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Medication Effects on Periurethral Sensation and Urethral Sphincter Activity

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Abstract

Aim—To characterize urethral neuromuscular function before and 2 weeks after medication therapy.

Methods—Premenopausal women without lower urinary tract symptoms were randomly allocated to one of six medications for 2 weeks (pseudoephedrine ER 120mg, imipramine 25mg, cyclobenzaprine 10mg, tamsulosin 0.4mg, solifenacin 5mg or placebo). At baseline and after medication, participants underwent testing: quantitative concentric needle EMG (CNE) of the urethral sphincter using automated Multi-Motor Unit Action Potential (MUP) software; current perception threshold (CPT) testing to measure periurethral sensation; and standard urodynamic pressure flow studies (PFS). Nonparametric tests were used to compare pre-post differences.

Results—56 women had baseline testing; 48 (85.7%) completed follow-up CNE, and 49 (87.5%) completed follow-up CPT and PFS testing. Demographics showed no significant differences among medication groups with respect to age (mean 34.3 ± 10.1), BMI (mean 31.8 ± 7.5), parity (median 1, range 0–7), or race (14% Caucasian, 80% African American). PFS parameters were not significantly different within medication groups. No significant pre-post changes in CNE values were noted; however, trends in amplitudes were in a direction consistent with the expected physiologic effect of the medications. With CPT testing, a trend toward increased urethral sensation at the 5 Hz stimulation level, was observed following treatment with pseudoephedrine (0.15 to 0.09 mA at 5Hz; $P=0.03$).

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Conclusion—In women without LUTS, pseudoephedrine improved urethral sensation, but not urethral neuromuscular function on CNE or pressure flow studies. Imipramine, cyclobenzaprine, tamsulosin, solifenacin, and placebo did not change urethral sensation or neuromuscular function.

Keywords

urethral sensation; urethral sphincter; electromyography

Introduction

The role of urethral neuromuscular function in the pathophysiology of lower urinary tract symptoms (LUTS) is poorly understood. Several medications used to treat LUTS affect urethral function, and significant changes in urethral sensation have been demonstrated in women with overactive bladder following 2 months of anticholinergic medication treatment (1).

Alpha1-blockers, which function at the urethral bladder neck, have also been shown to have efficacy in women with functional bladder outlet obstruction and other LUTS. Pummangura reported a significant difference in change from baseline mean urinary flow rates in 140 women randomized to 30 days of treatment with tamsulosin vs placebo (+0.7 vs -0.5 mL/sec, $P = 0.013$). Maximum flow rates were not significantly different in this study (2). Another small study showed decreased urethral pressures in a dose-dependent fashion following treatment with tamsulosin (3). A number of other medications, based on their mechanisms of action, should theoretically affect the sensory and/or motor function of the urethral sphincter. Furthermore, studies have shown increased sphincter activity in patients with urinary retention or voiding dysfunction, while decreased sphincter function has been observed in patients with recurrent stress urinary incontinence (4, 5).

Electrical stimulation is increasingly being used to assess urethral sensation in the lower urinary tract as well as afferent innervation of the urethra in women with lower urinary tract dysfunction (6–11). Current perception threshold (CPT) testing utilizes electrical stimuli at varying frequencies to activate different subpopulations of afferent nerve fibers (12–14). Concentric needle electromyography (CNE) is superior to surface electrodes in documenting striated urethral sphincter activity (15).

In this study, our primary aim was to characterize urethral function before and after 2 weeks of medication therapy, quantifying afferent innervation with CPT testing and efferent innervation with CNE in women with normal LUT function. This may provide increased insight regarding the impact of these medications on the neuromuscular function of the LUT, and may guide future research in women with LUT dysfunction.

Materials and Methods

This is a prospective, randomized, double-blinded pilot study of premenopausal women without urinary incontinence or other LUTS. Subjects with known neurologic disease that might alter urethral tone or sensation, those with a history of QTc prolongation or cardiac arrhythmia, currently pregnant, breastfeeding or less than 6 months postpartum, those taking

one of the study medications, and those with contraindications to the medications being tested were excluded. This study was approved by the Institutional Review Board at the University of Alabama at Birmingham. Participants were recruited through advertising, and the study was conducted at a university-based Urogynecology referral center. All participants provided written informed consent.

At the initial visit, participants underwent a complete medical history, physical examination, urinalysis and urine pregnancy test. We also obtained confirmation of postmenopausal status, surgical sterility or the use of reliable contraception throughout the duration of the study. Baseline current perception threshold (CPT) testing, urethral concentric needle electromyography (CNE), and a urodynamic pressure flow study (PFS) were performed on all participants.

Procedures

CPT testing of the urethra was performed using a Neurometer® device (Neurotron Inc, Baltimore, MD) (16). The Neurometer® is a constant current stimulator capable of delivering sine wave electrical stimuli at 3 frequencies, 2000 Hz, 250 Hz and 5 Hz, which selectively depolarize A- β , A- δ , and C fibers, respectively. Standardized CPT testing was performed in the urethra with subjects in the dorsal lithotomy position. Stimuli were applied to the urinary tract via a Urotrode™ Midurethral Catheter Electrode, positioned 1 cm distal to the balloon on a 9 French Foley catheter.

After draining the bladder and inflating the Foley balloon, the balloon was gently positioned at the urethrovesical junction, so the ring electrode lay at the mid-urethra. The ring electrode was connected to the Neurometer®, and testing initiated at 2000 Hz. Stimulus intensity was gradually increased until first perceived by the participant, and then decreased until no longer perceptible. CPT values were obtained using a semi-automated forced choice paradigm where randomly chosen pairs of stimuli were presented as “A” or “B” with a brief rest period until a consistent perception threshold was reached. We repeated the process at 250 Hz and 5 Hz.

For CNE testing, anesthetic cream containing 2.5% lidocaine and 2.5% prilocaine (EMLA cream, Astra, Westborough, MA) was applied to the external urethral meatus 10 minutes prior to the study to optimize subject comfort. An Alpine Biomed Keypoint.NET electromyography instrument (Alpine Biomed Corporation, Skovlunde, Denmark) was used to process all raw EMG signals using standard filter settings (range, 5Hz to 10 KHz). An amplifier gain of 50–100 μ V per division and sweep speed of 10ms per division were used because urethral sphincter motor unit action potentials (MUPs) are smaller than those in other skeletal muscles.

Two methods of quantitative electromyography (QEMG) were performed on all subjects. (1) Multi-Motor Unit Action Potential (MUP) analysis, which has been shown to be the most sensitive QEMG technique in distinguishing neuropathic from control muscles (17); and (2) interference pattern analysis (IPA) which reflects changes in MUP recruitment from weak effort to maximal contraction (18).

QEMG was performed using a concentric needle electrode. Multi-MUP analysis followed by IPA was performed at 3–4 insertion sites around the urethra. With the subject at rest and with slightly increasing pelvic floor muscle contraction, MUP activity was recorded using multi-MUP software. Quantitative MUP parameters, including amplitude, duration, area, rise time, number of phases and turns, and mean firing frequency were recorded. IPA was recorded at baseline and with the increase in muscle activity while asking subjects to incrementally increase voluntary contraction to maximum effort in order to recruit more MUPs. The mean rectified voltage (MRV) is the mean amplitude calculated over a 5-second period, and this value was used to compare pre- and post-treatment values.

The protocol for pressure flowmetry was developed in compliance with terminology from the International Continence Society Standardization Committee (19), as well as the technical recommendations from the Good Urodynamic Practice Guidelines (20).

Participants were instructed to void upon arrival, and a post-void residual volume was determined by catheterization. A 300 cc bladder fill was then performed through the catheter, the catheter was removed, and transurethral and transrectal pressure transducers were placed for the PFS. Voiding was performed in the seated position. Information obtained for the database included maximum flow rate (Qmax), average flow rate, time to Qmax, detrusor pressure at maximum flow rate, voided volume, and a calculated post-void residual (21). If a participant was unable to void with the catheters in place, they were removed and a non-instrumented uroflowmetry was performed. Participants were then assigned to take one of 5 medications or placebo based on a computer-generated randomization weighted more heavily to the 5 study medication groups (n=10 in each) compared to the placebo group (n=6). This unequal allocation maximized the number of women exposed to, and potentially benefit from, active drug. Medications included: pseudoephedrine ER 120 mg, imipramine 25 mg, cyclobenzaprine 10 mg, tamsulosin 0.4 mg, solifenacin 5 mg or placebo daily. Participants, researchers and research assistants were blinded to group assignment. Medications were taken for a period of 2 weeks, after which participants returned for repeat CNE, CPT and PFS testing.

Demographic characteristics were compared across study groups. Differences were assessed with analysis of variance (ANOVA) and Kruskal Wallis tests for quantitative measures and Fisher's exact test for categorical measures. Given small sample sizes the Kruskal Wallis test was used to evaluate differences between baseline, follow-up, and changes from baseline to follow-up, across the study groups. The sign test was used to examine pre-to-post changes from baseline to follow-up within each group. The baseline, follow-up, and change measures are presented as median (1st quartile–3rd quartile). To account for multiple hypothesis tests, a stringent significance level of 0.01 was used for all statistical tests. All analyses were conducted with SAS version 9.2 (SAS Institute Inc, Cary, NC). Adverse events were also collected.

Results

Patient flow was as noted in Figure 1. One hundred and three women were screened for participation and 56 were consented, randomized and underwent baseline testing. Forty-

eight (85.7%) completed follow-up CNE, and 49 (87.5%) completed follow-up CPT and PFS testing. There were no significant differences in demographic characteristics (Table I) among medication groups with respect to age, BMI, parity, race, prior hysterectomy or smoking. Participants were predominantly African-American, mildly obese, parous and non-smokers.

Median baseline CNE parameters were not significantly different across medications (Table II) and no significant pre-post changes in CNE values were noted ($p>0.01$). However, trends in amplitudes were in a direction consistent with the expected physiologic effect of the medications.

Median baseline CPTs were not significantly different across medication groups, and the placebo group showed no pre-post changes in CPT values (Table III; $p>0.01$). A trend toward improved urethral sensation, seen as a lower threshold at the 5 Hz stimulation level, was observed following treatment with pseudoephedrine (0.15 to 0.09 mA at 5 Hz; $p = 0.03$). No significant differences in pre-post CPT values were seen with other medications or placebo. There were no significant differences within medication groups with respect to the following PFS parameters: maximum flow rate, mean flow rate, time to Qmax, and detrusor pressure at peak flow (Table IV).

Discussion

In this cohort of healthy women without LUT symptomatology, median baseline CNE and CPT parameters were not significantly different across medication groups, and the placebo group showed no pre-post changes in any variables. No significant pre-post changes in CNE values were noted, however, trends in amplitudes were in a direction consistent with the expected physiologic effect of the medications. Specifically, post-treatment amplitudes of medications expected to increase urethral tone (pseudoephedrine, imipramine) trended higher, while those expected to relax the urethral sphincter (tamsulosin, cyclobenzaprine) trended lower. With respect to CPT testing, a trend towards increased urethral sensation was observed following treatment with pseudoephedrine (0.15 to 0.09 mA at 5Hz; $P=0.03$); in other words, C fiber pathways were activated with less stimulation after pseudoephedrine treatment. No other differences in pre-post CPT values were seen with other medications or placebo. Interestingly, PFS testing showed a slight decrease in Qmax following treatment with tamsulosin, but this finding is most likely related to the small sample size.

Medications were selected for our study based on their mechanism of action and expected effect on the urethra. As an α_1 blocker, tamsulosin is known to inhibit the effects of norepinephrine (NE) on the smooth muscle of the urethra, leading to sphincter relaxation and improvement in voiding parameters. Solifenacin, a muscarinic inhibitor, blocks the parasympathetic effect of acetylcholine (ACh) on μ receptors in the bladder wall, improving urine storage and decreasing overactive bladder contractions. Other anticholinergic drugs have been shown to improve urethral sensation (1) as well as to decrease urethral pressures (22). Pseudoephedrine is an α/β agonist that should cause contraction of the internal urethral sphincter via direct effect on α receptors and increase in NE release from presynaptic neurons. As a centrally acting skeletal muscle relaxant (related to tricyclic antidepressants

[TCAs]), cyclobenzaprine should theoretically decrease striated external urethral sphincter tone. While imipramine (a tricyclic antidepressant) has anticholinergic properties similar to solifenacin, it also has other sites of action. As a serotonin (5HT) and NE – reuptake inhibitor, this medication increases NE concentrations at the synaptic junction leading to stimulation of β receptors in the bladder wall and α receptors in the bladder neck and urethra, theoretically both relaxing the bladder and increasing urethral resistance.

This is the first human study of pseudoephedrine's effect on urethral function. As an α/β agonist, this medication should theoretically cause increased tone of the urethral sphincter via direct effect on alpha receptors and increased norepinephrine from presynaptic neurons. While the increased urethral EMG activity we report did not reach statistical significance, it is possible that longer duration of therapy could lead to a greater effect. Additionally, our sample size was based on previous work by Kenton et al and was capped by resources; the variability that we observed was substantially greater than this prior data, further limiting our ability to detect any significant differences that may exist. Another potential factor in our inability to show pre-post differences within the medication groups is the use of a young, asymptomatic patient population; the healthy urethra may be less affected by the study medications than in a population with LUTS.

One potential limitation of our study is the predominantly African-American subject population, leading to some concern for the generalizability of our results. However, previous work by Dr. Kenton showed no racial differences in urodynamic or CNE parameters in a similar, but more racially balanced, population of healthy controls (23). Strengths of this pilot study include random and blinded allocation to groups and our prospective, controlled collection of urethral EMG and CPT data in an asymptomatic population of women. The standardized methods used for collection allow for comparison with future studies. Though the small sample sizes and wide variability in study outcomes limited our ability to see differences between medication groups, our study adds to the pool of normative urethral CPT and EMG data and may be hypothesis-generating for further comparative studies. Future studies should address women with specific LUT symptoms, pre/post meds in order to clarify changes in afferent and efferent urethral function.

Conclusions

Though no significant changes were seen in CNE parameters, trends in pre-post changes suggest that certain medication effects on the urethra are quantifiable with CNE. Pseudoephedrine may improve urethral sensation in asymptomatic women. These findings will hopefully lead to further studies, which may help to clarify the role of the urethra in the etiology and potential treatment of female lower urinary tract dysfunction.

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Figure 1.
CONSORT flow diagram for the MUSE Trial

Demographics by randomization group, excluding those lost to follow-up and withdrawn consent. ANOVA and Fisher's exact test are reported unless otherwise noted.

Table 1

Characteristic	Pseudoephedrine (n=10)	Imipramine (n=10)	Cyclobenzaprine (n=10)	Tamsulosin (n=10)	Solifenacin (n=10)	Placebo (n=6)	p
Years of Age, mean $\pm$ SD	36.6 $\pm$ 9.2	33.1 $\pm$ 9.6	38.0 $\pm$ 10.4	35.5 $\pm$ 10.7	31.6 $\pm$ 12.2	28.7 $\pm$ 5.6	0.46
BMI, mean $\pm$ SD	32.6 $\pm$ 7.3	31.9 $\pm$ 6.4	31.9 $\pm$ 6.4	31.6 $\pm$ 6.1	32.3 $\pm$ 7.5	26.9 $\pm$ 5.7	0.64
Parity: median (range)	1.5 (0–7)	1.5 (0–5)	1 (1–6)	1.5 (0–2)	0.5 (0–3)	0 (0–3)	0.74*
Race, n (%)							0.26
White	1 (10%)	1 (10%)	2 (20%)	0 (0%)	2 (20%)	1 (33%)	
Black	9 (90%)	9 (90%)	8 (80%)	8 (80%)	8 (80%)	3 (50%)	
Other	0 (0%)	0 (0%)	0 (0%)	2 (40%)	0 (0%)	1 (17%)	
Hysterectomy, n (%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	>0.99
Tobacco Use, n (%)	2 (14%)	2 (20%)	4 (40%)	3 (30%)	2 (14%)	1 (7%)	0.93

* Kruskal-Wallis Test for equality of medians

Table II

Urethral Concentric Needle Electromyography Changes by Medication Group

Characteristic	Pseudoephedrine (n=8)	Imipramine (n=9)	Cyclobenzaprine (n=9)	Tamsulosin (n=10)	Solifenacin (n=8)	Placebo (n=4)	p
Amplitude	Baseline	110 (100, 164)	105 (72, 137)	131 (113, 167)	148 (94, 187)	131 (116, 183)	0.59
	Follow-Up	149 (111, 178)	107 (92, 115)	121 (104, 152)	120 (103, 177)	97 (78, 152)	0.79
	Change	-18 (-63, 50)	-15 (-40, 15)	12 (-12, 15)	11 (-35, 47)	36 (28, 42)	0.68
	Sign test p	>0.99	0.51	>0.99	0.75	0.13	
Duration	Baseline	5.6 (5.0, 6.0)	5.2 (4.9, 5.7)	6.3 (5.8, 6.9)	6.4 (5.0, 6.9)	6.0 (5.2, 7.4)	0.43
	Follow-Up	5.8 (5.2, 7.4)	5.6 (5.4, 6.4)	5.8 (5.5, 6.3)	6.9 (5.6, 7.5)	7.0 (6.2, 7.9)	0.61
	Change	-0.7 (-1.3, -0.1)	-0.9 (-1.5, 0.4)	0.3 (-0.8, 1.1)	-0.9 (-2.1, 0.8)	-0.8 (-1, -0.5)	0.64
	Sign test p	0.29	0.51	>0.99	0.75	0.13	
Turns	Baseline	0.6 (0.5, 1.1)	0.8 (0.2, 0.8)	0.9 (0.8, 1.2)	0.9 (0.5, 1.5)	0.6 (0.5, 1.0)	0.42
	Follow-Up	1.0 (0.5, 1.6)	0.6 (0.5, 0.8)	0.6 (0.6, 0.9)	0.8 (0.6, 1.2)	0.6 (0.3, 1.2)	0.91
	Change	-0.3 (-1.5, 1.0)	1.0 (0.7, 1.4)	-2.0 (-2.4, -0.1)	1.3 (-0.4, 3.1)	-0.1 (-2.0, 2.4)	0.26
	Sign test p	0.73	0.18	0.18	0.34	>0.99	

Median (IQR) of pre-, post-, and change in scores (pre-post). P-values reflect Kruskal-Wallis test of change across groups and sign test p-value for within-group change. Amplitude (μV), Duration (ms), Turns (n).

Table III

Current Perception Threshold and Pressure Flow Changes by Medication Group

	Pseudoephedrine (n=8)	Imipramine (n=9)	Cyclobenzaprine (n=9)	Tamsulosin (n=10)	Solifenacin (n=8)	Placebo (n=4)	KW p
2000 hz							
Pre	2.50 (1.34, 2.89)	2.92 (1.94, 3.18)	2.22 (2.04, 2.71)	4.35 (2.98, 6.11)	3.36 (1.75, 4.60)	3.55 (2.56, 5.03)	0.39
Post	2.16 (1.54, 2.54)	4.67 (3.97, 5.11)	2.53 (2.34, 3.80)	5.66 (3.96, 6.41)	3.06 (2.21, 4.40)	3.82 (2.64, 4.20)	<0.01
Difference:	0.16 (-0.45, 0.59)	-1.94 (-3.77, -0.29)	-0.49 (-1.38, -0.12)	-0.98 (-2.32, 0.10)	0.04 (-1.31, 1.76)	-0.08 (-0.40, 1.15)	0.29
Sign test p	>0.99	0.29	0.18	0.34	>0.99	>0.99	
250 hz							
Pre	0.72 (0.39, 1.30)	0.81 (0.34, 1.04)	0.83 (0.55, 1.25)	1.22 (1.04, 1.58)	0.79 (0.46, 1.33)	0.90 (0.58, 2.14)	0.69
Post	0.79 (0.36, 1.05)	1.23 (0.75, 1.87)	0.82 (0.59, 1.02)	1.43 (0.58, 1.65)	0.64 (0.34, 0.97)	1.04 (0.60, 1.76)	0.09
Difference:	0.1 (-0.06, 0.40)	-0.49 (-1.00, 0.07)	-0.14 (-0.25, 0.24)	-0.13 (-0.49, 0.28)	0.14 (-0.15, 0.34)	0.12 (-0.19, 0.55)	0.32
Sign test p	0.51	0.51	0.51	0.75	0.45	0.63	
5 hz							
Pre	0.19 (0.10, 0.61)	0.16 (0.67, 0.23)	0.22 (0.08, 0.38)	0.17 (0.13, 0.39)	0.28 (0.08, 0.45)	0.12 (0.07, 0.54)	0.95
Post	0.09 (0.06, 0.18)	0.31 (0.10, 0.56)	0.17 (0.06, 0.36)	0.42 (0.16, 0.76)	0.08 (0.06, 0.13)	0.12 (0.07, 0.50)	0.05
Difference:	0.06 (0.02, 0.52)	-0.12 (-0.28, 0.05)	0.00 (-0.03, 0.15)	-0.08 (-0.31, -0.03)	0.06 (0.02, 0.34)	0.03 (-0.00, 0.04)	<0.01
Sign test p	0.03	0.73	>0.99	0.18	0.22	0.63	

Thresholds are reported as median (IQR) in milliseconds. Kruskal-Wallis p-values are reported to compare median scores in all study groups. Sign test p-values are reported to evaluate 2-week changes within each group.

Table IV

Pressure Flow measures

		Pseudoephedrine	Imipramine	Cyclobenzaprine	Tamsulosin	Solifenacin	Placebo	p
Maximum Flow Rate (Qmax)	Pre	26.4 (22.5, 28.0)	24.0 (21.7, 31.3)	41.9 (36.9, 57.8)	42.9 (30.6, 50.3)	31.6 (26.3, 62.2)	34.9 (18.4, 42.5)	0.25
	Post	32.3 (30.8, 45.7)	33.4 (22.6, 48.1)	42.9 (23.8, 47.5)	40.5 (37.4, 54.8)	33.9 (26.1, 49.0)	25.6 (20.7, 32.1)	0.30
	Change	-7.3 (-11.4, 2.5)	-6.6 (-10.2, 0.0)	10.3 (-1.4, 15.5)	-5.6 (-17.6, 1.7)	5.0 (-2.7, 10.3)	10.4 (-8.9, 16.9)	0.14
	Sign test p	0.51	0.29	0.51	0.51	0.73	0.63	
Average Flow Rate	Pre	7.2 (6.1, 9.8)	5.7 (4.4, 9.2)	10.0 (8.3, 12.0)	10.3 (8.6, 12.0)	8.5 (6.6, 12.2)	7.9 (5.0, 10.6)	0.32
	Post	8.1 (5.4, 9.0)	7.2 (4.9, 11.6)	9.5 (7.0, 11.7)	10.6 (7.7, 11.7)	7.8 (7.1, 11.5)	7.3 (5.9, 9.5)	0.44
	Change	1.0 (-1.8, 2.1)	-0.9 (-2.4, 0.8)	-1.0 (-3.4, 2.5)	-2.3 (-3.9, 2.0)	0.9 (-3.7, 3.4)	-0.3 (-4.1, 4.3)	0.87
	Sign test p	>0.99	0.51	>0.99	0.51	0.73	>0.99	
Detrusor Pressure at Qmax	Pre	49.8 (32.7, 52.5)	43.6 (39.1, 56.9)	53.0 (41.0, 70.6)	42.8 (31.7, 48.5)	50.5 (25.0, 63.9)	33.1 (19.4, 35.5)	0.23
	Post	22.0 (21.5, 32.7)	49.0 (31.8, 57.1)	53.7 (47.8, 71.5)	48.2 (39.7, 59.2)	66.5 (34.4, 87.0)	46.0 (40.1, 52.9)	0.05
	Change	21.0 (8.2, 29.1)	-5.1 (-6.4, 2.1)	-4.7 (-10.1, 13.5)	-8.2 (-27.5, 10.4)	-2.6 (-32.0, 8.0)	-11.9 (-31.1, -7.0)	0.15
	Sign test p	0.18	0.51	>0.99	>0.99	0.45	0.13	
Time to Qmax	Pre	16.5 (7.4, 21.1)	25.6 (10.0, 43.8)	9.1 (8.5, 26.0)	14.0 (10.4, 23.1)	12.4 (9.1, 50.6)	34.7 (6.1, 83.5)	0.89
	Post	13.0 (10.9, 17.0)	10.4 (7.3, 26.6)	10.3 (3.6, 17.3)	6.8 (4.6, 21.5)	11.6 (9.1, 16.5)	8.9 (7.0, 20.3)	0.81
	Change	1.1 (-7.7, 9.9)	6.8 (-1.0, 22.5)	4.9 (-2.5, 15.7)	2.2 (-7.5, 7.8)	1.4 (-4.5, 40.9)	27.2 (-0.9, 63.3)	0.81
	Sign test p	>0.99	0.51	>0.99	0.51	0.73	0.63	
Voided Volume	Pre	312 (304, 330)	298 (261, 312)	320 (317, 353)	343 (279, 365)	329 (321, 362)	304 (189, 324)	0.10
	Post	320 (254, 326)	307 (260, 329)	308 (292, 312)	338 (307, 387)	298 (296, 309)	309 (297, 338)	0.24
	Change	24 (-22, 47)	0 (-38, 46)	25 (6, 101)	-21 (-90, 4)	27 (19, 56)	-21 (-130, 7)	0.07
	Sign test p	>0.99	>0.99	0.18	0.34	<0.01	0.63	
Residual	Pre	0 (0, 0)	2 (0, 39)	0 (0, 0)	0 (0, 21)	0 (0, 0)	1 (0, 112)	0.18
	Post	0 (0, 46)	0 (0, 40)	0 (0, 8)	0 (0, 2)	2.5 (0, 5)	0 (0, 7.5)	0.99
	Change	0 (-24, 0)	0 (-10, 2)	0 (-8, 0)	0 (0, 19)	-2.5 (-5, 0)	1 (-15, 112)	0.41
	Sign test p	0.25	>0.99	>0.99	0.38	0.13	>0.99	

Wilcoxon sign test p-values are reported to evaluate 2-week changes within each group.

Sign tests evaluate change within each group.