Low-molecular-weight heparins in the treatment of deep-vein thrombosis

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Authors' objectives
To compare the characteristics and clinical efficacy of low molecular weight heparins (LMWHs) and unfractionated heparin (UFH) in the treatment of deep-vein thrombosis. In addition, to discuss adverse effects, dosing and cost issues.

Searching
MEDLINE was searched from January 1984 to October 1997 for studies published in English or French.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) comparing the efficacy of LMWHs and UFH were included if they studied more than 50 patients. The follow-up periods ranged from 7 days to a median of 23 months.

Specific interventions included in the review
LMWHs and UFH, given either subcutaneously or as an infusion. The LMWH studies were of dalteparin, enoxaparin, tinzaparin and nadroparin. The doses were calculated on the basis of the patient's weight and the adjusted partial thromboplastin time. The duration of heparin treatment ranged from 5 days to 10 days. Warfarin treatment was started between day 1 and day 10. The patients were treated on both an in- and out-patient basis.

Participants included in the review
Patients who had had a first episode of symptomatic deep-venous thrombosis, as confirmed by objective tests including venography, duplex ultrasonography and impedance plethysmography.

Outcomes assessed in the review
The outcomes assessed were: total mortality, the percentage of venograms improved, recurrent thrombembolic events, and major bleeding complications.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction. Results pertaining to venographic assessment, recurrent thromboembolism, total mortality and bleeding complications were extracted.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review.

How were differences between studies investigated?
The individual studies were described. Heterogeneity among studies was not assessed.
Results of the review
Six RCTs were used to evaluated dalteparin (877 patients).
Two RCTs were used to evaluated enoxaparin (634 patients).
Four RCTs were used to evaluated nadroparin (882 patients).
One RCT was used to evaluated tinzaparin (432 patients).

The studies differed in when they started warfarin treatment, the definition of major bleeding events, and participants. Other problems encountered were the lack of intention to treat analysis and the lack of a predefined study protocol.

Most trials demonstrated no significant difference in the percentage of venograms improved, thrombus extension, incidence of recurrent thromboembolism and mortality. The incidence of bleeding complications (major and minor) with LMWHs was generally similar to that with UFH.

Cost information
The acquisition costs of UFH and the available LMWHs were presented. UFH was considerably cheaper than the LMWH at a daily drug cost of $1.44 to $4.30, compared with $83.70 for dalteparin and $80.80 for enoxaparin. The authors reported that cost-effectiveness data comparing the various LMWHs for the treatment of deep-vein thrombosis were not yet available.

Authors’ conclusions
LMWHs were as safe and effective as UFH. In view of this, and their more convenient method of administration, they can be considered valuable alternatives for the treatment of deep-venous thrombosis. Savings generated by the less intensive laboratory monitoring, and the possibility of early hospital discharge and out-patient therapy, may outweigh the higher acquisition costs of LMWHs. However, the long-term efficacy of LMWHs remains to be clearly demonstrated. LMWH should not be used interchangeably because of the lack of head-to-head comparisons.

CRD commentary
The aims of the review and the inclusion criteria were clearly stated. The details presented of the primary studies suggested that heterogeneity was present, thus a narrative review was appropriate.

By limiting the literature search to one database some relevant studies might have been omitted. Study validity was not discussed. More comprehensive details of the primary studies, such as the characteristics of the participants, would have been helpful. Some P-values, which were reported to have been unavailable from the original studies, could have been calculated from the data given.

In view of the problems highlighted, it is not possible to comment on the clinical efficacy of LMWHs and UFH for the treatment of deep-vein thrombosis.

Implications of the review for practice and research
The author states that additional studies are necessary before long-term anti-coagulation with LMWH becomes widely available. This research should address the following questions.

What is the optimal dose for each of the various LMWHs?
Is once-daily administration as safe and as effective as a twice-daily regimen?
Are the bleeding and recurrence rates truly lower than those observed with UFH?
Are LMWHs as safe as UFH in pregnancy?