Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses

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Authors' objectives
Comparative analysis of the efficacy of low molecular weight heparin (LMWH) and unfractionated heparin (UFH) for thrombosis prophylaxis after surgical interventions.

Searching
MEDLINE was searched from January 1988 to March 1996, and EMBASE from January 1990 to March 1996, for articles written in English, French, German, Italian or Spanish; the search strategy was outlined. References from retrieved publications were examined, and pharmaceutical companies were contacted for any unpublished studies.

Study selection
Study designs of evaluations included in the review
All randomised double-blind clinical trials comparing LMWH and UFH for prophylaxis against thromboembolic events after surgical interventions in general and orthopaedic surgery (including gynaecological, urological and malignant disease operations) were included. Studies including additions of dihydroergotamine (DHE) were eligible only if DHE was added to both treatment arms. Studies of organon were not included.

Specific interventions included in the review
LMWHs and fractions and fragments of UFH including monoembolex (doses of 3000, 3100, 10400 and 13600 anti-Xa units), fraxiparin (doses of 3400 and 4700 anti-Xa units), fragmin (doses of 2500, 5000 and 7500 anti-Xa units), embolex (dose of 3100 anti-Xa units), enoxaparin (doses of 2000, 4000 and 4800 anti-Xa units), clivarin (doses of 1750 and 2500 anti-Xa units), and logiparin (doses of 2500 and 3500 anti-Xa units).

Participants included in the review
Patients undergoing surgical interventions in general and orthopaedic surgery, including gynaecological, urological and malignant disease operations. No other patient characteristics were provided.

Outcomes assessed in the review
Incidence of deep vein thrombosis (DVT) and wound haematoma for comparisons of safety and efficacy. Analyses of other end points were presented, but due to the lack of comparability among studies these were restricted to subsets of the study population.

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 report the criteria used to assess validity, or how the validity assessment was performed.

Data extraction
The data were extracted by two independent reviewers, and any conflicts resolved through meetings with all reviewers.

Methods of synthesis
How were the studies combined?
Mantel-Haenszel estimates for odds ratios (ORs), 95% confidence intervals (CIs) and P-values were calculated.

How were differences between studies investigated?
Heterogeneity was assessed using the Breslow-Day test. Subgroup and sensitivity analyses using a random-effects model were also undertaken. Further sensitivity analyses were:

1. restriction of the analysis to the number of patients diagnosed with DVT, which is sometimes not equal to the number of patients initially randomised to the two treatments;
2. investigation of the effect of different diagnostic tests for the assessment of DVT on the estimation of a treatment effect; and
3. a safety analysis imputing other bleeding complications when wound haematoma was not reported.

Results of the review
Thirty-six double-blind studies (16,583 patients) were included.

The combined evaluation of studies in general and orthopaedic surgery showed a non significant reduction in the rate of DVT, with an OR of 0.92 (95% CI: 0.80, 1.05, p=0.19). In general surgery there was no increased efficacy in favour of high-dose LMWH (OR 0.88, 95% CI: 0.60, 1.30, P=0.53), but there was a higher incidence of bleeding complications (OR 1.47, 95% CI: 1.07, 2.01, p=0.02). Low-dose LMWH was equally efficacious (OR 1.03, 95% CI: 0.85, 1.26, P=0.76), but safer than UFH (OR 0.68, 95% CI: 0.56, 0.82, P<0.01). In the safety analysis of high- and low-dose LMWH versus UFH, the study results were affected by heterogeneity. In orthopaedic surgery there was a trend towards an increased efficacy for LMWH (OR 0.83, 95% CI: 0.68, 1.02, P=0.07) with equivalent safety (OR 0.96, 95% CI: 0.68, 1.36, P=0.83). The Breslow-Day tests and sensitivity analyses (including analysis using the random-effects approach and examination of differences in loss of patients, variations in diagnostic methods and safety results) showed that the analysis of efficacy was affected by heterogeneity, thus limiting the generalisability of the results.

Authors' conclusions
In general surgical patients, low-dose LMWH and UFH were equally efficacious while low-dose LMWH provided increased safety over UFH. High-dose LMWH in general surgery did not increase the efficacy of treatment, although safety was strongly decreased. In orthopaedic surgery, LMWH provides an increase in efficacy over UFH, while preserving an equal safety profile. Heterogeneity affects these analyses and the generalisation of the results to other patients. New clinical trials should not be initiated, but published data should be reanalysed at the individual patient level to identify the subgroups of patients and decrease heterogeneity.

CRD commentary
The review appears to adhere to most of the key criteria of a systematic review, with clearly-outlined objectives, review criteria, methods of pooling and assessment of heterogeneity, along with well-presented study details. The only elements of the review that lack discussion are the criteria for assessing validity, and the methods used for applying the relevance and validity criteria.

Bibliographic details

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Other publications of related interest

**Indexing Status**
Subject indexing assigned by NLM

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.