Low-molecular-weight heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review

Ribic C, Lim W, Cook D, Crowther M

CRD summary
The authors concluded that low molecular weight heparin could not be recommended routinely and that further trials were required to test patient-specific endpoints. The authors' conclusions were appropriate for the evidence presented.

Authors' objectives
To assess the effect of low molecular weight heparin thromboprophylaxis in medical-surgical critically ill patients in the intensive care unit.

Searching
MEDLINE was searched from 1950 to February 2008 for English-language articles. Reference lists of retrieved articles were examined and content experts were consulted to identify additional material.

Study selection
Prospective cohort and randomised controlled trials (RCTs) that used low molecular weight heparin for thromboprophylaxis in critically ill patients in medical, surgical, trauma or mixed intensive care units and evaluated clinically relevant outcomes (venous thromboembolism, bleeding or mortality) or laboratory outcomes (anti-factor Xa levels or thrombocytopenia) were eligible for inclusion. Retrospective audits, surveys of stated practice, case reports, case series, pilot trials, reviews, trauma and spinal cord injury patients were excluded.

Various low molecular weight heparin products were included in the studies (Dalteparin, Certoparin, Enoxaparin and Nadroparin). Most dosing schedules were once daily; there was one single-dose study. Included intensive care units were medical, mixed medical surgical and surgical trauma. Mean age of participants ranged from 58 to 72.9 years old. Length of follow-up ranged from 12 hours to five days. Patients were diagnosed with a range of conditions that included: renal insufficiency, sepsis, neurotrauma, intoxication, pneumonia, multitrauma, chronic obstructive pulmonary disease, perforated appendix and cerebral bleed. Control groups were varied. Where reported, patients treated with low molecular weight heparin products were compared with/without edema, with/without vasopressors, intensive care unit/medical patients, once-daily dosing/twice-daily dosing or compared with placebo.

Two reviewers independently selected studies for inclusion in the review. Disagreements were resolved by discussion.

Assessment of study quality
Study quality was assessed according to randomisation, concealment, blinding and confounders.

One reviewer performed the quality assessment.

Data extraction
One reviewer extracted mean and standard deviations for laboratory variables and proportion of patients with the outcome for clinical variables.

Methods of synthesis
The studies were combined by narrative synthesis.

Results of the review
Nine studies (n=627, range 10 to 223) were included in the review: one RCT, seven prospective cohorts and one case-control.
Anti-factor Xa levels (eight studies, n=406):

One nadroparin study found lower mean anti-Xa levels in patients on vasopressors compared to patients without vasopressors (prospective cohort, n=60). One dalteparin study found higher mean levels of anti-Xa levels in patients who received two to three inotropes compared to none or one inotrope (prospective cohort, n=10).

There was no difference in anti-Xa levels in patients with or without edema (one prospective cohort, n=14). There was no difference between patients who received once-daily or twice-daily dosing of certoparin (one prospective cohort, n=62).

Anti-Xa activity clearance was lower in critically ill patients who received enoxaparin compared to medical patients who received enoxaparin (one prospective cohort, n=29). Low molecular weight heparins did not appear to bioaccumulate based on trough anti-Xa levels (two prospective cohorts, n=157). Three studies had no control group (three prospective cohorts, n=246).

Clinical Outcomes:

One study found significantly lower incidence of venous thromboembolism in patients who received nadroparin (15.5%) compared to those who received placebo (28.2%). This study also found no effects of nadroparin on thrombocytopenia (one RCT, n=169). Two studies reported asymptomatic proximal leg deep vein thrombosis in 5.1% to 15.5% of patients who received dalteparin (two prospective cohorts, n=157). Overall bleeding (major and minor events) occurred in 14.6% of patients (one RCT, two prospective cohorts, n=378). No studies found an association between bleeding and the use of Dalteparin or Nadroparin. One study reported that mortality rates were the same in patients who received nadroparin compared to patients who received placebo (RCT, n=169).

Authors' conclusions

Low molecular weight heparin may be effective for thromboprophylaxis in medical-surgical critically ill patients, but evidence was not sufficient to recommend its routine use. Further trials were required to test patient important endpoints (incidence and clinical importance of venous thromboembolisms, bleeding, heparin-induced thrombocytopenia and mortality).

CRD commentary

This review addressed a clear research question supported by clear inclusion criteria. The search was limited to one database and included only English-language publications, which introduced a risk of language bias. Some attempts were made to identify unpublished material. Validity was assessed, but not reported; only study design was used to inform the results. Some steps were taken throughout the review process to minimise errors and bias. Narrative synthesis was appropriate given levels of heterogeneity among the trials. Given the clinical heterogeneity, small number of studies and overall number of participants in the review there was insufficient evidence to draw any conclusions. The authors conclusions reflect the results and are likely to be reliable.

Dr Lim had received funding from Leo Pharma and Pfizer. Dr Cook had received funding from Pfizer. Dr Crowther had received funding from or advised for Bayer, Artisan, Pfizer, Sanofi Aventis, Leo laboratories and Boehringer Ingelheim.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that large rigorous clinical trials were required to address the role of low molecular weight heparin in medical-surgical critically ill patients in the intensive care unit with respect to efficacy, safety and overall risk-benefit focused on patient outcomes.

Bibliographic details

Ribic C, Lim W, Cook D, Crowther M. Low-molecular-weight heparin thromboprophylaxis in medical-surgical

**PubMedID**
19327323

**DOI**
10.1016/j.jcrc.2008.11.002

**Original Paper URL**
http://www.jccjournal.org/article/S0883-9441(08)00241-4/abstract

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Anticoagulants /adverse effects /therapeutic use; Clinical Trials as Topic; Critical Illness; Factor Xa Inhibitors; Hemorrhage /chemically induced; Heparin, Low-Molecular-Weight /adverse effects /therapeutic use; Humans; Intensive Care Units; Postoperative Complications /mortality /prevention & control; Renal Insufficiency /chemically induced; Thrombocytopenia /chemically induced; Venous Thromboembolism /mortality /prevention & control

**AccessionNumber**
12009106182

**Date bibliographic record published**
02/12/2009

**Date abstract record published**
09/06/2010

**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.