Critical Review Form
Therapy

PGY-1

Perkins GD, Ji C, Deakin CD, et al; PARAMEDIC2 Collaborators. A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest. N Engl J Med. 2018 Aug 23;379(8):711-721.

Objectives: **"…to establish whether epinephrine is safe and affective as a treatment for cardiac arrest."**

Methods: **This multicenter, randomized controlled trial was conducted at five National Health Service ambulance services in the United Kingdom between December 2014 and October 2017. Adult patient suffering out-of-hospital cardiac arrest (OHCA) requiring advanced life support, provided by trial-trained paramedics, were eligible for enrollment. Exclusion criteria included known or suspected pregnancy, age < 16 years, cardiac arrest due to anaphylaxis or asthma, or administration of epinephrine prior to enrollment.**

Patients with initially unsuccessful attempts at resuscitation, regardless of presenting rhythm, were randomized in a 1:1 fashion to receive either epinephrine (1 mg intravenously or intraosseously every 3 to 5 minutes) or placebo (0.9% saline). Treatment was continued until return of spontaneous circulation, discontinuation of resuscitation, or handoff to clinicians at the hospital.

The primary outcomes was survival at 30 days. Secondary outcomes included survival to hospital admission, length of stay in the hospital and in the intensive care unit (ICU), survival to hospital discharge, survival at 3 months, and favorable neurologic outcome at hospital discharge and 3 months (defined as a modified Rankin scale score of 3 or less).

During the study period, 10623 patients were screened for eligibility and 8103 were randomized. Of these, 87% were found to be ineligible and 2 had unknown group assignments due to missing trial-pack numbers. This left 8014 patients, with 4015 in the epinephrine group and 3999 in the placebo group. The mean age was 69.7 and 69.8 years in the groups, respectively, and about 65% were male.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. Patients were randomized in a 1:1 fashion to receive either epinephrine (intravenous or intraosseous) or placebo (0.9% saline).

2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. "A randomization sequence was computer-generated by the minimization method with an overall assignment ratio of 1:1…the patient was randomly assigned to receive either parenteral epinephrine or saline placebo by the opening of a trial pack containing either agent. Uniquely numbered but otherwise identical-appearing trial packs contained 10 prefilled syringes, with each syringe containing either 1 mg of epinephrine or 0.9% saline." (p. 713) This should be sufficient to ensure allocation concealment.
3.	Were patients analyzed in the groups to which they were randomized?	Not exactly. The authors chose to use a "modified intention to treat analysis" for their primary analysis, "which included all the patients who had undergone randomization and were confirmed to have received the assigned intervention." (p. 713) It would appear, however, that all patients received the intervention to which they were randomized.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients in the two groups were similar with respect to age, gender, initial cardiac rhythm, cause of cardiac arrest, presence of witness to arrest, use of bystander CPR, and intervals between key events (e.g. time to arrival of EMS at scene, time until administration of trial drug, and time until arrival at hospital).
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. In addition to procedures used to ensure adequate blinding, patients enrolled were in cardiac arrest and hence in no position to be aware of treatment allocation.
2.	Were clinicians aware of group allocation?	No. "Uniquely numbered but otherwise identical-appearing trial packs contained 10 prefilled syringes, with each syringe containing either 1 mg of epinephrine or 0.9% saline." (p. 713) There is no chance of performance bias on the part of paramedics or clinicians influencing outcomes.
3.	Were outcome assessors aware of group allocation?	No. "Outcomes were assessed by research paramedics, who were unaware of treatment assignments." (p. 713)
4.	Was follow-up complete?	Mostly yes. For the primary outcome, only 4 patients in the placebo group and 3 patients in the epinephrine group were lost to follow-up at 30 days. An additional 4 patients in the placebo group and 3 patients in the epinephrine group did not have 30-day mortality information; 20 patients in the placebo group and 29 patients in the epinephrine group were lost to follow-up in neurologic analysis.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• For the primary outcome, significantly more patients in the epinephrine group survived to 30 days compared to the

		placebo group: 3.2% vs. 2.4%, OR 1.39 (95% CI 1.06-1.82). This results in a number needed to treat of 112. • Survival to hospital admission was much more common the epinephrine group compared to the placebo group (OR 3.59, 95% CI 3.14-4.12), but there was no difference in survival to hospital discharge with a favorable neurologic outcome (OR 1.18, 95% CI 0.86-1.61). Severe neurologic impairment (modified Rankin scale score 4 or 5) was more common among survivors in the epinephrine group (31% vs. 17.8%). • Survival at 3 months was more common in the epinephrine group (OR 1.41, 95% CI 1.07-1.87), but a favorable neurologic outcome at 3 months occurred in similar rates between the two groups (OR 1.31, 95% CI 0.94-1.81).
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Yes. Although this study was conducted in the UK, this patient population should be very similar to patients suffering OHCA in our community. The US and UK have similar ambulance systems, with paramedics providing the bulk of care, and hospital systems and standards of care would also be expected to be similar.
2.	Were all clinically important outcomes considered?	Yes. The authors considered not only short-term survival, but long-term survival and neurologic outcomes, as previously recommended by the Research Working Group of the American Heart Association Emergency Cardiovascular Care Committee. They did not look at societal costs of caring for patients who survived to hospital admission but whose long-term outcomes were poor, not did they address the psychosocial impact of such cases on family members.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While survival at 30 days (primary outcome) occurred somewhat more frequently in the epinephrine group, the odds of having a favorable neurologic outcome at discharge or at 3 months was not statistically higher in this group (though there was a trend towards improved outcome). It could be argued that given the societal costs of caring for the significantly higher number of patients who survive to hospital admission without improved neurologic outcomes that the risks outweigh the benefits. On the other hand, given the trend towards improved neurologic outcomes, and the statistically significant improvement in the primary outcome, it seems reasonable for now to continue to administer epinephrine for OHCA.

Limitations:

1. **The authors report using a modified intention to treat analysis, but what they report is actually a per protocol analysis. While they do not report any crossover, they do not specifically address this.**

2. **The primary outcome in this study was survival at 30 days, which does not take into account the importance of neurologic function.**

3. **Some research suggests that earlier administration of epinephrine in cardiac arrest is more beneficial (Hansen 2018); the median time elapsed between EMS arrival and trial drug administration was nearly 15 minutes in each group, which could result in an underestimation of the efficacy of epinephrine. In addition, the time required to randomize patients in and of itself could have prolonged this time period and potentially led to harm.**

Bottom Line:

This large, multicenter, randomized controlled trial found a small but statistically significant improvement in survival at 30-days with epinephrine administration in cardiac arrest compared to placebo, with a number needed to treat of 112. However, they also found an increase in neurologic impairment among survivors who received epinephrine and no significant difference in survival with a good neurologic outcome at hospital discharge or at 3 months between those who got and did not get epinephrine. These conflicting results will no doubt lead to continued controversy surrounding this topic.