Document Title: Minimizing Pain During Office Intradetrussor Botox Injection: A Prospective Randomized Controlled Trial Comparing Two Protocols

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STUDY DESCRIPTION – SECTION B

TITLE OF PROTOCOL	Minimizing pain during office intradetrussor Botox injection: A prospective randomized controlled trial comparing two protocols		
Principal Investigator	Eman Elkadry		
E-Mail Address	eelkadry@mah.harvard.edu		
P.I.'s Telephone	617-354-5452	P.I.'s Pager: n/a	Fax: 617-354-0495
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B1. PURPOSE OF PROTOCOL

Hypothesis

1. Pre-treatment with a buffered lidocaine solution provides superior pain control compared to a standard lidocaine procedure before intradetrussor botox injection

Primary Objectives:

1. Procedural pain associated with intradetrussor botox injections on a standardized Visual Analogue Scale

Secondary Objectives:

1. Patient satisfaction measured on a five point Likert scale
2. Willingness to undergo procedure again measured on a five point Likert scale
3. Adverse events
4. Demographic and clinical factors that predict high pain scores during the procedure

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Lidocaine is a commonly used amide-type local anesthetic. Lidocaine exists as both a quaternary water soluble structure, and a tertiary lipid-soluble structure. Only the tertiary lipid-soluble structure can cross the lipid bilayer of a cell membrane and thereby enter a neurons axoplasm and induce the desired effect. The ionization constant of lidocaine is 7.7 which means that at a pH of 7.7, 50% of lidocaine is available in the tertiary lipid-soluble structure. At a physiologic pH between 7.35 and 7.45 only around 44% of lidocaine is in the tertiary lipid-soluble structure. However, for lidocaine to be stable in solution, it is typically formulated as a hydrochloride salt and the pH of most commercially available lidocaine solutions are at a pH of 6.09.[1] In an acidic solution the majority of lidocaine is available in the quaternary water-soluble structure and at this pH only 2.5% of lidocaine is in the tertiary lipid-soluble structure. A Cochrane review found that increasing the pH of lidocaine prior to injection decreased pain and increased patient satisfaction perhaps because of the aforementioned pharmacokinetic principles[2]

Lidocaine is typically used as anesthetic for intradetrussor injections of onabotulinum toxin A for the treatment of refractory overactive bladder. In 2003, a technique for intradetrussor injections of onabotulinum toxin A was first described using only local anesthesia.[3] At that time, the procedure involved intrauerthral lidocaine. The procedure has evolved since that time and currently many physicians utilize protocols with both

utraurethral and intravesical lidocaine. At baseline intradetrusor onabotulinum toxin A injections are generally well tolerated and with reported mean VAS scores around 3.[4–6]

For patients with refractory overactive bladder, the standard of care is intradetrussor onabotulinum toxin A injections. In our clinical practice, the standard of care is to empty the bladder then retrograde fill the bladder with a 1:1 mixture of 1% lidocaine normal saline. This solution remains in the bladder for approximately 15 minutes prior to injection. Given that urine is typically acidic and commercially available lidocaine solutions are similarly acidic, it is likely that only a fraction of intravesical lidocaine is in the active tertiary lipid-soluble form. The goal of this study is to determine if we can improve the procedural pain of intradetrusor onabotulinum toxin A injections using a buffered solution compared to our standard solution.

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B3. DESCRIPTION OF RESEARCH PROTOCOL

A.Study Design – Overview, Methods, Procedures

Brief overview: This will be a prospective double-blinded randomized controlled trial comparing two pre-treatment protocols for patients undergoing intradetrussor botox injections to determine if a buffered lidocaine solution offers superior pain control.

Study Protocol: After approval by the IRB, providers will approach possible participants who are having intradetrussor botox injection for overactive bladder which is the standard of care for patients with refractory overactive bladder. If the patient meets eligibility criteria, consent forms will be signed and the patient will be randomized 1:1 to receive either our standard pretreatment regimen with 50 mL 1% lidocaine + 50ml of 0.9% normal saline or our buffered bicarbonate protocol with 50 mL 1% lidocaine + 45ml of 0.9% normal saline + 5 mL 8.4% sodium bicarbonate. The primary end point of this trial is to assess the pain scores measured on a Visual Analogue Scale (VAS) immediately following the procedure. Secondary end points include patient satisfaction, willingness to undergo repeat treatment and adverse events.

All subjects will be randomized 1:1 at the first intervention visit to one of the two protocols . At the completion of the procedure, patients will be asked to complete a brief questionnaire about their experience. Patients will follow up in clinic for a post-void residual check two weeks after the procedure as is standard for

our clinical practice.

Methods:
Standard protocol: 50 mL 1% lidocaine + 50ml of 0.9% normal saline
Bicarbonate protocol: 50 mL 1% lidocaine + 45ml of 0.9% normal saline + 5 mL 8.4% sodium bicarbonate

Inclusion criteria:
Female patient
Primary diagnosis of overactive bladder

Exclusion criteria:
Neurogenic bladder
Urinary retention

Outcome Measures:
The **primary** outcomes measures will include:

- Pain: The Visual Analogue Scale (VAS) consists of a straight line with the endpoints defining extreme limits such as 'no pain at all' and 'pain as bad as it could be' which was first described in 1923.[7] The patient is asked to mark his pain level on the line between the two endpoints. The distance between 'no pain at all' and the mark then defines the subject's pain. Studies vary on the definition of a clinically meaningful change in pain, but suggest that a difference of anywhere from 12% to 38% may be clinically significan[8–11]

The **secondary** outcomes measures will include

- Satisfaction
- Willingness to undergo repeat procedure
- Adverse events
    - Adverse events will be collected from the medical record and include postoperative urinary tract infections, hematuria, readmission, urinary retention, number of patient phone calls
- Pelvic Floor Distress Inventory (PFDI-20) Scores
    - The short-form version of the Pelvic Floor Distress Inventory has a total of 20 questions and 3 scales (Urinary Distress Inventory, Pelvic Organ Prolapse Distress Inventory, and Colorectal-Anal Distress Inventory). Total PFDI score measured on a 0-300 scale with higher scores equal to greater pelvic floor distress. As with the Total PFDI Score, higher subscale scores equal greater pelvic floor distress, on a 0-100 scale[14]

Sample size:
We are planning as study of a continuous response variable from independent controls and experimental subjects with one control per experimental subject. In a prior study looking at pain associated with intradetrusor botox, the response within each group had a standard deviation of 2.08. If the true difference between the experimental and control groups is 1.4 which would represent a 38% difference in pain scores, then we would need to enroll 36 controls and 36 experimental subjects to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 0.8. The type 1 error probability associated with this test of this null hypothesis is 0.05.

Study period:
November 2019 through November 2021

Data collection:
Baseline characteristics collected from the medical records and collected as part of routine clinical care for every patient:

- Age (years),
- Gravid (numeric value),
- Para (numeric value),
- BMI (height and weight)
- Race/ethnicity
- Medical history (fibromyalgia, use of chronic pain medications, chronic back pain)
- Surgical history (hysterectomy, prolapse surgery, urinary incontinence surgery)
- Pre-treatment Kegel strength
- Pre-treatment myofascial pain
- Pre-treatment POPQ
- Pre-treatment PFDI-20

B. Statistical Considerations

This is a prospective double-blinded randomized controlled trial comparing two pre-treatment protocols for patients undergoing intradetrussor botox injections to determine if a buffered lidocaine solution offers superior pain control. We are planning as study of a continuous response variable from independent controls and experimental subjects with one control per experimental subject. In a prior study the response within each group had a standard deviation of 2.08. If the true difference between the experimental and control groups is 1.4 which would represent a 38% difference in pain scores, then we would need to enroll 36 controls and 36 experimental subjects to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 0.8. The type 1 error probability associated with this test of this null hypothesis is 0.05.

All de-identified data will be shared with BIDMC who will help with the statistical analysis. We will analyze data with SAS 9.3 (SAS Institute, Cary, North Carolina). Descriptive statistics will be presented as medians with interquartile range (IQR), median with standard deviation or proportions, depending on data type and distribution. We estimate the risk ratio (RR) and 95% confidence interval (CI) for pre-specified risk factors. All tests will be two sided and P values <0.05 will considered statistically significant.

C. Subject Selection

Inclusion criteria:

1. Female patient
2. Age greater than 18
3. Willing and able to undergo in-office intradetrussor botox injectios
4. Primary diagnosis of overactive bladder

Exclusion criteria:

1. Urinary retention requiring intermittent self catherization
2. Neurogenic bladder
3. Requiring pretreatment with anxiolytic or opiate prior to in-office procedure

B4. POSSIBLE BENEFITS

Patients may benefit from this study. While the pain associated with intradetrussor botox injections is minimal, this protocol has the potential to decrease the pain associated with the procedure. Bicarbonate is already regularly used to buffer lidocaine for injections to improve patient pain and satisfaction. Patients may feel satisfaction knowing they are participating in a research study and can potentially help improve future care of patients.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

Possible risks include the potential loss of confidentiality. This risk will be minimized by the following methods. All patient data will be made anonymous and linked with a subject ID which will be stored separately from the data in locked cabinets and on a password protected drive behind the MAH firewall. Once the surveys are complete, the data will be completely deidentified and the master code linking the direct identifier to the dataset will be destroyed. Other potential risks include bladder pain, hematuria, urinary retention, urinary tract infections. These risks are all standard risks associated with cystoscopy and intradetrussor botox and should not be different between protocols. To date there have been no adverse events reported with the use of a buffered lidocaine solution for bladder instillations. In theory, buffering of the solution with sodium bicarbonate may cause precipitation of the dissolved lidocaine and thereby decrease efficacy, but in clinical practice this has not been demonstrated and studies looking at buffered lidocaine for injection found improved pain scores suggesting increased efficacy.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

The proposed study design includes an opt-in recruitment strategy. Patients meeting eligibility criteria will be identified by a co-investigator in the study during a routine clinical visit. Only patients of co-investigators will be recruited for the study and therefore no review of PHI or medical records will be needed.

Consent

Written informed consent will be obtained from study participants prior to the collection of any data or beginning treatment. Informed consent will occur in a private session before the cystoscopy procedure and patients will be consented by one of the members of the research team. Prospective study participants will be clearly informed that it is unclear whether one protocol has a benefit over another. Study staff will obtain consent and be able to answer any and all questions they may have. Study participants will be given the study coordinator's contact information should they have any further questions at a later time.

Subject Protection

It is unlikely that any subjects in the study will be vulnerable to coercion or undue influence. Study subjects will be clearly informed that participation in the study does not impact their care going forward.

B7. STUDY LOCATION

Boston Urogynecology Associates
725 Concord Avenue
Cambridge MA 02138

Data analysis to be completed at
Beth Israel Deaconess Medical Center
330 Brookline Ave, Boston, MA 02215