Optimization of OnabotulinumtoxinA (BTX-A) Injection for the Treatment of Neurogenic Lower Urinary Tract Dysfunction

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PROTOCOL TITLE:

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REVISION HISTORY

Not Applicable

Revision #	Version Date	Summary of Changes	Consent Change (Yes/No)
1	8/17/2023	Initial Protocol	
2	10/09/2023	There is only one follow up visit that will take place 4 to 6 weeks post Botox procedure; Dr. Julie Stewart has been added as a sub- I to the study	Yes
2.1	10/26/2023	Expanded indications to include all indications for injection of 200 or 300 units of Botox except painful bladder conditions such as interstitial cystitis (IC) or chronic pelvic pain (CPP)	Yes
2.2	11/30/20203	Adding a 6-12 months retrospective review to stay consistent with our specific aim	Yes

1. Study Summary

Urinary urgency, frequency, and urgency incontinence without urinary tract infection are components of a syndrome called overactive bladder (OAB). 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] For patients who are

inadequately managed with medications and conservative, third-line therapies are offered which include OnabotulinumtoxinA (BTX-A) or Botox injections.

BTX-A is a highly efficacious therapy with a reliable safety profile and demonstrable improvements in subjective and objective measures for OAB symptom control.[4-7] This procedure is quick and requires minimal equipment, making it ideal for the outpatient office setting. Despite BTX-A being a common practice, limited research has been done to optimize the injection technique for 200 or 300 units of BTX-A. This amount of BTX-A can be administered to patients who suffer from non-idiopathic OAB caused by conditions which include but are not limited to a neurological disorder, refractory idiopathic OAB[8], and radiation cystitis[9].

Neurological disorders such as Multiple Sclerosis (MS), Spinal Cord Injury (SCI), Parkinson's Disease (PD), Spina Bifida (SB), and stroke disrupt neural control of voiding and lead to the development of neurogenic lower urinary tract dysfunction (NLUTD), which develops when either the detrusor muscle fails to maintain effective contractions (voiding phase) or fails to relax appropriately with low pressures (storage phase), if the urethral sphincter (internal or external) fails to lower its tonicity and resistance, or if there is an asynchrony in events eventually leading to detrusor sphincter dyssynergia (DSD). Different patterns of NLUTD (including both storage and voiding) can arise depending on the level of injury or type of neurological disease. It can be characterized by urinary urgency, frequency and incontinence or urinary hesitancy and retention that leads to urinary tract infections (UTIs).

Management of NLUTD symptoms is complex. Treatment with BTX-A has been shown to decrease episodes of urinary incontinence and improve quality of life in this population. It has also been shown to ameliorate a multitude of devastating complications, such as upper tract deterioration, recurrent urinary tract infections, sepsis, and death.[10-11] According to the current manufacturer's recommendation, a standard 200-unit vial of Botox® should be diluted in 30cc of 0.9% saline and injected across 30 different sites in the detrusor muscle. Despite these guidelines, there are wide variations in administration techniques, raising the question of what the best depth and location for injection, optimal concentration, and volume of toxin per injection site is. The objective of this study is to determine the optimal injection schema for 200 or 300 units of intradetrusor BTX-A in the office setting.

We hypothesize that patients indicated for an injection of 200 or 300 units of BTX-A for all indications will be more willing to pursue additional sessions of BTX-A injections with a protocol utilizing less injection sites, while still maintaining effectiveness of the procedure.

2. Purpose of the Study / Objectives

Specific Aim 1: To evaluate patient satisfaction and perceived discomfort during office-based injection of intradetrusor BTX-A via two different administration protocols.
a. We will assess and compare validated questionnaires between two groups of patients receiving 20 versus 5 injections. We will assess and compare patient willingness to continue with treatment by the number of repeated sessions of BTX-A injections over 12 months of follow-up.

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Specific Aim 2: To evaluate treatment effectiveness between the two different administration protocols.
a. We will compare validated questionnaires between two groups of patients receiving 20 versus 5 injections.
b. We will compare procedure time between the two groups.

We will compare two common and specific adverse events (AEs) between the two groups including symptomatic UTIs, symptomatic gross hematuria, and new-onset incomplete bladder emptying necessitating de-novo bladder catheterization.

3. Background

Proper function of the lower urinary tract (LUT) is intricately regulated by the central nervous system. To achieve both storage and release of urine (voiding) the connections between the brain, spinal cord and peripheral innervations connected to the LUT must be intact[12]. During bladder filling, sympathetic nuclei at the T11-T12 spinal level mediate contraction of the urethral sphincter and relaxation of bladder wall through the hypogastric and pudendal nerves. Once it is deemed appropriate to void, tonic inhibition of the pontine micturition center (PMC) by cortical and subcortical centers is reversed.20 Parasympathetic nuclei at the S2-S4 spinal level extend their axons to pelvic ganglia via sacral roots and pelvic nerves to ganglia in the pelvic plexus and the bladder wall. Acetylcholine and noradrenaline released from postganglionic nerve terminals onto M3 muscarinic receptors induce bladder contraction, while simultaneous acetylcholine release from somatic axons relaxes urethral smooth muscles, all leading to effective bladder emptying.

Neurological disorders such as Multiple Sclerosis (MS), Spinal Cord Injury (SCI), Parkinson's Disease (PD), Spina Bifida (SB), and stroke disrupt neural control of voiding and lead to the development of neurogenic lower urinary tract dysfunction (LUTD), which develops when either the detrusor muscle fails to maintain effective contractions (voiding phase) or fails to relax appropriately with low pressures (storage phase), if the urethral sphincter (internal or external) fails to lower its tonicity and resistance, or if there is an asynchrony in events eventually leading to detrusor sphincter dyssynergia (DSD).

Different patterns of NLUTD (including both storage and voiding) can arise depending on the level of injury or type of neurological disease. It can be characterized by an overactive bladder (OAB) symptom complex which may include urinary urgency, frequency and incontinence or urinary hesitancy, and also retention that may lead to urinary tract infections (UTIs). Conditions such as radiation cystitis or BCG induced cystitis may also cause disruption of the neural control of voiding leading to lower urinary tract dysfunction and OAB[9].

Management of LUTD symptoms primarily due to storage dysfunction include various pharmacological agents (anticholinergics, antimuscarinics, beta-3- receptor agonists), intradetrusor injection of onabotulinumtoxinA (BTX-A) and tibial or sacral neuromodulation modalities. Despite the availability of different techniques to manage bladder function that have shown some improvement, it is important to continue to improve these treatment modalities to better serve individuals with LUTD due to storage dysfunction. The objective of this study is to determine the optimal injection schema for 200 or 300 units of intradetrusor BTX-A for all patients in the

office setting.

4. Study Design

This will be a single-blinded, parallel randomized control. Patients will be randomized into one of two groups:

-Schema 1: 200 or 300 units BTX-A reconstituted in 20 mL normal saline, injected into the bladder detrusor in 20 separate injections of 1 mL including the trigone.
-Schema 2: 200 or 300 units or more BTX-A reconstituted in 5 mL normal saline, injected into the bladder detrusor in 5 separate injections of 1 mL including the trigone
This trial will be designed and reported as outlined in the CONSORT guidelines.

Endpoints:
Primary Endpoints:
a. Change in patient willingness to repeat BTX-A injection procedure as assessed with an 11-point visual analog scale.
b. Change in discomfort in patients that undergo BTX-A injection, measured using the Numeric Pain Scale scores provided by patient prior to and following the treatment procedure.
c. Change in Patient Global Impression of Improvement score provided 6 weeks post-procedure.
Secondary endpoints:
a. Change in procedure times (from cystoscope insertion to removal).
b. Change in International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form.
c. Change in Neurogenic Bladder Symptom Score – Short Form
Safety endpoints:
a. Incidence of symptomatic UTI within the first 4- 6 weeks after the procedure.
b. Incidence of bleeding requiring admission or hospital/office evaluation related to the injection procedure.
c. Rate of bothersome incomplete bladder emptying requiring de novo catheterization within the first 4-6 weeks.

Demographic data: collected from the EMR for secondary analysis
- Age
- Gender/sex
- Race
- Body mass index (BMI)
- Diagnoses at the time of procedure – nature of neurogenic bladder
- Is the patient naive to BTX-A or not
- Number of total BTX-A procedures
- Past medical history
- Past surgical history

- Chronic narcotic use
- 3 or more symptomatic UTI in the last year
- Current Anticoagulation use
- Other GU relevant medications
- Mode of bladder emptying? Spontaneous voiding, CIC, Foley, SPT
- History of bladder augmentation?
- History of bladder outlet procedures
- Was anticoagulation stopped for the procedure?

Sample size and power calculation: Sample size was calculated by powering the primary outcome (11-point visual analog scale for willingness to repeat the procedure, Range: 0-10) between the two study arms. A continuous model was utilized. Cohen effect sizes were used with a power of 80% with statistical significance defined as an alpha of 0.05 for a target sample size of 74 patients. Accounting for a 5% drop out rate, our final target sample size will be 78 patients split between the two study groups (please see the randomization plan below).

Recruitment: Individuals with the diagnosis of OAB symptoms (frequency, urgency, UUI) who do not have a painful bladder condition and scheduled to undergo 200 or 300 units of intradetrusor BTX-A will be identified through the electronic medical record (EMR). The dosing amount will be determined by the physician who is indicating the patient for the BTX-A treatment based on clinical picture and is not influenced in any way by this study. We will recruit and sample from patients who are already scheduled for this therapy prior to study enrollment. Patients who meet inclusion criteria will be approached on the day of the procedure and consented in person if they are interested in participating.

5. Study Intervention

The study will include a clinic visit for the Botox procedure, a scheduled follow-up visit, and possibly a 15-minute phone call approximately 6 weeks after Botox injection.

During the clinic visit, the patient will rate the patient's willingness to repeat the procedure and pain level and fill out a short questionnaire called the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF) and Neurogenic Bladder Symptom Score-Short Form (NBSS-SF). At the follow-up visit, the patient will fill out the ICIQ-UI SF and NBSS-SF again to assess symptom improvement, Patient Global Impression (PGI) of Improvement score, and assess the patient's willingness to repeat the procedure. The questionnaire should take roughly 5 minutes to fill out. The component of the patient's participation that is being researched is the patient's willingness to repeat the procedure, response to questionnaires, and clinical response to the Botox. In addition, if the patient participates in the study, data from the medical record will be collected for this research. Types of data collected include demographic and baseline characteristics, procedural time, procedural response, discomfort with the procedure, and any procedural complications encountered. Besides 4-6 weeks follow-up, patients charts will retrospectively reviewed at the 6-12 months At 6 months to 1 year after their Botox injection, to see if additional therapies were pursued.

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Intervention	Procedure visit	Post-procedure visit (4-6 weeks after procedure visit)	12 months after procedure visit
Sign consent form	X		
ICIQ-UI SF Questionnaire	X	X	
NBSS-SF	X	X	
PGI score		X	
Numeric Pain Rating Scale	X		
Willingness to repeat procedure scale	X	X	
Randomization	X		
Chart review for whether patients continued Botox or underwent alternate therapies to Botox			x

6. 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[13].
c. We will only be studying patients who are already scheduled to undergo BTX-A injections for a dosage of 200-300 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.

7. Collaborative / Multi-site Research

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

8. 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-encrypted forms ofcommunication.
• Physical forms (consents and questionnaires) 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. Patients 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 4 to 6 weeks 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**
Names	Yes	No	
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	Yes	If required by the IRB and FDA to verify the data authenticity
Medical record numbers	Yes	No	
Phone numbers, fax numbers	Yes	No	

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Email address	Yes	No	

9. Data and Specimen Banking

As listed above.

10. Study Population

Inclusion

• Adult men and women (>18 years of age) with any diagnosis indicated for the injection of 200 or 300 units of BTX-A including radiation cystitis, or due to neurologic bladder secondary to neurological conditions such as MS, PD, CVA, myelomeningocele, SCI, or traumatic brain injury longer than 6 months prior to treatment.
• Participants must be able to provide informed consent, as well as understand and be willing to undergo follow-up procedures and completion of all questionnaires provided during the study.

Exclusion

• Symptomatic UTI at the time of procedure, defined as positive nitrites orhigh-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.
• Diagnosis of bladder pain syndrome or other chronic pain syndrome including fibromyalgia, chronic pelvic pain, pelvic floor dysfunction, levatormyalgia.
• Untreated bladder malignancy.
• Women who are currently pregnant or breast feeding.
• Contraindications to intradetrusor BTX-A injections.

11. Screening and Recruitment S R

All patients scheduled to undergo injection of 200 or 300 units of intradetrusor BTX-A for all indications other than bladder pain syndrome 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 Urology providers listed above: 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 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.

These patients will be approached on the day of the procedure and consented to 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.

12. Withdrawal of Subjects

Subjects would be withdrawn from the study if they are found to have symptomatic

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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)

13. 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 confidentiality. 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. Betsy Salazar, Hamida Rijab, Julu Benoy, research coordinators) and a research member during the telephone follow-up. 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 encounters. 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.

14. 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

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pregnancies. Pregnancy is an exclusion criterion 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.

15. Potential Benefits

1. Every patient in the study will benefit from intradetrusor BTX-A injections, ahighly effective treatment, as prescribed by their physician for theircondition.
2. A potential benefit to the individual could be reduced procedural discomfort due to an optimized injection protocol.

16. Financial and Economic Issues

-There is no cost to the patients associated with participation in this study.
-Patients will be compensated $100 for their participation in this study. They will receive $100 at the initial visit and another $50 after completion of the second round of surveys at their scheduled follow-up visit. If they miss the opportunity to fill out the survey at the follow-up visit, they will be contacted by phone.

17. 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 coordinator's 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.

18. 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 Urology offices at HMH TMC, West, Willowbrook, or Sugarland, 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 weeks 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

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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.

19. Waiver of Informed Consent and /or Authorization

We will be requesting HIPAA waiver for performing preparatory research activities such as reviewing patient's surgical and medical history and for the purpose of this study. The researchers have taken steps to minimize this risk. The research team will take proper precautions to ensure that any information regarding a patient's personal identity obtained in connection with this research will remain confidential. Patients will be assigned a unique study identification number. This number will be used to identify patients's study participation; their personally identifiable data will be stored separately. All study data will be stored in the secure and access-restricted REDCap research database maintained at Houston Methodist. Only the investigators and authorized study team members have access to the REDCap database. There are no plans to share any study data collected for this research with anyone outside of the study team; however, no one outside of the authorized study team would be able to link patients's study code with their personally identifiable information. Any inclusion of patient identifiers within the database will not be shared externally outside of the study team.

20. References

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