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

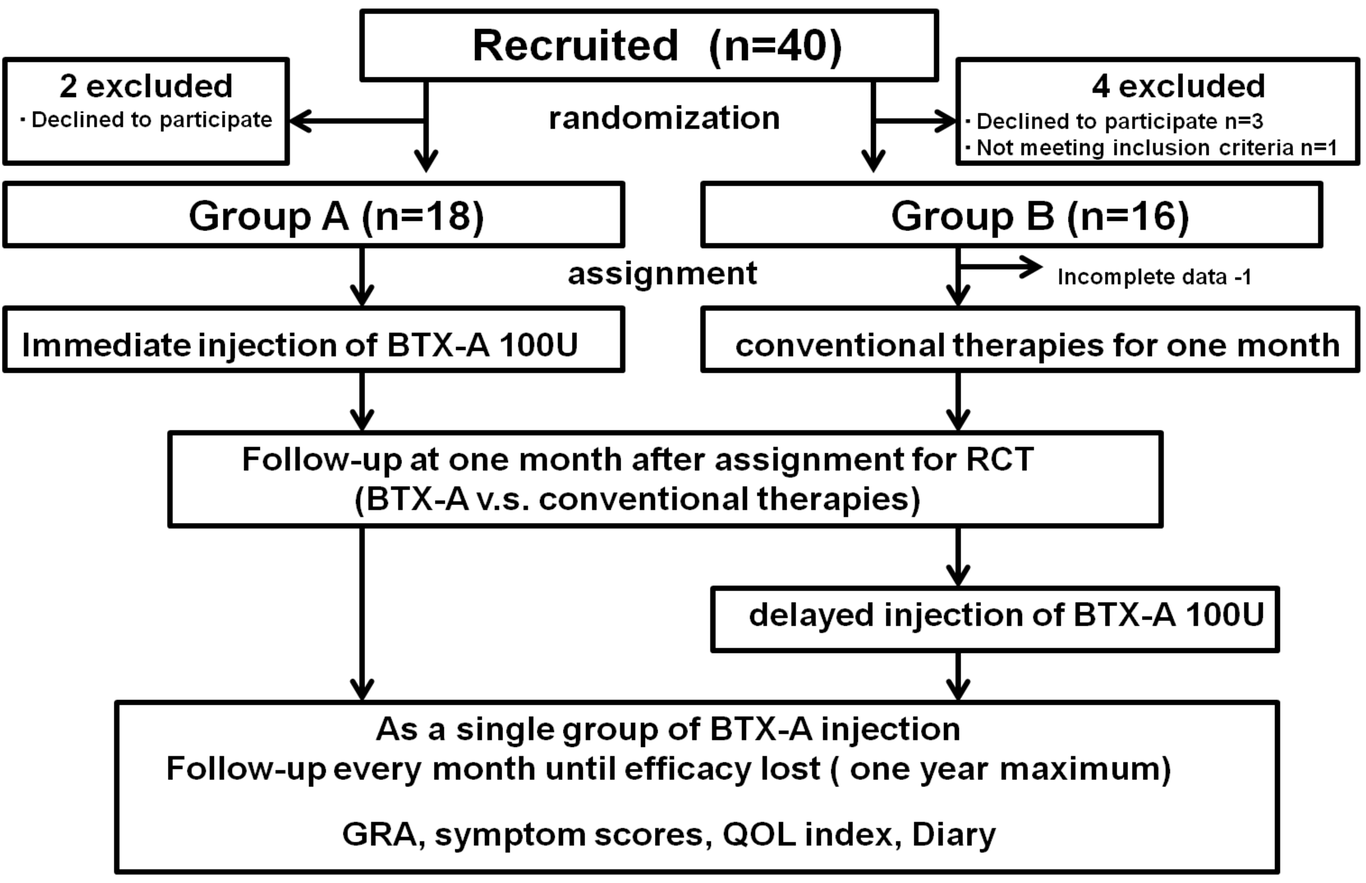
Yoshiyuki Akiyama[1, 2], Akira Nomiya[1], Aya Niimi[1], Yukio Yamada[1], Motofumi Suzuki[1], Tetsuya Fujimura[1], Yasuhiko Igawa[2] and Yukio Homma[1]

1 Department of Urology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
2 Department of Continence Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

## Aims of study

**To examine whether botulinum toxin A (BTX-A) is an alternative treatment for patients with interstitial cystitis (IC) refractory to conventional therapies.**

## Study design, Materials and Methods




### *Inclusion criteria*

- Past hydrodistension≧1 time
- Oral drugs/other intravesical therapies≧1
- O'Leary and Sant's symptom/problem index (OSSI/OSPI)≧6/6
- Visual analogue scale (0-10) for pain (VAS)≧ 3

### *The first month after assignment as a RCT*

- ***Primary endpoint*: Global response assessment (−3-+3) (GRA) (Responders≧+1: "slightly ~ improved" or better)**
- ***Secondary endpoints*: Symptom scores, QOL index, VAS, Diary**

### *From one month after assignment as a case series (n=34)*

·Group B patients received BTX-A injection

- ***Additional Secondary end points:***
  - Duration of efficacy (GRA≧0: "no change" or better)
  - Predictive factors for efficacy at 1month after BTX-A injection

## Results

### *Patient's demographics and baseline characteristics*

| | Group A (Immediate injection) | Group B (Delayed injection) | P value |
|---|---|---|---|
| No. (male / female) | 18 (4 / 14) | 15 (4 / 11) | 1 |
| Mean age (years) | 64.3 ± 13.2 [34 - 81] | 65.5 ± 15.1 [37 - 82] | 0.82 |
| Age at onset of IC (years) | 57.8 ± 15.9 [24 - 78] | 58.9 ± 13.2 [33 - 77] | 0.83 |
| Duration of IC (years) | 6.2 ± 3.9 [1 - 16] | 7.0 ± 5.1 [2 - 21] | 0.6 |
| No. Hunner type/non-Hunner type | 14 / 4 | 10 / 5 | 0.48 |
| Measured parameters at baseline | | | |
| OSSI | 14.2 ± 3.7 [7 - 19] | 13.3 ± 4.5 [2 - 20] | 0.62 |
| OSPI | 11.9 ± 2.8 [5 - 16] | 11.1 ± 3.8 [2 - 16] | 0.7 |
| VAS | 7.1 ± 2.3 [0 - 10] | 5.7 ± 3.0 [0 - 10] | 0.14 |
| OABSS | 8.5 ± 4.0 [1 - 15] | 8.2 ± 3.1 [2 - 12] | 0.93 |
| IPSS | 22.6 ± 6.0 [13 - 32] | 21.6 ±8.1 [3 - 33] | 0.9 |
| QOL index | 5.8 ± 0.4 [5 - 6] | 5.4 ± 1.0 [3 - 6] | 0.16 |
| Daytime frequency | 18.6 ± 8.0 [7 - 40] | 23.3 ± 13.6 [10 - 52] | 0.51 |
| Nocturia | 4.2 ± 3.1 [0 - 10] | 5.2 ± 5.1 [2 - 21] | 0.74 |
| Average voided volume (AVV) | 127.5 ± 73.1 [40 - 330] | 88.5 ± 42.1 [20 - 165] | 0.15 |
| Maximum voided volume (MVV) | 201.9 ± 131.6 [50 - 500] | 153.5 ± 74.8 [50 - 300] | 0.47 |
| Post void residual (PVR) | 53.9 ± 51.4 [0 - 112] | 30.8 ± 15.4 [16 - 60] | 0.77 |

| | Group A (Immediate injection) | Group B (Delayed injection) | P value |
|---|---|---|---|
| *Hydrodistension* | | | |
| Times on average [range] | 2.6 [1 - 8] | 2.5 [1 - 5] | 0.9 |
| Bladder volume at the last HD (mL) [range] | 516 ± 216 [250 - 1000] | 500 ± 301 [100 - 1200] | 0.85 |
| *Instillation* (No. patients) | | | |
| Heparin + lidocaine instillation | 6 | 4 | |
| DMSO instillation | 1 | 3 | |
| *Medicine* (No. patients) | | | |
| Anticholinergic agent | 3 | 2 | |
| NSAIDs | 11 | 11 | |
| Antihistaminic agent + steroid | 7 | 5 | |
| Suplatast tosilate | 4 | 11 | |
| Tricyclic antidepressant | 4 | 7 | |
| Others | 8 | 8 | |

The variables are expressed as mean ± SD [range]

OABSS: Overactive Bladder Symptom Score, IPSS: International Prostate Symptom Score, QOL: quality of life
DMSO: dimethyl sulfoxide, NSAIDs: non-steroidal anti-inflammatory drugs

### *GRA at 1 month and changes in parameter from baseline at 1 month*

| | Group A (n=18) | Group B (n=15) | P value |
|---|---|---|---|
| GRA | | | 0.01† |
| ≧ +1 | 13 | 4 | |
| ≦ 0 | 5 | 11 | |
| OSSI | -3.1± 3.9 [-12 - 4] | -0.8 ± 3.0 [-7 - 3] | 0.04* |
| OSPI | -2.9 ± 3.6 [-11 - 1] | 0.4 ± 3.5 [-5 - 8] | 0.02* |
| VAS | -1.9 ± 2.3 [-6 - 3] | 0.4 ± 2.7 [-4 - 8] | 0.01* |
| OABSS | -2.1 ± 3.1 [-12 - 1] | 0.1 ± 2.2 [-5 - 4] | 0.02* |
| IPSS | -2.8 ± 7.0 [-13 - 11] | 2.9 ± 3.3 [-10 - 13] | 0.01* |
| QOL index | -0.9 ± 1.5 [-4 - 1] | 0.1 ± 1.6 [-4 - 3] | 0.04* |
| Daytime frequency | -2.9 ± 5.1 [-15 - 5] | -1.4 ± 4.2 [-9 - 8] | 0.28 |
| Nocturia | -0.6 ± 2.4 [-5 - 5] | -0.1 ± 0.6 [-1 - 1] | 0.47 |
| AVV | 21.6 ± 48.0 [-20 - 160] | 1.2 ± 22.0 [-35 - 65] | 0.27 |
| MVV | 35.0 ± 78.5 [-50 - 230] | -11.2 ± 45.1 [-150 - 50] | 0.24 |
| PVR | 8.6 ± 45.8 [-50 - 100] | 16.7 ± 32.8 [-14 - 70] | 0.94 |

mean±SD [range]
Statistically significant †P<0.05 by Fisher's correct test, *P<0.05 by Wilcoxon rank-sum test

### *The change in parameters in all the patients at 1 month after BTX-A treatment*

| | baseline | 1 month | P value |
|---|---|---|---|
| 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 index | 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 |

mean±SD [range] Wilcoxon signed rank test statistically significant *$P$<0.05, **$P$<0.01, ***$P$<0.001

### *Univariate and multivariate logistic regression analysis for better response*

| | Univariate OR | Univariate 95% CI | Univariate P value | Multivariate OR | Multivariate 95% CI | Multivariate P value |
|---|---|---|---|---|---|---|
| Duration of IC ≧ 6 years / < 6 years | 7.39 | 1.11-147.64 | 0.03* | 6.01 | 0.768-128.241 | 0.09 |
| past HD frequency ≧ 3 times / ≦ 2 times | 12.00 | 1.80-240.87 | <0.01** | 10.35 | 1.441-214.464 | 0.02* |

### *The first month after assignment as a RCT*

- **Response rate (GRA≧+1) was significantly higher in BTX-A injection (Group A) than conventional therapies (Group B)**
- **All the symtom scores and QOL index significantly decreased in Group A than Group B, whereas none of all the diary variables showed significant changes**

### *From one month after assignment as a case series (n=34)*

- **The duration of efficacy was 6.4 months**
- **All the symptomatic parameters ecepting nocturia significantly improved at one month after BTX-A treatment**
- **Experience of the past hydrodistension ≧3 times was independent predictor**

## Conclusions

- **BTX-A injection is a vital treatment option for patients with refractory IC, especially for those who have received repeated hydrodistensions.**