

Review Article

Epinephrine in out-of-hospital cardiac arrest: A critical review

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BACKGROUND: Epinephrine is recommended in advanced cardiac life support guidelines for use in adult cardiac arrest, and has been used in cardiopulmonary resuscitation since 1896. Yet, despite its long time use and incorporation into guidelines, epinephrine suffers from a paucity of evidence regarding its influence on survival. This critical review was conducted to address the knowledge deficit regarding epinephrine in out-of-hospital cardiac arrest and its effect on return of spontaneous circulation, survival to hospital discharge, and neurological performance.

METHODS: The EMBASE and MEDLINE (through the Pubmed interface) databases, and the Cochrane library were searched with the key words "epinephrine", "cardiac arrest" and variations of these terms. Original research studies concerning epinephrine use in adult, out-of-hospital cardiac arrest were selected for further review.

RESULTS: The search yielded nine eligible studies based on inclusion criteria. This includes five prospective cohort studies, one retrospective cohort study, one survival analysis, one case control study, and one RCT. The evidence clearly establishes an association between epinephrine and increased return of spontaneous circulation, the data were conflicting concerning survival to hospital discharge and neurological outcome.

CONCLUSIONS: The results of this review exhibit the paucity of evidence regarding the use of epinephrine in out of hospital cardiac arrest. There is currently insufficient evidence to support or reject its administration during resuscitation. Larger sample, placebo controlled, double blind, randomized control trials need to be performed to definitively establish the effect of epinephrine on both survival to hospital discharge and the neurological outcomes of treated patients.

KEY WORDS: Emergency medicine; Epinephrine; Cardiac arrest; Prehospital; Out-of-hospital; Resuscitation

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INTRODUCTION

Cardiac arrest is a relatively common event with 40 000 occurring each year in Canada,^[1] a country with a population nearing 35 000 000.^[2] Approximately 70% of these are in the prehospital setting.^[1] Despite improvements in prehospital care, survival rates remain low. Estimates for survival to hospital discharge vary widely, both globally and regionally, with Canadian rates sitting between 4%–10%.^[3] There is an ongoing

discussion concerning interventions to improve survival rates. Some interventions have strong evidence such as prompt initiation of high quality CPR (*OR* 1.23–5.01),^[4] early defibrillation (*OR* 2.56, 95%*CI* 1.41–4.64),^[5,6] minimizing interruption in chest compressions (*OR* 2.33–3.01),^[7] and post resuscitation care initiatives.^[8–10] Conversely, interventions such as intravenous vasopressor drugs have a controversial role in resuscitation.

Epinephrine is recommended in the advanced

cardiac life support (ACLS) guidelines for use in adult cardiac arrest,^[11,12] and has been used in cardiopulmonary resuscitation since 1896.^[13] It is a non-selective alpha and beta adrenergic agonist, and its value in resuscitation is due largely to the alpha-1 receptor mediated vasoconstrictive activity.^[14] Alpha-1 activity increases diastolic blood pressure, which leads to increased coronary perfusion, as the coronary arteries receive blood during diastole. Yet, despite its long time use and incorporation into guidelines, epinephrine suffers from a paucity of evidence regarding its influence on survival.^[15]

Epinephrine use is also not without its risks. This drug can lead to a number of undesirable sequelae. Its vasoconstrictive properties, while beneficial in the short term, have been shown to reduce perfusion of cerebral microcirculation^[16,17] resulting in poor neurological outcomes.^[18,19] It also renders ventricular pacing foci irritable and increases the probability of ventricular arrhythmias post resuscitation.^[20] Furthermore, its action on beta-1 receptors has inotropic effects, which increase myocardial oxygen demand, and can exacerbate an existing ischemic insult.^[21] Consequently, patients can have residual ventricular dysfunction post-resuscitation. As a result of these issues, it has now come into question whether this drug is beneficial for long-term survival.

This critical review will synthesize the evidence concerning the use of epinephrine in out-of-hospital cardiac arrest (OHCA). Neurologically intact survival (a combination of the Utstein variables of neurological outcome at discharge from hospital and survival to hospital discharge) is generally accepted as the most relevant outcome.^[22,23] This will be reflected in the outcome measures of the included studies in this review. This review was conducted to address the knowledge deficit regarding epinephrine in OHCA.

Clinical question

Does epinephrine use in adult out-of-hospital cardiac arrest result in improved rates of neurologically intact survival to hospital discharge?

METHODS

A search was conducted to look for original research studies comparing the use of epinephrine versus no-epinephrine for adults in out-of-hospital cardiac arrest. Anticipating a paucity of randomized control trials (RCTs) on the subject, prospective cohort, and retrospective cohort observational studies were included in the review. Case reports, case series, and opinion

pieces were excluded. The preliminary search was conducted by a single reviewer. Selected articles were further scrutinized by a senior reviewer. The MEDLINE database was searched with no year restriction using the PubMed interface with the terms 'adrenaline', 'epinephrine', and 'cardiac arrest'. The search was limited to the English language. The search yielded 1570 results. The EMBASE database was searched, with no year restriction, using the terms 'adrenaline', 'epinephrine', 'cardiac arrest', and 'heart arrest'. The search was limited to out-of-hospital cardiac arrest. The search yielded 201 results. The Cochrane Library was also searched with no year restriction using the search terms 'adrenaline', 'epinephrine', 'drugs', 'cardiac arrest', 'resuscitation', and 'ventricular fibrillation'. This database yielded 1 protocol.^[24] The bibliographies of eligible trials and protocols were reviewed for additional eligible studies. Articles were excluded if they were not of the English language, or if they concerned in-hospital cardiac arrest, animal trials, or pediatric populations. This search strategy was formulated and revised with a medical librarian. The authors had no competing interests and no funding was received for this review.

In concordance with the Utstein Style guidelines for reporting data from out-of-hospital cardiac arrest,^[22,23] the primary outcomes to be analyzed in recruited studies are survival to hospital discharge and neurological performance. A secondary outcome examined will be ROSC. Included studies must be original research with statistical analysis that addresses one or more of these outcomes.

Study populations, interventions, outcomes, designs and quality will be assessed for heterogeneity. In addition, the Forest Plot will be visually inspected for heterogeneity, which will be assessed using the Chi-square test (P value <0.01) and I^2 models. A meta-analysis using a random effects model will be done if there is reasonable clinical and methodological similarity between studies.

Critical appraisal of included studies

Studies were reviewed for quality using assessment tools based on the recommendations of published systematic reviews of such tools.^[25] Observational studies were assessed using Project Methodology 5 from the Division of Information Services, University of Wales College of Medicine, and RCTs were assessed using the Critical Appraisal of Therapy Articles from the University of Oxford Centre for Evidence Based Medicine.

RESULTS

The search yielded nine eligible studies. These included five prospective cohort studies, one retrospective cohort study, one survival analysis, one case control study, and one RCT with a total of 601 subjects. Table 1 summarizes the key features of the nine included trials. The selected studies had significant heterogeneity with respect to population characteristics and poor methodological quality. The review team decided that a meta-analysis was not warranted and decided to present the results in a narrative-style review.

The earliest studies assessing the effect of epinephrine in adult out-of-hospital cardiac arrest were observational studies^[26–28] that examined differences in ROSC, survival, and neurological outcomes between OHCA patients treated with epinephrine and those not treated with epinephrine, within the same study population. The study by Holmberg et al^[27] demonstrated an association of decreased survival with the use of epinephrine (*OR* 0.43, 95%*CI* 0.27–0.66). Wang et al^[28] produced a similar association with a reported increased mortality (*HR* 1.57, 95%*CI* 1.20–2.07) using a multi-variable regression analysis of epinephrine administration in OHCA. Although Herlitz and colleagues^[26] found a comparable decrease in survival to the previous two studies (*RR* 1.58, *P*<0.01), they also found an increased rate of ROSC in patients with sustained VF who had received 3 defibrillatory shocks (*RR* 2.0, *P*<0.001) and in those who converted from VF to either asystole or electromechanical dissociation at any time during resuscitation (*RR* 1.76, *P*<0.001). However, for these studies, the untreated control groups were not case matched and were statistically different in areas such as arrival of paramedics, nurse present, use of lidocaine, and number of shocks administered. Accordingly, it was difficult to control the level of training of the emergency personnel and the effect of other drugs and treatment administered during resuscitation. Finally, there was an inherent selection bias as patients with prolonged cardiac arrest tend to be treated more aggressively with multiple measures such as intravenous pharmacotherapy.

Another group of observational studies,^[18,29,30] using a before-after approach, reflects modifications in resuscitation guidelines to allow EMS personnel to administer epinephrine in OHCA. Two of the included studies^[18,30] were based on a protocol change in Japan, where emergency life-saving technicians were permitted to establish an intravenous line and administer epinephrine according to Japanese Fire and Disaster Management Agency resuscitation guidelines since

2006. Before this period, epinephrine was administered only when patients were attended by a physician-manned ambulance. Hagihara et al^[18] conducted the larger of the two with an impressive sample size of 417 188 arrests. The epinephrine treated cohort of 15 030 patients was propensity matched to controls not treated with epinephrine to reduce differences between populations. The results revealed a reduction in one-month survival in patients treated with epinephrine (*OR* 0.46, 95%*CI* 0.42–0.51), poorer neurological outcomes reflected by a negative association with cerebral performance category (CPC) 1 and 2 (*OR* 0.31, 95%*CI* 0.26–0.36), and improved ROSC (*OR* 2.36, 95%*CI* 2.22–2.50) for the epinephrine treated group. Owing to attempts made by the authors to match populations and reduce bias and confounders, the study was given a high quality rating by the review team with its conclusions limited solely by its observational methodology. Yanagawa and colleagues^[30] also used before-after data from the modified Japanese guidelines. They conducted a retrospective study to examine factors associated with pre-hospital ROSC and good recovery (CPC 1 and 2). There was no significant association between epinephrine and neurological performance. However, there was a significant difference in the rates of epinephrine administration in the ROSC group, with epinephrine being positively associated with ROSC (*P*=0.0005). Yet, the populations were dissimilar, and despite multi-variable regression analysis, there were many confounding variables. A similar before-after study was conducted in Singapore by Ong et al,^[30] as epinephrine was incorporated into management of OHCA in October 2003.^[29] This study did not find any significant differences between the epinephrine treated population and those not treated with epinephrine with respect to survival to hospital discharge (or survival at 30 days post-arrest if still in hospital), and rates of ROSC. This study was disadvantaged by low sample size and a possible selection bias, as patients achieving early ROSC (thus better predicted survival) were included in the no-epinephrine group by default.

Ohshige and colleagues^[31] conducted a similar observational study comparing regions in Japan where emergency medical system services were either manned by emergency life-saving technicians (unable to administer resuscitative drugs at the time), or by physicians with a full scope of resuscitative capabilities. This study was also limited due to small sample size, and inability to control discrepancies in the level of training of personnel, dissimilarities between population groups, and differences in response time measures. No

Table 1. Summarizing the characteristics of studies comparing the use of epinephrine versus no epinephrine in out-of-hospital cardiac arrest.

Study	Description	Patients	Outcomes	Findings	Study quality
Hagihara et al 2012	Prospective cohort study	417 188 adult patients with OHCA, mean age 72 years, 63.5% male (epi), 58.8% male (no epi), VF/VT 13.7% (epi), 7.2% (no epi). Bystander CPR 45.1% (epi), 36% (no epi). Excluded cases were greater than 60 min from call to scene arrival or greater than 480 min from call to hospital.	ROSC, survival at 1 month, 1 month cerebral performance with CPC, and survival with no, mild, or moderate neurological disability with OPC	A positive association was detected between prehospital epinephrine use and ROSC before hospital arrival. A negative association was detected with respect to prehospital epinephrine use and both 1 month survival, and cerebral performance.	High: propensity matched controls to minimize confounders and bias; no individuals lost to follow-up; very large sample size.
Jacobs et al 2011	Randomized, double-blind, placebo-controlled study	601 adult patients with OHCA, mean age 65 years, 73% male, VF/VT in 46% of cases, 51% received bystander CPR. Cases excluded if loss of randomization or resuscitation not commenced.	Primary: survival to hospital discharge Secondary: ROSC, cerebral performance at hospital discharge with CPC	Nonsignificant increase in survival to hospital discharge in epinephrine group Significant increase in ROSC for epinephrine. Nonsignificant worse neurological outcomes in epinephrine group.	High: strong method of design; regression analysis to limit bias and confounders; main flaw in sample size due to ethical issues. Planned sample size was 5000.
Olasveegan et al 2011	Prospective cohort study	841 adult patients with OHCA, mean age 66, 71% male, VF/VT 32% (epi), 35% (no epi). Bystander CPR in 63%. Cases excluded if loss of randomization, or if unable to determine drug administration.	Primary: survival to hospital discharge Secondary: ROSC, survival to hospital admission, and neurological outcome at hospital discharge	Epinephrine associated with increased short term survival, but with decreased survival to hospital discharge, and decreased favourable neurological outcome.	Low: method of design flawed Confounding effects include selection bias and effects of other drugs.
Yanagawa and Sakamoto 2010	Case control study	713 adult patients with OHCA occurring between November 2005 and April 2007, mean age 69, 60% male, bystander CPR 34%. Patients excluded if untreated due to death or postmortem signs.	Prehospital ROSC and neurological outcome based on CPC	Epinephrine was associated with prehospital ROSC, but was not significantly associated with "good recovery".	Low: populations were divided based on prehospital ROSC and neurological recovery. The populations were dissimilar and despite multiregression analysis, many confounding variables present.
Ong et al 2007	Prospective cohort study	1291 patients in OHCA, mean age 64 years, 69% male, bystander CPR 19%, VF 20%, VT 0.7%. Exclusion criteria were traumatic cause, death, and younger than 8 years old.	Primary: survival to hospital discharge	No significant difference in survival to hospital discharge, ROSC, or survival to hospital admission. Neurological performance similar in both groups.	Moderate: confounders and bias adequately controlled in selection of controls and regression analysis. Limitations include low sample due to inadequate IV access and disparities in protocol (ie no other drugs given and only one dose of epi permitted).
Oshinge et al 2005	Prospective cohort study	434 patients in OHCA, mean age 69, 62% male. No exclusion criteria identified.	Primary: ICU admission rate and 1 month survival	No statistical difference between group resuscitated with epinephrine and reference group with no epinephrine.	Low: confounding variables as intravenous drugs was not the sole difference in care between groups, and the level of training of personnel differed. No regression analysis done to limit bias.
Wang et al 2005	Survival analysis	1496 patients with OHCA, mean age 67, 56.9 percent male, bystander CPR 46.4%, VF/VT 34.1%. Excluded paediatric patients.	Primary: elapsed time to death	Epinephrine was associated with increased risk of death both early (on day 1) and late (after day 1).	Low: potential for confounders as definitive controls not identified and case matched.
Holmberg et al 2002	Prospective cohort study	10966 cases of OHCA, mean age 67, male: 73.5% (epi) 71.3% (no epi), bystander CPR: 34.6% (epi) 30.5% (no epi), VF 51% (epi) 60.9% (no epi).	1 month survival	Survival rate significantly lower in those given epinephrine.	Susceptible to selection bias inherent in decision to administer epinephrine or not. Low: patient groups not comparable. Several differences indicated.
Herlitz et al 1995	Retrospective cohort study	1203 patients with OHCA in VF; median age: 71 years (epi), 70 years (no epi); 80% men, bystander CPR 20%. Exclusions: Any rhythm other than VF, discharge inadequate information.	ROSC, survival to hospital admission, survival to hospital discharge	Overall: patients in the two groups had similar initial rates of survival. Group treated with epinephrine with lower rates of survival to discharge. Certain rhythm defined subgroups with increased ROSC and survival to hospital.	Low: differences between groups. Difficult to account for actions of other drugs, level of training of personnel.

OHCA: out-of-hospital cardiac arrest; VF: ventricular fibrillation; VT: ventricular tachycardia; epi: epinephrine; ROSC: return of spontaneous circulation; CPC: cerebral performance category; OPC: overall performance category.

statistically significant difference in outcomes was found between the groups with respect to epinephrine.

The two most recently published studies^[19,32] included in this review are based on RCT data. However, they fundamentally differ as Olasveegan et al^[19] performed a *post hoc* sub-analysis on RCT data from another study related to the effect of intravenous drug access during cardiac arrest, whereas Jacobs and colleagues^[32] conducted a RCT focused on the effect of epinephrine in OHCA (to be discussed in further detail). An increase in ROSC with epinephrine treatment was shown in both. Olasveegan et al^[19] (*OR* 1.3, 95%*CI* 0.9–1.8) and Jacobs et al^[32] (*OR* 3.4, 95%*CI* 2.0–5.6) reported a decrease in favourable neurological outcome (*OR* 0.4, 95%*CI* 0.2–0.7), whereas Jacobs et al^[32] reported no statistical difference. The main difference between the two studies concerned the effect on survival to hospital discharge. Olasveegan et al^[19] reported a negative association with epinephrine (*OR* 0.5, 95%*CI* 0.3–0.8), while Jacobs et al^[32] reported a positive association (*OR* 2.2, 95%*CI* 0.7–6.3).

The study by Olasveegan et al expanded on data from a study examining the overall effect of intravenous access versus no intravenous access during resuscitation. There are a number of limitations to this study. The procedure, being physical in nature, precludes the use of blinding with the paramedic staff, albeit concealment of allocation of the study participants was maintained. Furthermore, 37 of the 433 patients randomized to the No-IV arm of the trial received epinephrine, and 85 of the 418 patients randomized to the IV arm did not receive adrenaline. Also, patients who obtained early ROSC, regardless of allocation status, were not administered epinephrine (or other intravenous drugs) and were allocated to the no-epinephrine group. The result of this variability is a selection bias in participants (similarly described by Ong et al). The study methodology also made it difficult to account for the use of other drugs during resuscitation efforts. Thus, this study is susceptible to much of the confounding and bias related error as the previous observational studies, regardless of its RCT methodology.

Jacobs et al^[32] have to date the highest quality and most methodologically sound data available. This study is a randomized, double blind, placebo-controlled trial in which OHCA patients were either administered a 1:1000 ampoule of epinephrine or a saline placebo. The results demonstrated a statistically significant increase in ROSC with epinephrine, and an increase in survival to hospital discharge ($P=0.15$) and decrease in good neurological outcome on discharge (CPC 1

or 2, $P=0.31$), which were not statistically significant. The main limitation of this study is its sample size. A power calculation performed by the authors (based on a baseline survival to hospital discharge of 5% with an absolute improvement in survival of 2%, alpha 0.05 and power of 80%) indicated that the sample size required for the study was 2213 patients per group. The planned total number was to be 5000, allowing for patients lost to follow-up, with participation from five emergency services systems in Australia and New Zealand. Despite approval from Institutional Ethics Committees, Crown Law and Guardianship Boards, four of the five EMS systems withdrew from the study due to concerns that the standard of care was being withheld.

DISCUSSION

The evidence clearly establishes an association between epinephrine and increased ROSC.^[16,17,23,27] However, the clinical significance of this outcome is uncertain with a number of studies reporting either no improvement or a decrease in survival to hospital discharge or a decrease in favourable neurological outcome.^[18,19,26,30]

With regard to survival to discharge, the evidence to date is inconclusive. The study by Jacobs et al,^[32] which is the only double-blind randomized controlled trial comparing epinephrine to placebo in OHCA, showed a trend towards increased survival to discharge in the epinephrine treated group. Unfortunately, the authors were unable to enroll the number of subjects planned in their sample size calculation, and this result did not reach statistical significance. In a letter to the editor, Youngquist and Niemann^[33] argue in favor of the benefit of epinephrine suggesting that this trend should not be ignored simply because the P value was 0.15. Such an 'all-or-nothing' interpretation of the data has been increasingly criticized by methodologists.^[34] They suggest that a Bayesian interpretation of the result is more appropriate than the classic Frequentist interpretation used, and subsequently re-calculated an *OR* of 2.1 (95%*CI* 0.8–6.6) with a posterior probability of 93% that the *OR* is greater than 1. They contend that, "while 93% is not certainty, it suggests that declarations regarding an absence of benefit from adrenaline in the setting of cardiac arrest are premature." The original authors reached similar conclusions when they re-analyzed their data using a Bayesian approach (*OR* 2.1, 95%*CI* 0.7–6.3).^[35] Like any *post hoc* analysis, the clinical significance of these arguments must be interpreted with caution, especially

in light of the non-statistically significant trend towards decrease in neurological performance found in this study and conflicting evidence from very large prospective cohort studies.^[18]

The opportunity cost of administering epinephrine must also be considered. Epinephrine must be administered through an intravenous line or intra osseous device and establishment of parental access may limit the effectiveness of other resuscitative measures including CPR. CPR has long been established as a vitally effective intervention with an *OR* for survival of between 1.23–5.01 in a recent meta-analysis.^[36] Interruptions in chest compressions cause a fall in diastolic pressure, which reduces coronary perfusion pressure resulting in a decrease in survival to hospital discharge of between 14%–18% for every 5-second increase in both pre- and peri-shock pause durations.^[36] Interruptions in chest compressions to establish parental access may diminish chances of survival. A randomized control trial where patients either received advanced cardiac life support with intravenous drugs or ACLS without intravenous drugs demonstrated no difference in survival to hospital discharge.^[37] Furthermore, another study^[38] showed no difference in survival to hospital discharge after institution of ACLS training (consisting of the addition of endotracheal intubation and intravenous line administration of medications).

In conclusion, although the results of this review exhibit the paucity of high quality published research supporting the use of epinephrine in OHCA, there is insufficient evidence to support changing current guidelines which recommend its administration during resuscitation. Larger placebo controlled, double blind, randomized control trials (approximately 5000 subjects)^[32] need to be performed to definitively establish the effect of epinephrine on both survival to hospital discharge and the neurological outcomes of treated patients. In the meantime, resuscitation efforts for OHCA should focus on those interventions that have been definitely associated with patient benefit: early, high quality CPR, minimizing the interruption of chest compressions, early defibrillation, and post resuscitation care.

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