

SELECTED ARTICLE

Vasopressin versus epinephrine for out-of-hospital cardiopulmonary resuscitation

Clinical question

Does the use of vasopressin for adult patients suffering a non-traumatic, out-of-hospital cardiac arrest improve the rates of survival to hospital admission (and discharge) better than epinephrine?

Article chosen

Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, Lindner KH; European Resuscitation Council Vasopressor during Cardiopulmonary Resuscitation Study Group. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004;350(2):105-13.

Objective

To determine whether vasopressin is more effective than epinephrine in improving rates of survival to hospital admission and, secondarily, survival to hospital discharge in adults requiring cardiopulmonary resuscitation (CPR) and vasopressor therapy after suffering non-traumatic, out-of-hospital cardiac arrest with ventricular fibrillation (VF), pulseless electrical activity (PEA) or asystole.

Background

Vasopressin, also known as arginine vasopressin (AVP) and antidiuretic hormone (ADH), is a vasoactive peptide released from the pituitary in response to hypovolemia or decreased central venous pressure. Although its primary role is to regulate extracellular fluid volume via renal mechanisms, it acts on both the kidneys and arterial system. In high concentrations, vasopressin increases systemic vascular resistance; hence, a potential role in resuscitation was proposed as early as the 1960s.¹

High endogenous vasopressin levels have been identified in canine cardiac arrest models² and, in a porcine model of VF and CPR, vasopressin was at least as effective as epinephrine in improving vital organ perfusion.³ Lindner and colleagues reported that in 8 patients with in-hospital cardiac arrests refractory to epinephrine all 8 had return of spontaneous circulation after rescue treatment with vasopressin, and 3 survived to hospital discharge.⁴

The first human randomized controlled trial (RCT) comparing vasopressin to epinephrine for cardiac arrest in-

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involved 40 out-of-hospital patients with VF.⁵ This trial showed significantly higher 24-hour survival in vasopressin-treated patients, but no difference in rates of survival to hospital discharge or in Glasgow Coma Scale scores at discharge. Another RCT compared vasopressin to epinephrine in 200 inpatients and showed no significant difference in 1-hour survival, survival to hospital discharge, or neurological outcomes (Mini-Mental State Examination scores and Cerebral Performance Category Scale scores).⁶

Population included / studied

In the Wenzel study, 1219 adult patients (<18 yr) from 33 communities in Austria, Germany and Switzerland with out-of-hospital cardiac arrest (VF, PEA or asystole) requiring CPR and vasopressor therapy were randomized to vasopressin or epinephrine. Patients who were pregnant, or had a documented terminal illness, or were in hemorrhagic shock or cardiac arrest after trauma, or had a lack of intravenous access, had a "do-not-resuscitate" order, or who were successfully resuscitated without the administration of vasopressors were excluded.

Study design

This double-blind, multicentre RCT was powered to demonstrate the superiority of vasopressin over epinephrine in improving rates of survival to hospital admission. Patients were randomized in blocks of 10 and stratified by centre, although the randomization method was not described. Patients received either vasopressin (40 IU) or epinephrine (1 mg) intravenously. If spontaneous circulation was not restored within 3 minutes, the same drug and dose was repeated. Failure to respond after the second dose ended study drug administration, and emergency physicians were permit-

ted to order additional epinephrine at their discretion.

Outcomes measured

The primary outcome was survival to hospital admission and the secondary outcome was survival to hospital discharge. Neurologic function in the surviving patients was assessed using a cerebral performance score. Multiple subgroup analyses were performed based on presenting cardiac rhythm and whether additional epinephrine was given following study drug administration.

Results

During recruitment, 80% of patients screened were excluded, but no reasons were provided. Of 1219 patients actually randomized, 33 were excluded from the analysis because of missing study-drug codes and 88 who were found to be ineligible were included in the analysis because of the intention-to-treat design. Eleven of 589 vasopressin patients (1.9%) and 9 of 597 epinephrine patients (1.5%) were lost to follow-up before hospital discharge, and 11 of 57 vasopressin patients (19.3%) and 12 of 58 epinephrine patients (20.7%) who survived to discharge were lost to follow-up before cerebral performance assessment.

Primary outcome analysis showed no difference between the 2 treatment groups with respect to hospital admission, hospital discharge or cerebral performance in survivors. Subgroup analyses showed no outcome differences between treatment groups for patients presenting with VF or PEA; however, patients presenting with asystole who re-

ceived vasopressin were significantly more likely to survive to hospital admission and discharge (Table 1).

In a secondary analysis of patients who received additional epinephrine following the assigned study drug, vasopressin recipients were more likely to survive to hospital admission (odds ratio [OR] = 0.6; 95% confidence interval [CI], 0.4–0.8) and to hospital discharge (OR = 0.3; 95% CI, 0.1–0.6). It should be noted that the reported ORs are inverted such that an OR <1 favours the experimental treatment, vasopressin.

Commentary

In order to interpret these results, several methodological and statistical issues need to be clarified. The primary end point, survival to hospital admission, is of questionable clinical importance but enables the enrolment of a smaller sample size and increases the likelihood of detecting a statistically significant difference. The secondary end point, survival to hospital discharge, is an outcome of greater interest, but also a relatively rare outcome that would have mandated a much larger sample size. The reported ORs for these outcomes were 0.8 (95% CI, 0.6–1.0) and 1.0 (95% CI, 0.7–1.5) respectively. Given that the CIs both include the value of 1.0, neither outcome is statistically significant.⁷

The authors performed many subgroup analyses and statistical tests looking for outcome differences between the 2 treatments. In fact, 29 statistical subgroup comparisons were made in addition to the primary analyses. One such analysis, based on rhythm (VF v. PEA v. asystole), suggested that if the initial rhythm was asystole, patients re-

Table 1. Primary and subgroup analyses of 1186 patients in study

Group/subgroup, outcome	Vasopressin, no. (and %)	Epinephrine, no. (and %)	Odds ratio (95% CI)	p value
All patients				
ROSC	145/589 (24.6)	167/597 (28.0)	1.2 (0.9–1.5)	0.19
Hospital admit	214/589 (36.3)	186/597 (31.2)	0.8 (0.6–1.0)	0.06
Hospital discharge	57/578 (9.9)	58/588 (9.9)	1.0 (0.7–1.5)	0.99
Ventricular fibrillation				
ROSC	82/223 (36.8)	106/249 (42.6)	1.3 (0.9–1.8)	0.20
Hospital admit	103/223 (46.2)	107/249 (43.0)	0.9 (0.6–1.3)	0.48
Hospital discharge	39/219 (17.8)	47/245 (19.2)	1.1 (0.7–1.8)	0.70
Pulseless electrical activity				
ROSC	21/104 (20.2)	17/82 (20.7)	1.0 (0.5–2.1)	0.93
Hospital admit	35/104 (33.7)	25/82 (30.5)	0.8 (0.5–1.6)	0.65
Hospital discharge	6/102 (5.9)	7/81 (8.6)	1.4 (0.5–4.7)	0.47
Asystole				
ROSC	42/262 (16.0)	44/266 (16.5)	1.0 (0.7–1.6)	0.87
Hospital admit	76/262 (29.0)	54/266 (20.3)	0.6 (0.4–0.9)	0.02
Hospital discharge	12/257 (4.7)	4/262 (1.5)	0.3 (0.1–1.0)	0.04

CI = confidence interval; ROSC = restoration of spontaneous circulation
Adapted with permission from Table 3, Wenzel V, et al. <17> © 2004 Massachusetts Medical Society.

ceiving vasopressin were more likely to survive to hospital admission (OR = 0.6; 95% CI, 0.4–0.9), but not to hospital discharge (OR = 0.3; 95% CI, 0.1–1.0). Therefore, when clinically important outcomes were measured, vasopressin did not prove superior to epinephrine, even in patients with asystole. This is contrary to the authors' conclusion.

In the subgroup of patients given additional epinephrine after the assigned study drug, vasopressin recipients were more likely to survive to hospital admission (OR = 0.6; 95% CI, 0.4–0.8) and to hospital discharge (OR = 0.3; 95% CI, 0.1–0.6). In the subgroup of patients with an initial rhythm of asystole who required additional epinephrine, vasopressin increased survival to hospital admission (OR = 0.5; 95% CI, 0.3–0.9) but no patients survived to hospital discharge, therefore analysis based on this outcome was not possible.

Interpretation of the multiple subgroup analyses is particularly difficult because of the lack of a priori hypotheses. In fact, the authors admit that the subgroup analyses were post hoc observations: the study was not powered to detect differences between subgroups; nor did the authors statistically adjust for the multiple comparisons made, and the large number of subgroup comparisons would be likely to yield a statistically significant result by chance alone.^{8,9} Had they corrected for multiple comparisons, none of the subgroup outcome differences would have achieved statistical significance.

In a companion Editorial,¹⁰ McIntyre proclaimed that "... practitioners should perhaps be encouraged to incorporate the use of vasopressin into their resuscitation protocols immediately." This suggestion was based on interpreting the data as demonstrating "... the success of vasopressin alone and vasopressin followed by epinephrine in refractory asystolic cardiac arrest — an important breakthrough in the science of resuscitation."¹⁰ This interpretation fails to consider the substantial statistical shortcomings and the fact that the subgroup analyses (i.e., possible benefit) conflict with the overall study results (no benefit), making it likely they are spurious effects.^{8,9} It is also important to note that these subgroup analyses and conclusions conflict with previously published trials comparing the 2 drugs.^{5,6}

Attacks on McIntyre's position were published in the May 2004 issue of the *Journal*^{11–14} along with responses by Wenzel and coauthors¹⁵ and by McIntyre and a colleague.¹⁶ A September 2004 commentary, by Werner, advocated a more cautious approach to the use of vasopressin in asystolic arrest.¹⁷

The multitude of post-hoc comparisons and statistical tests make this a very difficult study to read and interpret; however, if the rules of subgroup analyses and missing data accountability are applied, this study (the largest of 3 RCTs of vasopressin versus epinephrine in cardiac arrest)

demonstrates that vasopressin does not improve meaningful survival to hospital discharge.

Competing interests: None declared.

Key words: vasopressin; cardiac arrest; resuscitation; pre-hospital; out-of-hospital

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