DEM Journal Club

# Article Appraisal

**Article:** A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest Perkins et al

**Date of Journal Club:** September 18 2018

**Resident Reviewer Name(s) and Residency Affiliation:** Mark Sanderson (FRCPC), Adrianna Rowe (FRCPC)

**Faculty Methodology/Bio-statistics Resource Person:** Brian Grunau

## Background and Study Objective(s):

Current guidelines on management of out of hospital cardiac arrest call for repeated administration of intravenous epinephrine. Observational studies have demonstrated that the use of epinephrine in cardiac arrest is associated with increase rates of return of spontaneous circulation (ROSC), however this has never been shown in a randomized controlled trial. The use of supratherapeutic doses of epinephrine in cardiac arrest has been questioned in multiple observational studies and implicated in increasing rates of poor neurologic outcomes in survivors. A single randomized controlled trial has been initiated to investigate the use of epinephrine in cardiac arrest previously, however it was terminated early, reaching less than 15% of its anticipated enrolment.

## Study Design:

This was a multicenter, double-blind, randomized controlled trial performed at five National Health Service ambulance services in the United Kingdom. The trial population was adult patients (>16 years of age) with out-of-hospital cardiac arrest (traumatic and non-traumatic) attended by trial trained advanced life support paramedics. Exclusion criteria were obvious or presumed pregnancy, receiving epinephrine before the arrival of trial trained paramedics, or cardiac arrest caused by anaphylaxis or asthma. Patients who did not get ROSC after initial CPR and defibrillation were deemed eligible and randomized in a 1:1 assignment ratio to receive either 1mg of IV or IO epinephrine every three to five minutes, or identical pre-filled syringes of 0.9% normal saline. The primary outcome was the rate of survival at 30 days. Secondary outcomes included the rate of survival until hospital admission, lengths of stay in hospital and ICU, the rates of survival at hospital discharge and at 3 months, and rate of favourable neurologic outcomes at hospital discharge and 3 months (modified Rankin Score ≤ 3). Once patients arrived at an emergency department the treatment was at the discretion of the clinical teams, and further care (including prognostication) was not dictated by the study protocol, nor even recorded.

## Results:

Survival at 30 days from cardiac arrest was 130/4012 (3.2% in the epinephrine group and 94/3995 (2.4%) in the placebo group, corresponding to a number needed to treat of 112. The unadjusted odds ratio (OR) was 1.39 (95% CI = 1.06-1.89). Survival until hospital admission was significantly higher in the epinephrine group (947/3973 or 23.8%), than the placebo group (319/3982 or 8.0%) with an unadjusted OR of 3.59 (95% CI = 3.14-4.12). Similarly, survival to

hospital discharge was higher in the epinephrine group than the placebo group, 128/4009 (3.2%) and 91/3995 (2.3%) respectively (unadjusted OR 1.41, 95% CI = 1.08-1.86). Survival at 3 months was also higher in the epinephrine group. Survival with favourable neurologic outcome (mRS ≤3) at hospital discharge was 87/4007 (2.2%) and 74/3994 (1.9%) in the epinephrine and placebo groups respectively with an unadjusted OR of 1.18 (95% CI = 0.86-1.61; 3-month outcomes unadjusted OR 1.31, 95% CI 0.94-1.82). There was a greater proportion of poor neurologic outcome (mRS ≥ 4) in the epinephrine group.

## Validity of Results:

This was a well performed, and statistically rigorous multicenter randomized controlled trial. The internal validity of the trial is strong with a well-defined population, intervention, and primary outcome. The randomization was appropriate and successful and patients, healthcare workers, and study personnel were blind to treatments. We are unable to assess whether or not all patients were treated similarly once they had arrived at the emergency department and the ICU.

## Generalizability of Results:

In discussion with British Columbia Emergency Health Services (BCEHS) Emergency Physician Online Service (EPOS) staff it is not felt that the trial population or outcomes are significantly different from those encountered in British Columbia. Our pre-hospital protocols in BC are similar to those of the United Kingdom outlined in the trial. Different centers may expect different times to ambulance on-scene, time to first epinephrine administration, or time to transport to higher level of care with ICU or surgical services and therefore the results of this trial may not be generalizable to all centers. It should also be noted that average time from call to administration of agent was approximately 20 minutes in both groups, and that patients who had ROSC after initial CPR or defibrillation were not included in the trial. This limits the applicability of these results to patients unresponsive to initial therapy, and may not extend to patients who receive epinephrine early.

## The Bottom Line:

In this well performed multicenter, randomized, controlled trial the use of 1mg epinephrine in out of hospital cardiac arrest increased survival at 30 days. One of the secondary outcomes, favourable neurologic outcome at hospital discharge (mRS ≤3)–for which the study was not powered to detect a difference, was numerically higher in the epinephrine group but this was not statistically significant. Further study is required to elucidate the role of early epinephrine administration, low dose epinephrine or epinephrine infusion, in addition to how the impact of these strategies may differ between those with different initial cardiac rhythms.