Critical Review Form
Therapy

PGY-4

Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. JAMA. 2012 Mar 21;307(11):1161-8.

Objectives: **"to determine how epinephrine use in CPR before hospital arrival was associated with immediate and 1-month survival using national data from a whole sample of OHCAs [out-of-hospital cardiac arrest] between 2005 and 2008 in Japan." (p. 1162)**

Methods: **This prospective observational study was conducted using patients with OHCA from the Japanese national registry between 2005 and 2008. Outcomes were compared between patients who received epinephrine by EMS and those who did not. Patients were excluded for the following:**

1. **Age < 18 years.**
2. **Time from call to scene arrival > 60 minutes.**
3. **Time from call to hospital arrival > 480 minutes.**
4. **Data on epinephrine administration missing.**

The outcomes assessed were return of spontaneous circulation (ROSC) before hospital arrival, survival at one month, survival at one month with a cerebral performance category (CPC) score of 1 or 2, and survival at one month with an Overall Performance Category (OPC) score of 1 or 2. One month neurologic outcomes were assessed were assessed by chart review, as well as by in-person contact with the physician in charge of the patient. The etiology of cardiac arrest was determined by the physician in charge with the aid of the EMS personnel. The authors used propensity score matching for epinephrine use by multivariable logistic regression analysis, controlling for potential confounding factors. An adjusted odds ratio for each outcome was then calculated based on these propensity scores.

There were 431,968 cases of OHCA between January 1, 2005 and December 31, 2008, of which 417,188 were eligible. The overall mean age was 72. There were 15030 cases in which epinephrine was given (3.6%), with a yearly increase from 190 cases in 2005 to 8124 in 2008; there were 402,158 cases in which epinephrine was not given (96.4%).

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?	No. This was an observational study conducted using prospectively collected date from a national registry in Japan. There is a high risk of selection bias in this study, which the authors attempted mitigate by the use of propensity score matching.
2.	Was randomization concealed (blinded)?	N/A
3.	Were patients analyzed in the groups to which they were randomized?	N/A. Patients were analyzed according to whether or not they received epinephrine in the prehospital setting.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. Patients in the epinephrine group were more likely to have witnessed arrest (59.5% vs. 39.6%), were more likely to receive bystander chest compressions (45.1% vs. 36.0%), and were more likely to have a shockable initial rhythm (13.7% vs. 7.2%).
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. Although patients were not randomized or blinded, they were in cardiac arrest and hence would be unaware of any treatments administered. Survivors were not specifically blinded to treatment group allocation, but it is unlikely this would affect neurologic outcome results.
2.	Were clinicians aware of group allocation?	Yes. There is the risk of performance bias on the part of the clinicians.
3.	Were outcome assessors aware of group allocation?	Yes. Outcomes were assessed by the physician caring for the patient, and observer bias could potentially affect the results.
4.	Was follow-up complete?	Presumably yes. The authors do not mention being unable to assess all of the outcomes for any of the patients.
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	• Epinephrine was associated with an increase in ROSC in both the unadjusted data, and when adjustment was made for selected variables and all variables (Table 1). • For the unadjusted data, epinephrine use was associated with an improvement in 1-month survival, while it was associated with decreased 1-month survival when adjusted for selected variables and for all variables (Table 1). • Epinephrine was associated a decrease in survival with CPC 1 or 2 in the unadjusted model, when adjusted for selected variables and when adjusted for all variables (Table 1). • Epinephrine was associated a decrease in survival with OPC 1 or 2 in the unadjusted model, when adjusted for selected variables and when adjusted for all variables (Table 1). Table 3. Unconditional logistic regression analysis of outcomes in the epinephrine vs. no-epinephrine groups • Similar findings were noted when propensity matching was used to perform the logistic regression analysis (Table 2). Table 2. Conditional logistic regression analysis of outcomes in the epinephrine vs. no-epinephrine groups

Outcome	Unadjusted (OR, 95% CI)	Adjusted for selected variables (OR, 95% CI)	Adjusted for all variables (OR, 95% CI)
ROSC	3.75 (3.59-3.91)	3.06 (2.93-3.21)	2.36 (2.22-2.50)
1-month survival	1.15 (1.07-1.23)	0.43 (0.39-0.46)	0.46 (0.42-0.51)
CPC 1 or 2	0.61 (0.53-0.70)	0.21 (0.18-0.24)	0.31 (0.26-0.36)
OPC 1 or 2	0.63 (0.55-0.73)	0.22 (0.19-0.25)	0.32 (0.27-0.38)

Outcome	Unadjusted (OR, 95% CI)	Adjusted for propensity scores (OR, 95% CI)
ROSC	1.91 (1.78-2.05)	2.01 (1.83-2.21)
1-month survival	0.71 (0.64-0.79)	0.71 (0.62-0.81)
CPC 1 or 2	0.41 (0.33-0.52)	0.41 (0.33-0.52)
OPC 1 or 2	0.43 (0.36-0.51)	0.43 (0.34-0.54)

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In patients with ventricular fibrillation, epinephrine use did not affect the rate of ROSC, but was associated with a decrease in 1-month survival and survival with good neurologic outcomes (Table 1).

Table 3. Outcomes in patients with ventricular fibrillation
<table>
<tr><th>Outcome</th><th>Epinephrine, %</th><th>No-epinephrine, %</th><th>p-value</th></tr>
<tr><td>ROSC</td><td>21.1</td><td>22.3</td><td>0.21</td></tr>
<tr><td>1-month survival</td><td>15.4</td><td>21.3</td><td>< 0.001</td></tr>
<tr><td>CPC 1 or 2</td><td>6.1</td><td>13.5</td><td>< 0.001</td></tr>
<tr><td>OPC 1 or 2</td><td>6.2</td><td>13.5</td><td>< 0.001</td></tr>
</table>

In patients without ventricular fibrillation, epinephrine use was associated an increased rate of ROSC and 1-month survival, but a decrease in survival with a good neurologic outcome (Table 2).

Table 4. Outcomes in patients without ventricular fibrillation
<table>
<tr><th>Outcome</th><th>Epinephrine, %</th><th>No-epinephrine, %</th><th>p-value</th></tr>
<tr><td>ROSC</td><td>18.2</td><td>4.4</td><td>< 0.001</td></tr>
<tr><td>1-month survival</td><td>3.8</td><td>3.4</td><td>< 0.001</td></tr>
<tr><td>CPC 1 or 2</td><td>0.6</td><td>1.3</td><td>< 0.001</td></tr>
<tr><td>OPC 1 or 2</td><td>0.7</td><td>1.3</td><td>< 0.001</td></tr>
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<tr><td>2.</td><td>How precise was the estimate of the treatment effect?</td><td>See above. This was a very large study and hence the 95% CIs are relatively narrow.</td></tr>
<tr><td>III.</td><td>How can I apply the results to patient care (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>Were the study patients similar to my patient?</td><td>No. Only 3.6% of cases of OHCA included received epinephrine. This is very different from care in the US, where epinephrine is given in the majority of cases of OHCA. This suggests there may be other aspects of care of OHCA that would differ between Japan and the US.</td></tr>
<tr><td>2.</td><td>Were all clinically important outcomes considered?</td><td>Yes. The authors considered both short term outcomes (ROSC) and long-term outcomes with neurologic function assessment.</td></tr>
<tr><td>3.</td><td>Are the likely treatment benefits worth the potential harm and costs?</td><td>Uncertain. This study suggests that the use of epinephrine in OHCA improves ROSC but decreases 1-month survival and survival with a good neurologic outcome. However, this was an observational study that demonstrates</td></tr>
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		association but not necessarily causation. Despite the use of logistic regression to adjust for several known confounders and the use of propensity matching, it is possible that selection bias led to an imbalance in unknown confounders. Additionally, only 3.6% of the cohort in this study received epinephrine for OHCA; this is far different from the rates of epinephrine administration seen in the US, suggesting a difference in arrest care between Japan and the US. This may affect the external validity of the study and its application to our patient population.

Limitations:

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

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

3. **Only 3.6% of cases of OHCA were treated with epinephrine in this sample. This suggests that the care of OHCA is quite different in Japan compared to the US (external validity).**

4. **Initiation of IV access and administration of epinephrine both required "approval from an online emergency physician" (p. 1162) potentially leading to delays in epinephrine administration which some have proposed as an explanation for the apparent lack of efficacy (Attaran 2010).**

Bottom Line:

This large prospective observational study involving 417,188 patients with OHCA cared for in Japan suggests that the use of epinephrine in OHCA improves ROSC but decreases 1-month survival and survival with a good neurologic outcome. However, this was an observational study that demonstrates association but not necessarily causation. Despite the use of logistic regression to adjust for several known confounders and the use of propensity matching, it is possible that selection bias led to an imbalance in unknown confounders. Additionally, differences in the care of OHCA between Japan and the US may affect the external validity of the study and its application to our patient population.