

BEST IN CATEGORY PRIZE: MALE SEXUAL DYSFUNCTION

INTRACAVERNOSAL INJECTION OF BOTULINUM TOXIN IN THE TREATMENT OF ERECTILE DYSFUNCTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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HYPOTHESIS / AIMS OF STUDY

Erectile dysfunction affects a large proportion of mainly the aging male population. In the era of minimally invasive medicine, a novel treatment strategy emerges necessary to avoid morbid and irreversible surgeries. The aim of this review is to evaluate the role of botulinum toxin in treating erectile dysfunction.

STUDY DESIGN, MATERIALS AND METHODS

This study was based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. The study protocol on the part of human studies was registered on PROSPERO (CRD42021283751). A systematic review of literature of PubMed, Embase and Medline databases was conducted, in order to identify studies investigating the role of botulinum toxin to treat erectile dysfunction, published in English, from January 1990 through July 31, 2021. Evidence included human and animal data.

The study design was established according to the Population, Intervention, Comparator, Outcome, Studies (PICOS) process. Population: Patients with erectile dysfunction. Intervention: Intracavernosal injection of botulinum toxin. Comparator: Standard-of-care or other techniques. Outcomes: improvement of sexual function, improvement in erectile function. Studies: Case series, retrospective/prospective cohorts, comparative studies and randomized controlled trials (RCT) were included. Reviews, case reports, non-English language articles, congress abstracts, letters to editor, and editorial comments were excluded.

A meta-analysis was performed on three outcomes included commonly in at least two studies. Among the different parameters assessed were, Erection Hardness Score (EHS), Peak Systolic Velocity in cavernosal artery (PSV) and the Sexual Health Inventory for Men (SHIM) score.

RESULTS

Seven studies in total were included in our review including two pre-clinical studies. Table 1 summarizes the studies included. Figure 1 represent the respective meta-analysis done regarding EHS, PSV and SHIM. The Cochrane bias risk assessment was performed for the 3 studies from which data were extracted. A clear benefit was noted for intracavernosal injection (ICI) of botulinum toxin (BoNT-A) on PSV (Figure 1) with a HR of 10.82 [4.99, 16.65] and a heterogeneity of $I^2 = 61\%$. EHS results favored BoNT-A as well over placebo with a HR of 0.7 [0.47, 0.93] and a heterogeneity of $I^2 = 94\%$. As for SHIM score, with a heterogeneity of $I^2 = 85\%$, no statistically significant difference was found (HR 0.58 [-0.03, 1.20]) (Figure 1).

INTERPRETATION OF RESULTS

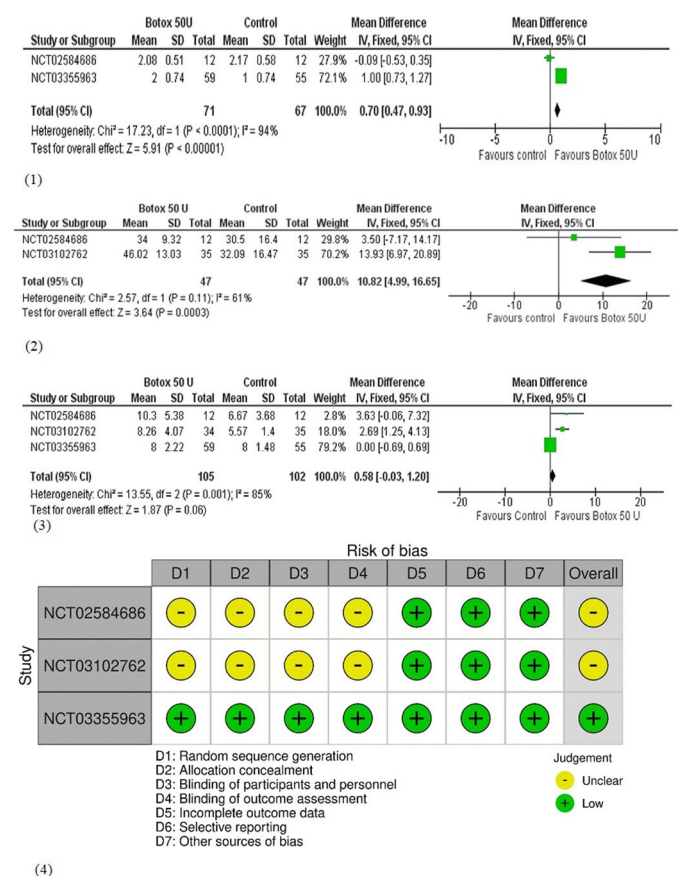
The rationale for using ICI of BoNT-A arises from its mechanism of action. One of the physiological hypotheses of its mode of action is that BoNT-A disables the exocytotic activity of presynaptic neurons by inhibiting neurotransmitter containing vesicles to fuse at the level of the synapse hence decreasing the influx of norepinephrine (NE) inhibiting the contraction of the cavernosal muscle cells. In addition to its effect on inhibiting NE release, BoNT-A increases the generation of nitric oxide (NO) by blocking the release of Acetylcholine (ACh) from cholinergic neurons which inhibits NO synthase [1]. The interplay of these effects results in a clinically inhibited cavernosal smooth muscle tone hence a more satisfactory blood flow is attained. This is the first systematic review to include 2 pre-clinical and 5 clinical studies results with a meta-analysis performed on 3 primary outcomes showing an efficacy of ICI of BoNT-A compared to other strategies on 2 of the 3 identified criteria, in particular EHS and PSV. There is, however, a narrative review in the literature from 2020 that supports the use of BoNT-A in male sexual pathologies extending to primary ejaculation, Peyronie's disease, and penile retraction [2].

The studies included in our review did not adapt a single treatment strategy, each studied different parameters and questionnaires during the study to objectify improvement in erectile dysfunction, there were different doses, serotypes and regimen of botulinum toxin as depicted in Table 1. However, the meta-analysis was done on the three similar trials adopting resembling regimens, and there was a significant benefit in PSV and EHS.

CONCLUDING MESSAGE

ICI of BoNT-A showed promising results in the first animal trials, these results were reproducible in the first human trials as well. BoNT-A may find its place in the therapeutic arsenal for the treatment of ED. Nonetheless, further studies and human trials are required to confirm the efficacy and durability of this novel treatment and bring forward more evidence.

FIGURE 1



(1) Forest plot assessing Erection Hardness score (EHS) (2) Forest plot assessing mean Peak Systolic Velocity (PSV) in the cavernosal arteries (3) Forest plot assessing the Sexual Health Inventory for Men (SHIM) (4) Graphical representation of the Cochrane

FIGURE 2

First author	Year of publication	Type of study	Participants (n)	Study design	Botulinum toxin dosage	Side effects	Efficacy
Young et al.	2017	Animal study	10 male rats	BoNT-A group vs. Control group	10 U	No side effects	*Significantly higher intracavernosal pressure (<= better erectile function) *Larger sinusoidal volumes but not statistically significant
Ghanem et al.	2017	Animal study	30 male rats	1 U of BoNT-A vs. 2 U of BoNT-A vs. control	Group receiving 1U Group receiving 2 U	No side effects	Significantly larger sinusoidal volume
Giuliano et al.	2019	Retrospective case series	47 male patients	One retrospective arm, abobotulinumtoxin molecule used as add-on therapy	250 U, then 500 U when the 250 U are ineffective	Local transitory pain on injection (2 patients)	* Total response rate 54% * IEF significant improvement by 4.7 for 250 U of abobotNT-A and by 5.6 for 500 U of abobotNT-A
Taleb et al.	2019	Prospective comparative study	45 male patients	100 U of BoNT-A vs. 50 U of BoNT-A vs. control stand-alone therapy	Group receiving 100 U Group receiving 50 U	Local transitory pain on injection	* Significant subjective improvement of IEF, EHS, SEP, GAS * Significant objective improvement on penile Doppler ultrasound * Improvement observed after 2 weeks and 3 months, but not durable to 6 months in some patients
El-Shaar et al. (NCT0355963)	2021	Randomized double-blinded placebo controlled trial	176 male patients	100 U of BoNT-A vs. 50 U of BoNT-A vs. control stand-alone therapy	Group receiving 100 U Group receiving 50 U	One hematoma One pain on injection site Four prolonged sustained erection successfully managed One priapism managed successfully No systemic toxicity	* Significant subjective improvement of IEF, EHS, SEP, GAS * Significant objective improvement on penile Doppler ultrasound * 40% response to treatment and successful sexual intercourse * Efficacy more durable at 6 months with 100 U of BoNT-A than 50 U
Ghanem et al. (NCT02584686)	Unpublished	Phase I randomized controlled trial	24 male patients	BoNT-A group vs. control group stand-alone therapy	50 U	No side effects	* Significant PSV improvement * Significant subjective improvement of EHS, SHIM, GAS * No difference for the SEP score
Ghanem et al. (NCT03102762)	Unpublished	Phase II randomized double-blinded placebo controlled trial	70 male patients	BoNT-A group vs. control group stand-alone therapy	100 U	No side effects	* PSV improvement trend * SHIM improvement trend * No effect on penile size or IELT

BoNT-A: botulinum toxin A; IEF: international index of erectile function; abobotNT-A: abobotulinum toxin A; EHS: erection hardness scale; SEP: sexual encounter profile; GAS: global assessment score; PSV: peak systolic velocity; SHIM: sexual health inventory for men; IELT: intravaginal latency time

Table summarizing all the studies included

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1. Giuliano F, Brock G. Botox for Erectile Dysfunction. The Journal of Sexual Medicine. 2017;14
2. Reddy AG, Dick BP, Natale C, Akula KP, Yousif A, Hellstrom WJG. Application of Botulinum Neurotoxin in Male Sexual Dysfunction: Where Are We Now? Sexual Medicine Reviews. 2021;9

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