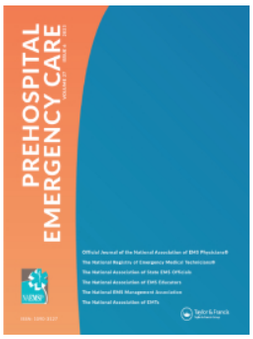

Prehospital Emergency Care

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ipec20

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To cite this article: Emma R. Wender, Catherine R. Counts, Molly Van Dyke, Michael R. Sayre, Charles Maynard & Nicholas J. Johnson (2023): Prehospital Administration of Norepinephrine and Epinephrine for Shock after Resuscitation from Cardiac Arrest, Prehospital Emergency Care, DOI: 10.1080/10903127.2023.2252500

To link to this article: https://doi.org/10.1080/10903127.2023.2252500

Accepted author version posted online: 29 Aug 2023.

Prehospital Administration of Norepinephrine and Epinephrine for Shock after Resuscitation from Cardiac Arrest

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Abstract

Introduction: Shock after resuscitation from out-of-hospital cardiac arrest (OHCA) is often treated with vasopressors. We examined whether infusion of epinephrine versus norepinephrine was associated with prehospital rearrest and neurologically favorable survival among OHCA patients.

Methods: This retrospective study included OHCA cases in Seattle, WA from 2014-2021 who had return of spontaneous circulation (ROSC) followed by vasopressor infusion. Our primary exposure was infusion of epinephrine or norepinephrine. Our primary outcome was prehospital rearrest. Secondary outcomes included survival and neurologically favorable outcome (Cerebral Performance Category score of 1 or 2). We used multivariable logistic regression to test associations between exposures and outcomes adjusting for key covariates.

Results: Of 451 OHCA patients with ROSC followed by vasopressor infusion, 253 (56%) received norepinephrine and 198 (44%) received epinephrine infusions. Those who received epinephrine were older (median 66 [IQR 53-79] vs 63 [IQR 47-75] years), but otherwise had similar baseline characteristics. Patients who received epinephrine were twice as likely to

rearrest (55% vs 25%). After adjustment, the difference in rearrest rates between epinephrine and norepinephrine persisted (OR 3.28, 95% CI 2.25-5.08), and the odds of pulses at hospital arrival were lower in the epinephrine group (OR 0.52 95% CI 0.32-0.83). After adjustment, there was no difference in neurologically favorable survival, survival to hospital admission, or survival to discharge.

Conclusion: Patients who received epinephrine infusions after ROSC suffered prehospital rearrest more frequently than those who received norepinephrine. Survival and neurological status at hospital discharge were similar. Future trials should examine the optimal approach to hemodynamic management for post-OHCA shock.

Key Words: Out-of-hospital cardiac arrest; epinephrine; norepinephrine; prehospital; vasopressor; emergency medical services

Introduction

Shock is present in most patients after spontaneous circulation is restored following out-of-hospital cardiac arrest (OHCA) (1). Post-arrest shock is often characterized by mixed cardiogenic and distributive physiology due to post-arrest myocardial stunning, global ischemia-reperfusion injury and inflammation, and persistent pre-arrest pathology (2, 3, 4). The optimal approach to hemodynamic management after OHCA is unknown (1). Norepinephrine and epinephrine are commonly used vasopressors with mechanistic differences. While both target the beta-1 adrenergic receptor on the myocardium and alpha-1 adrenergic receptor on the vascular smooth muscle, epinephrine has modestly greater affinity for beta-1, producing a more robust inotropic and chronotropic effect, especially at lower doses (5). Limited data exist comparing

epinephrine and norepinephrine after OHCA; and to our knowledge, no studies have compared vasopressor or inotropic agents in the prehospital setting (6, 7).

We investigated whether infusion of epinephrine compared with norepinephrine for post-arrest shock in the prehospital setting was associated with recurrent prehospital cardiac arrest. Secondarily, we examined associations between vasopressor agent and both survival and neurological outcome at hospital discharge. We hypothesized that, compared with norepinephrine, infusion of epinephrine would be associated with greater prehospital rearrest, lower survival, and worse neurological outcome.

Methods

Study population, design, and setting

This was a retrospective study of a prospectively collected registry including OHCA cases in Seattle, WA from January 1, 2014 to December 31, 2021. The study was approved by the University of Washington institutional review board. Qualifying OHCA patients were identified in the Seattle Fire Department's cardiac arrest registry, which has been previously described and includes detailed prehospital and in-hospital variables collected by trained abstractors in the Utstein format (8). We excluded patients who were under the age of 18, who never had return of spontaneous circulation (ROSC), who received only basic life support (BLS), who received advanced life support (ALS) from providers outside of Seattle's 9-1-1 system, whose resuscitation was terminated early due to Do Not Resuscitate orders, and who either did not receive epinephrine or norepinephrine infusions or received both types of infusions. We also excluded patients who were declared dead in the field even if they received vasopressor infusions because this population is systematically different from those in the study cohort due to their lack of survival. Rearrest status was not included in the cardiac arrest registry from 2014-2016.

Agency protocols

Patients in both groups were treated according to the Seattle Fire Department OHCA protocol. The protocol includes standing orders for intra-arrest care, but standing orders are not included for vasopressor selection after ROSC. Paramedics consulted by telephone or radio with an emergency physician at Harborview Medical Center for every patient receiving treatment for cardiac arrest. The choice of one vasopressor over another was based on individual clinician preferences and clinical judgement. Epinephrine was given in 0.5 mg boluses every 2 minutes during periods when the underlying rhythm was pulseless electrical activity or asystole and about every 4 to 8 minutes when the rhythm was ventricular fibrillation (9). Paramedics often initiate small fluid boluses after resuscitation unless volume overload is evident, but the total volumes of crystalloid fluid that patients received are not recorded. Typical airway management includes placement of an endotracheal tube as quickly as possible after completion of initial BLS measures, including chest compressions and defibrillation (10).

When preparing epinephrine infusions, 2 mg of epinephrine was mixed into a 250 mL bag of D5W. Norepinephrine infusions were prepared by mixing 8 mg of norepinephrine in a 250 mL bag of D5W. Epinephrine or norepinephrine infusions were administered to patients using microdrip administration sets with an initial rate of 2-9 mcg per minute. Infusion pumps are not used. The infusion rate was determined by the paramedic administering the medication and titrated to achieve a systolic blood pressure of approximately 90 mmHg. Because of the way these infusions are administered in this EMS system, it was not possible to obtain dosing information.

Outcome measures

Our primary exposure was prehospital-initiated infusion of epinephrine or norepinephrine. Our primary outcome was recurrent cardiac arrest (rearrest) in the prehospital setting after the initial ROSC. Key secondary outcomes included sustained ROSC defined as the presence of pulses at the time of hospital arrival, survival to hospital admission, survival to hospital discharge, and neurologically favorable outcome at the time of hospital discharge. Neurologically favorable outcome was defined as Cerebral Performance Category (CPC) score of 1 or 2.

Statistical analysis

Univariate statistics, including frequency counts and percentages, were used to describe the baseline characteristics of the study population. Characteristics were compared and described using Student's *t* test with means and standard deviations (SDs) if normally distributed. The Wilcoxon rank-sum test with medians and interquartile ranges (IQRs) was used for continuous variables that were not normally distributed. Categorical variables were compared using the chi-square and Fisher's exact tests, when appropriate. We used logistic regression to examine the association between primary and key secondary outcomes and vasopressor agent (norepinephrine or epinephrine) by adjusting for age, sex, initially shockable rhythm, bystander CPR, and witness status. A two-sided *p* value of less than 0.05 was used to establish statistical significance. Data analysis was performed using Stata version 17.

Results

Of 3,679 OHCA patients treated during the study period, 3,288 were excluded (Figure 1). Of the remaining 451 patients, 253 (56%) received norepinephrine and 198 (44%) received epinephrine infusions. Although patients who achieved ROSC but subsequently died on scene were excluded, only 7% of these patients received vasopressor infusions (Figure 1). Compared with norepinephrine, those who received epinephrine were older (median 66 [IQR 53-79] years vs 63

[IQR 47-75]), but otherwise had similar baseline characteristics, including epinephrine bolus dose and initial arrest rhythm (see Table 1).

Of the patients in this study, 99% received advanced airway treatment, with 94% having received endotracheal intubation. Of the patients who received advanced airways, 82% were placed prior to ROSC, and therefore prior to initiation of norepinephrine or epinephrine infusions.

Post-ROSC systolic blood pressure differed significantly between the norepinephrine and epinephrine groups (97 mmHg vs. 115 mmHg, $p < 0.05$). Blood pressure is the only post-resuscitation vital sign recorded in the registry used for this analysis.

In the unadjusted analysis, patients who received epinephrine were more likely to rearrest than those receiving norepinephrine (55% vs 25%, OR 3.54, 95% CI 2.38-5.28). This persisted after adjustment for age, sex, initial shockable rhythm, presence of bystander CPR, and witnessed event (OR 3.28, 95% CI 2.25-5.08). While the proportion of patients who rearrested was higher in the epinephrine compared with the norepinephrine group, the number of rearrests among patients who rearrested at least once was similar (1.5 vs. 1.7) (Table 2). After adjustment, the odds of pulses at hospital arrival were lower in the epinephrine group (OR 0.52 95% CI 0.32-0.83).

Overall survival to hospital discharge was 14%, and 10% were discharged with favorable neurological status (Table 2). After adjustment, we did not detect a difference in survival to discharge (OR 1.08, 95% CI 0.60-1.93) or neurologically favorable outcome (OR 0.89, 95% CI 0.45-1.77) (see Table 3).

We noted that the proportion of cases receiving epinephrine rather than norepinephrine increased over time (see Supplement Figure 1). We then added the year in which the OHCA occurred to the regression model and noted little change in the odds ratios (see Supplemental Table 1).

Discussion

In this retrospective study, we found that patients treated after OHCA who received epinephrine infusions rearrested more frequently than those who received norepinephrine infusions. However, these findings were attenuated by the time of hospital discharge.

There are several possible explanations for our findings. The first is confounding by indication. It is possible that paramedics selectively administered epinephrine to patients with higher illness severity and therefore higher rearrest risk. While we adjusted for covariates commonly associated with OHCA survival, residual confounding likely persists. Alternatively, aligned with several other studies detailed below, it may also be possible that epinephrine confers higher risk of rearrest and worse short-term outcome (7, 11). It is also possible that a personalized approach to shock assessment and resuscitation would confer improved outcomes, though invasive and non-invasive monitoring capabilities are limited in the prehospital setting (1, 12, 13).

Bougouin and colleagues conducted a retrospective cohort study of 766 patients at five hospitals in Paris, France treated with either epinephrine or norepinephrine for post-cardiac arrest shock in the intensive care unit setting. They also reported a higher incidence of early (within 48 hours) rearrest among patients treated with epinephrine (7%) compared with norepinephrine (2%). Unlike our study, these authors reported higher all-cause and cardiovascular-specific mortality associated with epinephrine use compared with norepinephrine, even after propensity matching, which may be due to longer duration of vasopressor exposure in the hospital compared with prehospital settings. While some prehospital critical care interventions, such as ventilator settings (14), have been shown to influence hospital treatments, it is unknown whether this holds true for vasopressor selection.

In a pilot randomized trial comparing epinephrine and the combination of norepinephrine and dobutamine for the treatment of cardiogenic shock after acute myocardial infarction among hospitalized patients, both vasopressors were found to be equally effective for augmenting mean arterial pressure (MAP) (6). However, the trial noted epinephrine was associated with lactic acidosis, gastrointestinal ischemia, and tachyarrhythmias. A different randomized trial comparing epinephrine and norepinephrine among patients with cardiogenic shock due to acute myocardial infarction, half of whom had cardiac arrest prior to randomization, was prematurely halted due to the increased rate of refractory shock in the epinephrine group, although MAP and cardiac index were no different (7). Finally, an observational study of hospitalized patients after OHCA showed that infusion of epinephrine was associated with higher all-cause mortality than norepinephrine, even after adjustment for markers of illness severity such as duration of CPR and intra-arrest epinephrine dosing (11).

A randomized controlled trial compared norepinephrine and epinephrine infusions, but it was limited to hospitalized patients with cardiogenic shock following acute myocardial infarction (7). Among the 57 randomized patients, approximately half received cardiopulmonary resuscitation prior to inclusion. Epinephrine was associated with a 30% higher incidence of refractory cardiogenic shock, and the study was terminated prematurely due to this safety outcome. Although refractory cardiogenic shock was explicitly defined, some aspects of their definition are potentially problematic, including persistent lactic acidosis, as lactic acidosis independent of tissue ischemia is a known byproduct of epinephrine administration. Notably, lactate concentrations were no different on hospital arrival in our epinephrine and norepinephrine cohorts (see Table 2).

There are several key limitations of this study. This was a retrospective analysis of a prospectively collected registry, and results should be interpreted cautiously and cannot show causality. The dosages for norepinephrine and epinephrine infusions were not recorded, thus limiting direct comparison of cumulative doses of the two drugs. Additionally, the timing of the drug administration was not consistently recorded, so it is possible that vasopressor infusions were administered after patients had already rearrested, though this is not standard in our EMS system. It is also unknown whether there was a correlation between the vasopressor used in the EMS setting and the vasopressor used in the emergency department and hospital settings. However, this notion of "therapeutic momentum", where therapies started in one setting are likely to be continued, exists for other prehospital interventions (14). These limitations should be considered in the context of the study's strengths: the investigation evaluated an important clinical question using a relatively large cohort with robust prehospital and hospital covariate and outcome measures.

Conclusion

Epinephrine infusion was associated with higher odds of prehospital rearrest compared with norepinephrine in this retrospective cohort study of patients with shock after out-of-hospital cardiac arrest. These data demonstrate a need for a randomized controlled trial comparing norepinephrine and epinephrine infusions for the treatment of post-resuscitation shock.

Declaration of Interest: The authors have no competing interests to declare.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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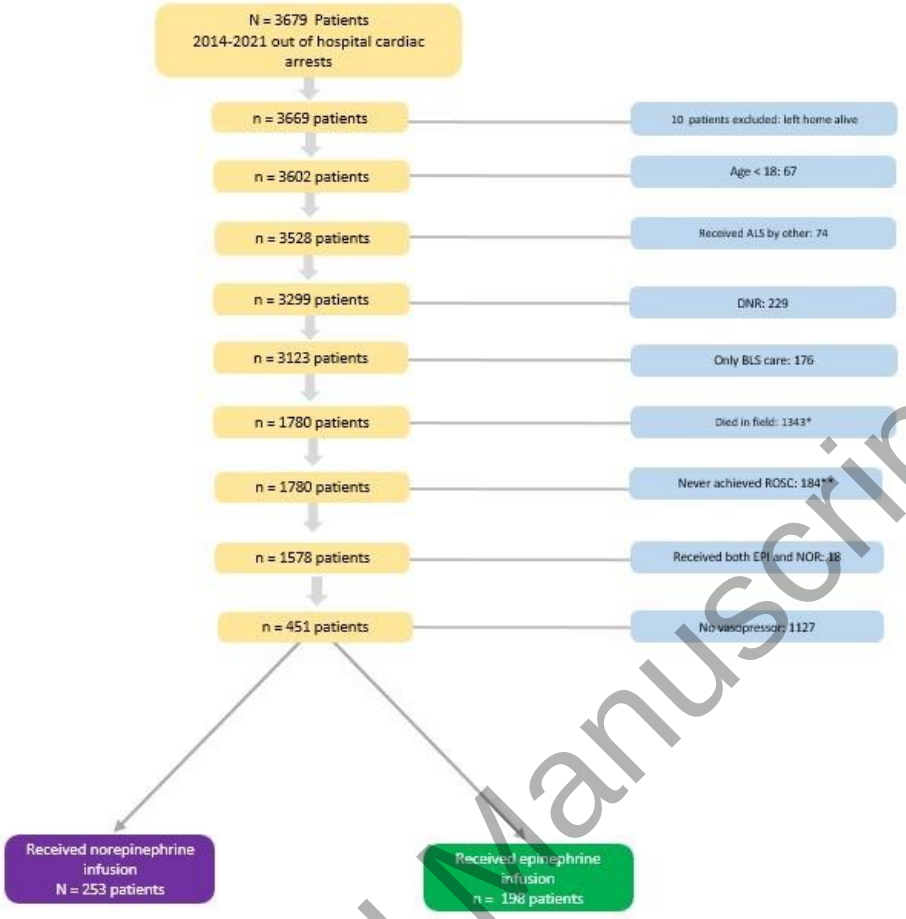

*Of patients who died in field, 30 received norepinephrine infusions, 32 received epinephrine infusions, 2 received both, and 1705 received neither
**Of patients who never achieved ROSC but were transported, 10 received norepinephrine infusions, 4 received epinephrine infusions, 0 received both, and 199 received neither
Figure 1: study cohort

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Table 1: OHCA characteristics and outcomes for prehospital norepinephrine and epinephrine infusions

Table 2: Hospital interventions and outcomes for prehospital norepinephrine and epinephrine infusions among OHCA patients
* Rearrest status missing for years 2014-2016

Table 3: Adjusted and unadjusted odds ratios of outcomes for patients who received norepinephrine or epinephrine infusions
OR odds ratio CI confidence interval ROSC return of spontaneous circulation
*Adjusted for age, sex, shockable rhythm, incident year, and witness status
** Rearrest status missing for years 2014-2016

Table 1: OHCA characteristics and outcomes for prehospital norepinephrine and epinephrine infusions

	Total		Norepinephrine infusion		Epinephrine infusion	
N/%	451	100%	253	56%	198	44%
Patient demographics						
Age (median, IQR)	64	(50-76)	63	(47-75)	66	(53-79)
Female	177	39%	107	42%	70	35%
Cardiac arrest demographics						
Arrested before EMS	377	84%	212	84%	165	83%
Bystander CPR	234	52%	127	50%	107	54%
Initial rhythm shockable	78	17%	36	14%	42	21%
Cardiac etiology	283	63%	155	61%	128	65%
Respiratory etiology	47	10%	25	10%	22	11%
EMS CPR performance						
Number of defibrillator shocks by EMS (mean, SD)	1.0	1.7	0.8	1.5	1.2	1.9
EMS chest compression fraction (median, IQR)	94%	(92%-96%)	94%	(92%-96%)	94%	(92%-96%)
ALS prehospital treatments						
Intravenous	373	83%	211	83%	162	82%
Intraosseous	160	35%	94	29%	66	33%
Advanced airway management	445	99%	249	98%	196	99%
Epinephrine bolus	434	96%	236	93%	198	100%
Epinephrine bolus dose (median, IQR)	2.5	(1.5-3.5)	2.5	(1.5-3.5)	2.5	(1.5-4.0)
Atropine	11	2%	6	2%	5	3%
Lidocaine	85	19%	38	15%	47	24%
External pacing	7	2%	4	2%	3	2%
Patient vital signs						
First post-ROSC systolic pressure (median, IQR)	98	(70-134)	88	(70-120)	110	(80-150)

Table 2: Hospital interventions and outcomes for prehospital norepinephrine and epinephrine infusions among OHCA patients

	Total		Norepinephrine infusion		Epinephrine infusion	
N/%	451	100%	253	56%	198	44%
Prehospital ROSC/rearrest						
Minutes to first ROSC (mean, SD)	24.3	10.2	24.2	9.8	24.5	10.7
Rearrest	172	38%	64	25%	108	55%
Number of rearrests (mean, SD)	1.6	0.9	1.5	0.7	1.7	0.9
Pulses on hospital arrival	358	79%	215	85%	143	72%
Count of rearrests by patient						
0 rearrests	148	33%	103	41%	45	23%
1 rearrest	97	22%	40	16%	57	29%
2 rearrests	50	11%	20	8%	30	15%
3+ rearrests	25	6%	4	2%	21	11%
Hospital						
Died in ED	117	26%	63	25%	54	27%
Admitted to hospital	334	74%	190	75%	144	73%
Lab values						
First pH (median, IQR)	7.0	(6.9-7.1)	7.0	(6.9-7.1)	7.0	(6.9-7.1)
pCO_2 (median, IQR)	65	(50-83)	61	(48-81)	70	(56-88)
pO_2 (median, IQR)	85	(52-193)	103	(53-232)	77	(50-179)
First lactate (median, IQR)	12.5	(9.2-16.0)	12.9	(9.6-17.0)	11.9	(8.5-16.0)
Post cardiac arrest care						
Targeted temperature management	241	53%	139	55%	102	52%
Coronary angiography	72	16%	36	14%	36	18%
Diagnosis of myocardial infarction	112	25%	64	25%	48	24%
ECPR/ECMO	5	1%	3	1%	2	1%
Outcome						
Discharged alive	62	14%	32	13%	30	15%
Full neuro recovery (CPC 1)	18	4%	9	4%	9	5%
Mild neuro impairment (CPC 2)	26	6%	15	6%	11	6%
Severe neuro impairment (CPC 3)	10	2%	6	2%	4	2%
Comatose (CPC 4)	8	2%	2	1%	6	3%

*Rearrest status was missing for the years 2014-2016

Table 3: Adjusted and unadjusted odds ratios of outcomes for patients who received norepinephrine or epinephrine infusions

Outcome	Epinephrine (n=198)	Norepinephrine (n=253)	Unadjusted OR, 95% CI	Adjusted OR, 95% CI*
Rearrest**	54.5% (108)	25.3% (64)	3.54 (2.38, 5.28)	3.38 (2.25, 5.08)
Sustained ROSC	72.2% (143)	85.0% (215)	0.47 (0.29, 0.75)	0.52 (0.32, 0.83)
Discharged alive	15.2% (30)	12.6% (32)	1.23 (0.72, 2.11)	1.08 (0.60, 1.93)
Good neurologic function	10.1% (20)	9.5% (24)	1.07 (0.57, 2.00)	0.89 (0.45, 1.77)

OR odds ratio CI confidence interval ROSC return of spontaneous circulation
*Adjusted for age, sex, shockable rhythm, and witness status
**Rearrest status missing for years 2014-2016