Using an anti-Xa level nomogram to adjust intravenous unfractionated heparin infusion for arrhythmia in pregnancy

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Hospital Venous Thromboembolism Standard Continuous IV UFH Anticoagulation Protocol and Nomogram (using aPTT levels)

- CBC, INR, PTT before heparin loading dose.
- Loading Dose: ________ (loading dose = 80 units/kg, maximum 5000 units)
- Heparin ________ units IV given in 50 mL NS over 30 minutes or given undiluted by IV push.
- Initial infusion: ________ (initial rate = 18 units/kg/hour up to 1300 units/hour)
- Initial rate at ________ units/hours = ________ mL/hour
- ** Heparin Concentration 25,000 units in 250 mL D5W (100 units/mL)**
- Draw PTT 6 hours after heparin loading dose.
- Adjust heparin dose and repeat PTT according to the table below.
# IV UFH Anticoagulation Protocol and Nomogram using aPTT levels

<table>
<thead>
<tr>
<th>PTT (in seconds)</th>
<th>Heparin Bolus dose (units)</th>
<th>Hold infusion (minutes)</th>
<th>Infusion Rate Change</th>
<th>Repeat PTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 50</td>
<td>5000</td>
<td>0</td>
<td>Increase by 2 mL (200 units)/hour</td>
<td>6 hours</td>
</tr>
<tr>
<td>50-74</td>
<td>0</td>
<td>0</td>
<td>Increase by 1 mL (100 units)/hour</td>
<td>6 hours</td>
</tr>
<tr>
<td>75-105</td>
<td>0</td>
<td>0</td>
<td>No change</td>
<td>Next am</td>
</tr>
<tr>
<td>106-135</td>
<td>0</td>
<td>60</td>
<td>Decrease by 1 mL (100 units)/hour</td>
<td>6 hours</td>
</tr>
<tr>
<td>Greater than 135</td>
<td>0</td>
<td>60</td>
<td>Decrease by 2 mL (200 units)/hour</td>
<td>6 hours</td>
</tr>
</tbody>
</table>
Problems with aPTT to monitor unfractionated heparin

- Issues:
  - Poor correlation with blood heparin concentration, varying response to aPTT reagents, aPTT’s responsiveness to other acute-phase reactants or other factors independent of heparin*
  - Subtherapeutic aPTT despite high doses of heparin**

- ACCP 2012 … reasonable to use anti-Xa levels in patients with VTE who require large doses of heparin***

**Levine M et al, Arch Intern Med 1994; 154:49-56
***Chest 2012;141(2):24S-43S
aPTT response in pregnancy is blunted

Coagulation factors change in pregnancy
- Fibrinogen, factors II, VII, VIII, X, XII, XIII – increase 20-200 %
- Thrombin activatable fibrinolytic inhibitor (TAFI), PAI-1, PAI-2 - increase

Result in aPTT
- aPTT has an attenuated response to heparin in pregnancy, therefore leading to the risk of incorrect heparin dosage
Coagulation Factor changes in pregnancy affecting the aPTT Pathway

Elements of haemostasis tested by the APTT

Fibrinolysis

http://www.practical-haemostasis.com
Re-write Heparin Infusion Nomogram using anti-Xa level in Pregnancy

- Concern, e.g. for the same blood sample, aPTT can be lower than therapeutic range whereas anti-Xa level is at target
Using anti-Xa level to adjust iv unfractionated heparin in pregnancy

- CBC, INR, PTT, anti-Xa level before heparin loading dose.
- Loading dose: Consider heparin 5000 units (U) IV given in 50 mL NS over 30 minutes or given undiluted by IV push. (80 U/kg, maximum 5000 units)
- Initial infusion: 18 U/kg/h up to a maximum of 1300 U/h. Heparin concentration 25,000 U in 250 mL D5W (100 U/mL).
- Anti-Xa level 6 hours after heparin loading dose or heparin infusion.
- Adjust heparin dose and repeat anti-Xa level according to the table below.
- Stop IV heparin 6 hours prior to predicted time of delivery.

<table>
<thead>
<tr>
<th>Anti-Xa level (U/mL)</th>
<th>Heparin bolus dose (U)</th>
<th>Hold infusion (minutes)</th>
<th>Infusion rate change</th>
<th>Repeat anti-Xa level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.20</td>
<td>5000</td>
<td>0</td>
<td>Increase by 2 mL (200 U)/h</td>
<td>6 hours</td>
</tr>
<tr>
<td>0.20-0.34</td>
<td>0</td>
<td>0</td>
<td>Increase by 1 mL (100 U)/h</td>
<td>6 hours</td>
</tr>
<tr>
<td>0.35-0.7</td>
<td>0</td>
<td>0</td>
<td>No change</td>
<td>Next am</td>
</tr>
<tr>
<td>0.71-0.85</td>
<td>0</td>
<td>60</td>
<td>Decrease by 1 mL (100 U)/h</td>
<td>6 hours</td>
</tr>
<tr>
<td>&gt;0.85</td>
<td>0</td>
<td>60</td>
<td>Decrease by 2 mL (200 U)/h</td>
<td>6 hours</td>
</tr>
</tbody>
</table>
Case

- G2P0 patient with complex congenital cardiac disease:
  - repaired cleft mitral valve for mitral stenosis and regurgitation
  - coronary artery bypass surgery for anomalous LAD
  - previous myocardial infarction
  - history of paroxysmal atrial fibrillation with ischemic stroke
- On lifelong anticoagulation.
Case...peri-delivery plan

• In her second trimester, recurrent episodes of rapid atrial fibrillation requiring electrical and chemical cardioversion

• Due to her high thromboembolic risk, and anticipating a potentially a long labor in a nulliparous woman, IV UFH was used to bridge before her planned induction of labor.
<table>
<thead>
<tr>
<th>Day/Time</th>
<th>aPTT (seconds, therapeutic 75-105)</th>
<th>Anti-Xa level (therapeutic 0.35-0.7)</th>
<th>Rate of heparin infusion (U/h)</th>
<th>Action based on aPTT nomogram</th>
<th>Action based on Anti-Xa nomogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 @ 10:30 h</td>
<td>32</td>
<td>0.46</td>
<td>N/A</td>
<td>Bolus 5000 units, then start infusion rate at 1300 U/h</td>
<td>Start IV UFH infusion at 1300 U/h</td>
</tr>
<tr>
<td>Day 1 @ 1810h</td>
<td>65</td>
<td>0.74</td>
<td>1300</td>
<td>Infusion rate increased by 100 U/h, aPTT level repeated in 6h</td>
<td>Infusion held for 60 min, then infusion rate decreased by 100 U/h, anti-Xa level repeated in 6h</td>
</tr>
<tr>
<td>Day 2 @ 0235 h</td>
<td>67</td>
<td>0.63</td>
<td>1200</td>
<td>Infusion rate increased by 100 U/h, aPTT repeated in 6h</td>
<td>No change</td>
</tr>
<tr>
<td>Day 2 @ 0750h</td>
<td>78</td>
<td>0.76</td>
<td>1200</td>
<td>No change, aPTT repeated next morning</td>
<td>Infusion held for 60 min, then infusion rate decreased by 100 U/h, anti-Xa level repeated in 6h</td>
</tr>
</tbody>
</table>

*Last dose of the enoxaparin was at 2000 h the day prior to induction*
Heparin Dose required to maintain therapeutic level

![Graph showing aPTT and Anti-Xa levels over days 1 to 4.](graph.png)
Patient went into active labor, hence heparin infusion was stopped.
aPTT was obtained 4 hours after and was at 36 and anti-Xa level 0.27. Epidural was given for normal aPTT,
Patient delivered vaginally
No postpartum hemorrhage
Case.....postpartum

- Postpartum, she was given LMWH prophylaxis about 12 hours postpartum, then increased to therapeutic LMWH 12 hours after.
- Usually we bridge to warfarin about 1 week postpartum (or 2 weeks post c-section).
Conclusion

• Use of anti-Xa level to guide UFH infusion in pregnancy to be feasible and reliable
• While similar nomograms have been published in the non-pregnant literature, none are currently available in pregnancy
• Due to the pitfalls of using aPTT in pregnancy, anti-Xa levels should be considered to be used to guide UFH dosing in pregnancy
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