Activated partial thromboplastin time monitoring in patients receiving unfractionated heparin for venous thromboembolism in relation to clinical outcomes

Vardi M, Laor A, Bitterman H

CRD summary
This review evaluated the association between activated partial thromboplastin time and clinical outcomes in patients with venous thromboembolism receiving subcutaneous unfractionated heparin (UFH). The authors concluded that subcutaneous UFH without anticoagulation monitoring may be a feasible treatment option. The authors' cautious conclusion reflected the evidence presented, but its reliability is unclear due to uncertainties in the review process.

Authors' objectives
To compare the association between activated partial thromboplastin time and clinical outcomes in patients with venous thromboembolism who received subcutaneous unfractionated heparin (UFH) or other treatments.

Searching
MEDLINE, Cochrane Peripheral Vascular Diseases Group Specialised Register and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to April 2009. Ongoing trials were searched via Cochrane Controlled Trials, UK National Research Register, Center Watch Clinical Trials Listing Service and National Institute of Health. Reference lists of relevant trials and reviews were scanned and authors and field experts were contacted to locate additional studies. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) that compared subcutaneous UFH to any other treatment in patients with venous thromboembolism were eligible for inclusion in the review. The outcome of interest was correlation between activated partial thromboplastin time and clinical outcomes.

All included trials involved patients with deep vein thrombosis (DVT) who received subcutaneous UFH compared with intravenous UFH or subcutaneous low molecular weight heparin. Various dosing regimens were reported in the paper. The intervention duration ranged from five days to the international normalised ratio (INR) target. Clinical outcomes included DVT resolution at the end of heparin treatment, recurrent DVT at three months, new pulmonary embolism during heparin treatment and at three months, new pulmonary embolism at routine lung scan at the end of heparin treatment, major or minor bleeding and death and venous thromboembolism during treatment and at three months.

Two reviewers independently selected trials for inclusion in the review. Discrepancies were resolved by discussion.

Assessment of study quality
Trial quality assessment was carried out using criteria set out by Schulz and Jadad on minimisation of selection bias, performance bias, attrition bias and detection bias. Trials were deemed to have a low risk of bias where all criteria were met, moderate risk where one or more criteria were partially met and a high risk where one or more criteria were not met.

The authors did not state how many reviewers carried out the quality assessment.

Data extraction
Data were extracted on the initial measurement (within 48 hours of treatment) and the maintenance measurement (last measure taken at least over 48 hours after treatment, or the mean of measures) from the test of anticoagulation (activated partial thromboplastin time). Data were also extracted to calculate odds ratios (OR) and 95% confidence intervals (CI) for therapeutic versus non-therapeutic activated partial thromboplastin time at the initial and maintenance measurement time points.
The authors did not state how many reviewers carried out data extraction.

Methods of synthesis
Correlations between activated partial thromboplastin levels and clinical outcomes were analysed by meta-regression using the method of maximum likelihood (Fisher scoring). Odds ratios and 95% CIs were pooled (using inverse variance weighting) for groups of studies at each time point in terms of new clinical pulmonary embolism following subcutaneous and intravenous UFH and major bleeding during subcutaneous and intravenous UFH. Statistical heterogeneity was assessed using the $X^2$ test. Subgroup analysis assessed clinical outcomes according to whether initial and maintenance activated partial thromboplastin levels were within desired limits.

Results of the review
Eleven RCTs (n=2,513) were included in the review, but only seven trials (n=852) were eligible for inclusion in the meta-regression. Follow-up ranged from acute phase only to 12 months. Two trials were double-blinded. One trial used intention-to-treat analysis. Assessor blinding was adequately reported in four trials. Most trials were considered to be at high risk of bias.

In patients who received subcutaneous and intravenous UFH, the maintenance measurement of activated partial thromboplastin time was significantly associated with the resolution of thrombus at the end of treatment ($p<0.0001$). The initial measurement was significantly associated with minor bleeding rate ($p<0.01$). The maintenance measurement was only significantly associated with minor bleeding rate in patients receiving subcutaneous UFH ($p=0.0132$). Where data were available, both treatments were significantly associated with the overall death rate at three months ($p<0.0035$). Activated partial thromboplastin time was not significantly associated with rates of recurrent DVT or rates of new clinical pulmonary embolism during treatment at three months, treatment-related major bleeding and death or venous thromboembolism during treatment. Subgroup analysis did not materially alter the results.

Trials that were not included in the meta-regression reported conflicting results.

Authors' conclusions
Weight-adjusted subcutaneous unfractionated heparin without anticoagulation monitoring may be feasible for patients with venous thromboembolism. There were no differences between subcutaneous and intravenous modes of administration in terms of clinical outcome.

CRD commentary
The review question was clear and supported by reproducible inclusion criteria for all except outcomes. A variety of outcomes were measured. A number of relevant sources were accessed in the search strategy. Attempts were made to minimise publication and language biases. An appropriate validity assessment tool was applied to the included study designs. The study selection process was carried out with sufficient attempts to minimise error and bias; the extent to which this was applied during data extraction and validity assessment was unclear. The chosen methods of analysis appeared to be appropriate, given the number of comparisons being made. Study details were provided, but patient characteristics were sparse. Given that most studies were deemed to be low quality, the author's cautious conclusion was appropriate. The extent to which this conclusion is reliable is potentially limited by uncertainties in the review process.

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

Research: The authors stated that a randomised clinical trial was required to confirm the findings of this review.

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