The Impact of Injection Location on the Efficacy of Intravesicular Onabotulinumtoxin A in Interstitial Cystitis

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BACKGROUND, RATIONALE, AND CONTEXT

Interstitial cystitis (IC), also referred to as painful bladder syndrome (PBS), is a heterogenous chronic disease of unknown etiology that impacts up to 8 million women in America.[1] Patients suffer from vague pelvic pain that can be exacerbated by bladder filling, and is often associated with urinary frequency and urgency.[2] Since Alexander Skene's inception of the term in 1887, research into the etiology and pathophysiology of this disease has not been successful in elucidating a specific mechanism, revealing more questions than answers. As a result, treatment is difficult. Although there are many oral, intravesicular, and procedural treatments available, many patients remain refractory and require a more substantial treatment. Onabotulinumtoxin A may be that treatment.

Onabotulinumtoxin A has long been considered an efficacious treatment for various bladder pathologies such as overactive bladder (OAB) and neurogenic bladder. For the treatment of IC current AUA guidelines list intradetrusor Onabotulinumtoxin A injections as a fifth-line treatment option with grade C evidence (observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data).[3] This option is based upon six observational studies that demonstrated highly variable amounts of short and long efficacy rates (from 20% to 86% at 3 months).[4–9] Since the release of these guidelines other studies have confirmed Onabotulinumtoxin A's efficacy.[10,11] While prior studies demonstrated the efficacy of intravesicular Onabotulinumtoxin A as a treatment, they largely did not address the importance of injection location. With the majority of bladder nociceptor and parasympathetic fibers located in the trigone,[10–12]it stands to reason that injections to this area should have a more significant effect on bladder pain than injections elsewhere. The purpose of this study is to identify the importance of injection location for intravesicular Onabotulinumtoxin A.

We hypothesize that injections into the trigone should be more effective in the treatment of IC than injections elsewhere in the bladder. The lack of evidence on this topic has been noted by several authors and is important to the understanding and future use of Onabotulinumtoxin A in the treatment of IC.

Objectives

The purpose of this study is to evaluate the efficacy of intravesicular Onabotulinumtoxin A injections for the treatment of interstitial cystitis (IC). Specifically, we hypothesize that trigonal Onabotulinumtoxin A injections is an effective treatment for IC and will result in more subjective and objective symptom relief than posterior wall Onabotulinumtoxin A injections.

Specific Aims

Patients diagnosed as having refractory IC will receive a one time dose of intravesicular Onabotulinumtoxin A with injections randomly assigned to either the posterior wall or trigone. Patients will be evaluated for subjective IC symptoms and objective flow performance prior to treatment as well as 30 and 90 days. This will test the hypothesis that intravesicular Onabotulinumtoxin A is an effective treatment for IC and that injections to the trigone are more effective than injections elsewhere.

MATERIALS AND METHODS

Design

This is a single center, prospective, randomized clinical trial. Subjects will consist of patients referred to the urology clinic at Wake Forest University Baptist Medical Center with interstitial cystitis for whom conservative management/oral medications have failed and Onabotulinumtoxin A is recommended. These patients will all have undergone evaluation by Dr. Robert Evans: an expert in the management of pelvic pain syndromes who sees >300 new patients each year.

Upon initial evaluation all subjects will undergo assessment including history taking and physical examination, urinalysis, subjective symptom assessment using self-reporting questionnaires, and objective symptom assessment using uroflowometry as well as the measurement of post void residuals.

After initial assessment subjects will be randomized into either the control or experimental cohorts. Subjects will receive a single dose of PO ciprofloxacin prior to injection unless culture or allergies dictate to use a different antibiotic. Each group will receive a total of 100 units of botox spread out among 10 separate injections. Subjects in the control group will have 10 injections made about the periphery of the trigone. Subjects in the experimental cohort will receive a one time dose of 100 units of Onabotulinumtoxin A diluted in 10 mL of preservative free normal saline and injected in 1.0 mL boluses in a set pattern across the upper aspect of the trigone of the urinary bladder. Meanwhile, those subjects randomized to the control cohort will also receive a one time dose of Onabotulinumtoxin A using the same dilution and number of boluses, but boluses will be administered at random sites on the posterior bladder wall (excluding the trigone). Post –treatment, subjects will remain at the site for at least 30 minutes for observation and will demonstrate their ability to void before leaving. All procedures will be performed using the facilities of Wake Forest Baptist Medical Center.

After the procedure subjects will be scheduled for clinical follow-up at 2 weeks for a measurement of post void residual and adverse event collection. At the day 30 and 90 day follow-up visits patients will again undergo evaluation including collection of adverse events, concomitant medications, history taking and physical examination, urinalysis, subjective symptom assessment using self-reporting questionnaires, and objective symptom assessment using uroflowometry as well as the measurement of post void residuals. At day 45 and day 60 we will call to verify if patient has had any adverse events or changes in concomitant medications. We will then analyze the data generated by these follow-up visits to measure the efficacy of Onabotulinumtoxin A injections for interstitial cystitis as well as impact of injection location, if any.

Procedures, Tests and Evaluations	Screening and Baseline Study Day 0 in Clinic	Week 2 Clinic visit	Day 30 Clinic Visit	Day 45 Phone call	Day 60 Phone call	Day 90 Clinic Visit
	Day 0	Day 14 ±3	Day 30 ±3	Day 45 ±3	Day 60 ±3	Day 90 ±3
Informed Consent	X					
Medical History/Demographics	X					
Medical History verification		X	X			X
Concomitant Medications	X	X	X	X	X	X
Inclusion/Exclusion Verification	X					
Physical Examination (PE)	X		X			X
Uroflowometry	X		X			X
Pregnancy Test	X[a]					
Antibiotic dose	X					
Post-Treatment Observation and Void	X[b]					
Urinalysis/Urine Culture	X		X			X
Questionnaires—PUF, O'Leary-Sant	X		X			X
Bladder Post-void Residual	X	X	X			X
IP injections	X					
AEs	X	X	X	X	X	X

a. For subjects who are of child-bearing potential
b. Subjects will remain at site on Day 0 after treatment for at least 30 minutes for observation. Subjects must also demonstrate their ability to void before leaving.

Subject selection criteria

Written informed consent will be obtained from all subjects before enrollment. Once participants have been appropriately consented, the minimal amount of clinical data required will be abstracted from their electronic medical record. Other extracted information will include their past medical history, such as comorbidities, current medications, and any symptoms of IC they experience. Furthermore, physical exam findings, laboratory results, intra-operative findings, and pathology reports will be reviewed. Patients will complete questionnaires that have been well-established to assist in IC diagnosis and assessment of disease severity and response to treatment, and are part of routine clinical diagnosis and treatment. These include the O'Leary-Sant Interstitial and the Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF). Each of these questionnaires are well established in the literature to help the urologist identify and treat patients with IC. Their scores on these questionnaires must >10 for either the ICSS or ICPI, and >10 on the PUF. Both the O'Leary/Sant questionnare and PUF questionnare ask about the voiding patterns and pain levels of IC patients.

Inclusion Criteria

Subjects should only be included if they meet the following conditions:

1. Adult females between the ages of 18 and 80 inclusive
2. Patients being treated for IC who are refractory to conservative management and oral therapy.
3. willing and able to initiate catheterization post-treatment

These patients will all have undergone evaluation by Dr. Robert Evans, an expert in the management of pelvic pain syndromes who sees >300 new patients each year. Subjects will be drawn from the patient population undergoing chronic management for their IC. The clinical diagnosis of IC will be based on the recently published AUA Guidelines definition: "An unpleasant sensation (pain, pressure, or discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms for more than six weeks duration, in the absence of infection or other identifiable causes."

Exclusion Critera

Subjects should be excluded if any of the following applies:

1. Any history of bladder cancer, uterine cancer, ovarian cancer, vaginal cancer, urethral diverticulum, spinal cord injury, stroke, Parkinson's disease, multiple sclerosis, spina bifida, cyclophosphamide treatment, radiation treatment to the pelvis, bladder tuberculosis, genital herpes.
2. Currently on or requiring anti-platelet/anti-coagulant concomitant therapy or having been on anti-platelet/ anti-coagulant therapy within the past 3 months

3. Pregnancy. Pregnancy is an absolute contraindication to undergoing these procedures. Thus, as part of their normal pre-operative work up, which is standard of care, pregnancy tests are administered if they are women of child-bearing age, are sexually active, and are within 10 days of the normal menstrual period. If positive, they will be excluded as they will not undergo the procedure.
4. An active urinary tract infection as shown during clean-catch urinalysis at screening visit. Subject may be re-screened if UTI is successfully treated and urinalysis is negative at rescreening.
5. A history of hypersensitivity or allergy to any botulinum toxin preparation
6. A post-void residual (PVR) urine volume >200mL at baseline
7. Treatment with botulinum toxin during the 12 week period prior to the trial
8. Current treatment with aminoglicosides or other drugs that interfere with neuromuscular transmission or with muscle relaxants.

Sample Size and Randomization

Each study arm will consist of 20 subjects for a total study population of 40. This number was chosen using estimates of symptom relief using our current patient population as reference.

Patients will be randomized to either the control or experimental cohort using a computer generated randomization table. Providers will not be aware of the subjects' cohort status until immediately prior to injection.

Power Analysis

We expect that treatment will result in a large effect and as such have set an anticipated Cohen's *d* as 0.95. Using this value along with standard study values of α=0.05 and β=0.80 we calculated a minimum total study group requirement of 38 subjects with 19 subjects in each arm.

Outcome Measure(s)

The primary outcome will be a measurement of subjective patient pain using the Pelvic Pain and Urinary Urgency Frequency (PUF) questionnaire and the O'Leary-Sant Symptom and Problem Indexes. Patients will be asked to complete this questionnaire prior to treatment administration and at 30 and 90 days post treatment. The PUF and O'Leary Sant are previously validated tools that have been used by numerous researchers to evaluate pelvic pain. Secondary outcomes will be objective data as to patient performance in uroflowmetry as well as measurement of post void residuals. Patients will

again undergo these assessments prior to treatment and at 30 and 90 days post treatment to assess objective treatment effectiveness.

Analytical Plan

Results will be analyzed initially using descriptive statistics. Comparison between groups will be done using chi square tests for proportions, and t-tests or ANOVA procedures for continuous variables. Regression analysis will be performed to identify independent outcome predictors. Other inferential statistical analysis will be conducted as appropriate.

Estimated Study Timeline

The study treatment duration is 90 days from first evaluation and treatment to final follow-up. We estimate that the total study time (including IRB approval, patient recruitment, treatment, and data analysis following treatment) to be approximately 1 year and 4 months.

Human Subjects Protection

Informed Consent: An IRB approved written informed consent will be obtained from each subject. Dr. Robert Evans or the study coordinator will consent each of the potential subjects. Informed consent will be acquired in the day hospital at Wake Forest University, or in the Wake Forest University Urology Out-patient Clinic.

Confidentiality and Privacy: Confidentiality will be protected by collecting only information needed to accomplish age and gender matching (i.e. patient's age and patient gender), minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a separate master log. The master log will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator and study coordinator will be responsible for the overall monitoring of the data and safety of study participants, and will ensure that the subjects'

information is not revealed. The principal investigator will be assisted by other members of the study staff.

Budget

Please see budget submitted separately as a spreadsheet. Letters on Wake Forest letterhead testifying to the institutional overhead costs will be forthcoming.

REFERENCES

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