

Faculty of Medicine, Cairo University Postgraduate Research Program Template

1. Proposed Study Title

Safety and efficacy of intra-cavernosal Botulinum toxin injection as an alternative line of treatment in patients with erectile dysfunction.

Degree: M.D

2.Candidate Name

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<p>2. Background and Rationale</p> <p>For over 4 decades BTX has been used to treat multiple neurologic disorders, such as blepharospasm, strabismus, focal dystonias, muscle spasms and spasticity, axillary hyperhidrosis, migraines and achalasia. It has been also used off-label to treat overactive bladder and urinary incontinence. BTX is a popular treatment for facial wrinkles in both FDA-approved (Glabella) and off-label (crow's feet, transverse forehead lines, lower face, and neck) indications (1,2).</p> <p>It has also been used recently to relieve a retracted penis (3).</p> <p>Botulinum toxin (BTX) is produced by the gram-positive anaerobic bacterium <i>Clostridium botulinum</i> and is considered among the most potent biologic neurotoxins. Its main mechanism of action is the strong inhibition of acetylcholine (Ach) release at the pre-synaptic cholinergic junction (2). BTX can also affect the autonomic nervous system through its high selectivity for cholinergic synapses which results in targeted blockade of cholinergic transmission, inducing strong relaxation (or may be even paralysis) of striated muscles (4). It has been also reported that BTX may also affect afferent nervous transmission via the inhibition of acetylcholine, adenosine tri-phosphate (ATP), glutamate, nerve growth factor and substance P, and a reduction in the axonal expression of nerve capsaicin and purinergic (P2X) receptors (5).</p> <p>Medical treatment of erectile dysfunction (ED), at its very core, attempts to induce erections by relaxing the smooth muscles of the corpora cavernosa and the lining small blood vessels.</p> <p>The study hypothesis: Evidence has been arising that Botulinum toxin injections can relax smooth muscles fibers in the treatment of obesity and hyperactive bladder. Would a similar effect on cavernosal smooth muscles help in the treatment of erectile dysfunction thus avoiding risks of repeated intra-cavernosal injections with vaso-active substances (e.g. Priapism and penile fibrosis) and surgical treatment options.</p>	
<p>3. Objectives</p> <p>To evaluate the safety and efficacy of intra-cavernosal Botulinum toxin injection as an alternative line of treatment in patients with erectile dysfunction - not responding to oral PDE5i - through cavernosal smooth muscle relaxation.</p>	
<p>4. Study Design</p> <p>Prospective, randomized double blind placebo control (RDBPC) study.</p>	
<p>5. Ethical committee approval</p>	

Yes

6. Study Methods

Population of study & disease condition

- Married male patients with erectile dysfunction

Inclusion criteria:

- Male patients will be included in the study recruited from Andrology, Sexology & STI's outpatient clinic, Kasr El Aini Hospitals, Cairo University, complaining of ED - not responding to oral PDE5i.
- Unable to develop erections sufficient for intercourse.
- A "No" response on Sexual encounter profile questions (SEP 2 & 3).

Exclusion criteria:

- Single patients.
- Any medical condition in which sexual activity is not advised.
- Any preexisting motor neuron disease (e.g myasthenia gravis).
- Neuropathies.
- Psychological disorders.
- History of reaction to toxin or albumin.
- Infection at the site of injection.
- Patients on aminoglycosides (may increase effect of botulinum toxin), penicillamine, quinine, chloroquine and hydroxychloroquine (may reduce its effect), calcium channel blockers, and blood thinning agents e.g. warfarin or aspirin (may result in bruising)

Methodology in details

Male patients complaining of ED - not responding to oral PDE5i - will be included in the study. All will be subjected for full history taking including assessment of intra-vaginal latency time, general and genital examination including measuring of the visible penile length at its flaccid state from the skin of the suprapubic area to the tip of penis, then stretched flaccid penile length and erected penile length from the pubic bone to the tip of the glans penis, at last penile girth at the mid shaft of the penis will be measured. Penile duplex with a trimix solution (20 ug alprostadil + 1 mg phentolamine + 30 mg papaverine) will be performed to assess erectile function. The patients will be randomized into a treatment group (35 patients) and a control group (35 patients).

All patients will sign an informed consent. A rubber band will be applied to the base of the penis. The skin will be prepped with alcohol swabs followed by intra cavernous injection of the treatment group by 100 units of BTX-A and intra-cavernous injection only with 1 ml saline

in the control group. Direct pressure will be applied for 2 minutes. The rubber band will be removed after 15 minutes.

Patients will be asked to resume their sexual activity using PDE5i on demand 2 weeks after intra-cavernous injection with BTX-A in the treatment group and saline in the control group. Assessment and follow up will be performed 2, 6 and 12 weeks after intra-cavernous injection with BTX-A in the treatment group and saline in the control group including measuring of the visible **penile length** at its flaccid state from the skin of the suprapubic area to the tip of penis, then stretched flaccid penile length and erected penile length from the pubic bone to the tip of the glans penis, **penile girth** at the mid shaft of the penis, assesment of **erectile function** using SEP2 & SEP3 questions, the global assessment question and SHIM questionnaire. Penile duplex with a trimix solution (20 ug alprostadil + 1 mg phentolamine + 30 mg papaverine) will be performed to assess erectile function 2 weeks after intra-cavernous injection with BTX-A in the treatment group and saline in the control group. Intra-vaginal latency time (**IVLT**) will be assessed in each patient 2, 6 and 12 weeks after intra-cavernous injection with BTX-A in the treatment group and saline in the control group. The rational for selecting the minimum 2-weeks waiting period is to give a chance for the BTX-A to reach its maximum effect.

Possible Risks

- Redness, pain and prolonged erections.
- Priapism.
- Possible injection site reactions (e.g. infection, fibrosis, bleeding, bruising or hematoma formation).
- Possible uncommon side effects of BTX-A (e.g. allergic reactions, rash, itching, headache, nausea, diarrhoea, stomach pain, loss of appetite, generalised weakness, muscle weakness, fever, cough, runny nose, flu symptoms, dizziness, drowsiness, anxiety, urinary tract infections, burning/painful urination, or difficulty urinating).

Primary outcomes

1. Comparison of Penile hemodynamics and response to ICI before and 2 weeks after BTX-A injection in the treatment group and saline injection in the control group.
2. Comparison of the SHIM score, SEP2 & SEP 3 questions, and the global assessment question before, 2, 6 and 12 weeks after BTX-A injection in the treatment group and saline injection in the control group.

Secondary outcomes

1. Comparison of penile size before, 2, 6 and 12 weeks after BTX-A injection in the treatment group and saline injection in the control group.
2. Comparison of intra-vaginal latency time (IVLT) before, 2, 6 and 12 weeks after BTX-A injection in the treatment group and saline injection in the control group.

Sample size (number of participants included)

- 70 male patients will be included in the study recruited from Andrology, sexology & STI's outpatient clinic, Faculty of medicine, Kasr al ainy hospitals, Cairo University.

Source of funding

- Sponsorships via investigators.

7. List of correlatives studies

1. Smaldone MC, Ristau BT, Leng WW. Botulinum toxin therapy for neurogenic detrusor overactivity. *UrolClin North Am.* 2010 Nov;37(4):567-80. doi: 10.1016/j.ucl.2010.06.001.
2. Carruthers JD, Carruthers A. The use of botulinum toxin type A in the upper face. *Facial PlastSurgClin North Am.* 2006;14(3):253-260.
3. Shaeer O, Shaeer K, Shaeer A. Botulinum toxin a (Botox) for relieving penile retraction. *J Sex Med.* 2009 Oct;6(10):2788-94.
4. Cavallini M, Cirillo P, Fundarò SP, et al. Safety of botulinum toxin A in aesthetic treatments: a systematic review of clinical studies. *Dermatol Surg.* 2014;40 (5):525-536.
5. Blasi J, Chapman ER, Link E, et al. Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25. *Nature.* 1993;365(6442):160-163
6. Sunil SM, Babu BG, Deepthi S, Veerabhadrappe AC, Vadavadagi SV, Punde P Botulinum toxin for the treatment of hyperfunctional lines of the forehead. *JIntSocPrev Community Dent.* 2015 Jul-Aug;5(4):276-82
7. Shamloul R, Ghanem H. Erectile dysfunction. *Lancet.* 2013 Jan12;381(9861):153-65
8. Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. *UrolClin North Am.* 2005 Nov;32(4):379-95
9. Small R. Botulinum toxin injection for facial wrinkles. *Am Fam Physician.* 2014Aug 1;90(3):168-75

8. Time plan (when to start/ when expected to finish/ when to publish)

- To start: Feb 2017
- To finish: Feb 2018