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Clinical paper

Lower-dose epinephrine administration and out-of-hospital cardiac arrest outcomes☆

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ABSTRACT

Background: International guidelines recommend administration of 1 mg of intravenous epinephrine every 3–5 min during cardiac arrest. The optimal dose of epinephrine is not known. We evaluated the association of reduced frequency and dose of epinephrine with survival after out-of-hospital cardiac arrest (OHCA).

Methods: Included were patients with non-traumatic OHCA treated by advanced life support (ALS) providers from January 1, 2008 to June 30, 2016. During the before period, providers were instructed to give epinephrine 1 mg intravenously at 4 min followed by additional 1 mg doses every eight minutes to patients with OHCA with a shockable rhythm and 1 mg doses every two minutes to patients with a non-shockable rhythm (higher dose). On October 1, 2012, providers were instructed to reduce the dose of epinephrine treatment during out-of-hospital cardiac arrest (OHCA): 0.5 mg at 4 and 8 min followed by additional doses of 0.5 mg every 8 min for shockable rhythms and 0.5 mg every 2 min for non-shockable rhythms (lower dose). Patients with shockable initial rhythms were analyzed separately from those with non-shockable initial rhythms. The primary outcome was survival to hospital discharge with a secondary outcome of favorable neurological status (Cerebral Performance Category [CPC] 1 or 2) at hospital discharge. Multiple logistic regression modeling was used to adjust for age, sex, presence of a witness, bystander CPR, and response interval.

Results: 2255 patients with OHCA were eligible for analysis. Of these, 24.6% had an initially shockable rhythm. Total epinephrine dose per patient decreased from a mean ± standard deviation of 3.4 ± 2.3 mg–2.6 ± 1.9 mg ($p < 0.001$) in the shockable group and 3.5 ± 1.9 mg–2.8 ± 1.7 mg ($p < 0.001$) in the non-shockable group. Among those with a shockable rhythm, survival to hospital discharge was 35.0% in the higher dose group vs. 34.2% in the lower dose group. Among those with a non-shockable rhythm, survival was 4.2% in the higher dose group vs. 5.1% in the lower dose group. Lower dose vs. higher dose was not significantly associated with survival: adjusted odds ratio, aOR 0.91 (95% CI 0.62–1.32, $p = 0.61$) if shockable and aOR 1.26 (95% CI 0.79–2.01, $p = 0.33$) if non-shockable. Lower dose vs. higher dose was not significantly associated with favorable neurological status at discharge: aOR 0.84 (95% CI 0.57–1.24, $p = 0.377$) if shockable and aOR 1.17 (95% CI 0.68–2.02, $p = 0.577$) if non-shockable.

Conclusion: Reducing the dose of epinephrine administered during out-of-hospital cardiac arrest was not associated with a change in survival to hospital discharge or favorable neurological outcomes after OHCA.

Introduction

Epinephrine has been used to treat patients with out-of-hospital cardiac arrest (OHCA) for over a century [1], yet its efficacy is debated. Current American Heart Association and European Resus-

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citation Council guidelines for adult cardiac arrest recommend administering 1 mg intravenous epinephrine every 3–5 min until return of spontaneous circulation (ROSC) is achieved regardless of cardiac arrest rhythm [2,3].

Epinephrine is believed to help achieve ROSC through its alpha-adrenergic vasopressor activity and has been shown to increase coronary and cerebral perfusion pressure during cardiopulmonary resuscitation (CPR) [4]. Paradoxically, evidence from pig models suggests that epinephrine use is associated with post-ROSC myocardial depression [5], has adverse effects on cerebral microvascular flow, and may increase severity of cerebral ischemia during CPR [1].

Observational studies indicate that prehospital epinephrine use for OHCA is associated with significantly decreased likelihood of survival to discharge and worse neurological outcomes [6,7]. A meta-analysis of randomized controlled trials using prehospital epinephrine for OHCA found that although higher doses of epinephrine were associated with increased rates of ROSC and survival to hospital admission compared to lower doses of epinephrine or placebo, there were no significant differences in survival to discharge or neurological outcomes at discharge [8]. Early but not late administration of epinephrine during attempted resuscitation may improve outcomes [9]. No randomized trial has shown significant benefit or harm for survival to hospital discharge or neurological outcome with epinephrine use for OHCA [3].

We evaluated the association of administration of a reduced dose of epinephrine with survival and favorable neurological outcomes after out-of-hospital cardiac arrest (OHCA).

Methods

Study setting

The structure of the Seattle Fire Department response to OHCA has been described previously [10]. In brief, a Seattle Fire Department basic life support (BLS) fire engine company initially responds to each call. A Seattle Fire Department advanced life support (ALS) ambulance responds to calls of higher acuity such as suspected cardiac arrest.

Since the founding of the Seattle Medic One program in 1970, the physicians leading the program integrated the latest research findings, when appropriate, into the clinical care guidelines for the organization. The State of Washington delegates decisions about which medications to carry in the ALS ambulance and the dosing of those medications to the medical directors for each emergency medical service (EMS). Traditionally, the Seattle guidelines have differed from the international guidelines for the treatment of cardiac arrest. From April 5, 2006 through September 30, 2012, Seattle Fire Department mobile intensive care paramedics administered epinephrine 1 mg at 4 min of resuscitation followed by additional 1 mg doses every eight minutes (min 12, 20, etc.) to patients with shockable rhythms. Epinephrine 1 mg was given every 2 min to patients with non-shockable rhythms.

Following the September 2011 publication of a randomized trial comparing epinephrine to placebo showing no difference in survival to hospital discharge and the March 2012 publication of a large observational study of OHCA patients in Japan that concluded that prehospital epinephrine use was associated with decreased chance of survival to one month, the epinephrine dosing protocol in Seattle was reduced [7,11]. On October 1, 2012, Seattle Fire Department mobile intensive care paramedics implemented a lower-dose epinephrine protocol for adult OHCA. Paramedics were instructed to give 0.5 mg at 4 and 8 min of resuscitation followed by additional doses of 0.5 mg every 8 min (minute 16, 24, etc.) when a shockable rhythm was present and 0.5 mg every 2 min when non-shockable rhythms were present. Shockable rhythms included ventricular fibrillation and pulseless ventricular tachycardia. Non-shockable rhythms include asystole, pulseless electrical activity, and indeterminate rhythms.

Throughout the study period, first responding emergency medical technician trained firefighters performed 2 min of cardiopulmonary resuscitation prior to the first analysis of heart rhythm with an automated external defibrillator (AED). Once paramedics arrived, the electrocardiograph (ECG) rhythm was assessed every 2 min. Thus, per dosing protocol, presence or absence of a shockable rhythm at each 2-min ECG rhythm check determined the treatment plan.

Data collection

Seattle Fire Department Medic One quality improvement staff prospectively collected information to describe patients with non-traumatic OHCA. Data was abstracted from dispatch center records, EMS field reports, audio recorded during resuscitations, and supplemental written data forms. Audio recordings of resuscitations were captured through Physio-Control LIFEPAK 500 AEDs and Physio-Control LIFEPAK 12 and 15 manual defibrillators. Defibrillator recordings were synchronized to the atomic clock time along with timelines generated by the dispatch center. Providers were trained to verbally identify treatments as they were being delivered. Outcomes were abstracted from hospital records and death certificates.

Outcome measures

The primary outcome was survival to hospital discharge with a secondary outcome of neurological function at the time of acute care hospital discharge. Neurological function was quantified using the Cerebral Performance Category (CPC) score system through evaluation of available hospital notes. CPC scores of 1 or 2 (little/no cerebral disability or moderate disability, respectively) were considered favorable neurological outcomes, whereas CPC scores of 3, 4, or 5 (severe disability, coma/vegetative state, or brain death, respectively) were considered unfavorable neurological outcomes.

Data analysis

Call-to-patient time intervals were calculated as the difference between when the 9-1-1 call was received at the EMS dispatch center and the time the first EMS defibrillator was turned on, which providers were instructed to perform immediately upon arriving at the patient's side. In cases where providers found a patient in cardiac arrest without a 9-1-1 call, call-to-patient interval was considered to be zero.

We considered all non-traumatic OHCA patients treated by Seattle mobile intensive care paramedics from January 1, 2008 to June 30, 2016. Seattle Fire Department's lower dose OHCA treatment protocol became effective October 1, 2012, so patients treated prior to this date were assigned to the higher dose cohort, and the later patients were assigned to the lower dose cohort. We excluded patients in which age was less than 18, no ALS care was provided, ALS agencies other than Seattle Fire Department (SFD) provided medications, do not resuscitate orders were present, arrest occurred after arrival of EMS, ROSC was achieved without ALS intervention or without epinephrine, epinephrine was first administered after ROSC was achieved, e.g. for hypotension, or survival data were missing.

Because the treatment protocols were different, we grouped patients based upon first recorded cardiac arrest rhythm as either shockable or non-shockable. Patients with an initial rhythm of ventricular fibrillation or ventricular tachycardia were consid-