Critical Review Form
Therapy

Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. Resuscitation. 2011 Sep;82(9):1138-43.

Objectives: **To evaluate the efficacy of epinephrine in the treatment of out-of-hospital cardiac arrest (OHCA) via a randomized placebo-controlled trial.**

Methods: **This randomized placebo-controlled trial was conducted with patients suffering OHCA attended by St. John Ambulance Western Australia (SJA-WA). Patients aged 18 years or older with OHCA of any cause, with resuscitation commenced by the paramedics were eligible for inclusion. Randomization occurred by a computer-generated schedule, and drug preparation occurred independently of the investigators. Study drugs (either 10 mL of 1:1000 epinephrine or 10 mL of 0.9% normal saline) were prepared in identical vials, distinguishable only by randomization number. Patients were randomized at the time that epinephrine was to be administered (i.e. after 3 unsuccessful shocks or after the establishment of an IV in cases of nonshockable rhythm). Per protocol, termination of resuscitation was allowed when asystole was present after a minimum of 20 minutes of maximal resuscitation efforts. In cases that were transported to the hospital, treating ED physicians were unaware of group assignment.**

The primary outcome was survival to hospital discharge. Secondary outcomes included pre-hospital return of spontaneous circulation (ROSC), survival to hospital admission, and cerebral performance category (CPC) scores at hospital discharge. An *a priori* subgroup analysis was planned based on shockable vs. nonshockable rhythms. Demographic and clinical information was obtained from the WA Ambulance Service Cardiac Arrest Registry, while outcome data was obtained from the state-based Emergency, Hospital Morbidity and Mortality data systems. For patients who survived to hospital discharge, CPC scores were obtained from the medical records by a reviewer blinded to study group allocation.

Between August 11, 2006 and November 30, 2009, there were 4103 cases of OHCA attended by the ambulance service. Of these, 601 eligible patients were randomized; in 67 cases the randomization number was not recorded, leaving 534 total subjects analyzed (262 in the placebo group and 272 in the epinephrine group). The mean age was 65 and 73% were male. The initial rhythm was ventricular fibrillation (VF) or ventricular tachycardia (VT) in 46% of cases. Bystander CPR was performed in 51% of cases.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "Randomisation occurred at the time that it became evident that the administration of IV adrenaline was indicated, and was actioned by selection of the study drug ampoule." (p. 1139)
2.	Was randomization concealed (blinded)?	Yes. "Study drugs were commercially prepared in identical 10 ml vials with tamperproof seals distinguishable only by a specific randomisation number. The drugs were prepared independent of the investigators and numbered according to a computer generated randomisation schedule." (p. 1139)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. All patients were treated according to group assignment with no crossover reported.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, location of arrest, % with cardiac etiology of arrest, initial arrest rhythm, and ambulance response interval. Rates of bystander CPR were higher in the placebo group compared to the epinephrine group (52.7% vs. 44.1%, p = 0.05).
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No. Patients were in cardiac arrest, and hence unaware of any and all interventions.
2.	Were clinicians aware of group allocation?	No. Study drugs were administered in identical 10 mL vials distinguishable only by randomization number.
3.	Were outcome assessors aware of group allocation?	No. ED clinicians, who presumably determined when to cease resuscitation efforts, were blinded to group allocation. Additionally "CPC scores are derived from medical chart review for patients surviving to hospital discharge, with the chart reviewer blinded to the study group allocation." (p. 1139)

4.	Was follow-up complete?	Yes. There was no loss to follow-up.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• ROSC was 3.4 times more likely among patients receiving epinephrine (23.5% vs. 8.4%), for an OR of 3.4 (95% CI 2.0-5.6). • Epinephrine was associated with an increase in the rate of survival to hospital admission among those who made it to the ED (25.4% vs. 13.0%; OR 2.3, 95% CI 1.4-3.6) • While survival to hospital discharge was nearly twice as high among patients who received epinephrine, this difference did not achieve statistical significance (4.0% vs. 1.9%; OR 2.2, 95% CI 0.7-6.3). • Survival with a good neurologic outcome (CPC 1 or 2) was observed in 5 patients in the placebo group (1.9%), compared to 9 patients in the epinephrine group (3.3%). Two patients in the epinephrine group survived with a CPC > 2. • For the sub group analysis, the improvement in rates of ROSC with epinephrine was more marked in patients with non-shockable rhythms (OR 6.9; 95% CI 2.6-18.4) than in those with shockable rhythms (OR 2.4; 95% CI 1.2-4.5).
2.	How precise was the estimate of the treatment effect?	See above. The study was underpowered to detect a statistically significant difference in the primary outcome, despite the outcome being more than twice as likely in the epinephrine group.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes and no. These were patients with OHCA provided EMS care in an industrialized nation. While the majority of the patients resided in a large urban area, ~27% did not, and presumably were cared for in a more rural setting in Western Australia. It is uncertain if rates of serious comorbidity were similar to those in our patient population.
2.	Were all clinically important outcomes considered?	No. While the authors considered ROSC, survival to hospital discharge, and neurologic function, they did not consider longer term outcomes. The

		Research Working Group of the American Heart Association Emergency Cardiovascular Care Committee has recommended that large trials designed to have a major impact should use longer-term endpoints at least 90 days out coupled with some neurological and quality-of-life assessment.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. The study demonstrated a significant improvement in ROSC and survival to hospital admission with the administration of epinephrine. Although it also demonstrated a two-fold improvement in survival to hospital discharge, this difference did not achieve statistical significance.

Limitations:

1. **Of five ambulance services the authors initially planned to include in the study, four withdrew prior to initiation of the study due to ethical concerns. The result was that the study remained underpowered to detect a statistically significant difference in the primary outcome.**

2. **The authors did not assess the effect of epinephrine administration on CPR quality.**

3. **Participation in the study by paramedics in the SJA-WA system was voluntary. The result was that only 40% of eligible patients were included, potentially leading to selection bias.**

4. **The study measured only short-term outcomes, including survival to hospital discharge. The Research Working Group of the American Heart Association Emergency Cardiovascular Care Committee has recommended that large trials designed to have a major impact should use longer-term endpoints at least 90 days out coupled with some neurological and quality-of-life assessment.**

5. **Around 27% of the population served by the SJA-WA system resided in a rural environment, which could affect the applicability of the results to our urban population (external validity).**

Bottom Line:

This randomized, blinded, placebo-controlled Australian study demonstrated a significant improvement in ROSC (OR 3.4, 95% CI 2.0-5.6) and survival to hospital admission (OR 2.3, 95% CI 1.4-3.6) with the administration of epinephrine. Although a two-fold improvement in survival to hospital discharge was also demonstrated, this difference did not achieve statistical significance (OR 2.2, 95% CI 0.7-6.3). Unfortunately, the study was limited by the unforeseen withdrawal of 4 of 5 EMS systems initially slotted to enroll patients.