Paraplegia Prevention by Oral Pretreatment with Memantine in a Rabbit Model


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Conflicts of interest:

• Dr Hiroshi Suzuki received some grant support from Daiichi Sankyo Co. Ltd. for measurement of serum memantine.

• Dr Takehito Yamamoto receives lecture fees from speaking at the invitation of Astellas Pharma Inc, Novartis Pharma, and Chugai Pharmaceutical Co. Ltd.
• Spinal cord injury (SCI): a devastating complication after TAAA repairs

• Combating SCI requires a multimodality approach including pharmacological approach
Background (2): NMDA receptor

Glycine

Glutamate

Memantine

Ischemic insult

Blocks only during its overactivation


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Objective

We evaluated the potential role of memantine for prevention of SCI following infrarenal aortic clamping in a rabbit model
Methods

• 30 NZW rabbits: 5 groups of 6 each

• Oral memantine pretreatment before surgery
  • Group 60-7 → 60mg OD for 7 days
  • Group 60-5 → 60mg OD for 5 days
  • Group 30-5 → 30mg OD for 5 days
  • Group 30-3 → 30mg OD for 3 days

• Group C → Control
• Paraplegic model:
  – Clamping of both aorta and IVC (infrarenal and proximal to bifurcations) for 45min

• Intraoperative monitoring: Vitals, motor evoked potentials (MEPs)

• Postoperative paraplegia evaluation: Modified Tarlov score at 6, 24, 48, and 72h
  – 0= no movement
  – 1= slight movement of lower limbs
  – 2= sits with support
  – 3= sits alone
  – 4= weak hop
  – 5= normal hop

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Methods contd…

• Serum memantine level:
  – Immediately after the surgery, 5ml blood sample centrifuged to obtain serum

  – Validated Liquid Chromatography-tandem Mass Spectrometry (LC-MS/MS) method

• Histopathology:
  – At 72h, Lumbar segments of spinal cords harvested → Hematoxylin & Eosin stain
Grading severity of ischemia

- Normal: none of the 4 quadrants showed evidence of ischemia
- Mild ischemia: only 1 quadrant ischemic
- Moderate ischemia: 2 quadrants ischemic
- Severe ischemia: 3 or all 4 quadrants ischemic
# Baseline and intraoperative variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 60-7</th>
<th>Group 60-5</th>
<th>Group 30-5</th>
<th>Group 30-3</th>
<th>Group C</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
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<tr>
<td>Body weight, mean±SD (kg)</td>
<td>3.2±0.1</td>
<td>3.2±0.2</td>
<td>3.2±0.1</td>
<td>3.1±0.2</td>
<td>3.2±0.2</td>
<td>0.617</td>
</tr>
<tr>
<td>Systolic BP, mean±SD (mmHg)</td>
<td>86±11</td>
<td>92±3</td>
<td>87±5</td>
<td>87±4</td>
<td>92±9</td>
<td>0.383</td>
</tr>
<tr>
<td>Heart rate, mean±SD (bpm)</td>
<td>158±13</td>
<td>159±11</td>
<td>163±10</td>
<td>170±29</td>
<td>151±9</td>
<td>0.372</td>
</tr>
<tr>
<td>Temperature, mean±SD (°C)</td>
<td>39.2±0.3</td>
<td>39.5±0.4</td>
<td>39.3±0.5</td>
<td>39.3±0.7</td>
<td>39.2±0.3</td>
<td>0.781</td>
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<tr>
<td><strong>Intraoperative characteristics</strong></td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Total operating time, mean±SD (min)</td>
<td>86±6</td>
<td>88±4</td>
<td>87±5</td>
<td>89±7</td>
<td>96±10</td>
<td>0.132</td>
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<tr>
<td>Systolic BP, mean±SD (mmHg)</td>
<td>67±17</td>
<td>78±8</td>
<td>78±5</td>
<td>69±15</td>
<td>74±9</td>
<td>0.391</td>
</tr>
<tr>
<td>Heart rate, mean±SD (bpm)</td>
<td>171±13</td>
<td>168±11</td>
<td>166±7</td>
<td>169±27</td>
<td>175±18</td>
<td>0.877</td>
</tr>
<tr>
<td>Temperature, mean±SD (°C)</td>
<td>37.7±0.4</td>
<td>38.4±0.5</td>
<td>38.1±0.7</td>
<td>37.9±0.5</td>
<td>38.4±0.4</td>
<td>0.108</td>
</tr>
</tbody>
</table>
Modified Tarlov score at 6, 24, 48, and 72h

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Motor Evoked Potentials

Loss of amplitude (%)

p=0.049

Reappearance of MEP, Yes (%)

p=0.073

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Serum memantine

\[ p = 0.421 \]

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Histopathology

Memantine group, H&E x20

Control group, H&E x20
Why memantine

• Favorable side effect profile

• Clinically approved for Rx of Alzheimer’s dementia

• Positive results on spinal protection by IV and intra-aortic injection (Ehrlich et al. JTCVS1999) → Disappeared from the literature for about a decade and half
Conclusions

- Oral memantine pretreatment was protective against spinal cord ischemia following aortic clamping in a rabbit model

- Spinal protection was achieved by 3-7 days of oral treatment, promising its potential clinical application
Thank you