Botulinum Toxin
Effects on the muscle & the patient

Steffen Berweck & A. Sebastian Schroeder

Specialist Centre Paediatric Neurology and Rehabilitation
Vogtareuth
Germany

Hauner Children’s Hospital
Ludwig-Maximilians-University Munich
Germany

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Functional repair of motor endplates after botulinum neurotoxin type A poisoning: Biphasic switch of synaptic activity between nerve sprouts and their parent terminals

ANTON DE PAIVA*†, FRÉDÉRIC A. MEUNIER*†, JORDI MOLGÓ‡, K. ROGER AOKI§, AND J. OLIVER DOLLY*¶

*Department of Biochemistry, Imperial College of Science, Technology, and Medicine, London SW7 2AY, United Kingdom; ‡Laboratoire de Neurobiologie Cellulaire et Moléculaire, Centre National de la Recherche Scientifique, Gif-sur-Yvette, 91198 Cedex, France; and §Allergan, 2525 Dupont Drive, Irvine, CA 92715

** Figures:**

- **Control vs BoNT/A**
- **Ratio integrated red:green intensities**

**Graphs:**

- **FM1-43 uptake ( Arbitrary Units)**
- **Time (days)**
- **Motor endplate in white, sprouts in black**
Overview

1. Ultrasound / CP Muscle
2. MRI / Histology Healthy Muscle
3. MRI / CP Muscle
4. Other indications
Variability of Muscle Size in CP

GMFCS I

GMFCS III
Ultrasound: BoNT & CP Muscle

Schroeder, Berweck, Heinen et al. 2006 Neuropediatrics
## Ultrasound: BoNT & CP Muscle

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unilateral CP</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>bilateral CP</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td><strong>Age (mean in months)</strong></td>
<td>69</td>
<td>54</td>
</tr>
<tr>
<td><strong>GMFCS Level (mean)</strong></td>
<td>1,8</td>
<td>2,2</td>
</tr>
<tr>
<td><strong>bodyweight (kg)</strong></td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td><strong>Dose/muscle (units/kg; mean)</strong></td>
<td>3,8</td>
<td>-</td>
</tr>
</tbody>
</table>
Ultrasound: 4-8 Weeks Follow-up

** minus 17%

** minus 21%
Ultrasound: 3-6 Months Follow-up

** after 4-8 weeks

** after 3-6 months
Overview

1. Ultrasound / CP Muscle

2. MRI / Histology Healthy Muscle

3. MRI / CP Muscle

4. Other indications
Paradigm

Participants:  Two healthy adults (47 & 31 years of age)
Injection site:  Lateral head of gastrocnemius muscle
Study design:  Double blinded regarding the sites of the verum and placebo
Dosage:  3 x 25 Units BoNT A (inco A), 2 ml/vial NaCl 0.9%  
Placebo | saline .9% contralateral GCL

Outcome:  MRI over time
           Histochemistry
MRI: BoNT & Healthy Muscle
12 Months Follow-up

Schroeder, Berweck, Heinen et al. 2009 MovDisord.
MRI: BoNT & Healthy Muscle
12 Months Follow-up
Fine structural analysis
Overview

1. Ultrasound / CP Muscle

2. MRI / Histology Healthy Muscle

3. MRI / CP Muscle

4. Other indications
9 year old boy

Unilateral right sided spastic CP

GMFCS Level I

Injection: 2x50 Units Botox

right soleus muscle

Schroeder, Berweck, Heinen et al. 2010 DevMedChildNeurol
Findings summary

1. focal neurogenic atrophy after BoNT/A-injection can be detected in healthy and CP muscle (ultrasound and MRI)

2. neurogenic atrophy corresponds to a high signal intensity pattern (MRI & histochemistry)

3. no inflammatory activity (light microscopy)

4. no significant fatty degeneration (MRI)
Overview

1. Ultrasound CP Muscle
2. MRI / Histology Healthy Muscle
3. MRI CP Muscle
4. Other indications
BoNT & Neurophysiology

Wohlfarth et al. 2007, Clin. Neuropharmacology

long-term up to 52 weeks

n = 2x26 healthy adults
EDB

4 weeks after injection

Wohlfarth et al. 2007, Clin. Neuropharmacology
Cosmesis

Procerus muscle
4 healthy adults
5x4 U onA (n=2)
saline solution (n=1)
no injection (n=1)

Koerte et al. 2012 Dermatologic Surgery, in press
Hypo-/Anhidrosis
onA/riB

Fig 1. Time course of both products. BOT, Botox and NBC-HA, Myobloc. The two-sided significance level was set to 5%. To assess the impact of gender, a mixed-effects model with the fixed factors log dose, gender and the random factor test individual was applied for each treatment group and anhidrosis separately. All analyses were performed with the statistics package R 2.10.1 (R Foundation, Vienna, Austria). The two-sided significance level was set to 5%. To assess the statistics package R 2.10.1 (R Foundation, Vienna, Austria). The two-sided significance level was set to 5%. To assess

Fig 2. Box plots showing effects on anhidrosis (left) and hypohidrosis (right) at week 3 for all injected doses and dilutions.
The gap between clinical effect and focal changes

Timecourse in months

Effect of BoNT

clinical effect

morphological effect

plasticity ?

muscle ?

central ?
Clinical implications: BoNT & Muscle

- The time course of neurogenic muscle atrophy and reinnervation following a single BoNT/A injection does not represent the clinical time-course we know from children with CP.

- The focal effect of BoNT/A should be taken into consideration when repeated BoNT/A injections into the same muscles are proposed?

Conclusion:
1. Follow the clinical need (?)
2. Injection within the same muscle, but at different injection sites (?)
3. Higher dilution (?)
4. Injection of other muscles relevant for the specific movement pattern within a patient (?)

5. Botulinum toxin is ONE therapeutic option for children with CP - combination with splinting, strengthening, and selective motor control training is neccessary
Thank you very much

Paediatric Neurology
Hauner Children’s Hospital, Munich, Germany:
Helene Auffermann
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Anita Laage Gaupp
Alexandra Sitzberger
Katharina Vill
Birgit Warken
Maren Jawad

Paediatric Neurology
Rehabilitations Centre, Vogtareuth:
Steffen Berweck
Christine Janssen

Clinic of Physical Medicine and Rehabilitation, Munich, Germany:
Josef Ilmberger
Cornelia Schlick

Integrated Center for Research and Treatment of Vertigo, Balance and Ocular Motor Disorders, IFB\textsuperscript{LMU}: Munich, Germany:
Verena Bruemmer
Klaus Jahn
Thyra Langhagen
Thomas Stephan

Dep. of Clinical Radiology, Munich, Germany:
Birgit Ertl-Wagner
Inga Koerte
Denise Steffinger

Bregenz, Austria:
Kurt Schlachter

Trondheim, Oslo, Norway:
Guro Andersen
Areej Elkamil
Torstein Vic

Perth, Australia:
Catherine Elliot
Siobhan Reid
Jane Valentine

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Katharine Alter
Siddhartha Sikdar