Increased Risk of Large Post-Void Residual Urine and Decreased Long-Term Success Rate After Intravesical OnabotulinumtoxinA Injection for Refractory Idiopathic Detrusor Overactivity

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Abbreviations and Acronyms

AE = adverse events
AUR = acute urinary retention
BCI = bladder contractility index
BoNT-A = onabotulinumtoxinA
CBC = cystometric bladder capacity
CIC = clean intermittent catheterization
IDO = idiopathic detrusor overactivity
OAB = overactive bladder
Pdet = voiding detrusor pressure
PVR = post-void residual urine
Qmax = maximum flow rate
QOL = quality of life
UTI = urinary tract infection
UUI = urgency urinary incontinence
VE = voiding efficiency
VUDS = videourodynamic study

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Purpose: Intravesical injection of onabotulinumtoxinA is effective for idiopathic detrusor overactivity refractory to antimuscarinics. However, safety is a major concern, especially in elderly individuals. We investigated the efficacy and safety of intravesical onabotulinumtoxinA injection for refractory idiopathic detrusor overactivity in the frail elderly population.

Materials and Methods: A total of 166 patients with urodynamic idiopathic detrusor overactivity refractory to previous antimuscarinics for more than 3 months received 1 intravesical 100 U onabotulinumtoxinA injection from 2004 to 2009. Frail elderly was defined as age greater than 65 years and 3 or more of certain criteria, including unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and/or low physical activity. Treatment results were assessed by the Patient Perception of Bladder Condition, voiding diary, urodynamic parameters and Kaplan-Meier estimates of survival plots.

Results: We evaluated 61 frail elderly patients, 63 who were elderly without frailty and 42 younger than 65 years. Large post-void residual urine volume (greater than 150 ml) after onabotulinumtoxinA injection was significantly higher in the frail elderly group than in the other groups (60.7% vs 39.7% and 35.7%, respectively, $p = 0.018$). Urinary retention developed in 7 frail elderly patients (11.5%), 4 (6.3%) who were elderly without frailty and 1 younger patient (2.4%) ($p = 0.203$). Recovery duration was significantly longer in frail elderly patients. The cumulative success rate was significantly lower in the frail elderly group than in the other 2 groups ($p = 0.009$).

Conclusions: Although safety and efficacy were similar between elderly patients without frailty and younger patients, an increased risk of large post-void residual urine volume and a lower long-term success rate in frail elderly patients were noted after intravesical onabotulinumtoxinA injection for refractory idiopathic detrusor overactivity.

Key Words: urinary bladder, overactive; onabotulinumtoxinA; frail elderly; quality of life; complications

THE prevalence of OAB increases with age and has a substantial impact on QOL.[1] Identifying and treating OAB in the elderly population is important because it is usually associated with an increased risk of falls, fractures and mortality.[2] However, conservative treatment and antimuscarinics may result in insufficient improvement and low compliance due to both-

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ersome AEs.[3] In addition, elderly patients usually show altered drug solubility, metabolism and clearance as well as increased polypharmacy, which may impact disease management.[4] Although clinical trial data indicate that antimuscarinics are generally effective and well tolerated in elderly patients,[5,6] these participants are generally relatively healthy, which may not reflect the true elderly population.

Frail elderly is usually defined as elderly with a clinical presentation or phenotype combining impaired physical ability, mobility, balance, muscle strength, motor processing, cognition, nutrition and endurance, including feelings of fatigue and exhaustion.[7,8] These patients are more vulnerable to complications. However, data specific to OAB treatment are limited in the frail elderly population. The International Consultation on Incontinence recommended behavioral intervention with the cautious addition and trial of antimuscarinic drugs for urinary incontinence in frail elderly individuals or those already in a state of decline.[9]

Intravesical injection of BoNT-A provides effective treatment for IDO and OAB.[10–15] White et al reported the short-term efficacy of intravesical injection of 200 U Botox® for refractory OAB with no treatment related complications in the elderly population.[16] We evaluated the short-term and long-term efficacy and safety of intravesical BoNT-A injection for refractory IDO in frail elderly patients.

MATERIALS AND METHODS

Patient Enrollment

In 2004 to 2009 we enrolled 166 patients diagnosed with urodynamic IDO who received intravesical injection of 100 U BoNT-A (Allergan, Irvine, California) for refractory OAB for the first time. Most patients lived in Hualien and were recruited at a tertiary teaching hospital, while others were referred from other hospitals around Taiwan. These frail individuals lived in the community and none lived in a nursing home. All patients had persistent urgency/UUI even with antimuscarinic use for more than 3 months.

Patients were requested to record a 7-day voiding diary before treatment. Urgency episodes and urgency incontinence were verified using a 7-day voiding diary at baseline and before each visit. Routine VUDS was performed at baseline to diagnose IDO and detect bladder outlet obstruction or intrinsic sphincter deficiency. VUDS was performed with terminology defined according to the International Continence Society recommendation.[17]

The study inclusion criterion was IDO refractory to previous antimuscarinics for more than 3 months. Exclusion criteria were UTI, bladder outlet obstruction, intrinsic sphincter deficiency, neurogenic bladder or greater than 150 ml PVR at enrollment. Frail elderly was defined as age greater than 65 years and 3 or more of certain criteria, including an unintentional weight loss of 4.54 kg in the last year, self-reported exhaustion, weakness (grip strength), slow walking speed and/or low physical activity.[12]

The hospital institutional review board and ethics committee approved this study. Each patient was informed of the study rationale and procedures. Written informed consent was obtained before treatment.

Botulinum Toxin Injection

Patients were hospitalized for treatment and received an intravesical injection of 100 U BoNT-A under intravenous general anesthesia in the operating room. Each BoNT-A vial was diluted with 20 ml normal saline to provide 40 suburothelial injections covering most of the bladder wall. A total of 40 suburothelial injections were performed with trigone sparing. The injection syringe was inserted in the urothelium at the posterior and lateral bladder walls using a 23 gauge needle and a 22Fr rigid cystoscopic injection instrument (Richard Wolf, Knittlingen, Germany). After BoNT-A injection, a 14Fr urethral Foley catheter was inserted, which remained for 1 day. Patients were discharged home the following day. Oral antibiotics were prescribed for 7 days. Antimuscarinics were discontinued at study enrollment and all patients were followed without repeat injection.

Clinical Assessment

All patients were closely monitored at 1 to 2 weeks, 1 and 3 months, and every 3 months thereafter until the response to BoNT-A disappeared. VUDS, a 7-day voiding diary and the QOL index according to the International Prostate Symptom Score were obtained at baseline and 3 months after treatment. The primary end point was the change in the Patient Perception of Bladder Condition, which is used to measure incontinence severity and treatment results.[18] All patients were requested to grade the treatment outcome at each visit. A Patient Perception of Bladder Condition decrease of 2 points was considered successful. The secondary end point was changes in the parameters of VUDS and the 7-day voiding diary. CBC, voiding Pdet, Qmax and PVR were recorded. VE was calculated according to the percent of voided volume of the total bladder capacity. The BCI is determined by the formula, BCI = Pdet at Qmax + 5 Qmax.[19] During followup, patients were requested to visit regularly until they could void with a PVR of less than 50 ml.

Procedure related AEs were recorded during followup after BoNT-A treatment. AEs included AUR (severe difficulty urinating with a PVR of greater than 350 ml, necessitating an indwelling catheter or CIC), gross hematuria, general weakness in the early stage, large PVR (greater than 150 ml), straining to void (difficult urination requiring abdominal straining to empty the bladder, which was not the pretreatment experience) and UTI (symptomatic or asymptomatic with a white blood count of greater than 10 cells per high power field on urinalysis) during followup. The indication for CIC determined by the patient, family or caretaker was PVR greater than 250 ml and difficulty emptying the bladder.

Other nonspecific AEs that developed after BoNT-A were also recorded based on patient self-report and chart recording. AEs were graded according to the surgical complication classification.[20]