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A Randomized Controlled Trial to Evaluate Botulinum Toxin A alone versus Botulinum Toxin A with hydrodistention for the Treatment of Refractory Overactive Bladder

(HydrA Study)

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Research Protocol

A Randomized Controlled Trial to Evaluate Botulinum Toxin A alone versus Botulinum Toxin A with hydrodistention for the Treatment of Refractory Overactive Bladder

(HydrA Study)

Joseph Malek, MD[1]

Isuzu Meyer, MD[1]

Tracey Wilson, MD[2]

L. Keith Lloyd, MD[2]

Alicia Ballard, MD[1]

David Ellington, MD[1]

Holly E. Richter, PhD, MD[1]

1. Division of Urogynecology and Pelvic Reconstructive Surgery, Department of Obstetrics and Gynecology, University of Alabama Birmingham, Birmingham, AL
2. Department of Urology, University of Alabama Birmingham, Birmingham, AL

Corresponding Author:

Joseph Malek, MD

1700 6th Avenue South, Suite 10382

Birmingham, AL 35233

Phone: (205) 996-5466

Fax: (205) 975-8893

Email: jmalek@uabmc.edu

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JM Malek: Protocol/project development, data collection, manuscript writing/editing

Abstract

The specific aim of this randomized, single-blinded controlled trial is to determine if hydrodistention at the time of intradetrusor injection of botulinum toxin A has additional benefit in patients with refractory overactive bladder (OAB) and urgency symptoms compared to intradetrusor injection of botulinum toxin A alone.

Consented patients will be randomized to hydrodistention at a pressure of 80 cm H_2O for 5 minutes, prior to the intradetrusor injection of 100 units of botulinum toxin A (hydrodistention group) or intradetrusor injection of 100 units of botulinum toxin A alone (botulinum toxin A alone group). The primary aim will be subjective improvement measured as change from baseline at 12 weeks using the OAB-q bother subscale. Secondary aims will include number of urgency urinary incontinence (UUI) episodes, total number of voids, percentage of patients requiring clean intermittent self-catheterization, elevated post-void residual, health related quality of life, patient global impression of improvement, patient satisfaction, rate of urinary tract infection post-operatively, and 24 week subjective improvement using the OAB-q.

Demographics and baseline data will be analyzed by Student's t-test and chi-squared test or Fisher's Exact test as appropriate.

Specific aims

Primary aim: To determine if hydrodistention at the time of intradetrusor injection of botulinum toxin A has additional symptomatic benefit in patients with overactive bladder (OAB) and urgency symptoms compared to botulinum toxin A injection alone in a single blind, randomized controlled trial using subjective improvement as measured by the OAB-q bother subscale at 12 weeks.

Secondary aims: Secondary aims will include number of urgency urinary incontinence (UUI) episodes, total number of voids, proportion of subjects requiring clean intermittent self-catheterization, elevated post-void residual, health related quality of life, patient global impression of improvement, patient satisfaction, rate of urinary tract infection post-operatively, and 24 week subjective improvement using the OAB-q.

Null hypothesis: In subjects with refractory overactive bladder, hydrodistention at the time of intradetrusor injection of botulinum toxin A will result in no difference in OAB-q score compared to botulinum toxin A injection without hydrodistention.

Background

Overactive bladder (OAB) is a common condition that affects approximately 17% of women in the United States [1]. Overactive bladder is defined by the International Continence Society as "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology" [2]. Approximately one third of these women will have urgency urinary incontinence (UUI) with the prevalence increasing with age [1]. The economic burden of this disease is significant with the estimated annual cost of OAB in the United States being $25 billion [3].

Anticholinergic medications have long been the mainstay of treatment for OAB but have significant side effects including dry mouth and constipation [4] which has led to poor patient compliance and high discontinuation rates in clinical practice [5]. Botulinum toxin A injected into the detrusor muscle during cystoscopy was Food and Drug Administration approved for the treatment of refractory OAB symptoms in 2013. This approval was based on two large randomized controlled trials that included 1,105 patients randomly assigned to placebo or 100

units of intradetrusor botulinum toxin A. A primary endpoint of 12 weeks showed a significant decrease in daily episodes of UUI episodes in the botulinum toxin A group compared to placebo [6,7]. Another double-blind, double-placebo-controlled, randomized trial compared anticholinergic use versus botulinum toxin A which showed a decrease in the number of episodes of UUI in the active group without any significant difference between treatments [8]. In this trial, both groups showed no significant differences in improvement in quality of life, but only 13% of patients in the anticholinergic group and 27% in the botulinum toxin A group reported complete resolution of UUI episodes [8]. Thus, we believe there is much room for improvement in the treatment of OAB symptoms.

Hydrodistention has been a treatment modality for interstitial cystitis (IC) since the early 1900s [9, 10]. It is thought that any efficacy for the treatment of IC is probably related to damage to mucosal afferent nerve endings in the bladder [11]. There are very limited studies on the use of hydrodistention for urgency and OAB symptoms. Dunn et al in a small study found that 14 of 20 patients with urgency and UUI reported resolution of their symptoms after prolonged bladder distention [12]. They also found that the bladder capacity in all patients increased after hydrodistention. In a retrospective review of patients undergoing hydrodistention, Cole et al found that in patients who had undergone the procedure for frequency and urgency symptoms with no pain component, 50% at 1 month, 19% at 3 months, and 7% at 6 months reported improvement in symptoms [13]. Other studies have shown no benefit from hydrodistention in the treatment of urgency and OAB symptoms [14, 15].

There are currently no studies investigating hydrodistention at the time of intradetrusor botulinum toxin A in patients with refractory OAB symptoms. We believe that patients may have additive benefit from a hydrodistention performed with botulinum toxin A injection as the

increased bladder capacity gained by the distention will be sustained for a longer period of time in the setting of botulinum toxin A.

Significance

No studies have been performed examining hydrodistention in the setting of intradetrusor botulinum toxin A for the treatment of refractory OAB symptoms.

Study Design

Inclusion criteria

1. Women with refractory overactive bladder symptoms, failing a credible behavioral therapy intervention and medical therapy or not tolerating medical therapy. Patients who are on medical therapy will stop the medical therapy for at least 2 weeks prior to botulinum toxin A treatment in the study
2. Female ≥ 18 years old
3. Desires further treatment for OAB symptoms.
4. Express understanding and ability to perform clean intermittent self-catheterization (CISC) if required.
5. Ability to consent
6. Ability to complete all study related items and interviews

Exclusion Criteria

1. Post void residual urine volume > 150 mL as assessed by catheter or ultrasound
2. History of intradetrusor botulinum toxin A injection
3. History of or current cancer of the genitourinary or gynecology tract

4. Neurogenic bladder
5. Interstitial cystitis
6. Current urinary tract infection (can be treated and re-considered for study)
7. Current active sacral neuromodulation device
8. Non-English speaking
9. History of chronic pelvic pain
10. Hematuria not previously evaluated

Intervention

Hydrodistention at a pressure of 80 cm H_2O for 5 minutes prior to intradetrusor injection of 100 units of botulinum toxin A (hydrodistention group) or intradetrusor injection of 100 units of botulinum toxin A alone (botulinum toxin A alone group).

Primary outcome

The primary outcome will be measured as change from baseline at 12 weeks using the OAB-q bother subscale which consists of eight questions assessing symptom bother with a possible score from 0 to 100 with a higher score indicating greater symptom bother.

Secondary outcomes

1. Number of UUI episodes as reported in a 3-day bladder diary at 12 weeks as measured in change from baseline.
2. Total number of voids reported in the 3-day bladder diary at 12 weeks as measured in change from baseline.

3. Proportion of subjects requiring clean intermittent self-catheterization (CISC) post-operatively as reported at 2 week post-operative visit. CISC will be initiated at post-void residual volumes of > 300 mL *or* > 150 mL in the presence of bothersome retention symptoms.
4. Post-void residual volume (PVR) at the 2 week follow-up visit measured with catheter or bladder scan.
5. Rate of urinary tract infection (UTI) as assessed by positive urine culture in patients having symptoms (dysuria, urgency, frequency, temperature ≥ 38 degrees Celcius, and/or suprapubic pain) at the 2 weeks post-operative visit. Subjects who call throughout the study complaining of symptoms but are unable to give a urine culture in clinic will also be treated and reported as having had a UTI.
6. Health related quality of life (HRQL) will be measured as a change from baseline at 12 weeks using the OAB-q HRQL subscale part which consists of 25 questions that assess HRQL addressing coping, concern, sleep, and social interaction where the scoring scale is from 0 to 100 with a higher score indicating a better quality of life.
7. Patient global impression of improvement at 12 weeks as measured using the Patient Global Impression of Improvement Questionnaire (PGI-I).
8. Patient satisfaction at 12 weeks as measured using Patient Satisfaction Questionnaire (PSQ).
9. Subjective outcome at 24 weeks using the OAB-q

Protocol in detail

Women seen in the urogynecology and urology clinics at University of Alabama at Birmingham who are seeking treatment for refractory OAB symptoms will be screened. Patients

who have failed a credible behavioral therapy intervention and medical therapy or not tolerating medical therapy will be evaluated for this study. Those patients satisfying the inclusion/exclusion criteria will be offered to participate in the study. Informed consent will be reviewed and signed with patients wishing to proceed.

At enrollment, any subjects who are using medical therapy including anticholinergic or β_3 agonist medications will stop these therapies for at least 2 weeks prior to treatment. Baseline clinical data including OAB-q and a 3 day bladder diary will be collected as well as clinical and demographic information. Data from subjects' urodynamic testing will be abstracted from the clinical chart if performed within the prior 12 months of the enrollment date. If no urodynamics testing is available then we will not collect this information for those subjects. Subjects will also be counseled on the possible need for clean intermittent self-catheterization (CISC) and instructions on how and when to perform CISC will be given in clinic. Subjects will be randomized the day of the scheduled procedure. Subjects will be blinded to which group they are assigned.

Subjects randomized to the botulinum toxin A alone group will undergo intradetrusor injection of 100 units of botulinum toxin A diluted in 10 cc of sterile normal saline and injected in volumes of 0.5cc in a grid-like pattern using rigid cystoscopy in the operating room under monitored anesthesia care (MAC) or general anesthesia. Those subjects randomized to the hydrodistention group will undergo hydrodistention of the bladder in the operating room just prior to the botulinum toxin A injection. The hydrodistention will be performed with a water pressure of 80 cm H_2O as measured by the height of the sterile water source above the pubic symphysis in the operative room. The bladder will be filled and noted to be full as evidenced by no further influx of water into the bladder. The bladder will be emptied and this volume will be

recorded as initial bladder volume. The hydrodistention will then be performed with the bladder filled at a pressure of 80 cm H_2O and noted to be full as evidenced by no further influx of water into the bladder. This volume will be held in the bladder for 5 minutes. Upon emptying, the volume will be recorded as the hydrodistention volume. After the hydrodistention, these subjectss will then receive intradetrusor injection of 100 units of botulinum toxin A in a grid like pattern using rigid cystoscopy as described above.

Subjects will be seen for a 2 week post-operative visit. It will be recorded if subjects have had to use CISC including how many days. CISC will be initiated at post-void residual volumes of > 300 mL *or* > 150 mL in the presence of bothersome retention symptoms. Subjects with symptoms of UTI including dysuria, urgency, frequency, temperature ≥ 38 degrees Celsius and/or suprapubic pain will have urine culture sent and treated accordingly for UTI. If subjects call with symptoms of urinary tract infection but are unable to present for urine culture will also be treated and reported as an UTI.

Subjects will follow up for scheduled post-operative care at a 6 and 12 weeks at which time they will complete the OAB-q, PGI-I, and PSQ for the 12 week primary outcome data. Subjects will complete a 3 day bladder diary during the week prior to the 12 week visit and bring the information with them to the visit. At the 24 week follow up visit, patients will complete the OAB-q. All follow up visits at 2 weeks, 6 weeks, 12 weeks, and 24 weeks will be plus or minus a 1 week window from the date of procedure.

Randomization/Allocation

Patients will be randomized to the hydrodistention group or botulinum toxin A alone group in a 1:1 fashion using variable size permuted blocks of 4, 6, and 8. This will be done by a

member of the research team on the day of the procedure. Subjects will be blinded to which group they are assigned. Allocation concealment will be ensured by using a centralized service to provide sequentially numbered, opaque, sealed envelopes.

Confidentiality

Extensive efforts will be made to ensure and maintain participant confidentiality. All identifying information will be maintained in a secure area at all times. Participants will be assigned a Study ID number at study enrollment taken from the randomization log. This Study ID will be used to label all data collection sheets.

Power analysis

A sample size of 27 patients per group provides 80% power to detect a difference of 15 points or more at a 0.05 level of significance. For this determination, we estimated the mean OAB-q bother score in the control group to be 45 and the standard deviation of the change in severity scores to be 19 points based on a prior studies by Coyne, et al [16, 17]. We hypothesized a 15 point difference to be meaningful based on feasibility, clinical significance, and prior reported minimally important difference (MID) [17]. Allowing for a 10% dropout rate, we will recruit a total of 60 patients, 30 per group.

Data analysis

Demographics and baseline data will be analyzed by Student's paired t-test and chi-squared test or Fisher's Exact test as appropriate.

Project schedule

- February to May 2016: start up and obtain IRB approval

- May 2016 until August 2017: Recruitment and Enrollment
- September 2017 to March 2018: Data analysis, manuscript completion

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