Critical Review Form
Therapy

PGY-4

Hansen M, Schmicker RH, Newgard CD, et al; Resuscitation Outcomes Consortium Investigators. Time to Epinephrine Administration and Survival From Nonshockable Out-of-Hospital Cardiac Arrest Among Children and Adults. Circulation. 2018 May 8;137(19):2032-2040.

Objectives: **"to evaluate the association between timing of the first dose of epinephrine and survival to hospital discharge among patients with OHCA [out-of-hospital cardiac arrest] who have initial nonshockable rhythms." (p. 2033)**

Methods: **This retrospective, observational chart review was conducted using data from the Resuscitation Outcomes Consortium (ROC) Epistry, a prospective registry of consecutive patients with OHCA. Patients of any age with an initial nonshockable rhythm (PEA or asystole) who received epinephrine and were enrolled in the Epistry between June 4, 2011 and June 30, 2015 were included. Patients in whom the time of epinephrine administration was not available were excluded, as were those who received epinephrine prior to an EMS-witnessed arrest, those who received epinephrine for a rearrest after initially having return of spontaneous circulation (ROSC) without epinephrine, and those with early ROSC (within 10 minutes of EMS arrival).**

The primary intervention being studies was the time, in minutes, between EMS arrival on scene and the first administration of epinephrine. The primary outcome was survival to hospital discharge. In a subset of patients enrolled in a study evaluating neurologic outcomes, a subgroup analysis was performed evaluating favorable neurologic outcome (defined as a modified Rankin Scale of < 3).

Out of 55568 cardiac arrests in the database, there were 26755 cases that met inclusion criteria. Among these, epinephrine was administered within 10 minutes of EMS arrival in 12238 cases and was administered more than 10 minutes after EMS arrival in 14417 cases.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	

1.	Were patients randomized?	No. This was an observational study conducted using prospectively collected date from a national registry in North America. There is a high risk of selection bias in this study, which the authors attempted mitigate by the use of logistic regression to control for certain known confounders.
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?	N/A
3.	Were patients analyzed in the groups to which they were randomized?	N/A. Patients were analyzed according to the amount of time between EMS arrival and epinephrine administration.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Mostly yes. Patients were similar with respect to age, gender, initial rhythm, use of bystander CPR, and enrollment site. **Patients in the early epinephrine group were much more likely to have EMS-witnessed arrest (14.8% vs. 6.7%).**
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. While this was not a blinded study, patients were in cardiac arrest and hence would not be aware of treatment allocation.
2.	Were clinicians aware of group allocation?	Not really. Again, this was not a blinded study, and EMS providers and subsequent care providers could theoretically be aware of the timing of epinephrine administration. However, given that this was a retrospective review of data, providers would not have been aware that this information would be used to study outcomes, and it is unlikely that knowledge of timing of epinephrine administration would have led to any performance bias.
3.	Were outcome assessors aware of group allocation?	Yes. No there is no mention of blinding of outcomes assessors. The primary outcome (survival to hospital discharge) is very objective and hence would not be subject to the risks of observer bias. For the subset of patients in whom neurological outcomes were assessed, it is possible that knowledge of group allocation could have potentially influenced outcome assignment. This is also unlikely, as the modified Rankin Scale scores were assessed in a different study in which timing to epinephrine

		administration was not an intervention being studied.
4.	Was follow-up complete?	Presumably yes. It would appear that primary outcome data was known for all patients enrolled in the registry.
II.	**What are the results ?**	

1.	How large was the treatment effect?	• Patients in the early group had a higher unadjusted rate of survival to discharge compared to the late group: 2.6% vs. 1.7% (RR 1.5, 95% CI 1.3 to 1.8).
		  ○ For patients with initial PEA, survival was 4.9% in the early group and 4.8% in the late group.
		  ○ For patients with initial asystole, survival was 1.5% in the early group and 1.0% in the late group.
		  ○ When evaluated in 2-minute increments, earlier administration of epinephrine was associated with increased rates of survival.
		• After adjusting for known confounders using multivariate logistic regression, survival rates were still lower in the elate epinephrine group compared to the early epinephrine group: OR 0.82, 95% CI 0.68 to 0.98.
		  ○ Each additional minute delay in epinephrine administration was associated with a 4% decrease in the odds of survival to hospital discharge (OR 0.96, 95% CI 0.95 to 0.98).
		• In a subgroup of 13290 patients with neurologic outcomes determined, survival with a modified Rankin Scale score < 3 decreased by 6% with each minute delay in epinephrine administration (OR 0.94, 95% CI 0.89 to 0.98).

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. This was a registry of patients suffering OHCA in North America (predominantly the US) and hence should be similar to patients seen in our setting (external validity). It is possible that an inordinate number of patients in the registry suffered arrest in rural settings, which

		would affect times to EMS arrival and EMS to hospital transport times, but this seems unlikely. It should be noted that this study only included patients with non-shockable initial rhythms (PEA/asystole) and these results do not apply to patients with ventricular tachycardia or ventricular fibrillation as the presenting rhythm.
2.	Were all clinically important outcomes considered?	No. The scope of this article was limited by data available in the registry. For about half of patients included, data regarding neurologic function was not available. For those patients in whom neurologic outcomes were known, this information was only known at the time of hospital discharge. The Research Working Group of the American Heart Association Emergency Cardiovascular Care Committee has recommended such studies evaluate long-term endpoints at least 90 days out. They were also unable to assess the cost of caring for patients who survived to hospital admission but not to hospital discharge and could not assess the psychosocial effects of such cases on friends and family.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes. Based on this evidence (while limited) it appears that earlier administration of epinephrine is beneficial in OHCA due to a nonshockable rhythm, without apparent associated harm. EMS protocols should include attempts at rapid administration of epinephrine in such cases, ensuring this does not adversely affect the quality of CPR provided.

Limitations:

1. **This was a retrospective, observational, non-randomized study subject to selection bias. This study demonstrates association but not necessarily causation.**

2. **Outcomes assessors were not blinded to timing of epinephrine administration, raising the possibility of observer bias.**

3. **The two groups were not well-balanced; patients in the early epinephrine group were much more likely to have EMS-witnessed arrest (14.8% vs. 6.7%).**

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.**

Bottom Line:

This retrospective, observational study using data collected in the Resuscitation Outcomes Consortium (ROC) Epistry demonstrated improved survival at hospital discharge when epinephrine was administered early by EMS (< 10 minutes after arrival) when compared to late administration in patients with OHCA due to a nonshockable rhythm. While this study was limited by its retrospective nature and lack of balancing between the groups, these findings persisted after adjustment for known confounders. It seems reasonable, given these findings, to ensure that EMS protocols involve the earliest possible administration of epinephrine for patients with OHCA and an initial rhythm of asystole or PEA.