Prevention of venous thromboembolism in neurosurgery: a metaanalysis

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CRD summary
The review evaluated the safety and effectiveness of heparin and mechanical devices in the prevention of venous thromboembolism and bleeding in neurosurgery patients. Low-molecular-weight heparin and intermittent compression devices were both effective in preventing venous thromboembolism. A combination of treatments may be appropriate for high-risk groups. Potential limitations in the review process made the reliability of the conclusions unclear.

Authors' objectives
To evaluate the safety and effectiveness of the prophylactic use of heparin and mechanical devices in the prevention of venous thromboembolism and bleeding in neurosurgery patients.

Searching
MEDLINE, EMBASE, BIOSIS Previews, Cochrane Central Register of Controlled Trials (CENTRAL), PASCAL, SciSearch, IPA and CRISP were searched from 1960 to August 2007 for publications in any language. Bibliographies of each retrieved article were handsearched. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) and prospective cohort studies that evaluated venous thromboembolism prophylaxis with either unfractionated heparin or low-molecular-weight heparin (LMWH) or mechanical venous thromboembolism prophylaxis with intermittent compression devices (ICDs) or compression stockings primarily in neurosurgical patients were eligible for inclusion. Studies were excluded if they were primarily of patients with penetrating or closed head injuries, spinal cord injuries or stroke. The trials included head-to-head trials that compared different mechanical prophylaxes, different heparin prophylaxes or mechanical versus heparin prophylaxis and placebo-controlled trials. The LMWH agents used were dalteparin, enoxaparin, nadroparin and fraxiparin; dosing regimens were reported in the paper. Craniotomy and spinal patients were included. Mean age ranged from 37 to 60 years. The proportion of males ranged from 30% to 62%. Eligible outcomes were objective assessments of deep venous thrombosis (DVT) (with Doppler compression sonography, impedance plethysmography, radiofibrinogen uptake scanning, autopsy or venography) and pulmonary embolism (with CT angiography, ventilation perfusion scanning, pulmonary angiogram or by autopsy) with the reporting of incidence. Outcomes reported were DVT, pulmonary embolism, minor bleeding events, major bleeding events, intracranial haemorrhage, reoperation for bleeding, death and whether death was study related.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Study quality was assessed by two reviewers independently using the Jadad scale. An adapted tool from McMaster was used to rate prognostic quality in terms of patient characteristics; selection criteria; selection bias; explained loss to follow-up; and relevance and objectivity of outcomes. Disagreements were resolved by consensus. One quality score was reported for each study; this appeared to be the prognosis quality rating.

Data extraction
The number of events for each outcome were extracted to calculate relative risk (RR) and 95% confidence intervals (CI).

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Relative risks for nine studies were pooled in a random-effects meta-analysis (DerSimonian and Laird). Overall and annualised rates were calculated for both RCTs and cohort studies combined. Heterogeneity was explored using $\chi^2$ and $I^2$ tests and visually using Galbraith plots. Publication bias was assessed using the methods of Begg and Berlin, Egger et al. and Duvall and Tweedie, and visually from funnel plots. A sensitivity analysis was carried out to assess the effect of study quality and other selected study characteristics with stratified analysis and random-effects meta regression.

**Results of the review**

Thirty studies were identified: 18 RCTs ($n=2,639$), of which six were double blind; and 12 cohort studies ($n=5,098$). The number of studies that investigated each intervention was: LMWH 11 studies; unfractionated heparin 12 studies; ICD 18 studies; and compression stockings 10 studies.

The reported mean Jadad score for the RCTs was 5.81 (range 2 to 8). The mean prognostic quality score was 7.0 (range 5 to 8) for the RCTs and 6.2 (range 3 to 8) for the cohort studies. Many studies were reported to show evidence of selection bias.

**Efficacy:** Meta-analysis of the RCTs for DVT or pulmonary embolism prophylaxis found only two statistically significant results: ICDs significantly reduced DVTs compared to placebo (RR 0.41, 95% CI 0.21 to 0.78; two studies, $I^2$ squared=0%) and LMWH significantly reduced DVTs compared to compression stockings (RR 0.60, 95% CI 0.44 to 0.81; two studies, $I^2$=0%).

Non-significant results were found for ICD versus compression stockings, LMWH versus ICD, LMWH versus unfractionated heparin and unfractionated heparin versus placebo. DVT rates and pulmonary embolism rates were reported and pooled for all studies; these gave similar results to those for the RCTs alone. Pulmonary embolism rates were lower than those for DVT.

**Safety:** Meta-analysis of the RCTs for intracranial haemorrhage, minor bleeding, major bleeding and death found only one statistically significant result: LMWH versus nonpharmacological prophylaxis significantly increased minor bleeding (RR 2.06, 95% CI 1.07 to 3.96; four studies, $I^2$=0%).

Non-significant results were found for unfractionated heparin versus nonpharmacological prophylaxis and LMWH versus unfractionated heparin. When rates of intracranial haemorrhage were compared for all studies, patients who received LMWH had significantly higher bleeding rates than those who received mechanical prophylaxis ($p<0.0005$), although patients who received unfractionated heparin did not have higher intracranial haemorrhage rates ($p=0.40$). There were no significant differences found for minor bleeding rates and major bleeding rates. Major bleeding rates were relatively low.

**Sensitivity analysis:** Sensitivity analysis found that prospective cohort trials reported lower rates of DVT than RCTs ($p=0.03$). Older patients and those who were treated for neoplasms had higher DVT rates. Patients who received preoperative heparin had lower rates of DVT than those who received their first dose postoperatively ($p=0.001$). There was no difference in rates of intracranial haemorrhage between heparin administered preoperatively, intraoperatively or postoperatively. After adjustment for age, neoplasm and study design, LMWH ($p=0.02$), unfractionated heparin ($p=0.001$) and ICD ($p=0.04$) prophylaxes had lower DVT rates than either compression stockings or placebo. After adjustment, patients with LMWH had a higher intracranial haemorrhage incidence than those with mechanical prophylaxis.

**Authors' conclusions**

In neurosurgical patients, LMWH and ICDs were both effective in preventing venous thromboembolism. There was no significant difference in the incidence of intracranial haemorrhage for LMWH prophylaxis compared to nonpharmacological methods. The pooled rates of intracranial haemorrhage and minor bleeding were generally higher with heparin therapy than with mechanical prophylaxis.

**CRD commentary**

The review addressed a well-defined question supported by explicit selection criteria. Relevant databases were searched for studies in any language, but it seemed that unpublished studies were not considered. Publication bias was
assessed. Study quality was assessed with suitable criteria, but the reporting of results was unclear. Quality assessment was carried out with efforts to reduce reviewer error and bias; it was unclear whether this process applied to other aspects of the review process. Relevant study details were reported, but no details of length of follow-up and loss to follow-up were given. There was little data relevant to the placebos used. Statistical heterogeneity was assessed and this was present for some outcomes, which suggested that the chosen method of synthesis was appropriate. Relative risks were not derived for the analysis of RCTs and cohort studies combined, which made comparisons difficult. It was unclear why relative risks were calculated for the meta-analysis of the RCTs only and not for all studies. Sensitivity analysis provided the basis for some recommendations for practice. In view of some potential limitations arising from the review process and uncertainties about the reported quality of included studies, the extent to which the authors conclusions are reliable is unclear.

Implications of the review for practice and research

Practice: The authors stated that a combination of prophylactic treatments might be beneficial for specific high-risk groups, such as patients undergoing craniotomy for neoplasm.

Research: The authors stated that further studies were needed in elderly patients and those undergoing craniotomy for neoplasm to compare therapy with LMWH and ICDs and determine benefits from chemical prophylaxis. RCTs with well-defined definitions of bleeding and other complications were required.

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