Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: a metaanalysis

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CRD summary
This review compared venous thromboembolism rates with twice- or three-times-daily unfractionated heparin regimens in hospitalised patients. The authors concluded that more frequent dosing reduces thromboembolism rates, but increases the risk of bleeding, and treatment should therefore depend on the patients' underlying risk for these factors. These conclusions might not be reliable as they are based on indirect comparisons of variable studies.

Authors' objectives
To assess whether three times daily prophylaxis with unfractionated heparin is superior to twice-daily dosing regimens for the reduction of venous thromboembolism rates in hospitalised medical patients.

Searching
MEDLINE, EMBASE, ClinicalTrials.gov, CRISP, the Cochrane Controlled Trials Register, ACP Journal Club, the Cochrane Database of Systematic Reviews and DARE were searched, without any language restrictions, from 1966 to the end of 2004 for relevant citations; the search terms were reported. The searches were supplemented by checking the bibliographies of relevant articles retrieved.

Study selection
Study designs of evaluations included in the review
To be eligible, the studies had to be randomised controlled trials (RCTs).

Specific interventions included in the review
To be eligible, studies needed to compare subcutaneously dosed unfractionated heparin with placebo or a suitable control (which was not further defined). Heparin had to be dosed at 5,000 U either two or three times a day. Of the 12 included studies, five assessed heparin given twice daily and seven assessed heparin given three times daily. Comparison groups included identical placebo (2 studies), low molecular weight heparin (5 studies), flubiprofen (1 study) and no treatment (4 studies).

Participants included in the review
To be eligible, the studies had to include nonsurgical hospital patients. Studies were excluded if the patient population included trauma, pregnant or paediatric patients. Three of the 5 studies giving heparin twice daily included high-risk patients, compared with only two of the 7 trials giving heparin three times daily. The populations of the remaining studies were considered to be moderate risk. Where reported, the mean age of the participants ranged from 58 to 83 years and the proportion of men from 27 to 88%. Settings included general medicine, intensive care units and coronary care units.

Outcomes assessed in the review
To be eligible, the studies had to have an objective assessment of deep venous thrombosis (DVT) (by Doppler compression sonography, impedance plethysmography, radiofibrinogen uptake scanning, autopsy or venography) and pulmonary embolism (PE) (by computed tomography angiography, ventilation perfusion scanning, pulmonary angiogram or autopsy). Studies had to report the incidence of DVT and PE. Other outcomes of interest were bleeding complications. In the included trials, the assessment of thromboembolism was by daily fibrinogen scan (7 studies), ultrasound (3 studies), autopsy (1 study), and D-dimer assessment and venography when positive (1 study).

How were decisions on the relevance of primary studies made?
Two authors independently selected articles for inclusion, with 100% agreement on first review.
Assessment of study quality
Two investigators independently rated trial quality using the Jadad criteria. Inter-rater agreement was high (kappa 0.97, p=0.0004) and any disagreements were resolved by consensus.

Data extraction
Three reviewers extracted the data independently and any differences were resolved by consensus. The following outcome data were extracted for each article: co-morbidity rates in study population, DVT event rate, PE event rate and bleeding complications (by major and minor bleeding events, where available). All rates (except minor bleeding) were calculated per 1,000 patient-days. The location of DVT was also extracted and, when the studies did not provide enough data to separate proximal from distal DVTs, all DVTs were considered to be proximal. For each trial, patients were stratified as being at high, medium or low risk for DVT according to predefined criteria.

Methods of synthesis
How were the studies combined?
The data were combined statistically in a meta-analysis using a random-effects model (DerSimonian and Laird). Publication bias was assessed using the Shapiro-Wilks normality test.

How were differences between studies investigated?
Heterogeneity was assessed visually with Galbraith plots and with the Mantel-Haenszel Q statistic. Heterogeneity was explored using meta-regression and stratified analyses. As baseline risk was found to be an important factor explaining the variance between studies, meta-regression was used to adjust for these differences when calculating subgroup p-values. To investigate the impact of the location of embolism on outcomes, two combined PE and DVT outcome groups were analysed: any PE or DVT, and only proximal DVT (popliteal and above) or PE. Sensitivity analyses were carried out to explore the possible dominance of any single study.

Results of the review
Twelve RCTs were included (n=7,978: n=1,664 for three-times-daily heparin treatment and n=6,314 for twice-daily heparin treatment). The numbers of participants in the individual trials ranged from 38 to 5,776.

The Jadad scores for the included trials ranged from 3 to 8. Quality problems included lack of blinding (6 studies), ineffective randomisation (6 studies), inadequate description of withdrawals and drop-outs (5 studies), and inadequate discussion of statistical methods (3 trials).

There were 87 DVTs in the 6,314 patients (5 RCTs) treated with twice-daily heparin, and 36 in the 1,664 patients (7 RCTs) treated with three-times-daily heparin. This corresponded to an event rate of 5.40 per 1,000 patient-days (95% confidence interval, CI: 1.65, 9.15) for twice-daily heparin and 3.01 per 1,000 patient-days (95% CI: 0.68, 5.25) for three-times-daily heparin, after adjustment for baseline risk. There was no significant difference between the treatment schedules.

There were 62 PEs with twice-daily heparin treatment and 8 PEs with three-times-daily heparin. This corresponded to an event rate of 1.50 per 1,000 patient-days (95% CI: 1.12, 1.88) for twice-daily heparin and 0.53 per 1,000 patient-days (95% CI: 0.04, 1.01) for three-times-daily heparin. The difference between the treatments was not statistically significant.

The combined event rates of DVT and PE after adjustment for baseline risk were 5.41 per 1,000 patient-days (95% CI: 2.47, 8.36) for twice-daily heparin and 3.46 per 1,000 patient days (95% CI: 0.97, 5.94) for three-times-daily heparin (no significant difference). For proximal DVT or PE, the event rate (after adjustment for baseline risk) was 2.34 per 1,000 patient-days (95% CI: 1.34, 3.34; 124 events) for twice-daily heparin and 0.86 per 1,000 patient-days (95% CI: 0.30, 1.4; 23 events) for three-times-daily heparin. This difference was statistically significant (p=0.05).

Definitions of bleeding events differed between the studies. The adjusted event rates for minor bleeding were 0.18 per patient (95% CI: -0.16, 0.52) for twice-daily heparin and 0.14 per patient (95% CI: 0.094, 0.184) for three-times-daily
heparin (no significant difference). For major bleeding, the adjusted event rates were 0.33 per patient (95% CI: 0.14, 0.52) for twice-daily heparin and 0.73 per patient (95% CI: 0.20, 1.27) for three-times-daily heparin. This difference was significant (p<0.001).

In the sensitivity analysis, 1 study with 5,776 patients, and which differed from the other studies in terms of results and outcome assessment method, was found to change the results. On excluding this study, adjusted event rates for DVT and for combined DVT or PE became significantly greater in the twice-daily heparin groups than in the three-times-daily heparin groups. The difference between treatment schedules in major bleeding rates was no longer significant.

Authors' conclusions
Unfractionated heparin three times a day appears to be superior to heparin twice a day in preventing clinically relevant venous thromboembolism events. However, this schedule might increase rates of major bleeding, therefore treatment needs to be individualised to patients depending on their underlying risk factors.

CRD commentary
This review had clearly stated inclusion criteria with respect to the study design, participants, interventions, and outcomes. The authors searched eight relevant databases without any language restrictions and made efforts to identify supplemental information. The review may be subject to publication bias as unpublished studies were not sought; the authors assessed publication bias but did not present the results. The review methods were well-reported and two reviewers conducted the study selection, quality assessment and data extraction processes independently, thereby reducing the likelihood of reviewer error and bias. The quality of the included studies was assessed and discussed.

The trial characteristics were well-described, but details on study populations were somewhat lacking, making the assessment of baseline risk for venous thromboembolism difficult; the authors acknowledged this problem. The trials also differed in terms of the comparator treatment and methods for detecting outcomes, and although the authors stated that they assessed heterogeneity, they did not present the results. The analysis carried out was an indirect comparison of two treatment schedules. Unlike a direct comparison, this carries an increased risk of bias and systematic differences between studies, especially as in this case the group of trials examining twice-daily heparin dosing regimens was dominated by one large trial which was quite different from the others. However, sensitivity analyses were carried out to examine the difference in results with or without the inclusion of this study. Although this review was generally well-conducted, the conclusions may not be reliable as they are based on indirect comparisons of heterogeneous studies.

Implications of the review for practice and research
Practice: The authors stated that in practice, heparin dosing regimens for hospitalised patients should depend on the patient’s risk for venous thromboembolism or bleeding, with patients at high risk from bleeding probably benefiting more from the twice-daily regimen and those at high risk from venous thromboembolism benefiting more from the three-times-daily regimen. Research: The authors did not state any implications for further research.

Bibliographic details

PubMedID
17296655

DOI
10.1378/chest.06-1861

Indexing Status
Subject indexing assigned by NLM
MeSH
Drug Administration Schedule; Fibrinolytic Agents /administration & dosage /adverse effects; Heparin /administration & dosage /adverse effects; Hospitalization; Humans; Thromboembolism /prevention & control; Treatment Outcome

AccessionNumber
12007000891

Date bibliographic record published
31/01/2008

Date abstract record published
31/01/2008

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.