Low molecular weight heparin-induced skin necrosis: a systematic review

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CRD summary
This review examined published reports of low molecular weight heparin-induced skin necrosis. The authors concluded that most patients have heparin-induced thrombocytopenia syndrome and most patients have a good outcome. The review methods were not reported and the conclusions did not adequately reflect the limited evidence from a small number of patients.

Authors' objectives
To examine published reports of low molecular weight heparin (LMWH)-induced skin necrosis.

Searching
The Cochrane Library, MEDLINE and EMBASE were searched using the reported search terms for reports published in English, German or French. In addition, reference lists were screened. One case at the authors' own hospital was also included.

Study selection

Study designs of evaluations included in the review
Reviews were excluded; no other inclusion criteria for the study design were specified. All of the included studies were case studies.

Specific interventions included in the review
Studies that evaluated LMWH were eligible for inclusion. Studies of other antithrombotic drugs were excluded. The included studies mostly evaluated dalteparin or enoxaparin; the other drugs evaluated were tinzaparin, tedelparin, certoparin, nadroparin and LMW heparin-dihydroergotamine. Where reported, the daily dose of LMWH ranged from 2,000 IU anti-factor Xa to 5,000 IU (mean 4,300 IU) and treatment was by injection into the abdominal wall, thigh or arm.

Participants included in the review
Inclusion criteria were not defined in terms of the participants. In the included studies, the reasons for LMWH administration included prophylaxis (including post-operative) of thromboembolism, treatment of established venous thromboembolism, acute coronary syndrome and atrial fibrillation. About half of the participants were female and the mean age was 62 years (range: 34 to 87). Some of the included studies reported that the patients had been previously exposed to heparin, most commonly a few days prior to the administration of LMWH.

Outcomes assessed in the review
Studies that assessed LMWH-induced skin necrosis were eligible for inclusion. Studies that assessed skin necrosis caused by underlying immunological diseases were excluded. The review also assessed the size and location of skin necrosis, the time from first administration of LMWH until skin necrosis started, heparin-induced thrombocytopenia, thrombocytopenia, other measures of coagulation state, switch anticoagulant and outcome.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The outcomes of interest were extracted from each study.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative and the number of studies reporting each outcome of interest was presented.

How were differences between studies investigated?
Heterogeneity was not formally investigated, but differences between the studies were apparent from the tables and text.

Results of the review
Twenty-one case reports (including the case reported by the review authors) were included (n=21).

The average time from first administration of LMWH until skin necrosis started was 7.6 days (range: 1 to 17).

The size of skin necrosis varied; most were small. Most lesions (16 out of 21) occurred locally at the injection site; skin necrosis at sites distant from the injection site was less common (5 out of 21).

Heparin platelet factor-4 antibody or heparin-associated thrombocytopenia tests were positive in 9 of the 11 studies in which their use was reported.

Severe thrombocytopenia was reported in 4 of 19 patients, while mild thrombocytopenia was reported in an additional 5 patients.

Fifteen of the 16 studies reporting various other measures of coagulation reported no abnormality of coagulation.

After the development of skin necrosis, anticoagulation was stopped in 2 patients. Fifteen studies reported a switch in anticoagulant, with the majority of patients being switched to either coumarin (5 patients) or unfractionated heparin (5 patients); others were switched to aspirin (3 patients) or hirudin (2 patients).

Most patients had a good outcome. One patient who was switched to coumarin developed a deep venous thrombosis, and 2 patients required debridement and reconstructive surgery with skin grafting.

Authors' conclusions
Most patients with LMWH-induced skin necrosis have evidence of the heparin-induced thrombocytopenia syndrome, although severe thrombocytopenia is rare. Most patients have a good outcome but some do require surgical treatment.

CRD commentary
The research question was defined in terms of the intervention and outcome; no inclusion criteria for either the participants or study design were specified. Three databases were searched and some attempts were made to reduce language bias. No attempts were made to minimise the possibility of publication bias. The methods used to select studies and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias. There was adequate information on the included studies. Reporting the number of studies with the outcomes of interest was an appropriate method of combining these case reports. However, the conclusions did not adequately reflect the limited evidence from a small number of patients.

Implications of the review for practice and research
Practice: The authors recommended that it is safe to switch patients who do not have the heparin-induced thrombocytopenia syndrome to unfractionated heparin; that patients with established heparin-induced
thrombocytopenia syndrome should be switched from heparin to hirudin; and that fondaparinux should be used in patients with heparin antibodies. The review did not present evidence about the efficacy of alternatives to LMWH.

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

Bibliographic details

Indexing Status
Subject indexing assigned by NLM

MeSH
Anticoagulants /adverse effects; Heparin, Low-Molecular-Weight /adverse effects; Injections; Male; Middle Aged; Multiple Trauma /surgery; Necrosis; Skin /pathology; Spinal Fractures /surgery; Thromboembolism /prevention & control; Time Factors

AccessionNumber
12005004764

Date bibliographic record published
30/04/2007

Date abstract record published
30/04/2007

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.