Role of Botulinum Toxin A as treatment for vulvodynia

Nina Bohm-Starke
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Disclosure: Campus Pharma, Ipsen
Background

Provoked vestibulodynia (PVD)

- Etiology – unknown, multifactorial?
- Life time prevalence 10-16%, during reproductive years.
- Significant impact on QoL and sexual health.
- Studies have shown that 90% of PVD patients have a dysfunction and increased tension/tonus/activity of the superficial pelvic floor muscles (PFM).
- It is thought that the PMF dysfunction is part of the mechanisms maintaining the pain, important to acknowledge during treatment.

Treatment of provoked vestibulodynia

Multimodal approach
- Pain management
- Psychosexual counseling
- Rehabilitation of pelvic floor function

Today, a more individualized treatment is possible!

Rehabilitation of the pelvic floor muscles

- Physiotherapy - various methods and techniques
- EMG biofeedback
- Botulinum toxin A (BTX-A)

sEMG guidance
Different formulations of BTX-A

Each of these neurotoxins is formulated differently, with unique characteristics, and these products are not interchangeable.
Indications for botulinum toxin A

Current FDA approved indications for BTX-A

- Neurological conditions: focal spasticity, blepharospasm, hemifacial spasm, cervical dystonia, chronic migraine
- Urinary bladder dysfunction: (neurogenic) overactive bladder
- Axillary hyperhidrosis

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989 (Dec)</td>
<td>FDA approval for strabismus, blepharospasm and hemifacial spasm (Botox® Medical)</td>
</tr>
<tr>
<td>2000 (Dec)</td>
<td>FDA approval for cervical dystonia (Botox® Medical)</td>
</tr>
<tr>
<td>2002 (Apr)</td>
<td>FDA approval for moderate/severe glabellar line ≤ 65 years (Botox® Cosmetic)</td>
</tr>
<tr>
<td>2004 (Jul)</td>
<td>FDA approves Botox® for axillary hyperhidrosis</td>
</tr>
<tr>
<td>2006 (Mar)</td>
<td>MHRA licence for Vistabel® (Allergan) for moderate/severe glabellar lines ≤ 65 years when psychological impact exists</td>
</tr>
<tr>
<td>2009 (Mar)</td>
<td>Licence as above for Azzalure® (Dysport)</td>
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<tr>
<td>2009 (Jul)</td>
<td>FDA approves Dysport®</td>
</tr>
<tr>
<td>2009 (Jul)</td>
<td>FDA approval for Xeomin®</td>
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<tr>
<td>2010 (Oct)</td>
<td>FDA approves Botox® for migraine</td>
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</table>
Of label use

- Cosmetics
- Anal spasm
- Vulvodynia
- Vaginismus
- Others...

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**BTX-A – mode of action**

- Reversible paralysis or weakness – the toxin is an endopeptidase which cleaves SNAP-25 and prevents release of acetylcholine and neurotransmitters from motor neurons.
- Lethal dose 0.09-0.015 µg iv, 0.7-0.9 µg inhale, 70 µg oral
- Approximately 3 months duration.

Simpson. Toxicon 2013
Jancovic. Mov Disord 2017

Possible nociceptive effect

- Nociceptive effect is unclear;
  - modulation and changes in surface expression of neurotransmitters and cytokines?
  - effect on other neurons, changes in pain sensitivity?
  - central effect via axonal transport?
  - reduction of neurogenic inflammation

Simpson. Toxicon 2013
Jancovic. Mov Disord 2017
Rational for using BTX-A for provoked vulvodynia

- To reduce the hypertonicity of the pelvic floor muscle and hamper the vaginismus reaction leading to less mucosal friction and pain during intercourse
- Possible effect on blood flow and ischemia in tensed muscles?
- Combine BTA-X with physiotherapy and other treatments
- We need studies!
## Published studies PVD

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>No of pat</th>
<th>Dose</th>
<th>Muscle</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dykstra et al 2006</td>
<td>Non-controlled</td>
<td>7</td>
<td>35 U 50 U</td>
<td>?</td>
<td>8.1-2.9, 30 d (effect 12w) 7.4-1.8, 30 d (effect 14w)</td>
</tr>
<tr>
<td>Bertolasi et al 2009</td>
<td>Non-controlled</td>
<td>39</td>
<td>20 U, Repeat inj</td>
<td>Levator ani EMG</td>
<td>Responders 63% Partial responders 15%</td>
</tr>
<tr>
<td>Damsted Petersen, 2009</td>
<td>RCT, double blinded</td>
<td>64</td>
<td>20 U Single inj</td>
<td>M Bulbocavernosus EMG</td>
<td>Both groups improved significantly on VAS 6 m</td>
</tr>
<tr>
<td>Pelletier et al 2011</td>
<td>Non-controlled</td>
<td>20</td>
<td>100 U Single inj</td>
<td>M Bulbospongiosus EMG</td>
<td>VAS 8.4-3.9, p&lt;0.001, 3 m</td>
</tr>
<tr>
<td>Pelletier et al 2016</td>
<td>Non-controlled</td>
<td>19</td>
<td>100 U Single inj</td>
<td>M Bulbospongiosus EMG</td>
<td>VAS reduction, p&lt;0.0001, 24 m</td>
</tr>
<tr>
<td>Nesbitt-Hawes 2013 Pelvic pain</td>
<td>Non-controlled</td>
<td>37</td>
<td>100 U Single or repeated inj</td>
<td>Mm puborectalis and pubococcygeous</td>
<td>VAS 54-30 (70%), 26 w VAS 51-23, (30%)</td>
</tr>
<tr>
<td>Morrisey 2015 Pelvic pain</td>
<td>Non-controlled</td>
<td>21</td>
<td>Up to 300 U</td>
<td>Spastic pelvic floor muscles? EMG</td>
<td>7.8-5.4, p&lt;0.01, 24 m</td>
</tr>
</tbody>
</table>
Studies on vaginismus

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>No of pat</th>
<th>Dose</th>
<th>Muscle</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brin, Vapnek 1997</td>
<td>Case report</td>
<td>1</td>
<td>10 + 40 U</td>
<td>Anterior vaginal wall</td>
<td>Intercourse possible after 2 injections</td>
</tr>
<tr>
<td>Shafik, El-Sibai 2000</td>
<td>Controlled but not blinded</td>
<td>8</td>
<td>25 U</td>
<td>M Bulbospongiosus</td>
<td>BT patients al improved, but not NaCl</td>
</tr>
<tr>
<td>Ghazizade, Nikzad, 2004</td>
<td>Non-controlled</td>
<td>24</td>
<td>150-400 U</td>
<td>Levator ani</td>
<td>75% Intercourse after first injection. No recurrence 24 m</td>
</tr>
<tr>
<td>Abbott et al. 2006</td>
<td>RCT, double blinded</td>
<td>60</td>
<td>80U</td>
<td>M puborrectalis M pubococcygeus</td>
<td>VAS 66-12. p&lt;.001 Cm H$_2$O 49-32, p&lt;.001</td>
</tr>
</tbody>
</table>
Current study at Danderyd Hospital

- RCT of 90 patients with PVD, 45 BTX-A and 45 placebo
- 50 Allergan U, 2 treatments, 3 months interval
- Injection of m bulbocavernosus using EMG guidance
- Primary outcome VAS (0-100) dyspareunia at 6 months
- Secondary outcome: reduction in PFM tone (vaginal manometer), QoL, FSFI/FSDS, anxiety and depression
Questions needed to be answered?

- What doses should be used?
- How many treatments is sufficient?
- What muscles to inject?
- Possible adverse events?
- How should we select vulvodynia patients suitable for BTX-A
What doses to use and how to inject?

- Published studies using 20–100 U onabotulinum toxin A (Botox®) have not reported any serious adverse events.
- EMG guidance or not – more concentrated formulas can be used= less volume= less pain
- Multiple injection sites – spread of the toxin, better effect?
- Intravaginally – through the vestibule
- Via the vestibule or perineum
M bulbocavernosus

- Easy to palpate when hypertone
- Easy to inject
- M transversus perinei?
Mm pubooccygeus/puborectalis?

- More lateral
- More difficult to inject?
Possible adverse event

- Painful!
- Serious adverse events are rare – spread of toxin?
- Concern about incontinence!
- Dose related
- Flu-like symptoms
- Allergic reactions
Who will benefit from BTX-A?

- We need studies to clarify which vulvodynia patients that might improve by BTX-A
  - only those with muscular component?
  - less effect with mucosal component?
  - combine with physiotherapy?
  - combine with other treatments?
Conclusions and concerns

- Botulinum toxin A will probably have a role in the treatment of provoked vestibulodynia
- Will all patients benefit or just those with hypertonicity/dysfunction of the pelvic floor muscles?
- Should we inject more muscles than we have done so far?
- Doses will probably be safe up to 100 Allergan Units, could we go higher??
- So far only off label use - FDA approval in the future?