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Comparative Study between Intracavernosal Injection of Botulinum Toxin type A [50 and 100 unit], Efficacy and Durability in the Treatment of Vascular Erectile Dysfunction

A.A.Taleb[1], M.El-Tabey[1],W.A.El-Shaer[1], H.M.Ghanem[2] and T.A.wahab[1]
[1]Urology Dept, Faculty of Medicine, Benha Univ, Benha, Egypt
[2]Andrology Dept, Faculty of Medicine, Cairo Univ, Egypt
E-Mail: Tamerdiab100@gmail.com

Abstract

Evidence has been arising suggesting that Botulinum toxin type A [BTX-A] injections can relax smooth muscles fibers in the treatment of obesity and Detrusor muscle over-activity, similar effect on cavernosal smooth muscles would help in the treatment of erectile dysfunction [ED] resistant to oral and intracavernous injection [ICI] therapy, thus it could be an alternative option for failed medical and other injectable therapy.. to compare safety, efficacy and durability of different doses of BTX-A [50 and 100 Unit] in the treatment of Vasculogenic Erectile Dysfunction after failure of other ICI therapy.. Forty-five patients with Vasculogenic erectile dysfunction who are failed treatment with non-surgical options were included at this study after elimination of all patients who are not matching eligible criteria or not complete the follow up program. The patients were randomized into 3equal groups, each group include 15 patients. Group [I] injected with 100U BTX-A, group [II] injected with 50U BTX-A and Control group injected with normal saline. All groups underwent follow up at 2 weeks, 3 months and 6 months intervals after injection, for assessment of all subjective data as, IIEF-5 Questionnaire [SHIM score], Erection hardness score [EHS], Sexual encounter profile [SEP 2 and 3], Global assessment score[GAS 2 and 3]. Also assessment of objective data by penile Doppler details.. Although 25 patients [55.6%] respond to BTX-A injection subjectively and objectively {13 patients [28.9%] in group [I] and 12 patients [26.7%] in group [II]}, but this impressive effect was not durable especially in group [II] as 9 patients [20%] show lost effect through complete follow up till 6 month in comparison to 5 patients [11.1%] in group [I] show same lost effect. Besides that, 5 patients [11.1 %] not responding to this treatment option {two patients [4.4%] in group [I] and 3 patients [6.7%] in group [II], also patients in Control group show non-significant subjective improvement. BTX-A could be a potential but not durable therapy for erectile dysfunction, as BTX-A [50 and 100 Unite] show almost same efficacy but, with complete follow up through 6 months, BTX-A 100U is more durable than 50U.

Keywords: Intracavernosal injection, Botulinum Toxin type A [BTX-A], Vascular Erectile dysfunction, Efficacy and Durability.

1.Introduction

1.1 Erectile dysfunction

Erectile dysfunction [ED] is widely accepted now as a persistent inability to achieve or maintain a penile erection sufficient to permit satisfactory sexual performance, reflecting a dramatic effect on quality of life for the man and his partner [1-7].

ED commonly occurs, and it's incidence increases with age, its prevalence is anticipated to increase from 152 million in 1995 to 322 million by 2025 [8-9].

ED is classified as psychogenic, organic, or mixed psychogenic and organic, 80% of cases are now considered to be organic in origin, but the final common pathway in the majority of subjects with organic ED is endothelial dysfunction[vasculogenic ED] [10-11].

Subjective and objective assessment should included at initial evaluation , medical, sexual, and psychosocial histories, as well as laboratory assays and complete Doppler study to identify possible comorbidities for a well-organized management [12-14].

Fifty years ago, psychotherapy was the mainstay treatment and undoubtedly was limited in its success. During the 1970s, penile prostheses combined with psychotherapy remained popular but relatively inaccessible. In the 1980s, intracavernosal injection [ICI] emerged, followed by intra-urethral therapy in the mid-1990s. The true revolution in the non-surgical management of ED was with the introduction of oral phosphodiesterase type 5 inhibitors [PDE5Is] in the late 1990s and subsequently. PDE5Is rapidly became the patient-friendly method of ED treatment and are currently considered as first-line monotherapy 15].

ICI has been used successfully since 1982 for patients with erectile dysfunction. Despite advances in oral and intraurethral treatments, ICI remains a very effective second line therapy for many patients [16-18].

Recently, the possibility of using stem cells or gene therapy has shown some early promise but disappointing clinical outcomes [19].

1.2 Botulinum toxin

One of the most potent toxins known to humans produced by Clostridium botulinum, resulting in generalized paralysis including

respiratory arrest and death, is Botulinum neurotoxin [BoNT] [20-21].

Although seven biochemical and serologic forms of BoNT [A, B, C1, D, E, F, and G] are known, only BoNT-A, BoNT-B, and BoNT-E can cause botulism in humans, whereas the remaining BoNT forms can cause disease only in animals. BoNT-A is the most commonly used form in medicine [22-23].

One of the newest putative therapeutic opportunities to be explored is the intracavernosal delivery of botulinum toxin A for ED. Most clinicians and the general public are familiar with its utility in dermatology suites and plastic surgery facial clinics for cosmetic indications. Intra detrusor delivery of Botox has been approved for patients with neurogenic and idiopathic detrusor overactivity. The potential for its use in facilitating long-acting cavernous smooth muscle relaxation through alteration of the balance within the penis between the permanent sympathetic contractile tone applied to cavernosal smooth muscle fibers responsible for flaccidity and the relaxed state of the cavernous smooth muscles induced by the activation of the parasympathetic nitric oxide [NO]-cyclic guanosine phosphate pathway in erection is a potential game changer **[**24].

Botulinum toxin A can inhibit norepinephrine, but not NO, release Thus, Botulinum toxin A could be responsible for a persisting modulatory effect on the erectile tissue facilitating an erectile response to sexual stimulation **[**19]

Currently, few real data on this pathway or treatment approach exist apart from a small basic animal study by De-Young et al25, and a pilot study from Egypt by Ghanem et al [**26**].

2. Patients and Methods

This was a prospective randomized double-blind placebo controlled study conducted in the outpatient setting. Ethical approval was obtained from the Institutional Ethics Committee before beginning.

2.1 Eligibility

Forty five patients with ranged age between 40 to 70 years old proved to be Vasculogenic ED by Penile Duplex, unable to develop erections sufficient for intercourse with "No" response on Sexual Encounter Profile questions [SEP 2 & 3], failing to respond to first and second line treatments for ED, and surgery is the only remaining treatment option for them were eligible for inclusion in our study Contrarily, patients with significant cardiovascular disease interfering with sexual activity, any history of an unstable psychiatric conditions and presence of penile anatomical abnormalities that would significantly impair erectile function were excluded from this study .

2.2 Baseline evaluation

All patients were assessed basally by full sexual history with scoring evaluation contained through, Sexual Health Inventory for Men score [SHIM], Erection Hardness Score [EHS], Sexual Encounter Profile [SEP-Questions 2 and 3] and Global Assessment Score [GAS]., then local penile examination to exclude any anatomical abnormalities followed by initial penile Doppler using a trimix solution [PGE1 10 ug + Phentolamine 1 mg + Papaverine 30 mg], finally all data were recorded to be followed up.

2.3 Randomization and allocation

Those patients equally randomized into 3 groups I, II. Injected by 100 and 50Unit BTX-A, and Control group injected with normal saline.

2.4 Procedure

In a recumbent position at controlled air-conditioned environment [24 °C], and promptly after the patient stripp of his clothes to minimize thermal effect, a fully stretched flaccid penile length which considered equivalent to erected penile length as described by Wessels et al27 was measured by same doctor using a tape from pubo-penile junction to distal glans, also a rigid ruler was applied to push suprapubic fat to confirm measurement and decrease inaccurate measures in obese patients, beside that, a mid-shaft penile girth was obtained using a rubber tape and all measures were approximated to the nearest 0.5 cm.

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

Botox [Onabotulinum toxin A; Allergan, Irvine, Ireland] diluted in isotonic saline injected through an insulin syringe intracavernosally 2cm proximal to coronal margin and 2cm distal to pubo-penile junction at right and left sides respectively followed by a fine massage at four sites of injection for 5 minutes and the band removed after 20 minutes.

2.5 Follow up

All patients in each group were evaluated at the following interval, 2 weeks, 3 months and 6 months after Botox injection subjectively and objectively as the same method described in basal assessment.

3. Results

Table (**1**) Three Groups Through Timeframe Evaluation

		Basal Median[IQR]	2w follow up Median[IQR]	3m follow up Median[IQR]	6m follow up Median[IQR]	Friedman test	P value
Group I	**Shim score**	8[7-9]	12[11-13]a	14[12-16]ab	11[8-15]ac	117.8	<0.001**
	EHS	1[1-2]	3[2-3]a	3[3-3]ab	2[2-3]ac	122.5	<0.001**
	SEP2	0[0.0]	36[58.1]	54[87.1]	30[48.4]		
	SEP3	0[0.0]	36[58.1]	54[87.1]	30[48.4]		
	GAS1	0[0.0]	54[87.1]	54[87.1]	54[87.1]		
	GAS2	0[0.0]	36[58.1]	54[87.1]	30[48.4]		
	Fully stretched penile length Mean ± SD	11.64±**1.12**	11.5[11-12.5]	12.5[11.88-14.5]ab	12.5[11.5-14]abc	112.2	<0.001**
	Fully stretched penile girth	8.5[7.5-9.5]	8.5[7.5-9.5]a	9[7.5-10]ab	8[7.5-9.5]c	38.97	<0.001**
	Cavernous artery diameter bef	0.6[0.5-0.75]	0.63[0.5-0.75]a	0.64[0.55-0.8]ab	0.65[0.55-0.8]ab	62.65	<0.001**
	Cavernous artery diameter aft	0.75[0.65-1.0]	0.9[0.75-1.15]a	0.95[0.85-1.26]ab	1.05[0.9-1.25]abc	127.44	<0.001**
	PSV	20[18-32]	33[31-35]a	33[32-34.25]a	32.5[28.5-37.5]a	85.72	<0.001**
	EDV	6[3-7]	5[3-6.5]a	4.5[3-5. 5]ab	3.5[3-5.62]a	31.77	<0.001**
	RI	0.8[0.7-0.84]	0.88[0.8-0.9]a	0.89[0.85-0.9]ab	0.84[0.77-0.89]abc	118.67	<0.001**
Group II	**Shim score**	8[8-9]	11[11-12]a	13[12-15]ab	8[8-10]abc	107.5	<0.001**
	EHS	2[1-2]	2[2-3]a	3[3-3]ab	2[2-2]abc	115.4	<0.001**
	SEP2	0[0.0]	27[45.8]	48[81.4]	11[18.6]		
	SEP3	0[0.0]	27[45.8]	48[81.4]	11[18.6]		
	GAS1	0[0.0]	49[83.1]	51[86.4]	51[86.4]		
	GAS2	0[0.0]	26[44.1]	48[81.4]	11[18.6]		
	Fully stretched penile length Mean ± SD	12.04±**1.3**	11.5[10.5-12.5]	12[11.5-13]ab	12.5[11.5-14]ab	61.59	<0.001**
	Fully stretched penile girth	8.5[8-9]	8.5[8-9]	9[8.5-9]a	8.5[8-9]c	94.57	<0.001**
	Cavernous artery diameter bef	0.6[0.4-0.75]	0.6[0.4-0.75]	0.65[0.45-0.75] ab	0.6[0.45-0.7] abc	38.04	<0.001**
	Cavernous artery diameter aft	0.85[0.6-1.05]	0.93[0.68-1.15]a	1.0[0.7-1.2]ab	1.0[0.7-1.15]abc	81.34	<0.001**
	PSV	22.5[19.5-37.5]	33.5[30-41]a	33[30-40]a	29.5[23.5-38]abc	112.13	<0.001**
	EDV	6.5[4-7.5]	6[3-6.5]a	5[3.5-5.5]ab	5.5[3.5-6.5]abc	65.23	<0.001**
	RI	0.8[0.7-0.84]	0.84[0.81-0.9]a	0.86[0.85-0.89]ab	0.81[0.76-0.84]abc	111.3	<0.001**
Control group	**Shim score**	8[7-9]	7[6-8]a	6[6-8]ab	8[6-10]bc	34.9	<0.001**
	EHS	1[1-2]	1[1-2]	1[1-1]	2[2-2]abc	50.52	<0.001**
	SEP2	0[0.0]	0[0.0]	0[0.0]	0[0.0]		
	SEP3	0[0.0]	0[0.0]	0[0.0]	0[0.0]		
	GAS1	0[0.0]	0[0.0]	0[0.0]	0[0.0]		
	GAS2	0[0.0]	0[0.0]	0[0.0]	0[0.0]		
	Fully stretched penile length Mean ± SD	12.12±**1.23**	12.5[11.5-13]	12[10.5-13]b	12 [10.5-13]b	13.0	0.005**
	Fully stretched penile girth	8.5[8-9]	8.5[8-9]	8.5[8-9]	8.5[8-9]	-	-
	Cavernous artery diameter bef	0.5L.5[0.4-0.65]	0.5[0.4-0.65]a	0.5[0.4-0.65]b	0.5[0.4-0.65]ac	12.7	0.005**
	Cavernous artery diameter aft	0.7[0.5-0.95]	0.7[0.5-0.95]	0.7[0.5-0.95]	0.8[0.7-0.95]abc	39.21	<0.001**
	PSV	31.5[18.5-37.5]	31.5[20.5-37.5]a	32[20.5-37.5]ab	32[20.5-37.5]a	25.36	<0.001**
	EDV	6[5.5-7]	7[6-7.5]a	7[6-7.5]a	6[3.5-7]abc	20.97	<0.001**
	RI	0.8[0.7-0.83]	0.8[0.75-0.82]	0.8[0.7-0.83]	0.8[0.7-0.83]	7.14	0.068

Although 25 patients [55.6%] respond to BTX-A injection subjectively and objectively {13 patients [28.9%] in group [I] and 12 patients [26.7%] in group [II]}, but this impressive effect was not durable especially in group [II] as 9 patients [20%] show lost effect through complete follow up till 6 month in comparison to 5 patients [11.1%] in group [I] show same lost effect. Besides that, 5 patients [11.1 %] not responding to this treatment option {two patients [4.4%] in group [I] and 3 patients [6.7%] in group [II]}, also patients in Control group show non-significant subjective improvement.

4.Discussion

As ED has a strong negative impact on quality of life and human psychological comfort [**28,29]** and it is believed that the disease is always hidden with insufficient treatment so, it was necessary finding a new trends in treatment [30].

Where cavernosal smooth muscles relaxation is the corner stone in erection physiology which is mediated by nitric oxide production resulting from stimulation of parasympathetic cholinergic and non-adrenergic non-cholinergic neurons.31so, sinusoidal smooth muscle relaxation effect of BoNT-A produce rational concept about its role in treatment.

Our belief in this treatment pathway was settled down after previous experiences of a small basic animal study by De Young et al**[25]** on old rats receiving Botox 10 U compared with controls and small human pilot study by Ghanem et al [26] which 12 patients received a single intracavernous injection of Botox 50 U with increased arterial flow and improved SHIM score after 2 weeks.

Our results confirm the results of Ghanem et al [26] in safety concern of Botox and its effective role in treatment of patients with refractory ED, beside that with application comparison between 50 and 100 U of BoNT-A, our results show same efficacy of 100 U than 50 U at initial follow up till 3 months but, with complete follow up till 6 months, BoNT-A 100 U show more durable action than 50 U with same safety.

5.Conclusion

BTX-A could be a potential but not durable therapy for erectile dysfunction, as BTX-A [50 and 100 Unite] show almost same efficacy but, with complete follow up through 6 months, BTX-A 100U is more durable than 50U.

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