Unfractionated Heparin vs Low Molecular Weight Heparin for the Prevention and Treatment of Venous Thromboembolic Disorders

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Overview

• What is unfractionated heparin? What is low molecular weight heparin?
• What are the mechanisms of action?
• Present indications for therapy
• Why debate?
• Review literature regarding use of unfractionated heparin versus low-molecular-weight heparin
• Particular patient populations
• Conclusions
<table>
<thead>
<tr>
<th>Low-Molecular-Weight Heparin (LMWH)</th>
<th>Unfractionated Heparin (UFH)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5,000 d (2,000-9,000 d)</strong></td>
<td><strong>15,000 d (3,000-30,000 d)</strong></td>
</tr>
<tr>
<td>De-polymerization and chromatography</td>
<td>Porcine intestine or bovine lung</td>
</tr>
<tr>
<td>Anti-factor Xa/Anti-factor IIa = 4/1</td>
<td>Anti-factor Xa/Anti-factor IIa = 1/1</td>
</tr>
</tbody>
</table>

**Figure 2.** Molecular weight distributions of LMWHs and heparin.
AT III + Heparin

HC II + Heparin

Prothrombinase Complex

Prothrombin

Thrombin

Fibrinogen → Fibrin (soluble)

Fibrin (soluble) + XIII

Cross-linked Fibrin (insoluble)

Extrinsic

Intrinsic

XII + Surface contact Prekallikrein HMWK

XIIa

XI

XIIa

Xa, Ca++ PL

IXa + Ca++ PL

IX

VII + TF Ca++

IXa, Xa or XIIa

VIIa + TF Ca++

IXa + Ca++ PL

VIIa + TF Ca++
UFH is Heterogeneous

- 1/3 binds to AT III
- Higher weights molecules bind plasma proteins, macrophages, EC’s, plts (PF4) more avidly
- Increase vessel wall permeability
- Decrease vSMC proliferation
- Increase osteoclast activity
- Two routes of excretion
LMWH- More Homogeneous, but not Pure!

- Smaller molecular weights mean less of a negative charge
- Less binding to platelet, macrophages, endothelial cells, and plasma proteins
- Requires an 18 saccharide molecule, which includes a unique pentasaccharide sequence that then binds with AT and thrombin
- Variable percentage of LMWH (25-50%) have this

<table>
<thead>
<tr>
<th>Binding Target</th>
<th>Biologic Effects</th>
<th>Clinical Consequences</th>
</tr>
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<tbody>
<tr>
<td>Thrombin</td>
<td>Reduced anti-IIa to anti-factor Xa ratio</td>
<td>Unknown</td>
</tr>
<tr>
<td>Proteins</td>
<td>More predictable anticoagulant response</td>
<td>Monitoring of anticoagulant effect unnecessary</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Cleared through renal mechanism</td>
<td>Longer plasma half-life. Once-daily SC treatment effective</td>
</tr>
<tr>
<td>Platelets</td>
<td>Reduced incidence of heparin-dependent antibody</td>
<td>Reduced incidence of heparin-induced thrombocytopenia</td>
</tr>
<tr>
<td>Osteoblasts</td>
<td>Reduced activation of osteoclasts</td>
<td>Lower incidence of osteopenia</td>
</tr>
</tbody>
</table>
UFH Indications & Dosing

- Treatment
  - Thromboembolism: 80 U/kg bolus, 18 U/kg/hr
- Thromboembolic prophylaxis
  - 5000 U SQ bid
- Bridging: 12-18 U/kg/hr
LMWH- Dosing

- Varies with the particular LMWH
- Enoxaparin
  - Prophylaxis - 30 mg sq bid or 40 mg sq qd
  - Treatment & Bridging - 1 mg/kg sq bid, or 1.5 mg/kg sq qd
- Dalteparin
  - Prophylaxis - 2500-5000 U sq qd for low & high risk
  - Treatment & Bridging
    - 200 U/kg sq qd for thromboembolic indications
Monitoring - UFH

- **aPTT** - measures defects in intrinsic pathway (60-80s)
  - For therapeutic ranges 1.5-2.5x normal
- **ACT** - for heparin levels > 1U/mL (170-220s)
- Heparin level
  - Protamine titration (0.2-0.4 U/mL)
  - Chromogenic assay (0.3-0.7 U/mL)
Monitoring - LMWH

- Usually unmeasured, so unclear!
- Anti-factor Xa level varies with the particular LMWH
  - Enoxaparin (0.6-1.0 IU/mL)
  - Dalteparin (1.05 IU/mL)
Why Debate?

• UFH had been the gold standard
  – Improved or similar outcomes
  – Less cumbersome with similar or decreased cost
• Should it be replaced? No
  – Inability to accurately measure anticoagulation levels
  – Not necessarily less cumbersome or cost effective
  – Specific patient populations
Inability to Monitor

- Anti-factor Xa levels
  - Variable across different LMWH species
  - Inconsistent correlation with anticoagulation
- aPTTT
  - Highly variable due to variety of reagents, lot and volume of blood collected
  - No way of standardizing across institutions

Is there a true comparison between therapeutic UFH and LMWH?
<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>UFH doses</th>
<th>LMWH doses</th>
<th># events @ 3 mo</th>
<th>Mortality &amp; bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galilei investigators (2004)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>720</td>
<td>&lt; 50 kg, 12500. &gt;50 kg 15000</td>
<td>Nadroparin 85 U/kg bid</td>
<td>4.2% vs 3.9%</td>
<td>3.3% vs 3.3%: 1.1% vs 0.8%</td>
</tr>
<tr>
<td>Kearon et al (2006)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>708</td>
<td>333 U/kg bolus, 250 U/kg bid</td>
<td>Enoxaparin/Dalteparin 100 IU/kg q12h</td>
<td>3.8% vs 3.4%</td>
<td>5.1% vs 6.2%: 1.1% vs 1.4%</td>
</tr>
</tbody>
</table>

- Do not have to sacrifice subcutaneous route of administration to achieve similar efficacy and safety profile as LMWH
- Cost for 6 days of tx: $37 vs $712<sup>6</sup>
• Prospective multi-center double-blind randomized non-inferiority trial of 1531 patients undergoing abdominal surgery into LMWH 1750 IU sq bid (n=655) vs UFH 5000 U sq bid (n=677)

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<th>Event</th>
<th>LMWH</th>
<th>UFH</th>
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<tbody>
<tr>
<td></td>
<td>(n = 648)</td>
<td>(n = 663)</td>
</tr>
<tr>
<td>% (no.)</td>
<td>95% CI</td>
<td>% (no.)</td>
</tr>
<tr>
<td>Deep vein thrombosis (DVT)</td>
<td>4.63 (30)</td>
<td>3.15–6.54</td>
</tr>
<tr>
<td>Pulmonary emboli (PE)</td>
<td>0.15 (1)</td>
<td>0.45 (3)</td>
</tr>
<tr>
<td>DVT and PE (patients)</td>
<td>4.78 (31)</td>
<td>3.27–6.72</td>
</tr>
</tbody>
</table>
Renal Failure

- Elevated anti-factor Xa levels when Cr Cl < 30 mL/min
- Increased risk of major bleeding (5.0% vs 2.4%, p=0.013)
19 volunteers given 0.4 mL of 100 mg/mL of enoxaparin, with blood samples taken q1h x 10h

Current ACCP guidelines recommend the use of unfractionated heparin for prophylaxis of thromboembolic complications in the obese
Priglinger U et al - Prospectively administered 40 mg of enoxaparin sq qd to 28 patients (16 ICU, 13 ward) and measure anti-factor Xa activity.
Inability to reverse accurately

- Unable to assess the degree of anticoagulation with any particular LMWH
- Unable to accurately titrate in the clinical setting how much protamine sulfate to give
- Experimental evidence that LMWH are more resistant to reversal than UFH

![Graph showing % Xa Neutralization for various agents.](image)
Conclusions

• Cannot reverse accurately
• Specific patient populations
  – Renal failure, critical illness, obese
• Caution with respect the liberal use of LMWH for the treatment and prophylaxis of venous thromboembolic disorders
  – “Apples & Oranges”
References


