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# Increased return of spontaneous circulation at the expense of neurologic outcomes: Is prehospital epinephrine for out-of-hospital cardiac arrest really worth it?☆

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ABSTRACT

*Introduction:* Current guidelines for the management of out-of-hospital cardiac arrest (OHCA) recommend the use of prehospital epinephrine by initial responders. This recommendation was initially based on data from animal models of cardiac arrest and minimal human data, but since its inception, more human data regarding prehospital epinephrine in this setting are now available. Although out-of-hospital return of spontaneous circulation (ROSC) may be higher with the use of epinephrine, worse neurologic outcomes may be associated with its use.
*Methods:* A systematic review of the literature was conducted by search of databases including PubMed, Embase, and OVID to identify studies comparing patients with OHCA who had received epinephrine before arrival to the hospital with those who had not. Studies were assessed for quality and bias, and data were abstracted from studies deemed appropriate for inclusion. A meta-analysis was conducted using a Mantel-Haenszel model for dichotomous outcomes. Outcomes studied were prehospital ROSC, survival at 1 month, survival to discharge, and positive neurologic outcome.
*Results:* A total of 14 studies with 655 853 patients were included for the meta-analysis. The use of epinephrine for OHCA before arrival to the hospital was associated with a significant increase in ROSC (odds ratio, 2.86; $P < .001$) and a significant increase in the risk of poor neurologic outcome at the time of discharge (odds ratio 0.51, $P = .008$). There was no significant difference in survival at 1 month or survival to discharge.
*Conclusion:* Use of epinephrine before arrival to the hospital for OHCA does not increase survival to discharge but does make it more likely for those who are discharged to have poor neurologic outcome. There is a need for additional randomized controlled trials.



## 1. Introduction

Survival after out-of-hospital cardiac arrest (OHCA) has been increasing due to improvements in community education efforts, clinical guidelines, and emergency medical services protocols but still remains low [1,2]. Of particular concern now is quality of life after successful resuscitation and how this may be impacted by specific components of resuscitation efforts. Recently, the use of epinephrine has been associated with poor neurologic outcome, which has brought the use of epinephrine for OHCA into question [3-7].

Current advanced cardiac life support guidelines for cardiac arrest dictate that 1 mg of epinephrine be given every 3 to 5 minutes during resuscitation of patients with OHCA [2]. Historically, this dosing finds its origins from canine studies, and dosing studies in humans have found no increasing efficacy with increased dosing, specifically in regard to prehospital return of spontaneous circulation (ROSC) [8-13]. Although the rate of ROSC has been found to be higher with prehospital epinephrine administration in previous studies, the concerns for poor neurologic outcomes have raised concerns about its use [4]. In addition, myocardial dysfunction, impaired cerebral microcirculation, increase in ventricular arrhythmias, and increased oxygen consumption are other reported concerns with epinephrine [14-17].

The aim of this study was to conduct a pooled analysis of previous observational and randomized studies to assess the effect of epinephrine when given before arrival to the hospital for OHCA with respect to survival rate and positive neurologic outcome. We hypothesize that epinephrine is associated with improved survival rate and neurologic outcomes when given to patients with OHCA.

## 2. Methods

### 2.1. End points

A systematic review of the literature was performed to identify manuscripts describing comparisons between those having received

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epinephrine and those not having received epinephrine before arrival to the hospital for OHCA. This was a newly conducted review with no previous review protocol having been established for it. The meta-analysis was conducted per the preferred reporting items for systematic reviews and meta-analyses checklist. The aim of the study was to compare resuscitation for OHCA with and without epinephrine using the following outcomes: prehospital ROSC, survival at 1 month, survival to discharge, and positive neurologic outcome. *Positive neurologic outcome* was defined as a cerebral performance category (CPC) of 1 or 2, which represents mild or moderate cerebral dysfunction but ability to perform activities of daily living independently [18].

### 2.2. Manuscript search and identification strategy

Manuscripts were identified using electronic databases including PubMed, EMBASE, and Ovid, which were queried using the following search terms: "epinephrine" or "adrenaline" in conjunction with "cardiac arrest." Only studies in English language were included for analysis. No specific restriction on year of publication was used. Resulting studies were then screened by title and abstract with manuscripts describing epinephrine use in OHCA retrieved in their entirety. References of these studies were then hand searched for additional relevant manuscripts. No direct contact with manuscript authors was made to obtain full-text manuscripts or data in case they were not available online.

The full-text manuscripts were then reviewed by 2 of the authors and assessed for quality (RL and SA). Any disparities in scoring of manuscripts were then independently reviewed by another author (RA). The Cochrane Handbook for Systematic Review of Interventions was used for quality evaluation. Published manuscripts available in full text were included in this review if they presented data from observational or randomized studies comparing outcomes of resuscitation with and without prehospital epinephrine for OHCA. Studies were included in this analysis if they included at least 1 of the outcomes identified above.

### 2.3. Data extraction

Next, data regarding baseline patient characteristics and identified outcomes were extracted from the manuscripts identified for inclusion. Trial-level data were extracted independently with use of a data collection form by 2 authors (SA and RL). The data extraction was then independently reviewed by another author (KN) to ensure integrity of the resulting data.

### 2.4. Bias analysis

Bias was assessed using the Newcastle-Ottawa assessment scale. Specifically, patient eligibility, randomization and concealment of allocation, blinding, completeness of outcome data, and statistical integrity were assessed using this scale.

### 2.5. Data analysis

Numeric data on baseline characteristics are presented as means with SDs or medians with ranges. Categorical data are presented as frequencies with absolute numbers as well as percentages. $P \le .05$ was considered statistically significant. The baseline comparison analysis was done using SPSS statistical software, version 20.0 (Chicago, IL). Meta-analysis and forest plot creation were done using RevMan 5.3(Cochrane Collaboration, Oxford, UK). A Mantel-Haenszel model was used for dichotomous outcomes and mean difference for continuous outcomes. Results are presented as pooled odds ratios with 95% confidence intervals or as mean difference where appropriate. Heterogeneity between studies was identified using $\chi^2$ and $I^2$ tests. For outcomes with no significant heterogeneity present, a fixed-effects model was used. Otherwise, a random-effects model was used if either the $P$ value was significant or the $I^2$ statistics was greater than 50%.

Sensitivity analyses were performed based on study design, study weight, sample size, year of publication, geographic region of study, and presence of a shockable rhythm (Table 1). For the neurologic outcome end point, we also conducted sensitivity analysis based on timing of assessment. Meta-regression was also formally conducted on all these variables as well except for timing of neurologic assessment.

## 3. Results

Initial search as outlined above yielded 1132 manuscripts after duplicates were removed. After reviewing the study titles and abstracts, full-text manuscripts were obtained for 19 studies. Of these 19 studies, 5 studies were excluded because either they did not report data regarding outcomes that we studied or they did not compare a prehospital epinephrine group with a nonepinephrine group. Fourteen studies were finally included in the analysis [3-7,19-27] (Fig. 1). There were a total of 655 853 patients across these studies with 48 755 (7.4%) having received epinephrine and 607 098 (92.6%) having not received epinephrine before arrival to the hospital. Thirteen of these studies were observational, and 1 was a randomized control trial. The study by Olasveengen et al was classified as an observational study, although the data were extracted from a previous study in which patients were randomized to intravenous access in the prehospital setting. The administration of epinephrine, however, was not randomized [3].

Of those having received epinephrine, 64.1% were male, whereas of those not having received epinephrine, 58.3% were male. Mean age of those receiving epinephrine was 65.9 ± 15.9 years, whereas the mean age of those not having received epinephrine was 65.7 ± 15.7 years.

**Table 1**
Study characteristics

| | Design | Timing of assessment of neurologic function | Epinephrine | | | Non-epinephrine | | |
|---|---|---|---|---|---|---|---|---|
| | | | n | Age | Males | n | Age | Males |
| Fukuda et al [5] | Observational | 1 mo after event | 770 | | | 6301 | | |
| Goto et al [6] | Observational | 1 mo after event | 23 676 | 70.3 ± 21.2 | 14886 | 185 901 | 70.2 ± 22.3 | 105 898 |
| Hagihara et al [7] | Observational | 1 mo after event | 15 030 | 72.4 ± 15.5 | 9546 | 402 158 | 72.4 ± 16.4 | 236 366 |
| Hayashi et al [19] | Observational | 1 mo after event | 1013 | 72.1 ± 15.0 | 660 | 2148 | 73.9 ± 15.2 | 1243 |
| Herlitz et al [20] (VF) | Observational | – | 417 | 60.0 ± 26.7 | 81 | 786 | 62.0 ± 24.4 | 79 |
| Herlitz et al [21] (asystole) | Observational | – | 344 | | | 878 | | |
| Herlitz et al [22] (PEA) | Observational | – | 276 | | | 472 | | |
| Jacobs et al [23] | Randomized | At discharge | 272 | 64.3 ± 17.5 | 193 | 262 | 64.9 ± 17.4 | 196 |
| Kaji et al [24] | Observational | – | 160 | 65.5 ± 6.4 | 79 | 24 | 60.3 ± 4.6 | 18 |
| Machida et al [25] | Observational | At discharge | 49 | 63.0 ± 18.0 | 33 | 443 | 64.0 ± 18.0 | 291 |
| Olasveengen et al [3] | Observational | At discharge | 367 | 66.0 ± 6.9 | 266 | 481 | 66.0 ± 6.9 | 337 |
| Holmberg et al [26] | Observational | At discharge | 4566 | 67.1 | 3356 | 6207 | 67.5 | 4426 |
| Ong et al [27] | Observational | – | 681 | 63.7 ± 15.5 | 456 | 615 | 63.3 ± 15.5 | 435 |
| Dumas et al [4] | Observational | At discharge | 1134 | 60.3 ± 16.0 | 797 | 422 | 58.3 ± 16.0 | 315 |

VF, ventricular fibrillation; PEA, pulseless electrical activity.