

## NO ADVERSE CHANGE IN AMBULATORY VOIDING FUNCTION AFTER TRIGONE ONABOTULINUMTOXINA DETRUSOR INJECTION IN THE RAT

**Hypothesis / aims of study:** Intradetrusor onabotulinumtoxinA (BTX) chemodenervation is an established therapy for appropriately selected patients who fail first and second-line treatments for overactive bladder. There has been much variability regarding the injection pattern of BTX described in the literature including templates which generally deliver the toxin to the posterior and lateral walls with or without sparing of the trigone. The aim of our study is to further characterize the physiologic effect of various BTX injection distributions on ambulatory voiding function in conscious awake rats.

**Study design, materials and methods:** Thirty-six adult female rats were divided into six (n=6) groups. Treatment animals received intradetrusor injection of 7.5 units BTX (in 25-125  $\mu$ L saline; 25  $\mu$ L/aliquot): intact control (no injection); saline vehicle control (5 aliquots); unilateral BTX (1 aliquot); trigone BTX (1 aliquot); posterior and lateral wall BTX (3 aliquots); whole bladder BTX (5 aliquots). Animals were acclimated and micturition frequency and voided volume were assessed using a 12-channel 100-gram load cell sensor array and metabolic cages. Measurements were obtained at baseline (day 0, 7) and following injection (day 14, 21, 28). On day 7, animals underwent detrusor injection via midline incision. On day 28, overactive bladder was induced with acetic acid bladder instillation (0.25%, 30-min). Bladder function was assessed using cystometry before and after acid instillation. Data analysis was performed in SAS Studio (Cary, NC, USA) using ANOVA, Pearson correlation and generalized linear regression to evaluate animals over time.

**Results:** One rat in the trigone group expired during recovery from anesthesia after injection. Diminished growth in body weight was noted in all BTX treated animals, with slowest growth noted after trigone injection. There was no overall correlation between rat weight and mean voided volume ( $r = -0.02$ ,  $p = 0.81$ ). Small volume voids were significantly associated with increased food intake ( $r = -0.21$ ,  $p = 0.006$ ) and greater stool output ( $r = -0.23$ ,  $p = 0.003$ ). Mean nocturnal voided volume was similar in control, vehicle, trigone and posterior-lateral groups. The ability to void small volumes was preserved in both the control and treatment groups with the exception of unilateral and whole bladder injection which demonstrated increased minimum ambulatory voided volumes. On cystometry, mean voided volume was the greatest in the control and trigone groups prior to acetic acid. Increased threshold pressure was noted in both the unilateral and whole bladder injection groups before and after acetic acid. Post void residual was decreased in all groups after acetic acid. Increased bladder weight was associated with increased ambulatory voided volume ( $r = 0.43$ ,  $p = 0.01$ ). The lowest number of voids and longest interval between voids was noted after unilateral and whole bladder BTX injection. Cystometric intercontractile interval correlated with increased nocturnal mean voided volume before ( $r = 0.33$ ,  $p = 0.05$ ) and after ( $r = 0.24$ ,  $p = 0.17$ ) acetic acid. Cystometric mean voided volume correlated with ambulatory nocturnal voided volume, however was almost 10-fold lower after saline instillation ( $r = 0.18$ ,  $p = 0.30$ ), and more closely approximated ambulatory voiding after acetic acid instillation ( $r = 0.30$ ,  $p = 0.08$ ).

**Interpretation of results:** Unilateral and whole bladder BTX injection resulted in elevated ambulatory nocturnal mean voided volumes, with higher pressure and smaller volume voids noted on cystometry. Trigone and posterior-lateral BTX injection patterns appear to preserve contractility, with threshold and peak contraction pressures similar to control animals. Future efforts should be directed at understanding the mechanism of trigone and unilateral injection.

**Concluding message:** There was no adverse change in ambulatory voiding function in the rat after a single 7.5 unit BTX injection to the trigone.

### Disclosures

**Funding:** Material support was provided by the SUFU Research Foundation grant for the Study of Chemodenervation funded by The Allergan Foundation. Dr. Dobberfuhr is supported by a KL2 Mentored Career Development Award of the Stanford Clinical and Translational Science Award to Spectrum (NIH KL2 TR 001083). **Clinical Trial:** No **Subjects:** ANIMAL **Species:** Rat **Ethics Committee:** Stanford University APLAC Protocol ID: 30707