Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke: a systematic review


CRD summary
This review evaluated the evidence on cerebral blood flow (CBF) thresholds for irreversible infarct core and penumbra in adult stroke patients. The authors concluded that use of cerebral blood flow thresholds in commercial software for imaging methods could not be recommended without further evaluation. This was generally a well-conducted review and the conclusions are likely to be reliable.

Authors' objectives
To evaluate the evidence on cerebral blood flow thresholds for irreversible infarct core and penumbra in adult stroke patients.

Searching
MEDLINE (January 1966 to March 2004), EMBASE (January 1982 to March 2004), The Cochrane Library (January 1993 to March 2004) were searched without language restrictions. Search terms were reported. Reference lists of primary studies and review articles were checked and experts and authors contacted.

Study selection
Studies of adults with acute ischaemic stroke that reported cerebral blood flow thresholds using any technique and follow-up brain computed tomography (CT) or brain magnetic resonance (MR) was used as the reference standard for diagnosing the finally infarcted area (based on accepted diagnostic criteria) were eligible for inclusion.

Participants had a mean age of 64 to 74.6. The proportion of males varied from 42.1% to 70%. Where reported, stroke severity was measured using patient level description (various measures), the National Institutes of Health Stroke Scale Score (NIHSS) and the European stroke scale. The index tests evaluated were positron emission tomography (PET) and perfusion/diffusion weighted magnetic resonance imaging (PW-DW MRI).

The approaches used to derive cerebral blood flow thresholds for penumbra using PET were lowest cerebral blood flow in non-infarcted tissue and 85% negative prediction limits based on probability curves. Threshold to derive cerebral blood flow thresholds for infarct core were highest cerebral blood flow in infarcted tissue and 95% positive prediction limits based on probability curves.

In studies that used PW-DW MRI, the thresholds used to derive cerebral blood flow thresholds for penumbra were best threshold based on discriminant analysis and best threshold from ROC curve. The threshold used to derive infarct core was best threshold from ROC (receiver operating characteristic) curve. Mean cerebral blood flow in regions diagnosed as penumbra and infarct were used to derive thresholds for both penumbra and infarct core in one study. The reference tests used were CT, magnetic resonance imaging (MRI), fluid attenuated inversion recovery (FLAIR) and diffusion weighted T2 weighted MRI (DW-T2W MRI). Cerebral blood flow threshold for penumbra and infarct were reported in most of the included studies. Prospective and retrospective cohort studies were included.

Two reviewers independently selected primary studies and disagreements were resolved by discussion with a third reviewer.

Assessment of study quality
The Standards for Reporting of Diagnostic Accuracy (STARD) and the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) criteria were used to assess methodological quality. Study design, study population, description of reference and index tests, independent and blind comparison between reference and index tests, co-registration of the index and reference tests and treatment administration were evaluated.

Two reviewers independently assessed validity and disagreements were resolved through discussion with a third reviewer.
reviewer.

**Data extraction**
The cerebral blood flow thresholds for penumbra and for infarct were extracted as reported in the primary studies. The time interval between the onset of symptoms and cerebral blood flow measurement and whether tissue reperfusion had occurred during this interval were also extracted. Authors were contacted for further information where necessary.

Two reviewers independently performed data extraction. Disagreements were resolved through discussion with a third reviewer.

**Methods of synthesis**
The studies were combined in a narrative synthesis and study details were presented in tables. A regression analysis was performed to assess whether there was evidence of an association between cerebral blood flow threshold value and time interval between the onset of symptoms and initial cerebral blood flow measurement.

**Results of the review**
Seven cohort studies were included in the review (n= 161): five prospective (n=70) and two retrospective (n=91)

A range of optimal cerebral blood flow thresholds for penumbra (14.1 and 4.8 mL/100g per minute) and infarct core (35.0 and 8.4 mL/100g per minute) were reported. Four studies reported sensitivity and specificity; two studies reported similar optimal thresholds of 29.5 and 24 mL/100g per minute and sensitivity and specificity (sensitivity of 91% and 88% and specificity of 73% and 66%). One study an optimal threshold of 14.1mL/100g per minute (sensitivity 72%, specificity 90%), which was a lower threshold that corresponded to a lower level of sensitivity and higher specificity than the two studies mentioned previously. One study reported a threshold of 35mL/100g (sensitivity 69%, specificity 85%).

Regression analysis showed no significant association between cerebral blood flow threshold value and time interval between the onset of symptoms and initial cerebral blood flow measurement.

**Authors’ conclusions**
The use of cerebral blood flow thresholds in commercial software for imaging methods could not be recommended without further evaluation.

**CRD commentary**
The review question was clear in terms of participants, outcomes and intervention. Published and unpublished sources were searched and databases were searched without language restrictions, which reduced the possibility of publication and language biases. Study selection, validity assessment and data extraction were performed in duplicate, which reduced the possibility of reviewer bias and error. The studies were predominately presented in a narrative synthesis, which was appropriate given the heterogeneity of the primary studies. This was generally a well-conducted review and the authors’ conclusions are likely to be reliable.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that adoption of standardised cerebral blood flow measurement techniques and measures of arterial reperfusion should be important considerations in future studies. They added that prospective studies on larger patient samples with blind comparison between index and reference tests were necessary to validate cerebral blood flow thresholds. Reporting of results should be based on ROC curves.

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