Management of anticoagulation following central nervous system hemorrhage in patients with high thromboembolic risk

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CRD summary
The review acknowledged the low quality of the evidence, but suggested that it may be important to restart anticoagulation earlier than thought previously with the timing and intensity modified based on perceived individual risks. Further research was needed. Evidence limitations suggest that the findings should be interpreted with caution, but the authors' recommendation for further research seems appropriate.

Authors' objectives
To identify the optimal timing and intensity for anticoagulation re-initiation following central nervous system haemorrhage in patients with high thromboembolic risk.

Searching
MEDLINE and EMBASE were searched between 1975 and February 2009 with no language restrictions. Search terms were reported. Reference lists of included studies were searched manually and further articles were sought through Web of Science.

Study selection
Studies that reported haemorrhages in or immediately adjacent to the central nervous system (as diagnosed by computed tomography scan or magnetic resonance imaging) in patients on anticoagulation medication (warfarin, heparin or low-molecular-weight heparin with or without antiplatelet, but not antiplatelet therapy alone) were eligible for inclusion. Studies were required to report patient follow-up and haemorrhagic or thromboembolic complications. Studies that included pregnant patients and patients with infective endocarditis or haemorrhagic transformation of an infarct were excluded.

Included studies were conducted between 1978 and 2008. Most patients received anticoagulation due to cardiac disease (atrial fibrillation, prosthetic heart valves and rheumatic heart disease). Other indications for anticoagulation included cerebrovascular disease, deep vein thrombosis or pulmonary embolism, ischaemic heart disease and peripheral vascular graft. Some patients had multiple indications. Where reported, a small proportion of haemorrhages were located in the spine (6.3%) and posterior fossa (8.3%). Others were in the supratentorial compartment. A small proportion of patients had haemorrhages related to a secondary cause (tumour, arteriovenous malformation or cirrhosis). Predictors of haemorrhagic and thromboembolic complications were investigated in the review.

Two reviewers screened studies for inclusion. Any discrepancies were referred to a third reviewer.

Assessment of study quality
Two reviewers independently assessed the quality of case series according to the Downs and Black 27-item checklist. Discrepancies were resolved through referral to a third reviewer.

Data extraction
Two reviewers independently extracted data on time to anticoagulation re-initiation and final intensities following anticoagulation resumption. Incidence and timing of haemorrhagic and thromboembolic complications were extracted. Where timing was described as emergent, time from presentation to surgery was assumed to be six hours. Where haemorrhagic or thromboembolic complications were reported as a short time after admission or surgery, the timing was assumed to be 12 hours.

Where patients experienced a second re-haemorrhage, both events were included in the analyses. Discrepancies were resolved through referral to a third reviewer.
Primary authors were contacted for further data, where necessary.

**Methods of synthesis**
Timings of complications and anticoagulation restart were presented as significance levels (p values) and frequency plots. Univariate statistical analyses were undertaken using Fisher's exact test, Mantel-Haenszel $X^2$ and Mann-Whitney U-test to assess the effects of patient characteristics of patients with and without re-haemorrhage or thromboembolism. Patient characteristics included age, haemorrhage location, cause of haemorrhage (trauma or not), haemorrhage type, anticoagulation type, reversal, strategy (no anticoagulation restarted, anticoagulation at same intensity or restarted at a lower intensity). Sensitivity analysis excluded grouped case series data.

**Results of the review**
Seventeen case series, six grouped case series and 40 case reports (n=492 participants) were included in the review. Three studies were prospective and 60 were retrospective. Case series scored between 2.0 and 12.7 on the Downs and Black checklist.

Haemorrhagic complications were experienced by 7.7% of patients (mostly within 72 hours of haemorrhage) and thromboembolic complications were experienced by 6.1% (mostly after 72 hours post-haemorrhage). Statistical analyses demonstrated a significant increase in risk of thromboembolic complications when anticoagulation was restarted after 72 hours (p=0.006). There was a trend towards an increase in haemorrhagic complications when anticoagulation was restarted before 72 hours, but this was not statistically significant (p=0.0727).

Univariate analyses identified that re-haemorrhage was more common in younger patients, where haemorrhage was caused by trauma, subdural haematomas and failure to reverse anticoagulation. Thromboembolic complications were more common in younger patients and patients with spinal haemorrhage, multiple haemorrhages and non-traumatic causes of initial haemorrhage. Patients restarted at lower intensity anticoagulation were significantly more likely to experience a thromboembolic complication than patients restarted at previous intensity anticoagulation (p<0.0001).

Other results were reported in the review. Sensitivity analysis results were not reported.

**Authors' conclusions**
Evidence based on low-quality studies suggested that it may be important to restart anticoagulation should earlier than thought previously, with the timing and intensity modified based on predictors of thromboembolic and haemorrhagic complications. The findings needed further exploration in a prospective study.

**CRD commentary**
The review question was clear and supported by clear inclusion criteria. The literature search was limited to two electronic databases. There were no language restrictions, which reduced potential for language bias. Only published data were sought, so potentially relevant data may have been missed. The quality of case series was assessed using previously published criteria. The authors acknowledged that the overall quality of the evidence was low. Each stage of the review process was undertaken in duplicate, which reduced risks of reviewer error and bias. The authors acknowledged that the evidence was based on a heterogeneous group of patients and most of studies were retrospective. Studies were published over a long time period during which medical practice changed. The studies were insufficiently powered. A large amount of missing data was not accounted for. Only a small proportion of patients experienced haemorrhagic or thromboembolic complications and statistical analyses were limited.

Evidence limitations suggest that the results should be interpreted with caution, but the authors' conclusions about the study limitations and need for further research seem appropriate.

**Implications of the review for practice and research**
**Practice:** The authors stated that the evidence suggested that clinicians should consider individual patient risks when selecting anticoagulant restart time and intensity.
Research: The authors stated that a prospective trial was needed to explore the findings and further research is needed in which relative morbidity of haemorrhagic and thromboembolic complications were taken into consideration.

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