Botulinum Toxin and Bladder Instillations

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Botulinum Toxin

Indications
Mechanism
Procedure
Outcomes
Adverse Effects

Bladder instillations for Bladder Cancer
Indications
AUA/SUO strategies for the BCG shortage
Intravesical agents

1 Botulinum Toxin
Botulinum Toxin

1820s
Justinus Kerner identifies food-borne botulinum toxin as cause of sausage deaths, Germany

1850s
C. botulinum identified

1895
Botulinum toxin identified

1920s
Edward Schantz prepares batches of crystallized toxin for animal experiments

1930s
Botulinum toxin is investigated as a biological weapon

1944
Dr. Allan Scott begins research in humans with strabismus

1978
FDA approves Botox® for blepharospasm, strabismus

1989
1996
Madonna, Tom Cruise et al. popularize Botox®

1999
FDA approves Botox® for OAB

2013
Why Intravesical?

Advantages of intravesical therapy
High concentration of pharmacologic agents directly to target (bladder) tissue
Avoid systemic effects

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Botulinum Toxin

Indications

Children
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Adults
Overactive bladder (urgency-incontinence, frequency, urgency)

• Inadequate response or intolerance of anticholinergic medication.

Neurogenic bladder: Urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., spinal cord injury, MS)

• Inadequate response or intolerance of anticholinergic medication.

Overactive Bladder

Randomized clinical trials in OAB wet: BTX vs antimuscarinics:

The ABC Trial

- Solifenacin 5mg (+NS injection) vs BTX 100 (+placebo) x 6 months
  - Option to escalate to solifenacin 10mg or trospium ER 60mg

Similar reductions in urgency/incontinence

BTX group had less dry mouth

BTX group had more urinary retention and UTI

Lorem ipsum

Lorem ipsum baseline

- Lorem ipsum
- Lorem ipsum

1. June 2012

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Bladder Structure and Function

Filling/Storage
- Store urine at a low pressure until socially appropriate time to void
- Emptying/voiding

Filling phase properties: Compliance
Change in volume relative to change in intravesical pressure (Hollow tank properties of bladder depend on neuromuscular and mechanical properties)
- Passive structures
  - Content of smooth muscle, collagen, elastin
  - Injury, obstruction, and denervation increase collagen content and impaired compliance
- Smooth muscle activity
  - CNS input required for compliance
  - Passive structures during filling to maintain smooth muscle compliance

Bladder Structure and Function

Filling phase: detrusor overactivity
Normal bladder smooth muscle is spontaneously active
- Gap junctions, bridges between smooth muscle cells, for elastic coupling
- Gap junctions can trigger spontaneous contractions aka microcontractions
- Interstitial cells aka myofibroblasts are also spontaneously active
- Located in suburothelial layer and the detrusor layer
- Non-contractile elements
- Believed to have a "pacemaker" function
- Propagate signals between detrusor muscle cells
- Smooth muscle and interstitial cells respond to cholinergic stimulation by M3 muscarinic receptor activation
- Both are involved in development of detrusor overactivity (storage failure)

Drug targets:
1. Botulinum Toxin
2. Botox 
3. OnabotulinumtoxinA
4. Oxybutynin

Bladder Structure and Function

Voiding phase
- Intravesical pressure = Pdet + Pabd, thus Pdet = Pves - Pabd
- Parasympathetic activation via acetylcholine leads to detrusor contraction
- Purinergic activation by ATP can also induce contractions

Muscle can use energy to generate force or shorten its length
- Force contributes to Pdet
- Velocity of shortening relates to urine flow (Q)
- If urethral resistance is low (women), Pdet may remain almost undetectable
- Mechanical power W = Pdet x Q
- Women open the urethra widely (high flow), and only need a low Pdet for the same voiding "power" as a man
- Voiding nomograms developed for men with obstruction are not applicable to women
Bladder Structure and Function

Voiding phase

Intersitial pressure = Pdet + Pabd, thus Pves = Pdet + Pabd

Parasympathetic activation via acetylcholine leads to detrusor contraction

• Parasympathetic activation by ATP can also induce contractions

Lately more prominent in disease states OAB, IC

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Botulinum Toxin and Bladder Instillations

1. Lim and Abrams 1995

Micromotions
Motor sensory network within the detrusor muscle wall

Neural control of the bladder

Neurogenic Bladder

Neuromuscular disease, injury, or dysfunction that alters the micturition cycle
Causing abnormalities in:

- Sensation (normal, absent, impaired)
- Detrusor activity (normal, overactive, areflexic, impaired contractility)
- Detrusor compliance (normal, decreased, increased)
- Smooth sphincter activity (synergic, dyssynergic)
- Striated sphincter activity (synergic, dyssynergic, bradykinetic, impaired voluntary control, fixed tone)
Neurogenic Bladder

Discrete neurologic lesions affect filling/storage and emptying/voiding in consistent manners that depend on:
The area of nervous system affected
The physiologic function of area affected
Whether lesion is destructive, inflammatory, or irritative

Option to escalate to anticholinergic: solifenacin 10mg or trospium ER 60mg

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Lorem ipsum baseline
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Lorem ipsum

Neurogenic Bladder

Common patterns:
Lesions above the brainstem
• Detrusor overactivity
DO Incontinence
Complete Spinal Cord Lesions T6-S2
• Absent sensation
• Detrusor overactivity
• Striated sphincter dysynergia
DO Incontinence
Urinary retention
Overflow incontinence

Neurogenic Bladder

Common patterns:
Trauma/disease below S2
• Detrusor areflexia
• Decreased compliance
• Absent striated sphincter control
Peripheral reflex arc interruption
• Can be motor or sensory neuropathy
• Detrusor areflexia
• Decreased compliance
• Fixed residual tone of striated sphincter
Botulinum Toxin

Mechanism of Action

Botulinum toxin (BTX) is a neurotoxin produced by Clostridium botulinum.
Seven subtypes: BTX subtype A has the longest duration of action.
Most clinically useful subtype

Dose units are not interchangeable

Four commercial forms of BTX A, wrapped by different proteins that modify its potency:
- OnabotulinumtoxinA (Botox)
- AbobotulinumtoxinA (Dysport)
- IncobotulinumtoxinA (Xeomin)
- Prosigne – exclusively produced in China

Some studies have investigated BTX subtype B
- RimabotulinumtoxinB (Miobloc, Neurobloc)

Mechanism

Botulinum toxin blocks neurotransmitter release

Most extensively studied in striated muscle, where acetylcholine release is blocked from motor nerve endings, causing paralysis.
- Effects last 2-4 months in striated muscle

BTX targets parasympathetic, sympathetic, and sensory nerve fibers in the bladder:
- Acetylcholine blockade is essential for impairing detrusor contractility
- Bladder sensory impairment is also important in clinical effect of BTX
- BTX inhibits spinal cord release of glutamate, substance P, and other neuropeptides
- BTX reduces firing from bladder afferent (sensory) nerves
- BTX inhibits bladder neurotrophins, unknown effect on plasticity, growth
- BTX effect lasts longer in detrusor smooth muscle (up to 12 months)
Mechanism

Botulinum toxin blocks neurotransmitter release
Impairs contractility
Relaxes resting tone / increases compliance
Impairs sensation

Botulinum Toxin

Procedure

Intravesical Injection

Check the Botulinum Toxin
Check formulation therapeutic (intravesical) – not cosmetic
Check expiration date (3yr post manufacture)
Store in refrigerator at 2–8 ºC
• Stable at 30ºC x7 days
The vial looks empty
• The vacuum-dried toxin looks like clear crystals
• Tiny volume
Prime the needle with reconstituted Toxin or NS

Reconstitute the Toxin
Sterile unpreserved normal saline (0.9% sodium chloride for injection)
• 10cc for 100 units, 30cc for 200 units
• Flush
Use immediately
Intravesical Injection

Injection procedure
- Classic injection template
  - Trigone sparing
  - 2mm needle depth
  - Injections 1cm apart
  - Aliquots:
    - 100 units: 20 sites in 0.5mL aliquots
    - 200 units: 30 sites in 1.0mL aliquots
  - Final injection with 1mL NS

Intravesical Injection

Documentation Best Practice

Dilution/reconstitution
- Lot number
  - Especially to differentiate Toxin obtained by practice versus specialty pharmacy
- Per insurance
  - Record number of units delivered
  - Record any wasted Toxin, if applicable

Repeat dosing
- When symptoms recur
- At 6 months

MAXIMUM DOSE: 400 units in 12 weeks

Botulinum Toxin

Outcomes
Outcomes in Overactive Bladder

Randomized clinical trials: BTX vs placebo
Success not related to existence of detrusor overactivity at baseline
Magnitude of effect vs placebo: 2 to 4-fold, not previously reported with antimuscarinics
- Decreases incontinence episodes: 23% completely dry with BTX
- Decreases frequency
- Decreases urgency
- Improves quality of life

Outcomes in Overactive Bladder

Randomized clinical trials in OAB wet: BTX vs antimuscarinics
ABC Trial
- Solifenacin 5mg (+NS injection) vs BTX 100 (+placebo) x 6 months
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Similar reductions in urgency incontinence
BTX group had less dry mouth
BTX group had more urinary retention and UTI

Outcomes in Neurogenics

Randomized clinical trials in NDO
Decreases incontinence episodes
Decreases urinary frequency
Improves quality of life (QoL)

Special populations
- Parkinson disease
- Multiple Sclerosis
- Spinal Cord Injury
Randomized clinical trials: BTX vs placebo\(^1\) 

Success not related to existence of detrusor overactivity at baseline\(^2\)\(^,\)\(^3\)

Magnitude of effect vs placebo \(^2\)-\(^4\)-fold, not previously reported with antimuscarinics

- Decreases incontinence episodes
- Decreases frequency
- Decreases urgency
- Improves quality of life

* Lorem ipsum *

Parkinson's Disease

1. Nitti 2013b
2. Rovner 2011
3. Kanagarajah 2012

Outcomes in Neurogenics

Special populations

- Parkinson's disease\(^1\)
- Improvement in frequency, incontinence episodes and QoL
- Duration up to 9 months

- Multiple Sclerosis\(^2\)
- Improvement incontinence and QoL

- Spinal Cord Injury

Outcomes in Neurogenics

- Improvement in bladder dyssynergia

Botulinum Toxin

Adverse Effects
Adverse Effects

Common side effects\(^2\)

Occur in the first 12 weeks
- Dysuria (12%)
- Urinary infection
- Hematuria
- Elevated post void residual (PVR)

Peaked at 2 weeks post treatment
8.7% had increase in PVR by ≥200mL

Discontinuation rates because of adverse effects were low (1.8%)\(^1\)

1. Mas 2010
2. Rose 2010

Adverse Effects

Uncommon side effects

Urinary retention (5.4%)\(^1\)
- Transient need for intermittent catheterization (cic)

Duration of cic usually till 6 weeks
- RCTs recommend caregivers teach cic prior to BTX

Transient muscle weakness reported with abobotulinumtoxin\(^2\)
- Caution in high risk patients
  - Children
  - Low pulmonary reserve
  - Myasthenia gravis

1. Mas 2010
2. Akbar 2007

Bladder Instillations

2
Background

Non-muscle invasive bladder cancer (NMIBC)
Field defect
BCG + surgery superior to surgery only
Multagent intravesical chemotherapy
- Lack high-quality data comparing to BCG
- Theoretically offer better efficacy and/or tolerability
  
  
  Doxorubicin + interferon-α (IFN)
  
  Gemcitabine + cisplatin

Bacillus Calmette-Guerin (BCG)
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Intravesical therapy for bladder cancer

Why intravesical therapy
Field defect
BCG + surgery superior to surgery only
BCG superior to single-agent intravesical chemotherapy regimens
Multagent intravesical chemotherapy
- Lack high-quality data comparing to BCG
- Theoretically offer better efficacy and/or tolerability
  
  
  Simultaneously target multiple points of cell replication
  Gemcitabine + docetaxel
  Carboplatin + gemcitabine + cisplatin

International BCG Shortage

Mounting drug shortages delay treatments for patients with bladder cancer

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AUA/SUO Strategies to optimize NMIBC care

Low risk disease
BCG should not be used for low-risk disease

Intermediate risk disease
Intravesical chemotherapy should be used as first-line option for intermediate-risk NMIBC
- Recurrent multifocal LG lesions requiring therapy
- MMC, gemcitabine, epirubicin or doxorubicin
If BCG would be administered as 2nd-line therapy for intermediate-risk NMIBC, use an alternative intravesical chemotherapy

High risk disease
High-risk NMIBC receiving induction therapy should be prioritized for full-strength BCG
- HG T1 and CIS
  - If not available, reduced ½-1/3 dose should be given
  - If no BCG, preferable alternative is MMC (induction + maintenance)
Other options: gemcitabine, epirubicin, doxorubicin, valrubicin or combination therapy
High-risk NMIBC receiving maintenance therapy
- Use ½ dose and limit dose to one year
  - If not available, maintenance therapy should not be given
  - If MMC induction was used, may also use MMC for maintenance
Patients with high-risk features should be offered initial radical cystectomy if appropriate
- HG T1 with GS, LVI, prostatic urethra involvement or variant histology
Oncologic risk with alternative intravesical agents is not well known

AUA/SUO Strategies to optimize NMIBC care

Additional notes
Split dosing
- Whenever possible when ½ or 1/3 doses are used, multiple patients should be treated on the same day to avoid waste
  - Work with pharmacy for appropriate safety precautions
Informed decision making with patients regarding ongoing BCG shortage
AUA awaiting guidance from CMS on billing
Enroll patients in clinical trials where feasible

AUA/SUO Strategies to optimize NMIBC care

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Botulinum Toxin and Bladder Instillations
Mitomycin C (MMC)

Mitomycin C
Crosslinks DNA

Gemcitabine

Gemcitabine
Requires active DNA synthesis for activity

Docetaxel

Docetaxel
Non-vesicant, microtubule polymerization stabilizer (inhibits cell division)
Cabazitaxel

Microtubule inhibitor (inhibits cell division)

Gemcitabine + Docetaxel

Combination Gemcitabine + Docetaxel

Administered as a sequence to optimize efficacy

- Gemcitabine (requires active DNA synthesis), docetaxel (inhibits cell division and thus DNA synthesis)
- Induction: 6 weekly instillations of 1g gemcitabine x1.5h, followed by 37.5mg of docetaxel x2h
- Monthly maintenance x2 years

Studied in BCG failure/intolerance (n=45)

- All but a few completed induction
- Disease-free survival 54% (1yr) and 34% (2yr)
- 15 failures underwent cystectomy
- 1/10 with invasive disease

1. Steinberg 2015 (9)

Cabazitaxel + gemcitabine + cisplatin

Combination: 2g gemcitabine, 5g cabazitaxel, cisplatin

Data from a phase 1 trial with prior BCG failure (n=9)

- Established doses
- Median four prior intravesical therapies
- All completed induction
- 7/8 had complete response

1. DeCastro (11)
References


Thank you.