Brief Report

Epinephrine for Out-of-Hospital Cardiac Arrest: An Updated Systematic Review and Meta-Analysis*

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Objectives: To perform an updated systematic review and meta-analysis of clinical trials evaluating epinephrine for adult out-of-hospital cardiac arrest resuscitation.

Data Sources: The search included MEDLINE, EMBASE, and Ovid Evidence-Based Medicine, clinical trial registries, and bibliographies.

Study Selection: Randomized and quasi-randomized controlled trials that compared the current standard dose of epinephrine to placebo, high or low dose epinephrine, any other vasopressor alone or in combination were screened by three independent reviewers.

Data Extraction: Randomized and quasi-randomized controlled trials that compared the current standard dose of epinephrine to placebo, high or low dose epinephrine, any other vasopressor alone or in combination were screened by three independent reviewers.

Data Synthesis: A total of 17 trials (21,510 patients) were included; seven were judged to be at high risk of bias. Compared to placebo, pooled results from two trials showed that standard dose of epinephrine increased return of spontaneous circulation (risk ratio, 3.09; 95% CI, 2.82–3.89), survival to hospital admission (risk ratio, 2.50; 95% CI, 1.68–3.72), and survival to discharge (risk ratio, 1.44; 95% CI, 1.11–1.86). The largest placebo-controlled trial showed that standard dose of epinephrine also improved survival at 30 days and 3 months but not neurologic outcomes, standard dose of epinephrine decreased return of spontaneous circulation (risk ratio, 0.87; 95% CI, 0.77–0.98) and survival to admission (risk ratio, 0.88; 95% CI, 0.78–0.99) when compared with high dose epinephrine. There were no differences in outcomes between standard dose of epinephrine and vasopressin alone or in combination with epinephrine.

Conclusions: Largely based on one randomized controlled trial, standard dose of epinephrine improved overall survival but not neurologic outcomes in out-of-hospital cardiac arrest patients compared with placebo. There is a paucity of trials with meaningful patient outcomes; future epinephrine trials should evaluate dose and method of delivery on long-term survival, neurologic function, and quality of life after cardiac arrest. (*Crit Care Med* 2020; 48:225–229)

Key Words: cardiac arrest; epinephrine; meta-analysis; resuscitation; systematic review

*See also p. 266.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Dr. Lin is an Investigator of the Cardiac Arrhythmia Network of Canada as part of the Networks of Centres of Excellence and is the Co-Principal Investigator of a Canadian Institutes of Health Research Project Grant for a clinical trial to evaluate low-dose epinephrine during cardiac arrest resuscitation, and he was an Evidence Reviewer for the C2015 International Liaison Committee on Resuscitation advanced life support Taskforce. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000004130

The International Liaison Committee on Resuscitation (ILCOR) identified the need for placebo-controlled trials to evaluate the routine use of vasopressors in out-of-hospital cardiac arrest (OHCA) (1). The aim of this systematic review is to expand and update our previous review to summarize the randomized controlled trial (RCT) evidence of standard dose of epinephrine (SDE) compared with placebo, higher doses of epinephrine, and other vasopressors alone or in combination with SDE in patients who experience OHCA.

MATERIALS AND METHODS

Eligibility Criteria

We included both RCTs and quasi-RCTs performed in adult (≥ 18 yr) nontraumatic OHCA patients treated by emergency medical services personnel. Interventions compared either: 1) SDE (1 mg per dose) to placebo, 2) SDE to high dose epinephrine (HDE; > 1 mg per dose), 3) SDE to low dose epinephrine (< 1 mg per dose), 4) SDE to any vasopressor in combination, or 5) SDE to any vasopressor alone, by either IV or intraosseous (IO) administration. Any vasopressor in combination was defined as

the use of two or more drugs (including SDE) administered concomitantly during resuscitation regardless of the order of drug administration. Studies whereby epinephrine was administered primarily via an endotracheal tube or intracardiac route were excluded due to differences in dose, pharmacokinetics, and pharmacodynamics compared with IV or IO administration.

Primary outcomes included survival and neurologic status at discharge, 30 days, 3 months, 6 months, and 1 year. Neurologic status was determined by Cerebral Performance Category (CPC), Glasgow Outcome Scale, or Modified Rankin Scale (MRS). Secondary outcomes included return of spontaneous circulation (ROSC), survival to hospital admission, all-cause mortality, and conversion from nonshockable to shockable rhythms.

Search Methods

We searched MEDLINE, EMBASE, and Ovid Evidence-Based Medicine Reviews for eligible RCTs and quasi-RCTs from the previous search date of July 1, 2013, to June 25, 2018 (elapsed time from the original systematic review) using a peer-reviewed, information specialist developed search strategy (**Appendix 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F139). We searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform registries and screened bibliographies to identify additional eligible articles.

Study Selection, Risk of Bias, and Quality of the Evidence

Studies were screened for eligibility by three review authors (T.A., A.C., M.P.) at the title/abstract and full-text review stages. Risk of bias (ROB) was assessed as outlined in the Cochrane Collaboration Tool for Assessing Risk of Bias. All screening and ROB evaluations were performed independently, in duplicate. Confidence in effect estimates was rated according to the quality of evidence using Grading of Recommendations Assessment Development and Evaluation (GRADE) approach. Additional systematic review methods are listed in **Appendix 2** (Supplemental Digital Content 1, http://links.lww.com/CCM/F139).

RESULTS

The literature search yielded 393 unique citations (**Fig. 1**). The gray literature search yielded one relevant ongoing trial

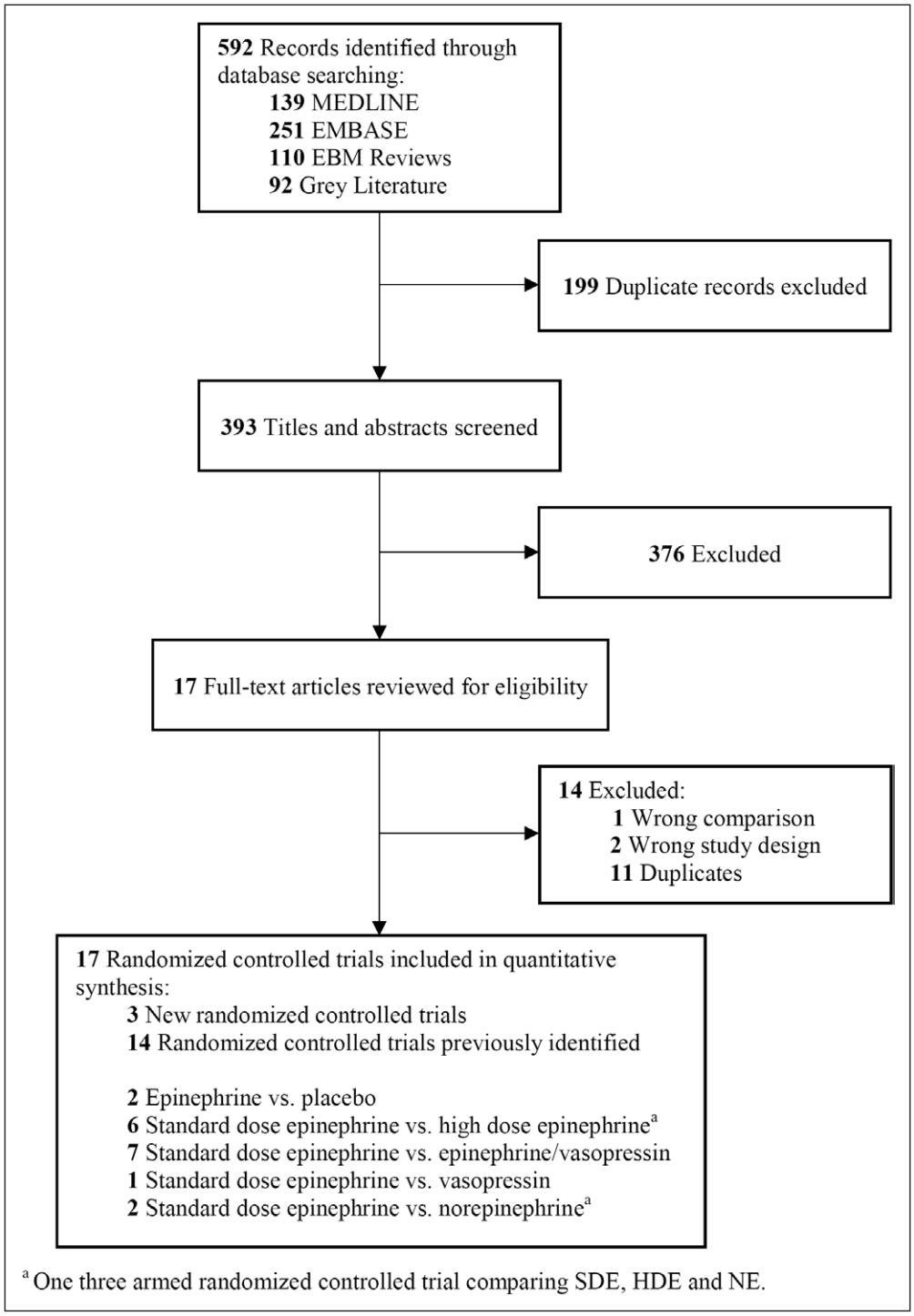

Figure 1. Study selection flow diagram. EBM = Evidence-Based Medicine, HDE = high dose epinephrine, NE = norepinephrine, SDE = standard dose of epinephrine.

(NCT03317197). Seventeen full-text articles were reviewed for eligibility of which three new RCTs met criteria for inclusion. The trials included one RCT of SDE versus placebo (2), one RCT of SDE versus epinephrine/vasopressin (3), and one RCT of SDE versus norepinephrine (NE) (4). The new studies were combined with the 14 RCTs identified in the previous systematic review (5) and grouped according to intervention for a total of 17 RCTs (n = 21,510) one of which included three treatment arms resulting in 18 comparisons (**Appendix Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F139).

Risk of Bias and Quality of Evidence Assessments

Seven studies were assessed as high ROB and ten assessed as low ROB. The quality of the evidence for each outcome ranged from very low to moderate quality across each comparison, assessed using the GRADE approach (**Appendix Figs. 1** and **2** and **Appendix Tables 3–7**, Supplemental Digital Content 1, http://links.lww.com/CCM/F139).

SDE Versus Placebo

Two studies (n = 8,548) compared SDE to placebo (2, 5). Patients who received SDE demonstrated higher ROSC (risk ratio [RR], 3.09; 95% CI, 2.82–3.39), survival to admission (RR, 2.50; 95% CI, 1.68–3.72), and survival to discharge (RR, 1.44; 95% CI, 1.11–1.86), however, there was no difference in neurologic outcome (CPC < 3 or MRS ≤ 3) at discharge (**Fig. 2**). Survival at 30 days was available for one trial (n = 8,014) which showed benefit with SDE compared with placebo (RR, 1.38; 95% CI, 1.06–1.79) similar to survival at 3 months (RR, 1.40; 95% CI, 1.07–1.84) (2). Although the same trial found no difference in favorable neurologic outcome (MRS ≤ 3) at 3 months between SDE and placebo (**Appendix Figs. 3** and **8**, Supplemental Digital Content 1, http://links.lww.com/CCM/F139).

SDE Versus HDE

Six studies (n = 6,744) compared SDE to HDE (5). Patients who received SDE had lower rates of ROSC than those who received HDE (RR, 0.87; 95% CI, 0.77–0.98). Four studies (n = 6,269) were pooled for survival to admission which demonstrated lower survival with SDE (RR, 0.88; 95% CI, 0.78–0.99). There were no differences in other measured outcomes between SDE compared with HDE (**Appendix Fig. 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/F139).

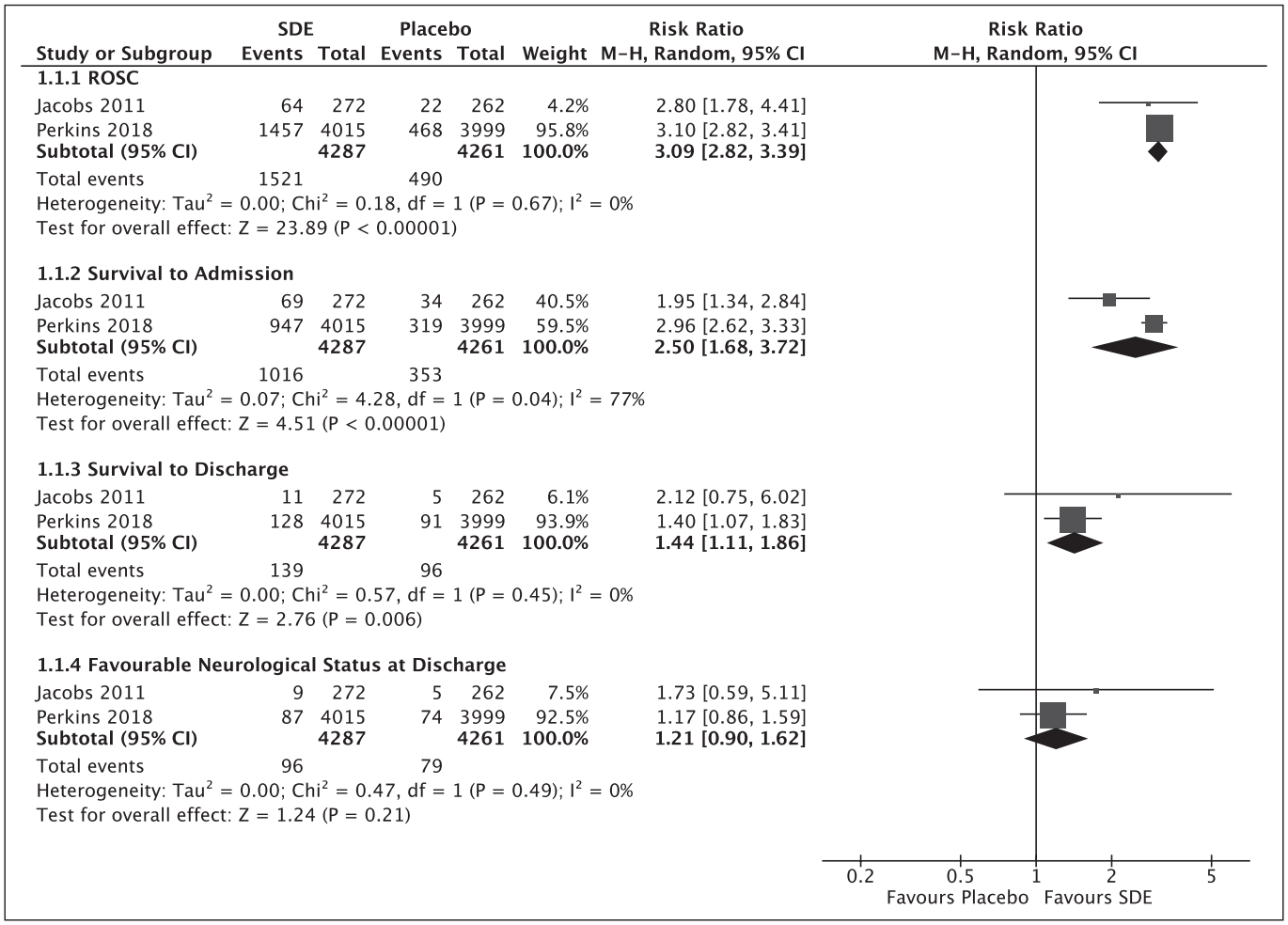

Figure 2. Risk ratios of studies comparing standard dose of epinephrine (SDE) to placebo using a random-effects model with Mantel-Haenszel (M-H) weighting for survival to return of spontaneous circulation (ROSC), survival to admission, survival to discharge and favorable neurologic status at discharge as measured by the Cerebral Performance Category (< 3) or Modified Rankin Scale (≤ 3). *df* = degrees of freedom.

SDE Versus Epinephrine/Vasopressin

Seven studies (n = 5,302) compared SDE to a combination of epinephrine/vasopressin (3, 5). There were no differences between treatments for all measured outcomes (**Appendix Fig. 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/F139).

SDE Versus Vasopressin

One study (n = 336) compared SDE to vasopressin (5). There were no differences in all reported outcomes. Survival to admission was not reported in this trial (**Appendix Fig. 6**, Supplemental Digital Content 1, http://links.lww.com/CCM/F139).

SDE Versus Norepinephrine

Two studies (n = 580) compared SDE to NE (4, 5). Patients who received SDE had lower rates of ROSC compared with NE (RR, 0.68; 95% CI, 0.50–0.94). However, there was no difference between treatments for all other measured outcomes (**Appendix Fig. 7**, Supplemental Digital Content 1, http://links.lww.com/CCM/F139).

DISCUSSION

SDE increased rates of ROSC, survival to hospital admission and discharge compared with placebo; however, there was no difference in neurologic outcomes at discharge. There was only one study that reported long-term outcomes with improved survival to 30 days and to 3 months but not neurologic outcomes (2), which represents the continued paucity of literature evaluating long-term outcomes and reflects the need for adequately designed trials to evaluate meaningful patient outcomes. The ILCOR has since called for the inclusion of a standardized core outcome set for cardiac arrest trials, incorporating survival, neurologic, and quality of life outcomes (6).

Epinephrine has multiple and complex adrenergic effects with a nonlinear dose-response relationship. Higher doses of epinephrine improve coronary perfusion but also disrupt cerebrovascular autoregulation leading to further neurologic damage (7), which paradoxically lead to better short-term survival but not long-term outcomes (**Appendix Fig. 9**, Supplemental Digital Content 1, http://links.lww.com/CCM/F139). OHCA patients receiving greater than or equal to 3 mg total had significantly higher mortality compared with lower doses (8), which may be due to subsequent doses of epinephrine having smaller, transient effects on coronary perfusion and cerebral oxygenation compared with the first two doses (9, 10). The Prehospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug administration In Cardiac Arrest (PARAMEDIC2) trial results showing improved survival but not neurologic outcomes may be the result of grouping dissimilar patients who received lower and higher cumulative doses of epinephrine (2).

In our subgroup analysis stratified by initial rhythm, SDE had lower rates of ROSC and survival to admission in pulseless electrical activity (PEA) and asystole patients compared with HDE (Appendix Fig. 9, Supplemental Digital Content 1, http://links.lww.com/CCM/F139). The PEA/asystole population is highly heterogeneous with different etiologies and survival rates compared with ventricular fibrillation (VF)/ventricular tachycardia (VT) patients. Future trials need to be powered to evaluate less heterogeneous populations, such as VF/VT, and to administer epinephrine in a timely manner to appropriately determine the efficacy of cardiac arrest treatments.

The Canadian Resuscitation Outcomes Consortium will be performing an RCT to evaluate different cumulative doses of epinephrine in OHCA resuscitation. The Epinephrine Dose: Optimal versus Standard Evaluation trial is a multicenter RCT across sites in Canada that will evaluate low cumulative dose (maximum 2 mg) of epinephrine compared with the current standard dose (NCT03826524).

This systematic review and meta-analysis has several limitations. For the majority of treatment comparisons, there was a small number of studies limiting our ability to pool data, and many of the studies had underpowered sample sizes resulting in imprecise effect estimates. There were only two placebo-controlled trials on SDE with the PARAMEDIC2 trial contributing the majority of patients to our meta-analyses (2, 5). Only one RCT reported the use of IV and IO separately but not based on outcomes to allow for subgroup analyses (2). Many of the included RCTs were also published prior to 2000 (5), and since that time, resuscitation guidelines have substantially changed in regards to chest compression ratios and an increased focus on chest compression quality.

Epinephrine administration during resuscitation is complex and the trial literature needs to be more robust to better evaluate its use. Furthermore, other vasopressors have not been sufficiently studied, particularly at different doses, against epinephrine in clinical trials. Adequately designed and powered RCTs focused on more homogeneous populations evaluating standardized long-term patient survival, neurologic outcomes, and quality of life measures are needed (6). This will enable future systematic reviews to meta-analyze consistent data across trials to improve the certainty of pooled effects.

CONCLUSIONS

Primarily based on one RCT, SDE improved overall survival but not neurologic outcomes in OHCA patients compared with placebo. Pooled analyses showed HDE improved short-term ROSC and survival to hospital admission but not survival or neurologic outcomes at discharge compared with SDE. There were no differences in survival between SDE and other vasopressors. Overall, there is a paucity of clinical trials evaluating long-term survival, neurologic, and quality of life outcomes.

ACKNOWLEDGMENTS

We wish to thank the team of the 2014 systematic review, the basis upon which our update was conducted.

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