High uterosacral ligament suspension by transvaginal natural orifice transluminal endoscopic surgery or laparoendoscopic surgery for uterine prolapse: a protocol for a non-inferiority randomized controlled trial

Tao Hou  
Meizhou People's Hospital

Li Chen  
Meizhou People's Hospital

Shan He  
Meizhou People's Hospital

Lishan Huang  
Meizhou People's Hospital

Ping Zhou  
Meizhou People's Hospital

Yang Chen  
Meizhou People's Hospital

Ye Liang  
Meizhou People's Hospital

Qijun Zhong  
Meizhou People's Hospital

Wen He (doctorhoman@163.com)  
Meizhou People's Hospital

Research Article

Keywords: High uterosacral ligament suspension, Transvaginal natural orifice transluminal endoscopic surgery, Laparoscopy, Uterine prolapse

Posted Date: November 8th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3388483/v1
Abstract

Introduction:

Uterine prolapse is a prevalent health condition that significantly impairs the daily activities and quality of life of women. High uterosacral ligament suspension (HULS) through conventional laparoscopy (cLap) is a frequently employed surgical procedure for treating uterine prolapse. In recent years, gynecological surgeons have increasingly considered transvaginal natural orifice transluminal endoscopic surgery (vNOTES) due to its favorable outcomes, including enhanced cosmetic appearance and expedited postoperative recovery. However, there is a lack of studies comparing the techniques of vNOTES-HULS and cLap-HULS. Therefore, this trial aims to compare the efficacy and safety of vNOTES-HULS and cLap-HULS for the treatment of uterine prolapse at stage 2 or higher, providing valuable insights for surgical decision-making.

Methods

A two-arm, single-center, non-inferiority randomized controlled trial (RCT) will be conducted to evaluate whether the vNOTES-HULS procedure is non-inferior to the cLap-HULS procedure in the repair of uterine prolapse. The study aims to recruit a total of 116 patients diagnosed with stage 2 or above uterine prolapse from Meizhou People's Hospital. These patients will be randomly allocated to either the vNOTES-HULS or cLap-HULS intervention. The primary objective of the study is to determine the rate of successful uterine prolapse treatment during the 1-year follow-up evaluation. Secondary outcomes include perioperative parameters, complications, costs, postoperative recovery, and quality of life assessed at 1-month, 1-year, and 5-year intervals.

Discussion

This study aims to compare the effectiveness of vNOTES-HULS and cLap-HULS in the treatment of stage II or higher uterine prolapse based on the Pelvic Organ Prolapse Quantification classification.

Trial registration:

The study protocol received approval from the Research Ethics Committee of the Meizhou People's Hospital (No. 2022-C-23) on October 3, 2022. It was registered into the Chinese Clinical Trials Registry on September 6, 2022 (no. ChiCTR2200063408). This study is currently in progress.

Background

Pelvic organ prolapse (POP) refers to the downward displacement of one or more pelvic floor components, leading to significant adverse effects on a woman's quality of life. The prevalence of
Symptomatic POP in China is approximately 9.6%, as reported recently [1]. Furthermore, in low- and middle-income areas, this prevalence increases significantly to 19.7% [2]. The projected upward trend in POP prevalence is expected to continue due to changing demographics, such as an aging society and limited access to healthcare facilities. Uterine prolapse is the most prevalent condition identified in advanced pelvic organ prolapse cases, as determined by the Pelvic Organ Prolapse Quantification (POP-Q) system [3]. Surgical intervention is usually necessary to address this condition, with affected individuals facing an estimated lifetime risk of approximately 20% of requiring POP surgery [4].

Surgical interventions for uterine prolapse include native tissue repair and mesh repair. However, concerns over severe postoperative complications, some of which led to the FDA's ban, have made autologous tissue repair the preferred technique for treating pelvic organ prolapse POP [5, 6]. Specifically, high uterosacral ligament suspension (HULS) has emerged as the favored method of autologous tissue repair, providing support to the upper one-quarter of the vagina, known as level I support in DeLancey's classification [7, 8]. Research indicates the success rate of HULS in repairing POP is favorable [9]. However, consensus is lacking regarding the optimal surgical approach. Advancements in conventional laparoscopic (cLap) technology have improved visualization, enabling abdominal HULS through laparoscopy. This approach offers superior visualization, improved suspension effect, and reduced surgical complications compared to the vaginal approach [10, 11]. Over the past decade, transvaginal natural orifice transluminal endoscopic surgery (vNOTES) has gained popularity as a minimally-invasive alternative to traditional laparoscopic procedures for gynecological conditions due to its numerous benefits, including reduced postoperative pain, faster recovery times, and superior cosmetic outcomes [12]. Although a few studies have reported the advantages of vNOTES-HULS for POP [10, 11], randomized controlled trials (RCTs) or large sample retrospective studies that compare the clinical outcomes between cLap-HULS and vNOTES-HULS in women with uterine prolapse are lacking.

Given the paucity of available data, this study aims to conduct a non-inferiority RCT to thoroughly assess the effectiveness and safety of vNOTES-HULS in the treatment of uterine prolapse at stage II or higher according to the POP classification, in comparison to cLap-HULS.

**Methods**

**Trial design**

The objective of this paper is to conduct a RCT using a two-arm, single-center, parallel-group design to evaluate the non-inferiority of vNOTES-HULS compared to cLap-HULS in the correction of uterine prolapse, as assessed by short-term and long-term outcomes. The study protocol is reported in accordance with the guidelines outlined in the SPIRIT Checklist for Trials (Additional file 1) [13]. The study will be conducted at the Department of Gynecology, Meizhou People’s Hospital in Guangdong, China, which is a university teaching hospital serving an estimated population of 20,000,000 individuals. The protocol and time schedule can be found in Fig. 1, following the guidelines provided by the Standard Protocol Items: Recommendations for Interventional Trials [14]. All surgical procedures, including
vNOTES-HULS and cLap-HULS, which involve concomitant hysterectomy or vaginal vault suspension, will be performed by two highly skilled pelvic floor surgeons, namely TH and LC. Both surgeons possess extensive experience in pelvic floor surgery and have been utilizing the vNOTES approach for gynecologic benign diseases since 2016. Due to the nature of surgical interventions, it is not feasible to implement a double-blind method. However, the allocation of surgical approaches will be concealed from the surgeons to ensure unbiased outcomes. Participant recruitment for this study began in September 2022 and is currently ongoing.

Participants

We are seeking participants aged 18 and older who have received a diagnosis of uterine prolapse and are willing to undergo either HULS and concomitant hysterectomy or vaginal vault suspension. The inclusion criteria for our study are as follows: (1) Participants must have a diagnosed uterine prolapse of POP stage ≥ 2 according to the POP-Q classification system. (2) This should be their first surgical treatment for POP. (3) Participants must express a desire for preservation of coital function. The exclusion criteria for this study are as follows: (1) Participants who are unable to tolerate surgical treatment. (2) Participants who have severe adhesions suspected during pelvic examination. (3) Participants who are suspected to have gynecological malignancy. (4) Participants who have a current urogenital tract infection. (5) Participants who have had a prior hysterectomy. The potentially eligible patients will be contacted by the researchers (LC and TH) who will explain the process of the study in detail to ensure that patients understand the entire research. Eligible participants will receive comprehensive information regarding the study’s objectives, methodology, expected benefits, and potential risks. Additionally, all enrolled participants will be informed that they retain the option to withdraw from the trial at any time.

Randomization

All participants will be randomly assigned to either the vNOTES or cLap-HULS group using a computer-generated randomization schedule with an allocation ratio of 1:1. The randomization schedule will only be accessible to the principal investigator (WH), who will inform the surgeons about the assigned treatment approach the day before the scheduled operation. The cLap procedure involves making four small skin incisions to insert a laparoscope and other surgical instruments into the abdominal cavity, while vNOTES does not require any abdominal incision. Therefore, blinding methods cannot be implemented for either the surgeons or the participants. However, to ensure unbiased data collection, a research nurse, who is not involved in the treatment, will collect the preoperative questionnaires and POP-Q measurements. The nurse will be unaware of the treatment allocation, thus preventing potential bias. The POP-Q measurement will be conducted during a follow-up appointment, enabling the research team to evaluate the progression of pelvic organ prolapse. The planned follow-up schedule is presented in Fig. 2.
Preoperative evaluation

Before undergoing surgery, all patients will receive standardized history and physical examinations administered by two designated specialists, TH and LC. The severity of symptoms related to POP, emotional state, and personal relationships will be assessed using the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire short form (PISQ-12) [15] and the Chinese version of the Pelvic Floor Impact Questionnaire Short Form-7 (PFIQ-7) [16]. These questionnaires will serve as indicators, and the scores will be recorded for each patient. Furthermore, all participants will receive counseling for HUSL. The specific surgical approach will be determined based on factors such as the size of the prolapse and the degree of pelvic floor muscle relaxation. After considering various factors, including the patient's preference for preserving the uterus, the extent of uterine prolapse (POP stage 2), and the patient's age (below 40 years), a decision has been made to proceed with uterine-preserving surgery. Alternatively, if uterine preservation is not desired, the patient will undergo HUSL with concomitant hysterectomy. Patients with uterine prolapse often experience accompanying vaginal prolapse. In our department, patients with stage 2 or higher vaginal vault prolapse typically undergo either anterior or posterior vaginal vault suspension.

Surgical procedures

Antibiotics (either Cefazolin sodium, 1g, i.v. or Azithromycin, 600 mg, i.v.) will be administered to all patients before surgery, following our hospital protocol. During the surgery, all patients will receive general anesthesia and be positioned in the Trendelenburg lithotomy position. The procedure will involve inserting a metal catheter into the bladder via the urethra for urine drainage. Patients scheduled for anterior vaginal vault suspension after anesthesia will have an indwelling urethral catheter inserted.

vNOTES-HULS with hysterectomy

The vNOTES establishment and hysterectomy procedure were previously described [17]. Briefly, the procedure begins by administering a submucosal injection of 0.9% NaCl solution to cushion the cervix. A circumferential incision is then made around the cervix. Next, a vicryl-1 suture is used by the surgeon to clamp, cut off, and tie the posterior and lateral ligaments of the uterus. The surgical process involves incising the anterior and posterior cul-de-sacs, followed by the insertion of a single-port device provided by Nantong Angel Medical Instruments Co., Ltd., China. The vNOTES platform is then established to inspect the peritoneal cavity. During the procedure, the Ligasure vessel sealer device is utilized to coagulate and cut the sacrouterine ligaments, bilateral infundibulopelvic ligaments, and the ligamentum ovarii proprium in cases requiring adnexectomy. All specimens are removed through the single-port device. Hemostasis is confirmed, and the pelvic and abdominal cavities are irrigated. To secure the proximal portion of the ligament, which is positioned approximately 4 cm distal to the sacral promontory, a non-absorbable suture is employed with a total of four stitches. Between the sutures there is 0.5 cm distance. In a hysterectomy procedure, each ligament is cut and clamped, with the sutures then being secured to their respective distal cervical parts. The same steps are repeated for the contralateral
ligament. Finally, the sutures are placed under tension, anchored to the vaginal stump, and secured with ties.

**vNOTES-HULS**

In patients who desire uterus preservation, the vNOTES platform will be established through posterior fornix. In these cases, the sutures of bilateral sacral ligaments will be tied to the fornix posterior finally. The other HULS procedures are the same as those in vNOTES-HULS with hysterectomy.

**cLap-HULS with hysterectomy**

The surgeon will initiate the surgery by establishing a pneumoperitoneum through the umbilical insertion of a Veress needle. Subsequently, the surgeon will insert an additional three trocars to gain entry into the abdominal cavity. A standard laparoscopic examination and hysterectomy will be conducted. The surgeon will perform coagulation and cutting of the bilateral round ligaments, uterine arteries, and cardinal ligaments in a cranial to caudal direction using bipolar and ultrasonic scalpels. The uterus and/or adnexa will be extracted through the colpotomy opening. Subsequently, the identical HULS procedures as those in vNOTES-HULS with hysterectomy will be carried out. Following a hysterectomy, the sutures of HULS will be secured to the vaginal stump. Alternatively, in patients who wish to preserve the uterus, the sutures of HULS will be tied to the fornix posterior.

Following HULS via vNOTES or cLap, the surgeon will evaluate the presence of anterior or posterior vaginal prolapse. If the prolapse is at stage 2 or beyond, the surgeon will proceed with an anterior or posterior colporrhaphy.

**Postoperative care and follow-up**

To minimize the risk of infections and other complications, patients undergoing surgery are routinely administered a course of either Cefazolin or Azithromycin as a standard prophylactic measure. The removal of the catheter typically occurs 48 hours after anterior colporrhaphy surgery. A comprehensive blood analysis, including a routine blood test and measurement of C-reactive protein (CRP) levels, is conducted on all patients 48 hours after the procedure. Postoperative pain in all patients is assessed using a Visual Analogue Scale (VAS) by a designated nurse named Weiqiong Li, once upon recovery and then at 24 and 48 h after surgery. Patients can generally be discharged when their postoperative blood test results are negative and they report no discomfort. Following their surgical procedure, all patients are given instructions to refrain from engaging in physically demanding activities, including exercise and sexual intercourse, for at least one month. Postoperative evaluation appointments are scheduled for all patients at 1 month, 1 year, and 5 years after the surgery. During each visit, patients undergo a standardized history assessment, which includes symptom evaluation of POP, completion of the PISQ-12 and PFIQ-7 questionnaires to assess sexual function and quality of life in relation to pelvic floor disorders, and revaluation for POP-Q in the clinic.

**Outcome measures**
The outcome data will be recorded at enrollment, upon completion of treatment following allocation, and during three follow-up periods: 1 month, 1 year, and 5 years post-surgery (Fig. 2). At the initial assessment, several baseline factors will be recorded, including age, body mass index (BMI), parity, surgical history, time since menopause and uterine prolapse, smoking status, medical and obstetric history, history of stress urinary incontinence, use of hormone replacement therapy, and history of constipation, chronic cough, and heavy lifting. All enrolled participants will undergo standard gynecological and pelvic examinations to evaluate the stage of uterovaginal prolapse using the POP-Q method. During their clinic visit, their scores on the PISQ-12 and PFIQ-7 questionnaires will be recorded. Participants will be reminded for follow-up during the phone call.

**Primary outcome measures**

The study aims to examine the success rate of uterine prolapse correction among women after one year of surgery. The primary outcome will focus on measuring the proportion of women who have achieved successful correction of the condition. The criteria for determining successful correction will be based on established clinical standards and guidelines.

**Secondary outcome measures**

The study will assess several secondary outcomes, which can be categorized into three groups: intraoperative parameters, postoperative parameters, and follow-up parameters. Intraoperative parameters will include the operation method, operation time, uterus weight, intraoperative complications, changes in hemoglobin level, and operative blood loss. Postoperative parameters will include postoperative pain scores (measured using the VAS at different time points: immediately after the operation, at 24 hours, and at 48 hours after surgery), defecation time after the surgery, fever (defined as an axillary temperature exceeding 38°C), urinary retention, vessel thrombosis, postoperative infection, urinary system injury, changes in postoperative POP-Q stage, length of postoperative hospital stay, and cost of hospitalization. Follow-up parameters will include the occurrence or recurrence of urinary incontinence, coital pain, recurrence of changes in POP-Q stage at 1 month, 1 year, and 5 years after surgery, scores from the PFIQ-7 at 1 month, 1 year, and 5 years after surgery, and scores from the (PISQ-12) at 1 year and 5 years after surgery.

**Statistical methods**

**Sample size calculation**

The study seeks to investigate whether vNOTES-HULS is a non-inferior alternative to cLap-HULS for managing uterine prolapse, as determined by the success rate one year after surgery. The assumptions for calculating the sample size are based on a 2019 meta-analysis and supplemented with data from our department. According to the meta-analysis, the anatomic success rate (defined as POP-Q < II stage) for patients undergoing cLap-HULS was about 95% [18]. In our department, the success rate for uterine prolapse treated with either cLap-HULS or vNOTES-HULS has been over 99% in more than 200 patients over the past few decades. Therefore, we hypothesize that the overall success rate will be approximately
97% for all cases. The sample size has been calculated with a non-inferiority margin of 10% (\(\beta = 0.2\) and one-sided \(\alpha = 0.025\)). A total of 92 patients (46 in each group) will be required for the study. Considering 20% potential dropouts, a total of 116 patients will be recruited (58 in each group).

Data collection and management

All data collected from electronic medical record, and relevant manual records will be recorded on the case report form by the blinded research staff, YL. Data entry, includes quality checks and validation through double entry. Missing data will be compared with the matching handwriting case report form and corrected accordingly. The data will be stored in a password-protected computer accessed only to WH. The identity and privacy of the participants will be strictly protected. Each enrolled participant will be assigned a unique subject ID number, which will represent their identity and be entered into the database. All data collection, transfer, processing, and storage will comply with data protection and privacy regulations throughout the study.

Data analysis

The raw data obtained will be analyzed using SPSS Statistics version 26 for Windows (SPSS Inc., Chicago, USA). Continuous data will be reported as mean ± standard deviation (SD), while categorical variables will be presented as frequencies and percentages. To compare continuous outcomes between the two groups, an unpaired Student's \(t\)-test will be utilized. For categorical outcomes, either Pearson's Chi-square test or Fisher's exact test will be employed. The paired \(t\)-test will be used to examine the before-and-after difference. In cases where there is a significant imbalance in baseline characteristics between treatment groups, a logistic regression adjusting model will be applied to adjust for the baseline covariates for binary outcomes. Missing data will be imputed using the multiple imputation method under the assumption of missing-at-random. Statistical significance will be determined as a two-sided value of \(P < 0.05\).

Oversight and monitoring

Data monitoring

In this single-center RCT with a relatively small sample size and low-risk intervention, a Data Monitoring Committee is not employed. Instead, the trial is overseen by a trial steering committee composed of experts in trial evaluation and governance from Meizhou People's Hospital. These committee members convene regular annual meetings to assess the progress of the trial and address any outstanding issues. Furthermore, the trial is registered and supervised by the Department of Health Science, Technology, and Education of the National Health Commission (https://www.medicalresearch.org.cn).

An interim analysis is conducted each year, and the corresponding analysis report is submitted to both the trial steering committee and the Department of Health Science, Technology, and Education of the National Health Commission. The report contains comprehensive information, encompassing ineligible patients, reasons for treatment cessation, adverse events and serious adverse events, protocol deviations
among enrolled participants, and the recurrence rate of all participants, among other relevant factors. Evaluating the report, the trial steering committee deliberates and proposes written recommendations to the study director, including decisions on whether to continue enrolling participants in the study.

**Protocol amendments**

Amendments to the protocol are permissible following discussion and adoption in the study committee meeting. Amendments to the protocol are allowed as long as they do not pose any medical, financial, or additional risk to the enrolled patients. All modifications to the protocol must be documented in writing and signed by the trial director. Approval from the Institutional Review Board is necessary for significant changes. The revised protocol will be uploaded to the clinical trial registry and distributed to clinical investigators.

**Reporting of adverse events**

Adverse events encompass any undesirable experiences that participants may encounter during the study, regardless of their relation to the intervention. Adverse events will be closely monitored throughout the study, from the implementation phase until its completion. Investigators will document all the pertinent details of the adverse events. The principal investigator will receive notification of any significant adverse events and assess their severity and possible causality. The ethics committee will be provided with a comprehensive record of all adverse events as part of the annual report.

**Dissemination plans**

The findings of this study will undergo a rigorous peer review process and will be published in a reputable scientific journal. In addition to publication, the results will be shared with the scientific community through national and international congresses. To ensure transparency and accessibility, the results will also be registered in the ClinicalTrials.gov registry. To reach a wider audience, the study results will be disseminated through social media channels of Meizhou People's Hospital.

**Discussion**

The surgical procedure known as HULS is commonly used to repair middle compartment POP via cLap. However, an emerging surgical technique called vNOTES, offers several advantages over cLap and vaginal approaches for treating uterine prolapse. These advantages include better exposure, scar-free cosmetic outcomes, reduced postoperative pain, lower complication rates, and faster recovery times [19]. Currently, there are no ongoing studies comparing the treatment efficacy of these two surgical procedures in women diagnosed with stage II or higher uterine prolapse.

The primary objective of this trial is to assess the success rate of vNOTES and cLap-HULS in the treatment of uterine prolapse at 1 year after surgery. If future research establishes the non-inferiority of vNOTES-HULS, it could be a justifiable alternative to cLap. Another consideration is to determine if HULS surgeries with hysterectomy would result in a higher rate of surgical success. It is also important to
examine the success rates at the 1-year mark after surgery and determine if there is a reduced rate of reoperation compared to uterus-preserving surgeries. Despite the controversy, hysterectomy is still performed on patients with uterine prolapse based on patient preference. Recent studies [20, 21] and our own data [17] suggest that vNOTES hysterectomy is a viable alternative to cLap hysterectomy and results in better postoperative outcomes, even for patients with enlarged uterine.

This trial has notable strengths. Firstly, the RCT design enhances the credibility and persuasiveness of its findings. Secondly, unlike previous studies that solely focused on the 1-year success rate, this trial comprehensively evaluates surgical outcomes immediately after the operation and during long-term follow-up. We analyze success rates and perioperative outcomes to gain a comprehensive understanding of the efficacy of the surgical procedure. This approach provides a complete picture of short-term and long-term outcomes, contributing significantly to the body of knowledge. One limitation is the inability to blind surgeons and patients due to trocar-related scars in the cLap group, which could potentially introduce bias.

The eventual results of the trial will contribute to the evidence base supporting the non-inferiority of vNOTES-HULS compared to cLap-HULS for the treatment of uterine prolapse. Additionally, these findings may prompt advancements in surgical management for pelvic floor dysfunction.

**Trial status**

At the time of manuscript submission, the study is in the phase of recruiting. The current version of protocol was 1.0 on July 1, 2022. The anticipated start date for the study is September 15, 2022. The last patient is expected to be included at the end of 2026.

**Abbreviations**

POP, Pelvic organ prolapse; POP-Q, Pelvic Organ Prolapse Quantification; HULS, high uterosacral ligament suspension; cLap, conventional laparoscopic; vNOTES, transvaginal natural orifice transluminal endoscopic surgery; RCTs, randomized controlled trials; PISQ-12, Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire short form; PFIQ-7, Pelvic Floor Impact Questionnaire Short Form-7; CRP, C-reactive protein; VAS, Visual Analogue Scale; BMI, body mass index.

**Declarations**

Acknowledgments

The authors wish to thank all of the patients, nurses, doctors and researchers who participated in this research.

Author’s contributors
WH and TH conceived the study. TH, LC, SH, LH, PZ CY and QZ participated in the participant recruitment and trial coordination. SH, LH, PZ CY and QZ will be responsible for data collection. WH will be responsible for quality analysis and data storage. WH and TH are the principal investigators and supervised writing the manuscript. All authors have read and approved the final manuscript.

Funding

This work is supported by the Peiyu Program Project of Meizhou People's Hospital (PY-C20222053). The funders of this study have no input into the study design, collection, analysis, and interpretation of data and in writing the manuscript.

Availability of data and materials

The full protocol, participant-level data, and statistical code are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The protocol of the present trial is registered in Chinese Clinical Trial Registry (ChiCTR2200063408). This study protocol (V.01, 1st July 2022) has been approved by the Research Ethics Committee of the Meizhou People's Hospital (No. 2022-C-23) on 3rd October 2022. No important protocol modifications have been made after approval. The study will be reviewed and conducted in accordance with in the Helsinki Declaration. All participants will be informed the detailed information on the aim, protocol and the possible adverse events related to the surgical treatments of the study in oral. All eligible participants will be requested a written informed consent before randomization.

Consent for publication

No identifying images or personal or clinical attributes of study participants are included in this manuscript nor will they be included in any reports on the trial findings.

Competing interests

The authors declare that they have no competing interests.

References


Figures
Figure 1

Flow chart of participating patients in the study. POP: Pelvic organ prolapse; vNOTES, vaginally assisted natural orifice transluminal endoscopic surgery; cLap: conventional laparoscopy; HULS: high uterosacral ligament suspension.
Figure 2

Content for the schedule of enrolment, interventions, and assessments. PFIQ-7: Pelvic Floor Impact Questionnaire short form; PISQ-12: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire short form; POP-Q: Pelvic Organ Prolapse Quantification (system).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITchecklist.docx