Study Protocol and Statistical Analysis Plan

PDS (polydiaxonene suture) versus prolene (polypropylene suture) as suture material for vaginal sacrospinous hysteropexy – a randomised controlled study

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1. Introduction

Lifetime risk for pelvic organ prolapse (POP) is high and around 3-6% of symptomatic POP are associated with symptoms connected to a decisive lower quality of life, including bladder and bowel issues as well as sexual dysfunction [1,2]. Therefore, these women should be offered feasible, safe, and functional treatment options. Individual treatment plans based on patient's expectations wishes and necessities should be chosen. Treatment options can range from conservative pessary application to various surgical repair methods [3,4], with 11-19% in women reported to be undergoing surgery for prolapse or incontinence [5] . As women have expressed more and more the desire to keep their uterus, uterine-preserving procedures such as vaginal sacrospinous hysteropexy (SSH) have become an increasingly utilized surgical option for the primary treatment of POP [3]. Sacrospinous hysteropexy is an uterine-preserving, well established surgical procedure that gained popularity after the publication of the SAFE U trail conducted by the Dutch research group of Detollenaere and Schulten et al. about its successful use [6,7]. Furthermore, several studies investigated the surgical outcomes after the different types of surgery and concluded that compared with vaginal hysterectomy with apical fixation, SSH has similar or possibly even better outcomes [8–10]. As such it has also become the most commonly performed uterine-preserving surgical technique at our institution.

However, it is crucial also to identify surgical variables that may have an impact on the outcomes of prolapse surgery: especially as the scientific evidence guiding the choice of suture material in sacrospinous hysteropexy is scant. In their SAFE U trail Detollenaere et al. used prolene as suture material, however patients reported buttock pain for some time after the intervention [6]. At our institution we mainly use

PDS sutures as a late resorbable suture material and noticed no such claims from patients.

The aim of this RCT is to investigate the effects of resorbable (PDS) versus non-resorbable (prolene) suture material in patients with symptomatic POP undergoing vaginal sacrospinous hysteropexy.

2. Experimental Plan

2.1 Study hypothesis

Primary study hypothesis is that patients receiving a sacrospinous hysteropexy with non-resorbable Prolene sutures (study group) experience a better subjective symptom improvement (evaluated by the prolapse domain score of the Deutscher Beckenboden Fragebogen [11]) assessed at 12 months after surgery, than patients with resorbable PDS sutures (control group).

The secondary hypotheses are, that the study group will have:

- better anatomical outcomes (better rate anatomical outcome in each compartment (change in POP-Q values from baseline) [12]),
- better condition-specific quality of life scores (changes in questionnaire from baseline),
- less postoperative complications (haematoma, vesico-vaginal fistula, ureteral obstruction, urinary tract infection, incomplete bladder emptying, overactive

bladder or stress incontinence symptoms, suture erosion, vaginal wound dehiscence, infection or granulation tissue, etc),

- lower use of pain killers for buttock pain during the hospital stay and in the 12 months postoperative period
- lower pain levels (assessed through the standardised Visual Analog Scale (VAS) and Numeric Rating Scale (NRS) [13]) at postoperative day 1, at discharge, at 4 to 6 weeks, 6 and 12 months.

2.2 Study design

This trial is a single-centre, prospective, randomized trial conducted with the aim of determining the superiority of non-absorbable prolene over absorbable PDS suture material with regard to the primary outcome in POP patients undergoing sacrospinous hysteropexy. The study will be a single-blind study, as it is impossible to blind the study surgeon for the surgical procedure to which the subject is assigned. However, all outcome assessors and the subjects will be blinded to the assigned treatment. Postoperative follow-up will take place after 4-6 weeks, 6 months and 12 months. Patients will undergo a standardized urogynaecologic examination that includes assessment of prolapse with POP-Q measurement [12]. Furthermore subjective outcome will be assessed with standardized questionnaires – our study participants will receive the German version of the pelvic floor questionnaire [11].

2.3 Study setting

This study will be conducted at the urogynaecologic outpatient clinic (Division of General Gynaecology and Gynaecologic Oncology, Department of Obstetrics and

Gynaecology, Medical University of Vienna). Enrolment, treatment, and data collection will be standardized by all sites according to the approved study protocol.

2.4 Participants and recruitment

The study population will consist of women aged 18 years or older who are referred to our urogynaecologic outpatient clinic due to symptomatic POP. Women with anterior vaginal wall prolapse and an indication for reconstructive pelvic floor surgery – including sacrospinous hysteropexy – can be included in this trial.

2.5 Randomization

Randomization will be performed by the randomizer of the Medical University of Vienna; subjects will be stratified by parity (Primipara / Multipara) and randomized in blocks of four. All subjects will receive a unique study number.

To prevent unmasking the actual procedures, the medical records will indicate the actual surgical procedure without stating the suture material used for anterior colporrhaphy. Intraoperative data collection will be conducted by the study surgeon rather than by other research staff.

2.6 Intervention

Sacrospinous hysteropexy will be performed in a traditional and standardized manner in accordance with our surgical policy. Any other concomitant procedures (e.g.,

anterior and/or posterior colporrhaphy, cystoscopy, etc.) will be performed in accordance with each surgeon's preferred technique.

Operative management: All patients will be operated by the vaginal route. They are prepared under strict aseptic conditions in the dorsal lithotomy position. The bladder is emptied preoperatively with a thin disposable catheter and antibiotic prophylaxis (cefazolin) is administered before incision. A vasoconstricting solution (combination of vasopression and NaCl) is administered and a high posterior colpotomy is made towards the posterior cervix. Blunt preparation towards the right Spina ischiadica to visualize the right sacrospinous ligament. Once 4 cm of ligamentum sacrospinale are visualised, two sutures will be placed through the ligament approximately 2 cm medial of the spina ischiadica. Depending on preoperative randomization, patients will receive either PDS sutures (PDS 0) or prolene (2-0) sutures. This suture will then be placed through the posterior cervical wall, but not yet knotted. First, the colpotomy will be closed via absorbable sutures (2/0 vicryl). Should additional procedures such as anterior and/or posterior colporrhaphy be indicated, they will be performed at this stage. Only after, the pre-laid fixation sutures will be tied, whereby the portio will come to lie about 4-6 cm cranial of the level off the vulva towards the sacrospinous ligament. Participating surgeons will be defined as high volume surgeons in prolapse surgery and will also be part of the urogynaecologic core team.

Perioperative management: is also standardized and includes preoperative single-shot antibiotics as well as vaginal pack and an indwelling urinary catheter for 24 hours after the surgical procedure. Patients will have postvoid residual volume measurement at the first postoperative day (when urinary catheter is removed). A postvoid residual volume of 2 x < 150 ml is defined as normal and no further follow-ups are necessary. Postvoid residual volumes of > 150 mL or greater will be

considered as abnormal. These patients' volumes will continue mechanical bladder drainage via clean intermittent (self)-catheterisation until the postvoid residual volumes are consistently less than 150 ml. Patients will receive standard analgesic therapy in accordance with the local hospital protocol (Metamizol 1g intravenously, 3 times a day).

Postoperative Management: The patients are instructed to rest for 2 weeks after the operation (not to work, to do sport, to do the cleaning and to carry more than five kilos). They are allowed to return to work after 4 weeks and to take part in sport or have intercourse after 6 weeks. Follow-up visits are scheduled postoperative after 4-6 weeks, 6 months and 1 year in our outpatient clinic due to our study protocol.

2.7 Inclusion and exclusion criteria

Inclusion criteria

- Anterior vaginal wall prolapse beyond the hymen (POP-Q point Aa or Ba >0) with a central defect.
- Apical vaginal vault prolapse beyond the hymen (POP-Q point C >0) with a central defect. Vaginal bulge symptoms
- Uterus-preserving reconstructive surgery via vaginal sacrospinous hysteropexy is planned

Exclusion criteria

- History of hysterectomy

- Reconstructive pelvic floor surgery using mesh or obliterative surgery is planned
- Reconstructive pelvic floor surgery with hysterectomy is planned
- Prior reconstructive pelvic floor surgery with mesh
- Known pelvic malignancy
- Known inflammatory disease
- Current systemic glucocorticoid or immunosuppressant treatment.
- Subject is unable or unwilling to participate

2.8 Data collection

At baseline, the following data will be collected: demographics and medical history data (age, body mass index, parity, menopausal and hormone therapy status, nutritional status, current smoking, previous hysterectomy and previous anti-incontinence surgery), and medical comorbidities (diabetes mellitus, connective tissue disorders), and data from the standardized urogynaecologic examination (POP-Q examination during maximal Valsalva, genital hiatus measurements and ultrasound of cervix, uterus, bladder, pelvic floor muscles and levator ani muscle hiatus).

Urogynaecologic examination evaluations is made using the POP-Q measurement system on maximum Valsalva effort in the seated semi-lithotomy position (a 45° upright sitting position). Objective anatomical cure is defined as a Ba point < −1. Symptoms, quality of life and sexuality are evaluated with the Deutscher

Beckenboden-Fragebogen. This Pelvic Floor Questionnaire consists of four domains: bladder, bowel, pelvic organ prolapse and sexual function. In every domain various questions assess severity and condition-specific quality of life. Every question is scored on a scale from zero to four. The sum of each individual domain is divided by the maximum reachable score and multiplied by ten, giving a value between zero (0= no symptoms) and ten (10=maximum of symptoms) for each of the domains. Baessler et al. has published the results of the validation study and scoring system [11].

To evaluate nutrition status, patients will receive the “Mini Nutritional Assessment”-Fragebogen (https://www.dgem.de/sites/default/files/PDFs/Screening/MNA-SF%20Deutsch-240513.pdf) and laboratory testing of albumin, electrolytes (sodium, potassium, magnesium, phosphate, and calcium), haematocrit, creatinine, blood urea nitrogen, and bilirubin.

Patients will be asked to complete the standardised Visual Analog Scale (VAS), Numeric Rating Scale (NRS) [13] and answer the following questions:

- “Do you experience a sensation of bulging or protrusion from the vagina?” and “Do you have a bulge or something fallen out that you can see in the vagina?” [6]
- “Do you experience pain in the rump?” and “Do you experience pain in the lower back?” and “Do you experience pain while walking?” [6]
- “What rate of postoperative recurrence would you accept and still opt for the surgery?” [14].

Furthermore, patients will answer the "Patient Global Impression of Improvement (PGI-I)" as it takes little effort for the patient and allows a precise result in terms of the rate of improvement after the operation [15]. One of the following answers can be given by each patient:

1. A lot better.
2. Much better.
3. A little better.
4. no change.
5. A little worse.
6. Much worse.
7. A lot worse.

Scheduled in-person follow-ups will occur at 4 to 6 weeks, 6 and 12 months after the operation. Each check-up will include a full urogynaecologic clinical examination including POP-Q, ultrasound and bloodwork as well as a written questionnaire identical to the one at baseline. In addition, an update of current medications, an assessment of new or continuing pelvic floor disorders and adverse events that occurred since the previous evaluation will be obtained by the study coordinator at each visit. All data will be anonymized and collected using case report forms by examiners or trained research coordinators who are blinded to the treatment assignment.

2.8 Primary and secondary outcome measures

The primary outcome is subjective symptom improvement (evaluated by the prolapse domain score of the Deutsche Beckenboden Fragebogen) assessed at 12 months after surgery.

The secondary outcomes are the anatomical outcomes (the rate of suboptimal anatomical outcome in each compartment (POP-Q point, change in POP-Q values from baseline), condition-specific quality of life (any changes in questionnaire Deutscher Beckenboden Fragebogen from baseline), postoperative complications (haematoma, vesico-vaginal fistula, ureteral obstruction, urinary tract infection, incomplete bladder emptying, overactive bladder or stress incontinence symptoms, suture erosion, vaginal wound dehiscence, infection or granulation tissue, etc), and use of pain killers during the hospital stay. In addition, patients‘ pain level will be assessed through the standardised Visual Analog Scale (VAS), Numeric Rating Scale (NRS) [13] and the earlier specified questions, patients’ improvement rate will be assessed through the "Patient Global Impression of Improvement (PGI-I).

2.9 Sample size and power considerations

Alteration of the prolapse domain score obtained from the pelvic floor questionnaire before and after intervention (between baseline and 12 months follow-up) will be compared between patients receiving continuous stitches versus simple interrupted stitches for anterior colporrhaphy. Schoenfeld at al. observed a mean prolapse domain score of 3.33 with a standard deviation of 2.2; we assume that the standard deviation of the pre- and post-interventional treatment will be equal, and that the correlation between the two values is 0.5, resulting in a standard deviation of the change between pre- and postinterventional value will be 2.2.; then, with 21 patients per group a difference of 2 between the changes in the two groups can be identified

with 80% power. Taking into account an expected dropout rate of 20%, 26 patients will be included per group.

2.10 Data analysis

Statistical analysis will be performed using SPSS and Excel software. Data will be calculated and graphed as mean plus minus standard error of mean (SEM).

Metric variables will be reported by mean and standard deviation resp. median and IQR, categorical variables will be reported by frequencies per group and timepoint. The primary outcome subjective symptom improvement after 12 months in either group will be analyzed by a t-test or a Man-Whitney-U-test depending on the distribution of improvements.

For the secondary endpoints, differences of rates of adverse events between the two treatment groups will be analysed by a Chi-squared test. Blood loss, use of pain killers and changes in condition-specific quality of life will be compared between groups analogously to the primary outcome.

Changes in POP-Q values from baseline over time will be analysed by a linear mixed model with fixed effects group, time, POP-Q point, age and BMI and random effect intercept per patient. Statistical significance will be set 0.05. No correction for multiple testing is performed because only one main hypothesis is considered.

3. Research facility

The patient screening will be performed at the urogynaecologic outpatient clinic of the Department of General Gynaecology and Gynaecologic Oncology, Medical University of Vienna, Austria. Infrastructure needed for this study is already present.

4. Ethical and legal aspects

4.1. Risks

The expected risk for the subjects involved in the study can be considered as minimal. Sacrospinous hysteropexy will be performed as a standard procedure. This procedure is clinical standard of care and is not an additional study related procedure. It is unclear if different suture material led to different adverse effects.

The only possible risk that patient's data might be released to public is minimized by anonymization of all data that will be saved at a password secured server. Data will be accessible by authorized staff only.

4.2. Publication of data

The results of the study will be published in an adequate timeframe.

4.3. Changes of the study protocol

If changes of the study protocol should occur, they will be documented carefully. If significant changes should be necessary, the ethic commission will be contacted and asked for permission.

4.4. Protection of data privacy

All data obtained from the subjects in this study will be handled with care and will not be passed to a third person. Every individual will be given a unique code to ensure the protection of personal data sample evaluation.

4.5. Written informed consent

Written informed consent will be obtained from every patient. Every participating patient will be informed thoroughly about the study. Every subject can withdraw from the study at any time.

5. References

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