Procedural Discomfort Related to Number of Intradetrusor Injections of OnabotulinumtoxinA for Idiopathic Overactive Bladder: A Randomized Control Trial of an Alternate Reconstitution Volume and Injection Template Protocol

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- Rachel High, MD- Department of Urogynecology

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-Departmental Funds

VERSION NUMBER/DATE:

Revision #	Version Date	Summary of Changes	Consent Change (Yes/No)
1	3/24/22	Initial submission	
2	6/7/22	All comments on initial submission were addressed – clarification was provided to study design with regards to recruitment and standard of care. We expanded upon protection of PHI and waver of HIPPA authorization. I elaborated on safety measures for the storage and usage of PHI that is collected from the EMR as part of this study. The Botox FDA medication information was provided	No
3	10/25/22	Adding Rachel High, MD as a Co-investigator and Removing Laura Oscar Thompson, MD-Resident, Department of Urology	No

4	09/14/2023	Removing Kathryn Williams, MD, Nadia Megahed, MD and Nickie Griffin	

Study Summary – N/A

Purpose of the Study/Objectives

Specific Aims/Purpose: The goal of this single-blinded, randomized control trial is to evaluate and optimize the technique for performing intradetrusor injections of BTX-A for the treatment of idiopathic overactive bladder. We will propose two different reconstitution and injection schema and study patient-centered outcomes related to procedural discomfort and symptom relief.

-*Primary Aim*: The primary aim of this study is to evaluate perceived discomfort using the Numeric Pain Scale (NPS) during office injection of intradetrusor BTX-A via two different injection techniques and reconstitution volumes.

-*Secondary Aims*: The secondary aims of this study are to evaluate treatment effectiveness and patient satisfaction of treatment with BTX-A using validated questionnaires. We will also compare procedure time and post-procedure complication rates between the two study groups.

Background

Urinary urgency, frequency, and urgency incontinence without urinary tract infection are components of a syndrome called overactive bladder (OAB).[1] OAB affects up to 27% of women in the United States and has been shown to negatively impact quality of life and increase rates of depression and sleep disturbances.[1-4] An algorithmic treatment approach to OAB has been recommended by the American Urological Association (AUA) and includes initiating therapy with conservative measures and behavioral modifications as first line, medication management as second line, and progression to referral for third line treatment including OnabotulinumtoxinA (BTX-A) injections, peripheral tibial nerve stimulation (PTNS), or sacral neuromodulation (SNM).[5,6] OAB is often refractory to conservative and medication management, with some studies demonstrating good response to medication in 56% and only 50% adherence to oral therapy.[7,8] Given unsatisfactory treatment response, side effect profile, and the cost of oral medications, more women are moving towards third line options for the treatment of refractory OAB. Injection of intradetrusor BTX-A is a highly efficacious therapy with a reliable safety profile and demonstrable improvements in subjective and objective measures for OAB symptom control.[4,9,10,11] This procedure is quick and requires limited equipment, making it ideal for the outpatient office setting. Despite BTX-A being a common practice, limited research has been done to optimize injection technique. The industry recommended dose of BTX-A for idiopathic overactive bladder is 100 units[12] and is most often reconstituted in 10 mL delivered in 20 injections (0.5 mL). This reconstitution volume and injection schema were developed arbitrarily and there are wide variations in injection techniques across practitioners. Given the paucity of data for procedural optimization, this study aims to analyze the way intradetrusor BTX-A injections are performed with a focus on the patient-centered outcomes of procedural discomfort and patient satisfaction.

Study Design

Hypothesis: We hypothesize that women undergoing intra-detrusor injection of 100 units of OnabotulinumtoxinA will have less procedural discomfort with a protocol utilizing a lower reconstitution volume and injection number, while still maintaining efficacy of the procedure.

Design: This will be a single-blinded, parallel randomized control trial (RCT) utilizing two study arms. This trial will be designed and reported as outlined in the CONSORT guidelines.[13]

Recruitment: Female patients scheduled to undergo injection of 100 units of intradetrusor BTX-A for the treatment of idiopathic overactive bladder will be identified through the electronic medical record (EMR). This is the standard of care/standard dosing for the treatment of OAB and we will recruit and sample from patients who are already scheduled for this therapy prior to study enrollment. Idiopathic OAB will be defined as "urinary urgency, with or without urgency urinary incontinence, usually accompanied by urinary frequency and nocturia, in the absence of urinary tract infection or other obvious pathology" and without evidence of neurogenic bladder.[1] These patients will be approached on the day of the procedure and consented in person if they are interested in participating.

Study Groups**:** The patients will be randomized to one of two groups:

- 100 units BTX-A reconstituted in 5 mL normal saline, injected into the bladder in 5 separate injections of 1 mL. One injection will be at the trigone
- 100 units BTX-A reconstituted in 10 mL normal saline, injected into the bladder in 10 separate injections of 1 mL. One injection will be at the trigone

Each of these methods of BTX-A injection into the bladder are considered to be standard of care and are performed routinely in our daily practice.

Randomization**:**

- Eligible and consenting subjects will be randomized with equal probability of assignment (1:1) to one of the two study arms (5 mL/5 injections vs 10 mL/10 injections). Randomization will occur on the day of the procedure immediately after consent.
- The randomization schedule will be generated using the NIH National Cancer Institute Clinical Trial Randomization Tool. Opaque folders with the study number, consent and envelope-sealed randomized group allocation will be created by the primary co-investigator and will be stored in a locked cabinet. The randomized allocation will be opened by the attending physician after the study consent has been completed and the BTX-A will then be prepared for injection.

Blinding: This will be a single-blind RCT. The patients will be blinded to their treatment allocation but for practical purposes, the attending physician will not be blinded given that they will be performing the injections.

Primary Outcomes:

1. The primary outcome of this study will be patient discomfort related to BTX-A injection.
2. This will be measured using a validated 11 point (0-10) pain scale – the Numeric Pain Scale (NPS). Patients will rate their discomfort via the NPS prior to and after injections. The measurement for comparison will be the difference in those values.

Secondary Outcomes:

1. Efficacy and patient satisfaction will be evaluated using the Overactive Bladder Symptom and Health-Related Quality of Life Short-Form (OAB-q SF) validated questionnaire.[15] The OAB-q SF is a condition-specific questionnaire developed to assess the symptom bother and health related quality of life (HRQL) impact of OAB. The form asks patients to detail their level of bother related to their bladder symptoms and how those symptoms have affected their lives in the last four weeks. There are 19 questions in total and answers are recorded by checking a box from 1-6. Raw scores are then transferred to a 0-100 scale using formulas provided in the validation literature.[15]

2. Procedure time will be recorded from the start of cystoscope insertion to cystoscope removal and procedure end.
3. Symptomatic urinary tract infection (UTI) within the first 30 days after the procedure will be recorded. Symptomatic UTI will be defined as positive nitrites or leukocyte esterase on urine dip or positive urine culture in addition to the presence of dysuria, hematuria, or urinary frequency/urgency in the 30 days after the procedure
4. Rate of bothersome incomplete bladder emptying requiring catheterization within the first 30 days of the procedure
5. Incidence of bleeding requiring admission or hospital/office evaluation related to the injection procedure

Demographic data: collected from the EMR for secondary analyses

1. Age
2. Race
3. Body mass index (BMI)
4. OAB diagnosis at the time of procedure – OAB with vs OAB without urinary incontinence
5. Number of total BTX-A procedures
6. Past medical history
7. Past surgical history
8. Chronic narcotic use
9. 3 or more symptomatic UTI in the last year
10. Anticoagulation use

Sample Size Calculation and Statistical Methods:

- The sample size was calculated by powering to the primary outcome of procedural discomfort as rated on the NPS. Cohen effect sizes were used with a power of 80%. The calculation accounted for a potential subject dropout rate of 20%. Three categorical variables (two degrees of freedom) will be utilized – Low discomfort vs. moderate discomfort vs. high discomfort – with a Chi-squared statistical analysis.
- Utilizing the above methods and an effect size of 30%, our target sample size will be 135 patients in total split between the two study groups.
- Variables will be defined as following on the NPS:
    - Low discomfort – 0-2
    - Moderate discomfort – 3-6
    - High discomfort – 7-10

Standard Practices and Considerations based on FDA recommendations for BTX-A:

1. Antiplatelet medications will be held for 72 hours prior to the procedure and can be restarted on the day after injection
2. Antibiotic prophylaxis will be prescribed for the day before, day of, and day after the procedure

Encounter 1

Scheduled visit for 100 units intradetrusor BTX-A

10 mL/10 injections
vs.
5 mL/5 injections

- Consent obtained and patient completes OAB-qSF
- Randomization → Reconstitution of BTX-A in 10 mL vs 5 mL (patient blinded) → Patient rates discomfort from 0-10 on NPS → BTX-A injected → patient rates discomfort from 0-10 on NPS

Data Collected from EMR:

- Demographic data → Age, Race, BMI, PMH, PSH, narcotic use, recurrent UTI, anticoagulation use
- Procedural data → UTI since procedure, Urinary retention requiring catheterization

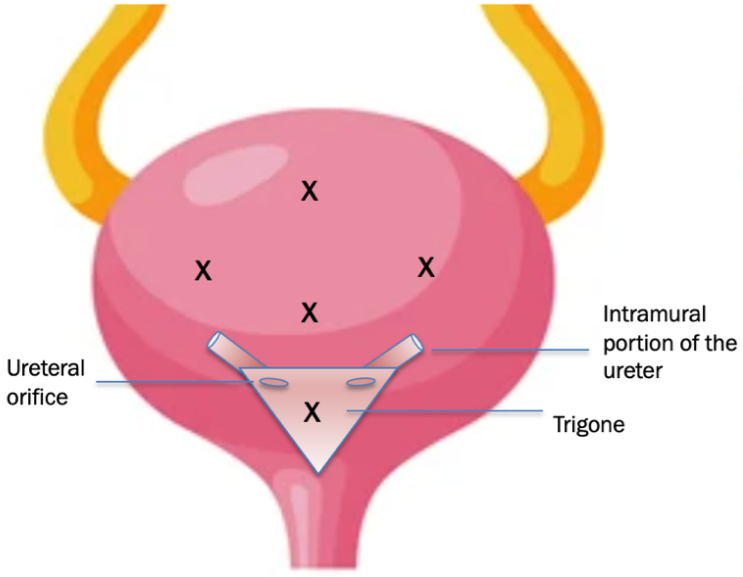
Encounter 2

Telephone call at 30 days post procedure

- OABq-SF completed again
- Overall satisfaction since procedure assessed via standardized telephone script

Study Intervention

- The patients will be randomized into one of two treatment groups. In each of these groups, a different volume of normal saline will be used to reconstitute (dissolve) the BTX-A. The same injection volume (1 mL) will be utilized between groups, leading to a different number of total injections between groups
- Group A: 100 units BTX-A reconstituted in 5 mL normal saline, injected into the bladder in 5 separate injections of 1 mL. One injection will be at the trigone
- Group B: 100 units BTX-A reconstituted in 10 mL normal saline, injected into the bladder in 10 separate injections of 1 mL. One injection will be at the trigone



- Anatomic definitions:
    - Ureteral orifice: opening of ureter into the bladder
    - Trigone: triagonal area of bladder muscle where ureteral orifices insert
    - Intramural ureter: portion of the ureter that runs within the bladder muscle
- The injection schema is diagramed above and will be performed according to the OnabotulinumtoxinA package insert for intradetrusor injections – 4 or 9 injections, respectively, will go into the posterior and lateral wall of the bladder and 1 injection will be placed into the trigone.
- As you can see from this schematic, all injections will be far from the ureteral orifices and away from the intramural portions of the ureter

Drugs, Biologics, Devices

a. Onabotuliumtoxin A (BTX-A) injections into the bladder will be evaluated in this research.
b. BTX-A is a commonly used therapeutic entity for the treatment of OAB and is FDA approved for this indication (12).
c. We will only be studying patients who are already scheduled to undergo BTX-A injections for the diagnosis of idiopathic OAB in the standard recommended dosage of 100 units.
d. This therapy is typically well tolerated with high patient satisfaction ratings for the treatment of OAB. The risks related to this therapy are described in the following sections.

Collaborative/Multi-site Research

This will be a single-site study within the Houston Methodist System in the departments of Urology and Urogynecology.

Data Privacy/ Confidentiality

- Protected Health Information (PHI) will be collected for this study through the electronic medical record
- Houston Methodist policies for PHI will be followed, including all requirements for all physical and electronic data security. Encrypted devices will be used and all information will be stored on HM password protected servers.
- All research team members will be CITI trained and registered through the HMRI. Only authorized study members will have access to physical (consents, OABs-QF forms) and electronic study data/PHI.
- Data will be primarily stored within the RedCap data management system through HM. Data will only be input on password protected computers through the Houston Methodist system and no data will be stored on desktops or in shared drives.
- Data will not be transmitted via email or other non-encripted forms of communication.
- Physical forms (consents, OABq-SF) will not be transported to personal residence and will be stored confidentially as listed above only in a Houston Methodist Building.
- We will collect only the minimum amount of PHI necessary and this will not be disclosed beyond Houston Methodist.
- PHI stored within RedCap will be de-identified. Patient's will be assigned a study number that will be included with their consent form. These files will be kept within a locked file cabinet within a locked office in Houston Methodist Smith Tower, only the PI and primary members of the research team will have access to these files. No photos or videos will be collected. The subjects will be de-identified immediately after recruitment.
- Per HMRI policy, the consents and physical/electronic study data that is collected will be kept for a minimum of 6 years. Physical files will be kept in a locked cabinet within the study coordinators locked office at Houston Methodist. The data collection timeframe is 30 days and there are no plans for long term outcome data. Therefore the data collected on physical forms will be confidentially shredded via the HM policy for disposal of PIH and discarded in PIH protected bins. The data stored through RedCap will be deleted.

- Accountable, complete, original, accurate, and legible records for the life of the study and required maintenance will be assured through the minimalization of research team members participating in recruitment and data collection. All team members will be permanent, contracted Houston Methodist employees that are research certified. Legible recording will be assured through the use of black/blue permanent ink on written forms in non-cursive text.

Identifier (or parts of)	Recorded	Disclosed	Comment
All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and elements of dates (including year) indicative of such age	Yes	No	Age will be recorded but not birthdate
Medical record numbers	Yes	No	
Names	Yes	No	The collection of names will occur on the consent forms only and will not be extracted from the EMR. The patients will be de-identified with a study ID number after consent and this ID number will be used for all data recording after consent.

Data and Specimen Banking: As listed above

Study Population

Inclusion Criteria	Exclusion Criteria
Women scheduled to undergo 100 units intradetrusor BTX-A injections in the office for the diagnosis of idiopathic OAB within the Houston Methodist departments of Urology and Urogynecology	Prior diagnosis of neurological conditions such as cerebral vascular accident within 6 months prior to treatment, Parkinson's Disease, Multiple Sclerosis, myelomeningocele, traumatic neurologic or spinal injury, or a former diagnosis of neurogenic bladder.
18 years of age or older	Symptomatic UTI at the time of procedure, defined as positive nitrites or high-volume leukocyte esterase on urine dip in addition to at least one of the following symptoms: dysuria, gross hematuria, suprapubic pain, frequency/urgency above baseline
Able to give informed consent in English or Spanish	Diagnosis of a bladder pain syndrome or other chronic pain syndromes including fibromyalgia, chronic pelvic pain, pelvic floor dysfunction, levator myalgia
Understand and are willing to undergo follow-up and complete all questionnaires as described in this protocol	Known bladder malignancy
	Previous history of bladder augmentation or reconstructive surgery not related to prolapse
	Pregnancy

Screening and Recruitment

Female patients scheduled to undergo injection of 100 units of intradetrusor BTX-A for the treatment of idiopathic overactive bladder will be identified through the electronic medical record (EMR). A trained, primary member of the research team will identify all patients scheduled for BTX-A as listed on the EPIC schedule for the Urogynecology and Urology providers listed above: Dr. Danielle Antosh, , Dr. Fiona Lindo, Dr. Ricardo Gonzalez, Dr. Julie Stewart, Dr. Rose Khavari, and Dr. Kathleen Kobashi. Without opening charts, a note can be placed on the schedule for female patients >18 yo to be evaluated for study qualification. The physician caring for the patient on the day of their scheduled BTX-A procedure will identify whether the patient meets inclusion/exclusion criteria for study enrollment based on the criteria listed in this protocol (inclusion and exclusion criteria are listed in the Study Population section above). By this process, the patients' information in the EMR will only be accessed by primary medical team members and will only be accessed by study team members after patients agree to enroll.

Idiopathic OAB will be defined as "urinary urgency, with or without urgency urinary incontinence, and is usually accompanied by urinary frequency and nocturia, in the absence of urinary tract infection or other obvious pathology" and without evidence of neurogenic bladder.[1] These patients will be approached on the day of the procedure and consented in person if they are interested in participating. Other than a detailed consent form, no recruitment materials or advertisements will be utilized as part of this study.

Withdrawal of Subjects

- Subjects would be withdrawn from the study if they are found to have symptomatic urinary tract infection on the day of the procedure – this would be defined by symptoms such as dysuria, frequency or urgency above baseline, or hematuria along with a urine dip that is positive for nitrites or leukocyte esterase.
- Subjects would be withdrawn if they are not able to tolerate the procedure itself and it is terminated prior to full injection of reconstituted BTX-A or if BTX-A was not able to be injected for other reasons (difficult anatomy, unable to pass scope or perform in the office)

Provisions to Protect the Privacy Interests of Subjects

- Privacy will be protected by ensuring that the patient interacts with and discloses information to only essential members of the research team to maximize confidentially
    - Caregivers that patients interact with during a typical BTX-A procedure include front desk staff for check in, the nurse/medical assistant helping with the procedure, a resident or fellow if present in clinic that day, and the attending staff.
    - Additional personnel patients would have to interact with to participate in the study would be a research member during the consent process (Dr. Miceli - Fellow, Hamida Rijab, Nickie Griffin - research coordinators) and a research member during the telephone follow-up (Dr. Miceli)
- The patient will be made to feel at ease with this research through a thorough explanation of the study protocol, the BTX-A procedure itself, and follow-up telephone encounter. All study members will be introduced by name and title and it will be well-explained that either injection protocol are standard ways that we perform BTX-A in the office every day.

Risks to Subjects

- The risks to the subjects participating in this study are only represent risks inherent to the nature of the BTX-A procedure itself – risks all subjects would be incurring regardless or participation or exemption given that we are only including patients who are scheduled for BTX-A prior to enrollment.
- Risks of undergoing intradetrusor BTX-A include: Post-procedural UTI (up to 10-30% in the literature, variations based on definition of UTI), bleeding requiring admission (<1%), and urinary retention (up to 5%).

- There is some risk of physical discomfort with injections, which we are hopeful to optimize with the results of this data. We ameliorate this risk through the instillation of local anesthetic into the bladder, which is standard protocol for all BTX-A injections and is recommended on the package insert/FDA approval for BTX-A.
- There should be no psychological, social, legal, or economic risks to the subjects.
- There is a small risk of loss of confidentiality that is inherent to the nature of any study participation. We will work to minimize this risk through the early de-identification of participants and through careful data storage by protected platforms as described above.
- BTX-A is considered to be pregnancy category C according to the package insert. This is based on animal studies, showing mostly reduction in fetal birth weight, as very limited studies regarding BTX-A in pregnancy have been performed in humans. A survey study of physicians who have performed BTX-A in pregnant women, knowingly or unknowingly, shows minimal risk.[14] For this research, the majority of our patients are post-menopausal. We do not perform BTX-A injections in women with known pregnancies. Pregnancy is an exclusion criteria for this study – all women of reproductive women will be screened for pregnancy.
- There are no risks to patients who do not participate as study subjects.

Potential Benefits

- Every patient in the study will benefit from intradetrusor BTX-A injections, a highly efficacious treatment, as prescribed by their physician for refractory overactive bladder symptoms.
- A potential benefit to the individual could be reduced procedural discomfort due to an optimized injection protocol.

Financial and Economic Issues

- There is no cost associated with participation in this study.
- Patients will not be compensated for their participation in this study.

Data safety plan

Standard methods to protect privacy will be maintained. The identities of study subjects will remain confidential. Only the PI, primary co-investigator, and study coordinator will have access to the names of the participants. All consent forms and randomization allocations will be stored in a locked cabinet in the study coordinators password-protected HMH office. Any electronic data will be securely stored in the primary co-investigator's (Miceli) office on a password protected office computer. This office is always locked and the computer is only opened through password protection. All data will be stored in Houston Methodist's electronic record keeping system RedCap for organization and analyses. All physical data/consents will be destroyed (shredded or erased from the computer hard drive) when use is no longer needed but not before a minimum of 3 years of data collection.

Informed Consent Documentation and Process

- Informed consent will be obtained from a member of the research team on the day of the BTX-A Procedure
- Patients undergoing intradetrusor BTX-A within the Urogynecology or Urology offices at HMH TMC, West, or Willowbrook will be identified the week prior and all subjects meeting criteria for inclusion will be approached about participation on the day of their scheduled procedure. If the subject fulfills inclusion criteria, the study team member (attending, fellow, research coordinator) will discuss the goal of the study and the process of BTX-A reconstitution and injection. If the patient is interested, the study requirements will be explained in detail - including requirements on the day of the procedure (short questionnaire, NPS rating prior to and after procedure) and 4 week follow up telephone call. The patient

will be given appropriate time to answer any questions she may have related to the study. Written information will be provided and the physician will allow adequate time for the subject to reflect flowing this discussion.

- If the patient agrees to participate, they will be consented in person by a member of the research team and will then be randomized. These documents will be safely stored as discussed above.
- A copy of the consent will be retained by the research coordinator in a locked file cabinet, and one copy will be given to the patient.

Waiver of Informed Consent and/or Authorization

A screening water will be requested preparatory for research (waver requested for feasibility, recruiting, access to charts, pre-screening). We are not requesting a waiver of informed consent.
The waiver of HIPPA Authorization will be required given the following:

- Requirement for the ability to screen patients for eligibility for the study to the absolute minimum extent required. It will not be feasible to conduct this research without the ability to screen for recruiting given that eligible patients will need to be identified prior to their scheduled procedure. The risk of this waiver only lies within the small possibility of loss of confidentiality that is inherent to any chart review for the purposes of academic study. These risks will be minimized by the measures described below.
- The data extracted from the EMR from the selected patient population will satisfy the objectives of this research which include evaluating discomfort related to BTX-A injections, peri-procedural factors and outcomes, and patient characteristics that may predict treatment satisfaction and response. The data that will be extracted from the EMR is listed in the Study Design portion of this document. We will extract the minimum information required to complete this study. We will not be able to satisfy the primary objectives of this research without the collection of demographic information, procedural details, and procedural outcomes that will be charted in the EMR.
- Security measures will be taken to assure that PHI will not be subject to improper use. All physical study data (consents, OABq-SF forms) will be kept in a locked cabinet inside a locked office that belongs to the primary researcher. Electronic information will be maintained in a password-protected database (RedCap). Only the researchers will have access to this data and it is password protected within the system.
- The procedural risk of this research is minimal. We will be studying a procedure via two techniques that are considered to be standard of care and are routinely performed in our office. We will not be introducing any study medications – the patients will receive 100 units BTX-A regardless of whether then choose to accept or decline enrollment into the study. The risk of a loss of confidentiality related to the collection of PHI is minimal due to the above mentioned safety precautions.

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