Innovative Treatment for Traumatic Brain Injury

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1.7 million people sustain a TBI each year in the United States.
- 52,000 die
- 275,000 are hospitalized
- 1.4 million are treated and released from an ED

TBI is the leading cause of death and disability in children and adults from ages 1 to 44.

Stochetti et al., 1996

Traumatic Brain Injury

- STC
  - About 350 severe TBI per year
  - About 175 AIS 4 or 5 per year
  - Mean ISS 33 ±11
  - Mean TRISS 55.4
  - Mean RTS 4.8
  - Mortality 27.2%

Primary injury occurs at the time of impact
- Only prevention treats this
- Secondary injury occurs in the minutes, hours and days following impact and is characterized by rebleeding, swelling and zones of ischemia
- We believe secondary injury can be prevented or mitigated by good care

Oxygenation

<table>
<thead>
<tr>
<th>$O_2$ Sats</th>
<th>Mortality (%)</th>
<th>Some Disability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 90%</td>
<td>14.3</td>
<td>4.8</td>
</tr>
<tr>
<td>60 – 90%</td>
<td>27.3</td>
<td>27.3</td>
</tr>
<tr>
<td>&lt; 60%</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Stochetti et al., 1996
ICU and Hospital Length of Stay (Mean days)

![Chart showing ICU and Hospital Length of Stay with significant differences marked by asterisks.](chart.png)

Mortality

![Chart showing mortality rates for field and hospital intubation with a p-value of 0.05.](chart.png)

Hypotension

<table>
<thead>
<tr>
<th>Condition</th>
<th>(%)</th>
<th>Good (%)</th>
<th>Dead (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>100</td>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>Neither</td>
<td>65</td>
<td>51</td>
<td>27</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>11</td>
<td>45</td>
<td>33</td>
</tr>
<tr>
<td>Hypotension</td>
<td>16</td>
<td>26</td>
<td>60</td>
</tr>
<tr>
<td>Both</td>
<td>8</td>
<td>6</td>
<td>75</td>
</tr>
</tbody>
</table>

Chesnutt et al., 1993

Survival vs. Lactate Clearance

![Chart showing survival vs. lactate clearance with time until lactate normalization.](chart.png)

Survival (%)

Time Until Lactate Normalization (Hours)

Moore, 2007

Balogh et al., 2003
Resuscitation

<table>
<thead>
<tr>
<th></th>
<th>Supra</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>85</td>
<td>71</td>
</tr>
<tr>
<td>IAH</td>
<td>42</td>
<td>20</td>
</tr>
<tr>
<td>ACS</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>MOF</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>Death</td>
<td>27</td>
<td>11</td>
</tr>
</tbody>
</table>

Damage Control Resuscitation

- Recognizes that resuscitation techniques must be part of damage control
- Works at preventing coagulopathy, not treating it
- Limits crystalloid and stresses early use of blood and clotting factors
- Tries to avoid iatrogenic resuscitation injury

Traumatic Brain Injury

- This supposes that all TBI is treated the same and that cerebral perfusion equals blood pressure
- This is not stratified by whether patients are bleeding
- Multiply injured patients may be different than those with isolated TBI

Principles of Compartment Syndrome

- Increased pressure
- Limited venous return
- Increased pressure
- Arterial insufficiency
**Compartments**
- Cranium
- Thorax
- Mediastinum
- Abdomen/Pelvis
- Muscle compartments

**Evolution of Trauma Care**
- High velocity weapons
- Multiple trajectories
- Prolonged operative care
- Technically satisfying but poor results
- Lethal triad-coagulopathy, acidosis and hypothermia

**Packing and Re-exploration For Patients With Nonhepatic Injury**
- 11 patients in 16 months
- ISS 17, PATI 48
- 17 major vascular injuries
- Mean OR transfusion needs 17 units Prbc’s
- All hypothermic, coagulopathic and acidic
- 7 survived

Talbert et al, 1992

**Damage Control**
- All but one of the non-survivors in the damage control group were really dead in the OR
- Survival in the 22 “maximum injury” subset was better with damage control (11% vs. 77%, p<.02)

Rotondo, et al 1993

**Abdominal Compartment Syndrome**

Physiologic Derangements

Increased Intra-abdominal Pressure
Intraabdominal Hypertension

- Physiologic alterations:
  - Hemodynamic
    - Venous return
    - Cardiac output
    - Systemic vascular resistance
  - Respiratory
    - Increased intra-thoracic pressure
    - Hypercarbia
    - Poor compliance

- Renal
  - Diminished urine output
    - Plasma flow, GFR, glucose reabsorption
    - Blood flow
  - Shunting from cortex to medulla
    - Arterial flow and vascular resistance
    - ADH

Secondary ACS (n=6)

- 0.5% of ICU admissions
- 13% of all mesh closures
- No evidence of abdominal injury
- Overall mortality 67%

Maxwell et al, 1999

Thoracic Compartment Syndrome

- Tension pneumothorax
- Massive hemothorax

Maxwell et al, 1999

Secondary ACS

- Resuscitation
  - 19 ± 5 liters
- PRBC’s
  - 29 ± 10 units
- NaHCO₃
  - 7.7 ± 1.9 amps
- Time to lap (all)
  - 18 ± 9 hours
- Time to lap (S)
  - 3.1 hours
- Time to lap (NS)
  - 25 hours

Maxwell et al, 1999
Mediastinal Compartment Syndrome

- Cardiac tamponade
- Cardiac swelling
- Severe blunt cardiac injury

ICH and ACS

- ICP and CPP with IAP
- Independent of CV and/or pulmonary dysfunction
- Reversed by decompression

ICH and ACS

- Intrathoracic pressure
- CVP
- Cerebral venous outflow
- ICP

ICH and ACS

- 29 year-old male in MCC
- SAH and SDH on initial CT
- ICP’s about 15 - 20 mmHg
- Initial response to 3% saline and mannitol, then barbiturates
ICH and ACS

- Post injury day #6, unilateral pupillary dilation and had decompressive craniotomy
- POD #2, again developed increasing ICP’s
- Urine output 30-40 cc/hr

Old versus New

**Old**
- CPP goal of > 55 mmHg
- Pentathol
- SIMV/PS and PC
- Mannitol given to keep osmo > 300 – 310
- Greater hyperventilation

**New**
- CPP goal of > 65 mmHg
- Propofol
- APRV (since 1994)
- Hypertonic saline
- CO2 maintained ~ 35 mmHg

Therapy for TBI

- Propofol lowers ICP but also blood pressure
- APRV increases mean airway pressure but causes RV dysfunction and passive hepatic congestion
- Hypertonic saline decreases ICP but increases total body water
- HOB elevation limits chest physical therapy

Traumatic Brain Injury

- ICP
- CPP and sedation
- Fluid and poor pulmonary hygiene
- Vent settings and intrathoracic pressure
- Intra-abdominal pressure

**TABLE 3. Parameters Before and After Abdominal Decompression**

<table>
<thead>
<tr>
<th></th>
<th>MAP (mmHg)</th>
<th>ICP (mmHg)</th>
<th>CVP (mmHg)</th>
<th>CI (L/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-decompression</td>
<td>29.5 ± 5.3</td>
<td>30.9 ± 4.0</td>
<td>39.9 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Post-decompression</td>
<td>27.5 ± 5.2</td>
<td>17.5 ± 3.2</td>
<td>18.9 ± 1.3</td>
<td>4.7 ± 1.4</td>
</tr>
<tr>
<td>P Value</td>
<td>NS</td>
<td>&lt; .0001</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
Decompressive Therapy

- Decompressive craniectomy
  - brain compliance
  - blood flow
  - cerebral oxygenation
- Decompressive laparotomy
  - intraabdominal and intrathoracic pressure
  - intracranial pressure

Comparison of ICP (Pre and Post DC and DL) by Sequence of Decompression

Cumulative Mean Airway Pressure

TBI-Induced Multicompartment Syndrome
Background

- Prompt recognition of both extent and duration of ICH and cerebral hypo- or hyperperfusion is critical in patients with severe TBI
- ICP and CPP tend to be documented intermittently
- Documented parameters reflecting the depth and duration of ICH can be subject to unrecognized artifact and/or recording errors
- Automated collection of real-time high-resolution data
  - Faster
  - More efficient processing of information
  - Automatic generation of multiple measures
  - Remote and instantaneous access

Continuous computerized monitoring at 6 sec intervals detects significantly more episodes and higher percentage of time spent with ICP > 20 mm Hg than with manual recording


Studies do not attempt to validate data acquisition or processing methodology by considering patient outcome

Methods

- Real-time patient VS were collected from the patient monitors (GE-Marquette-Solar-7000/8000) networked throughout the trauma center via VSDR every 6 seconds

- Potential artifacts are filtered by
  - removing first and last minute of data of patient stay
  - removing extreme outliers
  - a process of recording a moving median with a window-size of 5 data points (30 seconds)

- < 1% of data points discarded (1,990,000 remained)
- 5 min mean values calculated
- Plots of all cases were manually reviewed

Using automated (PTDa) or manual (PTDm) recordings the extent and duration of ICP and CPP above and below treatment thresholds were calculated as

‘Pressure times Time Dose’ (PTD, mmHg h)

- ICP > 20
- CPP < 60
- CPP > 100

3 time periods were evaluated

- TRU stay
- First 24 hours
- TRU + ICU = cumulative/total stay
Results

(A) Sample graph of a 2 hour block of automated ICP and CPP recordings at 6 second intervals superimposed with 5 minute mean (dark solid line)

(B) Calculation of PTD as the sum of all shaded areas above ICP>20 mm Hg and CPP<60 mmHg

Pressure Times Time Dose

- Automated measures of ICP>20 mm Hg and CPP >60 mm Hg correlate better with outcome than manual measures
- Total measure of PTD correlates better with functional outcomes over entire period of monitoring
- Daily mean PTD also correlates better with functional outcomes than manual measures

Total cumulative PTD as calculated from automated and manual data by favorable (GOSE >4) and unfavorable outcome (GOSE <5)

**p ≤ 0.002

Daily mean PTD as calculated from automated and manual data by favorable (GOSE >4) and unfavorable outcome (GOSE <5)

* p < 0.02
Results

• Total PTDa values of ICP20, CPP60 and CPP100 were also strongly correlated with
  – Length of ICU stay
  – Length of hospital stay

• PTDa values for ICP20 and CPP60 were correlated with discharge GCS scores

• PTDa of CPP60 during TRU stay was correlated with the need of craniectomy

Methods

The slope of cerebral perfusion pressure divided by intracranial pressure (CPP/ICP) as a Brain Trauma Index (BTI).

Results

Methods - Data Processing

• VSS “genes” of interest identified from these variables:
  - Brain trauma/vascular-pressure: ICP, CPP, BTI, SBP, MAP
  - Cardiac/shock: HR, SHP, Shock Index
  - Perfusion: SPO2

• Further characterized via conventional clinical thresholds:
  - ICP >20 and >30 mmHg
  - CPP <50, <60, and >100 mmHg
  - SBP <90, <100, <110, and <120 mmHg
  - MAP <60 and <70 mmHg
  - BTI <1.67, <2.0, and <3.0
  - HR >100, >110, and >120 bpm
  - SI >0.7, >0.8, >0.9, and >1.0
  - SPO2 <88% and <90%

• Assembly into “genes”
  - % time and PTD for VS and index segments above or below defined limits and # of episodes greater than, less than, or equal to 5, 10, 15, 20, 25, 30, 45, and 60 minutes.

• Final result = 588 VSS “genes” of potential use in prediction algorithms
  - 3 defined time segments: the first 12, 24, and 48 hours
  - 3 hospital-related outcomes: in-hospital mortality, hospital and ICU LOS >=14 days
  - 3 long-term functional outcomes: GOSE at 3, 6, 12 months
  - GOSE 1-4 = “favorable functional outcome”
  - GOSE 5-8 = “unfavorable functional outcome”

Methods - Data Processing
Results

Heat Map for all 588 VS features for first 12 hours: dark blue 0 - dark red 1.0

Cerebral Perfusion
n=60

- GOSE at 1 year
- Overall mortality 13.3%
- Admission SBP, GCS, Marshall Scores the same when good outcome (GOSE >4) compared to bad
- PTD, PTD/day, and % time SBP < 100 mmHg and <120 mmHg predicted mortality at 12, 24 and 48 hours (p<.04)
- % time SBP <100 mmHg in first 24 hrs predicted GOSE at 1 year (p=02)

Brenner et al, 2010

Cerebral Hyperoxia

- 1558 patients with TBI
- Mean GCS 8.3±4.7
- Mean ISS 31.9 ± 12.5
- Controlled for age, gender, ISS, MOI and admission GCS
- Patients with PO2 <100 had increased mortality (p=.03)
- Patients with PO2 >200 had increased mortality (p=.02) and lower DCGS (p=.004)

Brenner et al, 2010

Traumatic Brain Injury

- CVVHD
- Thoracic/mediastinal decompression
- Targeted volume resuscitation

Brenner et al, 2010

Focused Echocardiography

- 80% had EF obtained
- LV dysfunction in 56% of patients
- RV dysfunction in 25% of patients
- FREE answered a clinical question in 87% of patients
- FREE changed the planned care in 54% of patients

Ferrada et al, 2010
Summary

- Severe TBI is a whole body disease
- Body compartments connect
- Fluid therapies may precipitate pressure increases in multiple compartments
- Secondary brain injury may well be mediated by ischemia and/or inflammation
- Standard ICU care misses much of the picture

Summary

- New therapeutic tools will focus on non-brain therapies and better information
- These will be amalgamated in computer driven decision planning
- The future will be about creating a safer cocoon in which the damaged brain can live while healing
- Not every patient needs the same care
- Optimal personalized care may be defined by genetic make up