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ORIGINAL ARTICLE

Safety and efficacy of botulinum neurotoxin in the treatment of erectile dysfunction refractory to phosphodiesterase inhibitors: Results of a randomized controlled trial

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Abstract

Background: There has been recent interest in the use of botulinum neurotoxin (BoNT) in the field of Andrology, whereby it has been investigated in the treatment of penile retraction and premature ejaculation.

Objectives: To evaluate the safety and efficacy of intracavernosal BoNT-A injection in the treatment of patients with erectile dysfunction (ED) refractory to oral phosphodiesterase inhibitors (PDE5Is).

Patients and methods: A double-blind randomized placebo-controlled prospective comparative study conducted at one center and involved 70 patients with ED refractory to PDE5Is. At baseline, the following data were collected: erection hardness score (EHS), peak systolic velocity (PSV), end diastolic velocity (EDV), sexual health inventory for men (SHIM), and the sexual encounter profile 2&3 (SEP-2&3) questionnaires. Treatment group ($n = 35$) received a single ICI of 100 units of BoNT-A in 2 ml of saline and control group ($n = 35$) received a single ICI of 2 ml of saline. EHS, PSV, and EDV were assessed at 2 weeks post treatment. SHIM, SEP-2, SEP-3, and global assessment questionnaire (GAQ-Q1&Q2) were completed at 2-, 6-, and 12-weeks post treatment.

Results: Two weeks post treatment, the treatment group showed a statistically significant improvement in the mean EHS, PSV, EDV, and GAQ-Q1 positive responders ($p < 0.001$) compared to the control group. At 6- and 12-weeks post treatment, the treatment group showed a statistically significant improvement in the SHIM scores, SEP-2, and GAQ-Q1&Q2 positive responders compared to the control group. At 6 weeks, where there was a 5-point improvement in the mean SHIM score of the treatment group (10±5.9 from 5.4±1.7 at baseline) versus no improvement in the placebo group, 18 patients in the treatment group (53%) were able to have an erection hard enough for vaginal penetration versus only one patient in the control group.

Conclusion: BoNT-A is safe and effective as a potential treatment for ED refractory to PDE5I therapy.

KEYWORDS
Botulinum Neurotoxin, BOTOX, Erectile Dysfunction, Phosphodiesterase Inhibitors

1 | INTRODUCTION

Moderate to severe erectile dysfunction (ED) affects 5–20% of men worldwide. It is estimated that by the year 2025, 322 million men will suffer from ED.[1,2] ED is treated in a stepwise manner with oral (PDE5Is) being the first-line therapy for ED.[3,4] However, despite the fact that PDE5Is have revolutionized ED treatment, they do not work in all cases. Sildenafil Citrate is successful in up to 63% of men with ED and Tadalafil was shown to be successful in up to 52% of ED patients. It is more likely that patients with severe ED will have poor response to oral PDE5Is.[5,6] Second-line therapy includes transurethral alprostadil, intracavernosal injections of vasoactive substances (ICI), and vacuum pump therapy. However, many patients find second-line therapy too invasive and lacking in spontaneity.[7–9] Penile implants are used as a last resort when second-line therapy fails or is refused by the patient. Despite having a high patient and partner satisfaction rates (exceeding 80%), implant surgery is not free from complications, such as infection, erosion, autoinflation, and mechanical failure, and the surgery is both expensive and invasive.[4,10,11] Recent advances in the research for future ED therapies, such as low-intensity shockwave therapy, growth factor injection, gene therapy, stem cell therapy, and tissue engineering, can salvage ED patients from implant surgery as prosthesis surgery partially destroys the normal erection mechanism.[4]

Botulinum neurotoxin (BoNT) is produced by *Clostridium botulinum*, an anaerobic, gram-positive bacterium. Poisoning with BoNT can cause botulism, resulting in generalized paralysis, respiratory failure, and death.[12,13] There are seven serotypes of BoNT: A, B, C1, D, E, F, and G. BoNT-A is the most commonly used serotype for medical purposes. There are several commercially available forms: Botox (Allergan Pharmaceuticals, Parsippany, NJ, USA) is the most widely used and has the most medical applications.[14] Since its first use in 1977 for the treatment of strabismus in children, BoNT-A has since been used in aesthetic medicine and for the treatment of a number of disorders associated with overactive striated muscles, such as strabismus, esotropia, exotropia, focal dystonia, spasticity, and movement disorders.[15] BoNT-A has also been used in the management of some smooth-muscle disorders, such as achalasia, oesophageal spasm, ptyalism, hyperhidrosis, and intrinsic rhinitis, blepharospasm, muscle spasms and spasticity, axillary hyperhidrosis, and neurogenic detrusor muscle overactivity of the urinary bladder.[15–21] It is widely used in aesthetic medicine to treat facial wrinkles in the forehead, lower face, lateral eye, and in between the eyebrows.[22–27]

BoNT prevents the release of acetylcholine at the presynaptic membrane causing flaccid paralysis for up to 3 months.[28,29] BoNT can also inhibit the release of other neurotransmitters, such as noradrenaline, dopamine, glycine, and g-aminobutyrate. BoNT has been used for prostatic smooth-muscle relaxation in the management of lower urinary tract symptoms. It has also been found to inhibit noradrenaline release in the urethra and ano-coccygeus of rats.[16,30,31]

Erection depends on adequate cavernosal smooth muscle relaxation. PDE5Is and ICIs of vasoactive substances exert their effect by inducing corporal smooth muscle relaxation.[32] Since BoNT-A is a strong inducer of smooth muscle relaxation, it may be effective in the treatment of ED refractory to PDE5Is.[33]

There has been recent interest in the use of BoNT in the field of Andrology, whereby it has been investigated in the treatment of penile retraction and premature ejaculation.[34,35] The use of BoNT in the treatment of ED was first studied in 2016 by Ghanem et al., who performed an animal study followed by a human pilot study and showed promising results.[33,36–38]

This study investigated the safety and efficacy of BoNT in the treatment of ED refractory to oral PDE5Is with the aim of salvaging those patients from second- and third-line ED therapies by downgrading the level of their ED.

2 | PATIENTS AND METHODS

This is a double-blind randomized placebo-controlled prospective comparative study. Both the patients and the investigator were not aware if the active drug or the placebo were injected. It was registered at NIH ClinicalTrials.gov (https://www.clinicaltrials.gov/), number NCT03102762. The study protocol was approved by the local ethics committee.

2.1 | Study design

Seventy consecutive patients from a single high-volume Andrology unit presenting with ED, not responding to on demand PDE5Is, were recruited and randomly assigned to treatment group ($n = 35$) and control group ($n = 35$) using computer-generated randomization sequence. Sample size was calculated based upon the previous pilot study[36] with the difference between the two groups was 3 ± 5 in SHIM score. Using power 85% and 5% significance level, 51 patients were required. That number was increased to 59 to adjust for nonparametric usage and increased again to 70 to compensate for possible losses during follow up (20% more than calculated). Sample size was calculated using PS: Power & Sample Size Calculation Software Version 3.1.2 (Vanderbilt University, Nashville, TN, USA). A nonresponse to PDE5Is was defined as an erection not sufficient enough for penetration of the vagina or loss of the erection before completion of intercourse, after trying the highest dose of Sildenafil and Tadalafil on four separate occasions for each PDE5I. All the patients included in the study were PDE5Is failures, they were already on the highest dose of on demand Sildenafil or tadalafil and were unable to achieve an erection sufficient for penetrative intercourse, this was also demonstrated in their baseline questionnaires. After treatment, in order to avoid any bias, each patient was asked to use the same dose (highest) of the same PDE5I that he was using before the injection.

3 | INCLUSION AND EXCLUSION CRITERIA

All patients included were above 21 years old with regular sexual relation. Patients without regular sexual relations or younger than 21 years old or contraindicated for PDE5I treatment were excluded.

4 | METHODS

At baseline, all patients signed an informed consent form and had history taking as well as general and genital examination. Penile duplex with a trimix solution (20 μg alprostadil + 1 mg phentolamine + 30 mg papaverine) was also performed to assess the erection hardness score (EHS) and penile hemodynamics according to Standard Operating Procedures for Duplex Ultrasound: Standardization of Vascular Assessment of Erectile Dysfunction in order to achieve maximal cavernosal smooth muscle relaxation and possibly full erectile response.[39] The latter was done by measuring the peak systolic (PSV) and the end diastolic (EDV) velocities in the right and left cavernosal arteries and calculating the mean PSV and mean EDV. No cases of priapism needed intervention occurred. The patients also completed the validated Arabic translated version of sexual health inventory for men (SHIM), which consist of 5-point questionnaire consisting of five questions assessing the erectile function, and it gives a full picture of the capability of the male for initiation and maintenance of erection sufficient for successful intercourse.[40] They also completed sexual encounter profile 2&3 (SEP-2&3) questionnaires.

The patients were then randomized into a treatment group ($n = 35$) and a control group ($n = 35$). Patients in the treatment group received a single ICI of 100 units of onabotulinumtoxinA BoNT-A (Botox™; Allergan Pharmaceuticals, Parsippany, NJ, USA) diluted in 2 ml of normal saline. A tourniquet was applied at the base of the penis, the treatment dose was distributed along 4 points, right and left distal and proximal shaft using a 23G insulin syringe (the tourniquet was removed after 20 min). Patients in the control group received a single ICI of 2 ml of IV saline administered in the same manner as the treatment group. Patients in both groups were asked to resume sexual activity 1 week after treatment with the help of on demand PDE5Is trying the highest dose of Sildenafil and Tadalafil. ICI test, penile duplex, SHIM, SEP-2 & SEP-3, and global assessment question 1&2 (GAQ-Q1&Q2) were done at 2 weeks post treatment. We used penile duplex to compare the hemodynamics of the penile arteries before and after injection. SHIM, SEP-2&SEP-3, and GAQ-Q1&Q2 were completed at 6- and 12-weeks post treatment, respectively.

Statistical analysis was done using SPSS software (statistical package for the social sciences, version 21, SPSS Inc, Chicago, IL, USA). Frequency tables with percentages were used for categorical variables and descriptive statistics (median of minimum and maximum values) were used for numerical variables. Mann–Whitney test was used to compare quantitative variables, and the Chi-square test was used to analyze categorical variables. A p value of < 0.05 was considered statistically significant.

5 | RESULTS

The study was conducted from February 2017 to June 2018 at one Andrology unit. Seventy patients with ED refractory to PDE5Is were included in this study and were randomized into treatment and control groups with 35 patients in each group. The mean patient age was 54.3 ± 7.8 and 56 ± 9.1 in the treatment and control groups, respectively ($p = 0.16$). The underlying comorbidities identified were diabetes (treatment group 21, control group 22 patients) and cardiovascular disease (treatment group 10, control group 7 patients).

TABLE 1 Baseline characteristics of treatment and control groups

	Treatment	Control	*p* value
Age (mean ± SD)	54.3 ± 7.8	56 ± 9.1	0.167
SHIM (mean ± SD)	5.4 ± 1.7	5.7 ± 1.1	0.274
EHS (mean ± SD)	2.3 ± 0.6	2.1 ± 0.5	0.081
PSV (mean ± SD)	34.4 ± 11.7	31.3 ± 15.6	0.154
EDV (mean ± SD)	3.5 ± 3.7	4.5 ± 3.4	0.135
SEP-2 positive responders	3 (8.6%)	2 (7%)	0.643
SEP-3 positive responders	0	0	–

Abbreviations: EDV, end diastolic velocity; EHS, erection hardness score; PSV, peak systolic velocity; SEP-2&3, sexual encounter profile 2&3 questionnaires; SHIM, sexual health inventory for men.

At baseline, there were no statistically significant differences between the treatment group and the control group in the SHIM scores, EHS, penile hemodynamics, and SEP-2&3 positive responders (Table 1).

Patients in both groups had severe ED as evidence by low mean SHIM scores 5.4 ± 1.7 and 5.7 ± 1.1 in the treatment and control groups, respectively. The mean EHS in both groups showed that none of the patients achieved adequate rigidity (E3-4) in response to the ICI injection and the penile duplex parameters demonstrated vasculogenic ED (Table 1). The SEP questionnaire demonstrated that only three patients in the treatment group and two patients in the control group were able to have an erection hard enough for vaginal penetration and that those five patients lost the erections before completing coitus.

At 2 weeks post treatment, there was a statistically significant difference between the treatment and control groups in the mean EHS, PSV, EDV, and GAQ-Q1 positive responders favoring the treatment group ($p < 0.001$). The mean EHS in the treatment group demonstrates that patients were beginning to get some rigidity (E2.9 ± 0.8) and the penile duplex parameters demonstrate significant improvement of penile hemodynamics in the treatment group compared to baseline; the mean PSV increased from 34.4 ± 11.7 at baseline to 45.8 ± 13.2 and the mean EDV was reduced from 3.5 ± 3.7 at baseline to 1.7 ± 3.5. There was no statistically significant difference between the treatment and control groups in the SHIM score, SEP-2&3, and the GAQ-Q2 positive responders, although there was a positive trend favoring the treatment group (Table 2).

At 6- and 12-weeks post treatment, there was a statistically significant difference between both groups in the SHIM score, SEP-2, GAQ-Q1, and GAQ-Q2 positive responders favoring the treatment group. There was no statistically significant difference between both groups in the SEP-3 positive responders, although there was a positive trend favoring the treatment group (Tables 3 and 4).

TABLE 2 SHIM, EHS, SEP-2&3, and GAQ-Q1&Q2 and penile duplex parameters: 2 weeks post treatment

	Treatment	Control	*p* value
SHIM (mean ± SD)	6.7 ± 2.2	6 ± 2.8	0.059
EHS (mean ± SD)	2.9 ± 0.8	2.2 ± 0.6	<0.001
PSV (mean ± SD)	45.8 ± 13.2	31.9 ± 16.1	<0.001
EDV (mean ± SD)	1.7 ± 3.5	4.5 ± 3.9	<0.001
SEP-2 positive responders	7(20%)	3 (8.6%)	0.172
SEP-3 positive responders	1 (2.9%)	1 (2.9%)	1
GAQ-Q1 positive responders	17 (48.6%)	3 (8.6%)	<0.001
GAQ-Q2 positive responders	3 (8.6%)	2 (5.7%)	0.643

Abbreviations: EDV, end diastolic velocity; EHS, erection hardness score; GAQ-Q1&Q2, global assessment questionnaire 1&2; PSV, peak systolic velocity; SEP-2&3, sexual encounter profile 2&3 questionnaires; SHIM, sexual health inventory for men.

TABLE 3 SHIM, SEP-2&3, and GAQ-Q1&Q2: 6 weeks post treatment

	Treatment	Control	*p* value
SHIM (mean ± SD)	10 ±5.9	5.8±1.8	<0.001
SEP-2 positive responders	18 (53%)	1 (3%)	<0.001
SEP-3 positive responders	3 (8.8%)	0	0.072
GAQ-Q1 positive responders	22(64.7%)	0	<0.001
GAQ-Q2 positive responders	14 (41.2%)	0	<0.001

Abbreviations: GAQ-Q1&Q2, global assessment questionnaire 1&2; SEP-2&3, sexual encounter profile 2&3 questionnaires; SHIM, sexual health inventory for men.

The peak response was seen at 6 weeks post treatment, where there was a 5 point improvement in the mean SHIM score of the treatment group (10±5.9 from 5.4±1.7 at baseline) versus no improvement in the placebo group, 18 patients in the treatment group (53%) were able to have an erection hard enough for vaginal penetration versus only one patient in the control group, and three patients in the treatment group were able to have a hard erection long enough to have successful coitus versus none of the patients in the control group. Twenty-two (64.7%) patients in the treatment group reported improvement in their erections and 14 (41.2%) patients reported that the treatment improved

TABLE 4 SHIM, SEP-2&3, and GAQ-Q1&Q2: 12 weeks post treatment

	Treatment	Control	*p* value
SHIM (mean ± SD)	8.3 ±4	5.6±1.4	<0.001
SEP-2 positive responders	11 (32.4%)	1 (3%)	0.001
SEP-3 positive responders	2 (5.9%)	0	0.145
GAQ-Q1 positive responders	17 (48.6%)	0	<0.001
GAQ-Q2 positive responders	7 (20.6%)	0	<0.001

Abbreviations: GAQ-Q1&Q2, global assessment questionnaire 1&2; SEP-2&3, sexual encounter profile 2&3 questionnaires; SHIM, sexual health inventory for men.

TABLE 5 Comparison between sexual health index for men (SHIM) before, 2, 6, and 12 weeks after injection of BOTOX within the treatment group

	Mean	SD	*p* value
SHIM (B)	5.4	1.67	
SHIM (2W)	6.66	2.17	0.001
SHIM (B)	5.4	1.67	
SHIM (6W)	9.97	5.92	<0.001
SHIM (B)	5.4	1.67	
SHIM (12W)	8.26	4.07	<0.001

Abbreviations: B, before; 2W, at 2 weeks; 6W, at 6 weeks; 12W, at 12 weeks; SHIM, sexual health inventory for men.

TABLE 6 Comparison between sexual health index for men (SHIM) score before 2, 6, and 12 weeks after injection of saline within the control group

	Mean	SD	*p* value
SHIM (B)	5.69	1.08	
SHIM (2W)	6.11	2.82	0.44
SHIM (B)	5.69	1.08	
SHIM (6W)	5.77	1.82	0.73
SHIM (B)	5.69	1.08	
SHIM (12W)	5.57	1.399	0.23

Abbreviations: B, before; 2W, at 2 weeks; 6W, at 6 weeks; 12W, at 12 weeks; SHIM, sexual health inventory for men.

their ability to engage in sexual activity versus none of the patients in the control group. At 12 weeks post treatment, although still statistically significant compared to placebo, the response was beginning to decline.

Another comparison was done within the treatment group before the injection and 2, 6, and 12 weeks after injection as regards SHIM score (Table 5). This comparison showed statistically significant improvement of the SHIM score within the treatment group before and 2 weeks after injection in SHIM with a *p* value of 0.001 as well as before and 6 weeks after injection in SHIM with a *p* value of < 0.001 and before, and 12 weeks after injection in SHIM with a *p* value of < 0.001. However, the same comparison within the control group before the injection, 2, 6, and 12 weeks after injection as regards SHIM score (Table 6) showed that there was no statistical significance of the SHIM score within the control group before and 2 weeks after injection in SHIM with a *p* value of 0.44 as well as 6 weeks after injection in SHIM with a *p* value of 0.73 as well as before and 12 weeks after injection in SHIM with a *p* value of 0.23.

We compared the results of penile duplex before the injection and 2 weeks after injection within the treatment group (Table 7). It showed that there was statistically significant improvement as regards erection hardening score as well as PSV *p* values were < 0.001, but there was no statistically significant difference as regards EDV. On the other hand, the comparison of the results of penile duplex before the injection and

TABLE 7 Comparison of erection hardness score and penile duplex parameters between before and 2 weeks after injection of BOTOX within the treatment group

	Mean	SD	*p* value
EHS (B)	2.34	0.59	
EHS (2W)	2.89	0.76	<0.001
PSV (B)	34.4	11.7	
PSV (2W)	45.8	13.2	<0.001
EDV (B)	3.5	3.7	
EDV (2W)	1.7	3.5	0.244

Abbreviations: B, before; EDV, end diastolic velocity; EHS, erection hardening score; PSV, peak systolic velocity; 2W, at 2 weeks.

TABLE 8 Comparison of erection hardness score and penile duplex parameters between before and 2 weeks after injection of saline within the control group

	Mean	SD	*p* value
EHS (B)	2.14	0.49	
EHS (2W)	2.23	0.598	0.083
PSV (B)	31.3	15.6	
PSV (2W)	31.9	16.1	0.658
EDV (B)	4.5	3.4	
EDV (2W)	4.5	3.9	0.394

Abbreviations: B, before; EDV, end diastolic velocity; EHS, erection hardening score; PSV, peak systolic velocity; 2W, at 2 weeks.

2 weeks after injection within the control group (Table 8) showed that there was no statistically significant improvement as regards erection hardening score and all the penile duplex parameters.

Finally, we compared between diabetic patients and nondiabetic patients within the treatment group as regards SHIM before injection and also at 2, 6, and 12 weeks post injection. There was statistically significant difference before the injection between the two groups in favor of nondiabetic patients with $p = 0.019$. However, there was no statistically significant difference between the two groups at 2, 6, and 12 weeks post injection (Table 9).

During the follow-up period, no local or systemic complications occurred in either group.

6 | DISCUSSION

The present study showed that (53%) of the patients in the treatment group ($n = 18$) were able to have an erection hard enough for vaginal penetration. Twenty-two (64.7%) patients in the treatment group reported improvement in their erections and 14 (41.2%) patients reported that the treatment improved their ability to engage in sexual activity versus none of the patients in the control group. Also, 2 weeks post treatment, the treatment group showed a statistically significant improvement in the penile hemodynamics in the form of the mean EHS, PSV, and EDV ($p < 0.001$) compared to the control group. Finally, at 6- and 12-weeks post treatment, there was a statistically significant difference between both groups in the SHIM score, SEP-2, GAQ-Q1, and GAQ-Q2 positive responders favoring the treatment group.

TABLE 9 Comparison between diabetic and nondiabetic subgroups within the treatment group as regards sexual health index for men (SHIM) before injection and at 2, 6, and 12 weeks after injection of botulinum neurotoxin

		Mean	SD	*p* value
(B) SHIM	Diabetic	5.05	1.77	
	Nondiabetic	5.93	1.385	0.019
(2W) SHIM	Diabetic	6.38	1.83	
	Nondiabetic	7.07	2.61	0.454
(6W) SHIM	Diabetic	9.7	6.1	
	Nondiabetic	10.36	5.85	0.722
(12W) SHIM	Diabetic	7.8	3.76	
	Nondiabetic	8.86	4.55	0.601

Abbreviations: B, before; 2W, 2 weeks after injection; 6W, 6 weeks after injection; 12W, 12 weeks after injection.

The first human pilot study involving 24 men with severe vasculogenic ED refractory to PDE5Is; the patients were randomized to treatment and control groups (1:1). The treatment group received a single ICI of Botox 50 Units and the control group received a single ICI of 0.9% normal saline 1 ml. There was a statistically significant improvement in the mean PSV, SHIM score, and EHS in the treatment group. And 58% of the patients in the treatment group were able to engage in penetrative sex with their partners with the help of PDE5Is. There were no episodes of priapism or systemic toxicity from BoNT-A encountered in the treatment group.[36] These results are comparable to the results obtained from the present study as (64.7%) patients in the treatment group reported improvement in their erections and 14 (41.2%) patients reported that the treatment improved their ability to engage in sexual activity.

Another study was done by Giuliano et al. in 2019 to study the safety and efficacy of ICI of abobotulinumtoxinA (Dysportfi) as add on therapy to PDE5Is or prostaglandin E1 for ED. In this study, they treated 47 patients complaining of ED not responding to oral PDE5Is or ICIs with 250 and 500 units of abobotulinumtoxinA, respectively. They used the International Index of Erectile Function-Erectile Function IIEF-EF domain score before and 6 weeks after injection in the comparison. This study showed increase of the IIEF-EF domain score from 12.3 ± 5.6 to 14.8 ± 6.6. However, this study was not controlled. Also, they used abobotulinumtoxinA with two different doses 250 and 500 units with high response rate 54.5% and 52.9%, respectively, instead of onabotulinumtoxinA.[41]

The results of this study showed similar findings to the previous human study. This was a larger human study involving 70 patients randomized into treatment and control groups (1:1) extended up to 12 weeks. Baseline characteristics were similar between both groups. Based on the mean SHIM, EHS, penile duplex parameters, and SEP

questionnaire scores, at baseline patients in both groups suffered from severe ED. At 2 weeks post injection, patients in the treatment group showed statistically significant improvements in the EHS, GAQ-Q1, PSVs, and EDVs. There was also an improvement in the SHIM, SEP-2&3, and the GAQ-Q2 scores but not reaching statistical significance. This is similar to the onset of action of BoNT-A in other smooth muscle disorders, such as detrusor overactivity, which normally takes up to 2 weeks before exerting its neurotoxic effect.[21,42–45]

The peak subjective improvement in the quality of erections in the treatment group was observed at 6 weeks as evidenced by the statistically significant improvements in the SHIM, SEP-2, GAQ-Q1, and GAQ-Q2. These improvements were clinically meaningful as there was a 5-point increase in the mean SHIM score, and 53% (18) of the patients were able to achieve an erection hard enough to enable vaginal penetration compared to only three patients at baseline. These results are comparable to the study of Giuliano et al. in 2019 as they showed response rate 54.5% and 52.9% with two different doses of abobotulinumtoxinA 250 and 500 units, respectively, at 6 weeks post injection.[41] The response to the GAQ showed that 64.7% of the patients reported improvement in their erections and 41.2% reported that the treatment improved their ability to engage in sexual activity. The small number of positive responders to SEP-3 in the treatment group (three patients) may be attributed to the fact that all the patients had severe ED at baseline. The improvements were maintained at the 12 weeks follow-up but were starting to decline when compared to 6 weeks post injections. This coincides with the findings of the studies that looked into the use of BoNT-A injection in detrusor overactivity, which demonstrated that although BoNT-A is still active, yet there is decreasing treatment response compared with a placebo after 12 weeks.[21,42–45]

In the present study, there was no statistically significant difference between diabetic patients and nondiabetic patients within the treatment group as regards SHIM before injection and also at 2, 6, and 12 weeks post injection. This result was in agreement with the conclusion of Giuliano et al. study as they stated that the improvement was not affected by either the risk factor or the cause of ED.[41]

To date, two animal studies and two human pilot study have investigated the safety and efficacy of BoNT-A in the treatment of ED. In the first of the animal studies, by Ghanem et al., 30 male albino rats were divided into three equal groups: 10 received an ICI of saline 0.1 ml (control); 10 received an ICI of BoNT-A 1 unit; and 10 received an ICI of BoNT-A 2 units. The rats were sacrificed after 4 weeks and cavernosal tissue histological and immunohistochemical analyses were performed. The results showed a statistically significant larger mean resting sinusoidal diameter in the two treatment groups compared with the control group. There were no local or systemic side effects.

In another animal study, De Young et al. in 2017 investigated the use of BoNT-A ICI in 10 rats divided into treatment and control groups. There was a significant increase in the intracavernosal pressure in the treatment group and cavernosal histopathology showed a larger resting sinusoidal diameter compared to the control group.[46]

Priapism and systemic toxicity from BoNT-A were not encountered in any of the study patients nor were there any other local side effects. This result matched with the results of the previous two studies.[37,41]

7 | CONCLUSION AND RECOMMENDATION

This study has demonstrated that ICIs of 100 units of BoNT-A is a safe and effective potential treatment modality for ED refractory to PDE5Is. BoNT-A may thus have a role in the ED management protocol by downgrading the level of ED and reducing the number of patients requiring second-line or third-line therapy. Further multicenter randomized controlled trials with longer follow-up periods are warranted in order to further explore the therapeutic efficacy and clinical safety of BoNT-A in the treatment of different subsets and severity levels of ED. Unfortunately, we did not look into whether or not some of the patients would be able to function without using PDE5Is because we asked all the patients to use the same dose of the same PDE5I that they were using before treatment. However, this is something that can be investigated in future studies.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

Islam Fathy Soliman Abdelrahman: Methodology, study design, acquisition of the data, original draft preparation, review, and editing.

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REFERENCES

1. Ayta IA, McKinlay JB, Krane RJ. The likely worldwide increase in erectile dysfunction between 1995 and 2025 and some possible policy consequences. *BJU Int*. 1999;84:50-56.

2. Hatzimouratidis K, Amar E, Eardley I, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *Eur Urol*. 2010;57:804-814.
3. Ventimiglia E, Capogrosso P, Montorsi F, Salonia A. The safety of phosphodiesterase type 5 inhibitors for erectile dysfunction. *Expert Opin Drug Saf*. 2016;15:141-152.
4. Yafi FA, Jenkins L, Albersen M, et al. Erectile dysfunction. *Nat Rev Dis Primers*. 2016;2:16003.
5. Evans JD, Hill SR. A comparison of the available phosphodiesterase-5 inhibitors in the treatment of erectile dysfunction: a focus on avanafil. *Patient Prefer Adherence*. 2015;9:1159-1164.
6. Stuckey BG, Jadzinsky MN, Murphy LJ, et al. Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: results of a randomized controlled trial. *Diabetes Care*. 2003;26:279-284.
7. Bosshardt RJ, Farwerk R, Sikora R, Sohn M, Jakse G. Objective measurement of the effectiveness, therapeutic success and dynamic mechanisms of the vacuum device. *Br J Urol*. 1995;75:786-791.
8. Moreland RB, Kim N, Nehra A, Goldstein I, Traish A. Functional prostaglandin E (EP) receptors in human penile corpus cavernosum. *Int J Impot Res*. 2003;15:362-368.
9. Virag R, Shoukry K, Floresco J, Nollet F, Greco E. Intracavernous self-injection of vasoactive drugs in the treatment of impotence: 8-year experience with 615 cases. *J Urol*. 1991;145:287-292. discussion 92–3.
10. Jorissen C, De Bruyna H, Baten E, Van Renterghem K. Clinical outcome: patient and partner satisfaction after penile implant surgery. *Curr Urol*. 2019;13:94-100.
11. Trost LW, McCaslin R, Linder B, Hellstrom WJ. Long-term outcomes of penile prostheses for the treatment of erectile dysfunction. *Expert Rev Med Devices*. 2013;10:353-366.
12. Aoki KR. Physiology and pharmacology of therapeutic botulinum neurotoxins. *Curr Probl Dermatol*. 2002;30:107-116.
13. Chung E. Botulinum toxin in urology: a review of clinical potential in the treatment of urologic and sexual conditions. *Expert Opin Biol Ther*. 2015;15:95-102.
14. Aoki KR. Pharmacology and immunology of botulinum toxin serotypes. *J Neurol*. 2001;248(Suppl 1):3-10.
15. Munchau A, Bhatia KP. Uses of botulinum toxin injection in medicine today. *BMJ*. 2000;320:161-165.
16. Smith CP, Franks ME, McNeil BK, et al. Effect of botulinum toxin A on the autonomic nervous system of the rat lower urinary tract. *J Urol*. 2003;169:1896-1900.
17. Chapple C, Sievert KD, MacDiarmid S, et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. *Eur Urol*. 2013;64:249-256.
18. Cruz F, Herschorn S, Aliotta P, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. *Eur Urol*. 2011;60:742-750.
19. Cruz F, Nitti V. Chapter 5: clinical data in neurogenic detrusor overactivity (NDO) and overactive bladder (OAB). *Neurourol Urodyn*. 2014;33(Suppl 3):S26-31.
20. Escuder AG, Hunter DG. The role of botulinum toxin in the treatment of strabismus. *Semin Ophthalmol*. 2019;34:198-204.
21. Nitti VW, Dmochowski R, Herschorn S, et al. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. *J Urol*. 2013;189:2186-2193.
22. Jones DH, Kerscher M, Geister T, Hast MA, Weissenberger P. Efficacy of incobotulinumtoxinA for the treatment of glabellar frown lines in male subjects: post-hoc analyses from randomized, double-blind pivotal studies. *Dermatol Surg*. 2017;43(Suppl 2):S235-S41.
23. Kattimani V, Tiwari RVC, Gufran K, Wasan B, Shilpa PH, Khader AA. Botulinum toxin application in facial esthetics and recent treatment indications (2013–2018). *J Int Soc Prev Community Dent*. 2019;9:99-105.
24. Kim DW, Cundiff J, Toriumi DM. Botulinum toxin A for the treatment of lateral periorbital rhytids. *Facial Plast Surg Clin North Am*. 2003;11:445-451.
25. Matsudo PK. Botulinum toxin for correction of fronto-glabella wrinkles: preliminary evaluation. *Aesthetic Plast Surg*. 1996;20:439-441.
26. Qaqish C. Botulinum toxin use in the upper face. *Atlas Oral Maxillofac Surg Clin North Am*. 2016;24:95-103.
27. Sarrabayrouse MA. Indications and limitations for the use of botulinum toxin for the treatment of facial wrinkles. *Aesthetic Plast Surg*. 2002;26:233-238.
28. Montecucco C, Molgo J. Botulinal neurotoxins: revival of an old killer. *Curr Opin Pharmacol*. 2005;5:274-279.
29. Nigam PK, Nigam A. Botulinum toxin. *Indian J Dermatol*. 2010;55:8-14.
30. Leippold T, Reitz A, Schurch B. Botulinum toxin as a new therapy option for voiding disorders: current state of the art. *Eur Urol*. 2003;44:165-174.
31. MacKenzie I, Burnstock G, Dolly JO. The effects of purified botulinum neurotoxin type A on cholinergic, adrenergic and non-adrenergic, atropine-resistant autonomic neuromuscular transmission. *Neuroscience*. 1982;7:997-1006.
32. Gandaglia G, Briganti A, Jackson G, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. *Eur Urol*. 2014;65:968-978.
33. Ghanem H, Raheem AA, AbdelRahman IFS, Johnson M, Abdel-Raheem T. Botulinum neurotoxin and its potential role in the treatment of erectile dysfunction. *Sex Med Rev*. 2018;6:135-142.
34. Serefoglu EC, Hawley WR, Lasker GF, et al. Effect of botulinum-A toxin injection into bulbospongiosus muscle on ejaculation latency in male rats. *J Sex Med*. 2014;11:1657-1663.
35. Shaeer O, Shaeer K, Shaeer A. Botulinum toxin a (Botox) for relieving penile retraction. *J Sex Med*. 2009;6:2788-2794.
36. Ghanem H, Fathy I, Raheem AA, Shamloul R, Hamid MA. 024 The effect of botulinum toxin on penile vascular parameters and clinical outcome in patients with severe Ed: a pilot study. *J Sex Med*. 2017;14(1):S11.
37. Ghanem H, Raheem AA, Fathy I. 037 Safety and effectiveness of botulinum toxin in the treatment of severe ED: a pilot study. *J Sex Med*. 2017;14(2):e18.
38. Ghanem H, Soliman I, AbdulHamid M, Shamloul R. PS-08-016 Can intracavernosal botulinum toxin injection salvage vascular erectile dysfunction patients not responding to oral and intracavernous therapy? A pilot study. *J Sex Med*. 2016;13(5):S116.
39. Sikka SC, Hellstrom WJ, Brock G, Morales AM. Standardization of vascular assessment of erectile dysfunction: standard operating procedures for duplex ultrasound. *J Sex Med*. 2013;10:120-129.
40. Shamloul R, Ghanem H, Abou-zeid A. Validity of the Arabic version of the sexual health inventory for men among Egyptians. *Int J Impot Res*. 2004;16:452-455.
41. Giuliano F, Joussain C, Denys P. Safety and efficacy of intracavernosal injections of abobotulinumtoxinA (Dysport((R))) as add on therapy to phosphosdiesterase type 5 inhibitors or prostaglandin E1 for erectile dysfunction—case studies. *Toxins (Basel)*. 2019:11:283.
42. Denys P, Le Normand L, Ghout I, et al. Efficacy and safety of low doses of onabotulinumtoxinA for the treatment of refractory idiopathic overactive bladder: a multicentre, double-blind, randomised, placebo-controlled dose-ranging study. *Eur Urol*. 2012;61:520-529.
43. Dmochowski R, Chapple C, Nitti VW, et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. *J Urol*. 2010;184:2416-2422.

44. Sahai A, Khan MS, Dasgupta P. Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center, randomized, double-blind, placebo controlled trial. *J Urol*. 2007;177:2231-2236.
45. Tincello DG, Kenyon S, Abrams KR, et al. Botulinum toxin a versus placebo for refractory detrusor overactivity in women: a randomised blinded placebo-controlled trial of 240 women (the RELAX study). *Eur Urol*. 2012;62:507-514.
46. De Young L, Campbell J, Radomski S, Alzubaidi R, Brock G. 142 Intra-cavernosal injection of botulinum toxin to improve erectile function in older rats. *J Sex Med*. 2017;14(1):S40-1.

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