Novel treatments for disorders of consciousness?

THIBAUT Aurore
PhD Candidate
Coma Science Group
Cyclotron Research Centre
University of Liège, Belgium

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Motor disorder: spasticity

- Exaggeration of myotatic reflex leading to an involuntary muscle contraction after muscle stretching or a permanent muscle contraction.

**Aggravating factors:** Velocity of stretching
Fatigue and stress

**Side effects:** Muscle retraction (sarcomeres)
Irreversible stiffness of joints
Vicious positions and pain

Physiopathology is complicated
No clear treatment guidelines yet

Thibaut et al, *Brain Injuy*, 2013
Spasticity in DOC

Assess spasticity (MAS*) in VS/UWS and MCS (n= 65)

- **88%** (n=57) showed spasticity
- **60%** (n=39) had severe spasticity (MAS≥3)

- **Time since insult**: positively correlated with MAS scores

- **Pain** (*Nociception Coma Scale Revised*) : positive correlation

* MAS=Modified Ashworth Scale

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Thibaut et al, *submitted*
Soft splints

- **AIM:** Test the efficacy of soft splints on spastic upper limb to reduce spasticity in chronic VS/UWS & MCS

- **Avantages:**
  - Easy to apply
  - Patient can be alone
  - Soft and confortable
  - Several hours/day

Thibaut et al, *submitted*
Soft splints

- **AIM:** Test the efficacy of soft splints on spastic upper limb to reduce spasticity in chronic VS/UWS & MCS (n=17)

- **Avantages:**
  - Easy to apply
  - Patient can be alone
  - Soft and confortable
  - Several hours/day

- **Clinical benefits:**
  - Spasticity decrease on fingers flexors
  - Increase of hand opening

Thibaut et al, *submitted*
## Current treatments

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Study (first author, year)</th>
<th>Number of patients and etiology</th>
<th>Diagnosis</th>
<th>Placebo control</th>
<th>Reported functional outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopaminergic agents</strong></td>
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<tr>
<td>Amantadine</td>
<td>Giacino (2012)</td>
<td>184 TBI</td>
<td>MCS/VS</td>
<td>Yes</td>
<td>Positive</td>
</tr>
<tr>
<td>Schnakers (2008)</td>
<td>1 anoxic</td>
<td></td>
<td>MCS</td>
<td>No</td>
<td>Positive</td>
</tr>
<tr>
<td>Patrick (2006)</td>
<td>10 TBI</td>
<td>Low responsive level</td>
<td></td>
<td>No</td>
<td>No effect</td>
</tr>
<tr>
<td>Hughes (2005)</td>
<td>123 TBI</td>
<td>Coma</td>
<td>NA</td>
<td>NA</td>
<td>No effect</td>
</tr>
<tr>
<td>Saniova (2004)</td>
<td>41 TBI</td>
<td>Persistent unconsciousness</td>
<td>NA</td>
<td>NA</td>
<td>Positive</td>
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<tr>
<td>Meythaler (2002)</td>
<td>35 TBI</td>
<td>MCS</td>
<td>Yes</td>
<td>Positive</td>
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<tr>
<td><strong>Benzodiazepine sedative</strong></td>
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<tr>
<td>Bromocriptine</td>
<td>Brahmi (2004)</td>
<td>4 intoxication</td>
<td>Coma</td>
<td>No</td>
<td>Positive</td>
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<tr>
<td>Levodopa</td>
<td>Matsuda (2003)</td>
<td>3 TBI</td>
<td>VS</td>
<td>NA</td>
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<tr>
<td><strong>Nonbenzodiazepine sedative</strong></td>
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<tr>
<td>Zolpidem</td>
<td>Cohen (2008)</td>
<td>1 anoxic</td>
<td>Lethargic</td>
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<tr>
<td>Shames (2008)</td>
<td>1 anoxic</td>
<td>MCS</td>
<td>NA</td>
<td></td>
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<tr>
<td>Singh (2008)</td>
<td>1 TBI</td>
<td>MCS</td>
<td>NA</td>
<td></td>
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<tr>
<td>Brefel-Courbon (2007)</td>
<td>1 hypoxic</td>
<td>Akinetic mutism</td>
<td>Y</td>
<td></td>
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</tr>
<tr>
<td>Clauss (2006)</td>
<td>2 TBI, 1 anoxic</td>
<td>VS</td>
<td>NA</td>
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<tr>
<td>Clauss (2000)</td>
<td>1 TBI</td>
<td>Semi-comatose</td>
<td>NA</td>
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<td><strong>GABA agonist</strong></td>
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<tr>
<td>Baclofen</td>
<td>Sara (2007)</td>
<td>1 non-TBI</td>
<td>VS</td>
<td>No</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Deep Brain Stimulation (DBS) Intralaminar nuclei stimulation induces “recovery” from MCS

Giacino et al, NEJM, 2012
Zolpidem

Effect of Zolpidem in chronic disorders of consciousness: a prospective open label study

60 patients (32 MCS, 35±15y, 18 wo, 37 TBI, 4±5.5 y post insult)

Open label study

• 12 patients improved but no diagnostic change
• 1 patient: MCS ➔ EXIT
  Placebo control: no effect anymore
• At the group level: no effect

Thonnard et al., *Functional Neurology*, 2014
# Why direct current?

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Population</th>
<th>Effects</th>
<th>Authors</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Hemiplegic patients</td>
<td>Dexterity and strength</td>
<td>Hummel et al. Lancet, 2006</td>
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<tr>
<td></td>
<td>Spastic patients</td>
<td>Spasticity &amp; ADL (activity of daily life)</td>
<td>Wu et al., Arch Phys Med Rehabil 2012</td>
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<td></td>
<td>Alzheimer’s patients</td>
<td>Memory</td>
<td>Ferrucci et al. Neurology, 2008</td>
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<td></td>
<td>Aphasic patients</td>
<td>Language</td>
<td>Baker et al. Stroke, 2010</td>
</tr>
</tbody>
</table>

- Cheap & easy to use

Thibaut et al, Rev Neurol, 2013
Methods

- Direct current
- 2 mA; 20 minutes
- Anode: PFDL (F3)
- Randomised, double blind, sham controlled

Thibaut et al, *Neurology, 2014*
Results

- 55 patients (16f, 43±18y)
- 25 VS/UWS, 30 MCS
- 25 TBI, 30 NTBI
- 20 subacute, 35 chronic (>3m)

Thibaut et al, Neurology, 2014

* p<0.001
15 responders
Patient who showed new signs of consciousness after tDCS and not before tDCS or before and after sham

- 2 UWS; acute
- 13 MCS (5>1y post insult) $\Rightarrow$ 43% of MCS

- 2 UWS $\Rightarrow$ MCS (acute)
- 2 MCS $\Rightarrow$ EXIT (acute)
Neurophysiology

Prefrontal stimulation
- Increase of DMN connectivity (rsfMRI)
- Increase of α rhythm (EEG)

Motor stimulation
- rCBF increase in the left M1, right prefrontal cortex, right S1 (PET-scan)
- Functional connectivity increased within premotor, motor and sensorimotor areas (EEG)

Keeser et al., J Neurosci, 2011
Lang et al., Eur J Neurosci, 2005
Polania, Nitsche and Paulus, HBM, 2010
Responders vs Non-responders: PET

Responders (n=8) vs non-responders (n=17)

- Left prefrontal cortex (stimulated area) and thalamus were more preserved in responders as compared to non-responders.
Motor tDCS

88% of patients with DOC are spastic. Spasticity (MAS) correlates with NCS-r (Thibaut et al, submitted)

How to decrease spasticity?

- Cathodal tDCS: C3/C4
- 1 mA – 20 minutes
- 2 sessions (real/sham)
- MAS and CRS-R before and after
- tDCS coupled with 8 electrodes EEG
- Record cortical activity before and after
Motor tDCS

15 chronic patients (7 MCS, 40±15y, 8wo, 7 TBI)

Results

- no significant differences
  - Spasticity (MAS)
  - CRS-R

EEG: analyses in progress

Cathodal tDCS decrease motor response?
Chronic patients with fixed joints?
Repeated tDCS

**Effects last ± 90 minutes** (Hummel et al., *Lancet*, 2006)
→ Short improvement, back to initial state

**Daily stimulations (5 days)** (Fregni et al., *Pain*, 2006)
Improvement and extension of benefits
Randomized sham controlled double blind study

* tDCS = 20 minutes
Repeated tDCS

Chronic MCS – N=21 (4 excluded)

† 10 responders (out of 17 patients)

* <0.025
Repeteado tDCS en pacientes crónicos en casa o residencia de ancianos (estudio multicéntrico)

Protocolo:
• tDCS sobre la corteza prefrontal dorsolateral, 2 mA, 20 min
• 5 días por semana durante 4 semanas (2 sesiones de tDCS – real & sham)
• Estimulaciones realizadas por la familia (video)
• Evaluación: CRS-R antes – después de 4 semanas – dos meses más tarde
• Estudio doble ciego y aleatorizado (2 meses de lavado)
• Pacientes crónicos MCS (> 1 año post insult) en casa/residencia de ancianos
Consciousness \approx \text{connectivity}

transcranial Direct Current Stimulation

amantadine

zolpidem

Deep brain stimulation
