FULL PROTOCOL TITLE

Intradetrusor Onabotulinumtoxin A (Botox®) at the time of Transurethral Resection of the Prostate or Transurethral Waterjet Ablation of the Prostate for Mixed Lower Urinary Tract Symptoms

Principal Investigator:

Thomas W. Fuller, MD
Virginia Mason Franciscan Health
Department of Urology
1100 Ninth Ave C7-URO
Seattle, WA 98101
will.fuller@commonspirit.org
206-223-6772

Supported by:

Benaroya Research Institute

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CLINICAL SITES PARTICIPATING IN THE STUDY

Virginia Mason Franciscan Health

Principal Investigator:
Thomas W. Fuller, MD

PROTOCOL SYNOPSIS

TITLE	Intradetrusor Onabotulinumtoxin A (Botox®) at the time of Transurethral Resection of the Prostate or Transurethral Waterjet Ablation of the Prostate for Mixed Lower Urinary Tract Symptoms
NUMBER OF SITES	1
RATIONALE	Patients with longstanding obstructive lower urinary tract symptoms (LUTS) due to benign prostatic hypertrophy (BPH) can also develop symptoms of overactive bladder syndrome (OAB). Transurethral resection of the prostate (TURP) and Transurethral Waterjet Ablation of the Prostate (Aquablation®) are amongst the gold standard surgical treatments for BPH. However, in the immediate post-operative period, TURP and Aquablation® can also include OAB-like symptoms, including urinary frequency and urgency. For men with baseline OAB symptoms, this initial worsening of symptoms can be distressing. Botox® is an FDA approved medication with on-label indications to treat overactive bladder. The purpose of this study is to evaluate the outcomes of men who have Botox® concurrent with their TURP or Aquablation®.
STUDY DESIGN	This is an observational study to close knowledge gaps on the outcomes of patients who undergo these procedures concurrently.
PRIMARY OBJECTIVE	To identify whether concurrent Botox® and TURP or Aquablation® are effective at reducing post-operative irritative voiding symptoms.
SECONDARY OBJECTIVES	To identify whether concurrent Botox® and TURP or Aquablation® lead to higher rates of urinary retention, longer hospitalization.
NUMBER OF SUBJECTS	The goal will be to enroll 20 subjects
SELECT SUBJECT ENTRANCE CRITERIA	Inclusion Criteria: 1. Male ≥ 18 years of age and being scheduled to undergo TURP or Aquablation® and Botox® procedure. 2. Written informed consent obtained from subject and ability for subject to comply with the requirements of the study. Exclusion Criteria: 3. Non-English speaking 4. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.

	5. History of receiving Botox® in the bladder, within the previous 12 months.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Total expected duration of participation is four months. The study is expected to last approximately 2 years.
CONCOMITANT MEDICATIONS	All concomitant medications are allowed.
PRIMARY ENDPOINT	• 1 week post-operative visit for: trial of void, to assess for rates of postoperative urinary retention.
SECONDARY ENDPOINTS	• 4 and 12 week post-operative visits for: post void residual assessment via bladder scan, AUA symptom score, PGI-I, UDI-6, and VM Post Procedure questionnaires will be administered • Hospitalization readmission rates, urinary retention episodes
SAFETY EVALUATIONS	All subjects will be closely monitored per standard of care by their urology provider.
PLANNED INTERIM ANALYSES	None
STATISTICS **Primary Analysis Plan**	Descriptive statistics will be performed for demographic and survey data.

1. STUDY OBJECTIVES

1.1 Primary Objectives

To identify whether concurrent Botox® and TURP or Aquablation® are effective at reducing post-operative irritative voiding symptoms.

1.2 *Secondary Objectives*

To identify whether concurrent Botox® and TURP or Aquablation® lead to higher rates of urinary retention, longer hospitalization.

1.3 Primary Endpoint

1 week post-operative visit for: trial of void, to assess for rates of postoperative urinary retention.

1.4 Secondary Endpoints

Four and twelve-week post-op visits when AUA symptom score, VM Post Procedure Questionnaire, PGI-I, and UDI-6 questionnaires will be administered. Post void residual obtained via bladder scan.

Hospitalization readmission rates, urinary retention episodes.

2. BACKGROUND

2.1 Rationale

Patients with longstanding obstructive lower urinary tract symptoms (LUTS) due to benign prostatic hypertrophy (BPH) can also develop symptoms of overactive bladder syndrome (OAB). Transurethral resection of the prostate (TURP) and Transurethral Waterjet Ablation of the Prostate (Aquablation®) are amongst the gold standard surgical treatments for BPH. However, in the immediate post-operative period, TURP and Aquablation® can also include OAB-like symptoms, including urinary frequency and urgency. For men with baseline OAB symptoms, this initial worsening of symptoms can be distressing.

Botox® is an FDA approved medication with on-label indications to treat overactive bladder.

The purpose of this study is to evaluate the outcomes of men who have Botox® concurrent with their TURP or Aquablation®.

2.2 Supporting Data

Benign prostatic hypertrophy (BPH) is the natural growth of the prostate in aging men. BPH can eventually lead to an obstructed urinary stream, urinary

retention, and renal damage (1). It can additionally lead to both a hypocontractile as well as a hypercontractile, or overactive bladder (OAB). OAB is defined by irritative voiding symptoms, such as urinary frequency, urinary urgency, urge incontinence, and nocturia (2).

Transurethral resection of the prostate and Aquablation® are endoscopic procedures. In the case of TURP, a camera and resecting tool (resectoscope) are introduced via the urethra and the overgrown prostate is removed. This procedure is performed in the operating room under general or spinal anesthesia. Aquablation® is performed by placing a camera in the urethra and vaporizing prostatic tissue with a pressurized beam of water. Transurethral resection of the prostate and Aquablation® are considered amongst the gold standard treatment for BPH and obstructive LUTS (3,4,5).

However, for men with BPH and OAB, surgical treatment of BPH alone may not alleviate symptoms of overactivity (6). Furthermore, in the immediate post-operative period, TURP and Aquablation® can exacerbate symptoms of overactivity (7), causing distress to patients.

Overactive bladder has its own treatment pathway as outlined in the combined AUA/SUFU guideline (8,9). Botox® is administered as a 100 U starting dose via an endoscopic approach and can be up-titrated. The effect lasts, on average, 6-9 months at which point the injection can be repeated. Typically, Botox® injection is well tolerated and can be performed in the clinic with local anesthesia, although some patients prefer Botox® injection in the operating room (10). Recently, there has been rising concern regarding the safety profile of second line OAB treatments and a push to move to third line treatments for long-term management (11).

Currently, there is no data on the treatment outcomes or patient satisfaction of performing Botox® at the time of TURP or Aquablation®.

3. STUDY DESIGN

3.1 Observational Study

An observational study of the effect of Botox® injection at the time of TURP or Aquablation® will be performed.

If deemed eligible, participants will be invited to participate in this trial. The decision to accept or decline participation in the study will have no impact on whether they receive either treatment. After informed consent is obtained, patients will be administered the AUA symptom score and the Urinary Distress Inventory Short Form (UDI-6) as measures of baseline symptom severity and bother.

The International Prostate Symptom Score (IPSS) is a questionnaire that is widely used to assess LUTS in patients and assesses for incomplete emptying, frequency, intermittency, urgency, weak stream, hesitancy, and nocturia. The AUA quality of life score (AUA-QoL) asks how these symptoms affect quality of life. When administered as a combined questionnaire, this is referred to as the AUA symptom score. These scores are summed to produce an overall severity score, which can categorize patients as having mild (score 0-7), moderate (8-19) or severe (20-35) LUTS (12). The AUA symptom score is a benchmark in defining the severity of symptoms, and collection of these scores is recommended in the AUA guidelines as part of the initial management of BPH (3,4,13). The UDI-6 is a validated short form of the urogenital distress inventory, and it assesses for the impact and severity of urinary incontinence (14).

Participants will then undergo their TURP or Aquablation® and Botox® procedure with one of three surgeons in the department of Urology at Virginia Mason.

At approximately four weeks post-op, participants will have a visit with their provider. Symptoms will be assessed by re-administering the AUA symptom score, the UDI-6, PGI-I and the VM Post-Procedure Questionnaire to assess for change in symptoms as well as satisfaction with their procedure.

Participants will then have an approximate 3 month post-op visit, at which time the questionnaires will be re-administered. Patients will have the opportunity to follow-up with their provider sooner, if needed, based on individual symptoms.

The total expected duration of participation for any given participant is 4 months.

Demographic data, including comorbidities, urodynamics results, post-void residual, uroflow, operative length, estimated blood loss, length of stay, 30 day readmission rate, and 30 day rate of urinary retention will be collected for each subject via the electronic medical record.

All data will be entered into a secure password-protected clinical research database maintained on a Virginia Mason computer.

The goal is to enroll 20 patients based on an estimation of eligible subjects seen within the Virginia Mason urology outpatient clinic. The rate of enrollment is expected to be 1-2 patients per month.

We will be evaluating the impact of Botox® concurrent with TURP or Aquablation® relative to published rates of overactivity and bother after TURP or Aquablation® alone.

4. TARGET STUDY POPULATION SPECIFICS

4.1 Inclusion Criteria

1. Male ≥ 18 years of age, and being scheduled to undergo TURP or Aquablation® and Botox® procedure.

2. Written informed consent obtained from subject and ability for subject to comply with the requirements of the study.

4.2 Exclusion Criteria

1. Non-English Speaking

2. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.

3. History of receiving Botox® in the bladder, within the previous 12 months.

4.3 Data Collection Procedures

Virginia Mason Urology providers will identify patients for potential study participation.

Informed consent will be obtained for all subjects who wish to participate in this trial. Upon consent, study staff will obtain baseline and demographic data, administer AUA symptom score and the UDI-6. At follow up visits, the AUA symptom score, UDI-6, PGI-I, and VM post-procedure questionnaire will be obtained for participating patients. Additional data points under study will be obtained from the subject's electronic medical record.

5. STATISTICAL CONSIDERATIONS

5.1 Hypotheses

a. There is a high rate of bother from OAB symptoms in men with BPH

b. Botox® injection at the time of TURP or Aquablation® will improve irritative symptoms as compared to baseline.

c. Botox® injection at the time of TURP or Aquablation® will not increase procedural morbidity, urinary retention rate, or readmission rate.

d. Plan for future randomized, single-blind study to better evaluate symptomatic improvement pending the results of the study.

5.2 *Data Analyses*

Descriptive statistics will be performed for demographic and survey data. Additional analyses may be performed as appropriate.

6. DATA COLLECTION

6.1 Records to be kept

Clinical and demographic data is available through electronic medical records and will be entered directly into the study database. Any paper study documents that are generated, such as the questionnaires, will be securely stored and archived for 10 years following study completion.

6.2 Secure Storage of Data

All study data will be entered into a secure password-protected clinical research database maintained on a Virginia Mason computer. No PHI will be transferred outside of Virginia Mason.

6.3 Quality Assurance

The Clinical Research Program will assess the risk of this trial and will devise and implement an internal monitoring and/or auditing plan for this trial. This plan will be revised as necessary during the life of the trial based upon a variety of factors, including but not limited to: protocol amendments, staff turnover, enrollment metrics, and compliance issues noted.

7. HUMAN SUBJECTS

7.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and informed consent document/study information sheet and any subsequent modifications will be reviewed and approved by the IRB at Benaroya Research Institute at Virginia Mason prior to implementation. Informed consent will be obtained from all subjects prior to study entry following Good Clinical Practice and FDA guidelines.

7.2 Potential Risks

The risks associated with the completion of questionnaires are the potential to feel uncomfortable or upset and loss of confidentiality.

7.3 Subject Confidentiality

All paper records will be kept in a file cabinet within secure Virginia Mason offices during the trial. The database will be maintained on a Virginia Mason computer located on the secure Virginia Mason maintained network, which requires user login for access. Clinical information will not be released without written permission of the subject, except as necessary for monitoring

by the IRB, or CRP. All paper study records will be securely archived by CRP for 10 years following completion of the study.

7.4 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB or Investigator, as part of their duties to ensure that research subjects are protected.

8. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures of the journal for which it is submitted. Any presentation, abstract, or manuscript will be made available for review by the Benaroya Research Institute IRB.

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