Epinephrine in Out-of-Hospital Cardiac Arrest: Saving Lives or Prolonging Death?

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Editor's Note: *You are reading the 67th installment of Annals of Emergency Medicine Journal Club. As the Journal Club enters its second decade of publication, we are making a number of changes to the format. Dr. David Schriger, the originator of the Annals of Emergency Medicine Journal Club and its first editor, has retired from his Journal Club editorial role. The journal and his fellow editor are indebted to Dr. Schriger for his outstanding contributions and the success of this educational section. The Journal Club section welcomes Dr. Ryan Radecki and Dr. Rory Spiegel to the editorial staff. The Journal Club format has been revised and will focus on a monthly succinct review of high-impact articles from this journal and other premier medical journals relevant to emergency medicine. The reviews are followed by questions demonstrating principles by which readers–be they clinicians, academics, residents, or medical students–may critically appraise the literature. We are interested in receiving feedback about this feature. Please e-mail journalclub@acep.org with your comments.*

ARTICLE IN REVIEW

Perkins GD, Ji C, Deakin CD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. *N Engl J Med*. 2018;379:711-721.

What Question Did This Investigation Aim to Answer?

In adult patients with out-of-hospital cardiac arrest, what effect does the use of bolus-dose epinephrine have on patient survival?

What Study Design Did the Authors Choose?

Design: Prospective, pragmatic, multicentered, double-blinded, interventional, randomized, parallel-assignment clinical trial. Current Controlled Trials number ISRCTN73485024.

Setting: The trial was conducted by 5 National Health Service ambulance services in the United Kingdom.

Population: All adult patients who experienced sustained out-of-hospital cardiac arrest for whom advanced life support was attempted. Patients were excluded from enrollment if they had known or apparent pregnancy, were younger than 16 years, had cardiac arrest from anaphylaxis or asthma, or were administered epinephrine before the arrival of the trial-trained paramedic.

Intervention: Patients were randomly assigned to receive either intervenous or intraosseus epinephrine (1 mg) or placebo (10 mL of 0.9% saline solution) every 3 to 5 minutes.

Primary Outcome: Thirty-day survival.

Secondary Outcomes: Survival to hospital admission, hospital and ICU length of stay, survival to hospital discharge, 3-month survival, and the neurologic outcomes at hospital discharge and at 3 months.

How Did the Authors Interpret the Results?

The authors noted a statistically significant difference in the primary outcome, 30-day survival, which was 3.2% in the epinephrine group and 2.4% in the placebo group (unadjusted odds ratio for survival 1.39; 95% confidence interval 1.06 to 1.82; P=.02).[1] This 0.8% absolute difference in survival remained consistent at 3 months (3% versus 2.2%) and translated to a number needed to treat of 112 patients to prevent 1 death at 30 days. The authors also reported an increase in the number of patients who were transported to the hospital (50.8% versus 30.7%) and survived to ICU admission (14.1% versus 6.8%). Despite a small increase in overall survival, the authors reported no difference in the rate of neurologically intact survival in patients randomized to receive epinephrine versus placebo (2.2% versus 1.9%).[1]

How Might This Study Affect Your Clinical Practice in the Emergency Department?

In this large, high-quality randomized controlled trial, although epinephrine was demonstrated to increase the rate of 30-day survival, it did not increase the number of

patients who survived neurologically intact, leading to a higher number of survivors with severe neurologic disability.[1]

DISCUSSION POINTS

1. *The authors noted a statistically significant increase in 30-day survival, citing a 0.8% absolute difference in mortality, with a corresponding* P *value of .02. Although this was statistically significant, what is the clinical significance of such a difference in survival? Discuss the difference between statistical and clinical significance.*

The *P* value, first proposed by Fisher in the early 20th century, is defined as the probability, under the assumption of no effect or no difference (the null hypothesis), of obtaining a result equal to or more extreme than what was actually observed if the study were to be conducted a large number of times. The term "significant" was derived from "signify," or a test that indicates or provides support for rejecting the null hypothesis. Simply put, a *P* value is the probability that there is no difference between the 2 groups in question.[2] In this case, given the observed increase in survival of 0.8%, what is the likelihood that in reality there is no difference between epinephrine and placebo? The authors report a *P* value of .02, or a 2% probability that these results would be observed if there were in fact no difference between epinephrine and placebo.

With the increasing statistical power that comes with increasing sample size, it is inevitable that small statistical differences between groups will be observed because no 2 groups are identical. As such, it is important to differentiate between statistical significance and clinical importance. In the case of epinephrine in out-of-hospital cardiac arrest, we are asked to balance a 0.8% increase in survival to hospital discharge with the harms associated with its use. The harms are significant and clinically important. The resources required to stock epinephrine on ambulances across the country and to employ the staff with the appropriate skill level to administer intra-arrest medications are immense. More important, the use of epinephrine was associated with a significant increase in the risk of survival with neurologic devastation. Although more patients who received epinephrine were transported to the hospital (50.8% versus 30.7%) and survived to ICU admission (14.1% versus 6.8%), 31% of the survivors in the epinephrine group had a modified Rankin Scale score of 4 or 5 (unable to walk or bedridden) compared with 17% in the placebo group, with no increase in the number of patients with neurologically intact survival.

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REFERENCES

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2. Goodman SN. Toward evidence-based medical statistics. 1: The *P* value fallacy. *Ann Intern Med*. 1999;130:995-1004.