CJEM Journal Club

Improved neurologic outcomes after cardiac arrest with combined administration of vasopressin, steroids, and epinephrine compared to epinephrine alone

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Clinical question
Is a vasopressin, steroid, and epinephrine (VSE) protocol for in-hospital cardiac arrest resuscitation associated with better survival to hospital discharge with favourable neurologic outcome compared to epinephrine alone?

Article chosen
Mentzelopoulos S, Malachias S, Konstantopoulos D, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. *JAMA* 2013;310:270-9.

Objective
To determine if a VSE protocol during cardiopulmonary resuscitation with hydrocortisone administration in patients with postresuscitative shock at 4 hours after return of spontaneous circulation would improve survival to hospital discharge with favourable neurologic outcome.

Keywords: cardiac arrest, cardiopulmonary resuscitation, epinephrine, neurologic, randomized controlled trial, steroids, survival, vasopressin

BACKGROUND

Survival with favourable neurologic outcome after cardiac arrest, arguably the most clinically important outcome, has been the primary end point of several randomized clinical trials (RCTs).[1–4] Severe neurologic disability ranges from 25 to 50% among cardiac arrest survivors.[2–6]

In a 2009 single-centre RCT, Mentzelopoulos and colleagues implemented the vasopressin, steroid, and epinephrine (VSE) protocol in cardiac arrest resuscitation.[7] They demonstrated improved survival to hospital discharge. However, the study was not designed to evaluate neurologic outcomes.

POPULATION STUDIED

This current study enrolled adult patients experiencing in-hospital, vasopressor-requiring cardiac arrest according to the 2005 European Resuscitation Council guidelines for resuscitation.[8] Patients with cardiac arrests due to exsanguination, patients with terminal illness (life expectancy < 6 weeks), and those with steroid use before cardiac arrest were excluded.

STUDY DESIGN

The study was a multicentre, double-blind, placebo-controlled, and parallel-group clinical trial. Block randomization was performed using a computer-generated program. There was allocation concealment, and only the study pharmacist who prepared the intervention drugs was aware of allocation. The intervention consisted of the combination of vasopressin and epinephrine for the first five cardiopulmonary resuscitation (CPR) cycles along with methylprednisolone in the

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first CPR cycle. Four hours post return of spontaneous circulation (ROSC), the intervention group received stress-dose hydrocortisone if postresuscitation hypotension was present (mean arterial pressure < 70 mm Hg). The control group patients received standard advanced life support (ALS) epinephrine dose and normal saline placebo.

OUTCOMES

Primary outcomes were ROSC for 20 minutes or more and favourable neurologic status at discharge as defined by the Cerebral Performance Category (CPC) scores 1 and 2. Secondary outcomes included 1) blood pressure (BP) during and 20 minutes after ROSC; 2) BP and central venous saturation between days 1 and 10 after randomization; 3) the number of organ failure–free days; and the 4) incidence of steroid side effects (i.e., hyperglycemia, infections, and bleeding peptic ulcers).

RESULTS

Between September 2008 and October 2010, 300 patients were enrolled. There were 146 patients in the VSE group and 154 patients in the control group. Survival to hospital discharge with favourable neurologic outcome was achieved in 18 of 130 (13.9%) patients in the VSE group as opposed to 7 of 138 (5.1%) in the control group (OR 3.28, 95% CI 1.17–9.20, $p = 0.02$) (number needed to treat [NNT] of 11.4, 95% CI 6.1–52.9; relative risk [RR] 2.72). ROSC for 20 minutes or more was achieved in 109 of 130 (83.9%) patients in the VSE group as opposed to 91 of 138 (65.9%) in the control group (OR 2.98, 95% CI 1.39–6.40, $p = 0.005$) (NNT of 5.6, 95% CI 3.6–13.1; RR of 1.27).

In the VSE group, there was improved BP during CPR and 20 minutes after ROSC. There was better BP and central venous saturation until day 10 after randomization. More neurologic and renal organ failure–free days were noted in the VSE group. There was no difference in the incidence of steroid-associated complications.

STUDY CONCLUSION

The authors concluded that VSE during CPR along with stress-dose hydrocortisone for postresuscitative shock for in-hospital cardiac arrest was associated with increased survival to hospital discharge, with favourable neurologic outcome compared to standard ALS.

COMMENTARY

The findings of Mentzelopoulos and colleagues are of great interest, but the different study group characteristics, the underuse of therapeutic hypothermia, and the incomplete CPR quality monitoring constitute possible sources of bias. Additionally, steroids may impair myocardial injury healing. Of importance, the applicability to the emergency department (ED) of patients with in-hospital arrest may be limited.

First, the two study groups were not equal, despite appropriate randomization. It was possible to appreciate a greater incidence of respiratory depression and failure as a cause of cardiac arrest in the control group as opposed to the VSE group. In the latter, there was a trend toward more cardiac arrests caused by myocardial ischemia and infarction. Could specific etiologies have led to more futile resuscitations for the control group and poorer outcomes? A retrospective analysis by Wallmuller and colleagues in 2012 pointed toward better outcomes in patients with cardiac arrests of cardiac etiology as opposed to other causes (i.e., pulmonary).[9]

Therapeutic hypothermia was not consistently applied following the 2005 International Liaison Committee on Resuscitation (ILCOR) guidelines.[10] As per the supplement, only 16 patients with an initial rhythm of ventricular fibrillation or ventricular tachycardia received therapeutic hypothermia out of a total of 29 potentially treatable patients. If such a study was conducted today, the present 2010 ILCOR guidelines indicate, "induced hypothermia might also benefit comatose adult patients with spontaneous circulation after out-of-hospital cardiac arrest from a non-shockable rhythm."[11] Interestingly, nonshockable rhythms were also treated, although not consistently. If postresuscitative care were more rigorous, it would be difficult to predict whether the benefit in enhanced neurologic outcomes provided by the VSE compared to placebo would be accentuated or blunted.

The quality of CPR was not assessed for all patients. Good quality CPR is a proven contributor to favourable outcomes.[12] The 2010 American Heart Association (AHA) guidelines indicate that when "the arterial relaxation 'diastolic' pressure is < 20 mm Hg, it is

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reasonable to consider trying to improve quality of CPR by optimizing chest compression parameters or giving a vasopressor or both."[13] BPs obtained in the periarrest period indicate that good CPR was provided to both the VSE and control groups. Such monitoring was conducted on only a fraction of patients (see Table 3, *Hemodynamics, No (%)* row), and it is not possible to determine if similar quality of care (in less monitored settings) was provided to the remainder.

Additionally, steroids may impair myocardial healing after myocardial infarction,[14] as acknowledged by the authors. Postarrest myocardial function was not measured to determine if patients in the VSE group had worse cardiac outcomes. If favourable neurologic outcomes can be obtained without steroids, the latter should probably be avoided.

Notably, out-of-hospital cardiac arrests, which constitute a significant proportion of the cases treated in the ED, were specifically excluded from the study. This can compromise the generalizability of the results to the emergency population. The outcomes of the study may not be perfectly representative of cardiac arrests cared for by emergency physicians as only about 15% of the study population originated from the ED. In 2008, Kayser and colleagues demonstrated that "ED cardiac arrest patients... have better survival and neurological outcomes compared to patients arresting in other [hospital] locations."[15]

Although a CPC score of 2 is considered a favourable neurologic outcome in this study, the clinical status encompassed is that of "moderate cerebral disability." Patients are described as "disabled but independent": permanent memory and mental changes and hemiplegia can be present.[16] Perhaps a more relevant outcome would be the proportion of patients surviving with a CPC score of 1. As per personal correspondence with the study's first author, the raw data indicated that "for hospital discharge with a CPC score of 1, the VSE-to-control ratio was 3:1," although it was not mentioned if this is statistically significant.

CONCLUSION

One of the most important end points in cardiac arrest resuscitation is a favourable neurologic outcome. As indicated in the 2004 AHA cardiac arrest and cardiopulmonary resuscitation outcome reports, "survival without higher neurological function is suboptimal."[17] The study of Mentzelopoulos and colleagues is therefore of great relevance. It may be more prudent to wait for a validation study before emergency physicians universally adopt the VSE protocol, considering the potential risks, the possible trial biases, and the uncertain generalizability to an important segment of the ED population.

Competing interests: None declared.

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