Prophylactic Antibiotic Administration for Bladder OnabotulinumtoxinA Injection

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Single-Dose versus Multi-Dose Prophylactic Antibiotic Administration for Bladder OnabotulinumtoxinA Injection

Research Protocol

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Introduction

To date, no prospective trials have been conducted evaluating the outcomes of duration of antibiotic prophylaxis with bladder onabotulinumtoxinA injection. Antibiotic regimens vary widely from study to study, with differing indication (idiopathic vs neurogenic overactive bladder), pre-procedural urine studies (sterile urine culture, negative urinalysis, asymptomatic bacteriuria), route (intramuscular or oral), duration (zero to seven days), dose, and class of antibiotic (Aharony et al., 2020; Houman et al., 2019; Leitner et al., 2016; Bickhaus et al., 2020). In published studies, injection protocols have or have not included an antibiotic prophylactic treatment (Hermieu et al., 2014). Much of the original literature supporting onabotulinumtoxinA use for refractory overactive bladder does not provide specifics on antibiotic prophylaxis regimen (Aharony et al., 2020). The goal of this study is to determine if the incidence of post-procedure UTI is similar between single-dose and multi-day durations of peri-procedural antibiotics.

Background and Significance

Bladder onabotulinumtoxinA is a widely used third-line treatment option for patients with refractory overactive bladder, including symptoms associated with neurological disease. (Lightner et al., 2019). The most common adverse event related to bladder onabotulinumtoxinA injection is postoperative urinary tract infection (UTI). In some studies, rates of UTI are reported as high as 64% following bladder onabotulinumtoxinA (Yunfeng et al., 2022). Within our institution these rates are much lower at 11% (Martin et al., 2022).

Despite post-procedure UTI as a commonly reported adverse event, there are no specific guidelines for antibiotic prophylaxis for bladder onabotulinumtoxinA injection for prevention of UTI. The most recent American Urological Association (AUA) best practice statement for urologic procedures and antimicrobial prophylaxis does not provide specific recommendations for antibiotic prophylaxis for bladder onabotulinumtoxinA injection (Lightner et al., 2020). The recommendation for cystourethroscopy with minor manipulation with break in mucosal barriers, biopsy, fulguration, etc., is uncertain for the indication for antibiotic prophylaxis (Lightner et al., 2020). If prophylactic antibiotics are administered, a single dose of trimethoprim-sulfamethoxazole or amoxicillin/clavulanate is the recommended regimen, considering patient specific risk factors and prior urine culture results (Lightner et al., 2020). The product information guide from the manufacturer for bladder onabotulinumtoxinA recommends prophylactic antibiotics be administered 1–3 days pre-treatment, on the treatment day, and 1–3 days post-treatment to reduce the risk of procedure-related UTI (BoTox R, Allergan, Inc., Irvine, CA). Our own retrospective

study demonstrated no additional benefit from a multi-day course of antibiotic compared to single dose (Martin et al., 2022).

The current era of increasing healthcare-related costs, adverse events, and growing MDR (multidrug resistant organisms) calls for use of antimicrobials only when medically necessary and with the narrowest spectrum of activity with the shortest duration possible (Lightner et al., 2020). There is no high-level evidence to support the use of multiple doses of antimicrobials in the absence of preoperative symptomatic infection (Lightner et al., 2020). To date, no prospective trials have been conducted to evaluate the impact of duration of antibiotic prophylaxis on incidence of UTI after bladder onabotulinumtoxinA injection. The paucity of data has led to a lack of definitive guidance on best practice on an international level (Hermieu et al., 2014; Lightner et al., 2019). The goal of this study is to determine if duration of antibiotic prophylaxis is associated with the incidence of post-procedure UTI after office bladder onabotulinumtoxinA injection. Subjects will be randomized to receive one dose of pre-procedure antibiotic or one dose of pre-procedure antibiotic with continuation of the antibiotic for 3 days total. We hypothesize that a single dose of antibiotic prophylaxis is as effective as a multiple day course in the prevention of UTI with bladder onabotulinumtoxinA injection.

Study Design

Design & Population:

Men and women 18 years of age or older undergoing bladder onabotulinumtoxinA in the office will be randomized in a 1:1 ratio into one of two groups until the targeted sample size is met:

- The single dose group will receive one dose of oral antibiotic prior to bladder onabotulinumtoxinA injection.
- The multi-dose group will receive one dose of antibiotic prior to bladder onabotulinumtoxinA injection and additional antibiotics for a total of three days of antibiotic administration.

Random permuted block randomization with block sizes of 2, 4, 6, and 8 will be used to assign eligible patients to treatment groups, determined by a computer program.

Eligibility will be assessed based on the following inclusion/exclusion criteria:

Inclusion Criteria:

- Participants with planned in-office bladder onabotulinumtoxinA injection
- Men or Women Age ≥ 18
- Able to read, speak, and write in English
- No contraindication to injection of onabotulinumtoxinA - hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation
- Willingness and ability to initiate intermittent catheterization post-treatment if required
- No contraindication to oral antibiotics
- No active antibiotic therapy for any indication at the time of onabotulinumtoxinA injection

- Have not participated in this study before

Exclusion Criteria:

1. Any type of catheterization to empty the bladder
2. Unwillingness or inability to initiate intermittent catheterization post-treatment if required
3. Less than 3 months since last bladder onabotulinumtoxinA injection
4. Pregnant and/or breastfeeding
5. Active symptomatic UTI the day of the procedure - new or worsening frequency, urgency, dysuria, hematuria, suprapubic/flank pain, fevers or chills
6. History of recurrent UTI
7. Prior development of urinary retention or incomplete bladder emptying after bladder onabotulinumtoxinA injection requiring catheterization of any type

Sample Size:

Sample Size: 100

In its recommendations for development of new drugs for treatment of complicated UTI, the FDA suggests using a noninferiority margin of no more than 10%; however, this margin may be relaxed.

It is assumed that approximately 10% of patients will experience a UTI, based on our previous single institution study among a similar cohort of patients. Based on a one-sided 95% confidence interval (or equivalently 90% two-sided confidence interval) and no loss to follow-up, with 90% statistical power and 20 % inferiority margin the total sample size is 96 with 48 allocated to each group. **Want to add 20% to this number to account for drop out or loss to follow up.

Research Procedures

Protocol:

- After informed consent is obtained, urinalysis will be collected. Post-void residual will also be assessed by bladder scan if not already documented in the electronic medical record in the prior three months.
- Patients with positive urinalysis and symptomatic for UTI will be excluded from the study.
- Patients will be randomized in a 1:1 ratio to one of two groups.
    - Group 1 will receive one dose of antibiotic prior to bladder onabotulinumtoxinA injection.
    - Group 2 will receive one dose of antibiotic prior to bladder onabotulinumtoxinA injection. The same antibiotic will be continued for 3 days of total antibiotic administration with additional doses prescribed to the patient's pharmacy.
- Bladder onabotulinumtoxinA injection and dosing will be completed based on the surgeon's standard technique and template.
- Bladder onabotulinumtoxinA injection will be completed by staff or fellows in the Female Pelvic Medicine and Reconstructive Surgery division of the Genitourinary and Kidney Institute.
- Patients will be followed for 4 weeks after the procedure.

- At 4 weeks study investigators will contact the patient by phone to evaluate for any UTIs or adverse events not previously reported by the patient during the study period.
- Chart review will occur in 4 weeks to assess any unreported events.
- Other than this additional phone call, post-operative patient management will not deviate from the standard of care.
- Patients will be instructed to report symptomatic UTIs, urinary retention, or any other adverse events related to onabotulinumtoxinA or antibiotic to investigators.
- Patients that report symptoms suggestive of a UTI will result in obtaining a urine culture.
- Symptomatic, culture proven UTIs will be treated with appropriate antibiotics per the current AUA guidelines.
- Symptoms suggestive of urinary retention, such as increased urinary frequency, voiding small amounts of urine, or feelings of incomplete bladder emptying, will result in obtaining a post void residual (PVR) and urinalysis.
- Patients will undergo teaching to perform self, clean intermittent catheterization of the bladder per the discretion of the operating surgeon.
- Any adverse reactions to the prescribed antibiotic will result in discontinuation of the antibiotic and managed according to the severity of the reaction.

Antibiotic regimens:
Allergy, prior urine culture resistance or another contraindication to first line antibiotic will result in the patient being prescribed second line antibiotic and so forth.

First line:

Group 1: trimethoprim / sulfamethoxazole 800/160 mg once pre-procedure
Group 2: trimethoprim / sulfamethoxazole 800/160 mg once pre-procedure plus 800/160 mg every twelve hours for 6 total doses

Second line:

Group 1: cefalexin 500 mg once pre-procedure
Group 2: cefalexin 500 mg once pre-procedure plus 500 mg every twelve hours for 6 total doses

Third line:

Group 1: nitrofurantoin 100 mg once pre-procedure
Group 2: nitrofurantoin 100 mg once pre-procedure plus 100 mg every twelve hours for 6 total doses

Fourth line:

Group 1: ciprofloxacin 500 mg once pre-procedure
Group 2: ciprofloxacin 500 mg once pre-procedure plus 500 mg every twelve hours for 6 total doses

Aims:

Primary Aim:

- Establish noninferiority of the single dose antibiotic administration to the multi-dose antibiotic administration.

To assess this aim, the rate of postoperative urinary tract infection (UTI) within 4 weeks following bladder onabotulinumtoxinA injection will be compared between groups. Noninferiority will be declared if the incidence of UTI in the single dose group is not more than UTI incidence in the multiple dose group within statistical variability, by the prespecified noninferiority margin.

Secondary Aims:

- Characterize the rate of postoperative UTI in the 2-to 4-week period following bladder onabotulinumtoxinA injection in each group.
- Summarize rates of adverse events related to antibiotics in each group.
- Estimate the rate of symptomatic urinary retention requiring catheterization among refractory overactive bladder patients who experience a UTI.

Data Analysis

The analysis will be conducted using intention-to-treat (ITT) principles. Baseline characteristics of subjects in each group will be summarized using median (IQR) for continuous variables and frequency (percentage) for categorical variables. A 95% confidence interval for the difference between UTI rates (single dose minus multi-dose) will be calculated; noninferiority will be established if the upper limit of the 95% confidence interval exceeds the noninferiority margin.

An adjusted odds ratio will be estimated via logistic regression to determine and quantify the association between the treatment group and odds of experiencing urinary retention.

Incidence of adverse events will be summarized and compared using chi-square or Fisher's exact test, as appropriate.

All analyses will be performed using R statistical software by the Glickman Urological and Kidney Institute biostatistics team.

Data access and confidentiality:

- Data will be stored on the Cleveland Clinic Urology S drive. Lauren Gleich will have access.
- Patient study ID numbers will be assigned. A code linking study ID# to MRN will be kept separately and will be password protected. Lauren Gleich will have access.
- Informed consents and questionnaires will be stored in a locked cabinet in the Urology Department office in Q10 on CCF Main Campus. Lauren Gleich will have access. Transport to

this central locked cabinet from other CCF sites will be conducted by co-investigators in secure, locked bags/cases.

- Patient data and confidentiality will be protected by limited access and password protection as described above, as well as by destroying all PHI after manuscript publication. The PHI utilized in this study is limited to MRNs and dates and sites of service.
- All data shared from other sites will be de-identified before sharing with CC investigators. Data from CC GUKI site patients will not be shared with other sites until de-identified and summarized/analyzed in aggregate.

Adverse Events and Data Monitoring Committee (DMC)

The proposed study does not deviate from the current standard of practice and thus involves minimal risk to patients. We believe it does not warrant a data monitoring committee. Lauren Gleich, DO, and Emily Slopnick, MD, will be responsible for monitoring breaches in patient privacy and will report promptly to the IRB.

Consent

Recruitment will be undertaken in the Female Pelvic Medicine and Reconstructive Surgery section of the Glickman Urological and Kidney Institute at the Cleveland Clinic. Patients that fit the study criteria will be contacted by the co-investigator(s) either during an office visit when bladder onabotulinumtoxinA injection is scheduled or via MyChart message or mailed letter. Patients that express interest in the office or respond to MyChart message or mailed letter will be called on the phone by the co-investigator(s). Details of the study will be discussed, and questions answered at that time. The consent form will be signed in person by the patient at the time of the procedure, allowing adequate time between obtaining information about the study and signing the consent form. Consent forms will be stored in a secured location on Q10 in the Glickman Tower on Cleveland Clinic Main Campus. Consents obtained at other Cleveland Clinic sites will be transported to the Main Campus securely in a locked or password protected device.

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