Lessons on Urethral Lidocaine in Urodynamics ("LULU"): Impact of intraurethral lidocaine on cystometric parameters and discomfort, a RCT

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Abstract

Complex cystometric studies are often conducted to assess for and clarify incontinence. In current practice, intraurethral aqueous jelly is used to lubricate and insert urethral catheters for these studies. Patients commonly complain of urethral discomfort and/or pain with catheter insertion. Two percent lidocaine jelly has not been routinely used in practice for cystometric catheter insertion due to the unknown impact it may or may not have on complex cystometric parameters. Previous studies evaluating the use of 2% lidocaine jelly for office cystoscopy have not proven to consistently provide substantial relief of discomfort. However, a recent study using 2% lidocaine jelly for catheter insertion during complex cystometric evaluation did demonstrate significant relief of discomfort. Some studies have evaluated 2% lidocaine jelly use during complex cystometric evaluation in neurogenic populations, indicating a surprising increase in detrusor overactivity with 2% lidocaine jelly use. However, few studies have evaluated the impact of 2% lidocaine jelly in a non-neurogenic population. *If use of 2% lidocaine jelly was found to improve discomfort during complex cystometric studies in this patient population without substantially altering the study's findings, this could impact clinical practice in an important way.* Herein, we propose a randomized, double blind, controlled trial for patients undergoing complex cystometric evaluation. Patients will undergo routine complex cystometric evaluation for acquisition of baseline data using a small amount of intraurethral aqueous jelly for catheter lubrication. Then, they will be randomized to instillation of either placebo (additional intraurethral aqueous jelly, 5ml) or intraurethral 2% lidocaine jelly. Participants then undergo complex cystometry a second time. Normal variations in studies with placebo will be compared to variations within the 2% lidocaine jelly group to determine if

cystometric parameters are altered in any clinically important ways. Patient discomfort will also be evaluated by both the patient and the urodynamics advanced practice nurse.

Purpose of Study

This trial will assess whether use of intraurethral 2% lidocaine jelly meaningfully impacts sensation during filling (i.e., a change of more than 25% of first sensation, first desire to void, strong desire to void, or maximum cystometric capacity) and determine whether the use of intraurethral 2% lidocaine jelly meaningfully impacts pain/discomfort, filling metrics, and voiding metrics.

Hypothesis: In women without known voiding dysfunction being assessed for urinary incontinence by urodynamic studies (UDS), the use of intraurethral 2% lidocaine jelly during cystometry and pressure flow study (PFS) will not meaningfully impact sensation during filling and will decrease discomfort for patients.

Significance of the Study

Patients often complain that urodynamic bladder testing is uncomfortable and even painful, for some. Intraurethral lidocaine 2% jelly has been used to demonstrate increased patient satisfaction with comfort during this procedure. However, the effect of intraurethral lidocaine jelly on urodynamic test results has not been fully studied. Considering that lidocaine jelly is a local anesthetic, it may have a numbing effect, potentially increasing time to first sensation and bladder capacity, decreasing ability to empty the bladder, and may potentially mask detrusor overactivity (DO). However, if the local anesthetic has no effect on urodynamic

test results, one may consider changing practice to include intraurethral 2% lidocaine jelly with urodynamic testing to improve patient satisfaction and comfort.

Background of the Problem

Standard teaching for the performance of UDS is that after completion of the un-instrumented uroflowmetry, cystometry is completed using plain intraurethral aqueous jelly for insertion of the transurethral pressure catheter. Clearly, this can be a source of discomfort and pain for the patient. An alternative to plain lubricant, such as 2% lidocaine jelly, may relieve discomfort for patients but could theoretically impact or distort important cystometry findings, e.g., first or strong sensation and presence/absence of DO. Further, voiding could be affected if numbing the urethra blunts sensory nerves that serve to amplify bladder contractions and maintain efficient bladder emptying.(1, 2) A recent study of healthy volunteers randomized to intraurethral aqueous jelly versus 2% lidocaine jelly did not identify any detriment to voiding efficiency using lidocaine but did find greater interrupted flow patterns and more electromyography (EMG) activity during micturition when using lidocaine.(3) This study found no difference in pain perception between groups. Similarly, a meta-analysis of 9 randomized trials assessing lidocaine jelly versus plain jelly lubrication for office flexible cystoscopy did not suggest a significant difference in the efficacy of pain control using lidocaine.(4) Conversely, a different trial that compared water-based lubricant and 2% lidocaine jelly for UDS in women did find substantially less pain for patients using the lidocaine jelly.(5)

Neither of the above two trials of UDS in women compared participants *to themselves* to determine how filling and voiding metrics may change before/after lidocaine jelly was applied. It remains uncertain whether these parameters would change in clinically meaningful ways with the addition of lidocaine, and the possible benefit of lidocaine—i.e., decreased discomfort for the

patient—has not been definitively proven or disproven. Using patients as their own controls, this proposal aims to determine if the use of intraurethral 2% lidocaine jelly during cystometry and pressure flow study impacts filling and emptying measures while assessing patient discomfort at various time points during their procedures.

One prior study utilizing patients as their own control evaluated patients with urgency but no urge incontinence and reported DO on a repeat cystometry after no DO was observed on initial cystometry, indicating that lidocaine jelly may increase DO. (6) Additional studies have explored the effect of intravesical lidocaine on cystometric results within neurogenic populations, but few studies to date have looked at the effect of lidocaine jelly on cystometric parameters and DO in the normal population of patients with incontinence in the absence of neurogenic disease.

Methods & Analyses:

Urodynamic testing will be performed in procedure rooms by qualified advanced practice nurses in the field of female pelvic medicine and reconstructive surgery (FPMRS). Eligible patients meeting inclusion criteria will be consented for study participation prior to urodynamic testing. Standard urodynamic testing will be conducted, i.e., first un-instrumented uroflowmetry, then cystometry (including leak point pressure assessments, LPP) and a pressure flow study (PFS) with 1-2ml of aqueous jelly in the urethra. UDS will be completed with a dual-sensor 7-Fr catheter inserted through the urethra into the bladder and a second 7-Fr catheter in the vagina. Patch electrodes will be adhered peri-anally in the standard fashion for EMG. Patients will be filled with room-temperature sterile water at 60mL/min. Volumes at first sensation, first desire to void, strong desire to void, and maximum cystometric capacity will be recorded. Presence or absence of DO during cystometry will be documented. Other measures (detailed below) will be recorded during cystometry and PFS. After the patient voids for her first PFS, she will be

randomized (1:1) to either additional water-based lubricant (placebo) or lidocaine 2% jelly (5mL).

Randomization will be stratified by presence/absence of DO on the initial cystometry. A balanced randomization scheme will be generated with equal numbers of placebo and lidocaine. Identically appearing study drug syringes will be placed in consecutively numbered opaque envelopes by an unmasked study coordinator not participating in the procedure visit or study analyses. Both the urodynamic nurse and patient will be blinded to the type of lubricant. After randomization, the urethral catheter will be removed and 5mL of either placebo or 2% lidocaine will be injected into the urethra. The patient will sit for 5 minutes to allow lidocaine to take anesthetic effect. The catheter is then replaced, and cyostometry and PFS will be repeated. A continuous pain scale from 0 to 100 (visual analog scale) will be used by the patient to report her pain level during cystometry #1 (during catheter insertion and at maximum cystometric capacity), PFS #1, overall UDS #1, cystometry #2 (during catheter insertion and at maximum capacity), PFS #2, and overall UDS #2 discomfort. At the end of the procedure, the urodynamic nurse will also provide a subjective assessment of patient discomfort.

Planned Analyses & Power Calculation:

The primary outcome is the volume at which a participant perceives a strong desire to void. Statistical analyses will estimate the confidence interval for this outcome measure between the two arms of the study (i.e., using 2% lidocaine vs. aqueous jelly) through the standard calculation for the difference in means when standard deviations of the two arms are unknown, i.e., through the Student's t distribution. As it is thought that there will be no difference in the mean value of the two arms, the study will be designed as an equivalence trial. Since DO may alter findings, it is planned to stratify the randomization for DO in order to insure a balance between the arms for this variable. Prior to randomization, each patient will undergo a

baseline standard cystometry without lidocaine, and DO (present or absent) will be obtained from this evaluation. The observations from this *baseline cystometry* provide for an interesting and novel analysis: the baseline measure of volume at strong desire to void may serve as a covariate to adjust for individual patient variability. That is, comparisons of the difference in the baseline measure and the experimental measure will provide a patient "standardized" evaluation of her additional volume following the baseline. Analysis of the primary outcome will account for patient variability with standardization by the value of the baseline measure.

Beyond the primary outcome cystometric evaluations are numerous secondary outcomes such as pain/discomfort with filling and emptying, presence/absence of DO, and emptying metrics including flow rates, post-void residual, EMG activity, and detrusor pressures (max and at peak flow). Continuous measures will use the Student's t distribution as with the primary outcome. Binary and ordinal outcomes will be evaluated using logistic regression. The use of logistic regression for the ordinal outcomes is through the proportional odds model and combines with the cumulative logit link. All of these evaluations may incorporate the baseline urodynamic study metrics as a covariate (as described above for the primary outcome).

Assuming an average strong desire to void during cystometry (with plain lubricant gel) of 300mL, standard deviation of 100mL (3, 5), a non-inferiority margin of 75mL (i.e., 25% of 300mL), Power (1-β) of 0.80 and α of 5%, **31 participants per study arm** (i.e., 62 total) are needed to demonstrate "equivalence" in sensation during cystometry using plain lubricant gel versus lidocaine gel. Allowing for 12% participants being unable to complete the second half of the UDS, a total of **35 participants per study arm** (i.e., **70 total participants**) will be enrolled.

In the placebo group, the data from the two filling cystometry tests can be compared (sensation metrics, DO presence/absence, and compliance) to establish "normal variability". Anecdotally, patients commonly tolerate a second fill better. With this normal variability better

defined, we will be able to assess for changes attributable to the lidocaine in the group receiving the anesthetic jelly—specifically, whether volume of first sensation or bladder capacity is altered. We can also assess lidocaine's impact on bladder emptying by comparing voiding metrics. In patients with repetitive DO on their first cystometry, we will be able to assess whether they continue to demonstrate DO on their second cystometry with lidocaine.

Primary Outcome: Assess whether use of intraurethral 2% lidocaine jelly meaningfully impacts sensation during filling (specifically, strong desire to void).

Secondary Outcomes: Determine whether the use of intraurethral 2% lidocaine jelly meaningfully impacts the following:

Pain/ Discomfort

1. Measured by a visual analog scale during cystometry (catheter insertion and at maximum cystometric capacity), during PFS, and post-procedure
2. Provider perception of patient discomfort

Filling Metrics (besides sensation)

3. Presence/ absence of detrusor overactivity (DO)
4. Compliance (ΔVolume/ΔP_{det})

Voiding Metrics

5. Maximum flow rate (mL/sec)
6. Voiding pattern: normal, intermittent, interrupted
7. Detrusor void (yes/no) vs. Valsalva vs. mixed void
8. Voided volume and post-void residual (mL)
9. Voiding efficiency, i.e., voided volume/ (voided volume + PVR) (3)

10. P_{det}max (cm H_2O)
11. P_{det}peak flow (cm H_2O)
12. EMG activtity

Participant Eligibility

Inclusion Criteria	Exclusion Criteria
Female patients	Diagnosis of pelvic pain, interstitial cystitis, or bladder pain syndrome
>18 years of age	Known neurogenic disease impacting voiding/ continence (e.g., Parkinson disease, multiple sclerosis, myasthenia gravis, recent stroke)
Already scheduled (or being scheduled) for UDS to assess urinary incontinence	Active UTI
Able to speak and read in English	Pelvic organ prolapse that is unable to be easily reduced
	Pregnancy or breastfeeding
	Allergy or hypersensitivity to lidocaine or local anesthetics

Ethical Conduction

The study site will have a principal investigator and study coordinator, both skilled in conduct of IRB-approved clinical research, responsible for obtaining and appropriately documenting informed consent of each patient before beginning any study related procedure. Once patients have completed informed consent and have enrolled, each participant will be assigned a Participant ID that is an anonymous patient study number. Only the research coordinators and the site PI will have access to the list linking medical record number to participant ID. A research coordinator not involved in the care of the patient will have knowledge of whether a patient received lidocaine jelly or placebo (water based lubricant). The research coordinator and site PI will have the responsibility for securing original source documents containing any identifiable patient data. Each patient's study documents will be kept

under an individual tab in a binder, and the binder(s) will be stored in a locked cabinet and office. All information collected about the subject during the course of this study will be kept confidential to the extent permitted by law. Besides the specified study team, other access to study records or data would only be by the IRB or the study sponsor (SUNA) at their request. All information the subject has provided will be kept in a research record and stored in a locked office and on a secure, password protected computer. Research information will not be made a part of the participant's regular medical record. There is no personal information (name, social security number, etc.) about the subject that is associated with subject's research data; a Participant ID number will indicate a subject's identity on the research records. Patients routinely are escorted to exam rooms alone, but they may choose to have a family member or spouse present if that is her preference. The informed consent and the history and exam findings will be collected in a private room. The informed consent will be written and provided in English. Either the research coordinator or another member of the research team (PI or co-investigator) will be obtaining the consent, and the patient will sign and date/time her name to indicate understanding, which will be observed and countersigned by the person obtaining the consent. No matter what position of authority a research member has, the subject will be assured of the right to refuse to participate and/or the right to withdraw at any point in the study. The urodynamics nurse will be trained to minimize discomforts during the procedure.

A patient's Participant ID number will be provided to the central data collecting center (UTSW) with no personal information. Further, data will be entered using REDCap, a Web-based, HIPAA-complaint tool used by many major medical institutions. REDCap facilitates electronic form building and data collection. It has an automatic audit trail, report builder capability and data quality module. REDCap can export data to SAS, SPSS, R, STATA, or Microsoft Excel. The REDCap database will reside on a secure UTSW server with continuous backup. Only authorized personnel with designated rights can access this study, and that at

various levels. For example, a coordinator will be able to enter and check data, but cannot design screens. REDCap provides a protocol event schedule where specific forms are linked to events (visits) in the protocol. Authentication used in the REDCap application is compliant with the UT Southwestern Medical Center's Health System password and security standards.

Project Timeline

Research Task	Projected Time Course
Completion of IRB application, site review, project start-up processes, registration with *clinicaltrials.gov*	3 months
Participant recruitment, data collection (anticipating 5-6 procedures/ month)	12 months
Data analyses	1 month
Manuscript preparation/ submission/ edits, SUNA presentation preparation, final data entry in *clinicaltrials.gov*	2 months
TOTAL	**18 months**

Study Budget

Please see appendix A. Given that we will be conducting a 2nd CMG and PFS on patients already having urodynamic studies performed, we will not need any additional supplies other than the randomized jelly syringes. A registered nurse will prepare blinded jelly syringes of lidocaine vs. aqueous jelly solution. Research coordinator/urodynamicist time is included in the study budget. Salary support includes time for the nurse practitioner and/or physician(s) to submit to the IRB, VELOS, clinicaltrials.gov, and data entry within REDCap system, as well as time for consenting patients and performing additional complex cystometrogram with pressure flow study. It is estimated that the consent process and additional procedure time will be roughly 150 hours for 70 patients over the course of 12 months. Additional data entry support may be required, and this is calculated in the budget, as well.

Research Environment

UT Southwestern Medical Center (UTSW) is a large, research-oriented university, which provides an exceptional and highly interactive scientific and intellectual environment, as well as an extensive array of core laboratory and support facilities. UT Southwestern's research faculty include 22 members of the National Academy of Sciences, 15 members of the Howard Hughes Medical Institute, and 6 Nobel Laureates. The university supports an extensive number of seminar series, which routinely host outside speakers who are leaders in their fields. In addition, individual units and laboratories on campus support a wide variety of works-in-progress meetings and journal clubs, which provide abundant opportunities for scientific and collaborative interactions. The environment at UTSW is structured to encourage and support interactions between basic scientists and clinicians. The intellectual environment in the Department, as well as in neighboring departments and across campus, is outstanding. It provides a tremendous resource of expertise to the PI and SUNA for potential proposed studies. Numerous investigators on campus, who are leaders in their fields, work in areas closely related to the research interests of SUNA.

UTSW Outpatient Building FPMRS Clinic: The UTSW Female Pelvic Medicine & Reconstructive Surgery (FPMRS) clinic is staffed by Drs. Rahn, Schaffer, Florian, and Corton, 2 FPMRS fellows, and 2 nurse practitioners. The clinic is located in a building adjacent to Clements University Hospital. This outpatient clinic is fully equipped with 5 examination rooms and a urodynamic laboratory. Available equipment includes a Laborie® Aquarius XLS urodynamics system, Wolf® cystoscopy equipment, 2 portable Pathways 10 electrical stimulation units, 3 Uroplasty Urgent PC® Neuromodulation Systems, and a urodynamic chair. One bladder scanner is present in the clinic. Physicians see patients in nine ½-day sessions per week in this clinic and perform office diagnostic cystoscopy, periurethral bulking and Botox® injection. The nurse practitioners see patients 5 days per week for non-surgical management, including pelvic floor rehabilitation, pessary management, biofeedback, electrical stimulation and urodynamics. One nurse practitioner (the PI for this proposal) is permanently housed in this clinic so that she is

available 5 days per week for recruitment as well as treatment of patients in clinical studies. She conducts approximately 24-40 urodynamic bladder tests per month. In 2013/14, 1,721 patients were seen in the UTSW FPMRS Clinic.

Our division also participates in NIH funded multi-site clinical research trials through the Pelvic Floor Disorders Network, providing a strong foundation in clinical research. Research support is available by on-site registered nurses, clinical research coordinators, & biostatisticians, who can aid in the statistical data analysis and data entry.

The principal investigator, Christina Hegan, MS, APRN, WHNP-BC, is a current member of the Society of Urologic Nurses & Associates (SUNA), serving as Urodynamics Special Interest Group Leader. She has also presented at the 2018 SUNA urologic conference meeting, served on two patient fact sheet task forces, and recently submitted an abstract for presentation at the 2019 SUNA urologic conference. She has achieved several accomplishments in the last two years, including publication of two literature reviews online through the Interstitial Cystitis Association (ICA), three magazine articles published in the ICA Update, and a chapter published in an international textbook. She is currently serving as an interventionist in three NIH funded multi-site clinical research trials through the Pelvic Floor Disorders Network, and she has completed one phase 2 multi-site industry sponsored clinical trial as co-investigator.

Faculty sponsor & co-investigator, Dr. Joseph Schaffer, will be an important mentor in this project. With his many years of experience in pelvic floor medicine and reconstructive surgery, Dr. Schaffer has a strong record of accomplishment, producing quality based, statistically significant, and well-designed studies.

Additionally, co-investigator Dr. David Rahn will be an integral contributor and mentor on this project. Dr. Rahn also has a strong record of accomplishment, including receiving a recent

NIH grant for an investigational trial studying the role of vaginal estrogen in surgical healing. His study may help change practice by providing substantial proof or disproof of vaginal estrogen's ability to aid in the healing process, which has long been speculated.

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