Vasopressin for cardiac arrest: a systematic review and meta-analysis

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CRD summary
This review assessed the effectiveness of vasopressin compared with epinephrine in the treatment of cardiac arrest. The authors concluded that vasopressin has no clear advantage over epinephrine in this context. This appears to be a well designed and conducted systematic review, so the authors’ conclusions are likely to be reliable.

Authors’ objectives
To determine the effectiveness of vasopressin in the treatment of cardiac arrest.

Searching
MEDLINE, EMBASE, CINAHL and International Pharmaceutical Abstracts were all searched from inception to February 2004. The Cochrane CENTRAL Register (Issue 4, 2003) and DARE (first quarter of 2004) were also searched. The search terms used were reported and no language restrictions were applied. The reference lists of relevant studies, review articles and included studies were also manually checked, and ongoing trials and unpublished studies were sought electronically via web-based ongoing trials registers.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies were eligible for inclusion if the intervention group received intravenous vasopressin and the control group received intravenous epinephrine. Four of the included trials used the dose of 40 U of vasopressin; one trial used two different dosages, 0.5 U/kg and 1.0 U/kg body weight.

Participants included in the review
Studies of participants with cardiac arrest who had received cardiopulmonary resuscitation either in or out of hospital were eligible for inclusion. Three of the included trials investigated patients with out-of-hospital cardiac arrest, whilst two trials investigated patients with in-hospital cardiac arrest.

Outcomes assessed in the review
Studies that reported patient-important primary outcomes such as morbidity and mortality, rather than surrogate outcomes, were eligible for inclusion. The specific outcomes of interest were failure of return of spontaneous circulation (ROSC), death before hospital admission (if the cardiac arrest occurred out of hospital), death within 24 hours, death before hospital discharge, and the combination of number of deaths and neurologically impaired survivors.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed trials for inclusion in the review, with any disagreements resolved by consensus. External translators were used for assessing the eligibility of studies written in languages unfamiliar to the reviewers.

Assessment of study quality
Study quality was assessed using the 6-item Jadad scale. Two reviewers independently extracted data on the validity of the included studies, with any disagreements resolved by consensus.

Data extraction
Two reviewers independently extracted the data on the included studies, and the results were crosschecked using double
data entry. Any disagreements were resolved by consensus. Event rates were compared using risk ratios (RRs), although it was unclear whether these were extracted directly from the included studies or were calculated by the authors of the review.

**Methods of synthesis**

**How were the studies combined?**
The RRs from the studies were pooled using both a random-effects model (DerSimonian and Laird) and a fixed-effect model (Mantel-Haenszel), to produce estimates for the overall RR and 95% confidence interval (CI) for each pre-specified outcome.

Publication bias was assessed using the Egger test (Egger publication bias funnel plot).

**How were differences between studies investigated?**
The presence of statistical heterogeneity was investigated using the chi-squared test and quantified by calculating I². Both random-effects and fixed-effect models were produced for each outcome, and the results of these were compared. Subgroup analyses, which were defined a priori, were also performed to investigate possible differences between the studies.

**Results of the review**

Five RCTs (n=1,519) met the inclusion criteria.

There were no statistically significant differences between vasopressin and epinephrine in terms of any of the five pre-specified outcomes of interest: failure of ROSC (5 RCTs; RR 0.81, 95% CI: 0.58, 1.12), death before hospital admission (2 RCTs; RR 0.72, 95% CI: 0.38, 1.39), death within 24 hours (2 RCTs; RR 0.74, 95% CI: 0.38, 1.43), death before hospital discharge (5 RCTs; RR 0.96, 95% CI: 0.87, 1.05), or combination of the number of deaths and neurologically impaired survivors (3 RCTs; RR 1.00, 95% CI: 0.94, 1.07).

The results of the pre-specified subgroup analyses also showed no statistically significant difference between vasopressin and epinephrine. However, the presence of statistical heterogeneity was reduced, in particular for death before hospital discharge when based on initial rhythm.

The methodological quality of the included studies ranged from a Jadad score of 5 (highest quality) for 3 studies to a score of 2 for the remaining 2 studies, although one of these trials was only available as an abstract. Those scoring highly had adequate allocation concealment and blinding of the caregivers. All of the trials had similar rates of follow-up and performed an intention-to-treat analysis.

The funnel plot appeared asymmetric, indicating publication bias. However, no evidence of publication bias was found when using Egger's method for failure of ROSC (P=0.24).

The levels of inter-rater agreement at each stage were adequate to high, with kappa statistics ranging from 0.64 (agreement of quality assessment) to 0.72 (agreement for retrieval of full papers) to 1 (agreement of full papers to be included in the review).

**Cost information**
The authors stated that the use of vasopressin had substantial cost implications as 40 U of vasopressin cost approximately 15 times as much as 1 mg of epinephrine.

**Authors’ conclusions**
There was no clear advantage of vasopressin over epinephrine in the treatment of cardiac arrest.

**CRD commentary**
The review question was explicit in terms of the population, intervention, outcomes and study design of interest. A thorough search was performed, without language restrictions and unpublished literature was also sought. The authors assessed publication bias. The validity assessment, data extraction and screening of studies for inclusion were all performed in duplicate, thus minimising the possibility of reviewer bias and error.

Sufficient details of the primary studies were reported, allowing the reader to draw conclusions about the appropriateness of statistically synthesising the results of the studies. The techniques used for the data synthesis were appropriate and were well defined a priori, with the authors investigating possible sources of heterogeneity. This appears to be a well designed and conducted systematic review, so the authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that vasopressin should not be recommended in resuscitation protocols.

Research: The authors stated that future trials using the same outcomes should improve the precision of effect measures. They recommended that the subject be revisited on completion of the ongoing Pittsburgh trial.

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