Safety and efficacy of low molecular weight heparins for hemodialysis in patients with end-stage renal failure: a meta-analysis of randomized trials

Lim W, Cook D J, Crowther M A

CRD summary
This review compared the safety and efficacy of low molecular weight heparin (LMWH) with unfractionated heparin (UFH) for preventing thrombosis of the extracorporeal dialysis circuit. The authors concluded that there is limited evidence that LMWH is as safe and effective as UFH, and that larger higher-quality randomised controlled trials are required. The limitations of the evidence are reflected in the appropriately tentative conclusions.

Authors' objectives
To investigate the safety and efficacy of low molecular weight heparin (LMWH) in comparison with unfractionated heparin (UFH) for preventing thrombosis of the extracorporeal dialysis circuit.

Searching
MEDLINE (from 1966 to March 2004), EMBASE (from 1980 to week 13, 2004) and the Cochrane CENTRAL Register (Issue 1, 2004) were searched without any language restrictions; the search terms were provided. In addition, proceedings and papers in the FirstSearch databases were searched (April 2004), reference lists were checked, and clinical experts and pharmaceutical companies were contacted.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing LMWH with a different anticoagulant were eligible. Only LMWH commercially available in Canada was eligible. The included studies were of dalteparin, enoxaparin, nadoparin and tinzaparin, and compared LMWH with UFH, another LMWH, citrate or danaparoid. The LMWH dose varied and was established in different ways between studies. The UFH dose spanned the range of prophylactic to therapeutic-dose anticoagulation.

Participants included in the review
Studies of adult patients (18 years or older) with end-stage renal disease (ESRD) requiring intermittent haemodialysis or haemofiltration were eligible for inclusion. The participants in the included studies were all haemodialysis dependent without characteristics known to increase baseline bleeding risks. The mean age ranged from 45 to 69 years.

Outcomes assessed in the review
Studies measuring bleeding (bleeding symptoms and access compression times), thrombosis of the extracorporeal circuit, or anti-Xa levels were eligible for inclusion. The length of follow-up in the included studies ranged from assessment after a single dialysis to assessment after repeated dialysis up to 36 months.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed unmasked papers for quality, with any disagreements resolved by consensus. The inter-rater agreement was classified as good (k=0.64).

Assessment of study quality
Studies were assessed for concealment of treatment allocation, blinding, intention-to-treat analysis and outcome assessment using the Jadad scale. The studies were classified as low quality (score of 0 to 2) or high quality (score of 3 to 5). Two reviewers independently assessed unmasked papers for quality, with any disagreements resolved by
consensus. The inter-rater agreement was classified as good (k=0.64).

**Data extraction**
Two reviewers independently extracted the data. Authors were contacted where clarification was required. For each study, the number of patients with each of the outcomes of interest was extracted. Bleeding was classified as major (requiring hospitalisation or transfusion; bleeding into a critical organ or space, or leading to death) or minor (any other bleeding). The relative risk (RR) and 95% confidence interval (CI) were estimated for dichotomous outcomes, while the mean difference and 95% CI were estimated for continuous outcomes.

**Methods of synthesis**

How were the studies combined?
Studies comparing LMWH and UFH were pooled for each of the outcomes, using the Mantel-Haenszel random-effects model to estimate the pooled RR and weighted mean difference (WMD). The findings of the other studies were reported in a narrative synthesis.

How were differences between studies investigated?
Statistical heterogeneity was investigated using the I² statistic. Pre-planned sensitivity analyses were also carried out to investigate the effect of using a LMWH dose at therapeutic level (anti-Xa levels >0.05 IU/mL) and a follow-up of more than one month. There were insufficient data to explore the effect of LMWH type on the outcomes, as intended.

**Results of the review**

Seventeen RCTs (n=645) were included, eleven of which were included in the meta-analysis comparing LMWH and UFH. Eleven trials used a crossover design and six were parallel trials.

Most of the studies were rated as poor quality. Losses to follow-up were considerable (14.8% overall studies). The majority of the studies did not state whether the analyses were based on intention-to-treat or not.

**Bleeding.**

Most bleeding events across the studies were minor; few major events were reported.

LMWH compared with UFH: there was no statistically significant difference between LMWH and UFH in the number of major and minor bleeding events (6 RCTs; RR 0.96, 95% CI: 0.27, 3.43) or the vascular access compression time (5 RCTs; WMD -0.87, 95% CI: -2.75, 1.02). There was evidence of statistically significant heterogeneity in the pooling of bleeding events (I² 62.8%, P=0.03). The sensitivity analysis suggested similar results; significant heterogeneity was found for the analysis of studies with more than 1 month of follow-up (P=0.01), but studies using therapeutic doses were statistically homogeneous (P=0.24).

LMWH compared with other anticoagulants (3 RCTs): there were no difference between tinzaparin compared with dalteparin, reviparin compared with nadroparin, and dalteparin compared with danaparoid.

**Extracorporeal thrombosis.**

LMWH compared with UFH (5 RCTs): there was no statistically significant difference between LMWH and UFH in extracorporeal thrombosis (RR 1.15, 95% CI: 0.70, 1.91). There was evidence of statistically significant heterogeneity (I² 57.3%). The sensitivity analysis suggested similar results; significant heterogeneity was found for the analysis of studies with more than 1 month of follow-up (P=0.01), but studies using therapeutic doses were statistically homogeneous (P=0.72). LMWH compared with other anticoagulants (6 RCTs): no differences were found in the 3 RCTs comparing two LMWHs and 1 RCT comparing nadroparin with citrate. There was a trend towards lower filter clotting scores with citrate in comparison with dalteparin in 2 RCTs.

Anti-Xa levels (14 RCTs): the anti-Xa levels were reported for individual studies, although an overall synthesis was not reported.
Authors' conclusions
Compared with UFH, LMWH seems to be as safe in relation to bleeding complications and as effective in preventing extracorporeal circuit thrombosis. However, owing to the lack of large rigorous RCTs, only weak inferences can be made.

CRD commentary
The review addressed a clear research question using defined inclusion criteria. Several relevant databases were searched and attempts were made to locate unpublished studies. The review methodology was clearly described and appropriate steps were taken to minimise error and bias. The methodological quality of the studies was assessed and the findings were discussed in the context of study quality.

Relevant details of the included studies were provided. There was evidence of statistically significant heterogeneity for the main outcomes, while forest plots showed that the direction of the trend of treatment effect differed among studies. Possible sources of clinical and statistical heterogeneity were discussed and the authors drew attention to the weakness of the assumption on which the pooling was based, i.e. that there is a class effect of all LMWH. The limitations of the evidence are reflected in the appropriately tentative conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that large methodologically robust trials are required in this field. Future trials should compare one or more LMWH with UFH, and make direct comparisons between different LMWH.

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