Vasopressin for Cardiac Arrest

A Systematic Review and Meta-analysis

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Background: The current guidelines for cardiopulmonary resuscitation recommend vasopressin as an alternative to epinephrine for the treatment of adult shock-refractory ventricular fibrillation. The objective of this study was to determine the effectiveness of vasopressin in the treatment of cardiac arrest.

Methods: We performed a systematic review and meta-analysis of 1519 patients with cardiac arrest from 5 randomized controlled trials that compared vasopressin and epinephrine. Two reviewers conducted a systematic search of electronic databases, complemented by hand searches, to identify randomized trials. Reviewers evaluated the quality of the trials, extracted data, and derived pooled estimates using a random-effects model.

Results: There were no statistically significant differences between the vasopressin and epinephrine groups in failure of return of spontaneous circulation (risk ratio [RR], 0.81; 95% confidence interval [CI], 0.58-1.12), death before hospital admission (RR, 0.72; 95% CI, 0.38-1.39), death within 24 hours (RR, 0.74; 95% CI, 0.38-1.43), death before hospital discharge (RR, 0.96; 95% CI, 0.87-1.05), or combination of number of deaths and neurologically impaired survivors (RR, 1.00; 95% CI, 0.94-1.07). Subgroup analysis based on initial cardiac rhythm showed no statistically significant difference in the rate of death before hospital discharge between the vasopressin and epinephrine groups in any of the 3 subgroups: ventricular fibrillation or ventricular tachycardia (RR, 0.97; 95% CI, 0.79-1.19), pulseless electrical activity (RR, 1.02; 95% CI, 0.95-1.10), or asystole (RR, 0.97; 95% CI, 0.94-1.00).

Conclusions: There is no clear advantage of vasopressin over epinephrine in the treatment of cardiac arrest. Guidelines for Advanced Cardiac Life Support should not recommend vasopressin in resuscitation protocols until more solid human data on its superiority are available.

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SUDDEN DEATH FROM CARDIAC arrest is a major public health problem. The Centers for Disease Control and Prevention, Atlanta, Ga, has estimated that approximately 400,000 individuals in the United States experience a sudden cardiac arrest each year.1 Epinephrine has been the preferred medication for cardiopulmonary resuscitation (CPR) for more than 40 years.2

A retrospective study3 of adults who underwent resuscitation for out-of-hospital cardiac arrest found significantly higher plasma vasopressin concentration in successfully resuscitated patients than in nonresuscitated patients. This subsequent larger prospective study4 confirmed these findings. This highlighted the importance of vasopressin in cardiac arrest. In pigs with cardiac arrest, higher levels of vasopressin during CPR accompanied improved coronary perfusion pressure, myocardial blood flow, and coronary venous pH.5,8

In contrast, a randomized study9 with a porcine model showed that return of spontaneous circulation (ROSC) was significantly more likely in epinephrine-treated pigs than in vasopressin-treated pigs, despite improvement in myocardial and cerebral blood flow in the latter. Another animal study10 of CPR demonstrated that vasopressin improved coronary perfusion pressure but not neurologically normal survival.

The first published study11 of the effects of vasopressin in human cardiac arrest was a report of 8 adults with in-hospital cardiac arrest, in whom administration of intravenous vasopressin prompted ROSC after failure with intravenous epinephrine and defibrillation. In another human model of prolonged cardiac arrest, 40% of the pa-
tients who received vasopressin had a significant increase in coronary perfusion pressure. 12

In a small randomized trial 13 of out-of-hospital ventricular fibrillation (VF), the rates of successful resuscitation and survival for 24 hours were significantly higher in patients treated with vasopressin than in those treated with epinephrine. At that time, this was the only published study of its kind. Based on these findings, the resuscitation guidelines of the American Heart Association and the European Resuscitation Council recommended that vasopressin could be used as an alternative to epinephrine for the treatment of adult shock-refractory VF. 7 Since the development of these guidelines, more data from clinical trials on the use of vasopressin in CPR became available. 14 This warrants a systematic review of the evidence regarding the effectiveness of vasopressin in cardiac arrest. The objective of the present study was to determine the effectiveness of vasopressin in patients with cardiac arrest.

Subjects and Interventions

The subjects of this review were patients with cardiac arrest who underwent CPR in or out of the hospital. The experimental group received intravenous vasopressin, and the control group received intravenous epinephrine.

Outcome Measures

The outcome measures evaluated in this review were (1) failure of ROSC, (2) death before hospital admission (for out-of-hospital cardiac arrest), (3) death within 24 hours, (4) death before hospital discharge, and (5) the combination of number of deaths and neurologically impaired survivors.

SEARCH STRATEGY

Electronic searches of the following databases were conducted: MEDLINE (January 1966 to February 2004), EMBASE (1974 to February 2004), Cochrane Central Register of Controlled Trials (fourth quarter of 2003), CINAHL (1982 to February 2004), International Pharmaceutical Abstracts (1970 to February 2004), and Database of Abstracts of Reviews of Effects (first quarter of 2004). The search was limited to human data. No restrictions were made based on the language of the report. The following search terms were used: vasopressin.tw, heart arrest (MeSH), (cardiac adj25 arrest).tw, asystole.tw, ventricular fibrillation (MeSH), (pulseless adj25 electrical adj25 activity).tw, cardiopulmonary resuscitation (MeSH), (cardiopulmonary adj25 resuscitation).tw, and advanced cardiac life support (MeSH). The bibliographies of relevant publications, review articles, and included studies were also searched. Ongoing clinical trials and unpublished studies were searched via the Web on the following sites: http://www.controlledtrials.com, http://www.clinicaltrials.gov, and http://www.centerwatch.com.

DATA EXTRACTION AND SYNTHESIS

Two reviewers (K.A. and T.H.) independently selected trials for inclusion in this review. In the case of reports in languages with which the reviewers were unfamiliar, the services of external translators were sought. In assessing the methodological quality of trials, special significance was given to allocation concealment, outcome assessment, blindness, and completion of follow-up. The 6-item instrument developed and validated by Jadad et al 5 was used for quantification of the study quality. The same 2 reviewers independently performed data extraction, and the results were cross-checked by double-data entry. Disagreements were resolved by discussion and consensus. Agreement between reviewers concerning searches and quality assessment was measured, and Cohen κ statistics were calculated. Data entry and analyses were performed using Cochrane Review Manager software (RevMan version 4.2.3, Oxford, England). Heterogeneity between trials was tested by means of a standard χ² test using P < .10 to indicate heterogeneity. We chose to compare the event rates using risk ratios (RRs) as summary statistics because they were more consistent across the trials than odds ratios. The results of pooled estimates were reported as RRs with corresponding 95% confidence intervals (CIs). A random-effects model (DerSimonian-Laird method) 16 was used because of heterogeneity between studies. We also attempted analyses by using a fixed-effects model (Mantel-Haenszel test), 17 but the resultant estimates essentially did not change and hence will not be reported. Subgroup analyses of the trials were performed according to prespecified categories. The Egger test for publication bias was performed using Stata 7.0 software (StataCorp LP, College Station, Tex).

RESULTS

We identified 5 randomized controlled trials (Figure 1), of which 4 were published in English 13,14,18,19 and 1 in Chinese. 20 The characteristics of included studies are summarized in Table 1. One of them was published only as an abstract. 19 The subjects in 3 trials 13,14,19 were patients with out-of-hospital cardiac arrest.
while those in the remaining 2 trials\textsuperscript{18,20} had in-hospital cardiac arrest. Two trials\textsuperscript{14,18} addressed cardiac arrest with the initial rhythm of VF, asystole, and pulseless electrical activity, but 1 trial\textsuperscript{13} included only VF (Table 2). The remaining 2 reports\textsuperscript{19,20} provided no information on the initial rhythm. Two trials\textsuperscript{13,14} were performed in Europe, 1 trial\textsuperscript{18} in Canada, and another\textsuperscript{20} in China. The location of the trial was not reported in 1 study.\textsuperscript{19} Three trials\textsuperscript{13,14,18} used 40 U of intravenous vasopressin. One trial\textsuperscript{20} used 2 different doses, 0.5 U/kg of body weight (low dose) and 1.0 U/kg of body weight (high dose). Another one\textsuperscript{18} mentioned the use of 40 U of vasopressin but did not give the route of administration. A total of 1519 participants from these 5 trials were included in this review. One additional trial is in progress.

**METHODOLOGICAL QUALITY OF INCLUDED STUDIES**

Three trials\textsuperscript{13,14,18} have Jadad scores of 5 (highest methodological quality).

The 2 remaining trials\textsuperscript{19,20} each scored 2. The interrater agreement between the 2 investigators was 80% ($\kappa=0.64$). One trial\textsuperscript{19} was only reported in abstract form, and this precludes a thorough review of its methodological quality. Specific methodological issues are discussed herein.

**Allocation Concealment**

Allocation concealment was adequate in 3 trials\textsuperscript{13,14,18} In 2 trials,\textsuperscript{19,20} it was unclear whether the sequence of allocation of participants to groups remained concealed until after treatments were allocated. One study,\textsuperscript{20} listed as a randomized controlled trial in the Cochrane Central Register of Controlled Trials database, did not provide adequate information on the method of randomization.

**Masking**

In 3 trials,\textsuperscript{13,14,18} the patients and the persons providing care were un-
aware of the assigned treatment, minimizing performance bias. In the remaining 2 trials,\textsuperscript{19,20} the masking of persons providing treatment was unclear. Although not explicitly stated, it would seem safe to conclude that the patients who experienced cardiac arrest were unaware of the type of medication they received.

Detection Bias

In 2 trials,\textsuperscript{14,18} the outcome assessors were unaware of treatment assignment. The issue of masking outcome assessors was not explicitly addressed in the remaining 3 trials.\textsuperscript{13,19,20}

Attrition Bias

The rates of follow-up were similar in comparison groups in all 5 trials. All participants in all trials were analyzed as randomized (intention-to-treat analysis).

QUALITATIVE SYNTHESIS

Lindner et al\textsuperscript{13} reported a trial involving patients with VF resistant to defibrillation. Vasopressin increased 24-hour survival. The rate of ROSC, proportion who survived to hospital admission, proportion who survived to hospital discharge, and neurological outcomes did not differ significantly between the vasopressin group and the epinephrine group.

Li et al\textsuperscript{20} reported a trial comparing 2 different dosages of vasopressin in patients with inhospital cardiac arrest. Their findings indicated that high-dose vasopressin (1.0 U/kg) significantly increased the rate of ROSC and improved the survival rate compared with standard-dose (1.0 mg) and high-dose (5.0 mg) epinephrine.

Lee et al\textsuperscript{19} published their trial only in abstract form, with limited information available on all dimensions of the study. It was presented at the American College of Emergency Physicians Research Forum. The vasopressin group had a higher rate of ROSC and a better neurological outcome than the epinephrine group. To the best of our knowledge, this trial has not been published to date, and efforts to obtain additional detailed information were unsuccessful.

The trial by Stiell et al\textsuperscript{18} showed no statistically significant differences in the rate of ROSC, survival to 1 hour, survival to 24 hours, survival to hospital discharge, and neurological state of the survivors between the 2 groups.

Wenzel et al\textsuperscript{14} conducted the largest trial. There were no statistically significant differences in the rate of ROSC, survival to hospital admission, survival to hospital discharge, and cerebral performance among survivors between the 2 groups. Subgroup analyses showed advantages in survival to hospital admission and survival to hospital discharge in the vasopressin group in the subset of patients with asystole. No such difference was detected among the subset of patients with VF or pulseless electrical activity. Based on these findings, an accompanying editorial\textsuperscript{21} in the New England Journal of Medicine suggested that the American Heart Association should issue an interim guideline incorporating the use of vasopressin in patients with asystole.

The ongoing Vasopressin in Cardiac Arrest Research Project in Pittsburgh, Pa,\textsuperscript{22} explores whether the addition of vasopressin to the standard Advanced Cardiac Life Support protocol improves survival in out-of-hospital cardiac arrest. Three hundred twenty-four people may participate in the trial. The results are expected in 2005.

QUANTITATIVE SYNTHESIS

Statistical heterogeneity was detected in 4 of 5 outcome variables. When there are few trials, as in this review, $\chi^2$ test has a low power of detecting heterogeneity if it is present. The fact that $\chi^2$ statistics are bigger than their $df$s in every outcome measured (with different numbers of trials) also suggests the presence of heterogeneity. We quantified heterogeneity by calculating $I^2$ (Figures 2, 3, 4, 5, 6, and 7). The values of $I^2$ describe the percentage of total variation across studies that is due to heterogeneity rather than chance without depending on the number of studies in the meta-analysis.\textsuperscript{23}

There were no statistically significant differences between the vasopressin and epinephrine groups in all outcome measures (Figures 2, 3, 4, 5, and 6). A funnel plot was created to test for publication bias. The funnel plot appears asymmetric, but there is no evidence of publication bias using the Egger (weighted regression) method ($P = .24$ for bias) for failure of ROSC (Figure 8).

Clinical diversity such as variations in study location, study setting, and underlying cause of cardiac arrest among trials may have

<table>
<thead>
<tr>
<th>Source</th>
<th>Vasopressin, No./Total No.</th>
<th>Epinephrine, No./Total No.</th>
<th>Favor Vasopressin</th>
<th>Favor Epinephrine</th>
<th>Weight, %</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindner et al\textsuperscript{13} 1997</td>
<td>4/20</td>
<td>9/20</td>
<td></td>
<td></td>
<td>8.32</td>
<td>0.44 (0.16-1.21)</td>
</tr>
<tr>
<td>Li et al\textsuperscript{20} 1999</td>
<td>16/40</td>
<td>29/43</td>
<td></td>
<td></td>
<td>23.05</td>
<td>0.59 (0.38-0.91)</td>
</tr>
<tr>
<td>Lee et al\textsuperscript{16} 2000</td>
<td>1/5</td>
<td>4/5</td>
<td></td>
<td></td>
<td>3.00</td>
<td>0.25 (0.04-1.52)</td>
</tr>
<tr>
<td>Stiell et al\textsuperscript{14} 2001</td>
<td>42/104</td>
<td>39/96</td>
<td></td>
<td></td>
<td>27.47</td>
<td>0.99 (0.71-1.39)</td>
</tr>
<tr>
<td>Wenzel et al\textsuperscript{14} 2004</td>
<td>444/589</td>
<td>430/597</td>
<td></td>
<td></td>
<td>38.16</td>
<td>1.05 (0.98-1.12)</td>
</tr>
<tr>
<td>Total</td>
<td>758</td>
<td>761</td>
<td></td>
<td></td>
<td>100.00</td>
<td>0.81 (0.58-1.12)</td>
</tr>
</tbody>
</table>

| Total Events: Vasopressin | 507 | | | | | |
| Total Events: Epinephrine | 511 | | | | | |

Test for Heterogeneity: $\chi^2 = 12.08$ (P = .02), $I^2 = 66.9\%$

Test for Overall Effect: $z = 1.29$ (P = .20)

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contributed to heterogeneity. However, variations in initial rhythm seem to be the major factor responsible. For example, VF or ventricular tachycardia accounted for only 21% of the initial cardiac arrest rhythms in the trial by Stiell et al, whereas it accounted for all initial rhythms in the trial by Lindner et al (Table 2). When subgroup analysis based on initial rhythm was performed (thereby eliminating the related clinical heterogeneity), the statistical heterogeneity became less or nonexistent (lower $I^2$).

Table 2

<table>
<thead>
<tr>
<th>Source</th>
<th>Vasopressin, No./Total No.</th>
<th>Epinephrine, No./Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>609 (Vasopressin), 617 (Epinephrine)</td>
<td></td>
</tr>
<tr>
<td>Test for Heterogeneity: $\chi^2 = 3.36 (P = .07)$, $I^2 = 70.2%$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for Overall Effect: $z = 0.97 (P = .33)$</td>
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</tbody>
</table>

Figure 3. Death before hospital admission. CI indicates confidence interval; RR, risk ratio. For explanation of symbols, see legend to Figure 2.

Table 3

<table>
<thead>
<tr>
<th>Source</th>
<th>Vasopressin, No./Total No.</th>
<th>Epinephrine, No./Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>124 (Vasopressin), 116 (Epinephrine)</td>
<td></td>
</tr>
<tr>
<td>Test for Heterogeneity: $\chi^2 = 4.99 (P = .03)$, $I^2 = 80.0%$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for Overall Effect: $z = 0.90 (P = .37)$</td>
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</table>

Figure 4. Death within 24 hours. CI indicates confidence interval; RR, risk ratio. For explanation of symbols, see legend to Figure 2.

Table 4

<table>
<thead>
<tr>
<th>Source</th>
<th>Vasopressin, No./Total No.</th>
<th>Epinephrine, No./Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>747 (Vasopressin), 752 (Epinephrine)</td>
<td></td>
</tr>
<tr>
<td>Test for Heterogeneity: $\chi^2 = 8.05 (P = .09)$, $I^2 = 50.3%$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for Overall Effect: $z = 0.92 (P = .36)$</td>
<td></td>
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</tbody>
</table>

Figure 5. Death before hospital discharge. CI indicates confidence interval; RR, risk ratio. For explanation of symbols, see legend to Figure 2.

Table 5

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<thead>
<tr>
<th>Source</th>
<th>Vasopressin, No./Total No.</th>
<th>Epinephrine, No./Total No.</th>
</tr>
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<tbody>
<tr>
<td>Total</td>
<td>676 (Vasopressin), 677 (Epinephrine)</td>
<td></td>
</tr>
<tr>
<td>Test for Heterogeneity: $\chi^2 = 3.03 (P = .22)$, $I^2 = 33.9%$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for Overall Effect: $z = 0.11 (P = .91)$</td>
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</tbody>
</table>

Figure 6. Combination of number of deaths and neurologically impaired survivors. CI indicates confidence interval; RR, risk ratio. For explanation of symbols, see legend to Figure 2.
Pooled analysis of continuous data on neurological performance at the time of hospital discharge would have increased the statistical power in comparing the effects of vasopressin and epinephrine. We were unable to perform such an analysis because of the variations in the tools used to measure neurological performance in different trials.

Data on death before hospital discharge in subgroups based on initial cardiac rhythm were available in 3 trials. All of them were of the highest methodological quality (Jadad score, 5). There was no statistically significant difference in the rate of death before hospital discharge in subgroups concerning VF and ventricular tachycardia (RR, 0.97; 95% CI, 0.79-1.19), pulseless electrical activity (RR, 1.02; 95% CI, 0.95-1.10), or asystole (RR, 0.97; 95% CI, 0.94-1.00) (Table 3 and Figure 7). These summary estimates, however, should be interpreted cautiously because their meta-analysis reduced the number of studies from 5 to 2 or 3.

**COMMENT**

Based on the evidence summarized in this systematic review, we could not confirm any clear survival advantages for using vasopressin in patients experiencing cardiac arrest. One might argue that some of the CIs

**Figure 7.** Death before hospital discharge in subgroups. CI indicates confidence interval; RR, risk ratio. For explanation of symbols, see legend to Figure 2.

**Figure 8.** Egger publication bias funnel plot. Note that the 95% confidence intervals of the regression line’s y intercept include zero.

Figure 7). The small number of trials and differences in their characteristics precluded the use of meta-regression, a technique that can be used to investigate heterogeneity.
are too wide to demonstrate its superiority over epinephrine. Even if that is the case, the effect measures revealed by this review suggest that the magnitude of survival advantage that can potentially be offered by vasopressin would not be large from the perspective of an individual patient. However, from the public health perspective, small treatment effects could be translated to potentially large numbers of additional survivors in the United States alone, given the high prevalence of sudden cardiac arrest. More subjects from future trials using the same outcome variables should improve the precision of effect measures.

Our meta-analysis suggests that vasopressin may be at least equivalent to epinephrine relative to ROSC or survival. However, including vasopressin in the standard Advanced Cardiac Life Support algorithms has substantial financial and practical implications. The cost of 40 U of vasopressin is approximately 15 times greater than that of 1 mg of epinephrine.24 The cost associated with stocking vasopressin injection vials in every crash cart in all health care entities and emergency medical systems will be considerable. Such cost would be worthwhile if the certainty of the benefit of having extra survivors is proved beyond reasonable doubt. Neurologically normal survival (indicated by the combination of number of deaths and neurologically impaired survivors in this review) is the outcome that matters most for the patients and their families. Vasopressin did not perform any better than epinephrine in this regard.

It has been postulated that vasopressin use may be advantageous at later times because it has a more powerful vasoconstrictive effect under hypoxic and acidic conditions.25 If this theory were true, the studies of out-of-hospital cardiac arrest13,14 should give better results with vasopressin compared with in-hospital cardiac arrest.18,20 The data extracted in our review showed that such was not the case. Although response times may vary depending on the model of emergency care used in different regions of the world (as described further in this section), careful analysis of the trials included in this review showed that response times in studies involving out-of-hospital cardiac arrest were longer.

A sizable proportion of the patients in the vasopressin group also received epinephrine when the initial doses of vasopressin failed.13,14,18 The apparent effectiveness of vasopressin in some of these studies may be because of confounding effects of epinephrine.

The superiority of vasopressin over epinephrine in asystole in the trial by Wenzel et al14 must be viewed cautiously. In any given clinical trial, the observed treatment effect could vary across subgroups through random variation. A difference between subgroups is based on an observational comparison and may exist because of confounding by other factors. The information on whether each potential prognostic variable at baseline was equally distributed between the 2 comparison groups in the asystole subgroup could not be abstracted from the article. The risk of α error exists when performing multiple sub-analyses. Bonferroni adjustment26 or similar multiple testing adjustments may be necessary in such cases. Moreover, the upper limit of the CI around the odds ratio for death before hospital discharge in the asystole subgroup was 1.00, indicating that there could be no effect. In the asystole subgroup of our meta-analysis, the CI reached but did not pass 1.00. This suggests that there may or may not be a treatment effect. The trend slightly favored vasopressin, but it did not reach the statistically significant level.

Our review has some limitations. Not all outcomes of interest were available for every trial included. As a result, pooled estimates of some outcomes were derived from only 2 or 3 trials. There are many confounders in a cardiac arrest trial. Examples include bystander CPR, time to initiate CPR, time to intubation, time to first shock, and time to first Advanced Cardiac Life Support medication. Moreover, the Franco-German model of emergency care is different from the Anglo-American model. In the former, the ambulance is staffed with physicians, and downtime is different from that in the Anglo-American model. The study quality tools we used did not address these confounders. Therefore, pooling the results of the studies conducted in locations where the models of emergency care are different is another limitation of our analysis. The wide quality variation in the trials pooled, the possibility of confounding, and the nearly statistically significant difference in some end points could have affected the accuracy of the pooled estimates of the treatment effect, which, therefore, must be interpreted with caution.

Contrary to findings in animal trials, our synthesis of the published human trials demonstrated no clear advantage of vasopressin over epinephrine in the treatment of cardiac arrest. Similarly, there was no evidence of harm with the use of vasopressin. This subject should be revisited on the completion of the ongoing Pittsburgh trial.22 When a new treatment is not superior to an old treatment, using the less expensive and time-honored old treatment may be preferable. The American Heart Association and the International Liaison Committee on Resuscitation should consider our findings when revising the resuscitation guidelines in 2005.
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REFERENCES


