No difference in risk for thrombocytopenia during treatment of pulmonary embolism and deep venous thrombosis with either low-molecular-weight heparin or unfractionated heparin: a metaanalysis

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CRD summary

This was a generally well-conducted meta-analysis exploring the risk of thrombocytopenia in patients prescribed low-molecular-weight heparin or unfractionated heparin for venous thromboembolism. The authors performed a thorough quality assessment of the included studies and used appropriate statistical methods to combine the data. The conclusions seem reliable based on the evidence presented.

Authors' objectives

To compare the incidence of thrombocytopenia between low molecular weight heparin (LMWH) and unfractionated heparin (UFH) during treatment of pulmonary embolism (PE) and/or deep vein thrombosis (DVT).

Searching

Trials in English were identified through a computerised bibliographic search of MEDLINE, from January 1985 to June 2006; the search terms were reported. The references of retrieved reviews and meta-analyses were checked for additional studies, and publishers of included articles were contacted in an attempt to identify unpublished trials.

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 UFH of any type, preparation and route of administration for venous thromboembolism were eligible for inclusion if the planned follow-up was the same for LMWH and UFH. The specific thrombolytic drug therapies and doses were reported in the paper. All LMWH therapies were delivered subcutaneously, apart from one trial in which intravenous administration was used in addition to subcutaneous delivery.

Participants included in the review

Studies in patients with objectively diagnosed PE or DVT were eligible for inclusion. Objective diagnosis included pulmonary angiography, contrast venography, duplex ultrasound, Doppler scan, ventilation-perfusion scan, and/or computed tomographic scanning.

Outcomes assessed in the review

Studies that reported heparin-induced thrombocytopenia and heparin-induced thrombocytopenia with thrombosis were eligible for inclusion. Studies were required to define thrombocytopenia objectively, screen and measure platelet counts, and compare rates of thrombocytopenia for LMWH with UFH in the initial treatment of PE or DVT. For the primary analyses, ‘thrombocytopenia’ during LMWH or UFH therapy was defined as the occurrence of platelet counts in the range of 80,000 to 120,000/microL, or a decrease of at least 50% from a previously measured platelet level. A secondary analysis included all definitions of thrombocytopenia.

How were decisions on the relevance of primary studies made?

Two reviewers independently assessed studies for inclusion and any disagreements were resolved by consensus.

Assessment of study quality

Quality was assessed using a modified version of the criteria of Nuromohamed et al. (reference given). Trials were assessed for randomisation, explicit inclusion and exclusion criteria, description of clinical characteristics, description of bleeding complications, accurate diagnosis of DVT and PE, blinding, drop-outs and routine platelet counts performed. These criteria were used to assign a score of between 0 and 9. A study was considered to be of a high

quality if it met at least 8 of the 9 criteria. Two reviewers independently assessed the studies for validity.

Data extraction

The data extraction was carried out independently, in duplicate, with consensus resolution of any discrepancies. Data on the number of events in each group were used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for each study. Since the incidence of heparin-associated thrombocytopenia in some studies was zero, a 'minimax' approach was used to estimate ORs and 95% CIs.

Methods of synthesis

How were the studies combined?

The pooled ORs and corresponding 95% CIs were calculated using a Gaussian random-effects model, while controlling for treatment difference as a fixed effect. Likelihood ratios were used to assess the significance of the treatment terms (UFH versus LMWH) on the outcomes. Publication bias was assessed visually using a funnel plot.

How were differences between studies investigated?

Statistical heterogeneity was assessed using a chi-squared test. Additional analyses were pre-specified and included the addition of seven previously excluded studies defining thrombocytopenia differently. Further analyses included only studies that used an LMWH available in the USA.

Results of the review

Thirteen RCTs (n=5,275) were included in the review.

The methodological quality of the included studies was good; all studies were considered to be of a high quality.

There was no significant difference in heparin-associated thrombocytopenia between LMWH and UFH (OR 1.246, 95% CI: 0.80, 2.00, p=0.246). There was no evidence of statistically significant heterogeneity. The analyses that included additional studies did not change the results. There was no evidence of publication bias.

Authors' conclusions

There was no statistically significant difference in heparin-associated thrombocytopenia between LMWH and UFH. The rates of documented heparin-induced thrombocytopenia and heparin-induced thrombocytopenia with thrombosis were very low, and it was not possible to determine in any meaningful way whether or not there is a difference in risk between UFH and LMWH patients being treated for DVT and/or PE. There was no evidence from RCTs to support the contention that patients receiving treatment for PE or DVT with UFH are more prone to complications than those receiving LMWH.

CRD commentary

The review addressed a clear question in terms of the intervention, study design and outcomes of interest; information about the participants was limited. Search terms were reported and efforts were made to retrieve unpublished data. However, the restriction to one computerised database and English language publications may indicate that not all of the relevant data were included. Publication bias was assessed and no evidence of it found. The authors attempted to minimise bias and errors during the review process by carrying out the study selection, validity assessment and data extraction in duplicate.

The characteristics and quality of the included studies were presented clearly. The analysis of additional studies using a different definition of thrombocytopenia is inappropriate and negates the value of the inclusion criteria and quality assessment, although in this case it did not change the results. Sensitivity analyses of drug regimen and length of treatment might have been helpful. The authors' conclusions seem reliable based on the evidence presented.

Implications of the review for practice and research

Practice: The authors stated that current data do not warrant a choice between UFH and LMWH based on the avoidance of complications.

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

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