Efficacy and safety of anticoagulants in the prevention of venous thromboembolism in patients with acute cerebral hemorrhage: a meta-analysis of controlled studies
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CRD summary
The review found that early treatment with anticoagulants was associated with a significant reduction in pulmonary embolism and a non-significant reduction in death, with the trade-off of a non-significant increase in haematoma enlargement in patients with acute haemorrhagic stroke. Due to limited evidence of variable quality, the conclusions should be considered tentative.

Authors' objectives
To assess the efficacy and safety of anticoagulants for the prevention of venous thromboembolism in patients with acute haemorrhagic stroke.

Searching
MEDLINE, EMBASE (from January 1980 to November 2010), and The Cochrane Library (Issue 1, 2010) were searched; search terms were reported. Reference lists of retrieved studies were scanned. Abstracts from major international meetings were manually searched for unpublished studies.

Study selection
Randomised or non randomised studies that compared anticoagulants (unfractionated heparin, low-molecular weight heparin or heparinoid) with other treatments (intermittent pneumatic compression and/or elastic stockings or placebo) for the prevention of thromboembolism in patients with acute hemorrhagic stroke were eligible for inclusion in the review. Randomised trials were required to undertake randomisation within six days from haemorrhagic stroke onset; non-randomised studies were required to initiate treatment within six days from haemorrhagic stroke onset. Studies were required to use objective methods to assess one or more of the outcomes. Outcomes included symptomatic or asymptomatic deep venous thrombosis, symptomatic or asymptomatic pulmonary embolism, haematoma enlargement or re-bleeding, and death.

In the included studies, anticoagulant treatment included enoxaparin (20 to 40mg daily) or heparin (2,500 UI to 5,000 UI every eight to 12 hours). Initiation of treatment ranged from one to six days. Duration of treatment ranged from 10 to 14 days (where reported). Anticoagulant treatment was compared with compression stockings or no treatment. Deep venous thrombosis diagnosis was undertaken by Doppler or phleboscintigraphy; pulmonary embolism was diagnosis by computed tomography (CT) angiography or perfusion scintigraphy (where reported).

The authors did not state how many reviewers selected studies for the review.

Assessment of study quality
Studies were assessed for quality using criteria proposed by Schultz. These included proper generation of the treatment allocation sequence, proper concealment of the allocation sequence, blinding of the patient and the investigator assessing clinical outcomes to treatment allocation, and completeness of follow up.

Two reviewers independently assessed studies for quality, with disagreements resolved by consensus.

Data extraction
Data were extracted to calculate event rates and risk ratios (RRs) together with 95% confidence intervals (CIs). Where data were not available in the study publications, authors were contacted for further information.

Two reviewers independently extracted data, with disagreements resolved by discussion.

Methods of synthesis
Studies were pooled in meta-analyses. Summary effect estimates with 95% confidence intervals were calculated using a
Mantel-Haenszel random-effects model. Heterogeneity was assessed using the \(X^2\) test (\(p<0.1\) was considered significant) and quantified with \(I^2\).

Sensitivity analyses were undertaken to test the robustness of the results by excluding studies one at a time.

**Results of the review**

Four studies were included in the review (\(n=1,000\) patients). Two studies were randomised controlled trials (RCTs). One RCT reported allocation sequence and blinding of investigators. No patients were lost to follow-up in any of the studies, but one study did not report the duration of follow-up. Follow-up in the other studies ranged from 10 days to three months.

Compared with control treatments, anticoagulants were associated with a significant reduction in pulmonary embolism (RR 0.37, 95% CI 0.17 to 0.80; four studies).

There was no evidence of significant differences between groups in the rate of deep venous thrombosis or haematoma enlargement.

Compared to control treatments, anticoagulants were associated with a reduction (non-significant trend) in all-cause mortality (RR 0.76, 95% CI 0.57 to 1.03; three studies).

Sensitivity analyses changed some of the overall findings. With the removal of a study from the meta-analysis that contributed the most weight estimating pulmonary embolism rate, the summary estimate was no longer significant. With the removal of the same study (differently weighted) from the meta-analysis estimating haematoma enlargement, the results were statistically significant indicating risk of haematoma was increased with anticoagulants compared with control treatments. With the removal of one study from the meta-analysis estimating mortality, the results were statistically significant and indicated that risk of death was reduced with anticoagulants compared with control treatments.

There was no evidence of significant heterogeneity in any of the analyses.

**Authors’ conclusions**

In patients with acute haemorrhagic stroke, early anticoagulation treatment was associated with a significant reduction in pulmonary embolism and no significant reduction in death, with the trade-off of a non-significant increase in haematoma enlargement.

**CRD commentary**

The review addressed a clear research question. Inclusion criteria were appropriately specified, although a broad range of controlled study designs were eligible for inclusion. A range of relevant sources were used to identify unpublished or published studies, which minimised the risk of publication bias. Appropriate methods were used to assess studies for quality and extract data, but the authors did not state how many reviewers were involved in selection of studies, so reviewer error and bias could not be ruled out.

A valid tool was used to assess studies for quality, but few studies were identified and quality was variable. No details were reported on the characteristics of participants, so the applicability of the findings was unclear. Pooling of studies in meta-analyses was apprioriate; heterogeneity was assessed. Sensitivity analyses were undertaken to test the robustness of results; the findings were changed by the exclusion of some studies. The review was underpowered to provide more specific recommendations on the timing of therapy, types and doses of drugs to use for benefit.

The authors advocated caution in the interpretation of the results. Due to the limited evidence of variable quality, the conclusions should be considered tentative.

**Implications of the review for practice and research**

**Practice:** The authors stated that a low dose of heparin within the first days from stroke onset may be relatively safe in patients with cerebral haemorrhage.

**Research:** The authors stated that further RCTs were required to assess the efficacy and safety of early heparin...
administration in patients with intracerebral haemorrhage.

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