A randomized clinical trial of how to best position retropubic slings for stress urinary incontinence: Development of a study protocol for the mid-urethral sling tensioning (MUST) trial

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ABSTRACT

The goal of this trial is to compare two techniques for tensioning retropubic midurethral slings: a Mayo scissor between the tape and urethra vs. a Babcock clamp creating a measured loop underneath the urethra. The primary outcome is a composite of abnormal bladder function at 12 months post surgery. Abnormal bladder function is defined as bothersome stress incontinence or worsening over active bladder symptoms, a positive cough stress test, re-treatment of stress urinary incontinence, post-operative urinary retention requiring either catheterization beyond 6 weeks or surgical intervention. Secondary outcomes include the duration of post operative urinary retention, quality of life scores, and physical examination. This article describes the rationale and design of this clinical trial, which will be of interest to those who care for patient with pelvic floor disorders such as stress urinary incontinence.

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1. Introduction

In 1996, Ulmsten described the tension-free vaginal tape for stress urinary incontinence (SUI). The technique for placement was specified as having the sling "loosely placed – without elevation – around the urethra", and it was intended for intra-operative cough stress testing (CST) to be performed to determine the tension of the tape [1]. Since that introduction, a number of techniques have been described as CST can not always be performed in the operating theatre. Reasons for this include the tape being placed with the patient under general anesthetic or a deep sedative that does not allow the patient to follow commands. As such, others have advocated for intra-operative suprapubic pressure (Credé's maneuver) [2], the use of an instrument as a spacer between the urethra and tape [3], and a standardized way of measuring the amount of tape left in the suburethral space by using a Babcock clamp to create a loop of free tape [4].

Few studies on how retropubic tapes should be tensioned exist [5–9]. These papers have mixed results and are limited to evaluation of provocative cough stress testing in the operating room. Some studies have found that women with intra-operative cough stress test did not have different outcomes compared to those who had the tension of their tapes determined by placement of surgical scissors as a spacer [5,7]. In contrast, others found superior improvement in SUI symptoms when an intra-operative cough stress test was used rather than no provocative testing [6].

Given the minimal body of data on the best practice of intra-operative retropubic sling tensioning, a well designed trial of two standardized techniques is required. The impact of such a study would be far reaching. If a preferred technique could be determined by such a study, it could facilitate training, thus improving patient outcomes, decreasing complication rates, and setting a standard that provides medico-legal reference in the future.

2. Materials and methods

2.1. Rationale for tensioning methods used in this protocol

To determine which techniques were currently used by surgeons in Canada, an anonymous questionnaire was administered at an interdisciplinary Female Pelvic Medicine & Reconstructive Surgery (FPMRS) conference in Calgary, Alberta, Canada. This conference was attended by the majority of FPMRS surgeons in Western Canada, as well as a small proportion of surgeons from Eastern Canada. Of the 21 surgeons in attendance, 19 responded that they routinely performed retropubic midurethral slings. Respondents

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were asked "What is your practice for establishing the tension/tightness of a retropubic midurethral sling?" and given the opportunity to provide one or more responses. All answered the question with one to three answers. The most frequently reported technique was to place curved Mayo scissors between the sling and urethra (57.9%, n = 11). Other reported techniques included applied pressure on the bladder by the surgeon, "Credé's maneuver" (15.8%, n = 3), "eye balling" or visual inspection of tension without an instrument (15.8%, n = 3), the use of a Babcock clamp over a measured portion of the mesh (10.5%, n = 2), urethroscopy (5.3%, n = 1), placement of Metzenbaum narrow scissors between the sling and urethra (5.3%, n = 1), a dilator between the sling and urethra (5.3%, n = 1), a dilator in the urethra (5.3%, n = 1), and intra-operative cough testing (5.3%, n = 1).

In deciding which techniques to compare, it was decided that one arm of the study should evaluate the most frequently reported method and the technique used most often by the surgeons designing the study, use of Mayo scissors as a spacer. In choosing a second arm of the study, we wanted a highly reproducible technique that could be standardized between surgeons. Provocative techniques, such as intra-operative cough tests and Credé's maneuvers were decided against as level of sedation for coughing, and force used during Credé's, can not be standardized between patients and surgeons. Additionally, provocative measures can not be performed under general anesthetic (GA). In our experience, a significant portion of women opt for GA during their procedure. Visual inspection without an instrument was decided against, as there would be no way to objectively measure the amount of tension for each case. Dilators were decided against, as there was no consensus on what size of dilator should be used. While not a frequently reported technique, the use of a Babcock clamp over a measured portion of the mesh [4] was felt to be the most reproducible. This is because the distance in the "loop" held by the Babcock could be measured with a surgical ruler to an exact length for all cases.

2.2. Study design

We developed a randomized clinical trial (RCT) with superiority study design to be carried out at two Urogynecology centers in western Canada (Calgary and Edmonton, Alberta). Outcomes of retropubic mid urethral slings (Boston Scientific Advantage Fit) tensioned by two standardized non-provocative techniques: surgical scissor as a spacer vs. creation of a tape-loop with babcock clamp [3—5] will be compared. Study flow and design are shown in Fig. 1.

2.3. Participant selection

2.3.1. Inclusion criteria
Women aged 18 or older who have elected for surgical management of symptomatic stress urinary incontinence. They must have the ability to read and write in English for completing informed consent and quality of life forms. Patient must consent to participation in the RCT. Prolapse surgery at time of TVT placement is allowed within the study parameters.

2.3.2. Exclusion criteria
Women who elect for non-surgical management of their symptomatic stress urinary incontinence, or who decline participation in this RCT. Those who have had a prior incontinence procedure, or who have pre-existing urinary retention defined as post-void residual >100 mL are not eligible. Women who are clinically felt to have overactive bladder as the predominant cause of their urinary incontinence are excluded. Women who have
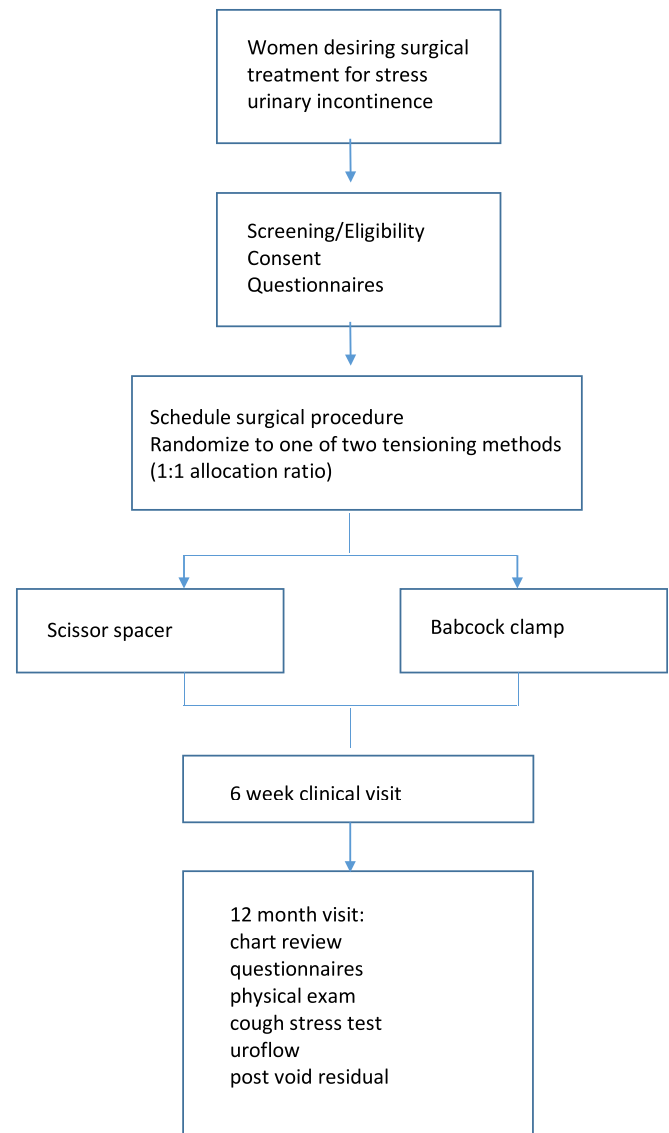

Fig. 1. Study design flow diagram.

asymptomatic stress urinary incontinence (latent SUI) are not included, as the lack of symptoms means the condition should have minimal impact on their quality of life and therefore, we would be unable to detect any positive difference in these parameters as a result of the surgical procedure.

2.4. Recruitment

Women referred to any of the collaborating clinicians, who fulfill the inclusion and exclusion criteria will be offered the opportunity to join the trial. The woman's clinician will briefly introduce the study, then the woman will be referred to the study nurse who is not involved in the woman's routine clinical care. The study nurse will explain the trial in full and provide detailed information. Women may have further discussion with their surgeon if they wish, and women who decide to participate will sign a consent form. Recruitment began in September 2015. During the first 7 months, 99 women enrolled in the study. Using a projected recruitment rate of 8—10 participants per month, enrollment is expected to finish in September 2018.

2.5. Compensation

No compensation is provided to study participants. Surgical procedures, including the purchase of the surgical device, hospital fees and physician payments, are in accordance with the provincial single payer universal health care system (Alberta Health Care).

2.6. Randomization

Participants will be randomized with equal probability to tensioning by scissor method or by Babcock method using a randomization service through the data manager at the University of Calgary Department of Obstetrics and Gynaecology. Permuted block randomization with blocks of varying size (1–4) will be employed. Randomization will be stratified by surgeon, and presence or absence of concomitant pelvic organ prolapse surgery. Randomization a few days prior to surgery will ensure that as many patients as possible will receive the allocated operation and reduce the chances that women will withdraw from the study or change their minds after randomization. Blinding of the surgeon will not be possible. Randomization information will be conveyed to the study surgeon by the principal investigator or the study nurse, by confidential phone call on day of surgery. The patient will remain blinded until the 12 month post operative visit. All post-operative assessments and examinations will be performed by a research nurse or physician at each site who did not perform the procedure and is blinded to treatment assignment.

2.7. Intervention

2.7.1. Scissor spacer

For the scissor spacer technique, curved Mayo scissors will be inserted in the space between the posterior urethra and plastic mid-line tab. The scissors will be advanced up to the hinge screw. The scissors will be kept at a neutral 0° angle parallel to the patient's posterior urethra. The scissors should not be forced against the pubic bone, unless they naturally come to lie there. By using the patient's own anatomy as the reference point, it will ensure the tape is positioned at the same angle for all participants regardless of the degree of trendelenburg and hip flexion they have been placed in. To ensure the scissor is at 0° to the urethra, the surgeon can inspect from the lateral aspect of the patient to see how the Mayo is in contact with the posterior urethra. To ensure there is no angling of the scissors, there should be no visible space between the posterior urethra and the hub of the scissor, as this occurs if the scissors are under traction towards the floor. There should also be no visible space between the posterior urethra and the tips of the scissors, as this occurs if the scissors are under traction towards the operating room ceiling. The tape will be tensioned so that the midline tab rests just flush against the screw hinge, without any pressure, ensuring the scissors are not pulled against the urethra. With the scissors in place, the tab will be cut and the plastic sheath removed from the mesh. The scissors will then be removed, the excess mesh tape trimmed at the suprapubic skin level and incisions closed. A 16 or 18 French foley catheter will placed at the start of the surgical procedure and will be left in place during these steps.

2.7.2. Babcock clamp

For the Babcock clamp technique, the protective tab will be cut off first and the protective sheath advanced 1 cm off midline on each side. Next a 1.5 cm of tape length will be measured out with a sterile surgical ruler (7.5 mm on each side of midline). The tape will be folded in the midline, and the clamp placed creating a 1.5 loop or "knuckle". The tape will then be tensioned by grasping both the suprapubic ends of the tape and protective sheath with Kelly clamps. The Kelly clamps will be used to pull the tape and sheath upward through the suprapubic skin incisions so that the Babcock clamp rests gently against the urethra. At this point, the protective sheath will be fully removed so the tape cannot be tensioned further. The Babcock is then released, ensuring exactly 1.5 cm of tape loose in the suburethral space. A 16 or 18 French foley catheter will be left in place during these steps [5].

2.8. Data collection, measures and outcomes, safety monitoring

2.8.1. Baseline & study measures

After consenting to join the study, baseline data will be extracted from the patient's chart including demographics, body mass index (BMI), parity, estrogen use and hormonal status. Presence or absence of vaginal atrophy, standardized POP-Q assessment of pelvic organ prolapse, uroflow parameters and post void residual will be recorded. All women will be asked to complete a questionnaire including pelvic floor symptoms and incontinence-related quality of life (Urinary Distress Inventory UDI-6, Incontinence Impact Questionnaire IIQ-7[10,11], International Consultation on Incontinence Modular Questionnaire for Female Lower Urinary Tract Symptoms – ICIQ-FLUTS [10]). Baseline and repeated study measures are shown in Fig. 2.

2.8.2. Considerations in the selection of the primary outcome

The primary outcome of the study is presence or absence of **abnormal post-operative bladder function,** a composite assessed at 12 months after surgery and composed of one or more of the following: 1) significantly bothersome SUI or OAB symptoms after surgery as measured on questions 1, 2, & 3 of the UDI-6, 2) a positive cough stress test in the office, 3) re-treatment for stress urinary incontinence (repeat surgery or pessary use), 4) post-operative urinary retention (presence of self-catheterization at 6 weeks post-operatively or beyond, or therapeutic intervention for retention at any time during the 12 months after, such as pelvic floor physiotherapy, sling lysis, urethrolysis, or sacral nerve stimulation). This composite outcome was chosen as it gives weight to suboptimal outcomes such as persistent SUI, de novo overactive bladder and post-operative urinary retention. Similar outcomes have been used in the past [12,13], and values from those trials can be used for sample size calculation.

2.8.3. Secondary outcome measures

The secondary outcomes of the study include: 1) rates of discharge from hospital with on-going need for catheterization, 2) duration of self catheterization after surgery in days, 3) standardized questionnaire scores (UDI-6 & IIQ-7, ICIQ-FLUTS), 4) standardized 1-h pad test values in grams of urine lost, 5) urine flow test parameters at 12 months, such as peak flow rate in milliliters/second and post-void residual in milliliters 6) new prescription of a medication to treat over-active bladder symptoms, determined by chart review 7) vaginal examination at 12 months (normal vs. abnormal palpation, and type of abnormality such as mesh erosion or tenderness during palpation).

2.8.4. Safety monitoring

At the midpoint of study enrollment (n = 159), an interim analysis of urinary retention rates at or beyond 6 weeks is planned. This safety endpoint has been chosen, as obstructed voiding is the outcome which has the greatest capacity for harm. A retention rate of 4.7% at 6 weeks is expected in the Mayo scissor group [13]. At mid-point enrollment, the study will be powered to detect a 4-fold increase in short term retention. In this event the study would be halted, as an increase of that magnitude would be too large for investigators to feel comfortable continuing.

Fig. 2. Study measured along protocol timeline.

2.9. Statistical analysis

Descriptive statistics (mean, standard deviation, median, interquartile range, proportions) will be calculated for baseline data. Baseline patient characteristics of age, ethnicity, nulliparity, smoking, menopausal status, presence of UUI symptoms before surgery and quality of life scores will examined to determine whether there are any major imbalances between the two treatment groups that would need to be adjusted for in the analysis of the primary or secondary outcomes.

Outcomes will be analyzed according to original treatment assignment (intent to treat). The primary analysis will compare the proportion of women with abnormal bladder function in each group (scissor method vs Babcock method) using the chi-square test. Differences in proportion will be presented along with 95% confidence intervals (CI).

Categorical secondary outcomes will be compared using the chi-square test or Fisher's exact test. Estimates for differences in proportions and 95% CI will be reported. Individual components of the composite primary outcome will be explored using the chi-square or Fisher's exact test. Continuous outcomes such as QoL scores will be compared using the student's t-test if normally distributed, or Mann-Whitney U test if not normally distributed.

Secondary analyses are planned to evaluate whether factors such as obesity, age, and pre-operative severity of incontinence (ISI) are risk factors for surgical failure. These analyses will include chi-square tests and t-tests, as appropriate, as well as logistic regression modelling.

This data will be managed in Microsoft Access with analysis carried out using SAS.

2.10. Sample size justification

Assuming a rate of 5.3% for bothersome post-operative SUI, and 6.3% for bothersome post-operative UUI [11], a conservative surgical revision rate for urinary retention of 1.1% [13], and a retention rate of 4.7% at $\geq$ 6 weeks post-operative [13], the additive value of our primary outcome is 17.4%. Acknowledging overlap within the groups (such as the likelihood that all women with surgical revision will fall into the retention group) we assume an overall rate of our primary outcome, **abnormal post-operative bladder function**, in the range of 15—16%. In a superiority trial study design, 276 patients (n = 138 each group) are required to have 80% power to detect a 10% difference in our primary outcome with a 90% two-sided confidence interval (alpha = 0.05). The 10% difference was chosen as our group determined this degree of improvement would be required in order for our practice to change in favor of the more complex Babcock method. Assuming a loss to follow-up rate of 15% based on a different midurethral sling trial conducted by our group [11], the total enrollment goal is 318 women.

3. Discussion

3.1. Study design challenges and limitations

The MUST trial is innovative and aims to characterize how two approaches on the tensioning of a retropubic sling affect the procedure's outcome. To our knowledge, this has not been done before.

The survey performed as part of trial development confirmed our suspicion that use of the Mayo Scissor is the most common method of tensioning a retropubic sling in Western Canada. The choice of comparison technique was challenging, as results showed no clear second favorite. We wanted the comparator to be a precise, standardized and reproducible method which could be described in detail for readers. The Babcock technique was chosen as it met those requirements.

The next challenge was engaging surgeons in the study, which requires them to deviate from their usual tensioning practice for half of surgical cases. Six surgeons were approached to take part in the trial after the protocol was finalized. Five agreed to take part; the individual who declined indicated they did not feel comfortable deviating from their usual practice.

One of the limitations of the study protocol is that we will not be performing a baseline pad test upon enrollment into the study. This means we can not objectively quantify the severity of leakage prior to surgery. Although this has not commonly been done in other studies of the TVT, the study authors desired to quantify the severity of leakage of each participant. If the severity of leakage is characterized, we can explore if the two techniques perform differently for women with mild or severe leakage. While we considered including an enrollment pad test, we ultimately chose not to based on our experiences with a previous clinical trial at our institution [11]. Experience from that trial gave us the impression that patients find pad-testing cumbersome, and so it was felt that use of pad testing at enrollment would be a barrier to participation due to additional upfront time requirements by patients. Instead we chose to use the Incontinence Severity Index [14] to qualify the severity of leakage experienced before and after surgery.

3.2. Strengths

The five participating surgeons represent two different Urgynecology departments in the province of Alberta. The large multi-site design is a strength, as it makes our study generalizable to

the readership's surgical practices. If the trial had a single participating surgeon, or a single site, it would difficult to say if outcomes reflected the two techniques or if the outcomes were influenced by regional practices or surgical expertise. By including surgeons with varied backgrounds, we can more confidently say the results are influenced mainly by the two techniques under study.

Another strength of this study is that we are looking at the impact of the two techniques on both patient centered subjective outcomes, as well as objective outcomes. It also characterizes the complications of surgery such as rates and duration of urinary retention, the need for post operative therapy for over-active bladder symptoms, as well as mesh erosion and vaginal pain. A detailed study of retropubic sling complications is valuable, given the recent increase in litigation involving mesh for prolapse and incontinence. Our trial follows these complications in the short term (first six weeks), as well as longer follow up to the 1 year mark.

We believe there will be broad interest in this study from gynecologists and urologists, as the data will give them the option to standardize practice. This study will be of particular interest to those who teach retropubic sling procedures, as the evaluation of the two techniques will allow educators to provide evidence-based instruction on the pros and cons of options for sling tensioning.

Acknowledgements

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