Clinical Study Summary Report

Sponsor: University College London (UCL)

Title of study: Open label pilot study to treat women with chronic urinary retention or voiding dysfunction due to a primary disorder of sphincter relaxation (Fowler's syndrome) with outpatient urethral injections of botulinum toxin A (BoNT-A)

Sponsor code: 08/0216

EudraCT Number: 2008-004858-33

Chief Investigator: Professor Clare Fowler

Study centre(s): Department of Uroneurology, NHNN

Studied period (years):2009 to 2012 (date of first enrolment): 25 Nov 2009 (date of last completed): 19 July 2012	**Phase of development:** Pilot study

Primary Objectives: To investigate if voiding can be restored in those with complete retention or flow rates improved by more than 50% in those with obstructed voiding by sphincter injection of BoNT-A.

Secondary Objectives: 1. To study the effect of the sphincter BoNT-A on reducing residual volume. A reduction to less than 100mls would be considered clinically significant. 2. Improvement in IPSS symptom score

Methodology:

5 women with complete urinary retention and 5 women with obstructed voiding with Fowler's Syndrome were included. Pre-treatment assessments included standard investigations appropriate for women with complete urinary retention or obstructed voiding- urine flow rate (if voiding), cystometry, urethral pressure profile, sphincter volume and sphincter EMG.

Treatment was given as an outpatient procedure following 1ml of 2% lignocaine injected either side of the urethral orifice.

Number of patients:

Planned: ten

Actual number enrolled and completed: 16 enrolled and 10 completed

Diagnosis and main criteria for inclusion:

INCLUSION CRITERIA

- Women 18 years old or over with diagnosed Fowler's syndrome and abnormal

sphincter function i.e. raised UPP {MUCP>(92 - patient age in years) cmH_2O} (Edwards and Malvern 1974), increased sphincter volume(if measured) (greater than 1.8 cm^3) and if voiding, evidence of obstructed outflow. (Sphincter EMG will be recorded at the time of injection.)

- Willing to give written informed consent
- Willing to attend the necessary follow up visits
- On effective contraception if sexually active - oral contraceptive pill (>3 months use), condoms, intrauterine contraceptive device, depot injection

EXCLUSION CRITERIA

- Previous urethral surgery (other than urethral dilatation)
- Neurological disease
- Pregnant or lactating women and those planning pregnancy
- Anticoagulant therapy at the time of inclusion.
- On drugs that might interfere with neuromuscular transmission (e.g. aminoglycosides)
- Pain thought to originate from the urinary tract
- Unsuitable past medical history e.g. frequent epilepsy, uncontrolled hypertension, severe coronary artery disease.
- Symptomatic Urinary Tract Infection with a positive urine culture
- Participation in a clinical trial involving an investigational product in the last 3 months
- Patients who are unable to understand or speak English, as this is a pilot study involving very few patients.

Test product, dose and mode of administration, duration of treatment:

100 U Botox® dissolved in 2mls of saline, injected1ml on each side into the striated urethral sphincter under EMG control

Endpoints

Primary

- To investigate if voiding can be restored in those with complete retention.
- Improvement in flow rates by more than 50% in those with obstructed voiding.

Secondary

- To study the effect of the sphincter BoNT-A on reducing residual volume. A

reduction to less than 100mls would be considered significant.

- Improvement in IPSS symptom score.

Statistical methods:
Descriptive- calculation of means

Summary – Conclusions
Mean symptom scores on the IPSS questionnaire improved from 20.9 (8-33) to 15.3 (8-25), and mean bother score reduced from 6.1 (4-7) to 3.5 (1-7) at week 10. As compared to a baseline mean flow rate of 8.12 mls/sec (3.4-10) in women who could void, the flow rate improved to 12.6 mls/sec (6.3-27.4) at week 10. Four out of five women in complete retention could void spontaneously, with a mean flow rate of 11.4 mls/sec at week 10. The mean post-void residual volume decreased from 315 mls (40-700) to 112 mls (0-230). The mean static UPP improved from 113 (86-139) to 92.2 (66-151) cmH_20 at baseline.
No serious side effects were reported. Three women with a history of recurrent urinary tract infections developed a urinary tract infection. None of the women developed stress incontinence. Seven out of the ten women opted to return for repeat injections.

In short, this pilot study demonstrates an improvement in patient-reported lower urinary tract symptoms, and objective parameters such as flow rate, post-void residual volume and UPP, ten weeks following urethral sphincter injections of botulinum toxin. No serious side effects were reported. However, a larger study is required to confirm the findings of this pilot study.

Arrangements for publication or dissemination of results:

Podium presentation at the Annual meeting of the International Continence Society in Barcelona in August 2013