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Is Epinephrine During Cardiac Arrest Associated With Worse Outcomes in Resuscitated Patients?

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ABSTRACT

BACKGROUND Although epinephrine is essential for successful return of spontaneous circulation (ROSC), the influence of this drug on recovery during the post-cardiac arrest phase is debatable.

OBJECTIVES This study sought to investigate the relationship between pre-hospital use of epinephrine and functional survival among patients with out-of-hospital cardiac arrest (OHCA) who achieved successful ROSC.

METHODS We included all patients with OHCA who achieved successful ROSC admitted to a cardiac arrest center from January 2000 to August 2012. Use of epinephrine was coded as yes/no and by dose (none, 1 mg, 2 to 5 mg, >5 mg). A favorable discharge outcome was coded using a Cerebral Performance Category 1 or 2. Analyses incorporated multivariable logistic regression, propensity scoring, and matching methods.

RESULTS Of the 1,556 eligible patients, 1,134 (73%) received epinephrine; 194 (17%) of these patients had a good outcome versus 255 of 422 patients (63%) in the nontreated group ($p < 0.001$). This adverse association of epinephrine was observed regardless of length of resuscitation or in-hospital interventions performed. Compared with patients who did not receive epinephrine, the adjusted odds ratio of intact survival was 0.48 (95% confidence interval [CI]: 0.27 to 0.84) for 1 mg of epinephrine, 0.30 (95% CI: 0.20 to 0.47) for 2 to 5 mg of epinephrine, and 0.23 (95% CI: 0.14 to 0.37) for >5 mg of epinephrine. Delayed administration of epinephrine was associated with worse outcome.

CONCLUSIONS In this large cohort of patients who achieved ROSC, pre-hospital use of epinephrine was consistently associated with a lower chance of survival, an association that showed a dose effect and persisted despite post-resuscitation interventions. These findings suggest that additional studies to determine if and how epinephrine may provide long-term functional survival benefit are needed. (J Am Coll Cardiol 2014;64:2360–7) © 2014 by the American College of Cardiology Foundation.

International resuscitation guidelines recommend administering epinephrine every 3 to 5 min during cardiac arrest resuscitation regardless of the initial rhythm (1). The alpha-adrenergic effects of epinephrine can increase coronary and cerebral perfusion pressure during the resuscitation period (2,3) and subsequently help achieve return of spontaneous circulation (ROSC). However, epinephrine may exert adverse effects during the post-resuscitation phase and contribute to myocardial dysfunction, increased oxygen requirements, and microcirculatory abnormalities (4–8).

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Although epinephrine can increase the likelihood of achieving ROSC, the balance of the effects of epinephrine on long-term survival remains uncertain. A randomized study found no overall survival effect of medication treatments that included epinephrine (9). In a large observational study, epinephrine was associated with a lower likelihood of long-term survival (10). In each of these studies, epinephrine was associated with a greater likelihood of ROSC, but the early potential benefit did not translate into a greater likelihood of long-term survival because outcomes among the epinephrine-treated patients were worse during the post-resuscitation phase.

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We sought to better understand the potential adverse effects of epinephrine when used during the post-resuscitation phase. We evaluated the relationship between use of epinephrine during resuscitation and survival among a cohort of patients resuscitated from out-of-hospital cardiac arrest (OHCA) and admitted to the hospital with ROSC. We also evaluated whether evidence-based post-resuscitation interventions, such as coronary reperfusion or hypothermia, may influence this epinephrine-survival relationship.

METHODS

STUDY DESIGN, PATIENTS, AND SETTING. We performed a cohort investigation of all patients who experienced nontraumatic OHCA, achieved ROSC, and were subsequently admitted to a large Parisian cardiac arrest–receiving hospital from January 2000 to August 2012. The appropriate institutional review board approved the study.

Management of OHCA involves mobile emergency units and fire departments that provide basic and advanced cardiac life support (ACLS). In suspected cases of cardiac arrest, the closest emergency unit is dispatched to the scene. Out-of-hospital resuscitation is performed by an emergency team, which includes at least 1 emergency physician trained according to international guidelines (1). When used, epinephrine is administered promptly at the beginning of ACLS or later if required. Patients in whom the resuscitation process fails are not transported to the hospital. Most patients who achieve ROSC are brought to the cardiac arrest–receiving hospital and admitted to the intensive care unit, where they are treated according to standard resuscitative guidelines including coronary angiography and mild therapeutic hypothermia. Procedures of post-cardiac arrest care have been described previously (11). Early coronary reperfusion and targeted temperature management are the most important components of these procedures.

DATA COLLECTION. The study hospital maintains an ongoing registry of all patients with OHCA who are admitted with ROSC. Information is prospectively collected according to Utstein recommendations (12). The registry includes characteristics such as age, sex, cardiovascular risk factors (hypertension, diabetes mellitus, and current smoking), location of cardiac arrest, witnessed status, bystander cardiopulmonary resuscitation (CPR), and initial cardiac rhythm as recorded by the automated defibrillator (ventricular fibrillation [VF]/ventricular tachycardia [VT] or pulseless electrical activity/asystole). The emergency medical service record is used to determine the time interval between the emergency call and successful ROSC as well as use of epinephrine, the timing of the first administration after cardiac arrest, and the total dose. Hospital data during the post-resuscitation phase include initial laboratory values, such as blood lactate levels (mmol/l), and procedures, such as therapeutic hypothermia, coronary angiography, and percutaneous coronary intervention (PCI).

Post-resuscitation shock was defined as the occurrence or persistence of arterial hypotension (mean arterial pressure <60 mm Hg or systolic blood pressure <90 mm Hg) sustained for more than 6 h after ROSC despite adequate fluid resuscitation and continuous vasopressor infusion (13). The definitive etiology of the cardiac arrest was confirmed at hospital discharge, considering all available data obtained during hospital stay. Acute coronary syndromes and/or primary ventricular arrhythmia were considered cardiac etiology. All other causes were considered to be extracardiac causes. The primary outcome was favorable neurological outcome at discharge, defined as a Cerebral Performance Category (CPC) of 1 or 2.

STATISTICAL ANALYSIS. Categorical variables were summarized with proportions and compared using Pearson chi-square test or Fisher exact test. Continuous variables were described with medians (and quartiles) or means and compared using Student *t* test or the nonparametric Wilcoxon test. Use of epinephrine was classified both dichotomously (any epinephrine vs. no epinephrine) and as a dose variable divided into 4 categories: none, 1 mg, 2 to 5 mg, and >5 mg.

We used multivariable logistic regression to evaluate the association between epinephrine and favorable neurological survival while adjusting for potential confounders. We also set up a propensity model to evaluate the relationship between epinephrine and

ABBREVIATIONS AND ACRONYMS

ACLS = advanced cardiac life support

aOR = adjusted odds ratio

CI = confidence interval

CPC = Cerebral Performance Category

CPR = cardiopulmonary resuscitation

OHCA = out-of-hospital cardiac arrest

PCI = percutaneous coronary intervention

ROSC = return of spontaneous circulation

VF = ventricular fibrillation

VT = ventricular tachycardia