Research in Practice: Epinephrine in Cardiac Arrest

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Disclosures

• I will ask you to look at research studies
• I am, in fact, a nerd
• I wasn’t always this way
Statistics is the most important science in the whole world: for upon it depends the practical application of every other science and of every art: the one science essential to all political and social administration, all education, all organization based on experience, for it only gives results of our experience.

To understand God's thoughts we must study statistics, for these are the measure of His purpose.
• “Immediately strip the sufferer; rub him strongly with dry coarse linen; put him as soon as possible into a well heated bed, and continue to rub him a considerable time together”

• “A strong and healthy person should force his own warm breath into the patient’s lungs; and the smoke of tobacco, if some was at hand, by means of a pipe, introduced into the mouth.”

• “The fumes of tobacco should be thrown up, as speedily and plentifully as possible, into the intestines by the fundament. Two pipes may be well lighted and applied; the extremity of one is to be introduced into the fundament; and the other may be blown through into the lungs.”
Evidence Based Practice

• Ensures the patient gets the best chance at treatment through
  – Ensuring that “logic” actually produces results
  – Filters out coincidences and clinician bias
  – Understanding variables, confounders

• Takes a really long time to do well
Levels of Evidence

- **Level I**: Systematic review or meta-analysis of randomized controlled trials (RCTs). Evidence-based clinical practice guidelines based on systematic reviews.
- **Level II**: A well-designed RCT.
- **Level III**: Controlled trial without randomization (quasiexperimental study).
- **Level IV**: Single nonexperimental study (case-control, correlational, cohort studies).
- **Level V**: Systematic reviews of descriptive and qualitative studies.
- **Level VI**: Single descriptive or qualitative study.
- **Level VII**: Opinion of authorities and/or reports of expert committees.
Seizure Treatment 1841

• Dr. Canstatt
Epinephrine in Cardiac Arrest

• 1901-Jokichi Takamine isolates the pure form of epinephrine
• 1960-Routine use of epinephrine proposed for inclusion in cardiac arrest management, based on the physiologic role of adrenaline and animal research that showed improved occurrence of ROSC
A+B=C Thinking

Systemic blood pressure is low or absent in cardiac arrest

Coronary Perfusion is low or absent in cardiac arrest

Epinephrine increases aortic blood pressure and therefore increases CPP

A higher Coronary Perfusion Pressure (CPP) increases the likelihood of ROSC

Epinephrine increases the incidence of ROSC

EPINEPHRINE SAVES LIVES!!
A+B=C Thinking

• If I exercise 30 more minutes per day, I will lose weight
• If I use my blinker, the car next to me will let me over
• If I tell my fall risk patient to push the call light before getting out of bed, they will do so
Why A+B=C Thinking Doesn’t Work

• All interventions have unintended side effects

• Interventions may be confounded by other factors

• May work only in certain circumstances
THE DEADLY FACTS ABOUT WATER!

**FACT!**
WATER CAN BE CHEMICALLY SYNTHESIZED BY BURNING ROCKET FUEL!!!

**FACT!**
OVER CONSUMPTION CAN CAUSE EXCESSIVE SWEATING, URINATION, AND EVEN DEATH!!!

**FACT!**
100% OF ALL SERIAL KILLERS, RAPEST AND DRUG DEALERS HAVE ADMITTED TO DRINKING WATER!!!

**FACT!**
WATER ONE OF THE PRIMARY INGREDIENTS IN HERBICIDES AND PESTICIDES!!!

**FACT!**
WATER IS THE LEADING CAUSE OF DROWNING!!!

**FACT!**
100 PERCENT OF ALL PEOPLE EXPOSED TO WATER WILL DIE!!!
Epinephrine for out of hospital cardiac arrest: A systematic review and meta-analysis of randomized controlled

Abstract

Objective: To evaluate the effectiveness of epinephrine, compared with control treatments, on survival at admission, ROSC, survival at discharge, and a favorable neurologic outcome in adult patients during OHCA.

Data source: MEDLINE and PubMed from inception to August 2018.

Study selection: Randomized controlled trials (RCTs) on adult patients after OHCA treated with epinephrine versus controls.

Data extraction: Independent, double-data extraction; risk of bias assessment with Cochrane Collaboration’s criteria.

Data synthesis: 15 RCTs representing 20,716 OHCA adult patients. Epinephrine, compared with all pooled treatments, was associated with a better survival rate to hospital discharge (RR: 1.16, 95% CI: 1.00–1.35) and a favorable neurologic outcome (RR: 1.24, 95% CI: 1.04–1.48). No difference was found in survival to hospital admission (RR: 1.02, 95% CI: 0.75–1.38) and ROSC when comparing epinephrine with all pooled treatments (RR: 1.13, 95% CI: 0.84–1.53). When epinephrine was compared with a placebo/no drugs, survival to hospital discharge (RR: 1.34, 95% CI: 1.08–1.67), ROSC (RR: 2.03, 95% CI: 1.18–3.51) and survival to hospital admission (RR: 2.04, 95% CI: 1.22–3.43) were increased, but there was not a favorable neurologic outcome (RR: 1.22, 95% CI: 0.99–1.51).

Conclusions: In OHCA, standard or high doses of epinephrine should be used because they improved survival to hospital discharge and resulted in a meaningful clinical outcome. There was also a clear advantage of using epinephrine over a placebo or no drugs in the considered outcomes.

Keywords: Out-of-hospital cardiac arrest, Epinephrine, Hospital survival, Fragility index.
Components of a research paper

• Abstract
  – Let’s you know if the paper addresses the question you are asking, provides a broad overview

• Introduction
  – Provides an overview of the topic, including what research has been conducted to date

• Methods
  – Describes how the study was conducted, including the question, sample size, protocol, data collection, and statistical models

• Results
  – Provides the outcomes of the study

• Discussion
  – Provides a summary of how this study relates to others, any anecdotal findings

• Limitations
  – Includes confounders and methodical concerns

• Conclusions
  – Provides the authors interpretation of conclusions and implications for practice
Things to Think About When Analyzing Research

• Sample and size
• Generalizability
• Design
• Primary/secondary outcomes
• Intervention and how implemented
• Measurements
• Clinical vs statistical significance
So, what question are we asking?

“It’s not a great mission statement, but we’ll revise it if things get better.”

• Does epinephrine administered during arrest:
  – Improve the chance of ROSC?
  – Improve survival?
  – Improve discharge to home?
  – Improve neurologic recovery?

• When you know your question you can start your search using key terms
- Google scholar
- Cochrane Database
- References from other papers
Key Words

- "systematic review" "meta-analysis", "guideline"
- "trial", "randomized", "vs", cute names
- "investigation"
- "association", "correlation", "single center"
- "summary", "review"
- "understanding", "concept mapping"
- "Position statement", "editorial"
Pre-hospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug administration In Cardiac arrest (PARAMEDIC-2): Trial protocol

Resuscitation 83 (2012) 921–932

Editorial

Adrenaline for the pharmacological treatment of cardiac arrest... going, going, gone?
Meta-Analysis/ Systematic Reviews

RCT #1

RCT #2

RCT #3
**Epinephrine for out of hospital cardiac arrest: A systematic review and meta-analysis of randomized controlled trials**

**Review article**

**Epinephrine for out of hospital cardiac arrest: A systematic review and meta-analysis of randomized controlled trials**

Maria Vargas, Paola Buonanno, Carmine Iacovazzo, Giuseppe Servillo

Objective: To evaluate the effectiveness of epinephrine, compared with control treatments, on survival at admission, ROSC, survival at discharge, and a favorable neurological outcome in adult patients during OHCA.

Methods: MEDLINE and PubMed were searched from inception to August 2018. Study selection: Randomized controlled trials (RCTs) on adult patients after OHCA treated with epinephrine versus controls.

Data extraction: Independent, double-data extraction; risk of bias assessment with Cochrane Collaboration’s criteria.

Data synthesis: 15 RCTs representing 2976 OHCA adult patients. Epinephrine, compared with all pooled treatments, was associated with a better survival rate to hospital discharge (RR 1.45; 95% CI 1.18-1.80) and a favorable neurological outcome (RR 1.24; 95% CI 1.04-1.48). No difference was found in survival to hospital admission (RR 1.02; 95% CI 0.75-1.38) and ROSC when comparing epinephrine with all pooled treatments (RR 1.39; 95% CI 0.84-2.32). When epinephrine was compared with a placebo plus drugs, survival to hospital discharge (RR 1.34; 95% CI 1.08-1.67), ROSC (RR 2.59; 95% CI 1.89-3.51) and survival to hospital admission (RR 2.04; 95% CI 1.29-3.28) were increased, but there was not a favorable neurological outcome (RR 1.22; 95% CI 0.89-1.65).

Conclusions: In OHCA, administration of high doses of epinephrine should be used because they improved survival to hospital discharge and resulted in a meaningful clinical outcome. There was also a clear advantage of using epinephrine over a placebo or no drugs in the considered outcomes.

Keywords: Out of hospital cardiac arrest, Epinephrine, Hospital survival, Fragility index.
Forest Plots

Fig. 3. Return of spontaneous circulation. VF = Ventricular Fibrillation; VT = Ventricular Tachycardia; PEA = Pulseless Electrical Activity.

Kempton, 2019
## Survival to discharge

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SDA Events</th>
<th>SDA Total</th>
<th>Adr/Vaso Events</th>
<th>Adr/Vaso Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ducros 2011</td>
<td>2</td>
<td>16</td>
<td>0</td>
<td>14</td>
<td>1.5%</td>
<td>4.41 [0.23, 84.79]</td>
</tr>
<tr>
<td>Gueugniaud 2008</td>
<td>33</td>
<td>1452</td>
<td>24</td>
<td>1442</td>
<td>30.2%</td>
<td>1.37 [0.81, 2.30]</td>
</tr>
<tr>
<td>Lindner 1997</td>
<td>3</td>
<td>20</td>
<td>8</td>
<td>20</td>
<td>8.6%</td>
<td>0.38 [0.12, 1.21]</td>
</tr>
<tr>
<td>Ong 2012</td>
<td>8</td>
<td>353</td>
<td>11</td>
<td>374</td>
<td>13.6%</td>
<td>0.77 [0.31, 1.89]</td>
</tr>
<tr>
<td>Wenzel 2004</td>
<td>58</td>
<td>597</td>
<td>57</td>
<td>589</td>
<td>46.2%</td>
<td>1.00 [0.71, 1.42]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2438</strong></td>
<td><strong>2439</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td>1.00</td>
<td><strong>1.00 [0.69, 1.44]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>104</strong></td>
<td><strong>100</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.04; \) \( \chi^2 = 5.33, \) df = 4 \( (P = 0.26); \) \( i^2 = 25\% \)

Test for overall effect: \( Z = 0.01 \) \( (P = 0.99) \)

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## Survival to discharge

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SDA Events</th>
<th>SDA Total</th>
<th>HDA Events</th>
<th>HDA Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown 1992</td>
<td>26</td>
<td>632</td>
<td>31</td>
<td>648</td>
<td>37.9%</td>
<td>0.86 [0.52, 1.43]</td>
</tr>
<tr>
<td>Callaham 1992</td>
<td>3</td>
<td>270</td>
<td>5</td>
<td>286</td>
<td>4.9%</td>
<td>0.64 [0.15, 2.63]</td>
</tr>
<tr>
<td>Gueugniaud 1998</td>
<td>46</td>
<td>1650</td>
<td>38</td>
<td>1677</td>
<td>54.7%</td>
<td>1.23 [0.80, 1.88]</td>
</tr>
<tr>
<td>Sherman 1997</td>
<td>0</td>
<td>62</td>
<td>0</td>
<td>78</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Stiell 1992</td>
<td>2</td>
<td>165</td>
<td>2</td>
<td>170</td>
<td>2.6%</td>
<td>1.03 [0.15, 7.23]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2779</strong></td>
<td><strong>2859</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>1.04</strong></td>
<td><strong>[0.76, 1.42]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>77</strong></td>
<td><strong>76</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.00; \) \( \chi^2 = 1.60, \) df = 3 \( (P = 0.66); \) \( i^2 = 0\% \)

Test for overall effect: \( Z = 0.22 \) \( (P = 0.83) \)
Our original questions

- Does epinephrine administered during arrest:
  - Improve the chance of ROSC? **Likely YES**
  - Improve survival? **Likely YES**
  - Improve discharge to home? **Maybe**
  - Improve neurologic recovery? **Probably NOT, may make it worse 😞**
In Summary

**Research**

[ri-surch, ree-surch], *noun*

1. what you are doing when you don’t know what you are doing