How frequently is venous thromboembolism in heparin-treated patients associated with heparin-induced thrombocytopenia?

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CRD summary
This review assessed the frequency of heparin-induced thrombocytopenia (HIT) associated with venous thromboembolism in patients given unfractionated or low molecular weight heparin for thromboprophylaxis or treatment. The authors concluded that unfractionated but not low molecular weight heparin is associated with high-frequency HIT. Poor reporting, inadequate literature searches, failure to address study quality and inappropriate synthesis mean that the authors’ conclusions are unlikely to be reliable.

Authors’ objectives
To assess the frequency of heparin-induced thrombocytopenia (HIT) in patients presenting with venous thromboembolism (VTE) during or following heparin therapy for thromboprophylaxis or treatment.

Searching
MEDLINE (November 1984 to November 2004) and the Cochrane Library (Issue 4, 2004) were searched. The search terms were reported and the MEDLINE search was restricted to RCTs. The text and bibliographies of summary articles, books and other related publications were screened, and personal files were reviewed. The review was limited to studies published in the English language.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and prospective or retrospective cohort studies that enrolled consecutive patients were eligible for inclusion in the review.

Specific interventions included in the review
Studies of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) used for prophylaxis or treatment were eligible for inclusion. The studies included in the review used both UFH and LMWH; UFH was administered either intravenously (IV) or subcutaneously, and LMWH (dalteparin, enoxaparin, fraxiparin and reviparin) subcutaneously. Some studies of acute VTE also administered a vitamin K antagonist in addition to heparin. Treatment duration was generally 7 to 10 days. Comparator study arms that administered selective factor Xa inhibitor fondaparinux were excluded. Some studies compared UFH with LMWH, while other studies only appeared to assess one form of heparin; it was unclear what treatment, if any, the comparator arms received in the latter studies.

Participants included in the review
Patients being treated or receiving prophylactic therapy for thrombosis were eligible for inclusion. Studies of both medical and surgical patients were included in the review. One study was conducted in a paediatric population; all other studies were conducted in adults. The studies included: patients with acute deep venous thrombosis or acute pulmonary embolism; medical patients, cardiac or neurological patients; patients who had undergone orthopaedic surgery or craniotomy; or paediatric intensive care patients.

Outcomes assessed in the review
The incidence of HIT associated with VTE, defined as an event that occurred in a patient with HIT, was the primary outcome included in the review. Studies were eligible for inclusion if they defined HIT, confirmed the diagnosis with laboratory testing, objectively documented new or recurrent VTE (deep venous thrombosis, pulmonary embolism or both), reported VTE for all patients and for patients with HIT, and at least one VTE occurred in the relevant study arms. The included studies typically defined HIT as a platelet count of <100 x10^9/L or a 40 to 50% decrease in count, with serologic confirmation. The duration of follow-up, where reported, ranged from 9 to 90 days.
How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the papers for inclusion in the review. Any disagreements were resolved through consensus.

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

Data extraction
The authors stated that the data were extracted and tabulated, but did not state how many reviewers performed the data extraction. The number of patients who received heparin, the number who acquired VTE, and the number who acquired HIT and VTE were extracted. The proportion of patients with HIT-associated VTE and the proportion of patients with any VTE, together with exact confidence intervals (CIs), were calculated for each study.

Methods of synthesis
How were the studies combined?
Summary odds ratios (ORs) were calculated together with 95% CI. The methods used to obtain summary measures were not reported.

How were differences between studies investigated?
Some differences between the studies were discussed very briefly in the narrative of the 'Results' section. Heterogeneity was not formally assessed, but the studies were grouped according to the following subgroups prior to pooling: type of heparin (UFH versus LMWH), method of administration (IV or subcutaneous), type of patients (surgical or medical).

Results of the review
Ten studies (n=6,219) were included in the review: six RCTs, three prospective cohort studies and one retrospective cohort study. Patient numbers were not reported separately according to study design.

All patients (10 studies, n=6,219): VTE occurred in 386 of the 6,219 patients; 32 of these patients had HIT.

Patients treated with UFH (5 studies, n=3,792): VTE occurred in 129 of the patients treated with IV UFH, of which 17 (13.2%) had HIT; and in 113 of the patients treated with subcutaneous UFH, of which 14 (12.4%) had HIT. There was no significant difference between groups treated with IV or subcutaneous UFH (OR 1.07, 95% CI: 0.50, 2.30, p=0.99).

Patients treated with LMWH (5 studies, n=2,427): VTE occurred in 144 of the 2,427 patients treated with LMWH; one of these patients had HIT.

There was a significantly higher incidence of HIT-associated VTE in patients treated with UFH than in those treated with LMWH (OR 21.0, 95% CI: 2.8, 156, p<0.001).

Authors' conclusions
VTE was associated with HIT infrequently in patients treated with LMWH, but frequently in patients treated with UFH.

CRD commentary
This was a confusing and poorly reported review. The review question and the inclusion criteria were clear and specific. The authors searched two relevant databases. Studies published in languages other than English were excluded from the review, and the authors did not report making any attempts to identify unpublished studies. These factors increase the possibility that some relevant studies might not have been included in the review, as does the limiting of the search to RCTs. The authors reported using appropriate methods to minimise bias and error in the selection of studies for the review. However, they did not report the use of such techniques when extracting the data. In addition, they did not
report carrying out an assessment of study validity; this is particularly problematic given the different types of studies included.

The decision to employ meta-analysis appears appropriate. However, the statistical pooling of randomised and non-randomised studies is rarely appropriate, particularly where subgroup or sensitivity analyses are not undertaken. In addition, the synthesis methods employed were poorly reported, and it was impossible to determine the actual methodology that was used. In view of these issues concerning the review methodology, reporting of methodology and the method of evidence synthesis, the authors' conclusions are unlikely to be reliable.

Implications of the review for practice and research
Practice: The authors stated the possibility of HIT if patients develop VTE during or soon after treatment with UFH. They further stated that if thrombocytopenia is present, alternative anticoagulation should be used until HIT is excluded.

Research: The authors did not state any implications for further research.

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