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A PROSPECTIVE RANDOMIZED CONTROL TRIAL OF BOTULINUM TOXIN A (BOTOX A) INJECTION FOR INTERSTITIAL CYSTITIS

Hypothesis / aims of study

Intravesical injection of BTX-A has been recently introduced as a new treatment for the refractory interstitial cystitis (IC) (1). However, the efficacy of this treatment is still controversial (2).

Study design, materials and methods

We recruited IC patients who had received hydrodistension at least once and one or more oral drugs for the relief of their symptoms yet remained to be symptomatic; six or more for both O'Leary and Sant's symptom index and problem index (OSSI/OSPI) and three or more for visual analogue scale for pain (VAS). Diagnosis of IC was made according to clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome (3).

Patients were randomly divided into two groups, Group A: immediate injection of BTX-A 100U after enrolment, or Group B: one-month delayed injection of BTX-A 100U after maintaining the conventional therapies for a month. As a primary endpoint, global response assessment (GRA) of seven grades was evaluated one month after assignment. Patients who rated the efficacy as better than +1 in GRA, which means "slightly improved", "improved" or "remarkably improved", were considered as responders to the BTX-A treatment. Symptom changes were compared between Groups at 1 month after randomization by OSSI/OSPI, VAS for pain, scale of quality of life (QOL), Overactive Bladder Symptom Score (OABSS), International Prostate Symptom Score (IPSS) and frequency volume chart variables.

The secondary endpoint was the duration of efficacy of BTX-A injection, presuming all the cases as a single group. GRA score of 0 (no change) or better was regarded as being "effective" and efficacy rate was evaluated using Kaplan Meier method. Predictive factors for maintaining efficacy were also explored.

Results

A total of 34 patients (25 women and 7 men) were enrolled. The mean age was 64.3 years (range 34-81) in Group A and 65.1 years (37-82) in Group B, respectively. All patients were compatible with the NIDDK criteria. After excluding two patients in Group B, 18 in Group A and 14 in Group B were evaluable. Response rate was significantly higher in Group A than Group B at one month (66.7% vs 21.4%, p=0.016). Symptoms scores including OSSI, OSPI, VAS, OABSS, IPSS, and QOL significantly decreased in Group A than Group B (Table 1).

The secondary analysis evaluated all patients (Hunner type IC: N=24, and non-Hunner type IC: N=10) received BTX-A injection. At one month after BTX-A injection the response rate was 73.5 %. All of the symptomatic parameters excepting nocturia significantly improved after BTX-A treatment (Table 2). Increases in average and maximal voided volumes were significantly larger in non-Hunner type IC than Hunner type IC. Univariate analysis for treatment failure indicated that experience of the past hydrodistension more than three times and the disease duration of more than six years were correlated with better outcomes (Table 3), while none of the other scores and indices showed above had significant relationship. Multivariate model based on these two significant variables indicated that only experience of the past hydrodistension more than three times was the independent predictor (p=0.045). The duration of efficacy was relatively short, with response rate 73.5% at one month, 58.8 % at three months, 26.5 % at six months and 11.8 % at 12 months (Figure 1). The mean time to loss of efficacy was 5.6 months.

Interpretation of results

The present study clearly indicated that intravesical BTX-A injection improved the symptoms and QOL impairment in patients with refractory IC. Predictive factors for better outcomes included a longer disease duration and a larger number of hydrodistension received.

Concluding message

Intravesical BTX-A injection could be an alternative treatment option for the patients with refractory IC, especially for those who have received repeated hydrodistension.

Table 1: Changes in parameter from baseline in Group A (N=18) and Group B (N=14)

	Group A	Group B	P value
OSSI	- 3.1 ± 3.9 (- 12 – 4)	- 0.4 ± 2.6 (- 7 – 3)	0.02*
OSPI	- 2.9 ± 3.6 (-11 – 1)	0.8 ± 3.3 (- 5 – 8)	0.01*
VAS	- 1.9 ± 2.3 (-6 – 3)	0.6 ± 2.8 (- 4 – 8)	<0.01**
OABSS	- 2.1 ± 3.1 (-12 – 1)	0.2 ± 2.2 (- 5 – 4)	0.02*
IPSS	- 2.8 ± 7.0 (-13 – 11)	2.9 ± 3.3 (0 – 13)	<0.001***
QOL	- 0.9 ± 1.5 (- 4 – 1)	0.4 ± 1.2 (- 2 – 3)	0.02*
daytime frequency	- 2.9 ± 5.1 (-15 – 5)	- 0.8 ± 3.7 (- 9 – 8)	0.15
nocturia	- 0.6 ± 2.4 (- 5 – 5)	0.0 ± 0.6 (- 1 – 1)	0.39
AVV	21.6 ± 48.0 (- 20 – 160)	2.1 ± 22.7 (- 35 – 65)	0.32
MVV	35.0 ± 78.5 (- 50 – 230)	- 12.1 ± 47.0 (- 150 – 50)	0.24
PVR	8.6 ± 45.8 (- 50 – 100)	16.7 ± 32.8 (- 14 – 70)	0.94

*P<0.05, **P<0.01, ***P<0.001 compared to Group B (Mann-Whitney's U-test)
AVV: Average Voided Volume, MVV: Maximal Voided Volume, PVR: Post Voided Residual

Table 2: Outcomes at baseline and 1 month after BTX-A treatment (N=34)

	baseline	1 month	P value
GRA		1.0 ± 1.6 (-3-3)	
OSSI	13.4 ± 4.1 (2-20)	10.7 ± 4.0 (4-19)	<0.001***
OSPI	11.5 ± 3.2 (3-16)	8.7 ± 3.9 (1-15)	<0.001***
VAS	6.7 ± 2.2 (0-10)	4.7 ± 2.5 (0-9)	<0.001***
OABSS	8.2 ± 3.6 (1-15)	6.6 ± 3.5 (1-14)	<0.001***
IPSS	23.1 ± 6.0 (12-33)	19.4 ± 7.9 (6-35)	<0.01**
QOL	5.8 ± 0.5 (4-6)	4.8 ± 1.3 (2-6)	<0.001***
Daytime frequency	20.1 ± 10.2 (7-44)	16.8 ± 8.0 (6-40)	<0.01**
Nocturia	4.5 ± 4.1 (0-20)	3.6 ± 3.0 (0-13)	0.167
AVV	111.4 ± 67.8 (20-330)	131.8 ± 78.6 (30-330)	0.04*
MVV	175 ± 112.6 (50-500)	217.7 ± 133.2 (50-550)	0.01*
PVR	47.8 ± 42.8 (0-112)	82.6 ± 73.8 (13-300)	0.06

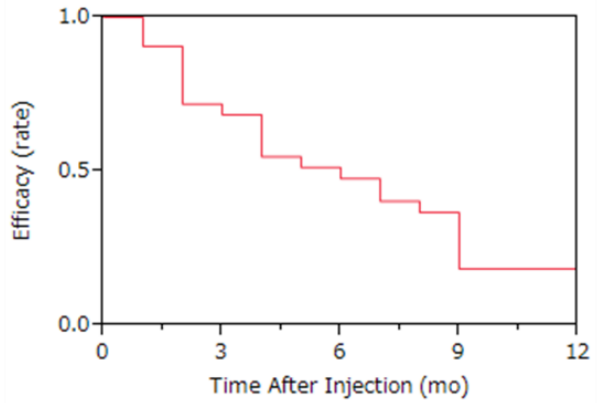
*P<0.05, **P<0.01, ***P<0.001 significant difference from baseline (Wilcoxon t-test)

Table 3: Univariate analysis of response factors at 1 month post treatment

	OR	CI	P value		OR	CI	P value
Sex				Duration of IC			
Female / male	2	0.334 - 10.941	0.43	≧6 years /<6 years	7.385	1.111 - 147.638	0.037*
Age				Past HD frequency			
≧65 years /<65 years	1.42	0.288 - 6.794	0.657	>2 times / ≦2 times	11.999	1.802 - 240.867	0.008**
Age at onset				Bladder capacity at the last HD			
<60 years / ≧60 years	2.75	0.533 - 21.007	0.236	< 500 ml / ≧ 500 ml	2.364	0.499 – 13.359	0.282
Non-Hunner type IC / Hunner type							
	1.647	0.308 - 12.753	0.574				

*P<0.05, **P<0.01 significant difference from non-responders (Fisher's exact test)

Figure 1: Kaplan-Meyer curve of efficacy rate



No. at risk	34	20	9	4	4

References

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