A Randomized Controlled Trial Comparing Retropubic KIM sling to TVT Exact Midurethral Sling

NCT number: NCT04985799

Document Date: April 15, 2021

A Randomized Controlled Trial Comparing Retropubic KIM sling to TVT Exact Midurethral Sling

BACKGROUND / RATIONALE

Midurethral slings (MUS) are recognized as a minimally invasive treatment of stress urinary incontinence (SUI). The retropubic route of MUS placement has a cure rate of 89.1%[1] with long term subjective cure rates ranging from 51-88%.[2] The Neomedic Knotless Incontinence Mesh (KIM) sling is a tension-free macroporous monofilament polypropylene knotless mesh designed to be resistant to elongation and deformation over time.[3] The KIM sling also offers a reusable trocar, which results in less waste and cost- savings. KIM sling trocars are available for the retropubic route or trans-obturator (TOT) route.

While studies have been performed comparing the TOT approach of the KIM sling to other slings, no studies have been performed to date with the retropubic (RP) approach. The RP and TOT approaches to MUS have been shown to be equivalent in the treatment of SUI.[4] Since the same mesh material of the KIM sling is used for both the TOT and RP approach, we can conclude that the RP route would show similar treatment success rates.

A type 1 macroporous (> 75um) polypropylene mesh is the most appropriate material for vaginal implantation.[5] Currently in our practice we use the Gynecare TVT Exact sling, which meets these requirements. However, Chapple et al suggest that the design and weave of synthetic mesh material can also have a significant effect on efficacy and safety;[5] therefore, the novel design of the KIM may be beneficial to reduce complications. If we can show there is similar efficacy with the RP approach of the KIM sling to the TVT Exact, there will be benefit of reduced costs and the potential for less complications. With this study, our aim is to show non-inferiority of the KIM sling to the Gynecare TVT Exact.

Given that the midurethral sling has been proven to be effective at treating stress urinary incontinence, and that lightweight, large pore mesh has less adverse effects, we propose a randomized trial to show noninferiority of the Neomedic KIM sling compared to the well-studied Gynecare TVT Exact sling. The study population will be patients that have clinically demonstrated SUI and have already chosen to pursue midurethral sling surgery for treatment. Validated questionnaires will be used to evaluate the subjective response to treatment, as a subjective outcome most closely relates to patient experience and satisfaction.

STUDY AIMS

Primary aim: Our primary aim is to assess to the non-inferiority of the retropubic Neomedic KIM sling compared to the Gynecare TVT Exact sling at 6 weeks.

We hypothesize that the KIM sling will be non-inferior to the TVT exact sling at 6 weeks postoperatively.

Secondary aims:

- To assess the non-inferiority in effectiveness of the retropubic Neomedic KIM sling compared to Gynecare TVT Exact at 1 year post-operatively.

- To assess safety of the Neomedic KIM sling compared to the Gynecare TVT Exact sling with regards to mesh exposure and reoperation for urinary retention or mesh complications at 1 year postoperatively.

STUDY DESIGN & METHODS

This is a randomized controlled, double-blinded, non-inferiority trial comparing effectiveness and safety of the Neomedic KIM midurethral sling to Gynecare TVT exact midurethral sling

Study Population

Inclusion criteria:

- Women ≥21 years based on medical chart review
- Diagnosis of SUI or mixed urinary incontinence based on medical chart review
- Objective evidence of SUI as indicated by positive cough stress test or urodynamic stress incontinence during urodynamic testing within the last year prior to enrollment. Medical chart will be reviewed.
- Planning surgery for SUI with/without POP surgery

Exclusion criteria:

- Current Pregnancy, desire for future childbearing, or ≤12 months postpartum at the time of enrollment
- Prior history of surgery for SUI based on medical chart review
- Bladder capacity <200mL on Urodynamic testing or PVR >150mL on Urodynamic testing or bladder scan.
- Non-ambulatory
- Current genitourinary fistula or urethral diverticulum based on pre-operative exam in the medical chart.

Outcome measures

Primary outcome: SUI treatment success at 6 weeks post-operatively. Treatment success will be based on a composite outcome of:

- Response of "No" on UDI-6 (subscale of PFDI-20), question #3 OR if answered "yes", must indicate "no bother"
- No re-treatment with a pessary, other incontinence device or repeat surgery (urethral bulking, Burch urethropexy, sling, or other procedure)

Secondary outcomes:

1. SUI treatment success at 1 year
    a. Uses same composite outcome criteria as primary outcome
2. Complication rates at 1 year
    a. Urinary retention
    b. Mesh exposure- determined by physical exam at 1 year
    c. Reoperation for urinary retention or mesh complications thru 1 year

Baseline characteristics will be used to define the study population. Variables to be collected:

- Age- number
- Race- Caucasian/ Black/ American Indian or Alaskan Native/ Asian/ Pacific Islander/ Other
- Ethnicity- Hispanic/ non-Hispanic
- BMI- number
- POP-Q points- number

- Smoking status- non-smoker/ current/ former
- Past medical history
    - Diabetes- yes/no
    - Charlson comorbidity index- number
- Past surgical history
    - Prior hysterectomy- yes/no
    - Prior prolapse surgery- yes/no
    - Prior surgery for SUI- yes/no
    - Prior bladder tack surgery- yes/no

Data of concurrent surgical treatment at the time of intervention, which will be used to define the study population:

- Hysterectomy
- Anterior repair
- Posterior repair
- Apical suspension
    - Uterosacral ligament suspension
    - Sacrospinous ligament fixation
    - Sacrocolpopexy

Study Intervention

The KIM sling is a tension-free Knotless Incontinence Mesh (KIM) sling. Any patient with female stress urinary incontinence can be a candidate for this sling. The KIM system provides support under the urethra to decrease stress urinary incontinence in patients, similar to other slings. As opposed to other slings on the market, KIM-specific benefits include being knotless which could decrease the friction between the permanent product and patient tissue which could decrease the risk of erosion or bacteria. The sling is placed via a short, outpatient procedure where a small vaginal incision is made with two exit points through the skin. Patients can be discharged on the same day of surgery. Of note, the KIM sling also allows for a reusable trocar system.[8]

Study participants will be randomized to receive the Gynecare TVT Exact sling or the Neomedic KIM sling in the operating room by a trained Urogynecologist.

Participating surgeons will undergo training on how to place KIM sling. This includes but is not limited to teaching or device representatives in the operating room for intraoperative questions. These surgeons already have experience in placing Gynecare TVT Exact slings, as this is the current standard of care. The KIM sling has subtle differences in placement which will be addressed at the training. All surgeons in the study will undergo one training together prior to the start of the study and will have individual help from device representatives.

Randomization, Concealment, and Blinding

The randomization schema will be created using Stata, and this schema will be uploaded into the REDCap database, where randomization will be performed and maintained. This technique will be used to prevent selection bias by concealing the allocations from those assigning participants until the moment of assignment. Randomization will occur in the operating room prior to performing the procedure. Assignment codes will remain within REDCap with access to the randomization for the research investigators. The randomization codes will not be broken unless knowing the sling type affects

the patient's health or if there is a complication postoperatively that requires knowing the type of sling placed.

Masking (Blinding)

This study will be double blinded. While the providers in the operating room placing the sling will not be able to be blinded, the subjects and data collectors will be blinded to the treatment assignment.

Study Procedures and Schedule

Procedures	Screening	Baseline	Intervention	6 weeks visit	6 month visit	1 year visit
Eligibility Assessment	X					
Informed Consent		X				
Medical History		X				
Study Intervention			X			
PFDI-20		X		X	X	X
PGI-I				X	X	X
Symptom Questionnaire				X	X	X
Physical Exam				X		X

Screening (within 6 months prior to enrollment)

Pre-screening will be performed through a provider visit, obtaining history, physical exam and urodynamics study if needed, where the patient will be evaluated for if they are eligible for a sling. If the patient is deemed eligible, they will verbally be consented to be screened for and contacted regarding the research study. The research coordinator will screen for eligibility and will contact the patient to further discuss the study. This screening will take place within 6 months prior to enrollment.

Enrollment / Baseline (Day 0)

- Informed consent
- PDFI-20
- Obtain baseline characteristics (medical history)

Visit 1 (Surgical intervention- within 6 months of enrollment)

- Intervention- randomized to treatment

Visit 2 (6 ± 2 weeks from intervention)

- PFDI-20
- PGI-I
- Symptom questionnaire
- Physical exam
- Adverse event / SAE assessment

Visit 3- phone (6 ± 2 months)

- PFDI-20
- PGI-I
- Symptom questionnaire

- Adverse event / SAE assessment

Final Visit (1 year ± 2 months)

- PFDI-20
- PGI-I
- Symptom questionnaire
- Physical exam
- Adverse event / SAE assessment

Statistical Analysis Plan

Strategies that Apply to all the Specific Aims

- To help ensure replicability of the research, the analysis plans will be reviewed and finalized prior to collection of data (a priori). For each specific aim, the analysis plans specify detailed steps for obtaining estimates of population parameters (e.g., treatment effects) and for making inferences.
- Descriptive graphical and tabular methods will be used to characterize the participants, visualize the data and examine relationships among variables.
- For each specific aim, the analyses will focus on the magnitude and direction of point- and interval-estimates of the population parameters of interest. To indicate precision, all statistical estimates of population parameters will be tabulated along with corresponding confidence intervals (CI) or standard errors (SE). The CI will be interpreted as the set of potential values of the population parameter that are most compatible with the observed data.
- All hypothesis tests yielding p-values that are deemed to be not statistically significant will be reported as being inconclusive. The proposed statistical analysis strategy acknowledges that no p-value can reveal the plausibility, presence, truth, or importance of an association or effect.

Plans for Aim 1:

To assess the non-inferiority in the effectiveness of the retropubic Neomedic KIM sling compared to Gynecare TVT Exact sling at 6 weeks, we will present the 2-by-2 contingency tables on SUI treatment success counts. Then, we will perform the one-sided hypothesis test of H_0: $(\mathrm{PTVT} - \mathrm{PKIM}) > \Delta$ vs H_a: $(\mathrm{PTVT} - \mathrm{PKIM}) \leq \Delta$, where PTVT is the proportion of success counts in the TVT sling group, PKIM is the proportion of success counts in the Neomedic KIM sling group, and Δ is the conjectured inferiority margin. We will use the chi-squared test to test the above hypothesis. In addition, we will provide the 95% confidence interval of $\mathrm{PTVT} - \mathrm{PKIM}$.

Plans for Aims 2:

We will perform a similar analysis for Aim 1 to compare effectiveness at 1 year.

To evaluate the complication rates of the retropubic KIM sling compared to the TVT Exact at 6 weeks and 1 year post-operatively, we will also present 2-by-2 contingency tables on complication counts (for urinary retention, mesh exposure and reoperation for mesh complications and urinary retention). We will perform a two-sided test on comparing the proportions of complications between KIM sling and TVT Exact sling groups. Again, such a test will be performed by using the chi-squared test. In addition, we will provide the 95% confidence interval of the differences of the proportions between these two groups.

Sample Size Rationale

Our statistical power calculation was based on prior studies showing retropubic sling success rate being 89-95%[1-5] and using 12-15% non-inferiority margin[6-9]. We based our sample size estimate on the following: 90% sling success with a 14% non-inferiority margin and 80% power, assuming a 20% dropout rate. If there is truly no difference between the standard and experimental treatment (90% in both groups), then 114 patients are required to be 80% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favor of the standard group of more than 14%. To assume a 20% dropout rate, we needed to enroll 144 participants for our primary outcome of treatment success at 6 weeks postoperatively. Sample size calculator used was https://www.sealedenvelope.com/power/binary-noninferior/.

Recruitment Strategy

Once a patient has been seen by a Urogynecology physician and plans to have sling surgery for SUI, the physician will notify the study team to screen for eligibility. After the study team determines eligibility, the patient will then be approached by the study team for recruitment.

Retention Strategy

The 6 week, 6 month and 1 year visits will be incentivized monetarily in order to enhance retention. Subjects will receive $25 with completion of the 6 week visit and $75 with completion of the 1 year visit. The 6 month visit will be performed over the phone and/or with REDCap surveys in order to reduce the burden on the participant.

Screen Failures

Those who are screened for the study but are not eligible will still undergo planned surgery for SUI but will not be enrolled or randomized to treatment. The patient will receive the treatment that is planned for with a shared medical decision-making process with their physician.

REFERENCES

1. Imamura M, Hudson J, Wallace SA, et al. Surgical interventions for women with stress urinary incontinence: systematic review and network meta-analysis of randomised controlled trials. BMJ 2019;365:l1842. (In eng). DOI: 10.1136/bmj.l1842.
2. Liu HH, Kuo HC. Durability of Retropubic Suburethral Sling Procedure and Predictors for Successful Treatment Outcome in Women With Stress Urinary Incontinence. Urology 2019;131:83-88. (In eng). DOI: 10.1016/j.urology.2019.05.015.
3. Marschke J, Reisenauer C, Mikkola TS, Schwab F, Tunn R, Huebner M. Comparison of two retropubic tension-free vaginal tape procedures in women with stress urinary incontinence: a randomized controlled multicenter trial. Arch Gynecol Obstet 2019;299(4):1015-1022. (In eng). DOI: 10.1007/s00404-019-05077-0.
4. Aniuliene R, Aniulis P, Skaudickas D. TVT-Exact and midurethral sling (SLING-IUFT) operative procedures: a randomized study. Open Med (Wars) 2015;10(1):311-317. (In eng). DOI: 10.1515/med-2015-0046.
5. Sun Y, Luo D, Yang L, et al. The Efficiency and Safety of Tension-Free Vaginal Tape (TVT) Abbrevo Procedure Versus TVT Exact in the Normal Weight and Overweight Patients Affected by Stress Urinary Incontinence. Urology 2017;110:63-69. (In eng). DOI: 10.1016/j.urology.2017.06.033.
6. Richter HE, Albo ME, Zyczynski HM, et al. Retropubic versus transobturator midurethral slings for stress incontinence. N Engl J Med 2010;362(22):2066-76. (In eng). DOI: 10.1056/NEJMoa0912658.
7. Albo ME, Richter HE, Brubaker L, et al. Burch colposuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med 2007;356(21):2143-55. (In eng). DOI: 10.1056/NEJMoa070416.

8. Barber MD, Kleeman S, Karram MM, et al. Transobturator Tape Compared With Tension-Free Vaginal Tape for the Treatment of Stress Urinary Incontinence: A Randomized Controlled Trial. Obstetrics & Gynecology 2008;111(3):611-621. DOI: 10.1097/AOG.0b013e318162f22e.
9. Karmakar D, Dwyer PL, Murray C, Schierlitz L, Dykes N, Zilberlicht A. Long-term effectiveness and safety of open Burch colposuspension vs retropubic midurethral sling for stress urinary incontinence—results from a large comparative study. American Journal of Obstetrics and Gynecology 2021;224(6):593.e1-593.e8. DOI: https://doi.org/10.1016/j.ajog.2020.11.043.