CRD summary
This review concluded that epinephrine provided short-term benefits in patients with cardiac arrest, particularly high-dose epinephrine compared to low-dose epinephrine. Vasopressors were generally equivalent to epinephrine. Insufficient information about the included studies, vote counting of results and a limited quality assessment make the reliability of the authors' conclusions unclear.

Authors' objectives
To evaluate the effectiveness of vasopressors in patients who suffer cardiac arrest.

Searching
PubMed, EMBASE and The Cochrane Library were searched to October 2011 for relevant studies in English; search terms were reported. Worksheets from the C2005 International Liaison Committee on Resuscitation were checked for additional studies. Reference lists of retrieved articles were reviewed.

Study selection
Studies of patients in cardiac arrest treated with vasopressors (including epinephrine, norepinephrine) compared to standard treatment were eligible for inclusion. Eligible studies were required to present data on clinical outcomes. Cardiac arrest was defined as asystole, pulseless electrical activity, pulseless ventricular tachycardia and ventricular fibrillation. Unpublished studies and studies of vasopressors used in traumatic cardiac arrest were excluded.

The comparisons made in the review were vasopressors compared to placebo and epinephrine. Evaluations were undertaken of high-dose compared to low-dose epinephrine, epinephrine compared to other vasopressors and the role of vasopressors in paediatric populations. Standard doses of epinephrine were 1mg. Outcomes evaluated were return of spontaneous circulation, survival of event, survival to hospital discharge and neurological outcomes.

It appeared that two reviewers independently performed the study selection.

Assessment of study quality
The retrieved studies were classified by level of evidence and were graded as good, fair or poor based on established criteria for each evidence level. Randomised controlled trials were classified as level one evidence, non-randomised trials were classified as level two evidence and studies that used retrospective controls were graded as level three studies. Level four studies were studies without control groups.

The authors did not state how many reviewers assessed methodological quality.

Data extraction
Survival outcome data were extracted as reported in the included studies.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
The results were summarised in a narrative review and reported under intervention and comparator subheadings.

Results of the review
Fifty-four studies were included in the review (23,752 patients, range seven to 2,984). Thirty-one studies were good quality, 11 studies were fair and 12 studies were poor.

Vasopressors compared to placebo: Three randomised trials, one retrospective study, one prospective observational study (4,078 patients) rated as good, fair and poor quality.
Improvements in return of spontaneous circulation and hospital admission were observed in two trials but no significant differences were observed in survival to hospital discharge.

**Vasopressin compared to epinephrine:** One meta-analysis, eight RCTs, four level three studies and one study each at non-randomised trials and one single-group study (6,440 patients).

A meta-analysis of three trials that compared vasopressin and epinephrine found no differences in failure of return of spontaneous circulation, death before hospital admission death within 24 hours and death prior to hospital discharge. All RCTs found neutral results of comparisons between vasopressins and vasopressins used with epinephrine compared to epinephrine alone.

**High-dose epinephrine compared to low-dose epinephrine:** One meta-analysis, eight RCTs, two non-randomised trials, three retrospective studies and three single group studies (8,443 patients).

Three randomised trials showed significantly improved rates of return of spontaneous circulation and two showed improved rates of hospital admission with high-dose epinephrine (dose not defined) compared to standard dose epinephrine (1mg). The other five clinical trials showed no differences between epinephrine doses in return to spontaneous circulation, survival to hospital admission and discharge and neurological outcomes.

**Alternate vasopressors compared to epinephrine:** Six RCTs and one single group study (3,067 patients).

Three randomised trials found no differences in outcomes with epinephrine compared to methoxamine in return of spontaneous circulation or survival to hospital discharge. Norepinephrine was associated with higher rates of initial return of spontaneous circulation compared to standard dose epinephrine but there were no differences in long-term survival or neurological outcomes (although there were trends observed towards worse cerebral performance with norepinephrine). Similar rates of return of spontaneous circulation were observed in one trial of phenylephrine and epinephrine.

**Vasopressors in paediatric populations:** Two RCTs, four retrospective studies and four single group studies (1,724 patients).

Five studies found no differences between high dose epinephrine and low dose epinephrine in return of spontaneous circulation, survival data and neurological outcomes.

**Authors’ conclusions**
Epinephrine was associated with improvement in short-term survival but no benefits in long-term survival were observed. Equivalent results were observed for vasopressin compared with epinephrine when used as an initial vasopressor during resuscitation from cardiac arrest. Short-term survival benefits were observed for high-dose epinephrine compared to standard dose epinephrine during resuscitation from cardiac arrest but no differences were observed between epinephrine dosages in long-term survival. There were limited data on use of vasoppressors compared with placebo and of vasopressors in the paediatric population.

**CRD commentary**
The review addressed a clear question. Broad criteria for the inclusion of studies in the review were outlined. Appropriate databases were searched for relevant studies. The authors acknowledged that the restriction to studies in English risked language bias and exclusion of unpublished studies risked publication bias. Steps to minimise reviewer error and bias were reported for study selection but not for quality assessment and data extraction processes. Little information was presented on the quality assessment so the reliability of the results was uncertain. Limited information was provided on the studies. There were no analyses of heterogeneity between the results of the included studies. Studies with a wide range of designs were included in the review and the use of vote counting of significant results for each study precluded any meaningful analysis of the results (vote counting can be misleading and does not account for sample sizes and differential study quality).

Methodological flaws (particularly the limited quality assessment and use of vote counting) make the reliability of the authors’ conclusions unclear.
Implications of the review for practice and research

**Practice:** The authors stated there was sufficient supporting evidence of short-term improvements in outcomes when vasopressors were used during resuscitation and that vasopressors should continue to be included in Advanced Cardiac Life Support guidelines.

**Research:** The authors stated there was insufficient evidence to support or refute vasopressin as an alternative to or in combination with epinephrine in patients with cardiac arrest. Further studies of vasopressors were required in paediatric populations.

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