### Alexanian (2013)

**Japan**

**Single-center, prospective, open labeled, randomized, competitive study**

Between September 2010 and February 2012, 40 IC patients who had received hydrodistension at least once and medical treatment of one or more oral drugs or intravesical agents, yet remained to be symptomatic, six points or higher on the IC and OSS and four points or higher for VAS for pain. Diagnosis for IC was made according to clinical guidelines for IC and hypersensitive bladder syndrome according to the NIDDK.

**Primary outcome measure:** OLS (OLS - SI, Prospective randomized double-blind study)

Full-analysis carried out using 36 patients (28 women, 8 men).

**Efficacy Assessment (Outcome) Measure**

Primary end point - response rate between two groups evaluated by GRA, a certific after allocation. Patients who rated the efficacy as better than +1 in GRA in the seven-point scale, meaning “slightly improved” or “remarkably improved” were considered responders in treated patients. Secondary endpoints were symptom changes from baseline compared a month after allocation by OLS(SI), VAS for pain, QOL based on the QOL index of the International Prostate Symptom Score, and the frequency volume chart.

**Findings**

All the symptom scores and QOL index significantly improved in group A compared with group B, whereas none of the pelvic floor variables showed significant changes. At all symptomatic parameters, except nocturia, significantly improved after BotoxA treatment. KPI: p < 0.001, CIQ > 2: p < 0.001, VAS: p < 0.001, DABSS: p < 0.001, ICIQ-SI: p < 0.03, QOL: p < 0.001, Daytime frequency (times/h): p = 0.10, Nocturia: p = 0.17. Average voided volume: p = 0.04, Maximum voided volume: p = 0.01. Additionally, univariate analysis showed that exposure to past HD more than three times and disease duration longer than 6 years were significant factors or better response.

### Manning (2013)

**Australia**

**Prospective, Intervventional study**

Double-blind study of 54 women with severe, refractory IC from three referral centers who were randomly allocated to treatment with hydrodistension + injection of normal saline or to hydrodistension + injection of BoNTA. The O’Leary Sant questionnaires, and bladder diary data were compared between BoNTA and control patients at baseline, and at 3 months of follow-up. Patients with no improvement after initial treatment had access at minimum 6 months after initial to BoNTA if they wished. Patients and doctors remained blinded to the initial treatment. Measurements were made beyond 3 months, but no further randomisation was possible due to inability of nonresponsive patients in either group to have BoNTA treatment.

From January 2004 until Feb 2009, 54 female patients with longstanding refractory IC/BPS were referred from urogynecology clinics in three centers. All study participants met NIDDK criteria, with majority having had multiple prior therapies. Being refractory was defined as having failed two or more recognised treatments. Study participants were >18 years of age.

**Primary outcome measure:** OLS (OLS - SI, Prospective randomized double-blind study)

54 female patients

**Secondary outcome measures** were frequency nocturia as measured by bladder diary, and complications such as adding difficulty.

**Findings**

OLS-P1 showed significantly greater improvement at 3 months in the BoNTA group (p = 0.04). No significant improvement in OLS-SI or total OLS scores between baseline and 3 months for BoNTA and control groups. IC/ICD patients were found to have repeated U/TI detected and treated at some time after cytoscopy and injection which was noted to be a confounding factor. Once the analysis was performed without U/TI patients, there was an overall improvement in BoNTA group in all measurements, including total OLS score (p = 0.02), OLS-SI (p = 0.08), OLS-P1 (p = 0.09) and question 4 of the OLS-P1 addressing the problem of bladder pain (p = 0.02). There was no significant difference in control or treatment group in number of patients requesting the BoNTA treatment after 3 months (p = 0.10).

### Gao HC (2013)

**Taiwan**

**Prospective, Intervventional study**

Thirty-one consecutive patients with IC/BPS who had failed conventional treatments were prospectively enrolled in this study from January 2006 to January 2010. Patients were requested to keep a bladder diary to assess frequency and nocturia. Baseline scores were assessed for O’Leary Sant questionnaires and the VAS responses. Video-urodynamic studies and postvoid residual sensitivity tests were performed. Patients with GRA < 2 result after treatment were considered to have a successful treatment outcome. Patients were admitted to the hospital for treatment where they received intravesical injection of botulinum, followed by cystoscopic hydrodistension. After BoNTA injection, a catheter remained for 1 day and patients were discharged on the next day. Oral antibiotics were prescribed for 7 days. Patients were monitored in the outpatient clinic 2 weeks later. During each follow-up visit, data from each of the GRA, diary, OSS, ICPI, ICSI, Pain VAS were recorded. Repeat injections were repeated 6 months after the first treatment, and patients were followed up in the same way. The BoNTA injection was repeated every 6 months for four times.

Evaluation of IC/BPS was established based on characteristic symptoms and cystoscopic findings. All patients had been treated with at least 2 of the following medications: oral pentoxyfylline or tricyclic antidepressant, intravesical instillations of heparin or hyaluronic acid for more than 1 year - but symptoms remained unchanged.

**Diagnosis of IC/BPS**

31 patients (27 female and 4 male)

**Primary and point - Global Response Assessment**

- 4 months after the fourth BoNT-A injection.
- Secondary outcome measures were ICSI, ICPI, OSSI, VAS, VBC, Frequency, Nocturna, QOL, CBC, IRC, Neq, Volume

**Findings**

As 6 months after the fourth BoNT-A injection, 19 of 31 patients (61%) had GRA >2 and 12 had a GRA <2. In the patients with GRA >2, OCSI, ICPI, VAS, VBC, frequency, CBC, and glomerulation grade all showed significant improvement. However, no significant change in measured parameters was noted in patients with GRA <2. Compared with the changes in observed change in measured parameters from baseline to endpoint, patients with GRA >2 had significantly greater changes in OCSI, ICPI, VAS, VBC, and CBC than those with a GRA <2. The therapeutic effects of OCSI, VAS, and glomerulation grade were slightly different after the second injection between patients with GRA >2 and GRA <2. Among the patients who were not satisfied with repeated BoNT-A injection, 5 women were found to have Hunner’s ulcer. GRA (p > 0.05), OSSI (p > 0.05), VAS (p > 0.05), FBC (p > 0.05), CBC (p > 0.05), QOL (p > 0.05), OCSI (p > 0.05) all showed significant improvement after repeated injections.

### Lee CL (2013)

**Prospective, Interventional study**

144 consecutive patients with IC/BPS who had failed conventional treatments were prospectively enrolled in this study from January 2008 to January 2011. Patients were requested to keep a bladder diary to assess frequency and nocturia. Baseline scores were assessed for O’Leary Sant questionnaires and the VAS responses. Video-urodynamic studies and postvoid residual sensitivity tests were performed. Patients with GRA > 2 result after treatment were considered to have a successful treatment outcome. Patients were admitted to the hospital for treatment where they received intravesical injection of botulinum, followed by cystoscopic hydrodistension. After BoNT-A injection, a catheter remained for 1 day and patients were discharged on the next day. Oral antibiotics were prescribed for 7 days. Patients were monitored in the outpatient clinic 2 weeks later. During each follow-up visit, data from each of the GRA, diary, OSS, ICPI, ICSI, Pain VAS were recorded. Repeat injections were repeated 6 months after the first treatment, and patients were followed up in the same way. The BoNT-A injection was repeated every 6 months for four times.

44 consecutive patients with IC/BPS who had experienced conventional treatment failure were prospectively enrolled. Diagnosis was established based on characteristic symptoms and cystoscopic findings. All patients had been treated with at least 2 of following medications: oral pentoxyfylline or tricyclic antidepressant and intravesical instillations of heparin or hyaluronic acid for more than one year with symptoms remaining unchanged.

**Diagnosis of IC/BPS**

44 consecutive patients with IC/BPS who had experienced conventional treatment failure were prospectively enrolled. Diagnosis was established based on characteristic symptoms and cystoscopic findings. All patients had been treated with at least 2 of following medications: oral pentoxyfylline or tricyclic antidepressant and intravesical instillations of heparin or hyaluronic acid for more than one year with symptoms remaining unchanged.

**Clinical Evaluation**

Classified as either 1 (10) or non-value (p = 0.10 - total 40 women)

**Global Response Assessment - 6 months after the 4th set of BoNT-A injections**

Global outcome score including ICSI and ICPI, VAS, Pain VAS, voiding diary, and diaryvoidness variables

**Findings**

Patients with non-ICP/BPS and GRA scores >2 had significantly decreased ICPI, ICOS, Pain VAS, Frequency and nocturia episodes, and increased FBC, cystometric bladder capacity. Patients with non-ICP/BPS and GRA <2 also had decreased ICSI, OSSI, VAS, VAS, and ICSI episodes, and increased FBC and maximal bladder capacity.

Patients with non-ICP/BPS and GRA scores >2 had significantly greater improvement than those with non-ICP/BPS and GRA scores <2 for ICSI (p<0.007), ICPI (p<0.06), and OSSI (p=0.04)
Table 3 Continued

<table>
<thead>
<tr>
<th>Country/Region</th>
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<tr>
<td>Italy</td>
<td>Prospective non-randomized study</td>
<td>81 consecutive patients with IC/BPS who failed conventional treatments were prospectively enrolled from July 2006 to August 2010. Patients were requested to keep a bladder diary to assess frequency and nocturia. Baseline scores were assessed for O'Leary Sant questionnaires and the VAS response. Urodynamic studies and postoperative cystoscopy were performed. Patients with GRA &gt;2 result after treatment were considered to have a successful treatment outcome. Patients with GRA &gt;2 result after treatment were considered to have a successful treatment outcome. Patients were admitted to the hospital for treatment where they received intravesical injection of botox, followed by cystoscopic hydrodistention. After BoNT-A injections, a catheter was retained for 1 day and patients were discharged on the next day. Oral antibiotics were prescribed for 7 days. Patients were monitored in the outpatient clinic 2 weeks later. During each follow-up visit, data from each of the GRA, diary, OIS, ICPI, UDI, PVI, VAS were recorded. Repeat injections were performed every 3 months after the first treatment, and patients were followed up in the same way. The BoNT-A injection was repeated every 6 months until patients felt that the treatment was successful up to 4 injections.</td>
<td>VAS decreased by 44%, 45%, and 79% (p&lt;0.01). The first injection improved VAS by 71%, 72%, and 79% (p&lt;0.01). All domains except weight and sleep showed significant improvement in the GRA and symptom variables showed persistent improvement with each repeated treatment. Overall, the GRA and symptom variables showed significant improvement after repeated BoNT-A treatment compared to baseline with initial treatment. All domains improved significantly comparing to baseline. All domains except for sleep showed significant improvement in the GRA and symptom variables showed persistent improvement with each repeated treatment. Overall, the GRA and symptom variables showed significant improvement after repeated BoNT-A treatment compared to baseline with initial treatment. All domains except for sleep showed significant improvement comparing to baseline. Patients with GRA &gt;2 result after treatment were considered to have a successful treatment outcome. Patients with GRA &gt;2 result after treatment were considered to have a successful treatment outcome. Patients were admitted to the hospital for treatment where they received intravesical injection of botox, followed by cystoscopic hydrodistention. After BoNT-A injections, a catheter was retained for 1 day and patients were discharged on the next day. Oral antibiotics were prescribed for 7 days. Patients were monitored in the outpatient clinic 2 weeks later. During each follow-up visit, data from each of the GRA, diary, OIS, ICPI, UDI, PVI, VAS were recorded. Repeat injections were performed every 3 months after the first treatment, and patients were followed up in the same way. The BoNT-A injection was repeated every 6 months until patients felt that the treatment was successful up to 4 injections.</td>
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