Brain cooling treatment in traumatic brain injury from bench to clinical Chi-Mei experience

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腦創傷中心 郭進榮

28-11-2010
CPP = MAP - ICP \geq 70 \text{ mmHg (2002)}
Brain trauma foundation (BTF) guideline

2000
CPP \geq 70 \text{ mmHg}

2003
CPP \geq 60 \text{ mmHg}
Publication (2006-2010)
1. Jinn-Rung, Kuo, Chong-Jeh, Lo, Che-Chuan, Wang, Chin-Li Lu, Shu-Chin, Lin, Chaio-Fang, Chen
   Measuring brain temperature while maintaining brain normothermia in severe traumatic brain Injury patients.
   Journal of clinical neuroscience (2010, accept)
2. Jinn-Rung, Kuo, Chong-Jeh, Lo, Chin-Li, Lu, Chung-Ching, Chio, Che-Chuan, Wang, Kao-Chang, Lin
   Journal of the Formosan Medical Association (2010, accept)
3. Jinn-Rung, Kuo, Chong-Jeh, Lo, Ching-Ping, Chang, Hung-Jung, Lin, Mao-Tsun, Lin, Chung-Ching, Chio
   Brain Cooling-Stimulated Angiogenesis and Neurogenesis Attenuated Traumatic Brain Injury in Rats
   The Journal of Trauma, Injury, Infection & Critical Care (2010, accept)
4. Jinn-Rung Kuo, Che-Chuan Wang, Huan-Fang Lee, Chung-Ching, Chio, Kao-Chang, Lin
   Hematoma density and Glasgow coma scale are independent predictors to outcomes in unilateral chronic subdural
   hematoma  Taiwan Crit. Care Med.2010;11:90-97
5. Kao-Chang, Lin, Jinn-Rung, Kuo
   The difference of osmotic effects between intact and disrupted blood brain barrier
6. Kao-Chang, Lin, Chih-Ho Chou, Wei-Lung Chang, Der-Shin Ke, Jinn-Rung Kuo (Correspondence)
   The Early response of mannitol Infusion in traumatic brain Injury  Acta Neurol Taiwan 2008;17:26-32
   Correlation of a high D-dimer level with poor outcome in traumatic intracranial hemorrhage
   European Journal of Neurology 2007; 14: 1073–1078
8. Chung-Ching Chio, Jinn-Rung Kuo, Sheng-Huang Hsiao, Ching-Ping Chang, Mao-Tsun Lin
   Effect of brain cooling on brain ischemia and damage markers after fluid percussion injury in rats
9. Jinn-Rung Kuo, Chong-Jeh Lo, Chung-Ching Chio, Ching-Ping Chang, Mao-Tsun Lin
10. Jinn-Rung Kuo, Chaio-Fan Chen, Cung-Ching Chio, Chin-Hung Chang, Che-Chuan Wang, Kao-Chang Lin
    Time dependent validity in the diagnosis of brain death using transcranial Doppler Sonography
    Journal Neurology Neurosurgery Psychiatry 2006;77:646–649
11. Jinn-Rung Kuo, Tsong-Chih Yeh, Kuan-Chin Sung, Che-Chuan Wang, Chi-Wen Chen, Chung-Ching Chio
    Intraoperative applications of intracranial pressure monitoring in patients with severe head injury
Hypothermic retrograde jugular vein flush (HRJVF) with 4 ℃ normal saline
Fluid percussion induced traumatic brain injury

液體衝撞腦創傷模型
Fluid Percussion Traumatic brain injury

Physiology
- ICP
- CPP
- MAP
- HR
- Tco
- Tb
- Microdialysis
  - Lactate
  - Pyruvate
  - Glutamate
  - Glycerol

Morphology
- TTC stain
  (Infarction volume)

Functional
- Motor (incline plane)
- Sensory (Propioception)

逆行性頸靜脈灌注選擇性腦低溫術
Mechanism?
Pathophysiology and outcome of TBI

Oxidative, Nitrostatic stress

Vascular alterations
- Hemorrhage
- Thrombosis
- ↓ Blood flow
- Ischemic necrosis
- Edema

Metabolic disturbances
- ↑ [Na⁺], [Cl⁻], [K⁺]
- ↑ [Ca²⁺]
- ↑ Glucose utilization
- ↓ ATP
- Acidosis

Biochemical alterations
- Lipid peroxidation
- ↑ Free radicals and fatty acid production
- ↑ Arachidonic acid release
- ↑ Eicosanoid synthesis

Cellular reactions
- Inflammation
  - ↑ Macrophages
  - ↑ Neutrophils and T cells
  - ↑ Reactive astrogia
  - Apoptosis

Fiber tract disturbances
- Demyelination
- Wallerian degeneration
- Apoptosis of oligodendrocytes
- Scar formation
Reactive oxidative and nitrostellative stress

Hydroxyl radical (OH•)
Superoxide (O₂•)
Nitric oxide (NO•)
NO synthase (一氧化氮合成酶)
Peroxynitrite (ONOO•)

Anti-oxidants

Superoxide dismutase (SOD)
Glutathione, Glutathione peroxidase (GPX)
Glutathione reductase (GRX)
Catalase
**Reactive oxidative stress**

ROS

\[ \text{O}_2 \cdot \overset{\text{SOD}}{\rightarrow} \text{H}_2\text{O}_2 \overset{\text{Catalase}}{\rightarrow} \cdot \text{OH} \overset{\text{Lipid peroxidation}}{\rightarrow} \text{MDA} \]

\[ \begin{align*} &\text{GSSG} &\text{GSH} &\text{GPx} &\text{H}_2\text{O} &\text{O}_2 \\
&\text{GR} &\text{NADPH} &\text{NADP}^+ &2\text{H}_2\text{O} \\
\end{align*} \]

**Reactive nitrostatic stress**

RNS

\[ \text{Arginine} \overset{\text{NOS} (\text{一氧化氮合成酶})}{\rightarrow} \text{NO} \overset{\cdot \text{O}_2}{\rightarrow} \text{ONOO}^- \overset{\text{peroxynitrite}}{\rightarrow} \text{Tyrosine} \overset{3}{\rightarrow} \text{3-Nitrosyltyrosine} \]

\[ \text{Brain injury} \]

**Oxidative pressure**

**Nitrosative pressure**
Mechanism?

1. 減少氧化及氮化自由基壓力 (oxidative, nitrostatic stress) 之傷害
2. 減少細胞凋亡 (apoptosis)
3. 刺激神經保護因子 (VEGF) 形成
4. 刺激神經新生 (Neurogenesis), 血管新生 (angiogenesis)
TUNEL (Apoptosis)

- TUNEL
- DAPI
- Merge

- Sham 72hr
- FPI 72hr
- Cooling 72hr

Number of apoptosis cells

<table>
<thead>
<tr>
<th>Sham</th>
<th>FPI</th>
<th>Cooling</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>40</td>
</tr>
</tbody>
</table>

- TUNEL
- DAPI
- Merge

- Sham 72hr
- FPI 72hr
- Cooling 72hr

Number of apoptosis cells

- Sham
- FPI
- Cooling

* Significance
† Significance
Brain injury

Active Caspase 3

Reactive oxidative stress (ROS)
Reactive nitroostative stress (RNS)

MDA, SOD, GPx, GR, Catalase

nNOS → 3-NT

Apoptosis

Neuron Apoptosis

Cell death

Neurogenesis (BrdU+NeuN)
Angiogenesis (BrdU+RECA-1)

Neuroprotection factor (VEGF)

Selective Brain cooling
Basic study

*Selective brain cooling
Retrograde jugular vein flush

TBI → ROS → RNS → Apoptosis → Outcome

attenuate

VEGF

Neurogenesis
Angiogenesis
**Basic study**

*Selective brain cooling  
Retrograde jugular vein flush

**Clinical study**

建立脳温資料

尋找適合病人

執行可行方法
Clinical application

Brain temperature monitor

110-4BT,
額溫
1. A significant temperature gradient exists between intracranial temperature (ICT) and rectal temperature (Tr)
The relationship between early brain hyperthermia within 24 hours of admission and GOS at 3 months.

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Intracranial temperature (ICT)</th>
<th>GOS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>postoperative</td>
<td></td>
<td>2+3</td>
<td>4+5</td>
</tr>
<tr>
<td></td>
<td>ICT &lt;= 38°C</td>
<td>305</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>(75.1)</td>
<td></td>
<td>(83.3)</td>
</tr>
<tr>
<td>Within 24 hours</td>
<td>ICT &gt; 38°C</td>
<td>(24.9)</td>
<td>24 (16.7)</td>
</tr>
</tbody>
</table>

2. Early brain hyperthermia within 24 hours of admission was associated with worse Glasgow outcome scale at 3 months.
Clinical application

脳溫監視器
Brain temperature monitor

Retrograde jugular vein approach
Prognostic predictors of outcome in an operative series in traumatic brain injury patients

Kuo JR, Lo CJ, Lu CL, Chio. CC, Wang, CC, Lin KC

Journal of formosan medical association (2010, accept)
The final model of multiple logistic regression was constructed by forward stepwise procedure, the adjusted odd ratio in predicting the Glasgow Outcome Scale (GOS 1 to 3, 4 to 5).

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>OR</th>
<th>Lower</th>
<th>Upper</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniectomy Vs craniotomy</td>
<td>2.78</td>
<td>16.17</td>
<td>2.07</td>
<td>126.39</td>
<td>0.008</td>
</tr>
<tr>
<td>Age</td>
<td>0.11</td>
<td>1.12</td>
<td>1.05</td>
<td>1.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pupil (both fixed vs at least one reactive)</td>
<td>4.37</td>
<td>78.68</td>
<td>6.39</td>
<td>968.59</td>
<td>0.001</td>
</tr>
<tr>
<td>Preoperative midline shift</td>
<td>0.17</td>
<td>1.19</td>
<td>1.00</td>
<td>1.42</td>
<td>0.050</td>
</tr>
<tr>
<td>ISS</td>
<td>0.39</td>
<td>1.48</td>
<td>1.11</td>
<td>1.97</td>
<td>0.007</td>
</tr>
<tr>
<td>Constant</td>
<td>-19.86</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kuo JR et al. JFMA 2010, accepted
Outcomes of early decompressive craniectomy in traumatic brain injury patients where hematomas were surgically removed

Kuo, J.R. Lo, C.J. Chio, C.C., Lin, K.C, Wang, C.C.

Clinical Neurology and Neurosurgery (2010, in revision 2)
The clinical data in continuous variables of the craniectomy and craniotomy patients

<table>
<thead>
<tr>
<th></th>
<th>Craniectomy</th>
<th></th>
<th></th>
<th>Craniotomy</th>
<th></th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>48</td>
<td>38.6</td>
<td>16.9</td>
<td>36</td>
<td>43.7</td>
<td>20.4</td>
<td>0.253</td>
</tr>
<tr>
<td>Admission GCS</td>
<td>48</td>
<td>8.3</td>
<td>3.3</td>
<td>36</td>
<td>9.0</td>
<td>3.3</td>
<td>0.207</td>
</tr>
<tr>
<td>Pre-op GCS</td>
<td>48</td>
<td>6.6</td>
<td>1.9</td>
<td>36</td>
<td>7.2</td>
<td>1.2</td>
<td>0.012*</td>
</tr>
<tr>
<td>Pre-op midline shift</td>
<td>48</td>
<td>11.4</td>
<td>5.0</td>
<td>36</td>
<td>10.5</td>
<td>6.0</td>
<td>0.413</td>
</tr>
<tr>
<td>Post-op midline shift</td>
<td>39</td>
<td>6.2</td>
<td>5.4</td>
<td>26</td>
<td>4.8</td>
<td>5.0</td>
<td>0.339</td>
</tr>
<tr>
<td>ICP</td>
<td>48</td>
<td>20.0</td>
<td>17.2</td>
<td>36</td>
<td>9.3</td>
<td>8.9</td>
<td>0.001*</td>
</tr>
<tr>
<td>MAP</td>
<td>46</td>
<td>73.0</td>
<td>12.1</td>
<td>36</td>
<td>72.5</td>
<td>8.5</td>
<td>0.989</td>
</tr>
<tr>
<td>CPP</td>
<td>46</td>
<td>51.2</td>
<td>21.7</td>
<td>36</td>
<td>63.3</td>
<td>13.0</td>
<td>0.011*</td>
</tr>
<tr>
<td>CCPI</td>
<td>46</td>
<td>7.9</td>
<td>12.4</td>
<td>36</td>
<td>13.7</td>
<td>14.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>ISS</td>
<td>48</td>
<td>27.3</td>
<td>4.1</td>
<td>35</td>
<td>27.5</td>
<td>4.2</td>
<td>0.983</td>
</tr>
</tbody>
</table>
The clinical data in continuous variables of the craniectomy and craniotomy patients

<table>
<thead>
<tr>
<th></th>
<th>Craniectomy</th>
<th>Craniotomy</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>19 (39.6)</td>
<td>9 (25.0)</td>
<td>0.161</td>
</tr>
<tr>
<td>male</td>
<td>29 (60.4)</td>
<td>27 (75)</td>
<td></td>
</tr>
<tr>
<td>Pre-op Pupil reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>both reactive</td>
<td>19 (39.6)</td>
<td>23 (63.9)</td>
<td>0.013*</td>
</tr>
<tr>
<td>one fixed</td>
<td>10 (20.8)</td>
<td>9 (25)</td>
<td></td>
</tr>
<tr>
<td>both fixed</td>
<td>19 (39.6)</td>
<td>4 (8)</td>
<td></td>
</tr>
<tr>
<td>GOS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17 (35.4)</td>
<td>8 (22.2)</td>
<td>0.015*</td>
</tr>
<tr>
<td>2+3</td>
<td>14 (29.2)</td>
<td>4 (11.1)</td>
<td></td>
</tr>
<tr>
<td>4+5</td>
<td>17 (35.4)</td>
<td>24 (66.7)</td>
<td></td>
</tr>
</tbody>
</table>
Recent clinical studies following decompressive craniectomy in severe traumatic brain injury

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patient</th>
<th>Timing</th>
<th>Outcome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>GOS 4-5</td>
<td>GOS 2-3</td>
</tr>
<tr>
<td>Albanese</td>
<td>2003</td>
<td>27</td>
<td>Early</td>
<td>18.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13</td>
<td>Late</td>
<td>38.5</td>
</tr>
<tr>
<td>Ucar</td>
<td>2005</td>
<td>100</td>
<td>Early</td>
<td>14.0</td>
</tr>
<tr>
<td>Jiang</td>
<td>2005</td>
<td>486</td>
<td>Late</td>
<td>34.1</td>
</tr>
<tr>
<td>Woertgen</td>
<td>2006</td>
<td>59</td>
<td>Early</td>
<td>30.4</td>
</tr>
<tr>
<td>Skolglund</td>
<td>2006</td>
<td>19</td>
<td>Late</td>
<td>68.4</td>
</tr>
<tr>
<td>Aarabi</td>
<td>2006</td>
<td>17</td>
<td>Early</td>
<td>38.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26</td>
<td>Late</td>
<td>57.7</td>
</tr>
<tr>
<td>Olivecron</td>
<td>2007</td>
<td>27</td>
<td>Late</td>
<td>71</td>
</tr>
<tr>
<td>Present</td>
<td>2007</td>
<td>46</td>
<td>Early</td>
<td>37.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Late</td>
<td>100</td>
</tr>
</tbody>
</table>
The perioperative neurological status in decompressive craniectomy is more severe than those in craniotomy patients.

37.0% of patients with traumatic brain injury who underwent early DC had beneficial effect on favorable outcome.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cOR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>aOR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td><strong>Demographic and pre-op characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.05 (1.00-1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>1.15 (1.04-1.27)</td>
<td>0.006</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.76 (0.22-2.57)</td>
<td>0.653</td>
</tr>
<tr>
<td>Time elapse to operation</td>
<td>1.00 (1.00-1.00)</td>
<td>0.134</td>
</tr>
<tr>
<td>Pre-op pupil reaction</td>
<td>8.23 (2.15-31.45)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pre-op pupil reaction at least one fixed vs. both reactive</td>
<td>14.79 (1.30-168.04)</td>
<td>0.030</td>
</tr>
<tr>
<td>Pre-op pupil reaction at least one fixed vs. both reactive</td>
<td>0.50 (0.29-0.86)</td>
<td>0.013</td>
</tr>
<tr>
<td>At least one fixed vs. both reactive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISS</td>
<td>1.32 (0.98-1.79)</td>
<td>0.072</td>
</tr>
<tr>
<td>Admission GCS</td>
<td>0.77 (0.63-0.95)</td>
<td>0.013</td>
</tr>
<tr>
<td>Pre-op GCS</td>
<td>0.50 (0.29-0.86)</td>
<td>0.013</td>
</tr>
<tr>
<td>Pre-op GCS</td>
<td>0.30 (0.10-0.95)</td>
<td>0.040</td>
</tr>
<tr>
<td>Pre-op GCS</td>
<td>0.50 (0.29-0.86)</td>
<td>0.013</td>
</tr>
<tr>
<td>Pre-op GCS</td>
<td>0.30 (0.10-0.95)</td>
<td>0.040</td>
</tr>
<tr>
<td>ISM</td>
<td>1.19 (1.03-1.37)</td>
<td>0.020</td>
</tr>
<tr>
<td>Craniectomy size</td>
<td>1.00 (0.98-1.02)</td>
<td>0.960</td>
</tr>
<tr>
<td><strong>Nagelkerke R²</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Post-op characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICP</td>
<td>1.04 (1.00-1.09)</td>
<td>0.066</td>
</tr>
<tr>
<td>MAP</td>
<td>1.00 (0.95-1.05)</td>
<td>0.980</td>
</tr>
<tr>
<td>CPP</td>
<td>0.97 (0.94-1.00)</td>
<td>0.060</td>
</tr>
<tr>
<td>CCPI</td>
<td>1.04 (0.97-1.11)</td>
<td>0.326</td>
</tr>
<tr>
<td>Post-op midline shift</td>
<td>1.22 (1.04-1.45)</td>
<td>0.018</td>
</tr>
<tr>
<td>Post-op midline shift</td>
<td>1.22 (1.04-1.45)</td>
<td>0.018</td>
</tr>
<tr>
<td>Post-op infarction</td>
<td>3.08 (0.33-28.77)</td>
<td>0.324</td>
</tr>
<tr>
<td><strong>Nagelkerke R²</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Care - Quality - Initiative - Culture 關懷 - 質量 - 鼓勵 - 文化**
Basic study

*Selective brain cooling
Retrograde jugular vein flush

Brain temperature monitor
- Underestimate the ICT with Tr, Tt

Clinical study

Prognostic predictors in sTBI
- Decompressive Craniectomy

Early decompressive craniectomy
- 37.0% : favorable outcome

Prognostic factors in craniectomy patients

Early brain hyperthermia within 24 hours of admission was associated with worse Glasgow outcome scale

) Old age, unresponsive pupil reaction,
  lower pre-op GCS score, and
  higher post-op midline shift values are
  associated with poor outcomes in TBI patients who underwent decompressive craniectomy.

TBI → ROS → RNS → Attenuate → Apoptosis → Outcome

VEGF → Neurogenesis → Angiogenesis
未來可能有價值之治療方法

Brain temperature monitor

Craniectomy + Local cooling
Conclusion

We suggest that early regional brain cooling in certain patients who had previously undergone decompressive craniectomy could be a promising treatment in severe traumatic brain injury.
Thanks for your attention