Low-molecular weight heparin for pulmonary embolism: A shot in the dark?

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Patient
A 71-year-old woman presents to the emergency department with right hip pain and the inability to bear weight after a fall. She is diagnosed with a mildly displaced hip fracture, and undergoes open reduction and internal fixation of the right hip the following day. The procedure is uneventful, but 3 days after surgery she develops acute shortness of breath associated with tachycardia and mild hypoxemia (pulse ox 90% on room air). A ventilation perfusion scan is performed and shows multiple areas of ventilation/perfusion mismatch bilaterally, interpreted as high probability for pulmonary embolism (PE).

Clinical Question
In a patient with non-massive acute PE, does low molecular weight heparin (LMWH) reduce the incidence of recurrent PE compared with unfractionated heparin (UFH)?

Where would you look for an answer to this question?

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How would you treat this patient?

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Turn the page for one possible approach.
Suggested Approach

Search Strategy

1. Cochrane Database of Systematic Reviews (4th Quarter 2004) using OVID interface:
   a. “low molecular weight heparin”
   b. “enoxaparen or dalteparin”
   c. “pulmonary embol$”
   d. combine [(a) or (b)] and (c)
   e. 28 studies—one of which pertained to the question: van Dongen et al—“Fixed dose subcutaneous low molecular weight heparins vs. adjusted dose unfractionated heparin for venous thromboembolism”

2. All years of MEDLINE (1966-November 2004 Week 3.) Using OVID interface:
   a. “exp Heparin, Low-Molecular-Weight” (limit human and English)
   b. “exp Pulmonary Embolism” (limit human and English)
   c. combine (a) and (b) and limit to meta-analyses
   d. 16 studies—one of which pertained to the question: Quinlan et al—“Low-Molecular-Weight Heparin Compared with Intravenous Unfractionated Heparin for Treatment of Pulmonary Embolism”

Study Characteristics and Results

<table>
<thead>
<tr>
<th>Study (Authors)</th>
<th>Quinlan et al</th>
<th>van Dongen et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>12 randomized trials including 1951 patients enrolled with objectively diagnosed symptomatic PE, or asymptomatic PE in setting of symptomatic DVT</td>
<td>22 randomized trials including 8867 patients enrolled with acute DVT or PE confirmed by objective tests</td>
</tr>
<tr>
<td>Study type</td>
<td>Meta-analysis</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>Intervention</td>
<td>Fixed-dose subcutaneous LMWH vs. dose-adjusted IV UFH</td>
<td>Fixed-dose subcutaneous LMWH vs. dose-adjusted IV or subcutaneous UFH</td>
</tr>
</tbody>
</table>

Main Outcomes* OR (95% CI)

<table>
<thead>
<tr>
<th>Study (Authors)</th>
<th>Quinlan et al</th>
<th>van Dongen et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any symptomatic VTE†</td>
<td>0.63 (0.33-1.18)</td>
<td>0.68 (0.55-0.84)</td>
</tr>
<tr>
<td>Recurrent PE‡</td>
<td>0.91 (0.45-1.85)</td>
<td>N/A</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.67 (0.36-1.27)</td>
<td>0.57 (0.39-0.83)</td>
</tr>
<tr>
<td>Minor bleeding‡</td>
<td>1.08 (0.73-1.59)</td>
<td>N/A</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.20 (0.59-2.45)</td>
<td>0.76 (0.62-0.92)</td>
</tr>
</tbody>
</table>

* Odds Ratios for LMWH vs. UFH
† Venous thromboembolism
‡ Outcomes not specifically assessed in van Dongen review

Validity of Evidence (Quinlan et al)

1. Addresses a focused clinic question.
2. Includes only randomized controlled trials with appropriate inclusion and exclusion criteria.
3. Outlines an exhaustive search for all relevant trials including MEDLINE, EMBASE and the Cochrane Library. Additional studies from bibliographies and unpublished data were also sought.
4. Assesses methodologic quality of individual trials. All studies had proper randomization and good follow-up. There is some concern about the quality of the individual trials since only 1 out of the 12 trials is double-blinded to treatment allocation.
5. No significant heterogeneity between trials.

Applying the Evidence to the Patient

1. Patient is similar to those in the studies. No reason to think that the results will not apply.
2. LMWH is feasible for the patient in question.

Summary

Both meta-analyses included large numbers of patients from randomized controlled trials with objectively diagnosed PE or VTE. Quinlan has the advantage of only including trials of patients with documented PE, which more closely pertains to the patient in the clinical question. The study was of excellent quality and showed no difference in rates of recurrent PE or mortality. It supports a trend towards a decrease in recurrent PE with the use of LMWH vs. UFH, without an increased rate of adverse events. The study by van Dongen et al further supports the use of LMWH in the combined group of patients with PE or DVT. Van Dongen shows a decrease in any symptomatic VTE, major bleeding, and all cause mortality in this group.

Conclusion

Low molecular weight heparin may be safely used in the initial treatment of sub-massive pulmonary embolism to prevent recurrent PE. It is at least equally efficacious and may be superior to UFH. In light of its superior pharmacokinetics and lower risk of heparin-induced thrombocytopenia in comparison to unfractionated heparin, it may be considered the treatment of choice in patients without contraindications to its use.

Bibliography

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