

Critical Review Form

Meta-analysis

Epinephrine in out-of-hospital cardiac arrest: A critical review. World J Emerg Med. 2013;4(2):85-91.

Objectives: “to address the knowledge deficit regarding epinephrine in OHCA [out-of-hospital cardiac arrest].” (p. 86)

Methods: This systematic review included original research articles evaluating the use of epinephrine compared to no-epinephrine in the treatment of adults with OHCA. Randomized controlled trials and observations studies were included, while case reports, case series, opinion pieces were excluded. MEDLINE (via PubMed), EMBASE, and the Cochrane Library were searched by a single reviewer for relevant articles assessing at least one of the following outcomes: 1) survival to hospital discharge, 2) neurological performance, and 3) return of spontaneous circulation (ROSC). The bibliographies of eligible studies were also reviewed to identify additional relevant articles. Only articles published in the English language were included.

Observational study quality was assessed using [Project Methodology 5](#), while randomized controlled trial quality was assessed using the Critical Appraisal of Therapy Articles worksheet from the [University of Oxford Centre for Evidence Based Medicine](#).

Nine eligible studies were identified: 5 prospective cohort studies, one retrospective cohort study, one survival analysis, one case control study, and one randomized controlled trial. A meta-analysis was not performed due to significant heterogeneity among the patient populations and the overall poor methodological quality of the included studies.

Guide	Question	Comments
I	<i>Are the results valid?</i>	
1.	Did the review explicitly address a sensible question?	Yes. While epinephrine is recommended in the advanced cardiac life support (ACLS) guidelines for the management of cardiac arrest, these recommendations are not based on solid clinical evidence. Epinephrine has several potential downsides that could result in decreased cardiac function and potentially worsen neurologic outcomes. It therefore seems reasonable to assess its efficacy.
2.	Was the search for relevant studies details and exhaustive?	Yes. The authors performed a detailed search of MEDLINE, EMBASE, and the Cochrane Library with the assistance of a medical librarian. The authors did not review conference abstracts, but would likely not have identified any additional methodologically sound research if they had.
3.	Were the primary studies of high methodological quality?	No. The authors identified 9 studies, of which only 2 were based on randomized controlled data, and one of these was a <i>post hoc</i> analysis of previously collected data. There were 3 retrospective cohort studies that did not attempt to match patients to similar controls. There were 3 before and after studies of varying methodological quality, and one observational studies that compared different regions of Japan with vastly different EMS capabilities.
4.	Were the assessments of the included studies reproducible?	No. The authors did not use any reproducible tools for evaluating study quality (Jadad scale , Cochrane “risk of bias” assessment tool , STROBE statement checklist), but rather assessed quality using critical appraisal forms similar to those used in our journal club.
II.	<i>What are the results?</i>	
1.	What are the overall results of the study?	<ul style="list-style-type: none"> • 3 retrospective cohort studies demonstrated increased mortality with the use of epinephrine, but were limited by differences in important prognostic factors between the groups (Holmberg et al, Wang et al, Herlitz et al). • A large before and after trial from Japan (Hagihara et al) using propensity matching to reduces differences between patient populations demonstrated improved ROSC with epinephrine use, but worsened one-month mortality and poorer neurologic outcomes (CPC 1 or 2). • Another before and after study from Japan (Yanagawa et al) demonstrated higher rates of epinephrine administration in patients with ROSC (p = 0.0005), but no association with neurological performance. The study was limited by dissimilar patient populations. • A before and after study from Singapore (Ong et al) did not find any differences in ROSC, survival to admission, or survival to hospital discharge among those treated with epinephrine and those not treated with epinephrine. • An observational study comparing regions in Japan with the capability to

give epinephrine to those without such capability found no differences in outcomes (Ohshige et al). This study was limited by small sample size, dissimilarities in patient population, and inability to control differences in the level of training of healthcare providers.

- Two randomized controlled trials were identified (Jacobs et al, Olasveegan et al). Both trials demonstrated an increase in ROSC; the study by Olasveegan demonstrated a decrease in favorable neurologic outcome, while Jacobs found no statistically significant difference; Olasveegan reported a decrease in survival to hospital discharge, while Jacobs reported a non-statistically significant increase in survival to discharge.

Table 1. Outcomes from prospective cohort studies

Primary author	Study Type	Outcome measure	Results (95% CI)
Holmberg	Retrospective cohort	Survival	OR 0.43 (0.27-0.66)
Wang	Retrospective cohort	Mortality	HR 1.57 (1.20-2.07)
Herlitz	Retrospective cohort	Mortality	RR 1.58
Hagihara	Before and after	ROSC One-month survival Good neurologic outcome	OR 2.36 (2.22-2.50) OR 0.46 (0.42-0.51) OR 0.31 (0.26-0.36)
Ong	Before and after	ROSC Survival to admission Survival to discharge	OR 0.9 (0.6 to 1.2) OR 1.0 (0.7-1.5) OR 1.7 (0.6-4.5)
Olasveegan	RCT	ROSC Survival to discharge Good neurologic outcome	OR 1.3 (0.9-1.8) OR 0.5 (0.3-0.8) OR 0.4 (0.2-0.7)
Jacobs	RCT	ROSC Survival to discharge Good neurologic outcome	OR 3.4 (2.0-5.6) OR 2.2 (0.7-6.3) OR 0.53 (0.17-1.6)

2. How precise are the results?

See above

3. Were the results similar from study to study?

No. All of the studies that assessed ROSC found improvements in the outcome with the use of epinephrine. While most of the observational studies demonstrated decreased survival to discharge with the use of epinephrine, many of these failed to achieve statistical significance, the study by Ong et al found a non-statistically significant increase in survival to discharge. Of the RCTs, one demonstrated a decrease in rates of survival to discharge, while the other demonstrated a non-statistically significance increased in survival to discharge. The three studies that assessed neurologic outcomes universally found decreased rates of good neurologic outcome among patients treated with epinephrine, but only 2 of these results achieved statistical significance.

III. *Will the results help me in caring*

	<i>for my patients?</i>	
1.	How can I best interpret the results to apply them to the care of my patients?	The current systematic review has compiled the results of 9 trials of varying methodological quality. The highest quality study on the subject (Jacobs et al) is a randomized controlled trial from Australia demonstrating improved ROSC with epinephrine use, with a non-statistically significant increase in survival to discharge, but a similarly non-statistically significant decrease in the rate of good neurologic outcomes. Unfortunately, the study's size was limited by withdrawal of 5 of the 6 EMS agencies initially set to enroll in the study. The remaining studies, by and large, demonstrate decreased survival and worse neurologic outcomes with the use of epinephrine in OHCA. The variable methodology makes it difficult to draw a definitive conclusion from these results, but does suggest that there is clinical equipoise regarding this topic, and suggests the need for a well done, large randomized controlled trial to better assess this controversy.
2.	Were all patient important outcomes considered?	Yes. The authors chose to address ROSC, survival to hospital discharge, and neurologic outcomes. The authors were unable to assess long-term neurologic outcomes.
3.	Are the benefits worth the costs and potential risks?	Uncertain. As described above, there is clinical equipoise regarding the use of epinephrine in OHCA, and further research is needed.

Limitations:

- 1. The date on which the search was conducted was not provided.**
- 2. A single author performed the literature search.**
- 3. Only articles published in English were eligible for inclusion.**
- 4. There was significant clinical and methodological [heterogeneity](#) between the included studies.**
- 5. The included studies were of overall poor methodological quality, although the authors failed to assess quality using easily reproducible scoring systems and/or checklists ([Jadad scale](#), [Cochrane "risk of bias" assessment tool](#), [STROBE statement checklist](#)).**
- 6. The authors did not assess for [publication bias](#).**

Bottom Line:

The current systematic review has compiled the results of 9 trials of varying methodological quality. The studies, by and large, demonstrate decreased survival and worse neurologic outcomes with the use of epinephrine in OHCA. The variable methodology makes it difficult to draw a definitive conclusion from these results, but does suggest that there is clinical equipoise regarding this topic, and suggests the need for a well done, large randomized controlled trial to better assess this controversy.