Low-molecular-weight heparin vs unfractionated heparin for perioperative thromboprophylaxis in patients with cancer: a systematic review and meta-analysis

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CRD summary
This review compared low-molecular-weight heparin and unfractionated heparin for prevention of death and adverse events caused by blood clots in cancer patients undergoing surgery. The authors found no evidence of a difference between the two treatments when administered before surgery. This was a generally well-conducted review and the conclusions were likely to be reliable.

Authors' objectives
To compare the benefits and harms of low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) for peri-operative prophylaxis of venous thromboembolism in patients with cancer.

Searching
MEDLINE, EMBASE, Web of Science and the Cochrane Central Register of Controlled Trials were searched to January 2007 without language restrictions. Search terms were reported. The authors also handsearched the proceedings of the American Society of Clinical Oncology (from 1982) and American Society of Hematology (from 2003), reviewed reference lists of included articles, relevant articles and related systematic reviews, and used the related articles function in PubMed to identify additional references.

Study selection
Randomised controlled trials in patients with cancer that compared LMWH with UFH were eligible for the review. Studies of patients with and without cancer were included if data for patients with cancer were reported separately. Outcomes of interest included mortality, deep venous thrombosis (DVT), pulmonary embolism, bleeding complications, thrombocytopenia and heparin-induced thrombocytopenia. All the included studies evaluated pre-operative administration of LMWH and UFH. Cancer site, details of surgery and LMWH and UFH treatment regimens varied among the included studies.

Two independent reviewers screened studies for inclusion and resolved disagreements by discussion.

Assessment of study quality
Two reviewers assessed validity independently based on criteria including allocation concealment, blinding, percentage follow-up, intention-to-treat (ITT) analysis, a priori sample size calculation and avoidance of early stoppage of the trial. Disagreements were resolved by discussion, with reference to a third reviewer if necessary.

Data extraction
For dichotomous outcomes, numbers of participants and events per treatment group were used to calculate a relative risk (RR) and 95% confidence interval (CI). Mean differences were calculated for continuous outcomes. Two reviewers extracted data independently using a standardised form. Discrepancies were resolved by discussion, with reference to a third reviewer if necessary. Data were extracted on an ITT basis.

Methods of synthesis
Studies were pooled by meta-analysis using random-effects models and a pooled RR or weighted mean difference calculated. Heterogeneity was assessed using the I² statistic, with values of 0-30 being considered low, 30-60 moderate and >60 severe; values of 90 or more were considered to allow pooling only with major caution. Subgroup analyses were performed for studies with UFH administration two and three times daily and for studies involving abdominal surgery. For DVT, separate analyses were performed for studies using a diagnostic workup triggered by clinical suspicion and those using a diagnostic workup triggered by venographic screening. A post-hoc analysis included all studies reporting on DVT regardless of detection method. Publication bias was assessed using funnel plots.
**Results of the review**

Fourteen RCTs (n = 5,502) were included. Sample sizes ranged from 50 to 1,116. Overall methodological quality was rated as moderate. All-cause mortality and clinically suspected DVT did not differ significantly between LMWH and UFH groups: pooled RR 0.89 (95% CI: 0.61, 1.28) for mortality and 0.73 (95% CI: 0.23, 2.28) for DVT. Seven RCTs (two with no events) reported mortality and six (four with no events) reported clinically suspected DVT. In the post-hoc analysis of all studies assessing DVT (12 RCTs, four with no events), risk of DVT was significantly lower with LMWH (RR 0.72, 95% CI: 0.55, 0.94). Subgroup analysis of DVT in the post-hoc analysis suggested that LMWH was superior to twice daily UFH, but not three times daily UFH. Values of $I^2$ were low for these outcomes. There were no significant differences in rates of pulmonary embolism, minor bleeding or major bleeding. Results of subgroup analyses were similar to those of the main analysis. The funnel plots did not suggest publication bias. Results for other outcomes were reported.

**Authors’ conclusions**

There appeared to be no survival benefit and no harm associated with LMWH compared with UFH in patients with cancer undergoing surgery.

**CRD commentary**

Inclusion criteria for participants, interventions, outcomes and study design were clear. The search covered a range of relevant resources without language restrictions. Risk of publication bias was assessed and found not to be significant. Validity was assessed using appropriate criteria, although the results were not explicitly used in the synthesis. Appropriate methods were used to minimise errors and bias during the review process. Relevant details of included studies were presented. Studies were pooled by meta-analysis and statistical and clinical heterogeneity was investigated. The authors’ conclusions reflected the evidence presented and were likely to be reliable. As noted by the authors, the absence of a significant difference between LMWH and UFH could result from either true equivalence or a lack of statistical power.

**Implications of the review for practice and research**

Practice: the authors stated that in choosing between LMWH and UFH, physicians should consider factors such as cost, ease of administration and patient preference.

Research: the authors stated that further RCTs were required to test the hypothesis that three times daily administration of UFH may be more effective than twice daily administration for prevention of DVT.

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