomodulin binds to thrombin & catalyzes the activity of proteins C & S.
- Absence of activated platelets limits pro-coagulant interaction.
- Activated clotting factors are preferentially cleared by the liver.
- Continuous release of fXa, thrombin, & fibrin activates the fibrinolytic system.
Drugs Affecting Coagulation

- Fibrinolytics and Thrombolytics
- Unfractionated Heparin
- Low Molecular Weight Heparin
- FXa Inhibitors
- Oral Anticoagulants

- Antiplatelet Drugs
  - NSAIDS
  - Thienopyridine derivatives
  - GP IIb/IIIa inhibitors
  - P2Y$_{12}$ Inhibitors

- Thrombin Inhibitors
- Herbal Medications
Fibrinolytic and Thrombolytic Pharmacology

- Act as exogenous plasminogen activators.
- Plasmin dissolves clots, proteins, and several coagulation factors.
- Clot lysis leads to elevations of fibrin degradation products which inhibit platelet aggregation.
- These drugs generally have short half lives (hrs) but thrombolytic effects last for days.
Thrombolytics & Fibrinolytics

- Streptokinase (Streptase)
- Tenecteplase (TNKase)
- Urokinase (Kinlytic)
- Reteplase (Retavase)
- Alteplase (Activase) tissue type plasminogen activator
Fibrinolytics, Thrombolytics and Regional Anesthesia

- Thrombolytic therapy poses a significant risk of spontaneous spinal or epidural hematoma.
- Generally not candidates for regional anesthesia.
- No recommendations for neuraxial catheter removal (perhaps monitoring fibrinogen levels)
- Limit sensory and motor block during infusions.
- Neuro checks at least every two hours.
IV & SQ Unfractionated Heparin Pharmacology

- Binds to antithrombin increasing it’s ability to inhibit thrombin (fIIa > fXa).
- Effects are dose dependent and effects increase disproportionately with increasing doses.
- Half life is 60-90 minutes and effects are easily reversed with protamine (1mg:100 units heparin).
- Effects can be monitored with measurement of aPTT, or activated clotting time (larger doses).
Unfractionated Heparin & Regional Anesthesia

- Twice daily dosing 5000 SQ is not a contraindication for regional anesthesia, there is significant uncertainty regarding thrice daily dosing*. 

- Be aware of the risk of HIT (check platelet count after 4th day of treatment).

- Intra-operative anticoagulation 1 hour after block placement is generally safe.

- Remove catheter 2-4 hours after last dose, 1 hour prior to next dose.
Low Molecular Weight Heparin Pharmacology

- The smallest of the heparin molecules.
- Effects $f_{Xa}>f_{IIa}$.
- Half lives are 3-5 times $> UFH$, significant anti $f_{Xa}$ activity present 12 hours after injection.
- Long half lives allow once or twice a day dosing.
- Effects are $\textit{not}$ reversed by protamine.
- Anti $f_{Xa}$ measures do not predict bleeding risk.
LMWH Currently Available

- Ardeparin (Normiflo)
- Enoxaparin (Lovenox & Clexane)
- Dalteparin (Fragmin)
- Certoparin (Sandoparin)
- Parnaparin (Fluxum)
- Tinzaparin (Innohep & Logiparin)
- Reviparin (Clivarin)
- Nadroparin (Fraxiparin)
Pre-operative LMWH & Regional Anesthesia

- Presume that patients on preoperative LMWH have altered coagulation

- Needle placement should occur > 10-12 hours after most recent dose.

- For patients on high doses, needle placement should occur 24 hrs after most recent dose.

- Peak anti-coagulant activity occurs 2-3 hours after administration.
Post-operative LMWH and Regional Anesthesia

**Twice Daily Dosing**
- Associated with increased risk of spinal hematoma, first dose should occur 24 hours post op.
- Epidural catheters should be removed two hours prior to the first dose of LMWH.

**Single Daily Dosing**
- First dose may be administered 6-8 hours post op. second dose 24 hours after the first.
- Epidural catheters can be maintained but should be removed 10-12 hours after most recent dose, at least 2 hours prior to subsequent dose.
Fondaparinux, Rivaroxaban, Idrabiotaparinunx, Apixaban: fXa Inhibitors

- Synthetic pentasaccharides with extended plasma ½ lives (F 21 hrs, I 135 hrs, R 5-9 hrs, A 10-15 hrs)

- Allows single-daily dosing.

- Antithrombotic effect is sustained and irreversible.

- Neuraxial techniques should be avoided in patients receiving these agents.
Oral Anticoagulants (Warfarin) Pharmacology

- Interferes with the synthesis of vitamin K dependent clotting factors.
- Factor activity of 40% allows for normal hemostatic function.
- INR is prolonged to 1.2 when factor VII 55% of baseline, 1.4 when at 40%.
- Effects are reversible with vitamin K or FFP administration.

<table>
<thead>
<tr>
<th>Factor</th>
<th>½ Life (hrs)</th>
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<tbody>
<tr>
<td>Factor VII</td>
<td>6-8</td>
</tr>
<tr>
<td>Factor IX</td>
<td>24</td>
</tr>
<tr>
<td>Factor X</td>
<td>25-60</td>
</tr>
<tr>
<td>Factor II</td>
<td>50-80</td>
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</tbody>
</table>
Oral Anticoagulants & Regional Anesthesia I

- For patients on long term warfarin therapy, discontinue warfarin 4-5 days early and allow INR to normalize.

- Patients should receive the first dose of warfarin < 24 hrs prior to block placement.

- Check INR if > 24 hrs or if a second dose has been given.

- Monitor patient’s INR daily if there is an indwelling epidural catheter.
Monitor and document sensory and motor function at regular intervals when patients with indwelling epidural catheters are receiving warfarin.

Epidural catheters should be removed when the INR is less than 1.5.

Continue neurologic assessment for 24 hours after removing the catheter.
# Antiplatelet Medication Pharmacology

<table>
<thead>
<tr>
<th>N.S.A.I.D.s</th>
<th>Thienopyridine Derivatives</th>
<th>GP IIb/IIIa Receptor Antagonists</th>
<th>P2Y&lt;sub&gt;12&lt;/sub&gt; Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Ticlopidine (Ticlid)</td>
<td>Abciximab (Reopro)</td>
<td>Ticagrelor (Brilinta)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Clopidogrel (Plavix)</td>
<td>Eptifibatide (Integrilin)</td>
<td>Prasugrel (Efient)</td>
</tr>
<tr>
<td>Naproxen</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Piroxicam</td>
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Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Inhibit platelet cyclooxygenase-1 and prevent synthesis of thromboxane A2.
- Patients receiving these drugs have normal platelet adherence and normal primary hemostatic plug formation.
- Platelet function is affected for the life of the platelet after aspirin, others have effects that normalize within 3 days.
NSAIDs and Regional Anesthesia

- No added risk of spinal or epidural hematoma.

- The concurrent use of other medications affecting coagulation increases the risk of bleeding complications.

- No specific timing interval or monitoring recommendations.
Thienopyridine Derivative Pharmacology

- Inhibition of ADP induced 1° & 2° platelet aggregation
  - Platelet to platelet binding
  - Platelet fibrinogen binding
- Effects are time and dose dependent
- Residual effects may be assessed by use of platelet function assays*:
  - Light Transmission Platelet Aggregometry
  - mTEG

*Anesthesiology, V 105, No 4, Oct 2006. 676-683
The risk of spontaneous spinal and epidural hematoma with these drugs is high, particularly if co-administered with other drugs affecting coagulation.

ACCP recommends discontinuation of:
- Clopidogrel at least 7 days
- Ticlopidine at least 10-14 days prior to surgery and regional blockade
GP IIb/IIIa Receptor Antagonist Pharmacology

- Interfere with:
  - Platelet-fibrinogen binding
  - Platelet-vWF binding
  - Block the final common pathway for platelet aggregation

- Platelet function returns to baseline after:
  - 8 hours for
    - Eptifibatide
    - Tirofiban
  - 24-48 hours for abciximab
GP IIb/IIIa Receptor Antagonists & Regional Anesthesia

- Neuraxial techniques should be avoided until platelet function has recovered.

- Platelet function returns to baseline after:
  - 8 hours for Eptifibatide and Tirofiban
  - 24-48 hours for Abciximab
**P2Y$_{12}$ Inhibitors**

- Act at the P2Y$_{12}$ ADP receptor to prevent signal transduction and platelet activation

- Onset is within 1 hour of a PO dose, effects last approximately 5 days.

- Indicated for treatment of acute coronary syndrome, unstable angina, non STEMI, and STEMI.
P2Y$_{12}$ Inhibitors & Regional Anesthesia

- Avoid neuraxial anesthesia techniques for 5 days after last dose (ticagrelor) and 7-10 days (prasugrel).

- May begin ticagrelor or prasugrel PO 6 hours after discontinuing epidural catheters.
Direct Thrombin Inhibitor Pharmacology

- Indicated for prevention and treatment of thrombosis in patients with HIT.

- Anticoagulant effects can be monitored by aPTT.

- Clinical effects present for 1-3 hours after IV administration.

- There is no pharmacologic reversal agent for these drugs.

- Hirudin derivatives
  - Desirudin (Revasc)
  - Lepirudin (Refludan)
  - Bivalirudin (Angiomax)

- L-Arginine derivatives
  - Argatroban (Acova)

- Others
  - Dabigatran (Pradaxa)
Direct Thrombin Inhibitors and Regional Anesthesia

- The performance of neuraxial techniques for patients receiving thrombin inhibitors is not recommended.
## Herbal Medications and Regional Anesthesia

<table>
<thead>
<tr>
<th>Herb</th>
<th>Important Effects</th>
<th>Perioperative Concerns</th>
<th>Normal Hemostasis in:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garlic</td>
<td>Inhibition of platelet aggregation, &amp; inc. fibrinolysis</td>
<td>↑ bleeding risk, especially in combination with other antiplatelet agents</td>
<td>7 days</td>
</tr>
<tr>
<td>Ginko</td>
<td>Inhibition of platelet activating factor</td>
<td>Ibid.</td>
<td>36 hours</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Increased PT and aPPTs in animals</td>
<td>↑ risk of bleeding, or ↓ effect of warfarin</td>
<td>24 hours</td>
</tr>
</tbody>
</table>
Current Thoughts on Anticoagulants & Regional Anesthesia

Questions?

Check out “Coagulate” at the App Store