Beta-blockers in Traumatic Brain Injury: In or Out?

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USA
Background

• Traumatic Brain Injury (TBI)
  – Significant cause of Trauma Mortality

• USA
  – 1.7 million head injuries
  – 1.4 million ED visits
  – 275,000 patients hospitalized
  – 50,000 deaths
Background

- Beta-Blockers (BBs)
  - Improve mortality after trauma

*Beta-Blocker Use is Associated With Improved Outcomes in Adult Trauma Patients*

Saman Arbabi, MD, MPH, Eric M. Campion, MD, Mark R. Hemmila, MD, Melissa Barker, RN, Mary Dimo, PharmD, Karla S. Ahrns, RN, Andreas D. Niederbichler, MD, Kyros Ipaktchi, MD, and Wendy L. Wahl, MD
Background

- Beta-Blockers
  - Improve mortality after severe TBI
Background

- Riordan et al 2007
- Salim 2007
- Inaba et al 2008
- Friese et al 2008
- Schroeppepel et al 2010, 2014

- ALL showed positive effects from BB
  - Some only in specific subgroups
Beta-Blockers in TBI

• WARNING!!

• UNPUBLISHED RESEARCH AHEAD
Beta-Blockers

- No PUBLISHED Randomized Clinical Trial

A Prospective Randomized Study Comparing Metoprolol to Placebo in The Management of Severe Traumatic Brain Injury

Hassan A Abu Khaber $^{(1, 2)}$, Akram M Fayed $^{(1, 2)}$, Ahmed A Khattab $^{(1, 2)}$

(1) Department of Critical Care Medicine, (2) Faculty of Medicine, University of Alexandria, Egypt.
Beta-Blockers

Graph showing heart rate over time for Control and Metoprolol treatments.
### Table (3): Absolute and relative risk reduction for mortality in different groups and subgroups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Absolute risk reduction</th>
<th>Relative risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality in Metoprolol vs. control</td>
<td>30%</td>
<td>47%</td>
</tr>
<tr>
<td>30 d-GOS (5) between Metoprolol and control (short-term mortality)</td>
<td>30%</td>
<td>60%</td>
</tr>
<tr>
<td>Mortality in early vs. late achievers</td>
<td>57.2%</td>
<td>86%</td>
</tr>
<tr>
<td>30 d-GOS (5) between early and late achievers (short-term mortality)</td>
<td>50.8%</td>
<td>91%</td>
</tr>
<tr>
<td>Mortality reduction between Metoprolol and control groups for patients above 40 years</td>
<td>53.4%</td>
<td>69.5%</td>
</tr>
</tbody>
</table>
Background

- Most studies don’t examine TYPE of BB

- Difference between drugs
  - Selective vs. non-selective
  - Lipophilic vs. nonlipophilic
  - Half life of drug
  - IV vs. PO
BETA BLOCKERS BLUNT THE EXAGGERATED PHYSIOLOGIC RESPONSE TO STRESS, THEREBY LOWERING BLOOD PRESSURE.
Study Purpose

Examine differences between different beta-blockers and their effect on mortality
Methods

- Patients who received ≥1 dose of BB
- Registry merged with pharmacy data
- Variables examined
  - Demographics, Injury & clinical data
  - Type & doses of beta-blocker used
- Propensity Score matching
Traumatic Brain Injury Patients
May 2006 – July 2011
N = 8,538

Exclusions
Children (aged <16 yrs. old)
N = 1238
Deaths in ED or 1st 24hrs
N = 301
Head AIS of 6
N = 35

Total TBI patients
N = 6964

Received Beta-Blockers
N = 1037
(14.9%)

No Beta-Blockers
N = 5927
(85.1%)

Received Beta-Blockers
N = 924
Matched Pairs

No Beta-Blockers
N = 924
Matched Pairs
## Demographics/Clinical Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>BB +ve N = 1037</th>
<th>BB -ve N = 5927</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57 ± 21</td>
<td>37 ± 18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>67.5%</td>
<td>66%</td>
<td>0.35</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>88%</td>
<td>84%</td>
<td>&lt;0.0001 overall</td>
</tr>
<tr>
<td>African-American</td>
<td>2%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>4%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>ISS</td>
<td>21.3 ± 22.0</td>
<td>9.7 ± 10.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Head AIS</td>
<td>3.3 ± 1.2</td>
<td>2.0 ± 1.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RTS</td>
<td>7.5 ± 7.6</td>
<td>6.8 ± 6.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Initial GCS</td>
<td>11 ± 5</td>
<td>14 ± 14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intubated</td>
<td>45%</td>
<td>10%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP in ED</td>
<td>149 ± 29</td>
<td>137 ± 22</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Beta-Blocker comparison

- No survival advantage with BB
- Head AIS 1,2
  - 98.8% survival with BB
  - 99.8% survival without BB \( P = 0.005 \)
- Head AIS 3,4,5
  - 87.4% survival with BB
  - 89.2% survival without BB \( p = 0.19 \)
## Propensity Matched Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>BB +ve N = 924</th>
<th>BB -ve N = 924</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55.9 ± 20.9</td>
<td>56.2 ± 19.9</td>
<td>0.68</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>67.3%</td>
<td>68.6%</td>
<td>0.55</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>87.3%</td>
<td>87.5%</td>
<td>0.83</td>
</tr>
<tr>
<td>African-American</td>
<td>2.5%</td>
<td>2.5%</td>
<td></td>
</tr>
<tr>
<td>Native American</td>
<td>4.1%</td>
<td>4.3%</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0.8%</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>ISS</td>
<td>20.4 ± 10.6</td>
<td>20.9 ± 12.9</td>
<td>0.43</td>
</tr>
<tr>
<td>RTS</td>
<td>6.8 ± 1.6</td>
<td>6.8 ± 1.6</td>
<td>0.99</td>
</tr>
<tr>
<td>Head AIS</td>
<td>3.3 ± 1.2</td>
<td>3.2 ± 1.2</td>
<td>0.97</td>
</tr>
<tr>
<td>GCS</td>
<td>11.4 ± 4.9</td>
<td>11.4 ± 4.8</td>
<td>0.81</td>
</tr>
<tr>
<td>Intubated</td>
<td>41.2%</td>
<td>38.5%</td>
<td>0.23</td>
</tr>
</tbody>
</table>
Propensity Matched Cohort

- Significant survival advantage with BB
- Head AIS 3, 4, 5
  - 88.7% survival with BB
  - 78.1% survival without BB \( p = 0.0001 \)
# Propensity Matched Cohort

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>BB +ve N = 924</th>
<th>BB -ve N = 924</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vent LOS</td>
<td>0 [0-80]</td>
<td>0 [0-30]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICU LOS</td>
<td>3 [0-92]</td>
<td>1 [0-59]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>7 [0-154]</td>
<td>2.5 [0-69]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Survival</td>
<td>91.5%</td>
<td>83.3%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Type of TBI

- No difference seen between groups
  - Epidural
  - Subdural
  - Subarachnoid
  - Skull fracture
  - Basal Skull fracture (25.2% vs. 21.2%, p=0.04)
  - Craniotomy
  - Craniectomy (1.2% vs. 0.1%, p=0.004)
## Propensity Matched Cohort

<table>
<thead>
<tr>
<th>Beta-blocker</th>
<th>Paired N</th>
<th>Survival BB +ve</th>
<th>Survival BB -ve</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Beta-blocker</td>
<td>924</td>
<td>91.5%</td>
<td>83.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>570</td>
<td>89.3%</td>
<td>80.0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Propranolol</td>
<td>48</td>
<td>97.9%</td>
<td>75.0%</td>
<td>0.002</td>
</tr>
<tr>
<td>Labetalol</td>
<td>79</td>
<td>81.0%</td>
<td>83.5%</td>
<td>0.57</td>
</tr>
<tr>
<td>Atenolol</td>
<td>54</td>
<td>100%</td>
<td>100%</td>
<td>1.00</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>40</td>
<td>95.0%</td>
<td>90.0%</td>
<td>0.32</td>
</tr>
</tbody>
</table>
Dosing affects survival

<table>
<thead>
<tr>
<th>Mortality [%]</th>
<th>0-9</th>
<th>10-99</th>
<th>100-999</th>
<th>1000-9999</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>10-99</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100-999</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>1000-9999</td>
<td></td>
<td></td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>
Summary

- Association between BBs and survival
- Not significant in mild TBI
- NO improvement in length of stay
- Metoprololol and Propranololol most effective
Limitations

- Single Institution
- Propensity scoring only quasi-randomized
- Low numbers for BBs other than Metoprolol
- No information on heart rate
2014 research paper

- Schroeppele et al. - Memphis
- Compared Propranolol in pts with TBI
- 78 patients compared to 349
Conclusions

- Association of BB with improved survival
- Not all BBs have this effect
ProTECTOR Trial

Progestosterone for the Treatment of Traumatic Brain Injury (ProTECTOR) is a research study to see if progesterone, a hormone naturally present in our bodies, is useful in the treatment of traumatic brain injury (TBI). Two small studies in Russia and Germany showed that progesterone may result in less brain swelling in people with TBI. The ProTECTOR trial will test these findings and determine if progesterone treatment is in adults with moderate to severe TBI.

PRESS RELEASE

Atlanta To Serve as National Epicenter for Promising Phase III Brain Injury Treatment Trial

The city of Atlanta will soon serve as the national epicenter for a groundbreaking National Institutes of Health (NIH)-sponsored Phase III trial for the treatment of traumatic brain injuries using the hormone progesterone.
Estrogen

Resuscitative Traumatic Brain Hemorrhage

People admitted to the hospital with brain injury and/or trauma will be drawn in the RESCUE-SH to determine whether a 28-day survival following treatment. The primary aim of the RESCUE-SH trial is to determine whether a 28-day survival following treatment. The primary aim of the RESCUE-SH trial is to determine whether a 28-day survival following treatment.
Erythropoietin

Figure 3. Kaplan-Meier Survival Curves of Erythropoietin Dosing Regimen Groups

Therapy for TBI

Is it all hopeless then?
**Purpose**

The investigators intend to determine the effect of adrenergic blockade on 1) short-term physiology, behavior, and cognition and 2) long-term neurological outcomes after Traumatic Brain Injury (TBI).

The primary hypothesis is that adrenergic blockade after severe TBI will be associated with increased ventilator-free days.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Injuries</td>
<td>Drug: IV Propranolol and Per Tube Clonidine</td>
</tr>
<tr>
<td>Craniocerebral Trauma</td>
<td>Drug: Placebo</td>
</tr>
<tr>
<td>Trauma, Nervous System</td>
<td></td>
</tr>
<tr>
<td>Traumatic Brain Injury</td>
<td></td>
</tr>
</tbody>
</table>
So, in or out?

- I say – IN
- AFTER Resuscitation
- HOLD parameters
- MORE doses are better than fewer
- ESPECIALLY in adrenergic storm