The Function Effect of Botulimun Toxin A (BtX-A) at the Calf Muscle in Lower Limb Lengthening

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INTRODUCTION

- **Major Concern in Human Distraction Osteogenesis**

- Distraction–induced muscle pain
- Use of analgesics
- Surrounding joint contractures
- Strenuous physiotherapy
- Surgical release
Human Studies of BtX-A on Spasticity

Post-stroke or Cerebral palsy

• The local injection of the BtX-A significantly reduced spasticity in lower limb muscles

Botulinum Toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial.

Kaji et al. J Neurol 2010;257:1330-1337

• Intramuscular BtX-A injections significantly reduced spasticity-related local pain

Management of Spasticity Associated Pain with Botulinum Toxin A

Animal Study of BtX-A in Distraction Osteogenesis

Effects of Botulinum Toxin A on Functional Outcome during Distraction Osteogenesis


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Fifteen tibia lengthening of New Zealand White rabbits (1.5mm/day, 20% lengthen gain)
v.s. Contra-lateral control group

• BtX-A injection at the gastrocnemius prior to DO decreased the amount of ankle equinus contracture

But, NO STUDY on human distraction osteogenesis
Pathogenetic mechanism

Limb Lengthening

- Inadequate adaptation of muscle, connective tissue, blood vessel, and nerve
- Strength imbalance between agonist and antagonist muscles

"Prophylactic Btx-A treatment may reduce muscle tension, spasm and pain" ??

- Stiffness of muscle and tendon
- Joint contracture
- Local pain
PURPOSE

To report the functional effect of botulimun toxin A (BtX-A) injection at the calf muscles in human tibial distraction osteogenesis

- A double blind prospective randomized study
HYPOTHESIS

- The **BtX-A local injection** at the calf muscle may...

  - **Decrease** Calf pain during distraction phase
  - **Increase** ROM of the knee and ankle joints
MATERIALS and METHODS

- **Patients selection**
  
  - 72 segments (36 patients)
  - Bilateral tibial lengthening
    - LON technique (20 segments)
    - LATN technique (52 segments)
  - Apr 2010 – Jan 2011 (min 2 years f.u.)

- **Inclusion criteria**
  - Familial short stature
  - Skeletally mature
  - No history of medical illness, fracture, soft tissue compromise, bony deformities or infection
  - Sufficient preop/follow-up radiographs

- **One leg**
  - INJECT ‘BtX-A’

- **The other leg**
  - INJECT ‘normal saline’
MATERIALS and METHODS

Random selection

One leg

INJECT ION

BtX-A 200 UNIT mixed with 20ml sterile normal saline

The other leg

INJECTION

Same amount of sterile NORMAL SALINE
MATERIALS and METHODS

**BOTOX® (Allergan, Inc.)**

Botulinum Toxin Type A
200 Unit (10 nanograms)
Mixed with 20cc sterile N/S

**Effect**
Acetylcholine release inhibitor
Neuromuscular blocking agent

**Maximum effect/Duration of effect**
6 weeks / 12 weeks (2-33 weeks)

**Dosage**
Recommendation: < 360 units in a 3 months interval
Lethal dose: 2700-3000 unit IV injection

However, safety and efficacy have not been established for distraction osteogenesis
MATERIALS and METHODS

- Demographics

<table>
<thead>
<tr>
<th></th>
<th>36 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tibia (segments)</td>
<td>72</td>
</tr>
<tr>
<td>Age at the time of 1\textsuperscript{st} stage surgery (years)</td>
<td>23 (16-35)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>72:10</td>
</tr>
<tr>
<td>BMI (kg/cm\textsuperscript{2})</td>
<td>22 (18-27)</td>
</tr>
<tr>
<td>Duration of follow up (months) (after the 1\textsuperscript{st} stage surgery)</td>
<td>29.5 (24.2-38.7)</td>
</tr>
</tbody>
</table>
**Surgical Protocol**

**BtX-A local injection**

- At the 6 spots at the gastrocnemius and soleus muscles
- Only for the randomly selected leg
- At the end of the index surgery
## Clinical Evaluations

<table>
<thead>
<tr>
<th>Clinical Evaluation</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Calf pain (VAS: 0-10 points)</td>
<td>BtX-A related adverse event</td>
</tr>
<tr>
<td>2. Range of motion (knee, ankle)</td>
<td>- Muscle weakness</td>
</tr>
<tr>
<td>3. Calf circumference (mm)</td>
<td>- Calf pain, myalgia</td>
</tr>
</tbody>
</table>

- **Double-blinded**

### Serial follow up
- Every 2 weeks during distraction phase
- Every 1 month thereafter until the end of consolidation phase
- Total 12 times follow up

### Side-to-side differences
- BtX-A - injected leg VS. Placebo-injected leg
RESULTS

- Radiographic results

<table>
<thead>
<tr>
<th>Variables</th>
<th>BtX-A legs</th>
<th>Placebo legs</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distraction rate (mm/days)</td>
<td>0.69 (0.50-0.96)</td>
<td>0.68 (0.51-0.97)</td>
<td>0.88</td>
</tr>
<tr>
<td>Final length gain (mm)</td>
<td>64 (45-81)</td>
<td>64 (43-81)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

No differences
Clinical result – Calf pain

Δ Pain VAS (Calf, 0-10 points)

Time series (POD#2wks ~ POD#48wks)

No differences
Clinical result – Knee range of motion

Δ Knee extension (degrees)

Δ Knee flexion (degrees)

Time series (POD#2wks ~ POD#48wks)

No differences
Clinical result – Ankle range of motion

No differences

Δ Ankle dorsi-flexion (degrees)

Δ Ankle plantar-flexion

Time series (POD#2wks ~ POD#48wks)
Clinical result – Calf circumferences

Δ Calf circumferences (mm)

No differences

Time series (Preop ~ POD#48wks)
Complications

No BtX-A related adverse event have been found
- Long term muscular weakness
- Calf pain, myalgia, muscle spasm
- Discomfort or pain at the injection site
- Dry mouth, tiredness, headache, nausea, etc.
Conclusion

The local injection of 200U BtX-A at one human calf muscle does **NOT** appear to **reduce calf pain nor help enhancing the ROM of the surrounding joints** during the tibial lengthening.

### BtX-A injected legs V.S. Placebo-injected legs

**No differences in…**

- Calf pain
- Range of motions (ankle, knee)
- Calf circumference
Conclusion

- Further studies on BtX-A would be needed with...

- Different dosages/dilutions
- Repeated injections
- More multi-level injections
- Various injection techniques
  (manual needle placement, US-guided injection, etc.)

Safety and Efficacy
Thank You for Your Attention