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ORIGINAL

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

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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 24h, 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 (1.6min 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 1. Characteristics of studies included in the meta-analysis.

Study	Methods	Patients	Interventions	Outcomes
Lindner KH, 1997	Double-blinded randomized trial	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 or pregnant patients; 100% ventricular fibrillation; 63%arrests witnessed	Vasopressin or epinephrine, as the initial vasopressor; epinephrine was given repeatedly after failure to respond to the initial vasopressor	Survival to admission and to hospital discharge, neurologic function by Glasgow Coma Scale score
Stiell IG, 2001	Triple-blinded randomized trial	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	Vasopressin or epinephrine, as the initial vasopressor; epinephrine was given repeatedly after failure to respond to the initial vasopressor	Survival at 1 h, survival to hospital discharge, ROSC, adverse outcome, neurological outcomes
Wenzle V, 2004	Double-blinded, prospective, multicenter, randomized, controlled clinical trial	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	Vasopressin or epinephrine, followed by additional treatment with epinephrine if needed	ROSC, survival to hospital admission, survival to hospital discharge, neurologic performance
Grmec S, 2006	Prospective observational cohort study, with a retrospective control group	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	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	ROSC, 24 hour survival, hospital discharge
Callaway CW, 2006	Randomized, placebo-controlled comparison	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	Vasopressin or Saline placebo after the first dose of intravenous epinephrine	ROSC, survived >30 days, time from dispatch to study drug, time from study drug to return of pulse
Gueugniaud PY, 2008	Multicenter randomized controlled study	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	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	Survival to hospital admission, ROSC, survival to hospital discharge, 1-Year survival, neurologic recovery

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

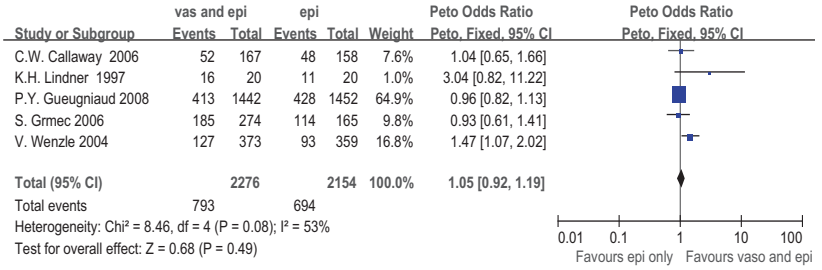

Figure 1. Return of spontaneous circulation.

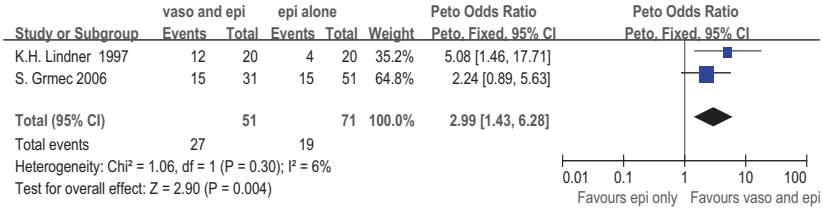

Figure 2.1. Survival rate at 24h.

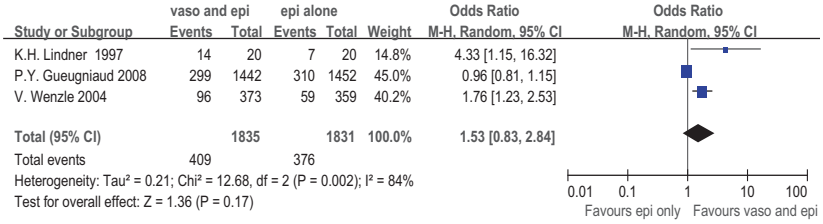

Figure 2.2. Survival rate on admission.

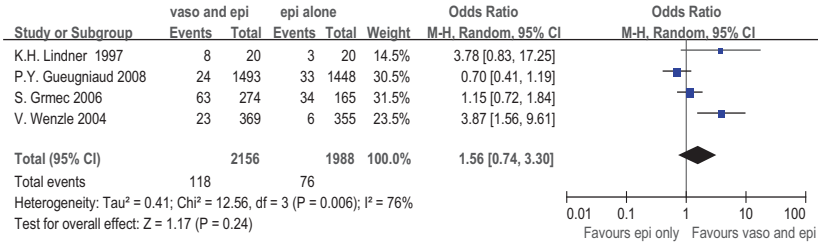

Figure 2.3. Survival rate at discharge.

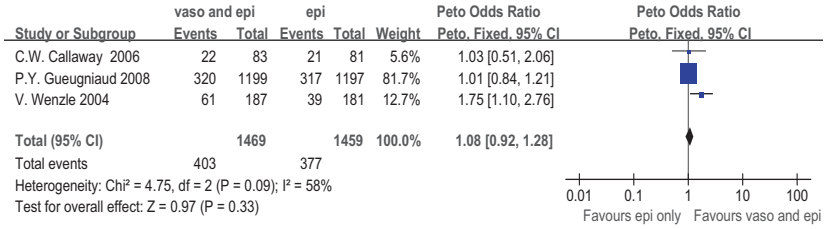

Figure 3.1. Return of spontaneous circulation following asystole.

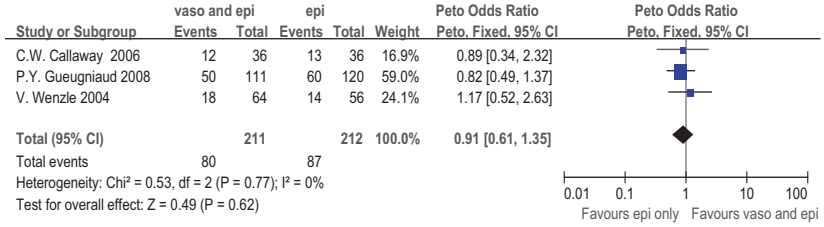

Figure 3.2. Return of spontaneous circulation following pulseless electrical activity.

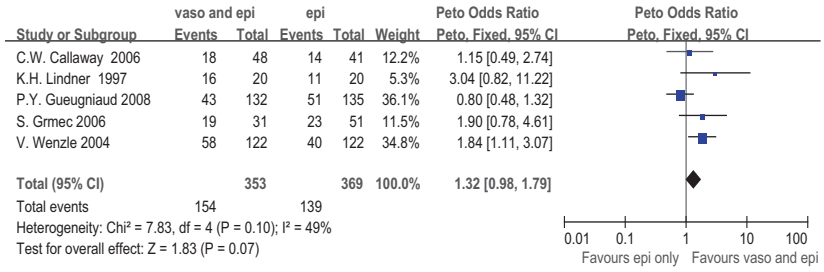

Figure3.3. Return of spontaneous circulation following ventricular fibrillation.

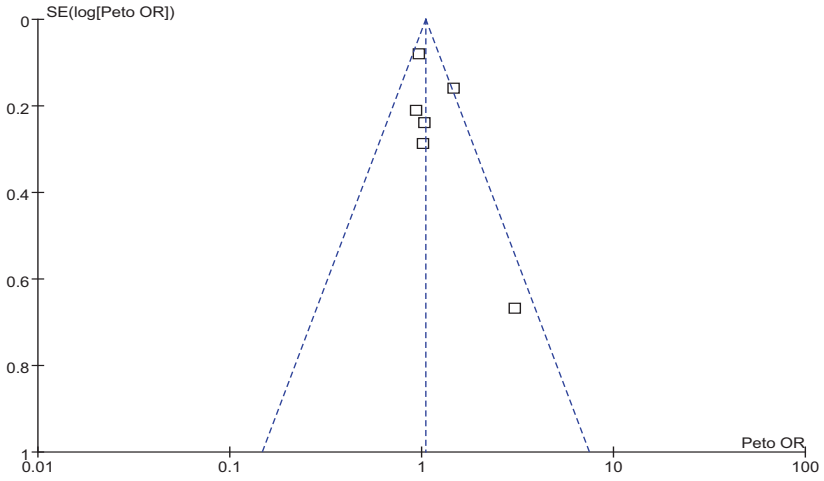

Figure 4. Funnel plot of all studies included in the meta-analysis.

only, perhaps because of a synergistic effect of epinephrine and vasopressin. (28-30)

Two previous meta-analyses have investigated whether vasopressin is superior to epinephrine in the management of cardiac arrest. The first, which included 2 human studies and 33 animal studies published before 2003, found vasopressin equivalent to epinephrine in humans, but significantly superior to epinephrine in animals. (31) In a second meta-analysis, which included 5 human studies, the investigators concluded that there is no clear advantage of vasopressin over epinephrine in the treatment of cardiac arrest in regard to failure of ROSC, hospital admission, hospital discharge and survival rates at 24 hours. And in the secondary analysis, subgroup analysis based on initial cardiac rhythm showed no statistically significant difference. (5) Another meta-analysis of the combination of vasopressin and epinephrine versus repeated doses of epinephrine alone ,which included 3 studies, found trends towards better ROSC but equivocal effects on survival. (32)

Our results, which include not only ROSC, hospital admission, hospital discharge and survival rates in the first 24 hours, but also subgroups based on initial cardiac rhythm, provide the best available estimates of efficiency between the addition of vasopressin to epinephrine and epinephrine alone. Despite the sensitivity of the search strategy used and the large number of published papers on this subject (485 studies), only six trials satisfied the strict inclusion criteria. In contrast to findings regarding patients with ventricular fibrillation, pulseless electrical activity or asystole, (4,10,23, 33-34) the results of clinical trials did not support the addition of vasopressin to epinephrine in cardiac arrest resuscitation, except in a subgroup looking at survival rate at 24h. For in- hospital patients, the vasopressin and epinephrine group failed to show any improvement compared with epinephrine for either 1 h survival or survival to hospital discharge. The combination of epinephrine and vaso-

pressin was not shown to be better than epinephrine alone. Although vasopressin is banked 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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