Drying Our Fears: The Role of Botulinum toxin in Managing Urinary Symptoms in SCI and MS veterans

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Presentation goals

• Review SCI genitourinary disorders and neurogenic bladder pathology
• Appropriate use of botulinum toxin to facilitate successful neurogenic bladder (NGB) management
Background

- Neurogenic bladder (NGB) described as bladder dysfunction resulting from neurological conditions most common being MS and SCI
- SCI and other neurological disorders often lead to both storage and emptying bladder dysfunction
Neurogenic bladder

• Storage bladder dysfunction
  – Neurogenic detrusor overactivity (involuntary detrusor contraction in setting of NGB) produces uncontrolled bladder emptying
  – Small bladder capacity
  – Poor bladder compliance
  – Weak external sphincter leads to urine leak with Valsalva and detrusor contraction
Neurogenic bladder

• Emptying bladder dysfunction
  – Detrusor Sphincter Dyssynergia (DSD)—involuntary urethral sphincter contraction during detrusor contraction
    • Bladder contractions against a closed sphincter leads to elevated bladder pressures and vesicoureteral reflux
    • Leads to bladder wall hypertrophy and eventually decreased compliance
  – Diminished detrusor contraction
    • Leads to incomplete emptying
Goals of NGB program

- Preserve renal function
- Preserve quality of life
- Decrease UTIs
- Decrease stone formation
- Facilitate bladder emptying while eliminating urine at regular and socially acceptable times
Preserve renal function

Hello Kidney
NGB management program

- Individualized approach
  - Patient’s preferences and social support
  - Consideration of upper extremities function
  - Lower extremity contractions
  - Individual anatomical variations
  - Urodynamics findings
  - Multidisciplinary approach preferred
NGB management program

• Start with the least invasive options
  – Maximize oral therapy
    • Anticholinergics
    • B-3 adrenergic receptor agonist
    • Alpha blockers for DSD
  – Clean intermittent catheterization
  – Local bladder and/or sphincter treatments
    • Botulinum toxin injections
    • Sphincterotomy
NGB management program

• Invasive surgical options
  – Sacral neuromodulation
  – Rhizotomy
  – Ileovesicostomy
  – Bladder augmentation with or without creation of Mitrofanoff channel
  – Ileal conduit diversion
Local bladder and sphincter treatments

• Intravesical and intrasphincteric botulinum injections can assist with successful SCI bladder program
• Intravesical botulinum injections addresses complications caused by neurogenic detrusor overactivity
  – Urgency, urge incontinence, poor compliance and bladder capacity
• Intraspheincteric injection addresses DSD
Clinical case

• MK is a 49 y/o female patient with MS
• She was wheelchair bound, but had good hand function
• Presented to me in 2005 with urge incontinence and recurrent UTIs
• UDS showed NDO, decreased bladder capacity (150cc) no DSD and incomplete emptying
• She was started on CIC every 4 hours and anticholinergic regimen
• UTIs have resolved with timely CIC and prophylactic antibiotics
Clinical case

• Her incontinence have improved, but did not resolve
• She was tried on several anticholinergic regimens and still continued to leak
• Part of her problem was small bladder capacity
Clinical case

• She decided against invasive surgical procedures
• 300 U of botox were injected in standard grid pattern
• She reported complete resolution of urge and incontinence in 2 weeks
• Repeat bladder capacity measurement showed 240cc 6 months later and 300cc in 12 months
• Patient reported sustained results for the past 5 years with every ~5 months intravesical botox regimen
Intravesical botulinum injections

• Botulinum toxin is produced by the spore-forming, Gram-positive, anaerobic Clostridium botulinum bacteria
• Toxin inhibit acetylcholine release at NM (neuromuscular) junction
• This causes smooth as well as striated muscle relaxation
• U. S. Food and Drug Administration (FDA) approved onabotulinum toxin A (Botox®) for treatment of detrusor overactivity associated with a neurogenic condition 8/2011
Indications

- Detrusor Overactivity associated with a Neurologic Condition
- Urinary incontinence due to DO associated with a neurologic condition (NDO)
- Adults who have an inadequate response to or are intolerant of an anticholinergic medication with NDO
Mechanism of Action

- Modulate acetylcholine and other biochemical messengers at presynaptic nerve terminals and noncholinergic mechanisms in the detrusor smooth muscle
- Preventing detrusor contraction
- Leading to transient smooth muscle paralysis and symptom alleviation
Mechanism of Action

• A broader mechanism of action suggested
  – BoNT (Botulinum toxin) blocks release of acetylcholine, ATP, and substance P
  – Leading to central desensitization and effectiveness in detrusor overactivity
Schematic diagram demonstrating normal of SNARE protein fusion and release of acetylcholine from nerve terminals

Smith CP, Chancellor MB. *J Urol* 2004;171:2128-2137
Botulinum formulations

- Three other BoNT (Botulinum Toxin) serotype preparations are available:
  - abobotulinumtoxinA (Dysport)
  - incobotulinumtoxinA (Xeomin)
  - rimabotulinumtoxinB (Myobloc)
- Not approved to treat NDO and cannot be used interchangeably.
The FDA approval was based on results of two subsequent phase 3 randomized clinical studies involving 691 patients. The studies assigned patients with NDO resulting from SCI or MS not adequately managed with anticholinergics to onabotulinumtoxinA 200 U, 300 U, or placebo.
Clinical Evidence
Chancellor, M. Part II: Current Treatment Options for Neurogenic Bladder Dysfunction. JULY 2012

• Primary end point was change from baseline in weekly urinary incontinence episodes at week 6
• Patients in the onabotulinumtoxinA 200 U and 300 U arms had significant decreases in weekly frequency of incontinence episodes vs. placebo
• Similar improvements noted in incontinence episodes, urodynamic parameters, and health-related quality-of-life scores
Two double-blind, placebo-controlled, randomized, multicenter studies

• Adults with UI due to detrusor overactivity associated with a neurologic condition4
• Diagnosed with MS (n=381)* or SCI (n=310)
• Spontaneously voiding or using catheterization
• 4.5 daily UI episodes (about 32/week) on average at baseline
• Had an inadequate response to or were intolerant of an anticholinergic medication
• Chancellor, M. Part II: Current Treatment Options for Neurogenic Bladder Dysfunction. JULY 2012 www.renalandurologynews.com
BOTOX® patients experienced a median 10-month duration of response (up to 48 weeks) based on patient qualification for retreatment.

- Placebo: median of 4 months (up to 18 weeks)

Duration of response: time to patient qualification for retreatment

Study 1

Study 2

Starting at week 12, patients could qualify for retreatment.

Starting at week 12, patients could qualify for retreatment.
BOTOX® patients showed a mean increase in maximum cystometric capacity of up to 63% (+150.8 mL) at week 6.

- Placebo: up to 5% (+12.1 mL)

Maximum cystometric capacity at baseline and week 6:

**Study 1**

<table>
<thead>
<tr>
<th>Placebo (n=129)</th>
<th>BOTOX® 200 U (n=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 259.1 mL</td>
<td>Baseline 253.8 mL</td>
</tr>
<tr>
<td>+5% +12.1 mL</td>
<td>+54% +135.9 mL*</td>
</tr>
<tr>
<td>Week 6 271.2 mL</td>
<td>Week 6 389.7 mL</td>
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**Study 2**

<table>
<thead>
<tr>
<th>Placebo (n=85)</th>
<th>BOTOX® 200 U (n=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 253.8 mL</td>
<td>Baseline 239.6 mL</td>
</tr>
<tr>
<td>+1% +2.8 mL</td>
<td>+63% +150.8 mL*</td>
</tr>
<tr>
<td>Week 6 256.6 mL</td>
<td>Week 6 390.4 mL</td>
</tr>
</tbody>
</table>

* P<.001

† Change from baseline represented by LS mean change based on an LOCF analysis using an ANCOVA model.
Procedure

• OnabotulinumtoxinA is injected intramuscularly at multiple sites throughout the bladder in an outpatient procedure.

• The recommended dose of onabotulinumtoxin A is 200 U per treatment
  – Some experts still using 300 U per treatment.

• Patients may be considered for reinjection when the clinical effect of the previous injection diminishes (median 42-48 weeks in clinical studies) but no sooner than 12 weeks from the prior bladder injection.
Adverse events

• The most common adverse events are incomplete bladder emptying and urinary tract infections
  – Urinary retention reported in up to 30% of patients
• Distant botulinum spread have not been reported for intravesical injections
Contraindications

- Active infection
- Known hypersensitivity to botulinum agents
- Relative contraindications
  - preexisting neuromuscular disorders
- Pregnancy (Class C) and nursing mothers
- Bladder outlet obstruction
Cost Effectiveness

• Vanderbilt University Medical Center study 2010
  – Priya Padmanabhan*, Harriette Scarpero, Douglas Milam, Roger Dmochowski, David Penson, Nashville, TN

• Procedure surgical costs were derived from the Medipac database of the hospital billing system using Current Procedural Terminology (CPT) codes. Hospital center costs were determined from Diagnosis Related Group (DRG) reimbursement files. Drug costs were calculated using Center for Medicare and Medicaid Services (CMS) Average Selling Price.

• All costs were reported in 2008-2009 US dollars

• BoNTA was found more cost effective choice over a five-year period in the treatment of NGB patients over augmentation cystoplasty
Cost Effectiveness

- Jennifer M. Wu,* † Nazema Y. Siddiqui, Cindy L. Amundsen,† Evan R. Myers,‡ Laura J. Havrilesky§ and Anthony G. Visco

Duke University, Durham, North Carolina

- Botulinum toxin A injection was cost-effective compared to anticholinergic medications for the treatment of refractory urge incontinence

- Anticholinergics become cost-effective if patients are highly compliant with medications or if the botulinum procedure costs increase substantially
Intrasphincteric botulinum injection

- Thirteen patients (1 F, 12 M) suffering urinary retention due to DSD were randomised to receive one transperineal injection of 100 IU BTx Botox° in 4 ml of 9% saline (botulinum group, (BG)) or 4 ml of 0.5% L (lidocaine group, (LG))

- The preliminary results demonstrated the superiority of BTx compared to L in improving clinical symptoms and DSD in spinal cord injured patients

- The botulinum toxin injection was efficacious for 3 months in 46% of the patients and longer than 3 months in 23% of them. The efficacy was shorter than 3 months in the remaining 31% of patients. Mean follow-up was 80±49 days

- No infection or bleeding complications
Intrasphincteric botulinum injection

- Described in pediatric population
  - 20-50 U injection into 4 quadrants at the external sphincter

- In multiple sclerosis patients with DSD, a single transperineal injection using striated sphincter electromyography injection of 100 U botulinum A did not decrease post-voiding residual urine volume*
Conclusions

• Successful NGB management encompasses reduction in NGB related complications and improvement in symptoms

• Intravesical BoNT injections are effective in treatment of NGB
  – Urinary retention is most common side effect

• Supported by clinical data
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References

- Chancellor, M. Part II: Current Treatment Options for Neurogenic Bladder Dysfunction. JULY 2012 www.renalandurologynews.com
- Data on file, Allergan, Inc.
- BOTOX® Prescribing Information, November 2011.
- Placebo controlled, randomised, double blind study of the effects of botulinum A toxin on detrusor sphincter dyssynergia in multiple sclerosis patients P Gallien, J-M Reymann, G Amarenco, B Nicolas, M de Se`ze, E Bellissant