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Vaginal hysterectomy versus vaginal assisted NOTES hysterectomy (VANH): a protocol for a randomised controlled trial

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ABSTRACT

Introduction Natural Orifice Transluminal Endoscopic Surgery is a minimal invasive technique using natural body orifices like the vagina. Benefits of a vaginal assisted NOTES hysterectomy (VANH) are no visible scars, less blood loss, shorter surgery time and it allows more women to undergo a hysterectomy in a day-care setting compared with the total laparoscopic hysterectomy. Trials comparing vaginal hysterectomy (VH) and VANH are lacking. The aim of this study is to compare hysterectomy by VANH versus VH for same-day discharge (SDD), complications, surgical outcomes, postoperative recovery, quality of life, costs and cost-effectiveness.

Methods and analysis The study is a single-blinded, multicentre, randomised controlled trial. Eligible women with benign indication for hysterectomy will be randomly allocated to the VH (control) group or the VANH (intervention) group. The primary outcome is SDD. We calculated a sample size of 124 women assuming 27% SDD difference with an alpha of 0.05 and power of 0.8. A total of 83 patients will be included in the VANH-group and 41 patients in the VH-group, using an enrolment ratio of 2:1. Secondary outcomes are; surgery-related complications, surgical outcomes, postoperative recovery, quality of life, costs and cost-effectiveness.

Ethics and dissemination The study was approved on 27 May 2021 by the Ethics Committee of the Zuyderland Medical Centre Heerlen. The first patient was randomised on 8 July 2021. The last participant randomised should be treated before 31 December 2022. The results will be presented in peer-reviewed journals and at scientific meetings within 4 years after starting recruitment.

Trial registration number NCT04886791.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Randomised controlled trial.
⇒ Multicentre study.
⇒ Blinding of participants.
⇒ Limited generalisability.

INTRODUCTION

Hysterectomy is one of the most performed gynaecological surgeries worldwide.[1 2] In the Netherlands they yearly perform about 8000 hysterectomies.[3] The most common benign indications to perform a hysterectomy are uterine leiomyomas (51.4%), abnormal uterine bleeding (41.7%), endometriosis (30%) and prolapse (18.2%).[2 4–6]

The four approaches to perform a hysterectomy for a benign disease are abdominal hysterectomy (AH), vaginal hysterectomy (VH), (total) laparoscopic hysterectomy ((T)LH) and robotic-assisted hysterectomy.[7 8]

The VH is the approach of preference for a benign indication because of quicker recovery and the least amount of complications.[4] Compared with an LH, it is more difficult during a VH to perform an opportunistic salpingectomy and to inspect the abdominal cavity.[9]

The rate of VH and AH has decreased since the introduction of laparoscopy and the number of LH has significantly increased between 2002 and 2012.[10]

In 2004, a novel approach of endoscopic surgery was described, 'Natural Orifice Transluminal Endoscopic Surgery' (NOTES) by researchers at the John Hopkins University.[11] It is a surgical technique using natural orifices of the body (eg, mouth, anus, urethra, vagina) to perform scarless surgery.[12] The first vaginal assisted NOTES hysterectomy (VANH) was performed in 2012.[13]

The Vaginal NOTES (vNOTES) has been described for multiple indications, for example, hysterectomy, adnexectomy, cystectomy, salpingectomy in case of an ectopic pregnancy, myomectomy and sacrocolpopexy.[14–16] The HALON trial was the first randomised controlled trial (RCT) which compared LH with VANH.[17] This trial showed VANH was non-inferior to LH. VANH had a significantly shorter surgery time, allowed more women

to undergo a hysterectomy as a day-care procedure and less postoperative complications compared with LH.[17] A recent published review of Housmans supports this data.[16]

No studies have been performed comparing the VH with VANH. Because the VH is the preferred method to perform a hysterectomy for a benign indication,[18] there is a need to compare VH with VANH. The aim of this RCT is to compare VH with VANH performed as a same-day discharge (SDD) procedure.

METHODS AND ANALYSIS

Aims and outcome measures

The aim of this study is to compare VH with VANH.

The primary outcome is the proportion of SDD. Secondary outcomes are complications scored by Clavien Dindo classification,[19] surgical outcomes (conversion rate, surgery time, blood loss, number of performed opportunistic salpingectomies per group), postoperative recovery (using the EuroQol 5-dimensions 5-levels (EQ-5D-5L) questionnaire and Recovery Index-10 (RI-10) respectively) pain first 7 days postoperative (measured using the Numerical Rating Scale (NRS)), quality of life, costs (eg, intervention and hospital costs, using an adapted version of the iMTA Medical Consumption Questionnaire (iMCQ)[20] and cost-effectiveness. Generally, the ovaries will not be removed, unless explicitly requested by the patient. This will be noted and taken into account.

We hypothesise that women who underwent a VANH procedure are more often able to be treated in an SDD setting.

Patient and public involvement

No patient involved.

Study design, participants

The design of this study is a single-blind, multicentre, RCT. The participating centres (Zuyderland Medical Centre Heerlen and Catharina Hospital Eindhoven) are both non-university teaching hospitals. Patients of 18 years and older of age, Dutch speaking, with a benign indication for a VH and who have given written and oral informed consent are eligible to participate in this study. Exclusion criteria are history of more than one caesarean section, endometriosis, rectal surgery or pelvic radiation, suspected rectovaginal endometriosis, history of pelvic inflammatory disease, virginity, pregnancy, need for concomitant prolapse or incontinence surgery or a contraindication for general anaesthesia.[21] The recruitment has started July 2021 and is ongoing.

Procedures, recruitment, randomisation and collection of data

Patients scheduled for a VH for a benign indication will be informed about the study during their visit at the outpatient clinic. Eligible patients who fulfil the inclusion criteria will be identified and counselled by the research coordinator or staff of the participating centres.

Eligible patients will also be counselled about an elective salpingectomy during surgery. They will be informed, that when participating in this study, it is only possible to undergo the surgery under general anaesthesia. To secure blinding of the participants, general anaesthesia is necessary because a VANH can only be performed using general anaesthesia. Unblinding of the patients is only permissible when a patients life is in danger due to the surgery.

Patients will be informed about the aims, methods, reasonably anticipated benefits and potential hazards of the study. They will be assured that their participation is voluntary and that they are free to discontinue participation at any time. They will be notified that refusal to participate or decision to withdraw will not affect their care. When a patient does not want to participate in the RCT, they are asked to participate in a prospective cohort.

After receiving informed consent, the randomisation procedure with permuted block randomisation will be conducted by the data management programme of Zuyderland Medical Centre. This programme is only accessible for the principal investigator. This principal investigator will inform the attending physician via central telephone about the randomisation. Only 'group A' or 'group B' will be noted in the patient file, without specifying the planned type of surgery. Randomisation will be 1:2 for VH group and the VANH group with a block length of six. Patients are randomly divided in both study groups, using allocation concealment. The study will be single blind with the participants blinded to their treatment allocation.

Online supplemental figure 1 shows the study flowchart. With exception of the baseline questionnaires and the NRS pain score, all questionnaires will be sent by email and the patients will be reminded twice if not completed within 1 day (the first 7 days postoperative) and 1 week (other questionnaires). When a patient decides to discontinue, all the data that is collected until that specific moment can be used. The following baseline characteristics will be collected preoperatively: age, body mass index, ethnicity, education level, vaginal parity, medication use, intoxications, comorbidities, surgical history, indication of surgery, chronic pain defined as pain >6 months not related to indication of surgery and NRS for pain before surgery.

Health-related quality of life (HRQoL) is measured with the EQ-5D-5L, which examines the patient's HRQoL on the day of the interview.[22 23] It comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with five response levels (no problems to extreme problems) and a Visual Analogue Scale (VAS).[24] The EQ-VAS records the patient's self-rated health with endpoints labelled 'the best health you can imagine' at the top and 'the worst health you can imagine' at the bottom. Responses to the EQ-5D dimensions can be converted into an index score representing HRQoL.

The RI-10 questionnaire is a standardised questionnaire to measure five levels of recovery. This includes, for example, feelings, pain, mobility and self-care.

Costs will be calculated by estimating individual resource use by means of a questionnaire based on the iMCQ,[20] completed by patients. The questionnaire has a recall period of 6 weeks. Questions focus on resource use outside the hospital (eg, general practitioner visits, medication), and the use of informal care and productivity losses. Costs within the hospital will be collected using hospital records.

Interventions

All participants will be counselled for SDD. The surgery will be scheduled in the morning before 12:00.

VANH group

Participants will be admitted to the day-care ward. Preoperative cefazolin 2 g and 500 mg metronidazole will be administered intravenously. Elective salpingectomy will be performed on patients' request. During surgery, the surgeon will estimate surgical feasibility and safety of performing elective salpingectomy. The participants receive the standard pain medication according to the local pain protocol. When a patient reports an NRS-score of 4 or higher, additional pain medication will be proposed.

VH group

Participants will be admitted to the day-care ward. Preoperative cefazolin 2 g and 500 mg metronidazole is administered intravenously. Elective salpingectomy will be performed on patients' request. During surgery, the surgeon will estimate surgical feasibility and safety of performing elective salpingectomy. The participants receive the standard pain medication according to the local pain protocol. When a patient reports an NRS score of 4 or higher, additional pain medication will be proposed.

Statistical issues

Sample size

We are arranging a study of independent cases with an enrolment ratio of 1:2 in favour of the VANH group (1 VH vs 2 VANH).

According to literature, the mean postoperative hospital stay after a VH is 1.13 days to 2.2 days.[25–29] A recently performed pilot study showed the feasibility of SDD after a VH with an SDD percentage of 63%.[30] The HALON trial reported SDD in 77% of the patients undergoing a VANH procedure.[17] We hypothesise 50% SDD is feasible in the control group and 77% SDD in the intervention group. With an alpha of 0.05 and a power of 0.8 and an enrolment ratio of 1:2, this will result in a total of 36 patients in the control group and 72 patients in the intervention group. Taking 15% lost to follow-up in account, we have to include 124 patients of which 41 patients randomised in the control group and 83 patients in the intervention group.

Data analysis

The data will be analysed using SPSS (V.26), based on an intention-to-treat principle a per-protocol analysis will be performed, the data will be stratified for centre. If the treatment effect is homogenous across centres we will also perform an un-stratified analysis.

Differences in baseline/patient characteristics between the VANH and VH group will be will be analysed by an independent sample t-tests or a Mann-Whitney U tests in case of non-normal distribution for numerical variables. For categorical variables, the χ^2 tests or the Fisher's exact tests will be used. Depending on the number of missing values, the missing values will be excluded or imputed. Imputation of the results will be executed according to the guidelines of Jakobsen *et al*.[31] The primary outcome, that is, proportion of SDD between both groups, will be analysed by univariable and multivariable logistic regression analyses.

For numeric secondary outcomes, the independent sample t-test will be used. The categorical secondary outcomes will be analysed using univariable and multivariable logistic regression analyses.

An economic evaluation will be performed alongside the clinical trial to determine the cost-effectiveness of VANH compared with VH. The evaluation adopts a societal perspective and has a time horizon of 3 months and adheres to the Dutch guideline for economic evaluations in healthcare and the Dutch manual for costing research.[32 33] Societal costs over the study period will be calculated by multiplying individual resource use (as collected with the adapted iMCQ and using hospital records) with the costs per unit. The quality-adjusted life year (QALY) is the health outcome of choice in the economic evaluation and is calculated using the EQ-5D-5L index scores at baseline, 6 and 12 weeks, by means of the area under the curve method. Cost-effectiveness is then expressed in the incremental cost-effectiveness ratio (ICER): the difference in costs between the two treatments divided by the difference in QALYs. Bootstrapping techniques will be used to summarise the uncertainty in estimates of incremental costs, effects and the ICER. In addition, the probability of VANH being more cost-effective compared with VH, for a range of maximum monetary values that a decision-maker might be willing to pay for a QALY gained, is presented in a cost-effectiveness acceptability curve. Several one-way sensitivity analyses and scenario analyses will be performed to assess the robustness of results.

DISCUSSION

Since vNOTES is an upcoming minimally invasive surgical technique, valuable research is needed to define the indications for VANH.

Recent evidence shows VANH to be an effective and safe technique with potential benefits like shorter surgery time, a higher percentage of surgery in a day-care setting

and less postoperative complications compared with LH.[16 17 34 35]

To our knowledge, the VANH trial is the first multicentre RCT to compare VH with VANH as SDD procedure and investigates complication rates, treatment-related outcomes, postoperative recovery and quality of life and cost-effectiveness.

It is important to compare the VANH with the VH for benign indications. This research contributes to gain insight in the safety and feasibility of this new emerging technique. It contributes to a safe implementation and further development of this method.

ETHICS AND DISSEMINATION

The VANH trial protocol and the informed consent documents have been approved on 27 May 2021 by the Ethics Committee of the Zuyderland Medical Centre Heerlen. The protocol of the VANH trial is registered at the ClinicalTrials.gov register; on 24 May 2021.

All eligible women will receive a patient information folder with details about the design of the study, the aim and background of the study and the pros and cons of participating in this study. Written informed consent will be obtained from all participants. This will be obtained by the principal investigator (IB), the project leader (MMLHW) or the subinvestigator (NACS). There is also an insurance for the participants (see online supplemental file 2).

In case of important modifications of the protocol or the informed consent documents, the Ethics Committee of Zuyderland Medical Centre Heerlen, all trial participants and ClinicalTrials.gov will be informed.

The VANH trial is non-commercial and investigator driven. All authors declare that there are no competing interests.

An encrypted Excel key file has been made. In this file, the participants number will be linked to the concerning study number. Only the (head)investigators have access to this file. The obtained data will be saved in an electronic case report form (CRF) in the programme 'Research Manager', for which a password is necessary. Here as well only the (head)investigators have access. All paper documents, like the informed consent, baseline questionnaires and CRF papers, will be stored in a chart. This chart will be stored in a locked closet. On the informed consent forms no study number will be mentioned, thus the study number can not be tracked back to the participant.

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Contributors IB and MMLHW were responsible for the development of the trial protocol. IB was responsible for the logistical aspects of the trial. MMLHW, HAAMvV, AD and NACS managed the trial in the different hospitals and commented on the protocol and the paper. LH and IB were responsible for the trial coordination. All authors read and approved the final paper.

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