Intracavernosal Injection of Botulinum Toxin Type A in the Treatment of Vascular Erectile Dysfunction: A pilot study

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Disclosures

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Rationale

- Evidence has been arising suggesting that Botulinum toxin type A (BTX-A) injections, through relaxation of smooth muscles fibers, can be used in the treatment of: Detrusor muscle over-activity; premature ejaculation; vaginismus and post-coital dyspareunia; as well as aesthetic issues of the penis and scrotum.

- BTX-A has not been shown to have vasodilator or vasoconstrictive properties.

- BTX-A blocks the release of neurotransmitters from autonomic and somatic nerve endings at presynaptic level causing neuromuscular blockade.


Objective

- To evaluate the safety and efficacy of Botulinum toxin A in the treatment of severe vasculogenic erectile dysfunction (ED), not responding to PDE5i or Intra-cavernosal injection therapy (ICI) by inducing smooth muscle relaxation.
Concerns

- Systemic Toxicity
- Priapism
Animal safety study 20 (200 gm white rats)
Sinusoidal diameter in rats after BTX-A

The average diameter of blood vessels was significantly enlarged in rats that received BTX-A IC. Average diameter in the control group was (13.32±2.8), in Group 1 (26.2±6.5), and in Group 2 (22.57±5.97); P < 0.05 (P=0.000027 for group 1 and 0.0003 for group 2).
Introduction: Botulinum Toxin type A (BTX-A) has been suggested to relax smooth muscles in various indications including detrusor muscle hyperactivity and obesity treatment. Penile erection depends mainly on cavernosal smooth muscle relaxation. Studies are underway to assess a possible role for intracavernosal injection (IC) of BTX-A in improving erectile function, through cavernosal smooth muscle relaxation. Histologic effects of IC injection of BTX-A need to be studied in an animal model.

Aim: The aim of this work is to study the histological effects and safety of intracavernous injection (IC) of BTX-A in an animal model.

Methods: 20 white rats (200 gm) were included in this study. Group 1 (10 rats) received IC 1 unit of BTX-A, Group 2 (5 rats) received 2 units, and Group 3 (control, 5 rats) received an equivalent volume of normal saline. The rats were observed for any clinical local or systemic adverse effects (penile changes, respiratory changes). After 1 month the rats were sacrificed and cavernosal tissue was subjected to histological examination using H&E and Masson trichrome stain. Assessment of the data was obtained using Leica Qwin 500 image analyzer computer system (England). Area % of C.T. in all groups was measured using an objective lens of magnification 10. Four fields were measured for each specimen and the average was recorded. Diameter of blood vessels was calculated in X20 power fields. Four fields were randomly selected for each specimen and the average diameter of blood vessels was recorded.

Quantitative data were summarized as means and standard deviations and compared using Student’s T test on Microsoft excel 2010 software. Results were considered significant when probability (p) < 0.05.

Results: No clinical local or systemic adverse effects were noted from the IC BTX-A injection.

Blood vessel diameter: The average diameter of blood vessels was significantly enlarged in rats that received BTX-A IC. Average diameter in the control group was (13.32±2.8), in Group 1 (26.2±6.5). and in Group 2 (22.57±5.97); P < 0.05 (P=0.000027 for group 1 and 0.0003 for group 2).

Conclusions: IC injection of BTX-A resulted in statistically significant increase in intracavernous vascular diameter. This might potentially assist in the treatment of erectile dysfunction. However, the small group size didn’t allow us to draw conclusions regarding change in collagen content. No clinical or histological adverse effects were noted.
Patients & Methods

- Ethics committee approval
- Informed consent
Patients & Methods

- Prospective
- Single-blind randomized pilot study
- 24 patients refractory vascular ED
Patients & Methods

Inclusion criteria:
- Male patients between 40 and 70 years.
- Vascular ED proved by penile duplex.
- Unable to develop erections sufficient for intercourse.
- A "No" response on Sexual encounter profile questions (SEP 2 & 3)
- Failing to respond to PDE5i’s and ICI therapy with penile implant surgery as the only remaining treatment option.

Exclusion criteria:
- Significant cardiovascular disease interfering with sexual activity
**Patients & Methods**

Penile duplex with a **trimix** solution (PGE1 10 ug + Phentolamine 1 mg + Papaverine 30 mg)

**Treatment Group**
- 12 patients
- ICI of BTX-A 50 units

**Control Group**
- 12 patients
- ICI 1 ml saline

**Daily Sildenafil 100mg**
Intra-cavernosal BTX-A injection

- A rubber band is placed on the base of the penis.
- 50 units BTX-A diluted in 1ml saline
- 25 units BTX-A is injected laterally, in each corpus.
- 2 min direct pressure
- The rubber band is cut after 25 minutes.
Patients & Methods

**Baseline & 2 weeks & 2 months after treatment**
- Penile color Doppler exam

**Baseline & 4 weeks after treatment**
- SHIM
- Erection hardness score (EHS)
- SEP
- Global assessment question (GAQ)*

*GAQ not done at baseline*
# Results

<table>
<thead>
<tr>
<th></th>
<th>Treatment group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td><strong>PSV Rt</strong></td>
<td>25.553</td>
<td>34.985</td>
</tr>
<tr>
<td><strong>PSV Lt</strong></td>
<td>22.637</td>
<td>35.012</td>
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<td><strong>EDV Rt</strong></td>
<td>4.102</td>
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<td><strong>EDV Lt</strong></td>
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<td>5.913</td>
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<tr>
<td><strong>RI</strong></td>
<td>0.71</td>
<td>0.82</td>
</tr>
</tbody>
</table>
Results

![Graph showing mean PSV over time](image)
Results

![Graph showing the Mean RI over time with a trend line from Baseline to 2 weeks]
Results

- Mean SHIM Treatment Group
- Mean SHIM Control Group
- Mean EHS Treatment Group
- Mean EHS Control Group

Before Treatment
After Treatment

Graph showing comparisons between different groups.
Sexual Encounter Profile

Patients who answered Yes after treatment

- SEP Q-2
- SEP Q-3

Treatment (n=12)
Control (n=12)
Global Assessment Question (GAQ)

Patients who answered Yes after treatment
Adverse Events

- No systemic side effects

- 1 case of prolonged erection, in the treatment group, during the post-treatment penile colour Doppler study with the trimix injection which resolved after 2.5 hours with an intra-cavernosal injection of ephedrine.
Conclusion

The results suggest a possible benefit of intra-cavernosal BTX-A in the treatment of patients with severe refractory ED and may lead to a reduction in the number of patients requiring penile implant surgery.
Further Research

- Highly-powered, double-blind RCTs to assess the true therapeutic efficacy in various populations of ED (e.g. milder forms/other types).
- Optimum dose for ED; number and distance of injection points; duration of effects.
- Is the mechanism of action in ED mediated through the classic effect on smooth muscles or is there perhaps a novel role that needs to be further explored?