D-dimer testing in the diagnosis of cerebral vein thrombosis: a systematic review and a meta-analysis of the literature

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CRD summary
This generally well-conducted review concluded that D-dimer may be a useful diagnostic tool in the management of patients with suspected cerebral vein thrombosis. Although based on a relatively small number of studies and participants, the authors’ conclusions reflected the available data and are likely to be reliable.

Authors’ objectives
To assess the accuracy of D-dimer testing for the diagnosis of cerebral vein thrombosis.

Searching
MEDLINE and EMBASE were searched from inception to July 2011 without language restrictions. Search terms were available from the authors. Conference abstracts from the International Society on Thrombosis and Haemostasis and the European Neurological Society were also searched. The bibliographies of retrieved articles were screened for additional studies.

Study selection
Studies were eligible for inclusion if they assessed the performance of D-dimer testing for the diagnosis of cerebral vein thrombosis and used angiography, magnetic resonance imaging, magnetic resonance venography, or computed tomography venography as the reference standard to confirm diagnosis. Included studies were required to report a minimum of sufficient data to allow the calculation of sensitivity.

Half of the included studies assessed the accuracy of D-dimer testing in participants with suspected cerebral vein thrombosis; the remaining studies included only those with confirmed cerebral vein thrombosis. D-dimer tests used in the included studies were Enzyme-Linked Immunoassay (ELISA), immuno-turbidimetric methods, latex immunoassay and qualitative immunoassay. Most included studies used a diagnostic threshold of over 500ng/mL. Reference standards varied across studies (details were reported in the article).

Two reviewers independently assessed studies for inclusion; any disagreements were resolved by discussion, or consultation with a third reviewer.

Assessment of study quality
The methodological quality of included studies that assessed the accuracy of D-dimer testing in patients with suspected cerebral vein thrombosis was assessed using a modified version of the QUADAS tool; two items ‘Were index test results interpreted without knowledge of the reference standard results?’ and ‘Were un-interpretable/intermediate test results reported?’ were omitted.

Two reviewers independently assessed study quality; any disagreements were resolved by discussion, or consultation with a third reviewer.

Data extraction
Data were extracted on the sensitivity and, where possible, specificity of D-dimer testing. The results of studies that evaluated potential predictors of false negative D-dimer results were also extracted. Study authors were contacted for additional information where needed.

Two reviewers independently extracted data; any disagreements were resolved by discussion, or consultation with a third reviewer.

Methods of synthesis
A bivariate random-effects regression model was used to calculate summary estimates of sensitivity and specificity,
with 95% confidence intervals (CIs).

**Results of the review**
Fourteen studies (1,134 participants, range 5 to 343) were included in the review. Withdrawals were not explained in 30% of included test accuracy studies. Approximately 73% of studies did not report whether the reference standard was interpreted blind to index test results. The description of the index test was unclear in approximately 15% of studies. Other QUADAS criteria were met by all studies.

Seven studies (926 participants) evaluated D-dimer accuracy in patients with suspected cerebral vein thrombosis. The pooled estimate of sensitivity from these studies was 93.9% (95% CI 87.5 to 97.1) and the pooled estimate of specificity was 89.7% (95% CI 86.5 to 92.2).

Potential risk factors for false negative D-dimer results included isolated headache (two out of three studies), longer duration of symptoms (two out of four studies), and limited sinus involvement (combined results of three studies).

A sensitivity estimate derived from all study participants with objectively confirmed cerebral vein thrombosis was also reported.

**Authors’ conclusions**
D-dimer may be a useful diagnostic tool in the management of patients with suspected cerebral vein thrombosis.

**CRD commentary**
This generally well-conducted review reported a clear research objective and defined appropriate inclusion criteria. A number of sources, including conference proceedings, were searched for relevant studies and no language restrictions were applied, which reduced the possibility of missing relevant studies. Measures to minimise error and bias were applied throughout the review process.

The methodological quality of included studies was assessed and reported in the article. Appropriate meta-analytic methods were used to produce summary estimates of sensitivity and specificity. The reference standard used by studies in the bivariate meta-analysis varied, but all studies included magnetic resonance venography in the reference standard.

Although based on a relatively small number of studies and participants, the authors' conclusions reflected the available data and are likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors did not specify any recommendations for clinical practice.

**Research:** The authors stated that future prospective studies were needed to confirm their preliminary findings and to develop a clinical model for the stratification of patients with suspected cerebral vein thrombosis into high, moderate and low pre-test probability. D-dimer test performance data were also needed for pregnant patients.

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