PROTOCOL
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The Impact of Retropubic Lidocaine vs Saline on Postoperative Urinary Retention Following Midurethral Sling: A Randomized Placebo Controlled Trial

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Objective

To compare the impact of retropubic lidocaine versus normal saline on postoperative urinary retention in patients undergoing retropubic midurethral sling placement.

Background/Hypothesis

Stress urinary incontinence (SUI) affects millions of women worldwide and has a profound impact on the quality of life of older individuals, their subjective health status, levels of depression and need for care[6].Midurethral sling placement was introduced in 1995 and remains the current gold standard for surgical management of SUI[5].Although the advantages of midurethral sling surgery include its high success rates and minimally invasive approach, approximately 10-50% of women experience acute postoperative urinary retention and are subsequently sent home with an indwelling foley catheter or clean intermittent self catheterization[2].Urinary retention is anxiety provoking for most patients and adds morbidity, cost, and increased utilization of healthcare resources[2].Additionally, catheterization of the urinary tract results in increased risk of urinary tract infection and potential need for antibiotics[8].

Several mechanisms could explain the inability to void postoperatively, including nerve conduction impairment from anesthesia. Multiple studies have investigated the use of various types of anesthesia and downstream effects on postoperative urinary retention. It is postulated that denervating the regional pelvic nerves for pain control may lead to denervation of the bladder for a transient period of time, blocking both the afferent and efferent pathways of the voiding mechanism, affecting the urethral retro-resistance pressure, and impacting urethral length thereby contributing to voiding dysfunction postoperatively[3,4,11].

Two of the most commonly used local anesthetic agents in surgical practice are lidocaine and bupivacaine. Lidocaine as a local anesthetic is characterized by a rapid onset of action, typically within 2-5 minutes of injection, and intermediate duration of efficacy. Therefore, it is often favored in the outpatient setting for pre-incisional injections. Of note, however, its effects generally only last up to 2 hours. Epinephrine (adrenaline) vasoconstricts arteries, delaying the resorption of lidocaine, and thus almost doubles the duration of anesthesia. Bupivacaine, on the other hand, has a slower onset of action, approximately 5-10 minutes after injection, but its effects last much longer, typically about 4-8 hours[1].

Our current practice of midurethral sling placement involves injection of lidocaine with epinephrine into the retropubic and suburethral space with the threefold purpose of hydrodissection, hemostasis, and pain reduction. Interestingly, several studies report varying rates of postoperative urinary retention and postoperative pain depending on the type of local anesthetic used (if any) for hydrodissection; however, the data is sparse and invites a more thorough investigation. For example, one study investigated the use of bupivacaine versus normal saline injected suburethrally on postoperative voiding function and pain in patients undergoing retropubic midurethral sling. These authors found no difference in voiding dysfunction between the study and placebo groups; however, the use of bupivacaine did lower pain scores at 6 hours postoperatively[5].A similar study compared urinary retention and pain control when bupivacaine versus saline for hydrodissection is used while placing tension-free vaginal tape midurethral slings. Hydrodissection fluid was placed subcutaneously, into the space of Retzius bilaterally, suburethrally, and periurethrally. These authors concluded that bupivacaine did not increase the risk of failing a postoperative voiding trial; however, there was a trend toward a difference with a 19% reduction in voiding trial success (47% pass rate in the bupivacaine group vs 66% in the saline only cohort, $p = 0.14$) and a statistically significant elevated PVR in the bupivacaine group compared with the control group. In addition, bupivacaine was not seen to improve immediate postoperative pain after placement of a tension-free vaginal tape[2].A third study[7]reported that while bupivacaine did decrease postoperative pain scores following retropubic midurethral sling placement, reported pain was in fact low in both the intervention and placebo groups. Of note, there was also a trend toward increased voiding trial failure in the bupivacaine group (33% vs 18% in the controls ($p = 0.082$)). In this study, injections were performed into each of the two trocar paths “deep behind the pubic bone” and into the vaginal incision.

The aforementioned studies vary considerably in the quantity and composition of local anesthetic used intraoperatively, the location of injection, and in the administration of voiding trials postoperatively. Sample size of each study was also small and thus perhaps underpowered to detect statistically significant differences. Therefore, based on the limited existing data, we hypothesize that patients receiving retropubic normal saline compared to local anesthetic (e.g., lidocaine) will have a reduction in rates and duration of postoperative urinary retention following retropubic midurethral sling placement.

Aim 1: to compare the incidence of urinary retention following retropubic midurethral sling placement in those women receiving normal saline vs lidocaine for retropubic hydrodissection. We will compare rates of failed retrograde voiding trials between patients receiving normal saline and those receiving the same quantity of lidocaine. This will be completed using a standardized retrograde voiding trial 1-2 hours postoperatively (as outlined in "Data and Statistical Methods" below). We hypothesize that patients receiving normal saline will have a reduction in postoperative urinary retention following retropubic midurethral sling placement.

Aim 2: to assess postoperative pain in women receiving retropubic normal saline vs lidocaine during midurethral sling placement. Postoperatively, subjects will be asked to assess their pain using a VAS scale administered by nursing personnel at 2 hours (+/- 30 minutes) and again at 6 (+/- 30 minutes) hours following surgery, during the time of routine vital sign assessment. The subsequent pain assessments will be completed by the patient via an at-home form from discharge through postoperative day #7. Narcotic use will be queried through the electronic medical record as well as with a pain diary administered at time of discharge until postoperative day #7.

Aim 3: to examine differences in patient satisfaction and quality of life following retropubic midurethral sling placement between women receiving retropubic normal saline vs lidocaine at time of midurethral sling placement. Differences in patient satisfaction will be compared using multiple questionnaires at multiple time points. Patients will be asked to complete the American Pain Society Patient Outcome Questionnaire (APS-POQ-R) on POD #1. Patients will be asked to rate their satisfaction with surgery on a Likert scale (with 1 being the least satisfied and 5 being the most) at their 6-week postoperative follow up visit. We hypothesize that women receiving normal saline for hydrodissection will have improved patient satisfaction, mood, and quicker return to activities, as evidenced by lower APS- POQ-R scores and higher Likert scores compared to those receiving lidocaine.

Study Entry and Recruitment

Subjects with stress incontinence or stress-predominant mixed urinary incontinence who are scheduled to undergo a retropubic midurethral sling with or without concomitant anterior repair at West Penn Hospital, Bethel Park Health and Wellness Pavilion, Wexford Health and Wellness Pavilion, and Jefferson Hospital of the Allegheny Health Network, will be offered participation in the study. Study subjects may also be recruited via the MyChart app. The MyChart app is a secure app accessible only by the patient. Only the patient can access their medical information through this app by setting up a secure account using their social security number, birthday, username, and password. The patient can log in securely by providing their username and password, or via biometrics (i.e., face recognition). If the research staff reaches out to the subject via telephone and the subject does not answer, a follow-up message will be sent to the subject via the MyChart app, with the statement that initial contact attempt was made by phone. The message will include the following:

A recent review of your records indicated that you may be eligible to participate in an ongoing research study. The Retropubic Lidocaine study is looking to determine if the numbing medicine we standardly use during surgery impacts your ability to empty your bladder postoperatively. If you are interested in participating, you would be randomly selected to get our standard numbering medicine (lidocaine and epinephrine) or placebo (saline and epinephrine) at the two sling exit sites in your pubic area while in the operating room. This study does not require any additional in-person visits. There will be a few questionnaires we would ask you to complete during your recovery. If you are interested in learning more about our study, please call (412) 578-4216, or email shannon.buono@ahn.org. If you respond to this message indicating your interest, you are giving your permission for the study staff to receive your phone number and/or email address indicated in your medical records and reach out to you directly.

Inclusion criteria includes the following: age 18 years or older, English speaking, and competent to give consent. Exclusion criteria includes a known intolerance or allergic reaction to local anesthetics, planned spinal anesthesia for the procedure, planned concomitant prolapse repair other than anterior repair, or preoperative voiding dysfunction as evidenced by a post-void residual (PVR) of 150 mL or greater. On average, our institution treats 60-80 patients per year with midurethral slings.

Informed consent will be obtained at the preoperative appointment. Demographic information including age, weight, height, body mass index (BMI), allergies, obstetrical, gynecological, medical, and surgical history will be collected from those subjects who agree to participate. Preoperative bladder testing obtained as part of routine clinical care will also be recorded,

Patients will be randomized in the preoperative area on the day of surgery to prevent randomization of patients who may go on to cancel or postpone surgery. Randomization will be created using a random numbers table with blocking into groups of 4. On the day of surgery, the operating room pharmacist will prepare 20 cc of either study drug, 0.5% lidocaine with epinephrine 1:200,000, or normal saline with epinephrine 1:200,000 in identical appearing 20cc syringes to be injected retropubically. Our group's routine clinical practice will inject the randomly assigned 20cc syringe retropubically along the path of the midurethral sling trocars. Suburethral injection of local anesthetic will be performed at surgeon discretion. Surgical teams, anesthesia teams and patients will be blinded to allocation assignment. The investigational drug pharmacist will maintain the randomization sequence.

Standard postoperative care will then be followed. Before discharge, as part of routine clinical care, all subjects will undergo a postoperative voiding trial as outlined below. A routine postoperative evaluation will be performed by the primary surgeon at a 6-week interval following surgery.

Table 1. Timeline of data collection

			Time of Data Collection/Evaluations					
Data	Baseline	Intervention	Surgery	Postoperative assessment				
				2 h (+-30 mins)	6 h (+- 30 mins)	24h	Week 1	Week 6
Retrograde Voiding Trial				x				
VAS pain score	x			x	x			
Narcotic requirements	x		x	x	x	x	x	
Pain Diary						x	x	
Demographic factors	x							
Intraoperative factors			x					
Side effects (APS-POQ-R)						x		
Satisfaction Likert Scale								x
Patient satisfaction and mood (APS-POQ-R)						x		

Variables and measures

Postoperative Urinary Retention

The primary outcome is postoperative voiding trial failure, defined as being discharged from the hospital with an indwelling catheter or instructions for clean intermittent self-catheterization (CISC). Duration of catheterization will also be measured and recorded on the postoperative diary. As part of routine clinical care, a retrograde voiding trial will be completed 1-2 hours postoperatively using the following protocol and parameters:

Retrograde Voiding Trial:

- Confirm that all urine is drained from the bladder with the indwelling catheter in place
- Backfill 300 mL of sterile saline into the bladder through the indwelling catheter
- Clamp catheter, deflate the balloon, and remove the catheter
- The patient should be asked to void within 1 hour into a urine collection container in the toilet
- Record voided volume

Passed void trial: patient voids at least 200 mL Failed void trial: patient voids <200 mL or cannot void at all within 1 hour of test

In the event that all 300 mL of sterile saline are unable to be instilled into the bladder due to patient discomfort or bladder spasms, the test is still considered passed if >2/3 of instilled bladder volume is voided.

All patients who meet criteria for failure as described above are discharged from the hospital with either an indwelling catheter or CISC.

Postoperative pain

Visual Analog Scale (VAS) pain: Pain will be measured 2 hours (+/- 30 Minutes) and 6 hours (+/- 30 minutes) following surgery by VAS pain scales. VAS pain scales are unidimensional measures of pain intensity that are easily completed and scored. Subjects place an “X” on a 10-centimeter (cm) VAS line at the point that represents their pain intensity. The score is calculated by measuring the distance in millimeters (mm) along the 10 cm line where 0 represents “no pain” and 10 represents “worst pain.” Scores range from 0-100mm. They have been widely used in diverse populations to assess pain. VAS pain scores will be used as the outcome measure in this study because they are easy to complete and because they are easily compared to prior studies. The 2-hour VAS score will be completed prior to discharge. The 6-hour VAS score will be returned via mail since patients are routine discharged a few hours after sling surgery.

Pain diary: Pain diaries will also be used in order to assess postoperative pain in the home setting. Pain diaries will be provided to all participants at time of discharge to be completed from POD #0 until postoperative day #7. Patients will be asked to register their pain intensity at home on a VAS scale once every morning and every evening. These will be returned by the patient via mail in self-addressed stamped envelopes.

Narcotic requirements
Morphine equivalents: Doses of narcotic pain medications administered to subjects during the intra- and postoperative period will be abstracted from the EMR. Narcotics will be converted to morphine equivalents, in grams, using an equianalgesic dosage table. Narcotic use following hospital discharge will be measured by a 7-day diary, which will also be converted to morphine equivalents. Morphine equivalents have been widely used in the study of postoperative pain.

Patient satisfaction and mood
APS-POQ-R: The APS-POQ-R is a validated questionnaire used to assess QOL and satisfaction with pain control over the 24 hours following an operation. It is preferred over more global measures of QOL since it is validated for acute pain in the setting of recent surgery. This questionnaire was designed to assess satisfaction with pain control and impact of pain on mood and emotional well-being. It contains twelve items across six subscales: pain severity and relief, impact of pain on mood/emotions, adverse effects, satisfaction, participation in decision making, and non-pharmacological methods of pain management. We are specifically interested in the impact of pain on satisfaction (item 9), mood/emotions (item 5 a-d) and adverse effects (item 6 a-d, see below). These subscales use a 0-10 rating scale. This measure has good internal consistency (alpha=0.85) and validity.

Patient satisfaction
Likert Scale: The Likert Scale is the most widely used approach to scaling responses in survey research and contains five tiered responses which users quantify on a visual analogue scale. The administration of such is easily comprehended, provides an effective and clinically relevant means of assessing patient satisfaction, and can readily be used in clinical practice. To determine satisfaction, patients will be asked to rate their satisfaction with surgery on a Likert scale (with 1 being the least satisfied and 5 being the most) at their 6-week postoperative follow up visit.

Sample Size Calculation

The rate of postoperative urinary retention following midurethral sling at our institution is 35% (data unpublished). To detect a clinically significant reduction of postoperative urinary retention of 20%, 72 subjects per group would be needed to provide 80% power with a two-sided alpha of 0.05. After adjusting for a 5% loss to follow-up rate, 75 subjects per arm would be required.

Data Collection & Storage

The patient's electronic medical record will be reviewed for demographic and surgical information. Data entry will be completed and stored on a password protected network drive within the health system firewalls. Each patient will be assigned an alphanumeric code for data collection. The key linking patients with their respective codes will be recorded in an encrypted file on password-protected computer in the research coordinator's locked office. The de-identified parameters will be tabulated in Excel spreadsheets. Security will be maintained by limiting login access to members of the study team. Data security will be monitored at monthly research meetings.

Potential Risks, Issues, and Solutions

General risks associated with the study include the possible loss of confidentiality and increased pain secondary to lack of lidocaine in the placebo arm. Since clinical practice regarding retropubic lidocaine varies widely and many surgeons do not use lidocaine or do not use any form of hydrodissection retropubically, we do not think that a placebo of normal saline is unreasonable or places the patient at undo risk. Because both placebo and study drug will contain epinephrine, bleeding risk should not differ between the groups.

Patients that do not undergo surgery after enrollment: To prevent non-adherence to the study intervention, we will not randomize subjects until the day of surgery in the preoperative area. Once randomized, all participants will be followed and analyzed in an intention to treat analysis. Subjects who are lost prior to randomization, for example those that cancel surgery or are not medically cleared will be excluded from analysis.

Competing events: We plan to exclude those women with severe dementia that will be unable to accurately complete study questionnaires/VAS pain scores. Because patients with terminal diseases or those expected to have poor follow-up do not usually receive elective sling surgery, these events should not occur in a high percentage of subjects, if at all.

Missing data: Subjects with missing void trial results or those that do not complete/return questionnaires and diaries will still be included in the final analysis. To reduce the chance of missing data, members of the study team will call subjects or personally visit them in their hospital room to provide reminders for completion of VAS pain scales and APS-POQ-R questionnaires. Study nurses will call the patient at 1 week to remind them to complete and return their pain diary. We will also emphasize the importance of the data and need for completeness with subjects at the time of enrollment. By keeping data collection short (limited short forms with study participation ending on POD#7), we will not overburden the subjects.

Study Duration

This study will include patients who undergo midurethral sling placement. Enrollment for this study is expected to last for two years in order to achieve adequate sample size. Once enrolled, patients will be followed from date of surgery until six week postoperatively.

Table 2. Timeline

	Year 1				Year 2				Year 3			
	Q 1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Train research staff												
Baseline data collection												
Follow-up data collection												
Analysis												
Write manuscript												
Disseminate findings												

Data and Statistical Methods

Aim 1: to compare the incidence of urinary retention following retropubic midurethral sling placement in those women receiving normal saline vs lidocaine for retropubic hydrodissection. Rates of postoperative urinary retention will be compared between groups using chi squared testing. Duration of urinary retention measured in days will be compared using t-tests or nonparametric testing as appropriate. To adjust for other factors that may impact voiding trial results, logistic regression analysis will be performed and will include variables identified as significant ($p>0.01$) on univariable analysis as well as intraoperative narcotic use, age, and estimated blood loss. All analyses will be performed using intention to treat. Data analyses will be done using SPSS and Matlab.

Aim 2: to assess postoperative pain in women receiving retropubic normal saline vs lidocaine during midurethral sling placement. VAS scores will be measured on a scale of 0-100mm with higher scores indicating worse pain. Change from baseline in VAS pain scores will be compared at each time point with t-tests. Narcotic requirements measured in morphine equivalent grams will be compared by t-tests (and

Wilcoxon rank-sum tests if non-parametric). Both VAS pain scores and narcotic requirements will be compared in an intention to treat analysis. Multivariable logistic regression analyses will be used to identify independent risk factors that predict pain at 2, 6 and 24 hours postoperatively. We plan to adjust for operating time, estimated blood loss, urinary retention, and concomitant procedures, as all of these may predict worse postoperative pain. Anything found to be different at baseline will also be included as covariates.

Aim 3: to assess patient satisfaction in women receiving retropubic normal saline vs lidocaine during midurethral sling placement. Patient satisfaction Likert scale questionnaires will be compared using t-tests with lower scores indicating worse satisfaction. T-tests (and Wilcoxon rank-sum tests if non-parametric) will be used to analyze results of individual APS-POQ-R questions.

Data and Safety Monitoring Plan

A data safety monitoring board will be established which shall consist of the co-investigators annually submitting safety and AE information to the IRB. In addition, we will proactively monitor for allergic reaction to lidocaine, epinephrine, and normal saline throughout the first 6 hours following surgery. Hospital readmission will be proactively monitored through POD #7. We will also monitor closely for heightened rates of postoperative urinary retention. As mentioned previously, approximately 10-50% of women experience acute postoperative urinary retention. Should this number exceed 80% (assessed via administration of standardized retrograde voiding trial) in those women receiving retropubic normal saline, we would consider stopping further study enrollment pending further investigation.

Furthermore, an interim analysis will be performed at 12 weeks and/or following the enrollment of 30 subjects, whichever event comes sooner. At that time, we plan to investigate the presence of any serious events like blood transfusions or operating room take backs. We also plan to run a preliminary analysis on the rate of failed voiding trials between the two study arms. This report is to be reviewed by the IRB.

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