Is the Statistical Deck Stacked in Observational Resuscitation Studies?

Michael Levy MD, FAEMS, FACEP, FACP
Medical Director Anchorage Fire Department
Medical Director State of Alaska Emergency Programs
Medical Director EMS Kenai Peninsula Borough
Disclosure

• Chief Medical Advisor Stryker Emergency Care
Resuscitation Time Bias in Observational Resuscitation Studies

Have you tried the Scientific Method?
Pathways to Scientific Knowledge

• Randomized clinical trials: formerly constructed to answer a clinical question by controlling variables and having enough data to reach a conclusion that has statistical significance. Commonly used to show a causal relationship between the use of a drug or device and a clinical outcome

• Observational trials: study A type of study in which individuals are observed or certain outcomes are measured. No attempt is made to affect the outcome. There can be associations of interventions and outcomes but cannot show causality
Types of bias in observational studies

• Selection bias: selection of individuals, groups or data for analysis in such a way that proper randomization is not achieved, thereby ensuring that the sample obtained is not representative of the population intended to be analyzed

• Information bias: results from wrong or inexact recording of individual factors

• Confounding: a risk factor for the disease under study is associated with the exposure of interest but is not causal

• Immortal
Resuscitation Time Bias

• A unique situation in which an exposure is more likely to occur the longer the cardiac arrest continue. Since length of resuscitation is strongly associated with worse outcomes, this will bias the result toward a harmful effect of the exposure
Resuscitation Time Bias

• Pertains to observational studies of exposures (e.g. drugs, airway management)
• An exposure is more likely to occur the longer the cardiac arrest continues.
• Length of resuscitation is strongly associated with worse outcome, tends to bias the results toward a harmful effect
• This bias is the reverse of immortal time bias
Resuscitation Time Bias

• Interventions that occur intra-cardiac arrest related to time:
  • Interventions are more likely to be implanted the longer the duration of the cardiac arrest
  • Once ROSC is achieved or cardiac arrest is terminated without ROSC, the interventions cannot be performed
  • These interventions may result in ROSC thereby shortening the duration of arrest
Fig. 2.

Resuscitation time bias. Graphical example illustrating resuscitation time bias. Due to the way the exposure is defined, patients in the exposed group have longer cardiac arrest. Since longer cardiac arrests are associated with poor outcomes, this artificially favors the unexposed group, biasing the results.
Example

• Japanese study 2012 examined association between epinephrine administration and outcomes of OHCA.
  • Did not adjust for timing of epinephrine administration (likely to occur late)
  • Worse survival was found

• A second study with same data adjusted for time of administration
  • Their results showed favorable outcome more likely with epinephrine for both shockable (OR 1.36 95% CI: 1.13,1.63) and nonshockable OR 1.78 95/5 CI: 1.49,2.13)
<table>
<thead>
<tr>
<th>Outcome parameters (N (%)</th>
<th>All (N=49)</th>
<th>sCPR (N=19)</th>
<th>mCPR (N=30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROSC anytime</td>
<td>40 (82%)</td>
<td>19 (100%)</td>
<td>21 (70%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Survived to hospital admission, all VF/VT</td>
<td>36 (73%)</td>
<td>18 (95%)</td>
<td>18 (60%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Good cerebral performance, CPC 1</td>
<td>23 (47%)</td>
<td>13 (68%)</td>
<td>10 (33%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Moderate disability, CPC 2</td>
<td>3 (6%)</td>
<td>1 (5%)</td>
<td>2 (7%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Severe disability, CPC 3</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

sCPR = standard manual-only CPR, mCPR = manual transitioning to mechanical CPR, ROSC = Return Of Spontaneous Circulation, CPC = Cerebral Performance Category,
Survivors from Standard vs Mechanical CPR

<table>
<thead>
<tr>
<th>CPR Type</th>
<th>0 min</th>
<th>2 min</th>
<th>3 min</th>
<th>5 min</th>
<th>7 min</th>
<th>9 min</th>
<th>11 min</th>
<th>13 min</th>
<th>15 min</th>
<th>17 min</th>
<th>19 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>10</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Mechanical</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>13</td>
</tr>
</tbody>
</table>

Survivors
**Outcome**

- CPR Time Course to First ROSC or Termination

**Legends**

- Time in standard (manual) CPR
- Time in manual then mechanical CPR
- No ROSC
- ROSC, Resuscitation terminated in field
- ROSC, Resuscitation terminated in ED
- Survived to hospital admission
- Survived to discharge, CPC 3
- Survived to discharge, CPC 1-2

**Patients**

- Time from Start of CPR (min): 0 to 60

**Office of the Medical Director**

Michael Levy MD
Resuscitation Time Bias

Odds of Success Low
Require Time Data!!
Conclusions

• Resuscitation research is hard!
• Observational studies are convenient and can yield helpful information
• Controlling variables by cohort matching implies that we know all of the variable
• Be VERY skeptical of observational studies looking at an intervention such as device or drug IF TIME of EXPOSURE is not specifically listed
Thank you

Michael Levy MD
mike.levy@anchorageak.gov

@mklevy10