Intradetrusor Injections of Botulinum Toxin A in Adult Patients with Spinal Dysraphism

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Purpose: The aim of the current study was to determine the outcomes of botulinum toxin A intradetrusor injections in adult patients with spina bifida.

Materials and methods: All patients with spinal dysraphism who underwent intradetrusor injections of botulinum toxin A from 2002 to 2016 at a total of 14 centers were retrospectively included in analysis. The primary end point was the global success of injections, defined subjectively as the combination of urgency, urinary incontinence and detrusor overactivity/low bladder compliance resolution. Univariate and multivariate analysis was performed to seek predictors of global success.

Results: A total of 125 patients were included in study. The global success rate of the first injection was 62.3% with resolution of urinary incontinence in 73.5% of patients. All urodynamic parameters had improved significantly by 6 to 8 weeks compared to baseline, including maximum detrusor pressure (−12 cm H_2O, $p < 0.001$), maximum cystometric capacity (86.6 ml, $p < 0.001$) and compliance (8.9 ml/cm H_2O, $p = 0.002$). A total of 20 complications (3.6%) were recorded for the 561 intradetrusor botulinum toxin A injections, including 3 muscular weakness complications. The global success rate of the first injection was significantly lower in patients with poor compliance (34.4% vs 86.9%, OR 0.08, $p < 0.001$). On multivariate analysis poor compliance was associated with a lower global success rate (OR 0.13, $p < 0.001$). Female gender (OR 3.53, $p = 0.01$) and patient age (OR 39.9, $p < 0.001$) were predictors of global success.

Conclusions: Intradetrusor botulinum toxin A injections were effective in adult patients with spina bifida who had detrusor overactivity. In contrast, effectiveness was much lower in adult patients with spina bifida who had poor bladder compliance. The other predictors of global success were female gender and older age.

Key Words: urinary bladder, overactive; spinal dysraphism; adult; botulinum toxins, type A; urodynamics

Abbreviations and Acronyms

BTX-A = botulinum toxin A

MS = multiple sclerosis

NDO = neurogenic detrusor overactivity

SCI = spinal cord injury

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SPINA bifida is the most common congenital cause of neurogenic bladder with an incidence of 1/10,000 births in developed countries.[1,2] Lower urinary tract symptoms are present in more than 90% of patients with spina bifida[3] and until recent years urinary complications have been the leading cause of death in these patients.[4,5]

Intradetrusor BTX-A injections have revolutionized the management of neurogenic bladder since its first description in 2000 by Schurch et al.[6–8] The DIGNITY (Double-blind investigation of purified neurotoxin complex in neurogenic detrusor overactivity) randomized, controlled trials lead to the licensing of onabotulinum toxin A for NDO but they included only patients with SCI and patients with MS.[9,10] Neurological lesions in spina bifida cases are typically incomplete, sometimes mixed with central and peripheral alterations and frequently with a patchy distribution, and they do not exactly match the pattern of lesions seen in traumatic SCI or MS cases, resulting in distinct bladder dysfunctions in the spina bifida and MS/SCI populations.[3,11]

To date sparse data have been reported on the efficacy of intradetrusor BTX-A injections in patients with spinal dysraphism and no adult patients were included in any available studies in the literature.[11] The aim of the current study was to report the outcomes of BTX-A intradetrusor injections in adult patients with spina bifida.

METHODS

Study Design

All adult patients with spinal dysraphism who underwent at least 1 intradetrusor injection of BTX-A from 2002 to 2016 for detrusor overactivity and/or poor bladder compliance at a total of 14 centers were included in this retrospective study. Patients with a history of augmentation cystoplasty were excluded from analysis. Patients underwent botulinum toxin injection only if they were able and willing to perform clean intermittent self-catheterization and they had not received therapeutic botulinum toxin for any indication in the previous 3 months.

The primary end point was the global success of injections, defined subjectively as the combination of clinical success (urgency and urinary incontinence resolution) and urodynamic success (detrusor overactivity/low bladder compliance resolution) more than 12 weeks in duration as previously described.[12–14] Secondary resistance was defined as failure of at least 2 consecutive intradetrusor BTX-A injections after successful initial injections. This retrospective chart review was approved by the local ethics committee at each institution.

Botulinum Toxin A Injections

Due to the retrospective multicenter study design injection techniques as well as doses were not standardized. For each injection the type of botulinum toxin A (onabotulinum toxin A vs abobotulinum toxin A) was collected as well as the injected dose and complications graded according to the Clavien classification.[15] Injections were performed on an outpatient basis. No standardized re-injection policy was used and the approach in that regard (fixed timing vs symptom recurrence) varied according to local protocols.

Pretreatment and Posttreatment Evaluation

Clinical and urodynamic assessments were performed before and 6 to 8 weeks after the first intradetrusor BTX-A injections. Urodynamic data were collected, including maximum cystometric capacity in ml, bladder compliance in ml/cm H_2O, maximum detrusor pressure in cm H_2O, maximum urethral closure pressure in cm H_2O and volume at the first uninhibited detrusor contraction in ml. The filling rate ranged from 10 to 30 ml per minute according to institutional habit. Urodynamic studies were done according to the ICS (International Continence Society) recommendations.

A low compliance bladder was defined as a bladder with compliance less than 20 ml/cm H_2O.[16] Compliance was calculated by reading the urodynamic traces (ie no automated compliance calculation was used). Urodynamic traces were independently reviewed at each participating institution and there was no central review for study purposes.

Spina bifida was categorized as open or closed spinal dysraphism according to the Tortori-Donati classification.[17] Based on the clinical evaluation the sensory motor level of re-injection was categorized as sacral, lumbar or thoracic. Urodynamics were not repeated after each re-injection when the first injection succeeded. Injections were performed thereafter at physician discretion.

Statistical Analysis

The mean ± SD is reported for continuous variables and proportions are reported for nominal variables. Nominal variables before and after injections were compared by the McNemar test with the paired Student t-test applied to compare continuous variables with time. Factors predictive of global success were investigated using univariate and multivariate logistic regression analysis. Multivariable models included covariates at $p < 0.2$ on univariable analysis. For continuous variables the OR is expressed as a range according to the change in the regressor over the entire range. Comparisons were made with the chi-square test for nominal variables and the Mann-Whitney test for quantitative variables. Statistical analyses were performed using JMP®, version 12.0 software. All tests were 2-sided with significance considered at $p < 0.05$.

RESULTS

Patient Characteristics

After excluding 53 children and 4 patients with a history of augmentation cystoplasty 125 patients who underwent a total of 561 intradetrusor BTX-A injection courses were included in study. There were 1 to 17 courses per patient. Table 1 summarizes patient characteristics. The urodynamic [T1]