Journal Club Handout

Name: Dean Bell
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Background and Overview

Article Title/Citation:

Study objectives/purpose:
The aim was to investigate the reliability of diagnostic methods such as neurologic examination, serum concentrations of neuron-specific enolase (NSE), and median nerve somatosensory-evoked potentials (SEP) to predict poor outcome in patients treated with mild hypothermia after in- and out-of-hospital CPR.

Brief Background: (why issue is important, summary of previous literature)
Outcome prediction in cardiac arrest is primarily based on literature published prior to the use of mild therapeutic hypothermia in the post arrest population. Recent single centre series have raised questions regarding the predictive abilities of neurologic exam, biochemical markers, and electrodiagnostic testing when mild therapeutic hypothermia has been used. No large series has been examined in post arrest patients who have received hypothermia. Previous best evidence was most cogently summarized in a 2006 publication from the American Academy of Neurology (Wijdicks EF, Hijdra A, Young GB, et al. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006;67:203–210).

Methods

Study design and Methodology: (type of trial, Randomization, blinding, Controls, study groups, Length of study, etc.)
1. Multicenter prospective cohort study in 10 Dutch mixed medical-surgical ICU’s.
2. Presumably consecutive admissions to each center meeting entry criteria.
3. Data not available for patients admitted after CPR but not eligible or not enrolled in the study.
4. No randomization; no control group; no blinding (including outcome assessment).
5. Consent- obtained initially from a surrogate after admission and later from patient if they became capable.
6. IRB approval from all participating hospitals.

Patient selection and Enrollment: (Inclusion/Exclusion criteria, sample Size etc.)
1. Inclusion: adult patients admitted to ICU following CPR who remained comatose and who received therapeutic hypothermia.
2. Exclusion: pre-existing disease with life expectancy <6 months, severe disability before CPR, CPR secondary to hypovolemic shock, lack of consent.
Interventions: (if applicable)
None, however specific tests were performed to determine their impact on outcome prediction.

Tests done:
1. Neurologic examination (GCS and brainstem reflexes) at 48 and 72 hours after CPR (attending ICU physician or neurologist). Results available to treating physicians.
2. Blood samples for NSE on admission; 12 hours after target temp 32-34 degrees; and 48 hours after collapse. Samples frozen and analyzed later. Results NOT available to treating physicians.
3. Cortical N20 median nerve SEP “during hypothermia” and repeated after rewarming in patients who remained in a coma and were judged to have cleared sedative drugs and metabolites. SEP results during hypothermia were NOT available to treating physicians.

The study protocol contained no guidelines for withholding or withdrawing treatment. These decisions were left to the treating physicians (and presumably patient representatives). In the Netherlands SEP in comatose normothermic patients are used to predict prognosis and absent SEP were a reason physicians used to withdraw treatment.

Outcome measures/Endpoints:
1. Outcome determination
   a. Glasgow Outcome Scale at 1 week; 1 month; and 6 months after admission via telephone
2. Primary outcome was GOS 1-3 (death, vegetative state, severe disability) at six months.
3. Secondary outcomes
   a. Death or vegetative state (GOS 1-2) at one month
   b. Mortality at one week; one month; and six months

Statistical analysis:
• Patient characteristics described by distribution with mean±SD if continuous or normally distributed; median and interquartile range for non normally distributed characteristics.

• Categorical variables expressed as percentage and chi square used for differences.

• GOS used as reference variable for patient outcome.

• Percentages of correct identification were expressed as sensitivity and specificity. False positive rate (FPR) was calculated as 1-specificity. Confidence intervals were calculated for the FPR.
• Sensitivity, specificity and FPR were calculated for the following predictors or neurologic outcome:
  1. Physical exam- 72 hour motor score, pupillary light response, corneal reflexes
  2. NSE at several intervals- admission, during hypothermia, 36 and 48 hours after collapse
  3. SEP during hypothermia and normothermia

• ROC curve calculated for NSE

Results

Enrollment & Baseline Characteristics:
Enrollment ran between December 2007-August 2009. A total of 391 patients were included. We are not given any information about patients with cardiac arrest who were admitted to the units but not enrolled in the study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean (SD)</td>
<td>64 (13.4)</td>
</tr>
<tr>
<td>Gender, male, % (n)</td>
<td>73.1 (286)</td>
</tr>
<tr>
<td>Presenting rhythm, % (n)</td>
<td></td>
</tr>
<tr>
<td>VF or VT</td>
<td>76.5 (299)</td>
</tr>
<tr>
<td>Asystole or PEA</td>
<td>21.5 (84)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Location of CPR, % (n)</td>
<td></td>
</tr>
<tr>
<td>OHCA</td>
<td>86.7 (339)</td>
</tr>
<tr>
<td>IHCA</td>
<td>12.3 (48)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Time collapse to bystander</td>
<td>2 min (0–5)</td>
</tr>
<tr>
<td>BLS, median (IQR)</td>
<td></td>
</tr>
<tr>
<td>Time collapse to ROSC, median (IQR)</td>
<td>20 min (11–30)</td>
</tr>
<tr>
<td>Time from CPR to ≤34°C, median (IQR)</td>
<td>315 min (218–450)</td>
</tr>
<tr>
<td>Medical history, %</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>21.5</td>
</tr>
<tr>
<td>Heart failure</td>
<td>16.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13.6</td>
</tr>
<tr>
<td>COPD</td>
<td>10.5</td>
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</tbody>
</table>

BLS = basic life support; COPD = chronic obstructive pulmonary disease; CPR = cardiopulmonary resuscitation; IHCA = in-hospital cardiac arrest; IQR = interquartile range; OHCA = out-of-hospital cardiac arrest; PEA = pulseless electrical activity; ROSC = return of spontaneous circulation; SD = standard deviation; VF = ventricular fibrillation; VT = ventricular tachycardia.
Summary of primary & secondary outcomes: (including subgroup analysis etc. include both efficacy and safety parameters)

- After 6 months 199 patients (51%) had died, and 149 (75%) of these deaths occurred in the first week after admission. Treatment was withdrawn (62%) or restricted (26%) in these 149 patients dying within the first week.

- Poor outcome (GOS 1-3) was found in 208 (53%) of the complete group at 6 months.

- 72% of the patients who recovered had a good recovery

- Outcome after out-of-hospital arrest was better (52% poor outcome) versus in-hospital arrest (75% poor outcome)

- Poor outcome more common with asystole/PEA (83%) versus VF/VT (47%)

- 42 patients had absent SEP after rewarming. All 42 patients died. Treatment was withdrawn in 33 patients and limited in 7 (DNR order).

- Three patients with absent SEP during hypothermia recovered to good outcomes. These were examined post-hoc in a sample with 10 others. Two neurophysiologists reviewed the sample and concluded that the three SEP should have been classified as “undeterminable” rather than “absent”.

Pertinent figures/diagrams:

![Table 2: Outcomes](image-url)
Brief summary of Authors’ main discussion points:

- 72 hours after CPR absent pupillary light response (FPR 1; 95% CI 0-7) or absent corneal reflexes (FPR 4; 95% CI 1-13) are reliable to predict poor outcome in patients who received therapeutic hypothermia following CPR.

- Absent SEP N20 response may be reliable at 72 hours post CPR. (FPR 0; 95% CI 0-18)

- Motor score at 72 hours following ROSC should no longer be used as a predictor in daily clinical practice (FPR 10; 95% CI 6-16).

- NSE >33 μg/L does not reliably predict poor outcome. Higher cut off (80 μg/L) may be a better discriminator.

- SEP results may represent a “self-fulfilling prophecy” as these results were available to treating physicians and used to limit treatments.

Author’s conclusions:

- In patients with persisting coma after CPR who were treated with hypothermia motor scores 72 hours after CPR, and serum NSE levels are not reliable for outcome prediction.

- Poor outcome can be reliably predicted with:
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- Absent pupillary light response or absent corneal reflexes 72 hours after CPR
- Bilateral absence of cortical N20 response of median nerve SEP

In daily practice decisions about prognostication in the individual patient should not be based on one test but on full clinical condition.

Your Discussion and Conclusions

**Study strengths:**

- Largest series published in the era of therapeutic hypothermia.
- First multicenter study employing hypothermia.
- Attempted to standardize testing and timing of tests.
- Masked NSE levels and SEP during hypothermia from treating physicians.
- FPR for were higher in this study than in 2006 AAN paper (AAN absent pupils/corneal FPR=0; 95% CI 0-3 at day 3; absent N20 FPR=0.7; 95% CI 0-3.7)

**Study limits, weaknesses, Potentials for bias:**

- Cohort study with no intervention.
- Time frames for prognostic evaluations were established in patients from the pre-hypothermia era.
- This selection of time frames limits exploration of the effects of hypothermia.
- Still a small cohort with some low event rates resulting in relatively wide confidence intervals for predictors.
- No idea how many patients were excluded from the study, why they were excluded, or what happened to them.
- After rewarming results of the neuro exam and SEP were available to treating physicians.
- Potential “self-fulfilling prophecy” with SEP which were used (when absent) to withdraw treatment.
- Incomplete data as not all diagnostic methods were performed at all points in all patients. Early deaths resulted in no 72 hour exams, NSE not done after 48 hours, SEP not done in off hours.

**Applicability & impact:**

- Likely practice changing as motor response at 72 hours following CPR has been a standard used to initiate discussion about limitation of treatment.
- Indicates a role for SEP monitoring in this patient population.
- Raises questions about our ability to prognosticate before 72 hours after ROSC.

**Additional thoughts/Comments:**

- In conjunction with other articles this indicates that a multi-modality approach needs to be employed in decision making for patients who remain comatose following therapeutic hypothermia.
This approach could involve imaging (CT/MRI) and techniques such as EEG and SEP monitoring. We have not been systematically using these modalities in this population.


I was struck at outcome improvements noted between one month and six months. At one month 59% of the cohort had GOS 1-3 but at 6 months this was down to 53%. GOS 4-5 was 40% at one month but up to 44% at 6 months. Decreases in vegetative, severe disability and moderate disability were seen at 6 months.

Conclusions and Recommendations:

- Don’t use 72 hour post CPR motor response to predict outcome or justify withdrawal of treatment in patients treated with hypothermia.
- Should we wait until 72 hours after normothermia before considering prognostication and limitation of treatments?
- We must investigate the barriers to getting SEP testing in our units.
- We should consider the literature on EEG as an outcome predictor in this population.
- We should also consider the role of neuro-imaging to help with outcome prediction.
- Raises a major question about how and where we are currently delivering care to post arrest patients- not all hospitals have SEP or EEG availability. Not all can provide PCI to post arrest patients. Should we consider regionalizing post arrest care?