Metaanalysis of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage

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CRD summary
This review concluded that tirilazad had no effect on clinical outcome after subarachnoid haemorrhage, but did decrease symptomatic vasospasm in five trials. Poor reporting of the review process means that the reliability of the authors' conclusions cannot be determined.

Authors' objectives
To evaluate the effects of tirilazad after subarachnoid haemorrhage.

Searching
Clinical trials were found through searches that were not described. The Cochrane Library was also searched (Issue 3, 2008) and additional studies sought through examination of the references of papers obtained and contact with authors.

Study selection
Trials of tirilazad conducted in patients with subarachnoid haemorrhage appeared to be eligible for inclusion. The main outcome of interest was clinical outcome at three months measured on the Glasgow Outcome Scale (unfavourable outcome). Secondary endpoints were symptomatic vasospasm (defined by clinical criteria described in paper) and occurrence of cerebral infarction on computed tomography at three months. Safety endpoints were phlebitis, pulmonary complications, sepsis, hypotension, intracranial haemorrhage/re-bleeding, brain oedema and increased intracranial pressure.

The randomised controlled trials (RCTs) were conducted in neurosurgical centres in Europe, Australia, New Zealand, South Africa and North American between 1990 and 1997. The mean age of included patients ranged from 51 to 53 years. The majority of trials included males and females (two trials were 100% female). Included trials compared tirilazad with placebo and used doses of tirilazad ranging from 0.6 to 15mg/kg/day, administered over 10 days. One trial was a dose ranging study. Treatment was within 48 to 72 hours of subarachnoid haemorrhage.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they systematically assessed validity, but blinding, method of randomisation, completion rates and comparison of baseline characteristics were reported.

Data extraction
Patients that had received at least one dose of medication were included in the analysis. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated for each outcome.

The authors did not state how data were extracted for the review, or how many reviewers performed that data extraction.

Methods of synthesis
Odds ratios and 95% confidence intervals were pooled using fixed-effect or random-effects models for homogenous or heterogeneous results respectively. The random-effects model used was the maximum likelihood method. A bivariate random-effects model was also used to relate treatment effect size to the risk of events in the control group while controlling for haemodynamic therapy. Dose was divided into low (\leq 6 \text{mg/kg/day}) or high (>6\text{mg/kg/day}), and treatment-response and dose-response relationships were modelled using logistic regression analyses. Clinical outcome was analysed as a dichotomous variable; unfavourable outcomes were classified as severe disability, vegetative state or death. Logistic regression was used to determine the effect of tirilazad after adjustment for potential confounding variables. Analyses were also performed to determine if there was an interaction between tirilazad and two dependent
variables (Glasgow Outcome Scale and symptomatic vasospasm) and gender; use of anticonvulsants and World Federation of Neurosurgical Societies (WFNS) grade. Statistical heterogeneity, publication bias were assessed and sensitivity analyses were performed (details not reported).

Results of the review
Five RCTs were included (n=3,819 patients; 3794 included in the analysis). All RCTs were randomised, double blinded and placebo controlled; randomisation was in blocks of four and stratified by treatment centre. Four RCTs reported completion rates. 80% of placebo patients and 81% tirilazad patients completed treatment; it was reported that there was no significant baseline differences between groups.

Tirilazad was associated with a significant decrease in symptomatic vasospasm (OR 0.80, 95% CI 0.69 to 0.93; five RCTs). Sensitivity analysis showed that exclusion of any one of three trials significantly influenced the meta-analysis result. A tirilazad dose greater than 6mg/kg/day was associated with significantly decreased odds of symptomatic vasospasm (OR 0.75, 95% CI 0.61 to 0.93; two RCTs) but this was not significant for doses of less than 6mg/kg/day. The odds of symptomatic vasospasm also decreased progressively with increasing dose of tirilazad (number of trials unclear). Logistic regression analyses showed that tirilazad was independently associated with decreased vasospasm, but had no effect on Glasgow Outcome Scale or cerebral infarction. There were no significant interactions between tirilazad and gender, use of anticonvulsants and WFNS grade when considering Glasgow Outcome Scale and symptomatic vasospasm. Results were similar with adjustment for anticonvulsant use and whether sedation affected reliability of symptomatic vasospasm diagnosis.

Tirilazad was not significantly associated with unfavourable outcome (as measured by Glasgow Outcome Scale) (five RCTs) or cerebral infarction (four RCTs) compared with placebo.

Publication bias was not indicated. Significant statistical heterogeneity was only present for the outcomes of cerebral infarction (p=0.02) and the subgroup analysis for this outcome (less than 6mg/kg/day tirilazad dose) (p=0.01).

There was no significant difference between tirilazad and placebo groups in the likelihood of phlebitis (four RCTs), pulmonary complications (two RCTs), sepsis (four RCTs), hypotension (three RCTs), intracranial haemorrhage/re-bleeding (five RCTs), brain oedema (two RCTs), increased intracranial pressure (four RCTs) or arrhythmias (one RCT).

Authors' conclusions
Tirilazad had no effect on clinical outcome but did decrease symptomatic vasospasm in five trials of aneurysmal subarachnoid haemorrhage.

CRD commentary
The research question was supported by inclusion criteria for participants, intervention and study design, but these were not clearly stated. The searches were not well described but appeared to be limited. It was not clear whether any language restrictions were imposed or whether the searches were restricted to published studies, so publication and language biases could not be ruled out. The authors did appear to have assessed validity but the criteria were not described. The review process was not described, so it was not known whether reviewer error and bias was a possibility. Meta-analysis appeared to be appropriate and heterogeneity was examined. Poor reporting of the review process means that the reliability of the authors' conclusions cannot be determined.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that the dissociation between outcome and symptomatic vasospasm needs to be studied.

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