The usefulness of neuron-specific enolase in cerebrospinal fluid to predict neurological prognosis in cardiac arrest survivors who underwent target temperature management: a prospective observational study

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Disclosures

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The usefulness of neuron-specific enolase in cerebrospinal fluid to predict neurological prognosis in cardiac arrest survivors who underwent target temperature management: a prospective observational study

I have no relevant financial relationships with commercial interests to disclose.
Methods for neurological prognostication

- Non-invasive
- Much utilized and studied for CA
- Sensitivity to sedation?
- Difficult to standardize – interrater variability

- Easily studied
- Easily interpreted
- Low availability outside academic centre
- Limited sensitivity

- Quantification of brain injury
- Easy to understand
- No standard available
- No agreement on cut-off

- Easily accessible
- Low cost
- Interrater variability
- Sensitivity to analog-sedation

- Evidence is limited

ERC/ESICM guidelines: Suggested prognostication algorithm

Serum biomarkers commonly face the challenge of contamination; for example, NSE is also found in red blood cells (RBCs) and platelet, and post-cardiac arrest patients commonly have hemolysis, which raises the NSE levels without necessarily reflecting brain injury. Although harder to obtain, CSF samples have the advantage that the biomarker need not be transported across the blood-brain barrier for detection, thus greatly reducing the contamination issue.
Hypothesis

- NSE molecular weight: 45000 Da
- Blood brain barrier: < 500 Da
- BBB disruption (vasogenic edema): 24 hours of ROSC

Park et al, *Resuscitation*, 2019

Measuring NSE in the CSF prior to BBB disruption such as cytotoxic edema state, could yield earlier and more accurate values than the serum

Stammet et al, *JACC*, 2015
Hypothesis

CSF

NSE 45 kDa

< 500 Da

Blood
Methods

- Prospective single-centre observational cohort study of adult comatose OHCA survivors

- December 2017 to November 2018

- Inclusion criteria: OHCA patients > 18 years old who had been treated using TTM

- Exclusion criteria: traumatic CA, receiving ECMO, ineligible for lumbar puncture (brain CT showed severe cerebral edema),

- The primary outcome was the 6-month neurological outcome (poor neurological outcome: CPC 3 – 5)

- Approved by the Institutional Review Board (IRB) of Chungnam National University Hospital
Measurement of CSF vs Serum NSE levels

- Time: 0, 24, 48, and 72 hours after ROSC
- Serum NSE: venipuncture
- CSF NSE: lumbar drainage

Analysis
- GC Labs (Yongin, Geonggi-do, Korea)
- Electrochemiluminescence immunoassay (COBAS® e801, Roche Diagnostics, Mannheim, Germany)
- Analytic measurement range: 0.1 - 300 ng/ml (normal values < 16.3 ng/ml)

Hermetic™ lumbar catheter kit (Integra Neurosciences, Plainsboro, NJ, USA)
Results

- 34 patients enrolled
- Good outcome group: 18 (52.9%)
- Poor outcome group: 16 (47.1%)

Cardiac arrest survivors who underwent target temperature management (n = 41)

Patients included for analysis (n = 34)

Severe brain edema (n = 1)
Traumatic cardiac arrest (n = 2)
Declined any further treatment (n = 2)
Extracorporeal membrane oxygenation (n = 2)
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Cohort, (N = 34)</th>
<th>Good Outcome, (N = 18)</th>
<th>Poor Outcome, (N = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>46.5 (36.8-58.3)</td>
<td>45.5 (36.8-63.8)</td>
<td>51.5 (37.3-57.8)</td>
</tr>
<tr>
<td>Sex, male, N (%)</td>
<td>24 (70.6)</td>
<td>15 (83.3)</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index score, median (IQR)</td>
<td>1.0 (0.0-3.0)</td>
<td>0.5 (0.0-4.0)</td>
<td>1.0 (0.0-2.5)</td>
</tr>
<tr>
<td>Witness arrest, N (%)</td>
<td>23 (67.6)</td>
<td>14 (77.8)</td>
<td>9 (56.3)</td>
</tr>
<tr>
<td>Bystander CPR, N (%)</td>
<td>26 (76.5)</td>
<td>17 (94.4)</td>
<td>9 (56.3)</td>
</tr>
<tr>
<td>Shockable rhythm, N (%)</td>
<td>12 (35.3)</td>
<td>11 (61.1)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Cardiac aetiology, N (%)</td>
<td>11 (32.4)</td>
<td>9 (50.0)</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>No flow time, min (IQR)</td>
<td>1.5 (0.0-12.3)</td>
<td>0.5 (0.0-5.0)</td>
<td>5.0 (0.3-20.8)</td>
</tr>
<tr>
<td>Low flow time, min (IQR)</td>
<td>16.5 (8.0-30.0)</td>
<td>8.5 (4.8-20.0)</td>
<td>27.0 (15.0-41.3)</td>
</tr>
<tr>
<td>LP time, min (IQR)</td>
<td>270.0 (235.8-372.6)</td>
<td>245.5 (200.0-446.8)</td>
<td>285.0 (252.0-328.3)</td>
</tr>
</tbody>
</table>

IQR, Interquartile range; CPR, Cardiopulmonary resuscitation; LP, Lumbar puncture
Serial Comparison of CSF and serum NSE levels

**Serum NSE after ROSC**
- $P = 0.078$

**Serum NSE after 24 hr**
- $P = 0.008$

**Serum NSE after 48 hr**
- $P < 0.001$

**Serum NSE after 72 hr**
- $P < 0.001$

**CSF NSE after ROSC**
- $P = 0.001$

**CSF NSE after 24 hr**
- $P < 0.001$

**CSF NSE after 48 hr**
- $P < 0.001$

**CSF NSE after 72 hr**
- $P < 0.001$
### Prognostic performance using CSF NSE vs. serum NSE

<table>
<thead>
<tr>
<th>Time</th>
<th>Cut-off (ng/ml)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive Predictive value</th>
<th>Negative Predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RO SC</td>
<td>53.7</td>
<td>50.0 (24.7-75.3)</td>
<td>100.0 (81.5-100.0)</td>
<td>100.0</td>
<td>69.2</td>
</tr>
<tr>
<td>24 hr</td>
<td>99.9</td>
<td>93.8 (69.8-99.8)</td>
<td>100.0 (81.5-100.0)</td>
<td>100.0</td>
<td>94.7</td>
</tr>
<tr>
<td>48 hr</td>
<td>136</td>
<td>93.8 (69.8-99.8)</td>
<td>100.0 (81.5-100.0)</td>
<td>100.0</td>
<td>94.7</td>
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<tr>
<td>72 hr</td>
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**BBB intact (cytotoxic edema)**

- **CSF ROC for CPC 3-5 at ROSC**: AUROC (95% CI) = 0.831 (0.660-0.938)
- **CSF ROC for CPC 3-5 at 24 hr**: AUROC (95% CI) = 0.967 (0.831-0.999)
- **CSF ROC for CPC 3-5 at 48 hr**: AUROC (95% CI) = 0.783 (0.599-0.910)
- **CSF ROC for CPC 3-5 at 72 hr**: AUROC (95% CI) = 0.896 (0.733-0.975)

**BBB disruption (vasogenic edema)**

- **CSF ROC for CPC 3-5 at ROSC**: AUROC (95% CI) = 0.831 (0.660-0.938)
- **CSF ROC for CPC 3-5 at 24 hr**: AUROC (95% CI) = 0.967 (0.831-0.999)
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Neuron-Specific Enolase as a Predictor of Death or Poor Neurological Outcome After Out-of-Hospital Cardiac Arrest and Targeted Temperature Management at 33°C and 36°C

Serum NSE has high sensitivity and specificity at 48 and 72 h

- Sensitivity: 0.58 (0.52 – 0.64)
- Specificity: 0.98 (0.96 – 0.99)

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<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>ROSC</td>
<td>53.7</td>
<td>0.50 (0.25-0.75)</td>
<td>1.00 (0.82-1.00)</td>
</tr>
<tr>
<td>24 hr</td>
<td>99.9</td>
<td>0.94 (0.70-1.00)</td>
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Discussion

<table>
<thead>
<tr>
<th>Table 2: NSE Cutoff Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoff (ng/ml)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>NSE Youden</td>
</tr>
<tr>
<td>NSE 5</td>
</tr>
<tr>
<td>NSE 4</td>
</tr>
<tr>
<td>NSE 3</td>
</tr>
<tr>
<td>NSE 2</td>
</tr>
<tr>
<td>NSE 1</td>
</tr>
<tr>
<td>NSE 0</td>
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</tbody>
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<table>
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<tr>
<th>48 h</th>
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<tbody>
<tr>
<td>NSE Youden</td>
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<td>NSE 5</td>
</tr>
<tr>
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<table>
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<tr>
<td>NSE Youden</td>
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<td>NSE 3</td>
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</table>

Stammet et al, JACC, 2015
Limitation

- This was a single-centre prospective study with a small number of patients; therefore, a multicentre study is required to enhance the generalization of these findings.

- Of 48 patients achieving ROSC during the study, 7 (14.6%) were excluded because TTM had not been undertaken. This might have caused selection bias and could limit the generalization of our findings.

- Before analysing samples, we did not assess the objective haemolytic index, such as the Roche haemolysis index. However, CSF is less likely to haemolyse than serum, so the haemolysis effect was likely to limited.

- The maximum measurement range was 300 ng/ml. Samples with values above the measurement range were not diluted and analysed. However, the maximum value of the CSF NSE in the good outcome group was 136 ng/ml on 48 h after ROSC, which was not difficult to differentiate the poor outcome group.
Conclusion

**CSF NSE** values were shown to have *early, high predictive, and high sensitivity* values for predicting poor neurological outcome in comatose OHCA survivors treated with TTM. These values showed better performance than other serum biochemical markers such as NSE. A large sample, multi-centre study is warranted to identify the exact association between CSF NSE values and neurological outcomes.
Thank you!

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If you have any question, please let me know by e-mail
Cranial Computed Tomography, Lumbar Puncture, and Clinical Deterioration in Bacterial Meningitis: A Nationwide Cohort Study

- Nationwide prospective cohort study
- Community-acquired bacterial meningitis
- From 2006 to 2014

Of 1533 episodes, 47 (3.1%) had deterioration

Cerebral herniation following LP in bacterial meningitis is a rare event (range, 0.1%-3%, but likely to be closer to 0.1%)

CSF opening pressure was evaluated in 19 patients and exceeded 30 mmHg in 15 (79%).
Relationship between optic nerve sheath diameter measured by magnetic resonance imaging, intracranial pressure, and neurological outcome in cardiac arrest survivors who underwent targeted temperature management

Changshin Kang¹, Jin Hong Min¹, Jung Soo Park¹,²,³, Yeonho You¹, Insool Yoo¹,², Yong Chul Cho³, Wonjoon Jeong¹, Hong Joon Ahn¹, Seung Ryu¹, Jinwoong Lee¹, Seung Whan Kim¹, Sung Uk Cho³, Se Kwang Oh³, In Ho Lee³,⁴, Byungkook Lee⁵, Donghun Lee⁶, Minjung Kathy Chae⁷

Fig. 3 – Comparison of the ICP (A) and ONSD (B) for different neurological outcomes at each time point. ICP, intracranial pressure; ONSD, optic nerve sheath diameter.
• Lumbar CSF drainage: safe & valuable tool

• Select patients with discernible basal cisterns


• Lumbar CSF drainage: treat refractory increased ICP


Chungnam National University: Consent form

<table>
<thead>
<tr>
<th>Date of Birth</th>
<th>Date of Death</th>
<th>Relationship</th>
<th>Signature</th>
</tr>
</thead>
</table>

Signature:

Family signature
Neuron-Specific Enolase (NSE)

• CSF : Serum = 1:1

• Biological half life : 48 hours

• Total mass of proteins in the brain: 1.5%

• CSF : Blood = 165 ml : 4000 ml