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ORIGINAL ARTICLE

Therapeutic outcome and patient adherence to repeated onabotulinumtoxinA detrusor injections in chronic spinal cord-injured patients and neurogenic detrusor overactivity

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botulinum toxin A;
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spinal cord injury

Background/Purpose: To investigate the continuous therapeutic effects and urinary incontinence severity after repeated detrusor injections of 200-U of onabotulinumtoxinA (BoNT-A) in chronic spinal cord-injured (SCI) patients.
Methods: Between 2006 and 2010, patients with chronic SCI and refractory neurogenic detrusor overactivity (DO) were treated with repeated sets of 200-U BoNT-A injected into 20 sites every 6 months. All patients underwent urological examinations and video-urodynamic studies at baseline and after each BoNT-A treatment. The outcomes were measured using Urogenital Distress Inventory 6-item short form (UDI-6) for urinary incontinence. The severity of urinary incontinence and urodynamic parameters were compared after each BoNT-A injection.
Results: A total of 59 SCI patients with a mean age of 42.1 ± 13.1 years were enrolled. The UDI-6 incontinence scores persistently improved for up to three injections. The rate of dryness and mild incontinence reported by patients persistently improved from 25.4% at baseline to 74% at 3 months after the fourth injection, but decreased slightly after the fourth injection. The overall satisfaction rate after single or repeated injections was 59.3% (35 patients), and the failure rate was 33.9% (20 patients), and discontinuation rate owing to adverse events (2 recurrent UTI, 2 autonomic dysreflexia) was 6.8% (4 patients). Among the 20 patients who reported failure to treatment, 10 patients (16.9%) reported no significant improvement after one or repeated injections, eight converted to augmentation enterocystoplasty.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: Repeated 200-U BoNT-A injections every 6 months for neurogenic DO in chronic SCI patients provided a satisfactory initial outcome. However, only 20% patients continued the repeated treatment.

Introduction

Spinal cord injury (SCI) is a significant cause of morbidity and mortality in developing countries, with a global annual incidence of 1:25,000.[1] Neurogenic voiding dysfunction and urinary symptoms in patients with SCI lead to several complications. If not well managed, high intravesical pressure will damage the upper urinary tract, causing renal scarring and chronic renal insufficiency, which impair the quality of life.[2] The first-line treatment for SCI induced neurogenic detrusor overactivity (DO) is antimuscarinic agents with or without clean intermittent catheterization (CIC).[3,4] However, most of the patients have an incomplete response to antimuscarinic agents, which can also cause undesirable systemic side effects.[5]

OnabotulinumtoxinA (BoNT-A) detrusor injections were introduced in 2000 as a minimally invasive treatment option for neurogenic DO.[6] In addition to the benefit of decreased detrusor pressure to prevent renal damage, it significantly improved quality of life.[7] In 2011, a global Phase 3 clinical trial concluded both 200-U and 300-U injections provided the same therapeutic effect.[8] However, most previously published studies used 300-U BoNT-A detrusor injections; only a few studies focused on 200-U BoNT-A injections for the treatment of neurogenic DO. As most patients with neurogenic DO require repeated treatments, the efficacy and safety of multiple BoNT-A injections need to be addressed. This study investigated the therapeutic effects of repeated 200-U BoNT-A injections in the detrusor muscle for the treatment of urinary incontinence and refractory neurogenic DO among SCI patients. We also investigated the adherence of SCI patients to repeated BoNT-A injections throughout the study course.

Methods

Patients with SCI and neurogenic DO, requiring CIC or not, and who were refractory to antimuscarinic treatment were consecutively enrolled in this prospective study. Video-urodynamic studies (VUDS) were routinely performed prior to enrollment to prove the presence of DO with or without detrusor sphincter dyssynergia, and exclude the patients with detrusor underactivity, anatomical obstruction, or intrinsic sphincter deficiency. Patients were also excluded if they had an active urinary tract infection at enrollment, urinary tract cancer, history of lower urinary tract surgery, or chronic systemic diseases such as congestive heart failure and chronic renal failure.

VUDS was performed according to the recommendations of the International Continence Society.[9] The urodynamic parameters of cystometric bladder capacity (CBC), maximum flow rate (Qmax), post-voiding residual (PVR) volume, voided volume, involuntary detrusor contraction (IDC) and voiding detrusor pressure at Qmax (Pdet.Qmax) were recorded in detail. In addition, the lower urinary tract symptoms were evaluated using the Urogenital Distress Inventory short form (UDI-6) questionnaire.

The patients were designed to receive initial four repeated injections each of 200-U of BoNT-A (Allergan, Irvine, CA, USA) in the detrusor muscle at baseline and every 6 months thereafter. The BoNT-A injections were performed under light intravenous general anesthesia in the operating room. The 200-U BoNT-A was diluted with 20 mL of normal saline and the diluted solution was injected into 20 sites in the bladder wall, excluding the bladder trigone. The patients were evaluated every 3 months for the therapeutic effects, quality of life in urinary incontinence, and VUDS for evaluation of the bladder condition.

All patients were scheduled for four sets of BoNT-A injections (Phase I). However, patients were also allowed to withdraw from the trial if they were dissatisfied with the treatment outcome, having intolerable adverse events, or were effective to treatment but did not want to continue the injection. After completion of four sets of BoNT-A injection and follow-up, patients were allowed to receive two additional BoNT-A injections every 6 months (Phase II) if they wished to continue this mode of treatment for their urinary incontinence. The causes of discontinuation of BoNT-A injection were analyzed, and patients were considered to have effective treatment based on their subjective reports.

This study was approved by the Ethics Committee of Tzu Chi General Hospital, Hualien, Taiwan (TCGH 098-53 and 098-088); written, informed consent to participate was obtained at enrollment. All patients had been informed and educated for CIC after treatment. Patients had to agree to perform CIC prior to when they were enrolled in the study.

The primary efficacy parameter was the severity of urinary incontinence (caused by all etiologies) as perceived by the patient's subjective scoring of urinary leakage at each follow-up visit. The incontinence severity score was adapted from three incontinence items from the UDI-6. The severity of urinary incontinence was graded as dry if the sum of UDI-6 incontinence items was 0, mild in the sum of 1—3, moderate in the sum of 4—6, and severe in the sum of 7—9. Secondary efficacy parameters were the changes in VUDS parameters at 3 months and 6 months after each set of BoNT-A injections. Any adverse events were also recorded throughout the study. Urinary tract infection was defined as a febrile episode with a white blood cell count of more than 10 cells per high-power field on urinalysis. Asymptomatic pyuria was not considered an adverse event.

Results

A total of 59 patients with SCI and neurogenic DO were enrolled in this study, including 21 women and 38 men.

Their mean age was 42.1 ± 13.1 years (range: 22–74 years) and the mean injury duration was 8.7 ± 8.1 years. Higher-level SCI was the most common, including 26 patients with cervical SCI, 28 with thoracic SCI, and five with lumbar SCI. Among all patients, 39 were classified as ASIA-A, 9 ASIA-B, 5 ASIA-C, 5 ASIA-D, and 1 ASIA-E according to the American Spinal Injury Association (ASIA) Classification.[10] All patients had urinary incontinence at enrollment.

After the first injection, 7 patients did not come back for follow-up because of adverse events (in 4 patients) or failed treatment (in 3 patients). Only 52 patients were available for the second follow-up visit. However, not all patients continued the subsequent BoNT-A injections because of different causes. Among all patients, 43 received two sets of BoNT-A injection and required follow-up visits, 31 received three sets, 27 received four sets, 15 received five sets, and only 11 received six sets of injection. Fig. 1 shows the flow diagram of patients. The overall satisfaction rate after single or repeated injections was 59.3% (35 patients), the failure rate was 33.9% (20 patients), and the discontinuation rate due to adverse events (2 individuals had recurrent UTI, 2 individuals had autonomic dysreflexia) was 6.8% (4 patients).

Fig. 2 shows the continuous change in incontinence severity among patients who received repeated BoNT-A injections and follow-up. The initial therapeutic effect of the first 200-U BoNT-A injection was satisfactory. At 3 months after the first injection, 33 (63.5%) of 52 patients reported completely dry (7 patients, 13.5%) or mild incontinence (26 patients, 50%). The rates of dry (6 patients, 11.5%) and mild incontinence (22 patients, 42.3%) declined slightly at 6 months after the first injection, but returned to a higher level 3 months after the second injection (dry: 13 patients, 30.2%; mild incontinence: 15 patients, 34.9%). The incontinence severity improved consistently up to the time of 3 months after the fourth injection (dry: 8 patients, 29.6%; mild incontinence: 12 patients, 44.4%).

The subjective symptoms of incontinence as assessed by the UDI-6 improved dramatically during the course of the first three sets of injections at both 3 months and 6 months after injection. Moderate and severe incontinence was noted in 74.6% of patients at baseline, but in only 25.9% and 44.4% at 3 months and 6 months after the fourth injection, respectively. The therapeutic effect decreased gradually after the fourth injection. The percentage of moderate and severe incontinence was 46.7% and 36.4% at 3 months after the fifth and sixth injections, and 50% and 40% at 6 months after the fifth and sixth injections, respectively.

The changes in urodynamic parameters after repeated BoNT-A injections are given in Table 1. Significant increases in CBC and PVR volumes, and a significant decrease in Pdet.Qmax were noted 3 months and 6 months after each set of BoNT-A injections. The CBC, bladder compliance, and Pdet.Qmax were consistent throughout the treatment course. CBC increased from 228 mL at baseline to more than 400 mL, but slightly decreased after the fourth set of injections. The Pdet.Qmax decreased to less than 25 cmH_2O, which is considered a level safe enough to prevent upper urinary tract damage. Furthermore, the PVR volume also increased along with the incremental CBC increase.

Of the 52 study patients with available follow-up after the first injection, adverse events occurred in 13 patients (25%) who developed urinary tract infection and in four patients (7.7%) who had post-operative gross hematuria. By contrast, the occurrence of IDC in urodynamic studies was

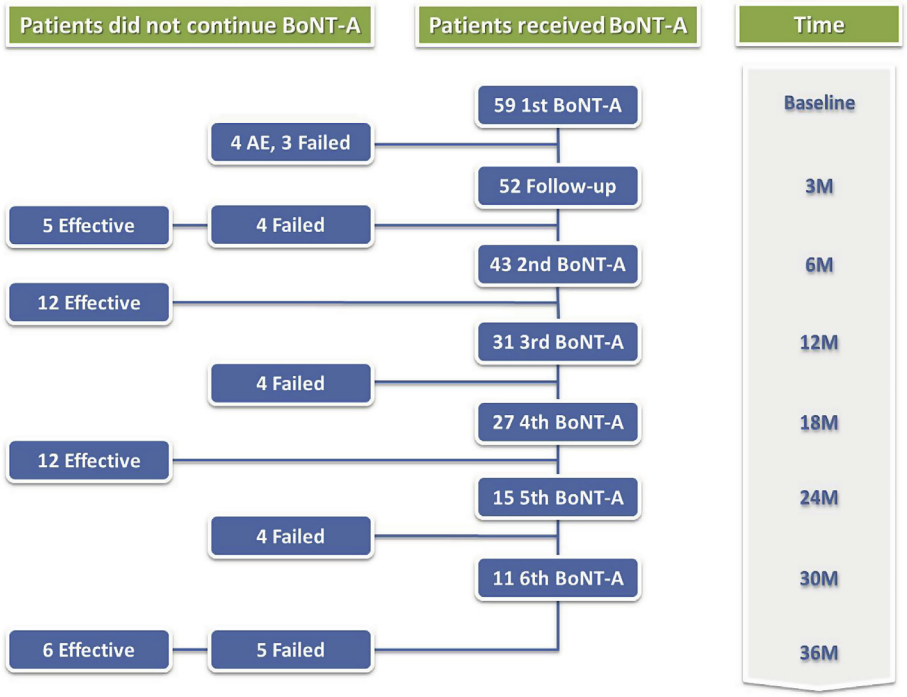

Figure 1 The flow diagram of patients receiving repeated BoNT-A injections, and the number of patients with effective results and failed the treatment. BoNT-A = onabotulinumtoxinA.

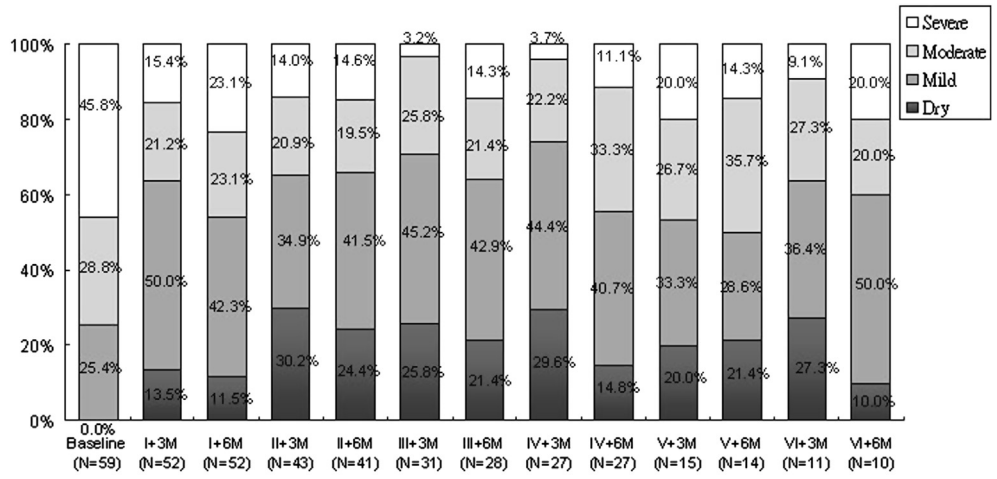

Figure 2 Urinary incontinence severity at 3-month and 6-month follow-ups after each set of 200-U BoNT-A detrusor injections. Parentheses indicate available follow-up patient numbers. BoNT-A = onabotulinumtoxinA.

noted in 93.2% (53/59 patients) of patients at baseline. After BoNT-A injection, the incidence of IDC decreased at 3 months, and increased slightly at 6 months after each injection (Fig. 3). Nonetheless, we still observed that IDC was consistently higher at 6 months than at 3 months after each injection, which indicated that the therapeutic effect was greater at 3 months, but decreased at 6 months after each BoNT-A injection.

After the first BoNT-A injection 17 of the 52 patients did not continued treatment because they were satisfied to the first treatment ($n = 5$) or second treatment ($n = 12$). Overall, 20 individuals reported failure to one or repeated BoNT-A injections, 10 (16.9%) individuals had improvement fluctuated after repeated injections, and 10 (16.9%) individuals reported no significant improvement after one or repeated injections. Eight patients with ineffective BoNT-A treatment outcome converted to augmentation enterocystoplasty for permanent correction and a better treatment outcome.

Discussion

Minimally invasive BoNT-A injections into the detrusor muscle improved clinical and urodynamic parameters and quality of life in patients with refractory neurogenic DO in several open-label studies.[11–13] In our previous study, the success rate was 73.3% in SCI patients with neurogenic DO who received a single set of detrusor injections of 200-U BoNT-A, and the therapeutic effects lasted for 3–9 months (mean: 5.3 months).[14] Based on this preliminary result, the injection protocol was designed as repeated injections every 6 months in order to observe the consistency of therapeutic effects of the repeated sets of BoNT-A injections.

The dose of BoNT-A for neurogenic DO treatment was controversial until the recent global Phase 3, multicenter trials, in which both 200-U and 300-U of BoNT-A significantly reduced urinary incontinence and improved urodynamic parameters and quality of life in patients with neurogenic DO. No clinically relevant difference in efficacy or duration of effect was observed between the two doses, and the 200-U dosage had fewer adverse effects.[8,15] After BoNT-A treatment, 62.9% of patients in the 200-U group and 61.6% in the 300-U group achieved the subjective primary treatment goal of dryness.[16] This evidence indicates that 200-U BoNT-A injections provide a satisfactory initial outcome. The US Food and Drug Administration approved the 200-U BoNT-A dosage for the treatment of neurogenic DO associated with conditions such as SCI and multiple sclerosis in 2011.

Bladder management for neurogenic DO should meet three main objectives: low-pressure urine storage, low-pressure voiding, and adequate urine drainage.[12] However, from the patient's point of view, the most important goals of treatment are continence and good tolerability of therapy. Kalsi et al[7] measured the changes in the quality of life at 4 weeks and 16 weeks after treatment with BoNT-A detrusor injections using the short form of the UDI-6 and Incontinence Impact Questionnaire. The results showed significant improvement after treatment, which is compatible with our previous study.[17] In another study, the proportion of patients without IDC 6 weeks after treatment with 200-U of BoNT-A was 64% (81/127).[15] In this study, we found no urodynamic IDC in 42.6% (23/54) of patients 3 months after the first 200-U BoNT-A injection, whereas the proportion was 52.4% (22/42) at 3 months after the second 200-U injection. Nonetheless, the occurrence of IDC fluctuated after each injection. It is possible that 200-U of BoNT-A might not be adequate in abolishing all IDC, especially at 6 months after injection when the BoNT-A effect has waned.

Haferkamp et al[18] reported resprouting of the nerve endings after an interval of about 9 months after BoNT-A detrusor injection, with no significant ultrastructural detrusor changes found in the biopsy tissue. Owing to the reversible pharmacological effect of BoNT-A, repeated BoNT-A injections are necessary to maintain a satisfactory outcome. Grosse et al[19] found that repeated 300-U BoNT-A detrusor injections on demand slightly reduced the average interval between the third and fourth treatments compared to the interval between the first and second, and the

Table 1 Changes in the urodynamics parameters 3 months and 6 months after each set of 200-U BoNT-A detrusor injections.

	Baseline 1st BoNT-A ($n = 59$)	3 mo after 1st BoNT-A ($n = 54$)	2nd BoNT-A ($n = 47$)	3 mo after 2nd BoNT-A ($n = 42$)	3rd BoNT-A ($n = 39$)	3 mo after 3rd BoNT-A ($n = 31$)	4th BoNT-A ($n = 27$)	3 mo after 4th BoNT-A ($n = 27$)	5th BoNT-A ($n = 27$)	3 mo after 5th BoNT-A ($n = 15$)	6th BoNT-A ($n = 12$)	3 mo after 6th BoNT-A ($n = 11$)	6 mo after 6th BoNT-A ($n = 10$)
GFR (mL/min)	89.7 ± 21.1	85.2 ± 26.0	88.3 ± 21.8	95.2 ± 25.4	90.0 ± 22.6	86.0 ± 22.0	85.2 ± 23.3	85.4 ± 22.6	83.9 ± 24.3	87.8 ± 23.1	82.8 ± 28.6	83.5 ± 24.6	86.0 ± 35.3
CBC (mL)	231 ± 138	371 ± 167	319 ± 183	377 ± 155	397 ± 170	387 ± 112	370 ± 129	463 ± 137	414 ± 175	422 ± 134	377 ± 112	465 ± 137	399 ± 120
Pdet.Qmax (cmH_2O)	37.4 ± 20.4	20.6 ± 16.9	25.3 ± 23.8	16.3 ± 16.3	20.4 ± 16.9	17.6 ± 16.1	24.8 ± 21.0	16.1 ± 17.8	20.9 ± 18.9	23.7 ± 22.7	30.8 ± 26.6	26.7 ± 28.2	20.5 ± 24.2
Qmax (mL/s)	5.24 ± 5.41	2.96 ± 4.42	2.40 ± 3.69	2.64 ± 4.08	1.90 ± 3.77	2.42 ± 4.25	2.44 ± 4.46	1.96 ± 4.00	2.37 ± 3.71	2.73 ± 5.55	3.42 ± 6.39	2.45 ± 5.72	3.40 ± 10.1
Volume (mL)	80.2 ± 95.5	65.6 ± 116	41.0 ± 66.4	58.2 ± 101	31.6 ± 61.1	44.8 ± 68.1	45.6 ± 74.9	32.6 ± 58.2	60.6 ± 94.8	40.3 ± 75.3	47.4 ± 82.4	34.7 ± 82.7	50.1 ± 138
PVR (mL)	151 ± 111	305 ± 191	278 ± 189	319 ± 181	366 ± 183	342 ± 148	324 ± 151	431 ± 149	353 ± 178	381 ± 155	330 ± 146	430 ± 179	349 ± 150
Compliance (mL/cmH_2O)	35.4 ± 36.8	33.6 ± 39.4	36.6 ± 48.1	25.0 ± 17.5	32.9 ± 25.5	33.4 ± 31.9	38.5 ± 49.6	35.2 ± 29.8	40.1 ± 54.1	43.2 ± 48.4	56.2 ± 82.3	54.7 ± 55.4	25.0 ± 18.6

BoNT-A = onabotulinumtoxinA; CBC = cystometric bladder capacity; GFR = glomerular filtration rate; Pdet.Qmax = detrusor pressure at the maximum flow rate; PVR = postvoid residual volume; Qmax = maximum flow rate.

second and third treatments. However, this difference was not statistically significant. According to the results of the extended Phase 3 clinical trial, the median time to patient retreatment request was greater for 200-U and 300-U BoNT-A than for placebo (256 days and 254 days, respectively, vs. 92 days).[15] When the patients develop botulinum resistance, subsequent injections might be less effective. When the therapeutic results of these studies and our results are compared, too frequent injections for neurogenic DO might not have advantage in the long-term success.

Incontinence is the most bothersome factor that affects the quality of life in SCI patients. We found that after the fourth 200-U BoNT-A injection, although CBC and Pdet.Qmax were still in the acceptable range, the percentage of patients with moderate or severe urinary incontinence increased, which caused a high withdrawal rate during the study period and a decrease in the satisfaction rating. In this study, 10 patients discontinued BoNT-A treatment because of the perception of no significant improvement and 10 other patients discontinued the treatment because of the fluctuated therapeutic outcome not meeting their expectations. This result is also compatible with a previous study showing that post-treatment changes in CBC and Pdet.Qmax did not correlate with the changes in the quality of life scores or those of the symptom severity recorded in bladder diaries.[7]

In a recent report of patients receiving intravesical BoNT-A for overactive bladder over a period of 7 years, 61.3% (84/137) of patients had discontinued intravesical BoNT-A therapy at 36 months, with a 63.8% (51/80) discontinuation rate at 60 months.[20] The main reasons for discontinuation were tolerability issues, mainly urinary tract infections and the need for CIC. Primary and secondary losses of efficacy were of secondary importance. Therefore, patients with neurogenic DO may also discontinue repeated BoNT-A injections for the same reasons. Urinary retention was not defined as an adverse event because the therapeutic effect was defined as complete dryness so that urinary retention was a necessary effect. Nonetheless, study has shown that about 70% of patients require periodic CIC.[12] SCI patients might have unrealistic expectations regarding the BoNT-A treatment; however, the improvement of urinary incontinence severity after repeated BoNT-A injections could not meet the patients' expectations.

Although the effects of BoNT-A were promising, the maintenance rate is very low in this study. We assumed that this was mainly because the therapeutic effect did not meet their initial expectations. Although CBC and Pdet.Qmax were still in the acceptable range after repeated BoNT-A injections, the percentage of improvement in urinary incontinence was not so significant. By contrast, most patients were inconvenient to take medical treatment because of restrictive activity. The last problem was the adverse effect of UTI. Around one-third of patients got UTI after BoNT-A injection. The high percentage of UTI may be because of urinary retention and failure to perform CIC regularly.

One of the limitations of this study is the small number of patients and lack of a control arm. The second limitation is that some of the patients dropped out of the study because of lack of satisfaction with the treatment or

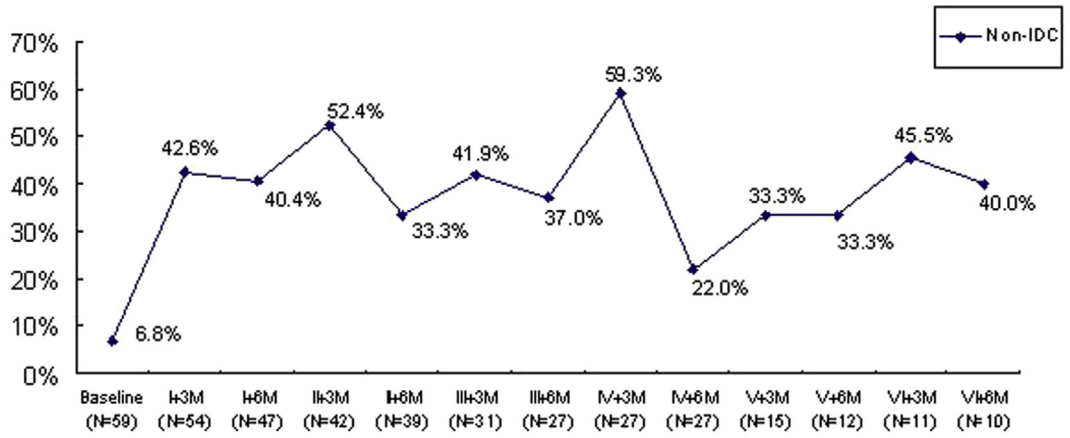

Figure 3 Percentage change in patients without involuntary detrusor contraction (non-IDC) at 3-month and 6-month follow-ups after each set of 200-U BoNT-A detrusor injections. Parentheses indicate the number of patients at each time point. BoNT-A = onabotulinumtoxinA; IDC = involuntary detrusor contraction.

preference for a permanent correction such as enterocystoplasty. However, the overall study results can reflect the real life practice of patients' acceptance of this novel treatment modality for neurogenic DO and urinary incontinence.

In conclusion, repeated 200-U BoNT-A detrusor injections every 6 months provide a satisfactory initial outcome for treatment of patients with neurogenic DO and urinary incontinence due to chronic SCI. However, the improvement in incontinence severity was not consistent after each injection, and the patients' adherence rate to repeated BoNT-A injections was not high as we expected.

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