

Epinephrine compared to placebo in cardiac arrest resuscitation

Tudor Botnaru, MD, CM*; Jerrald Dankoff, MD, CM†

Clinical question

Does epinephrine (adrenaline) used in the context of out-of-hospital cardiac arrest improve outcomes?

Article chosen

Jacobs IG, Finn JC, Jelinek GA, et al. Effect of adrenaline on survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial. *Resuscitation* 2011;82:1138-43.

Objective

To determine the effect of epinephrine in out-of-hospital cardiac arrest on patient survival to hospital discharge, prehospital return of spontaneous circulation, and neurologic outcomes.

Keywords: adrenaline, cardiac arrest, cardiopulmonary resuscitation, epinephrine, out-of-hospital, randomized controlled trial, resuscitation, survival

BACKGROUND

Despite epinephrine being the standard of care in certain cardiac resuscitation algorithms for many decades, previous studies, with clinical outcomes as the primary end point, have demonstrated equivocal effectiveness.¹⁻³ An overall case fatality of more than 90% indicates that there is potential for further gains.⁴ This study is the first randomized, controlled trial comparing epinephrine to placebo in out-of-hospital cardiac arrest.

STUDY DESIGN

The study was a randomized, double-blind, placebo-controlled trial of out-of-hospital cardiac arrest patients

attended by the St. John Ambulance Western Australia (SJA-WA). Patients found to be in cardiac arrest by the emergency medical service (EMS) team were randomized to receive either intravenous epinephrine or saline placebo (centrally distributed using a computer-generated randomization schedule and prepared by independent investigators). Such a protocol was possible as the SJA-WA was operating under a no-drug administration policy at that time. This approach was based on the perceived lack of evidence for improved survival with epinephrine and potential adverse effects on other resuscitation interventions such as chest compressions.

POPULATION STUDIED

The population studied included patients with cardiac arrest from any cause, age 18 years or older, resuscitated by paramedics of the SJA-WA. The enrolment period was August 11, 2006, to November 30, 2009.

OUTCOMES MEASURED

The primary outcome was survival to hospital discharge. The secondary outcomes were prehospital return of spontaneous circulation (ROSC) for greater than 30 seconds and neurologic outcome classified as per the Cerebral Performance Category score.

RESULTS

The results were analyzed on an intention-to-treat basis and per protocol basis, with findings essentially

From the *Emergency Medicine Residency Program, McGill University Health Centre, Montreal, QC, and †Department of Emergency Medicine, Sir Mortimer B. Davis Jewish General Hospital, Montreal, QC.

Correspondence to: Dr. Tudor Botnaru, Emergency Medicine Residency Program, McGill University Health Centre, 687 Pine Avenue West, Room A4.62, Montreal, QC H3A 1A1; tudor.botnaru@mail.mcgill.ca.

This article has been peer reviewed.

unchanged. A non-statistically significant improvement in survival to discharge from hospital with epinephrine (OR 2.2 [95% CI 0.7–6.3], $p = 0.15$) was found (Table 1). For secondary outcomes, there was benefit in prehospital ROSC (OR 3.4 [95% CI 2.0–5.6], $p < 0.001$) and admission to hospital (OR 2.3 [95% CI 1.4–3.6], $p < 0.001$). In terms of favourable neurologic outcome, no OR was provided, but one can calculate a number needed to treat of 71, with the lower end of the 95% CI reaching 24.

Epinephrine used in nonshockable rhythms achieved increased rates of prehospital ROSC (OR 6.9 [95% CI 2.6–18.4], $p < 0.001$) and admission to hospital (OR 2.5 [95% CI 1.3–4.8], $p = 0.005$). Only two patients in the epinephrine group and none in the placebo group survived to discharge from hospital, rendering further statistical calculations impossible. In shockable rhythms, prehospital ROSC and admission to hospital were also improved when epinephrine was used compared to placebo (OR 2.4 [95% CI 1.2–4.5], $p = 0.009$, and OR 2.2 [95% CI 1.2–4.1], $p = 0.01$, respectively), but, again, benefit in survival to discharge from hospital was statistically insignificant (OR 2.0 [95% CI 0.6–6.0], $p = 0.23$) (Table 2).

COMMENTARY

The article by Jacobs and colleagues attempted to challenge one of the cornerstones of cardiac resuscitation. Unfortunately, the study has several limitations. To start, it was underpowered for the primary outcome secondary to a large number of excluded patients. As a result, no valid comment can be made as to the value—or lack thereof—of epinephrine with respect to ultimate survival rates. Second, details regarding postresuscitation care were not provided. Finally, other critical variables potentially affecting outcomes were not measured.

The study was underpowered, as acknowledged by the authors. Initially, each treatment group was planned

to enrol 2,213 patients. Unfortunately, there were only 272 patients in the epinephrine arm compared to 262 patients in the placebo arm. Among the excluded patients, 2,513 were confirmed dead prior to resuscitation efforts. Although not statistically significant, there was a trend toward an increased survival to hospital discharge and better neurologic function at discharge, both in favour of epinephrine compared to placebo. Within the 95% CI, there is up to a sixfold increase in odds ratios favouring epinephrine over placebo in terms of hospital discharge. Although the study is underpowered, as Youngquist and Niemann point out in their letter to *Resuscitation*, we should be careful in interpreting the p value.⁵ A Bayesian interpretation of the results, contrary to the frequentist interpretation, supports some degree of evidence for epinephrine benefit in terms of survival.

It is unclear as to what was included in the postresuscitation care. Therapeutic hypothermia following ROSC has been shown to improve neurologic outcomes.^{6,7} The 2010 American Heart Association (AHA) guidelines recommend that “a comprehensive and structured approach to post-cardiac arrest care be implemented in a consistent manner.”⁸ This includes hypothermia. As per personal correspondence with the author (Jacobs, June 30, 2012), the latter is an accepted clinical practice in Australian intensive care units but was not monitored in the study.

Furthermore, variables of potential importance were not accounted for. The 2010 International Liaison Committee on Resuscitation (ILCOR) guidelines indicate that although there is “inadequate evidence for the optimal timing... of drug administration,” faster drug delivery could possibly lead to better outcomes.⁹ A useful addition to the Jacobs and colleagues study would have been to assess the time from cardiac arrest to first drug administration. Of note, the ambulance response time was provided. For both the epinephrine and the placebo group, it was above 10 minutes, which is suboptimal, as determined by previous studies.^{10–12}

Table 1. Outcomes for patients receiving placebo versus epinephrine

Outcome	Placebo ($n = 262$)	Epinephrine ($n = 272$)	OR (95% CI)	p value
ROSC achieved prehospital	22	64	3.4 (2.0–5.6)	< 0.001
Survival to hospital discharge	5	11	2.2 (0.7–6.3)	0.15

Adapted from Jacobs IG et al.
ROSC = return of spontaneous circulation.

Table 2. Patient outcomes for epinephrine versus placebo by shockable and nonshockable initial cardiac arrest rhythm

	Shockable (n = 245)			Nonshockable (n = 289)		
	Placebo	Epinephrine	OR (95% CI) p value	Placebo	Epinephrine	OR (95% CI) p value
ROSC achieved prehospital	17	32	2.4 (1.2–4.5) 0.009	5	32	6.9 (2.6–18.4) < 0.001
Survival to hospital discharge	5	9	2.0 (0.6–6.0) 0.23	0	2	NA

Adapted from Jacobs IG et al.
NA = not applicable; ROSC = return of spontaneous circulation.

Finally, the quality of cardiopulmonary resuscitation was not measured or controlled for, which may also have had an impact on survival.¹³

CONCLUSION

The 2010 ILCOR guidelines indicated that there is insufficient evidence to suggest that “vasopressors improve survival to hospital discharge and neurological outcome.”⁹ They also called for “placebo-controlled trials to evaluate the use of any vasopressor in adult and pediatric cardiac arrest.”⁹ Equipoise is elegantly defined by Freedman as a “state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial.”¹⁴ Based on the Jacobs and colleagues article, advocating equipoise in its entirety is harder. In fact, as per personal correspondence with the author (Jacobs, June 30, 2012), epinephrine is now part of the SJA-WA guidelines. Unfortunately, being underpowered, the study does not allow us to arrive at valid conclusions about clinical outcomes as defined by the 2010 ILCOR guidelines. One may argue, however, that a Bayesian analysis supports improved survival in patients receiving epinephrine. Interestingly, in one of the largest observational studies ever, Hagihara and colleagues came to a different conclusion.¹⁵ Among patients with out-of-hospital cardiac arrest, although the use of epinephrine was associated with an improved ROSC, it led to decreased chances of survival and good functional outcomes 1 month after the event. These findings are counterintuitive considering our understanding that this medication improves cerebral and coronary perfusion.¹⁶ Equipoise remains regarding the clinically significant benefits of epinephrine, and further research is warranted.

Competing interests: None declared.

REFERENCES

- Herlitz J, Ekstrom L, Wennerblom B, et al. Adrenaline in out-of-hospital ventricular fibrillation. Does it make any difference? *Resuscitation* 1995;29:195-201, doi:[10.1016/0300-9572\(94\)00851-6](https://doi.org/10.1016/0300-9572(94)00851-6).
- Olasveengen TM, Sunde K, Brunborg C, et al. Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. *JAMA* 2009;302:2222-9, doi:[10.1001/jama.2009.1729](https://doi.org/10.1001/jama.2009.1729).
- Ong ME, Tan EH, Ng FS, et al. Survival outcomes with the introduction of intravenous epinephrine in the management of out-of-hospital cardiac arrest. *Ann Emerg Med* 2007;50:635-42, doi:[10.1016/j.annemergmed.2007.03.026](https://doi.org/10.1016/j.annemergmed.2007.03.026).
- Ornato JP, Becker LB, Weisfeldt ML, et al. Cardiac arrest and resuscitation: an opportunity to align research prioritization and public health need. *Circulation* 2010;122:1876-9, doi:[10.1161/CIRCULATIONAHA.110.963991](https://doi.org/10.1161/CIRCULATIONAHA.110.963991).
- Youngquist ST, Niemann JT. Regarding effect of adrenaline on survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial. *Resuscitation* 2012;83:e105, doi:[10.1016/j.resuscitation.2011.09.035](https://doi.org/10.1016/j.resuscitation.2011.09.035).
- The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve outcome after cardiac arrest. *N Engl J Med* 2002;346:549-56, doi:[10.1056/NEJMoa012689](https://doi.org/10.1056/NEJMoa012689).
- Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557-63, doi:[10.1056/NEJMoa003289](https://doi.org/10.1056/NEJMoa003289).
- Hazinski MF, Chameides L, Hemphill R, et al. Highlights of the 2010 American Heart Association guidelines for CPR and ECC 2010. Available at: http://www.heart.org/HEARTORG/CPRandECC/Science/Guidelines-Highlights_UCM_317219_SubHomePage.jsp/ (accessed Nov 24, 2012).
- Morrison LJ, Deakin CD, Morley PT, et al. Part 8: Advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Circulation* 2010;122(16 Suppl 2):S345-421, doi:[10.1161/CIRCULATIONAHA.110.971051](https://doi.org/10.1161/CIRCULATIONAHA.110.971051).
- Lyon RM, Cobbe SM, Bradley JM, et al. Surviving out of hospital cardiac arrest at home: a postcode lottery? *Emerg Med J* 2004;21:619-24, doi:[10.1136/emj.2003.010363](https://doi.org/10.1136/emj.2003.010363).
- O’Keeffe C, Nicholl J, Turner J, et al. Role of ambulance response times in the survival of patients with out-of-hospital

- cardiac arrest. *Emerg Med J* 2011;28:703-6, doi:[10.1136/emj.2009.086363](https://doi.org/10.1136/emj.2009.086363).
12. Pell JP, Sirel JM, Marsden AK, et al. Effect of reducing ambulance response times on deaths from out of hospital cardiac arrest: cohort study. *BMJ* 2001;322:1385-8, doi:[10.1136/bmj.322.7299.1385](https://doi.org/10.1136/bmj.322.7299.1385).
 13. Abella BS, Alvarado JP, Myklebust H, et al. Quality of cardiopulmonary resuscitation during in-hospital cardiac arrest. *JAMA* 2005;293:305-10, doi:[10.1001/jama.293.3.305](https://doi.org/10.1001/jama.293.3.305).
 14. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;317:141-5, doi:[10.1056/NEJM198707163170304](https://doi.org/10.1056/NEJM198707163170304).
 15. Hagihara A, Hasegawa M, Abe T, et al. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. *JAMA* 2012;307:1161-8, doi:[10.1001/jama.2012.294](https://doi.org/10.1001/jama.2012.294).
 16. ECC Committee, Subcommittees, and Task Forces of the American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005;112 Suppl 24:IV-1-203.