Anticoagulation in Acute Ischemic Stroke

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An Introduction to Heparin

What is Heparin?

- Heterogeneous collection of straight chain anionic sulfated mucopolysaccharides usually obtained from animal lung or intestine
- Potentiates activity of antithrombin III - an endogenous inhibitor of coagulation factors IIa, IXa and Xa
- Binds to platelets and plasma proteins

Heparinoids and Low Molecular Weight Heparins

Pharmacological

- Reduced anti-IIa effect, primary effect on Xa
- Reduced platelet interaction
- Reduced plasma protein binding

Clinical

- Assay activity as anti-Xa units
- Longer half-life
- Reduced bleeding

Intravenous Heparin for Partial Stable Stroke

- 225 patients with acute ischemic stroke and partial motor deficits
- Onset within 48 hours
- Exclusions:
  - Progression within 1 hour
  - Diastolic BP > 110
  - Cardiac source
Progression at 7 days

- Heparin - 19/112 (17%)
- Placebo - 22/113 (19.5%)
- \( p = 0.62 \) - 95% CI -8.7 to +13.7%
  - No difference in number improved, overall functional status or death

Late Results

- Three months
  - No difference in functional activity level
- One year
  - Higher mortality in heparin group (\( p < 0.01 \))
  - No difference in functional activity level

Source: Ann Internal Med 1986: 105:825-828
Clinical Trials of Anticoagulation in Stroke

Recently Published Clinical Trials

- International Stroke Trial (IST)
- Lancet 1997; 349: 1569-1581
- Hong Kong Nadroparin Trial (HK)
- Trial of ORG 10172 in Acute Stroke Treatment (TOAST)
- Journal of the American Medical Association 1998; 279: 1588-1593

Trial Format

<table>
<thead>
<tr>
<th></th>
<th>IST</th>
<th>HK</th>
<th>TOAST</th>
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<tbody>
<tr>
<td>Entry</td>
<td>&lt;48 hrs</td>
<td>&lt;48 hrs</td>
<td>&lt;24 hrs</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Dead/Dependent</td>
<td>Dead/Dependent</td>
<td>Good</td>
</tr>
<tr>
<td>Duration</td>
<td>6 months</td>
<td>6 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Drug</td>
<td>Heparin</td>
<td>Nadroparin</td>
<td>ORG 10172</td>
</tr>
<tr>
<td>Class</td>
<td>LMWH</td>
<td>Heparinoid</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>5000 SC BID</td>
<td>4100 SC QD</td>
<td>7200 IV/day</td>
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<tr>
<td></td>
<td>12,500 SC BID</td>
<td>4100 SC BID</td>
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</tr>
<tr>
<td>Time</td>
<td>14 days</td>
<td>10 days</td>
<td>7 days</td>
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Recurrent Ischemic Stroke

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<tbody>
<tr>
<td>Time</td>
<td>14 days</td>
<td>10 days</td>
<td>7 days</td>
</tr>
<tr>
<td>HD</td>
<td>3.2%</td>
<td>2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>LD</td>
<td>2.6%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>3.8%</td>
<td>1%</td>
<td>1.1%</td>
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Percent with Poor Outcome

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<tr>
<td>HD</td>
<td>62.6%</td>
<td>45%</td>
<td>24.8%*</td>
</tr>
<tr>
<td>LD</td>
<td>63.1%</td>
<td>52%</td>
<td></td>
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<tr>
<td>Control</td>
<td>62.9%</td>
<td>65%</td>
<td>26.3*</td>
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<tr>
<td>Results</td>
<td>Negative</td>
<td>p=.007</td>
<td>Negative</td>
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Intracranial Hemorrhage

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<tbody>
<tr>
<td>Time</td>
<td>14 days</td>
<td>10 days</td>
<td>10 days</td>
</tr>
<tr>
<td>HD</td>
<td>1.8%</td>
<td>0%</td>
<td>2.2%</td>
</tr>
<tr>
<td>LD</td>
<td>0.7%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.4%*</td>
<td>1.0%</td>
<td>0.6%</td>
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*p<.05

Major Extracranial Hemorrhage

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<tbody>
<tr>
<td>Time</td>
<td>14 days</td>
<td>10 days</td>
<td>10 days</td>
</tr>
<tr>
<td>HD</td>
<td>2%</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>LD</td>
<td>0.6%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.4%*</td>
<td>1%</td>
<td>1.6%</td>
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*p<.05 HK data for major GI hemorrhages only
Additional Studies

Fraxiparine in Ischemic Stroke Study
Death / Dependency at Six Months

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LD</th>
<th>HD</th>
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<tbody>
<tr>
<td>Number</td>
<td>250</td>
<td>272</td>
<td>245</td>
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<tr>
<td>Death</td>
<td>68</td>
<td>73</td>
<td>73</td>
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<tr>
<td>Barthel &lt;85</td>
<td>74</td>
<td>82</td>
<td>75</td>
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<tr>
<td>Combined</td>
<td>56.8%</td>
<td>57.2%</td>
<td>59.2%</td>
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Fraxiparine is the proprietary name for nadroparin


Heparin
Complications in Patients with Cerebrovascular Disease

- Symptomatic CNS hemorrhage in 1-4%
- Serious non-CNS hemorrhage in 2-3%

Sources:
Camerlingo et al: Archives of Neurology 1994; 51:462-467

Anticoagulant Treatment in Progressing Stroke
Unblinded, randomized trial of heparin (125 mg IV x 1, IM q6H x 2) then phenindione PT 2-3x control for 3 weeks. Number recovered or improved at 6 months:

- Control 19/38
- Anticoagulation 26/38 (p=.16)

Source: British Medical Journal 1961 2:70-73

Anticoagulant Therapy in Thrombosis in Evolution
Unblinded, randomized trial of heparin (50 mg IV q4h if < 1 week until dicumarol therapeutic) then dicumarol for PT 15-25%. Progression of deficit:

- 1 month - control 10/67 vs Rx 8/61
- 6 months - control 13/67 vs Rx 8/61
• 12 months - control 18/67 vs Rx 9/61


**Heparin Treatment of Progressing Stroke-I**
Prospective study of 36 patients who worsened after admission and were then treated with heparin for 7 hours to 21 days. Further progression:

- Carotid 13/19
- Vertebrobasilar 2/8
- Lacunar 2/9


**Heparin Treatment of Progressing Stroke-II**
Retrospective chart review of 69 patients:

- 27 (39%) continued to deteriorate
- 2 due to CNS hemorrhage
- 12 (17%) stabilized
- 30 (44%) improved
- 10 (14%) developed hemorrhagic side effects

Additional Studies and Conclusions

Cerebral Embolism Study Group
Un-blinded, prospective randomized study of clinically diagnosed cardio-embolic stroke within 48 hours treated with heparin for 48 hours then warfarin. Results at 14 days:

- Stroke - control 2/21 vs Rx 0/24
- Death - control 2/21 vs Rx 0/24

Source: Stroke 1983; 14:668-670-1662

International Stroke Trial
Atrial Fibrillation

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<th>Control</th>
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<tbody>
<tr>
<td>Number randomized</td>
<td>1557</td>
<td>1612</td>
</tr>
<tr>
<td>Recurrent Ischemic Stroke</td>
<td>2.8%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>2.1%</td>
<td>0.4%</td>
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<tr>
<td>Total New Stroke</td>
<td>4.9%</td>
<td>5.3%</td>
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Data for first 14 days

Source: Lancet 1997; 349:1569-1581
Trial of ORG 10172 in Acute Stroke Treatment (TOAST)

Cardioembolism

<table>
<thead>
<tr>
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<th>ORG 1072</th>
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<tbody>
<tr>
<td>Number randomized</td>
<td>143</td>
<td>129</td>
</tr>
<tr>
<td>Recurrent Stroke</td>
<td>0%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

Data for first 7 days

Source: Journal of the American Medical Association 1998; 279: 1588-1593

Retrospective Stroke Subtype Analysis

- Five subtypes analyzed for two different endpoints in addition to 4 analyses for total group = 14 analyses
  - \( p < .05/14 = p < .0036 \)
- Large artery atherosclerosis
  - Favorable outcome \( p = .04 \)
  - Very favorable outcome \( p = .02 \)
- No significant difference

Cardiac Embolism Conclusions

- IST showed no benefit for the subgroup with atrial fibrillation
- TOAST showed no benefit for the subgroup with cardioembolism

Summary

Patients with lower extremity paralysis should receive DVT prophylaxis with low dose anticoagulation. Anticoagulation with heparin or heparin like drugs has no beneficial effect on:

- Progression or early recurrence
- Long term functional status
- Any subgroup of patients
References

International Stroke Trial (IST)
Lancet 1997; 349: 1569-1581

Hong Kong Nadroparin Trial: "Low-molecular-weight heparin for the treatment of acute ischemic stroke"

Trial of ORG 10172 in Acute Stroke Treatment (TOAST)
Journal of the American medical Association 1998; 279: 1265-1272

Rothrock & Hart: "Antithrombotic therapy in cerebrovascular disease."

Camerlingo et al. "Immediate anticoagulation with heparin for first-ever ischemic stroke in the carotid artery territories observed within 5 hours of onset."
Archives of Neurology 1994; 51:462-467

Haley et al. "Failure of heparin to prevent progression in progressing ischemic infarction."
Stroke 1988; 19:10-14

Annals of Internal Medicine 1986; 105:825-828

Slivka & Levy: "Natural history of progressive ischemic stroke in a population treated with heparin."
Stroke 1990; 21:1657-1662

Stroke 1983; 14:668-670-1662

Baker et al:
Neurology 1962 12:823-835

Carter:

Fisher:
Neurology 1961 11:119-131

www.strokecenter.org