Neuroanesthesia and Intensive Care

Best evidence in anesthetic practice

Treatment: vasopressin neither improves nor worsens survival from cardiac arrest

Article appraised

Stiell IG, Hébert PC, Wells GA, et al. Vasopressin versus epinephrine for inhospital cardiac arrest: a randomized controlled trial. Lancet 2001; 358: 105–9.

Structured abstract

Question: Does vasopressin, as the initial vasopressor, improve one-hour survival compared to epinephrine in inpatients with cardiac arrest?

Design: Multicentre, randomized controlled trial. Patients, caregivers, study investigators, and adjudication committee were blinded.

Setting: Emergency rooms, critical care units, and wards of three teaching hospitals in Canada from July 1997 to November 1998.

Patients: Two hundred inpatients with cardiac arrest from asystole, pulseless electrical activity, or refractory ventricular fibrillation. Exclusion criteria were age < 16 yr; documented terminal illness; do-not-resuscitate status; hospital admission < 24 hr after trauma; cardiac arrest before arrival to hospital, or in the operating, recovery, or delivery rooms, or from obvious exsanguination; or previous enrollment in the study. Study was approved by the research ethics committees; informed consent was not obtained.

Intervention: All patients were treated according to the American Heart Association Advanced Cardiac Life Support (ACLS) protocols. The intervention was applied whenever the ACLS protocol indicated epinephrine. One hundred and four patients were allocated to vasopressin 40 U *iv*; 96 patients were allocated to epinephrine 1 mg *iv*. Both groups received epinephrine 1 mg *iv* every three to five minutes if there was no return of pulse.

Main outcomes: One-hour survival was the primary outcome. Survival to 24 hr, 30 days, and hospital discharge; cognitive function (mini-mental state examination and five-point cerebral performance score); return of pulse; and adverse events were secondary outcomes.

Main results: Analysis was per protocol. There were no differences in survival to one hour, 24 hr, 30 days, or hospital discharge, or in cognitive function, return of pulse, and adverse events between the two groups. The sample size was powered to detect a 20% absolute difference in one-hour survival.

Conclusion: Vasopressin neither improved nor worsened survival in cardiac arrest from asystole, pulseless electrical activity, or refractory ventricular fibrillation when compared with epinephrine.

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Commentary by A. Denault, Y. Beaulieu, S. Bélisle

Is there always a simple solution for a complex problem? Vasopressin is recommended in the current Advanced Cardiac Life Support (ACLS) guidelines,[1] as a "class 2b intervention" (acceptable, not harmful, supported by fair evidence), in the treatment of ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) refractory to defibrillation. The initial drug can be either epinephrine 1 mg every three to five minutes or vasopressin 40 U intravenously. In patients unresponsive to a single dose of vasopressin, epinephrine may be used. For cardiac arrest from other dysrhythmias, treatment with vasopressin remains indeterminate from lack of scientific evidence.

The current ACLS recommendation for vasopressin was strongly influenced by one randomized clinical trial (RCT). Lindner *et al.* randomized 40 out-of-hospital patients, with persistent VF refractory to defibrillation, to either vasopressin 40 U or epinephrine 1 mg as the initial drug.[2] Subsequently, the ACLS algorithm was

TABLE Comparison of rates of survival in the two RCTs of vasopressin use in cardiac arrest

	Return to pulse (%)		Survival > 20 min or to hospital admission (%)		Survival at 24 hr (%)	
	Vasopressin	*Epinephrine*	*Vasopressin*	*Epinephrine*	*Vasopressin*	*Epinephrine*
Stiell *et al.*	60	59	43	40	26	24
Lindner *et al.*	80	55	70	35	60*	20

RCTs = randomized controlled trials; * $P = 0.02$

applied. Survival at 24 hr was significantly better with vasopressin (60%; epinephrine, 20%; $P = 0.02$). The proportion of patients discharged from hospital was encouraging (vasopressin, 40%; epinephrine, 15%) but was not statistically significant. Times to treatment were 6.1–6.5 min for emergency medical services response time and 7.8–8.6 min from cardiopulmonary resuscitation (CPR) to drug administration.

Since the publication of the current ACLS guidelines, Stiell *et al.* randomized 200 patients with pulseless electrical activity (48%), asystole (31%), VT (3%), or VF (18%) to receive either vasopressin 40 U or epinephrine 1 mg as the initial medication during in-hospital cardiac arrests.[3] The authors observed no difference in the survival rate at one hour (vasopressin, 39%; epinephrine, 35%) and at 30 days (vasopressin, 13%; epinephrine, 14%). Subgroup analysis suggested that vasopressin improved survival in patients with cardiac arrests of unknown etiology (one-hour survival: vasopressin, 38%; epinephrine, 13%) but worsened survival in patients less than 70-yr-old (survival to discharge: vasopressin, 10%; epinephrine, 24%). Times to treatment were very rapid: 1.4–1.9 min from collapse to CPR and 1.1–1.3 min from CPR to ACLS. The Table compares rates of survival between the two studies. Both groups of investigators recommended a large RCT before widespread use of vasopressin.

Why were differences in survival seen in the two trials? As there are multiple pathophysiological mechanisms for cardiac arrests, expecting one drug to be suitable for all cardiac arrests is unrealistic. To significantly improve our patients' prognoses, we may need to go beyond the recovery of pulsatile circulation. The time from collapse to drug administration may also represent an important issue. Vasopressin was administered much later in Lindner's trial compared to Stiell's trial. Compared to epinephrine, vasopressin exerts a greater vasoconstrictive effect under hypoxic and acidotic conditions;[4] thus, vasopressin use may be advantageous at later times. The rapid response times in Stiell's trial may explain partly the lack of difference observed between these two drugs.

What can we conclude? First, the two studies examined different populations and clinical scenarios. Second, the efficacy of drug therapy is poor (Table). Finally, the use of vasopressin is controversial but has been associated with a significantly better survival at 24 hr in patients with out-of-hospital VF. Considering the poor prognosis of cardiac arrest, a bolus of either epinephrine or vasopressin as the initial drug in the treatment of VF is reasonable until more powerful trials are conducted. Vasopressin should remain available in the resuscitation cart.

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Commentary by G. Peachey

Intravenous vasopressin 40 U is now included in the American Heart Association's (AHA) 2000 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care[1] for the treatment of unstable ventricular tachycardia (VT) and ventricular fibrillation (VF). A number of human and animal

studies suggest potential benefit with vasopressin.[2–4] Vasopressin has a longer half-life than epinephrine and acts hemodynamically through V_1 smooth muscle receptors without impairment from acidosis. These characteristics may improve coronary perfusion pressure; however, there is little evidence that vasopressin improves survival in patients with unstable VT or VF. Insufficient evidence prevents determination of its role in asystole, pulseless electrical activity (PEA), or prolonged cardiac arrest refractory to epinephrine.

Stiell *et al.* should be congratulated for furthering our knowledge of vasopressin's clinical value. Their multicentre, triple-blind prospective study compared the safety and effectiveness of vasopressin to epinephrine as the first-line *iv* agent for in-hospital cardiac arrests. Inclusion and exclusion criteria for enrollment and statistical analysis were appropriate. Primary outcomes were the presence of a continuous pulse and measurable pressure for at least one hour postresuscitation. Secondary outcomes included survival to hospital discharge and neurological outcomes. In contrast to other studies, in which coronary perfusion pressure, cerebral perfusion, and return of spontaneous circulation were interpreted as efficacy, this study's endpoints were more clinically significant.

No difference in survival between the two groups led the authors to disagree with the current AHA recommendation of vasopressin as an alternative agent for cardiac arrest. In contrast, Lindner *et al.* studied out-of- hospital VF arrests and found a larger proportion of patients were successfully resuscitated following initial vasopressin therapy compared to epinephrine.[5] However, the sample size was small (40 patients) and survival to hospital discharge was not different. In Stiell *et al.*'s study, response times were shorter. As well, the study did not limit vasopressin therapy to unstable VT or VF. Only 21% of the 198 patients presented with unstable VT or VF, which would be appropriately treated with vasopressin according to the AHA guidelines. There were no differences in outcomes in this subgroup.

Some investigations have shown that vasopressin increases coronary perfusion pressure and vital organ blood flow in prolonged cardiac arrest and PEA.[2–4] These studies had small sample sizes and did not demonstrate improved survival. Stiell *et al.*'s results add support to these findings. Seventy-nine percent of their patients presented with asystole or PEA; no differences were seen in outcomes.

Epinephrine was used as a rescue drug in patients without initial response to vasopressin. Eighty-seven percent of patients in the vasopressin group received epinephrine, which was comparable to the proportion of patients (81%) in the epinephrine group that required additional doses. In some studies, compared to epinephrine, vasopressin plus epinephrine results in similar left ventricular myocardial blood flow but significantly decreases cerebral perfusion. Stiell *et al.* demonstrated neither benefit nor harm from vasopressin plus epinephrine compared to multiple doses of epinephrine.

In summary, no differences in outcomes between vasopressin and epinephrine were found. Vasopressin may still be appropriate in the presence of severe acidosis; however, further studies of different doses and arrest conditions are needed to clarify vasopressin's role in emergency cardiac care.

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