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Kuo Y[1], Lee C[2], Jiang Y[2], Kuo H[2]

1. *Department of Urology, Taipei City Hospital, Taipei, Taiwan,* ***2.*** *Department of Urology, Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan*

THERAPEUTIC EFFECTS OF INTRAVESICAL ONABOTULINUMTOXINA INJECTION ON IC/BPS REFRACTORY TO CONVENTIONAL TREATMENT - A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED STUDY

Hypothesis / aims of study

Intravesical onabotulinumtoxinA (BoNT-A) injection has been demonstrated to be beneficial for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS) yet the therapeutic efficacy has not been validated by a placebo controlled study. We conducted a randomized, double blind, placebo controlled trial to elucidate the effects of intravesical BoNT-A injection on IC/BPS.

Study design, materials and methods

Patients with IC/BPS refractory to conventional treatment for at least 6 months were recruited in this study. All the subjects were randomized in a 2:1 ratio to receive hydrodistention plus intravesical suburothelial injection of BoNT-A 100 U (group B) or equivalent amount of normal saline (group N) in a 20 sites setting. Post-baseline study visits/assessments were conducted at weeks 2, 4 and 8. The primary endpoint was improvement of pain visual analogue scale (VAS). The secondary endpoints included changes in the O'Leary-Sant symptom index (ICSI) and problem index (ICPI), global response assessment (GRA), functional bladder capacity (FBC), frequency, nocturia, maximum flow rate (Qmax), voided volume (VV), post-void residual urine (PVR), and cystometry bladder capacity (CBC). Patients with Hunner's ulcer, PVR >150 mL or active urinary tract infection were excluded. An improvement of pain VAS $\geqq$2 or GRA $\geqq$1 was defined as treatment success. Safety was assessed by evaluating adverse events (AE).

Results

A total of 53 patients (6 male, 47 female, aged 50.8±13.9) including 36 in group B and 17 in group N were enrolled in this study. At 8 weeks after intravesical injection, significant differences in VAS, ICSI, ICPI, OSS, GRA, FBC, frequency, nocturia and PVR could be observed in group B while only significant improvements in ICSI, ICPI and OSS could be revealed in group N when compared with those at baseline (Table 1). Moreover, significantly greater decrease of VAS and increase of PVR could be demonstrated in group B than those in group N after 8 weeks follow-up. The overall successful rates of intravesical injection for treating IC/BPS were 59.3% (16/27) in group B versus 46.7% (7/15) in group N by VAS (p=0.525) and 70.4% (19/27) in group B versus 53.3% (8/15) in group N by GRA (p=0.325). There was no significant difference in prevalence of AE between the two groups (Table 2).

Interpretation of results

The significant improvements in ICSI, ICPI and OSS after normal saline injection disclosed the remarkable influence of placebo effects on subjective symptoms. However, the significant differences in VAS, ICSI, ICPI, OSS, GRA, FBC, frequency, nocturia and PVR at 8 weeks in group B indicated the comprehensive therapeutic effects of intravesical BoNT-A injection at the cost of moderate increase of PVR. The significantly greater decrease of VAS in group B than that in group N confirmed the key action of BoNT-A therapy on pain reduction in IC/BPS patients. Although the overall successful rate seemed higher in group B than in group N, the current study failed to generate a significant difference due to its small sample size.

Concluding message

The results of this randomized, double blind, placebo controlled trial demonstrated single intravesical injection of BoNT-A is effective to release the pain symptom in patients with IC/BPS refractory to conventional therapy. The adverse events are acceptable. Large scale studies are warranted.

Table 1. Comparison of the parameters at baseline and 8 weeks after treatment, and comparison of changes of the parameters at 8 weeks between the two groups

		Group B (N=27)	Group N (N=15)	P-value[#]
VAS	BL	5.48±2.39	3.40±2.69	
	8W	2.85±3.01*	2.60±1.72	0.049
	Change	-2.63±2.94	-0.80±2.51	
ICSI	BL	13.37±3.92	12.93±3.24	
	8W	8.89±4.86*	9.40±4.84*	0.465
	Change	-4.48±3.89	-3.53±4.19	
lCPI	BL	13.04±2.85	12.0±3.44	
	8W	7.30±4.94*	8.07±4.38*	0.276
	Change	-5.74±4.56	-3.93±5.93	
OSS	BL	26.41±6.44	24.93±6.24	
	8W	16.19±9.66*	17.53±8.89*	0.316
	Change	-10.22±7.96	-7.40±9.75	
GRA	BL	0	0	0.646
	8W	1.56±1.42*	1.40±1.59	

	change	1.56±1.42	1.40±1.59	
FBC (mL)	BL	162.04±107.35	132.0±59.06	
	8W	225.93±110.50*	193.33±95.67	0.941
	change	63.89±100.52	61.33±114.88	
Frequency	BL	14.07±6.82	14.93±9.97	
	8W	10.96±5.87*	12.93±10.86	0.493
	change	-3.11±5.26	-2.00±4.44	
Nocturia	BL	3.52±1.48	4.60±2.80	
	8W	2.63±1.39*	3.60±2.61	0.834
	change	-0.89±1.53	-1.00±1.81	
Qmax (mL/s)	BL	9.47±5.58	10.13±3.64	
	8W	9.76±7.10	9.63±4.93	0.760
	change	0.29±4.92	-0.50±7.91	
VV (mL)	BL	235.29±139.39	268.62±187.57	
	8W	247.76±136.97	243.75±87.89	0.545
	change	12.47±145.42	-24.88±133.24	
PVR (mL)	BL	32.60±59.32	70.50±87.83	
	8W	102.0±132.41*	36.0±53.37	0.038
	change	69.40±140.21	-34.50±74.99	
CBC (mL)	BL	277.05±119.34	315.44±147.80	
	8W	322.60±140.06	279.78±81.71	0.199
	change	45.55±159.98	-35.67±137.26	

*p <0.05 when compared with baseline. #comparison of changes of parameters between the two groups. 8W: 8 weeks, BL: baseline, CBC: cystometry bladder capacity, FBC: functional bladder capacity, GRA: global response assessment, ICPI: IC problem index, ICSI: IC symptom index, OSS: ICSI+ICPI, PVR: post-void residual urine, Qmax: maximum flow rate, VAS: visual analogue scale, VV: voided volume.

Table 2. The adverse events presented at 4 and 8 weeks after intravesical injection of BoNT-A or normal saline for IC/BPS.

4 Weeks	**Group B**	**Group N.**	**8 Weeks**	**Group B**	**Group N**
None	17 (63%)	11 (84.6%)	None	17 (63%)	12 (93.3%)
Dysuria	9 (33%)	1 (7.7%)	Dysuria	8 (29.6%)	1 (6.7%)
UTI	--	1 (7.7%)	UTI + Dysuria	1 (3.7%)	--
Hematuria	1 (4%)	0	Retention	1 (3.7%)	--
P=0.239			P=0.196		

UTI: urinary tract infection.

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