Review Article

Epinephrine in Out-of-hospital Cardiac Arrest: Helpful or Harmful?

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Abstract

Objective: Epinephrine is the primary drug administered during cardiopulmonary resuscitation (CPR) to reverse cardiac arrest. The evidence for the use of adrenaline in out-of-hospital cardiac arrest (OHCA) and in-hospital resuscitation is inconclusive. We conducted a systematic review on the clinical efficacy of adrenaline in adult OHCA patients to evaluate whether epinephrine provides any overall benefit for patients.

Data Sources: The EMBASE and PubMed databases were searched with the key words "epinephrine," "cardiac arrest," and variations of these terms.

Study Selection: Data from clinical randomized trials, meta-analyses, guidelines, and recent reviews were selected for review.

Results: Sudden cardiac arrest causes 544,000 deaths in China each year, with survival occurring in <1% of cases (compared with 12% in the United States). The American Heart Association recommends the use of epinephrine in patients with cardiac arrest, as part of advanced cardiac life support. There is a clear evidence of an association between epinephrine and increased return of spontaneous circulation (ROSC). However, there are conflicting results regarding long-term survival and functional recovery, particularly neurological outcome, after CPR. There is currently insufficient evidence to support or reject epinephrine administration during resuscitation. We believe that epinephrine may have a role in resuscitation, as administration of epinephrine during CPR increases the probability of restoring cardiac activity with pulses, which is an essential intermediate step toward long-term survival.

Conclusions: The administration of adrenaline was associated with improved short-term survival (ROSC). However, it appears that the use of adrenaline is associated with no benefit on survival to hospital discharge or survival with favorable neurological outcome after OHCA, and it may have a harmful effect. Larger placebo-controlled, double-blind, randomized control trials are required to definitively establish the effect of epinephrine.

Key words: Adrenaline; Cardiac Arrest; Cardiopulmonary Resuscitation; Epinephrine; Return of Spontaneous Circulation

Introduction

Cardiac arrest is a substantial public health problem.[1] Data from previous studies suggest that >3 million sudden cardiac deaths occur worldwide every year, and survival is lower than 8%.[1] Overall, 544,000 sudden cardiac deaths occur in China each year with survival in <1% of cases (compared with 12% in the United States).[2,3] Survival from sudden cardiac arrest in China is much lower than in many countries. Many conditions may cause cardiac arrest, with coronary artery disease being one of the most common causes.

Epinephrine has been the cornerstone of cardiac resuscitation and advanced cardiac life support (ACLS) from the birth of modern cardiopulmonary resuscitation (CPR) in the early 1960s.[4] The provision of epinephrine is currently suggested by both the American Heart Association (AHA) and the European Resuscitation Council in both shockable and nonshockable rhythms.[5] Epinephrine is vital to improving the return of spontaneous circulation (ROSC). However, standard-dose epinephrine does not increase and may actually reduce long-term survival and neurological recovery after CPR.

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In this article, we systematically reviewed whether the use of intravenous adrenaline, according to current cardiac arrest guidelines, is helpful or harmful.

Current Guidelines

The administration of adrenaline has long been recommended for the use during ACLS, based predominantly on animal studies.[6] Epinephrine is an endogenous catecholamine with high affinity for α- and β-adrenergic receptors present in cardiac and vascular smooth muscle.[7] β-adrenergic effects are more pronounced at low doses while α-adrenergic effects are more pronounced at higher doses.[7] Epinephrine has beneficial effects in patients during cardiac arrest, primarily because of its α-adrenergic effects, resulting in improved coronary perfusion pressure which is associated with an increased probability of ROSC in animals and humans.[8,9] However, the effect on cerebral perfusion remains controversial.[5] A Class IIb recommendation from the 2015 updated AHA guidelines states that "standard-dose epinephrine may be reasonable for patients with cardiac arrest," with doses of 1 mg of 1:10,000 epinephrine administered intravenously every 3–5 min.[10] It may be reasonable to administer epinephrine as soon as feasible after the onset of cardiac arrest due to an initial nonshockable rhythm (Class IIb recommendation).[10] For initial shockable rhythms, such as pulseless ventricular tachycardia or ventricular fibrillation (VF), defibrillation is recommended as the first-line treatment, with chest compressions. However, the optimal timing of epinephrine administration is unknown.[10] High-dose epinephrine is not recommended (Class III recommendation).[10]

Potential Beneficial and Detrimental Effects of Epinephrine

Beneficial effects of epinephrine

The findings from randomized trials and observational studies indicate that epinephrine increases coronary perfusion pressure and the likelihood of ROSC during CPR.[11] Administering epinephrine during CPR increases the probability of restoring cardiac activity with pulses, which is an essential intermediate step toward long-term survival.[12] The potential beneficial effects are attributed to the stimulation of α-receptors, which constrict the arterioles and increase aortic pressure during chest compressions.[13] When CPR fails to generate a coronary perfusion pressure >15–20 mmHg (1 mmHg = 0.133 kPa), return of cardiac mechanical activity rarely or never occurs.[14] Epinephrine, with its potent vasopressor and inotropic properties, can rapidly increase diastolic blood pressure to facilitate coronary perfusion and help restore organized myocardial contractility.[7] In a systematic review and meta-analysis, investigators addressed an advantage of standard-dose adrenaline (SDA) over placebo and high-dose adrenaline (HDA) over SDA in overall survival to admission and ROSC, which is consistent with previous reviews.[15]

In the first and, to date, only randomized, double-blind, placebo-controlled trial of adrenaline in patients with out-of-hospital cardiac arrest (OHCA), Jacobs *et al*.[16] reported a significant increase in ROSC associated with epinephrine and a nonsignificant increase in survival to hospital discharge or worse neurological outcomes in patients administered epinephrine. Nakahara *et al*.[17] reported that patients receiving early (<10 min) adrenaline had significantly higher rates of neurologic intact survival and any survival than those who did not receive early adrenaline, after adjusting for potential confounders. Hayashi *et al*.[18] reported that the effectiveness of adrenaline in patients with OHCA depended on the time of its administration. When adrenaline was administered in the early phase, there was an improvement in neurologic outcome from OHCA secondary to VF. Atiksawedparit *et al*.[19] published a meta-analysis reporting a higher rate of prehospital ROSC in the epinephrine group while no difference in survival to discharge was found. Studies in patients with cardiac arrest outside hospital have consistently found that epinephrine increases aortic relaxation pressure and increases coronary perfusion pressure, increasing the chances of achieving ROSC.

Detrimental effects of epinephrine

Epinephrine increases coronary perfusion pressure by decreasing blood flow to all other organs, an effect that may persist after the restoration of pulses.[12] On the basis of observational data and limited clinical trials, standard-dose epinephrine does not increase and may actually reduce long-term survival and neurological recovery after CPR.[11] Potentially harmful effects are α- and β-receptor mediated and include reduced cerebral microvascular blood flow and exacerbation of neurological outcome. Cardiovascular instability, such as increased myocardial work and increased risk of tachydysrhythmia, promotes thrombogenesis and platelet activation after ROSC and adverse immunomodulatory and metabolic effects.[10,12,20] Experimental studies have shown that β-blocker treatment may mitigate some of these deleterious effects.[21] An animal study indicated that epinephrine reduced capillary blood flow in swine brain.[22] Epinephrine-induced cerebral hypoperfusion persisted during CPR was attributable to the α-1 agonist effects of reduced cerebral microcirculatory blood flow and increased cerebral ischemia, determined by decreased brain tissue pO_2 and increased pCO_2.[4] Epinephrine also has adverse effects on myocardium mediated by β-receptor stimulation.[4] Epinephrine impairs myocardial function despite increasing coronary perfusion pressure.[4] Epinephrine is known to increase the frequency of transitions from PEA to ROSC and extend the time window for the development of ROSC at a cost of greater cardiovascular instability after ROSC, with a higher rate of rearresting.[23] Similarly, the total dose of epinephrine is associated with impaired lactate clearance for hours and gastric mucosal perfusion after CPR in humans.[11,12]

Hagihara *et al*. conducted a prospective nonrandomized analysis of over 400,000 patients with OHCA in Japan,

finding an increase in ROSC with epinephrine, but no increase in survival or functional outcome. Greater ROSC occurred in the epinephrine group, although this was associated with lower survival at one month and worse neurologic outcome.[24] Dumas *et al*.[25] examined a cohort of patients who achieved ROSC and found that prehospital adrenaline was associated with a lower chance of survival. Investigators also reported that adrenaline administration was associated with worse survival and neurological outcome that was not improved by postresuscitation hypothermia.[25] In a trial *post hoc* analysis, Olasveengen *et al*.[26] found that "adrenaline was associated with short-time survival but also with decreased survival to hospital discharge and survival with favorable neurological outcomes." A study conducted by Sanghavi *et al*.[27] in 2015 reported that no evidence implies epinephrine associated with improved neurologic outcome, survival to discharge, and total survival. There is conflicting evidence on long-term survival and functional recovery, particularly neurological outcomes, in patients with cardiac arrest outside hospital.

Effect of dosage, timing subgroups of patients

The total dose and timing of epinephrine affects patient outcome.[28] The current 1 mg bolus dose of adrenaline was derived from animal studies in the 1960s.[12] The optimal dose of epinephrine is not known, although increasing the cumulative dose may worsen survival and neurological outcome.[10] Lin *et al*.[15] compared SDA (1 mg every 3–5 min) with placebo, SDA with HDA (>1 mg/dose), SDA with the combination of adrenaline and vasopressin, and SDA with vasopressin alone. There was no benefit of adrenaline in survival to discharge or neurological outcomes.[15] There were improved rates of survival to admission and ROSC in the SDA versus placebo and HDA versus SDA studies.[15] However, there are no studies examining smaller doses (e.g., 1 μg/kg) or infusions of adrenaline in clinical studies.[29] Some studies suggested that the earlier epinephrine is administered in cardiac arrest, particularly in nonshockable OHCA, the greater its effect.[30]

Several studies have identified different etiologies in subgroups with shockable and nonshockable rhythms, and it seems reasonable that there are differences in treatment strategies.[31] In the initial shockable rhythm cohort, the ratios of prehospital ROSC, 1-month survival, and 1-month favorable neurological outcomes in the nonepinephrine group were significantly higher than those in the epinephrine group.[32] However, in the initial nonshockable rhythm cohort, the ratios of prehospital ROSC and 1-month survival in the epinephrine group were significantly higher than those in the nonepinephrine group, and there was no significant difference between the epinephrine and nonepinephrine groups for 1-month favorable neurological outcomes.[32] Several studies have identified dissimilar etiologies in shockable and nonshockable subgroups and it seems reasonable to assume that differences in treatment strategies will emerge.[26]

Nevertheless, future studies should consider whether different effects of epinephrine are observed in clinically distinct subsets of patients, such as those with non-VF cardiac arrest, or at distinct times after cardiac arrest.[11]

Summary of studies evaluating epinephrine is listed in Table 1.

Potential Future Directions of Epinephrine

There is an urgent need for larger sample, high-quality, double-blind, randomized controlled trials and should include long-term follow-up in order to improve understanding and inform clinical practice. The evidence to date suggests that epinephrine may still have a role in resuscitation, possibly by continuous infusion rather than bolus administration, or in doses smaller than 1 mg or when delivered very early, or when combined with other therapies.[33]

Three phases of cardiac arrest can be considered: electrical, circulatory, and metabolic.[3] The use of epinephrine in cardiac arrest increases the chance of achieving ROSC. The circulatory phase targets perfusion and epinephrine could increase coronary blood flow and perfusion pressure through α-adrenergic peripheral vasoconstriction. Epinephrine's beta-stimulation may have deleterious effects, resulting in postresuscitation cardiac dysfunction. Beta-adrenoceptor blockade treatment may mitigate some of these harmful effects, maximizing the function of epinephrine. The use of beta-blockade could reduce myocardial oxygen requirements, improve postresuscitation myocardial function, diminish arrhythmia recurrences, and prolong survival. Prearrest beta-blockade seemed to yield better postresuscitation myocardial and neurologic function in addition to the increase in postresuscitation survival. Several studies illustrate that future research may focus on the promotion of microvascular flow rather than maximizing pressures in large arteries. Randomized controlled trials remain the gold standard and their use in comparing standard-dose epinephrine (1 mg every 3–5 min) to placebo, no intravenous access to drug administration of existing and new drugs, appears justified.

Conclusions

Prehospital epinephrine administration may improve ROSC but does not improve survival to discharge or neurologic outcomes after OHCA. Although there is no clear evidence of long-term benefits following the use of epinephrine in OHCA, there is insufficient evidence to support changing current guidelines which recommend its administration (1 mg every 3–5 min) during resuscitation. Therefore, there is a need for further clinical trials to examine whether lower doses or alternative regimes of epinephrine administration. Furthermore, the most important aspect of care in cardiac arrest is BLS measures, including adequate compressions and early defibrillation.

Table 1: Summary of studies evaluating the effects of epinephrine

Study	Year	Description	Outcomes	Findings
Sanghavi *et al*.[27]	2015	Retrospective cohort study	Survival to hospital discharge, to 30 days, and to 90 days; neurological performance	No epinephrine associated with improved neurologic outcome, survival to discharge, and total survival
Lin *et al*.[15]	2014	Systematic review and meta-analysis	Primary: Survival to hospital discharge Secondary: ROSC, survival to hospital admission, and neurological outcome at hospital discharge	No benefit of epinephrine in survival to discharge or neurological outcomes. There were improved rates of survival to admission and ROSC with SDA over placebo and HDA over SDA
Atiksawedparit *et al*.[19]	2014	Meta-analysis	ROSC and survival to discharge	A higher rate of prehospital ROSC in the epinephrine group while no difference in survival to discharge
Dumas *et al*.[25]	2014	Prospective cohort study	Survival to hospital admission, and neurological outcome at hospital discharge	Prehospital epinephrine was associated with a lower chance of survival and worse neurological outcomes
Nakahara *et al*.[17]	2013	Retrospective cohort study	Overall and neurologically intact survival at 1 month or at discharge	Significant increase in neurologic intact survival and survival at 1 month
Hayashi *et al*.[18]	2012	Prospective cohort study	neurological outcome at hospital discharge	When epinephrine was administered in the early phase, there was an improvement in neurologic outcome
Hagihara *et al*.[24]	2012	Prospective cohort study	ROSC, survival at 1 month, 1 month cerebral performance with CPC, and survival with no, mild, or moderate neurological disability with CPC	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
Olasveengen *et al*.[26]	2012	Prospective cohort study	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 favorable neurological outcome
Jacobs *et al*.[16]	2011	Randomized, double-blind, placebo-controlled study	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 group. Nonsignificant worse neurological outcomes in epinephrine group

ROSC: Return of spontaneous circulation; SDA: Standard-dose adrenaline; HDA: High-dose adrenaline; CPC: Cerebral performance category.

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Conflicts of interest

There are no conflicts of interest.

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