Vasopressin and epinephrine versus epinephrine in management of patients with cardiac arrest: a meta-analysis

ABSTRACT

Objective. A combination of vasopressin and epinephrine may be more effective than epinephrine alone in cardiopulmonary resuscitation (CPR), but evidence is lacking to make clinical recommendations. This meta-analysis compares the efficacy of vasopressin and epinephrine used together versus epinephrine alone in cardiac arrest (CA).

Methods. We searched MEDLINE and EMBASE for randomized trials comparing the efficacy of vasopressin and epinephrine versus epinephrine alone in adults with cardiac arrest. The primary outcome was the return of spontaneous circulation (ROSC) and the survival rate on admission and discharge. We also analyzed ROSC in subgroups of patients presenting with different arrest rhythms, such as asystole, pulseless electrical activity (PEA), ventricular fibrillation (VF).

Results. We analyzed 6 randomized trials out of 485 articles. We did not find evidence supporting the superiority of vasopressin and epinephrine used in combination, except for the survival rate at 24h 2.99 95% CI(1.43,6.28). No evidence supports the conclusion that vasopressin combined with epinephrine is better than epinephrine alone for ROSC, even amongst subgroups of patients.

Conclusion. This systematic review of the efficacy of vasopressin and epinephrine use found that its combined use is better for 24h survival rate but only in one study which included 122 patients. Further investigation will be needed to support the use of this combination for cardiac arrest management.

Key words: cardiopulmonary resuscitation, meta-analysis, epinephrine, vasopressin

Introduction

Survival rates for cardiac arrest patients, both in and out of hospital, are poor. Furthermore, survival without severe neurological impairment has not improved over the past few decades. Epinephrine has been used during cardiopulmonary resuscitation for more than 100 years, (1-3) but has become controversial because it is associated with increased adverse effects. An increasing body of evidence from laboratory investigations suggests that vasopressin may represent a promising alternative vasopressor for use during cardiac arrest and resuscitation. Several clinical trials have demonstrated superior survival rates with the use of vasopressin instead of epinephrine. (4,5) Recently, the potential benefit of the administration of both drugs has drawn researchers’ attention. There have been several human studies in which some patients received both vasopressin and epinephrine. Among those trials, some have reported more desirable outcomes with the administration of both drugs, including increased ROSC and survival rate. (6-8) The current international guidelines for CPR recommend the use of vasopressin during cardiac resuscitation as
a secondary alternative. This recommendation could lead to the use of vasopressin for millions of cardiac arrests worldwide. However, some clinical studies yielded contrasting findings. Therefore, our aim was to investigate the effectiveness of vasopressin and epinephrine for the treatment of patients with cardiac arrest.

**Materials and methods**

We searched MEDLINE, from January 1966 to December 2008, and EMBASE, from January 1950 to December 2008, for research papers. Keywords used in this search were (cardiac arrest) or (cardiopulmonary resuscitation) or (cardiopulmonary-cerebral resuscitation) and [epinephrine or adrenaline] and [vasopressin or argipressin or (antidiuretic hormone)].

In MEDLINE, the search was limited by the search words “Publication Date since 1966/01/01 till 2008/12/31”, “English” and “Human”. We excluded those research papers with the following keywords: “case reports”, “letter”, “review”, “practice guideline”, “review literature”, “review of reported cases”, “review, academic”, “review, multicase”, “review, tutorial”, “scientific integrity review”, “congresses”, “ interview”, “overall”, “comment”, “news”, “newspaper article” and “address”. In EMBASE, the search was limited by the search words: “Publication Date since ‚1950 till 2008”, “English” and “Human”. The search strategy was reviewed by library personnel to ensure that it was complete. We did not limit the articles published as abstracts only. The references of articles were searched for citations which may have been missed by the electronic search.

Eligible patients had a cardiac arrest and had been treated with CPR. The diagnosis of cardiac arrest and CPR was based on International guidelines. The process of diagnosis and management was registered according to the Utstein model. We looked at randomized trials comparing vasopressin to epinephrine for adults with cardiac arrest. Patients in the treatment groups were those who suffered a cardiac arrest and who had received vasopressin and epinephrine during CPR. The sequences of drug administration were not restricted. Patients in the control groups were those who experienced a cardiac arrest and were treated by CPR with epinephrine alone. Efficacy was compared between the treatment and control groups. The incidence of the ROSC, survival rate at 24 h, survival to hospital admission, survival to hospital discharge and neurologic outcome were recorded.

Odds ratio (OR) and 95% confidence intervals (95% CI) were calculated for the articles included. Pooled estimates of the odds ratio and 95% CI were obtained by the fixed-effects model of Peto with Review Manager 5.0 software. When there was heterogeneity, OR and 95% CI were obtained by the random-effect model of Mantel-Haenszel with Review Manager 5.0 software. Publication bias was assessed by Funnel plot.

**Results**

The search retrieved 485 papers, and 8 of them were cohort studies on cardiopulmonary resuscitation, vasopressin and epinephrine. Among the 8 articles, one was limited to 10 patients and was published in abstract form only. The reports do not provide detailed information of treatment protocols or its study populations. One of the 8 papers just describes the comparisons of vasopressin and epinephrine for CPR. Two articles were finally excluded from this meta-analysis. Only six cohort studies were included in this meta-analysis to be analyzed for the effect of the association of vasopressin and epinephrine in CPR. Participants and the selected study design characteristics of the six cohort studies included in the meta-analysis are detailed in table 1. (7-12)

Finally, the study by Stiell et al. was an in-hospital study in which time to initial drug administration was rapid (1.6 min to CPR, 2.8 min to Advanced Cardiovascular Life Support (ACLS)), but the other five studies were out-of-hospital studies. The methodologies for the six studies were deemed too different to be compared and thus a meta-analysis was not attempted to combine in-hospital and out-of-hospital arrests together.

**Comparing the outcome of vasopressin and epinephrine versus epinephrine alone for CPR**

1. We compared the rate of ROSC between the vasopressin and epinephrine and epinephrine alone groups. The rate of ROSC was compared between two groups in five articles. Among the five articles, none concluded that the combination group did increase the rate of ROSC (1.05, 95%CI [0.92, 1.19]). This meta-analysis indicates that compared with epinephrine alone, the combination group did not improve outcome (figure 1).

2. We compared the survival rate between the two groups. First, the 24 h survival rate was compared between the two groups. Two articles included and one concluded that patients receiving vasopressin or epinephrine had an improved 24 h survival rate. Second, three articles compared the survival rate on admission. Two concluded significant differences between the two groups, while the others had contrary results. The last survival rate we compared was the survival on discharge. Five articles did this comparison, with only one finding significant differences. However, a meta-analysis indicates that the combination of vasopressin and epinephrine only significantly improved the 24 h survival rate (2.99, 95%CI [1.43, 6.28]) (figure 2.1-2.3).

3. We compared the rate of ROSC according to the subgroups of patients with cardiac arrest, selected according to the Utstein Consensus Conference. Subgroup analyses were made between the vasopressin and epinephrine group and epinephrine alone group. Although one out of three included studies revealed that the combination group increased the rate of ROSC among patients with asystole and one of five studies indicated a significant difference in patients with ventricular fibrillation (VF), our meta-analysis did not show a convincing conclusion (1.08
<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Patients</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindner KH, 1997</td>
<td>Double-blinded randomized trial</td>
<td>Subjects (n= 40) in Ulm with out-of-hospital cardiac arrest, average age 65 years, 72.5% men; excluded cardiac arrest resulting from trauma or terminally ill patients or those with exsanguinations; 57% ward patients, 22% ICU; 30% asystole, 47% pulseless electrical activity, 18% ventricular fibrillation</td>
<td>Vasopressin or epinephrine, as the initial vasopressor; epinephrine was given repeatedly after failure to respond to the initial vasopressor</td>
<td>Survival to admission and to hospital discharge, neurologic function by Glasgow Coma Scale score</td>
</tr>
<tr>
<td>Stiell IG, 2001</td>
<td>Triple-blinded randomized trial</td>
<td>Subjects (n = 200) in Canada with in hospital cardiac arrest, average age 70 years, 63% men; excluded cardiac arrest resulting from trauma or terminally ill patients or those with exsanguinations; 57% ward patients, 22% ICU; 30% asystole, 47% pulseless electrical activity, 18% ventricular fibrillation</td>
<td>Vasopressin or epinephrine, as the initial vasopressor; epinephrine was given repeatedly after failure to respond to the initial vasopressor</td>
<td>Survival at 1 h, survival to hospital discharge, ROSC, adverse outcome, neurologic outcomes</td>
</tr>
<tr>
<td>Wenzl V, 2004</td>
<td>Double-blinded, prospective, multi-center, randomized, controlled clinical trial</td>
<td>Subjects (n= 1219) in Europe with out-of-hospital cardiac arrest, average age 66 years, 70% men; excluded cardiac arrest resulting from trauma or terminally ill patients or those successfully defibrillated without drugs, hemorrhagic shock, pregnancy; 45% asystole, 16% pulseless electrical activity, 40% ventricular fibrillation; 75% arrests witnessed</td>
<td>Vasopressin or epinephrine, followed by additional treatment with epinephrine if needed</td>
<td>ROSC, survival to hospital admission, survival to hospital discharge, neurologic performance</td>
</tr>
<tr>
<td>Grmec S, 2006</td>
<td>Prospective observational cohort study, with a retrospective control group</td>
<td>Subjects (n= 530) in the city of Maribor in Slovenia with out-of-hospital cardiac arrest, 56% men, average age 60 years; excluded cardiac arrest resulted from trauma or terminally ill patients or those successfully defibrillated without drugs, severe hypothermia; 25% ventricular fibrillation; 51% arrests witnessed</td>
<td>Vasopressin after three doses of adrenaline, adrenaline 1 mg every three minutes or vasopressin 40 IU as first-line therapy, if failed, adrenaline 1 mg was given every three minutes</td>
<td>ROSC, 24 hour survival, hospital discharge</td>
</tr>
<tr>
<td>Callaway CW, 2006</td>
<td>Randomized, placebo-controlled comparison</td>
<td>Subjects (n = 325) in the City of Pittsburgh with out-of-hospital cardiac arrest, average age 67 years, 61% men, excluded cardiac arrest resulting from trauma; 50% asystole, 22% pulseless electrical activity, 15% ventricular fibrillation; 45% arrests witnessed</td>
<td>Vasopressin or saline placebo after the first dose of intravenous epinephrine</td>
<td>ROSC, survived &gt;30 days, time from dispatch to study drug, time from study drug to return of pulse</td>
</tr>
<tr>
<td>Gueugniaud PY, 2008</td>
<td>Multicenter randomized controlled study</td>
<td>Subjects (n= 2894) in Lyon with out-of-hospital cardiac arrest, average age 61 years, 74%men; excluded cardiac arrest resulting from trauma or terminally ill patients or those successfully defibrillated without drugs, pregnancy; 83%asystole, 8% pulseless electrical activity, 9% ventricular fibrillation; 75% arrests witnessed</td>
<td>Vasopressin and epinephrine or epinephrine and saline placebo intravenously, the same combination repeated after the first administration failed within 3 minutes, epinephrine was given if still failed</td>
<td>Survival to hospital admission, ROSC, survival to hospital discharge, 1-Year survival, neurologic recovery</td>
</tr>
</tbody>
</table>

ICU, intensive care unit; ROSC, return of spontaneous circulation.
95%CI [0.92, 1.28] and (0.91, 95%CI [0.61, 1.35]). When pulseless electrical activity (PEA) was the initial rhythm, ROSC did not differ between groups in our meta-analysis (1.32, 95%CI [0.98, 1.79]) (figure 3.1-3.3).

Potential Publication Bias
Potential publication bias (for the primary endpoint) was based on visual analysis of the funnel plot. The distribution is roughly symmetrical; thus, there is no strong evidence of publication bias (figure 4).

Discussion
For patients in cardiac arrest, administration of epinephrine appears to increase myocardial oxygen demand and consumption, decreases myocardial adenosine triphosphate (ATP) with pro-arrhythmic effects, and increases myocardial lactate levels. (13-17) It may cause severe tachycardia immediately after ROSC, (18,19) and the most serious side effect of epinephrine is the increase in myocardial oxygen consumption during VF and myocardial dysfunction in the post-resuscitation phase. (20) The recently published European Resuscitation Council CPR Guidelines state that ‘current evidence is insufficient to support or refute the routine use of any particular drug or sequence of drugs’; the respective CPR algorithm primarily recommends injection of 1 mg epinephrine every 3–5 minutes, while vasopressin may also be injected. (21) In contrast, the approach of the American Heart Association CPR guidelines is more liberal, stating that ‘one dose of vasopressin may replace either the first or second dose of epinephrine’. (22)

Vasopressin has been shown to increase coronary perfusion pressure and brain perfusion more effectively than epinephrine. (4,23) Since it was found that endogenous vasopressin levels in successfully resuscitated patients were significantly higher than levels in patients who died, (2) it was postulated that it might be beneficial to administer vasopressin during CPR. Other properties unique to vasopressin may also contribute to its synergistic effects with epinephrine. The V2 receptor vasodilatory activity of vasopressin may mitigate end organ hypoperfusion that results from multiple doses of epinephrine. (21) Combining both drugs may combine both beneficial effects and avoid complications of injecting excessive dosages of one drug alone. In a series of animal studies, the group of subjects that received vasopressin and epinephrine appeared to have a more rapid rise in coronary perfusion pressure, (24) higher levels of left ventricular myocardial blood flow during CPR, (25) higher resuscitation rates, and improved cerebral blood flow (25,26,27) than the group that received epinephrine.
Figure 3.1. Return of spontaneous circulation following asystole.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Peto Odds Ratio Peto, Fixed, 95% CI</th>
<th>Peto Odds Ratio Peto, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.W. Callaway 2006</td>
<td>22</td>
<td>83</td>
<td></td>
<td>1.03 [0.51, 2.06]</td>
<td></td>
</tr>
<tr>
<td>P.Y. Gueugniaud 2008</td>
<td>320</td>
<td>1199</td>
<td></td>
<td>1.01 [0.84, 1.21]</td>
<td></td>
</tr>
<tr>
<td>V. Wenzle 2004</td>
<td>61</td>
<td>187</td>
<td></td>
<td>1.75 [1.10, 2.76]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1469</td>
<td>1459</td>
<td>100.0%</td>
<td>1.06 [0.92, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>403</td>
<td>377</td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity: Ch² = 4.75, df = 2 (P = 0.09); I² = 58%</td>
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<tr>
<td>Test for overall effect: Z = 0.97 (P = 0.33)</td>
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Figure 3.2. Return of spontaneous circulation following pulseless electrical activity.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Peto Odds Ratio Peto, Fixed, 95% CI</th>
<th>Peto Odds Ratio Peto, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.W. Callaway 2006</td>
<td>12</td>
<td>36</td>
<td></td>
<td>0.89 [0.34, 2.32]</td>
<td></td>
</tr>
<tr>
<td>P.Y. Gueugniaud 2008</td>
<td>50</td>
<td>111</td>
<td></td>
<td>0.82 [0.49, 1.37]</td>
<td></td>
</tr>
<tr>
<td>V. Wenzle 2004</td>
<td>16</td>
<td>64</td>
<td></td>
<td>1.17 [0.52, 2.63]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>211</td>
<td>212</td>
<td>100.0%</td>
<td>0.91 [0.61, 1.35]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>80</td>
<td>87</td>
<td></td>
<td></td>
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<tr>
<td>Heterogeneity: Ch² = 0.53, df = 2 (P = 0.77); I² = 0%</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.49 (P = 0.62)</td>
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</table>

Figure 3.3. Return of spontaneous circulation following ventricular fibrillation.

Figure 4. Funnel plot of all studies included in the meta-analysis.
vasopressin was not shown to be better than epinephrine alone. Although vasopressin is ranked in a Class IIb recommendation in cardiac arrest that requires fair-to-good evidence with a majority of experts considering it an ‘optional or alternative intervention’, there is insufficient evidence to advocate the use of vasopressin plus epinephrine in CPR temporally.

This meta-analysis has some limitations. Firstly, we included three trials in the analysis that had recruited a small proportion of patients (about 7%) who had experienced CPR. Exclusion of these trials did not affect the outcome of our analysis apparently. Secondly, the dose and the sequence of the two drugs differed between included trials. Thirdly, the included trials represented participants with a clinically heterogeneous level of risk (although statistical heterogeneity was low), which was directly related to the method of selection of the comparison group in each study. As has been reported, the funnel plots showed a relatively symmetric distribution, but the point cloud did not have a distinctive funnel form. This was probably due to the relatively high heterogeneity and to the small number of primary studies included in the meta-analysis. Therefore a publication bias may have also occurred. The majority of the included studies were performed at single sites, so therefore same staff could have treated both cases and controls with a possible contamination bias.

Conclusion
We failed to detect a trend favoring the combination of vasopressin and epinephrine, except for the survival rate at 24h. However, only 122 patients in two studies were involved in this comparison. We have no idea whether a proposal of the use of vasopressin and epinephrine should be recommended, unless further large randomized controlled trials show more evidence of improved outcome. There is a need for randomized controlled trials (RCTs) to evaluate the addition of vasopressin to epinephrine in cardiac arrest. However, there is no adequate evidence to advocate the use of epinephrine plus vasopressin for cardiac arrest at this point in time.

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REFERENCES


