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Intra-cavernous injection of BOTOX® (50 and 100 Units) for treatment of vasculogenic erectile dysfunction: Randomized controlled trial

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Abstract

Background: Erectile dysfunction (ED) is a socioeconomic problem.There are several options for its management including intra-cavernosal injection (ICI).

Objective: To compare the safety, efficacy, and durability of ICI of onabotulinum toxin-A (BTX) in different doses (50 and 100 U) against placebo (saline) in the management of vasculogenic ED non-responding to pharmacological therapy (phosphodiesterase type 5 inhibitors or/and ICI of trimix).

Materials and Methods: A prospective randomized double-blind placebo-controlled trial was conducted between July 2016 and February 2019. A total of 176 patients were randomly assigned (1:1:1) to one of the treatment sequences: Botox 100 U group (BTX-100; 62 patients), Botox 50 U group (BTX-50; 59 patients), or placebo group (55 patients). All patients were followed up for 6 months.

Results: Significant improvement in all parameters, that is, SHIM score & Erection Hardness Score (EHS), Sexual Encounter Profile (SEP), Global Assessment Score (GAS), and Doppler parameters ($p < 0.001$) was observed in patients of BTX-100 and BTX-50 groups with maximum improvement at 3rd month of treatment. Around 40% of patients were responders and were able to engage in sexual intercourse. Patients in placebo group did not experience significant improvement ($p = 0.264$). It was noted that at the 2nd week and 3rd months after treatment, there was no statistically significant difference in the improvement of these parameters in BTX-100 and BTX-50 groups ($p > 0.05$). In the 6th month, there was a statistically significant difference between the aforementioned groups in favor of BTX-100 ($p < 0.01$).

Conclusions: Only one-time ICI of BTX (50 U and 100 U) is effective and safe for the treatment of refractory ED. This agent has a considerable long duration of action, particularly BTX-100U seems to be more durable.

KEYWORDS
botox, erectile dysfunction, ICI, PDE5Is, SHIM score

1 | INTRODUCTION

Erectile dysfunction (ED), which is defined as a persistent inability to achieve or maintain a penile erection sufficient to permit satisfactory sexual performance, represents a significant medical challenge with an immense sociomedical and economical burden.[1]

The prevalence of ED is usually associated with other medical comorbidities such as cardiometabolic syndrome, neuropsychological disorders, and depression. The prevalence of ED is anticipated to affect about 1/3 billion patients by the year 2025[2] with actual increase in its incidence among juniors.[3]

Several treatment modalities for ED are available including the penile prosthesis, intra-cavernous injection (ICI), intra-urethral therapy, and oral phosphodiesterase type 5 inhibitors (PDE5Is). Despite the advances in oral and intra-urethral treatments, ICI remains a viable and effective second-line therapy for many patients.[4-7] Recently, application of stem cells and gene therapy for ED treatment has shown some early promise but disappointing clinical outcomes.[8]

Although the current modalities for ED treatment demonstrate some degree of clinical success, many of these modalities suffer from inherent disadvantages such as the modest efficacy, lack of durability, and short-term efficacy, and sometimes debilitating side effects.[8] Thus, the development of effective, safe, and durable treatment of ED, particularly the refractory vasculogenic erectile dysfunction, is a pressing and unmet medical need.

Approximately four out of five patients with ED are attributed to organic etiologies with multiple signal transduction pathways converge to endothelial dysfunction.[9] Thus, an effective therapy of vasculogenic ED should be directed toward this factor.

Onabotulinum toxin-A (BTX) is widely used for the treatment of various medical conditions.[8,10] BTX exerts multiple pharmacological effects, which may qualify BTX as therapeutic candidate for treatment of ED. For instance, it blocks the release of acetylcholine and norepinephrine-mediated sympathetic pathway and increases the expression of vascular endothelial growth factor and CD31.[11] The expression of these factors and the activation of its downstream signaling cascades enhance vasodilation and endothelial cell proliferation and thus are involved in the pathophysiology of ED. These findings represent the theoretical and molecular rationale for the potential effects of BTX in the treatment of vasculogenic ED. Indeed, several reported a durable efficacy of BTX in the treatment of several vasospastic disorders such as Raynaud's phenomenon.[12]

Indeed, until now, there is no well-conducted human study that investigated a suitable dose of BTX-A as an ICI for the treatment of ED. Thus, we carried out this prospective, randomized, double-blinded, and controlled trial to test the hypothesis that treatment with BTX-A (50 or 100 U) can exert a durable, safe, and beneficial therapeutic effect for management of drugs non-responders ED patients.

2 | PATIENTS AND METHODS

This is a prospective randomized double-blind placebo-controlled trial conducted between July 2016 and February 2019. After obtaining an institutional review board approval, all recruited patients in the trial were asked to sign well-informed written consent form according to the Declaration of Helsinki. This study was registered in ClinicalTrials.gov with ID: NCT03355963.

2.1 | Sample size

Sample size was calculated by the G*Power (version 3.1.9.2), with respect to the primary end point: the change in Sexual Health Inventory for Men (SHIM) score from baseline to 2 weeks, 3 and 6 months ≥4 points, expected standard deviation was 5 for the change in SHIM score based on previous available data.[13] with α error 5% and a power of 80%, using effect size 0.2, number of groups was 3, and number of measures was 4, using ANOVA model (repeated measures between factors). A priori computed required sample size was 50 patients per group (total 150 patients). Considering possible attrition rate, the number of enrolled patients in this study was increased to 176 patients.

2.2 | Eligibility

Male patients (age 40–70 years) with vasculogenic ED, insufficient erection for intercourse, "No" response on Sexual Encounter Profile questions (SEP 2 and 3), and not responding to any pharmacological agents (oral PDE5Is or/and ICI of Trimix [including high-dose trimix[14]]), and 3rd line of treatment is the only remaining option, were eligible for this study. Contrarily, patients with significant cardiovascular disease interfering with sexual activity, any history of unstable psychiatric conditions, and the presence of anatomical, hormonal, or neurological abnormalities that would significantly impair erectile function and men with history of radical pelvic surgery were excluded.

2.3 | Baseline evaluation

All patients were assessed by: full medical and sexual history, SHIM score, Erection Hardness Score (EHS), SEP (Questions 2 and 3) and Global Assessment Score-1,2 (GAS), local penile examination to exclude any anatomical abnormalities and penile Doppler to confirm vasculogenic ED and to categorize participants according to standard operating procedures (using trimix of alprostadil 10 mg +phentolamine 1 mg + papaverine 30 mg).[15]

2.4 | Randomization and allocation of recruited patients

Out of screened patients for ED who were attended to outpatient urology clinics of Banha University Hospital, only 176 were eligible for final randomization [1:1:1] to 1 of 3 treatment sequences (Figure 1):

Group I (BTX-100): 62 patients received ICI with BTX 100 U.

Group II (BTX-50): 59 patients received ICI with BTX 50 U.

Group III (Placebo): 55 patients were received ICI with Saline.

The random allocation process was performed according to the sequential computer-generated table. All patients and caregiver/assessor were masked to treatment allocation; only the corresponding author had full access to data all over the study periods. The data were unmasked after full study completion.

2.5 | Treatment procedure

In a recumbent position at controlled air-conditioned environment (24°C), promptly after the patient slips off his clothes to minimize thermal effect, a fully stretched flaccid penile length which considered equivalent to erected penile length as described by Wessels et al[16] was measured by a rigid ruler firmly applied to pubis (from pubis to glans tip in the dorsum) and a mid-shaft penile girth was measured by a tape. All measures were approximated to the nearest 0.5 cm.

A rubber band was placed at the root of the penis, and the skin was sterilized by 70% alcohol spray followed by application of povidone-iodine using sterile gauze.

BOTOX® vial (onabotulinumtoxin-A; Allergan) was prepared by the corresponding author as follows:

for patients of BTX-100 group, the vial (100 U vial) was diluted in 1 ml normal saline, for patients of BTX-50 group the vial was diluted in 2 ml of normal saline and only 1 ml contained 50 U was used for injection. While for patients in placebo group, 1 ml of normal saline in insulin syringe. A specialist, who was blinded to the study design, performed the injection. The solution was injected into 4 different injection sites 1 inch proximal to corona and 1 inch distal to pubopenile junction at right and left cavernosa, respectively. Following injection, a fine massage was applied to the injection sites for 5 min and the band was removed after 20 min.

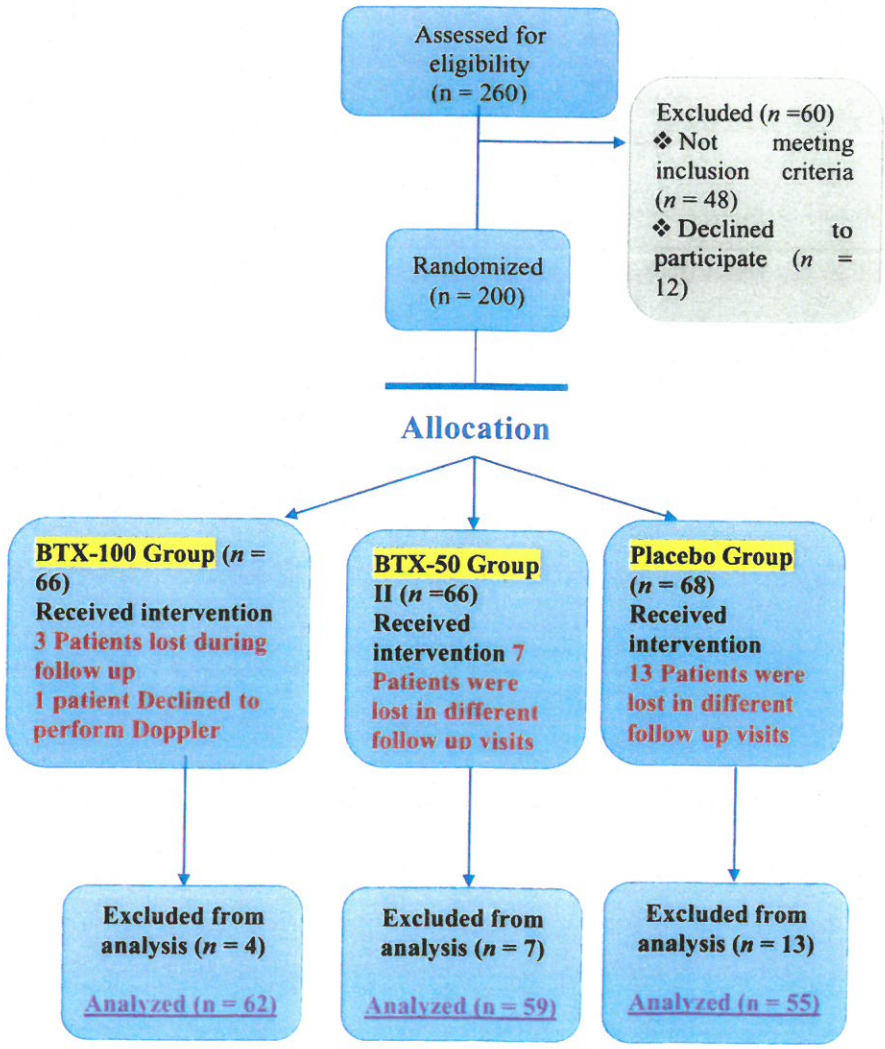


FIGURE 1 Flow diagram illustrating the study design

TABLE 1 Baseline characteristics of study patients

	BTX 100 U (N = 62)	BT 50 U (N = 59)	Placebo group (N = 55)	p Value
Age (year; median-IQR)	55.5 (49–64)	57 (50–62)	54 (49–61)	0.685
Period of ED (month; median-IQR)	6.0 (6.0–9.0)	6.0 (6.0–9.0)	9.0 (6.0–12.0)	0.087
Cause; (N, [%])				
AI	20 (32.3)	16 (27.1)	18 (32.7)	0.960
VOD	26 (41.9)	27 (45.8)	22 (40.0)	
Mixed	16 (25.8)	16 (27.1)	15 (27.3)	
Co-morbidity (N; [%])				
DM	14 (22.6)	16 (27.1)	12 (21.8)	0.866
HTN	23 (37.1)	21 (35.6)	14 (25.5)	
DM+HTN	11 (17.7)	8 (13.6)	11 (20.0)	
IHD	1 (1.6)	1 (1.7)	1 (1.8)	
None	13 (21.0)	13 (22.0)	17 (30.9)	
Serum testosterone (ng/dl; median-IQR)	588 (450–691)	571 (444–691)	587.5 (450–717)	0.887
SEP2, Median (IQR)	0 (0.0)	0 (0.0)	0 (0.0)	
SEP3, Median (IQR)	0 (0.0)	0 (0.0)	0 (0.0)	
GAS1, Median (IQR)	0 (0.0)	0 (0.0)	0 (0.0)	
GAS2, Median (IQR)	0 (0.0)	0 (0.0)	0 (0.0)	
Penile girth, Cm, median IQR	8.5 (7.5–9.5)	8.5 (8.0–9.0)	8.5 (8.0–9.0)	0.446

Note: Data expressed as frequency (N = number, % = percentage); median (interquartile range [IQR]).

Abbreviations: AI, Arterial Insufficiency; DM, Diabetes Mellitus; ED, Erectile Dysfunction; GAS, Global Assessment Score; HTN, Hypertension; IHD, Ischemic Heart Disease; SEP; Sexual Encounter Profile; VOD, Veno-Occlusive Dysfunction.

All patients were strictly instructed to not use any PDE5Is or other ICI agents for ED all over the study period.

2.6 | Follow-up

All patients were evaluated subjectively and objectively at 2 weeks, 3 months, and 6 months following post-treatment by the same method as described in basal assessment.

The primary end point is improvement of SHIM score (≥4 points increase[9]). Secondary end points are, "yes" response of SEP questions, EHS, penile length, girth, and GAS assessments.

2.7 | Statistical analysis

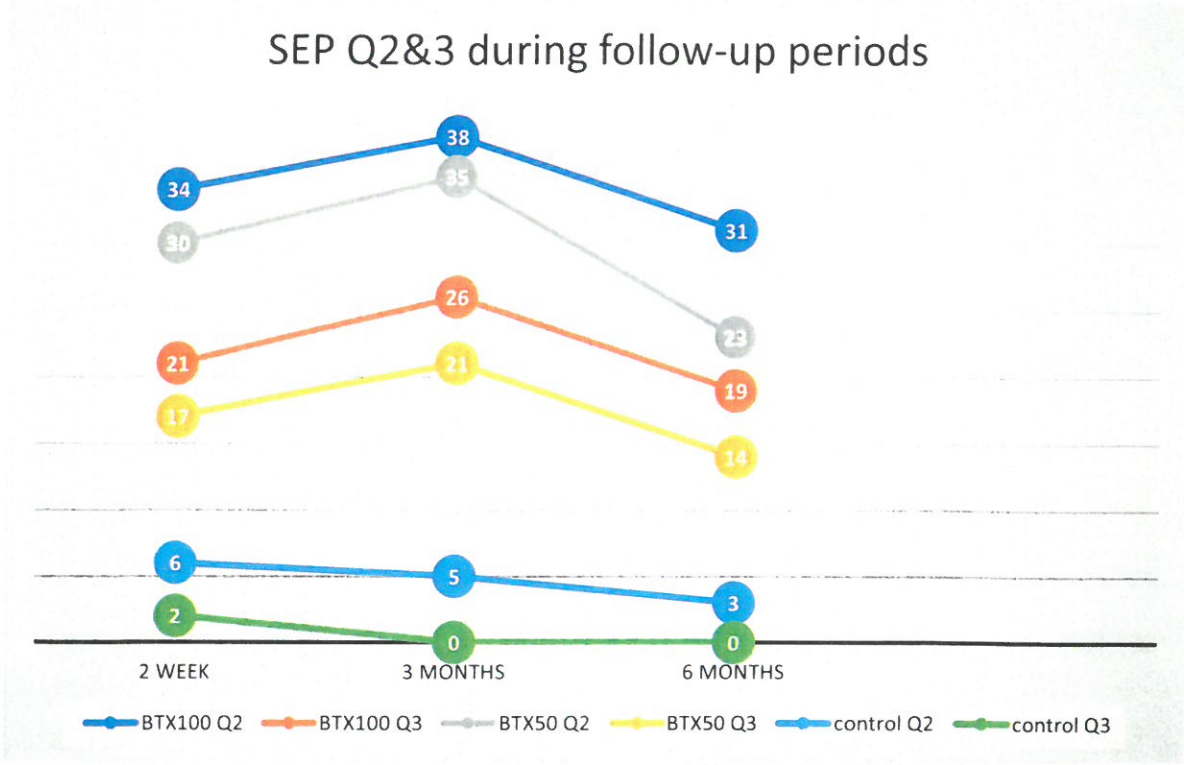
Data were handled by SPSS ver. 23 (SPSS, Inc.). Shapiro-Wilk was used as a test of normality. Quantitative data were presented in median and interquartile range (IQR). Kruskal-Wallis test was used for assessing differences of end points among three groups at baseline, 2 weeks, 3 months, and 6 months and adjusted by Bonferroni's correction. Mann-Whitney test was used for pairwise comparisons if the difference was statistically significant.

Qualitative data (SEP, GAS) were presented as number and frequency. Different comparisons of categorical data were performed by chi-square test. p value <0.05 was considered statistically significant.

3 | RESULTS

Baseline and demographic data of the participants are shown in Table 1. There were no statistically significant differences in these baseline characteristics between all groups ($p > 0.05$).

There was a significant improvement in all subjective parameters, that is, SHIM and EHS scores (Table 1), SEP-Q2&3 (Figure 2), and GAS-Q1&2 (Figure 3), all over the post-treatment periods ($p < 0.001$) in patients of BTX-100 and BTX-50 groups. The maximum improvement occurred in the 3rd month of treatment. While patients of the placebo group did not experience significant improvement as compared to the baseline measurements ($p = 0.264$) It was noted that at the 2nd week and 3rd months after treatment, there was no statistically significant difference in SHIM scores, EHS, SEP, and GAS in BTX-100 and BTX-50 groups ($p > 0.05$). However, in the 6th month, there was a statistically significant difference between the aforementioned groups in favor of BTX-100 ($p < 0.001$).



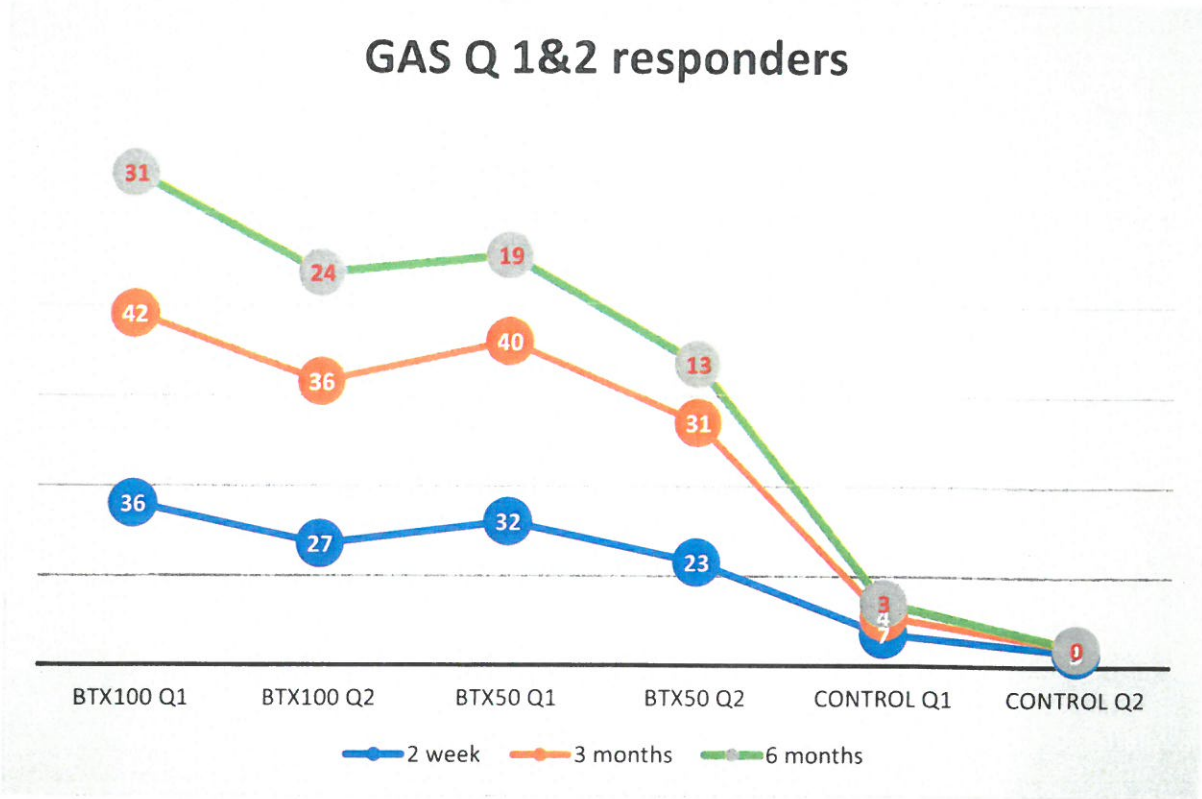
Parameter	Time Interval	BTX-100 IU (N=62)	BTX-50 IU (N=59)	placebo group (N=55)	P value
SEP2, Yes (N, %)	Baseline	0(0.0%)	0(0.0%)	0(0.0%)	-
	2 weeks	36(58.1%) [a]	27(45.8%) [a]	0(0.0%) [AB]	<0.001*
	3 months	54(87.1%) [ab]	48(81.4%) [ab]	0(0.0%) [AB]	<0.001*
	6 months	30(48.4%) [ac]	11(18.6%) [A bc]	0(0.0%) [AB]	<0.001*
SEP3, Yes (N, %)	Baseline	0(0.0%)	0(0.0%)	0(0.0%)	-
	2 weeks	36(58.1%) [a]	27(45.8%) [a]	0(0.0%) [AB]	<0.001*
	3 months	54(87.1%) [ab]	48(81.4%) [ab]	0(0.0%) [AB]	<0.001*
	6 months	30(48.4%) [ac]	11(18.6%) [A bc]	0(0.0%) [AB]	<0.001*

FIGURE 2 SEP Questions 2 and 3 of study groups during follow-up visits. Data expressed as Number & percent *: significance ≤0.05 (chi square test), A: significance vs BTX-100 IU, B: significance vs BTX50 IU a: significance vs baseline, b: significance vs 2weeks, c: significance vs 3 months SEP = Sexual Encounter Profile

Regarding the objective parameters, treatment with BTX (either 100 or 50 IU) did not cause any significant change in penile girth ($p > 0.05$). On the other hand, treatment with BTX-100 or BTX-50 resulted in a significant increase in stretched penile length and Doppler parameters as compared with the corresponding pretreatment values (Table 2).

As expected, in placebo group, there were no significant changes in penile girth, stretched penile length, or Doppler parameters (Table 2).

During treatment and follow-up periods, some adverse events occurred; one patient of BTX-50 group had injection site penile pain which was managed by psychological support and analgesics. Another patient from the control group had injection site trivial hematoma which was managed by compression with analgesics and ice-pack. Four patients (three patients from BTX-100 and one patient from BTX-50 groups) developed a prolonged sustained erection during penile Doppler examination at three months which managed conservatively. At 6th month, one patient from the BTX-100 group



Parameter	Time Interval	BTX-100 IU (N=62)	BTX-50 IU (N=59)	placebo group (N=55)	P value
GAS1, Yes (N, %)	Baseline	0(0.0%)	0(0.0%)	0(0.0%)	-
	2 weeks	54(87.1%) [a]	49(83.1%) [a]	0(0.0%) [AB]	<0.001*
	3 months	54(87.1%) [a]	51(86.4%) [a]	0(0.0%) [AB]	<0.001*
	6 months	54(87.1%) [a]	51(86.4%) [a]	0(0.0%) [AB]	<0.001*
GAS2, Yes (N, %)	Baseline	0(0.0%)	0(0.0%)	0(0.0%)	-
	2 weeks	36(58.1%) [a]	26(44.1%) [a]	0(0.0%) [AB]	<0.001*
	3 months	54(87.1%) [ab]	48(81.4%) [ab]	0(0.0%) [AB]	<0.001*
	6 months	30(48.4%) [ac]	11(18.6%) [A bc]	0(0.0%) [AB]	<0.001*

FIGURE 3 GAS Questions 1 and 2 of study groups during follow-up visits. Data expressed as Number & percent *: significance ≤0.05 (chi square test), A: significance vs BTX-100 IU, B: significance vs BTX50 IU; a: significance vs baseline, b: significance vs 2weeks, c: significance vs 3 months. GAS = Global Assessment Score

had priapism which resolved by ICI of ephedrine. No systemic side effects were noted.

4 | DISCUSSION

Our findings suggest that BTX might provide a safe, effective, and relatively durable improvement of ED. Several mechanisms are proposed for the potential therapeutic effect of BTX in the treatment of many vasculogenic disorders, including ED. For instance, BTX inhibits sympathetic adrenergic or cholinergic vasoconstriction, sensory nerves, and/or endothelial exocytosis of endothelin 1, which are involved in the pathophysiology of erectile dysfunction.[8,17] Mounting evidence suggests that the effects BTX are mediated by non-nitric-oxide-mediated mechanism. Instead, it inhibits the neuronal membrane fusion with the synaptic vesicles that contain

TABLE 2 Comparison of the subjective and objective parameters between groups

Parameter	Time interval	BTX-100 IU (N = 62)	BTX-50 IU (N = 59)	Placebo group (N = 55)	p_c Value
SHIM score, median (IQR)	Baseline	8.0 (7.0–9.0)	8.0 (8.0–9.0)	8.0 (7.0–9.0)	-
	2 weeks	12.0 (11.0–13.0)	11.0 (11.0–12.0)	8.0 (7.0–9.0)	<0.001[a*]
	3 months	14.0 (12.0–16.0)	13.0 (12.0–15.0)	8.0 (5.0–11.0)	<0.001[a*]
	6 months	14.0 (12.0–15.0)	8.0 (8.0–10.0)	8.0 (6.0–9.0)	<0.001[a*]
	p_c Value	<0.001[a**]	<0.001[a**]	0.264	
EHS, median (IQR)	Baseline	1.0 (1.0–2.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)	
	2 weeks	3.0 (2.0–3.0)	2.0 (2.0–3.0)	1.0 (1.0–2.0)	<0.001[a*]
	3 months	3.0 (3.0–3.0)	3.0 (3.0–3.0)	1.0 (1.0–2.0)	<0.001[a*]
	6 months	2.0 (2.0–3.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)	<0.001[a*]
	p_c Value	<0.001[a**]	<0.001[a**]	1	
Stretched penile length, Cm, median (IQR)	Baseline	12.0 (10.5–13.0)	12.0 (10.5–13.0)	11.5 (10.5–12.5)	
	2 weeks	12.3 (11.0–13.0)	12.0 (11.0–13.0)	12.0 (11.0–12.5)	0.168
	3 months	12.5 (11.5–13.5)	13.0 (11.5–13.5)	11.8 (10.5–12.5)	<0.001[a*]
	6 months	13.0 (12.0–14.0)	12.5 (11.5–13.5)	11.5 (10.5–12.5)	<0.001[a*]
	p_c Value	<0.001[a**]	<0.001[a**]	0.576	
Penile girth, Cm, median (IQR)	Baseline	8.5 (7.5–9.5)	8.5 (8.0–9.0)	8.5 (8.0–9.0)	
	2 weeks	8.5 (7.5–9.5)	8.5 (8.0–9.0)	8.5 (8.0–9.0)	1
	3 months	8.5 (7.5–9.5)	8.5 (8.0–9.0)	8.5 (8.0–9.0)	0.51
	6 months	8.5 (7.5–9.5)	8.5 (8.0–9.0)	8.5 (8.0–9.0)	1
	p_c Value	0.236	0.448	1	
Change of CAD, mm, median (IQR)	Baseline	0.20 (0.10–0.30)	.20 (.15–0.35)	0.22 (0.10–0.35)	
	2 weeks	0.30 (0.23–0.40)	0.30 (0.20–0.40)	0.20 (0.15–0.35)	0.012
	3 months	0.35 (0.30–0.45)	0.35 (0.25–0.42)	0.20 (0.15–0.35)	<0.001[a*]
	6 months	0.35 (0.30–0.43)	0.30 (0.22–0.35)	0.25 (0.15–0.35)	<0.001[a*]
	p_c Value	<0.001[a**]	<0.001[a**]	0.544	
PSV, cm/sec, median (IQR)	Baseline	20.0 (18.0–32.0)	22.5 (19.5–37.5)	31.8 (20.0–37.5)	0.147
	2 weeks	33.8 (32.0–40.0)	32.0 (27.5–40.0)	31.5 (19.0–37.5)	0.006
	3 months	34.0 (33.0–40.0)	33.0 (30.0–40.0)	30.0 (19.0–37.5)	<0.001[a*]
	6 months	37.5 (30.0–39.0)	29.0 (25.0–38.0)	32.0 (20.0–37.5)	<0.001[a*]
	p_c Value	<0.001[a**]	<0.001[a**]	1	
EDV, cm/sec, median (IQR)	Baseline	6.0 (3.0–7.0)	6.5 (4.0–7.5)	6.0 (5.5–7.0)	
	2 weeks	5.0 (3.0–6.5)	6.0 (3.5–6.5)	7.0 (6.0–7.5)	<0.001[a*]
	3 months	4.5 (3.0–5.0)	5.0 (3.5–5.5)	7.0 (6.0–7.5)	<0.001[a*]
	6 months	3.5 (3.0–6.0)	6.0 (4.0–7.0)	7.0 (6.0–7.5)	<0.001[a*]
	p_c Value	<0.001[a**]	<0.001[a**]	0.416	

Data expressed as median and interquartile range (IQR).

Abbreviations: CAD, Cavernosal Artery Diameter; EDV, End Diastolic Velocity; EHS, Erection Hardness Score; GAS, Global Assessment Score; N, number; PSV, Peak Systolic Velocity; SHIM, Sexual Health Inventory for Men; p_c Value, is adjusted by Bonferroni method.

[a]Significance <0.05 (Kruskal-Wallis test).

*Inter-groups pairwise comparison (Mann-Whitney U test): at 2 weeks and 3 months: BTX-100 vs. BTX-50 $p > 0.05$; BTX-100 vs. placebo and BTX-50 vs. placebo $p < 0.001$; at 6 months: BTX-100 vs. BTX-50 and BTX-100 vs. placebo $p < 0.001$; BTX-50 vs. placebo $p > 0.05$.

**Intra-group pairwise comparison (Friedman test): BTX-100 group: baseline vs. 2 weeks, baseline vs. 3 months, baseline vs. 6 months, 2 weeks v 3 months and 2 weeks vs. 6 months $p < 0.001$; while; 3 months vs. 6 months $p > 0.05$. BTX-50 group: baseline vs. 2 weeks, baseline vs. 3 months, 2 weeks vs. 3 months and 2 weeks vs. 6 months $p < 0.001$; while; baseline v 6 months $p > 0.05$.

norepinephrine neurotransmitters. So, preventing release of norepinephrine rather than nitric oxide.[8] These effects might lead to a decrease in the tone of resistance penile vessels, an increase in resting blood flow, and reduction in persistent cavernosal smooth muscle tone. BTX-A injection induces sinusoidal dilatation of cavernous tissue which seems to be mediated by smooth muscle relaxation.[18,19]

Ultimately, these effects are responsible for, at least in part, facilitating an erectile response to sexual stimulation through its modulatory effect on the erectile tissue[8,20]

Despite the six-item erectile function (EF) domain of the International Index of EF (IIEF) is adapted as a clinical trial end point, in this study, response was defined as four point improvement in SHIM score.[9] Earlier published study suggested that the minimal clinically important difference varies according to ED category, based on six-item IIEF-ED.[19]

In this novel study, there were highly statistically significant improvements in SHIM score and EHS in the BTX-treated patients ($p < 0.001$) within 2 weeks after injection. This was in agreement with a small pilot study by Ghanem and his colleagues.[20] This improvement was maximum at 3rd month of follow-up with no statistical difference between BTX-100-treated and BTX-50-treated groups ($p > 0.05$). This improvement was diminished in the BTX-50 group while endured in BTX-100 at the 6th-month post-treatment ($p < 0.01$).

There are only three preclinical animal studies that investigated the effect of ICI of Botox in rates of different species and ages. The results of these preclinical studies concluded that BTX improves erectile function in aging rats proclaimed by increased intra-cavernosal pressure[20-22] and increased sinusoidal volume in BTX-treated treatment groups compared to control ($p < 0.001$). These effects led to the enhancement of cavernosal smooth muscle relaxation and increased penile blood flow during sexual stimulation.[20,22]

Data from a newly published uncontrolled retrospective study by Giuliano and coworkers confirmed that the response rate was 54% at 6 weeks.[23] In the present study, the response rate was maximum at the 3rd month and was about 61%. This relatively low difference in the response rate reported in our study and by the Giuliano group may attribute to the fact that we used onabotulinumtoxin-A (50 or 100 U) as monotherapy while Giuliano et al injected abobotulinumtoxin-A (250 or 500 U), in combination with pharmacotherapy as an additive. These botulinum toxins are dissimilar in the purification method. In addition, the dose of BTX in our study is remarkably higher than that used in the study by Giuliano et al[23] Furthermore, the relatively smaller sample size of Giuliano et al study (only 47 patients were included) and the difference in the demographic characteristics of the study subjects could account for the observed difference in response in our study and the previous one.

In the current study, there was statistically significant ($p < 0.001$) improvement in penile hemodynamics (PSV, EDV, and average cavernosal artery diameter) among the two active treatment groups but not in placebo group. It is noteworthy that there was profound improvement in PSV in both active treatment groups, while the improvement in EDV was modest. This observation could be explained by inherent effect of BTX on penile smooth musclure[11,12]

Some previous studies reported a significant effect of placebo in improvement of ED.[9,24] However, the current study revealed no significant improvement in SHIM score in the placebo groups throughout the different study follow-up visits ($p_c = 0.264$). This apparent discrepancy between our finding and the other studies could attribute to ambivalence of included patients, as we included severe vasculogenic ED patients only while other studies had different inclusion criteria and thus recruited patients with mild to severe ED and treated by PDE5Is. Indeed, the lack of placebo effects was also reported in other studies whereas insignificant effect of placebo was observed in ED patients managed by low-intensity extracorporeal shock wave therapy.[25,26]

Regarding complications, only 4% (5/121) of patients from treatment groups had an adverse event. All of these adverse effects were likely related to ICI of trimix during Doppler study rather than the direct effect of BTX. We argue that ICI of Botox may improve the sensitivity of the cavernous tissues to the trimix effects. A recent study reported complications in 16% of patients underwent ICI. These complications were as follows: plaque or scar formation (10%), penile pain (2%), bruising (1%), restlessness (1%),tissue damage(1%), and 1% headache.[27] The authors of the same study claimed that 27% of their patients complained of penile shortening while 1/5 of them developed a new curvature of their penises.[27] This is may be due to recurrent trauma due to repeated injections. On the contrary, patients in treatment groups in our study reported an increase of penile length while there was no new penile curvature reported. The proposed mechanism for this lengthening may be due to BTX-induced relaxation of cavernosal muscles. Additionally, despite that patients were assessed by the same assessor (which was blinded), intra-observer fallacy cannot be excluded.

The discontinuation rate for ICI pharmacotherapy is relatively high and may range from 30% to 80%. This relatively high dropout rate is attributed to several factors including the development of adverse effects, unacceptance by the patient/partner, physical or psychological discomfort, lack of durability of the effect, patient's anxiety concerning penile injections, and the high the treatment.[6,27,28]

In the present study, the dropout rates were 9% in the treatment groups and 20% in the placebo group, respectively. Nonetheless, the number of patients in each group remained above minimal calculated sample size (50 patients per group). The relatively high dropout rate in the placebo group is likely due to ineffective treatment and patient unsatisfaction.

It is worth mentioning that the single ICI of BTX for the management of ED demonstrated durable effects with acceptable adverse events. This important characteristic imparts a clinical advantage for the wide application of ICI BTX in the treatment of ED. Furthermore, ICI of BTX is administered by well-trained medical provider and therefore minimizes the patient's concerns and anxiety.

This study has several limitations. First, different cohorts of ED patients should be included with various causes such as post radical prostatectomy, spinal cord injury, and pelvic trauma patients. Second, patient inclusion may be better enlarged to include all

PDE5Is non-responder. Third, longer follow-up periods are needed to determine how long the action of BTX lasts. Lastly, further studies with intent-to-treat analysis are also required.

5 | CONCLUSIONS

Treatment of refractory ED by single ICI of BTX was found to be effective, durable, and safe. All noted complications were related to ICI of vasoactive agents during subsequent follow-up penile Doppler studies. While ICI of BTX helped around 40% of patients to restart their sexual activities, around 60% of patients were still not able to complete intercourse.

This novel application of ICI BTX demonstrated a considerable long duration of action, which lasts at least for 3–6 months. Although both 50 U and 100 U are effective and safe, BTX-100 appears to be more durable. Further studies with different doses are warranted to confirm current results.

CONFLICT OF INTEREST

None.

AUTHOR'S CONTRIBUTION

W. El-Shaer: Project development, Data Collection, Manuscript writing & editing, supervising, & Data analysis; H. Ghanim: Project development, supervising; T. Diab: Data collection & Data analysis; A.A. Taleb: supervising, & Data analysis; W. Kandeel: Manuscript writing & Data Collection.

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