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THE CUTTING EDGE: RESEARCH UPDATE

# Assessment of epinephrine efficacy in out-of-hospital cardiac arrest

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## Background

Epinephrine has been a cornerstone of cardiac resuscitation for over 50 years and continues to be recommended by the recent updates of the advanced life support guidelines. However, there is limited evidence about its effects on survival and neurologic outcomes [1].

Epinephrine has potentially beneficial effects in cardiac arrest, through its vasoconstrictor activity on arterioles, mediated by α1 and α2 receptors. The augmented vascular tone increases the aortic diastolic pressure, which generates higher coronary perfusion pressures, thereby increasing the probability of return of spontaneous circulation (ROSC). When cardiopulmonary resuscitation (CPR) does not generate coronary perfusion pressure of more than 15 mmHg, ROSC rarely occurs and after more than few minutes' arterial tone tends to collapse, making vasoconstrictors essential for restoration of cardiac activity.

On the other hand, adrenaline has potentially harmful effects on the heart, mediated by beta-adrenoreceptors, which increase the myocardial oxygen demand and exert a pro-arrhythmogenic effect. This further worsens the mismatch between oxygen delivery and consumption, especially in acute coronary syndromes, thus increasing the risk of recurrent cardiac arrest. In addition, alpha-receptor stimulation causes platelet aggregation, which promotes thrombosis and might worsen acute ischemia. Finally, vasoconstriction induced by epinephrine impairs microvascular blood flow in the cerebral cortex, increasing the severity of cerebral ischemia during CPR and for at least 10 min after ROSC.

There is only a small randomized controlled trial (RCT) comparing directly epinephrine with placebo, showing higher rates of ROSC in patients receiving epinephrine, while the results on mortality are inconclusive. Further trials have compared standard-dose epinephrine (1 mg) with high-dose epinephrine (5–10 mg) or with epinephrine and vasopressin, without showing evidence of better outcomes [2]. In large observational studies, receiving epinephrine and increasing epinephrine dosage are strongly associated with worse survival and neurological outcome after cardiac arrest [3].

At present, well-designed randomized controlled trials assessing safety and effectiveness of epinephrine in cardiac arrest are lacking.

## Summary

Perkins et al. conducted a multicenter randomized double-blind placebo-controlled trial (PARAMEDIC-2) to establish whether epinephrine is a safe and effective treatment for cardiac arrest [4]. The study was conducted by five National Health Service ambulance services in the United Kingdom.

Adult patients who had an out-of-hospital cardiac arrest were included in the study. Exclusion criteria included known or apparent pregnancy, an age of less of 16 years, cardiac arrest from anaphylaxis or asthma, previous administration of epinephrine and traumatic cardiac arrests (only in one ambulance service).

Randomization was provided with concealed assignment. If initial attempts at resuscitation (including CPR and defibrillation) were unsuccessful, the patient was randomly assigned to receive 1 mg of epinephrine or 0.9% saline. Administration timing was consistent with resuscitation protocols of European Resuscitation Council Guidelines.

The primary outcome was the rate of survival at 30 days. The secondary outcomes were the rate of survival until hospital admission, the lengths of stay in the hospital and in the intensive care unit (ICU), the rates of survival at hospital discharge and at 3 months and the neurologic outcomes at hospital discharge and at 3 months.

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The study included 8014 patients: 4015 were assigned to the epinephrine group and 3999 to the placebo group. As concern primary outcome, data were available for 4012 patients in the epinephrine group and 3995 patients in the placebo group. The rate of survival at 30 days was higher in the epinephrine group than the placebo group: 3.2% (130 patients) vs 2.4% (94 patients), unadjusted odds ratio for survival 1.39 (95% confidence interval [CI] 1.06–1.82; $p = 0.02$).

The proportion of patients who survived with a favorable neurologic outcome until hospital discharge was not significantly different between the epinephrine and placebo group, 87 of 4007 patients [2.2%] and 74 of 3994 patients [1.9%], respectively, unadjusted odds ratio 1.18% (95% CI 0.86–1.61).

More survivors in epinephrine group had severe neurologic impairment, 39 of 126 (31%) vs 16 of 90 (17.8%) in the placebo group, considered as a score of 4 or 5 on the modified Rankin score.

The authors concluded that, even if there was a higher rate of 30 day survival with the use of epinephrine, it was associated with a higher neurological impairment, so that there was not difference in rate of favorable neurological outcome between groups.

## Strengths of the study

- The study deals with a relevant clinical topic on a drug extensively recommended and routinely administered in cardiac arrest patients, but without conclusive evidence of safety and effectiveness. Making RCT placebo-controlled trial on this topic could raise ethical issues, but the authors had carefully managed them in the protocol design. The study is well-designed and follows a rigorous methodology.
- The outcomes of the study are both clinically and ethically relevant (30-day survival, neurologic outcomes and the consequent quality of life).

## Question mark

- Since the high number of patients that had died between ROSC and 30 days, we wonder if this difference could have been influenced by in-hospital patients' management, thus underlying the need for extreme care in the first days' conduct.
- According to what authors reported for sample size calculation, there was a smaller proportion of survived patients than expected. We wonder if the reference population considered in study design was adequately chosen.
- Even though there was no statistically significant difference in the neurological outcome between epinephrine and placebo group, we wonder if the neurologic outcome is relevant to test epinephrine efficacy. Even if it is important to consider patients' functional status and the consequent quality of life, both can be significantly influenced by many other interventions. Therefore, a conclusion about this topic appears to be beyond the scope of this trial.

## Sponsorship

The trial was funded by the Health Technology Assessment Programme of the National Institute for Health Research, with legal sponsorship provided by the University of Warwick. The funders had no role in the trial design, in the collection or analysis of the data, or in the writing of the manuscript. The Warwick Clinical Trials Unit undertook data management.

## Clinical bottom line

The results of this study support guidelines recommendations showing an increased rate of survival among out-of-hospital cardiac arrest patients treated with epinephrine.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Statement of human and animal rights** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with human and animals performed by any of the authors.

**Informed consent** None.

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