Timing of initial administration of low-molecular-weight heparin prophylaxis against deep vein thrombosis in patients following elective hip arthroplasty: a systematic review


Authors' objectives
To perform a systematic review of the literature to assess the efficacy and safety of once-daily subcutaneous low molecular weight heparin (LMWH) administered at different times in relation to surgery, compared with oral anticoagulation prophylaxis.

Searching
Potential studies were identified from MEDLINE and by manually reviewing the reference lists of original articles and review articles. Abstracts of conference proceedings were also reviewed, and investigators and pharmaceutical companies were contacted. Abstracts were eligible for inclusion if the study methods and results were reported in full. The investigators of individual studies for inclusion in the review were also contacted, where necessary, to obtain specific information relating to that study. The studies included in the review were published from 1993 to 2000.

Study selection

Study designs of evaluations included in the review
The review was confined to randomised controlled trials in which random assignment to treatment groups could be identified from the study report.

Specific interventions included in the review
The review aimed to identify all studies that compared once-daily subcutaneous LMWH, given as prophylaxis, with oral anticoagulants in the prevention of deep-vein thrombosis (DVT). Although the investigators sought studies of the LMWHs lexane, clivarin, CY216, CY222, dalteparin, enoxaparin, framin, fraxiparine, logiparin, certoparin, nadroparin, parnaparin, reviparin, tinzaparin, and the oral anticoagulants warfarin or coumadin, the actual interventions included in the studies reviewed were:

- tinzaparin (post-operative and usual dose, 75 IU/kg per day);
- warfarin (post-operative and usual dose, INR 2-3, adjusted daily; or 5.0 to 7.5 mg pre- and post-operative and INR 2.5 for usual dose; or post-operative 5 to 10 mg and usual dose INR 2-3);
- nadroparin (once-daily pre-operative 3,075 IU, post-operative and usual dose given according to body weight);
- acenocoumarol (4 mg pre-operative, 2 mg post-operative and INR 2-3 usual dose);
- dalteparin (pre-operative 2,500 IU, post-operative 2,500 IU, usual dose 5,000 IU; or post-operative only 2,500 IU and usual dose 5,000 IU).

The timing for pre-operative medication varied from the day before surgery, to less than 2 hours before surgery. For post-operative medication it was between 4 to 6 hours and 18 to 24 hours following surgery.

Participants included in the review
Participants undergoing elective hip arthroplasty were included in the review. The mean age ranged from 63 to 67 years (1,501 men and 1,988 women) and 293 patients had cancer.

Outcomes assessed in the review
The outcomes assessed included the frequency of major outcomes: all DVT, proximal vein thrombosis and major bleeding complications, as defined by the investigators. Only studies on patients undergoing elective hip arthroplasty, which objectively documented the presence or absence of DVT and proximal vein thrombosis by bilateral ascending...
contrast phlebography and used objective methods for assessing major bleeding complications, were eligible. The risk of DVT appeared to be the primary outcome in the review.

How were decisions on the relevance of primary studies made?
Two investigators independently evaluated studies for inclusion in the review and any disagreements were resolved by discussion. The investigators were not blinded to the journal, author or institution. The agreement between the two investigators for selecting the studies for inclusion in the review was 100% (k=1.0).

Assessment of study quality
Four criteria were reviewed to assess the quality and strength of the studies: proper randomisation derived from the use of a randomised numbers table or a computer program; masking of the allocation sequences from the investigators, staff and patients involved in the study; use of double-blinding; and determining the proportion of patients who underwent successful phlebography. Two investigators extracted data relating to the quality of the studies included in the review.

Data extraction
Two investigators independently extracted data from the primary studies. The investigators were not masked to the journal, author or institution. The baseline data extracted were: patient age and gender, name of intervention (drug), timing of prophylaxis, frequency of administration, dosage, if the study was double-blind, and the timing of and the number of patients having successful venography. Clinical data included: the type of hip arthroplasty (cemented or not); the duration of and type of anaesthesia (general, regional or combined); if the arthroplasty was primary or a revision; if graduated stockings were used; the number of patients that had previous venous thromboembolism and the number diagnosed with cancer. The outcomes data were categorised by the timing of prophylaxis (remote from surgery or in close proximity) and included the number of clinical events by treatment group (DVT, proximal deep-vein thrombosis and major bleeding).

For each primary trial, the absolute risk reduction (ARR), the relative risk reduction, the odds ratio (OR), the number-needed-to-treat to prevent one thromboembolic event and the number-needed-to-harm to cause one major bleeding event, were calculated for each major outcome.

Methods of synthesis
How were the studies combined?
It was planned that the results of the individual studies would be combined using a meta-analysis. However, because of statistical heterogeneity, no statistical pooling was carried out. Funnel plots examined interstudy variations in the ORs for three major outcomes in relation to sample size, to assess the potential for publication bias.

How were differences between studies investigated?
Logistic regression was used to test the effect of close proximity administration of prophylaxis on these rates. By incorporating oral anticoagulant group event rates as controls it was possible to take into account the contribution of non-systematic between-study variation. Secondary analysis was performed to examine the effect of the one study that used a unilateral phlebogram on the main outcomes. The Mantel-Haenszel test was used to investigate statistical heterogeneity.

Results of the review
Four primary studies, recruiting 3,519 patients, were included in the review. Two of the studies were double-blind. Two of the studies administered LMWH remote from surgery and two in close proximity to surgery.

Heterogeneity was positive between studies for total and proximal DVT (p<0.2 for each outcome). A separate examination of the LMWH and oral anticoagulant arms revealed significant interstudy variability (LMWH p=0.004; oral anticoagulants p=0.01). Among the oral anticoagulant arms, heterogeneity was attributable to the low event rate in one study. A mixed-effects analysis indicated that a significant (p=0.008) decrease in DVT rates in the studies using
close proximity to surgery prophylaxis protocols accounted for the heterogeneity between the LMWH arms. For proximal DVT, the results were heterogeneous, with the timing of initiation of prophylaxis accounting for a statistically-significant (p=0.004) component of variability. There was no strong indication of heterogeneity in the results for major bleeding events. Analysis using the chi-squared test, the Fisher exact test and the t-test found that the clinical characteristics of patients were comparable across treatment groups within each study.

For LMWH given at half the usual dose in close proximity to surgery (less than 2 hours before surgery or 4 to 6 hours after surgery), a large and statistically-significant ARR for DVT was observed in 2 trials with two pre-operative interventions (ARR 11.2, 95% CI: 3.2, 19.2 and OR 0.49, 95% CI: 0.29, 0.82; ARR 13.3, 95% CI: 7.6, 18.9 and OR 0.38, 95% CI: 0.25, 0.58) and one post-operative intervention (ARR 10.9, 95% CI: 5.1, 16.7 and OR 0.48, 95% CI: 0.32, 0.72). No reduction in the risk of DVT was observed in patients given LMWH 12 to 24 hours before surgery or 18 to 24 hours post-operatively (ARR not reported; ORs 0.87 and 1.01, CIs not reported). Major bleeding was significantly more frequent in only one of five study arms which gave LMWH in close proximity to surgery (for centrally adjudicated major bleeding); the ARR was 4.4 (95% CI: 1.3, 7.5) and the OR was 2.07 (95% CI: 1.22, 3.50). The risk of minor bleeding, thrombocytopenia and wound haematomas were similar and low for each study across the randomised groups (data not shown).

Inverted funnel plots of study OR versus sample size were uninformative because of the similarity of the sample sizes among the studies, and were not presented.

Authors' conclusions
The interval between surgery and the first administration of LMWH is a critical variable that significantly influences the occurrence of DVT in patients undergoing elective hip arthroplasty. LMWH begun in close proximity to surgery and initiated at half the usual high-risk dose was more effective than LMWH given 12 hours pre-operatively or 12 to 18 hours post-operatively. LMWH given 4 to 6 hours after surgery provided superior efficacy compared with oral anticoagulation, and with no increased risk of major bleeding. However, while LMWH given 2 hours before surgery had a large impact on reducing the risk of DVT, it was associated with an increased risk of major bleeding. The findings of this review suggest that delayed initiation of LMWH (which is current practice in North America) to 12 to 24 hours post-operatively results in suboptimal antithrombotic effectiveness without evidence of a substantive safety advantage.

CRD commentary
The review was well conducted with the authors following a methodological check-list of 15 review criteria. The review process was described in detail and two authors independently selected the studies and abstracted data for the review, with any discrepancies resolved through discussion. Statistical heterogeneity was explored between the different studies. This was found to be positive and, therefore, the results from the individual studies were not pooled. Given the review's aims to assess the effect of the timing of LMWH administration, it may have been better to have searched for studies that randomised participants to LMWH delivered at different timings, rather than including only studies that compared this drug with oral anticoagulants. The review could have been improved by searching other important electronic databases rather than relying on just MEDLINE. Consequently, there is a potential that some relevant studies were not identified and included in the review, and the assessment of publication bias was not informative.

Some discrepancies were found in the tables presenting the patient characteristics in each study. However, it is unlikely that this has any effect on the conclusions in the review. It would have been helpful if the authors had also tabulated the data for non significant findings. Information about the risk of DVT in patients in each study, such as smoking status, could have assisted in exploring the internal and external validity of the findings. Furthermore, the authors did not explore the potential reasons why one study observed an increased risk of major bleeding while this was not observed in another study using a similar intervention. More importantly, the effect of the interventions on mortality was not considered. The authors' conclusions on the timing of LMWH delivery are based solely on secondary analyses and should be treated with caution.

Implications of the review for practice and research
Practice: The authors state that the current practice in the USA and Canada of delayed initiation of LMWH to 12 to 24 hours post-operatively results in suboptimal antithrombotic effectiveness without evidence of a substantive safety advantage.

Reviewer’s statement: The practice of giving LMWH in close proximity to patients undergoing elective surgery for hip arthroplasty should be given serious attention.

Research: The authors do not discuss implications for research.

Reviewer’s statement: This review has highlighted the importance of the timing of the administration of prophylaxis treatment to primarily reduce the risk of DVT in patients undergoing elective hip arthroplasty.

Bibliographic details

PubMedID
11525697

Original Paper URL
http://archinte.ama-assn.org

Indexing Status
Subject indexing assigned by NLM

MeSH
Administration, Oral; Anticoagulants /administration & dosage; Arthroplasty, Replacement, Hip /adverse effects; Drug Administration Schedule; Elective Surgical Procedures /adverse effects; Heparin, Low-Molecular-Weight /administration & dosage; Humans; Injections, Subcutaneous; Odds Ratio; Randomized Controlled Trials as Topic; Research Design; Risk; Venous Thrombosis /etiology /prevention & control

AccessionNumber
12001008378

Date bibliographic record published
31/08/2003

Date abstract record published
31/08/2003

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.