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ONABOTULINUM TOXIN-A FOR OVERACTIVE BLADDER

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Abstract

The propose of this study is to evaluate the effect of Botulinum A intradetrusor injection on patients with overactive bladder refractory to oral anticholinergics and safety of the drug.

Patients with overactive bladder (excluding patients with neurological or pathological causes) were enrolled in this study, those patients did not benefit of oral medications with anticholinergic effect, and they were assessed for history of their problem and kept a urinary diary for three days before the start of the procedure. They were also examined, and ultrasound for post voiding residue with urinary flow rate was kept in records. Injection of 200 IU of onabotulinom toxin-A in the detrusor muscle. The drug effect was studied one month after injection on patient's symptoms, including day and night frequency, urgency and urge incontinence by keeping a three days' urinary diary postoperatively. The maximum flow rate and the post voiding volume were also measured. Postoperative complications in the form of haematurea, urinary tract infection and retention of urine were recorded.

There was a significant decrease in the number of voiding during both day and night from 10.7±1.68 SD, 2.09±0.93 SD to 4.407±1.394 SD, 1.257±0.752 SD respectively which is statistically significant difference (t (135) =6.377, P≤0.001), (t (135) =0.837, p≤0.001), this was associated with a reduction in the number of episodes of incontinence from 1.37±0.975 SD to 0.6815±0.676 SD. The postvoiding volume was increased remarkably. Complications includes urinary tract infection and retention of lower tract local effects only.

In conclusion, the use of onabotulinom toxin-A in the treatment of refractory overactive bladder is effective in reducing patients' symptoms and discomfort as well as being a safe option for treatment.

Introduction

Overactive bladder (OAB) is a group of symptoms including frequency, nocturea, urgency and urge incontinence that exists in a patient after excluding pathological and neurological causes. The patient might pass urine more than eight times during day time and more than one time during night with strong desire to pass urine with or without involuntary passage of urine. These symptoms can affect the quality of life of those patients to a degree that can have a financial impact by changing the productivity of those patients[1,2].

The treatment of overactive bladder can be in the form of behavioral therapy as first line treatment and the second line treatment will be in the form of oral drugs either antimuscrinic or β 3-adrenoceptor agonist, and the third line is in the form of intradetrusor injection of Botox, peripheral tibial nerve stimulation or sacral neuromodulation. Patients with overactive bladder usually are treated by the first two lines of treatment if there condition persist and it is unresponsive then they are shifted to the third line of treatment. One way is by the injection of the detrusor muscle with onabotulinum toxin- A. Botox is a neurotoxin protein produced by the bacterium Clostridium botulinum a gram positive anaerobic bacterium[3,4], there are several indications for Botox in addition to overactive bladder it may be used for focal hyperhidrosis, blepharospasm, strabismus, chronic migraine as well as the wildly spread cosmetic use. Botox is broken into 7

neurotoxins (labeled as subtypes A,B,C,D,E,F and G) they are different serologically and antigenically but similar structurally There are two main commercial types: botulinum toxin type A and botulinum toxin type B. The subtype for overactive bladder is onabotulinum toxin-A, it act by attaching to the presynaptic nerve terminals at specific high affinity sites thus preventing the release of acetylcholine and blocking the neurotransmission as a result the muscle involved will be paralyzed .This was the principle by which Botox was used in overactive bladder to control the involuntary detrusor muscle contraction and it's undesirable urinary symptoms.

Materials and methods

From march 2016 a total of 135 patients with overactive bladder(after excluding other pathological and neurological causes for their symptoms) were treated with intradetrusor injection of onabutulinom toxin-A in Basrah General Hospital, this was done by the same surgeon using G21F cystoscope and the procedure was carried out under general anesthesia using a flexible endoscopic needle (Figure 1) in a way that the injection site forms a wheel by inserting the needle end to about 0.5 cm in the bladder wall (Figure 2). The dose used was 200 IU for all patients and it was injected in 20 different sites avoiding injecting the trigon and the ureteric orifices (Figure III).

Figure 1: Flexible endoscopic injection needle

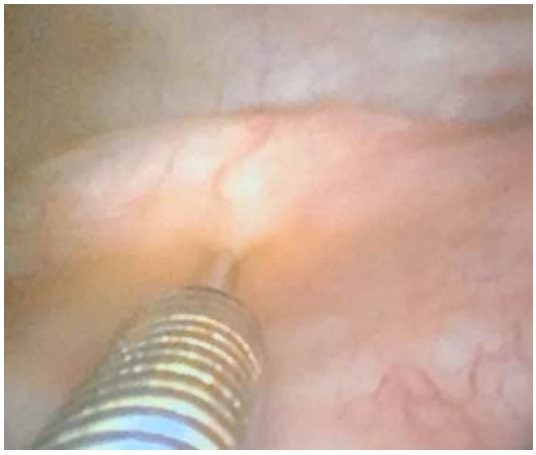

Figure 2: Flexible needle endoscope bladder injection site (wheel)

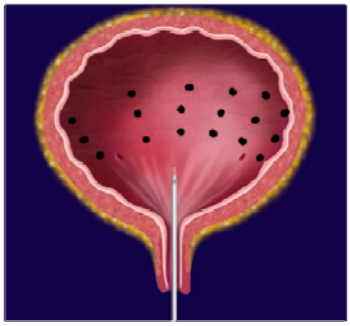

Figure 3: injection pattern for intradetrusor injections of Botox for overactive bladder

Data was collected from those patients one month after the injection regarding episodes of incontinence, day and night frequency by a three day urinary diary, an ultrasound was done to check for post voiding residual volume and a flow rate measurement to determine the maximum flow rate these data were compared to those obtained as baseline before the injection.

During early post-operative period, patients were checked for early bleeding and urinary tract infection by general urine examination, also patients who developed retention of urine were instructed to perform clean self-intermittent catheterization for a period that lasted for six weeks.

Data was interpreted by the use of SPSS version 23 calculating means and standard deviation and comparing paired samples using a T test.

Results

In this study 135 patients were enrolled, excluding all patients with pathological and neurological causes for their symptoms, they were 83 females and 52 males (Table I).

The age range was 21-65 with a mean age of 41.8 years ± 12.6 SD (Table II).

Table I: Gender distribution

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	**female**	83	61.5	61.5	61.5
	male	52	38.5	38.5	100.0
	Total	135	100.0	100.0	

Table II: Age distribution

	N	Minimum	Maximum	Mean	Std. Deviation
age	135	21.00	65.00	41.8148	12.60075
Valid N	135				

The mean number of voiding during day before the injection of onabutulinom toxin-A was 10.7±1.68 SD while the mean number of voiding during the night was 2.09±0.93 SD. The mean number of urge incontinence before the injection was 1.37±0.975 SD, while the mean of post voiding residual volume was 33.4ml±21.45 SD and the mean Q max was 15.03 ml/sec±3.96 SD before the injection. The following parameters were recorded one month following the injection, the mean number of voiding during the day was 4.407±1.394 SD which was a statistically significant difference ($t(135)=31.93$, $P\leq0.001$).the mean number of voiding during night was 1.257±0.752 SD this was also statistically significant (t

(135)=8.29,p≤0.001). The mean of urge incontinence one month after injection was significantly reduced from that before, 0.6815±0.676 SD (t (135)=6.63, P≤0.001), there was a significant change in both the post voiding volume and Q max following onabutulinom toxinA injection, the post voiding volume increased to a mean of 98.53 ml ± 18.8 SD (t (135)= -27.78, P≤0.001) while the Q max was significantly reduced to a mean of 10.296 ml/sec±2.11 SD(t (135)=11.67,P≤0.001) (Table III).

Table III: Paired t Test

		Paired Differences					t	df	Sig. 2-tailed
		Mean	Std. Dev.	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Freq. – freq. P.O.	6.37778	2.32079	.19974	5.98272	6.772	31.930	134	.000
Pair 2	Noct. – Noct..P. O.	.83704	1.17313	.10097	.63734	1.036	8.290	134	.000
Pair 3	Incon. – incon. P.O.	.68889	1.20612	.10381	.48358	.894	6.636	134	.000
Pair 4	Qmax – Qmax P.O.	4.74074	4.71891	.40614	3.93747	5.544	11.673	134	.000
Pair 5	PVRV – PVRV P.O.	-65.11	27.228	2.343	-69.75	-60.48	-27.78	134	.000

P O: post-operative, Noct: nocturea, Incon: incontinence, Qmax: maximum flow rate PVRV: post voiding residual volume

Four patients 5.4% had retention post operatively and they required clean intermittent self-catheterization for a period of six weeks. Thirteen 17.55% patient developed sever urinary tract infection, they were treated by appropriate antibiotic according to culture and sensitivity, and seven patients 9.45% reported developing macroscopical hematuria for few days post operatively.

Discussion

The use of onabotulinum toxin A have revolutionized the treatment of overactive bladder in the last decade[5]. There was a lot of controversy regarding the recommended dose a dose range from 100 I.U. up to 300 I.U. was used for patients with variable bladder dysfunction with variable results, we have used a mid-point dosage of 200 I.U., we can see from our results that there was a better response to the 200 I.U. dose than the 100 I.U. as seen in a study by Victor W. in 2013[6] were the incontinence episode was reduced from 2.65 to 0.87 comparing to our study the reduction was from 1.37 to 0.68 episodes of incontinence .The mean number of day voiding was reduced from 10.7 to 4.407 per day in our study comparing to 11.7 reduced to 11.2 using the 100 I.U. dose conducted by Victor W, Nitti et al in 2016[7] the increased dose was associated with a better reduction in day time voiding frequency .Kessler et al reported that the mean post voiding volume after injecting

300I.U. was increased from 10 ml to 140 ml while in our study using the 200I.U. the mean volume increased from 33.4 to only 98.53 which is an important factor in minimizing the incidence of retention and the need for clean intermittent catheterization[8]. Linda Brubaker reported an incidence of post injection urinary tract infection of 44% which was higher than that reported by our study it was 17.55% which is almost half the incidence in their study[9], the incidence of culture positive urinary tract infection was 9.7% reported by Greer T. in 2016[10], these results are close to what was found in this study indicating that local complications in the form of urinary tract infection are tolerable. The data collected reported 5.4% patients had retention requiring clean self-intermittent catheterization which is very close to the reported 4% incidence of retention found by a study done by Nitti VW et al in 2013, the same result was found in similar studies[11]. This was solved by self-catheterization for six weeks. The maximum flow rate was found to decrease from 15.03ml/sec at baseline to 10.296 ml/sec after the injection which seems to be related to the increase in the post voiding volume which is related to the decrease bladder detrusor activity, this was in contrast to what was reported in 2016 by Yuh-Chen Kuo and Hann-Chorng Kuo[12] in their study they had an increase in maximum flow rate form 15.51ml/sec at base line to 17.69 ml/sec., this difference could be attributed to the difference in timing of measuring the maximum flow rate of urine which is done after three months in their study and by that time probably the effect of the drug will start to fade away in comparison to the one month post injection time of measurement of the flow rate in this study during which the effect is at its maximum.

Conclusion

This study can verify that using Botulinum Toxin A is effective in relieving the symptoms of overactive bladder with a dose dependent relationship, and low incidence rate of serious complications making it a safe procedure that can be tolerated by patients and strongly recommend it for refractory cases of overactive bladder.

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