Article Type: Randomised Controlled Trial

Hysterectomy by Transvaginal Natural Orifice Transluminal Endoscopic Surgery versus laparoscopy as a day-care procedure: a randomised controlled trial.

Running title: Day- care hysterectomy by vNOTES or laparoscopy: a randomised trial

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ABSTRACT

OBJECTIVE

To compare hysterectomy by Transvaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) versus total laparoscopic hysterectomy (TLH) as a day-care procedure.

DESIGN

Parallel group, 1:1 randomised single-centre single -blinded trial, designed as a non-inferiority study with a margin of 15%.

SETTING

Belgian teaching hospital.

POPULATION

Women aged 18-70 years bound to undergo hysterectomy for benign indication.

METHODS

Randomisation to TLH (control group) or vNOTES (experimental group). Stratification according to uterine volume. Blinding of participants and outcome assessors.

MAIN OUTCOME MEASURES

The primary outcome was hysterectomy by the allocated technique. We measured the proportion of women leaving within 12 hours after hysterectomy and the length of hospital stay as secondary outcomes.

RESULTS

We randomly assigned 70 women to vNOTES (n=35) or TLH (n=35). The primary endpoint was always reached in both groups: there were no conversions. We performed a sensitivity analysis for the primary outcome, assuming one conversion in the vNOTES group and no conversions in the TLH group: the one-sided 95% upper limit for the differences in proportions of conversion was estimated as 7.5%, which is below the predefined non-inferiority margin. . More women left the hospital within 12 hours after surgery after vNOTES: 77 versus 43%, difference 34% (95%CI, 13 to 56%), P=0.007. The hospital stay was shorter after vNOTES: 0.8 versus 1.3 days, MD, -0.5 days, (95%CI, -0.98 to -0.02), P=0.004.

CONCLUSIONS

vNOTES is non-inferior to TLH for successfully performing hysterectomy without conversion. Compared to TLH, vNOTES may allow more women to be treated in a day-care setting.

FUNDING

No funding by any third party.

KEYWORDS

Randomised controlled trial, vNOTES, laparoscopic hysterectomy, day-care surgery, core outcome set.

TRIAL REGISTRATION

Trial registration: ClinicalTrials.gov NCT02631837; www.clinicaltrials.gov —HALON study.

TWEETABLE ABSTRACT

RCT: vNOTES is just as good as laparoscopy for successful hysterectomy without conversion but allows more day-care surgery.

INTRODUCTION

Hysterectomy is worldwide the most frequently performed major surgical procedure in gynaecology. There are currently four approaches to hysterectomy: abdominal hysterectomy (AH), vaginal hysterectomy (VH), laparoscopic hysterectomy (LH) - either totally laparoscopic (TLH) or laparoscopy-assisted (LAVH) - and robotically-assisted hysterectomy (RH). A Cochrane review including 47 randomised trials (RCTs) in 5102 women advises VH to be the preferred technique in women in whom this is feasible. When VH is not applicable, LH may be used as an alternative approach, but at the cost of an increased risk of urinary tract injury.[1] Overall hysterectomy rates and the proportions of the different types vary markedly across countries. Based on data of the National Institute for Health and Disability Insurance in Belgium in 2016 the relative contribution of the different techniques was as follows: AH 18%, VH 28%, LAVH 17% and TLH 31%. Out of 11364 hysterectomies only 86 procedures (0.7%) were done as a day-care surgical procedure.

Natural Orifice Transluminal Endoscopic Surgery (NOTES) uses the natural orifices of the human body as a surgical access route. Its first use in an animal model was reported in 2004.[2] Su et al. published the first series of 16 women undergoing transvaginal NOTES (vNOTES) hysterectomy in humans in 2012.[3]

We report on the first randomised controlled trial of Transvaginal Natural Orifice Transluminal Endoscopic Surgery hysterectomy for benign disease. The study objective was to compare vNOTES hysterectomy with total laparoscopic hysterectomy (TLH) as a day-care procedure. Our study hypothesis was that the new experimental technique (vNOTES) was non-inferior to the established effective technique (TLH) for successfully removing the uterus while being superior for one or several secondary outcomes predefined in the study protocol (Appendix S1). The non-inferiority design was based on the superiority of TLH to avoid open surgery when vaginal hysterectomy is not feasible. [1]

METHODS

Study design and participants

Our study, the Hysterectomy by trans-Abdominal Laparoscopy Or NOTES (HALON) – a parallel group 1:1 randomised controlled non-inferiority trial- was conducted from December 2015 to June2017 at the department of Obstetrics and Gynaecology of the Imelda hospital, a teaching hospital in Belgium. The study was approved by the ethics board of the Imelda hospital (B689201526261**)** and was conducted in compliance with the ICH Good Clinical Practice guideline and the Belgian Law of May 7, 2004 related to experiments on humans. The trial was registered as NCT 02631837. We published the study protocol as an open access paper.[4]

Women between 18 and 70 years were eligible for the study if they were scheduled to undergo hysterectomy for benign disease. Common surgical indications for hysterectomy were: symptomatic uterine fibroids, adenomyosis, high grade cervical dysplasia, treatment refractory dysfunctional uterine bleeding, atypical endometrial hyperplasia and BRCA positive women 45 years of age or older. Women with a history of rectal surgery, suspected

rectovaginal endometriosis, suspected malignancy, pelvic inflammatory disease (PID), active lower genital tract infection, virginity or pregnancy were not eligible. There were no limitations with respect to the Body Mass Index (BMI) or uterine volume. All participants needed to provide written informed consent before surgery.

ProceduresOn the day of the planned hysterectomy (Thursday or Friday) all participating women were admitted to the surgical day-care unit from 07:30 am. The nursing staff administered clindamycin cream on admission. All surgeries were scheduled as a first or second case from 08:00 am. All hysterectomies were done by one surgeon (JFB); he had introduced NOTES in our department since November 2013 and had performed at least 200 vNOTES procedures before the beginning of the trial. In women allocated to the experimental arm the surgeon (JFB) performed a vNOTES hysterectomy (VNH) (Video S1). First, four superficial non therapeutic skin incisions were made in all women of the vNOTES group, identical to those in the control group to blind participants, personnel of the day-care unit and the outcome assessor. The surgeon (JFB)created access to the peritoneal cavity by circumcising the cervix, performing an anterior and posterior colpotomy, and cutting the uterosacral ligaments as done in conventional vaginal surgery when possible (VANH technique: Vaginally Assisted NOTES Hysterectomy). In some cases classical colpotomy was not possible: the surgeon (JFB) used the vNOTES port (GelPOINT® Advanced Access Platform, Applied Medical, Rancho Santa Margarita, California, US) and the endoscopic instruments to make an anterior or posterior incision in the vaginal vault (TVNH technique: Total Vaginal NOTES Hysterectomy). After obtaining access to the peritoneal cavity a vNOTES port was inserted through the vagina into the peritoneal cavity to establish a pneumoperitoneum. This device enables inserting several trocars through a single port. A standard 10 mm rigid mm 0° laparoscope (Olympus Corporation, Tokyo, Japan) was used

through one trocar and two endoscopic instruments (Olympus Corporation, Tokyo, Japan) through the other two trocars. The ureters were identified but not routinely dissected. The surgeon performed the hysterectomy by dissecting from caudally to cranially using endoscopic instruments with bipolar coagulation (HiQ+ Bipolar, Olympus Corporation, Tokyo, Japan; Voyant, Applied Medical, Rancho Santa Margarita, California, US). The Fallopian tubes were removed in all women after counseling, the ovaries were removed when indicated. At the end of the hysterectomy, the surgeon removed the vNOTES port and the uterus through the vagina. The vaginal cuff was closed similar to conventional vaginal surgery.

In women allocated to the control arm, the surgeon performed a TLH using the laparoscopic closed entry technique with the insertion of a Veress needle (Karl Storz, Tuttlingen, Germany), one 10 mm intra-umbilical primary trocar and three 5 mm accessory trocars. A standard 10 mm rigid mm 30° laparoscope (Olympus Corporation, Tokyo, Japan) was used. The ureters were identified but not routinely dissected. A Hohl uterine manipulator (Karl Storz, Tuttlingen, Germany) was used. The hysterectomy was performed by dissecting from cranially to caudally using bipolar coagulation. The vaginal cuff was sutured laparoscopically using intracorporeal knot tying.

At the end of all hysterectomies a vaginal plug (betadine gauze 10cmx5m) was left in place to be removed after 3 hours together with the Foley catheter. Cefazolin 2g and metronidazol 1.5g were administered intravenously at the beginning of each procedure. The care given by the anaesthesiologists and the nursing staff was standardized and similar in both groups. A study specific pain protocol was developed by the anesthesiologists involved in the trial (PADM and ILR). A nursing protocol was written by a senior nurse of the surgical day-care

unit (IV) for the purpose of standardising nursing care .. At 6:00 pm the outcome assessor (JJAB) evaluated the condition of all participants. He checked the vital parameters and enquired if women preferred to leave the day-care unit or not. In accordance with the day-care unit discharge policy participants were discharged when assessed as well enough and able to cope independently or with assistance from a partner or relative who stayed with them at home. The outcome assessor ensured that clinical notes were completed and filed correctly in the electronic patient file. A discharge letter was handed for the family physician as well as telephone numbers for contact in case of adverse events. Follow-up visits by the outcome assessor were done at days 7 and 42. Questionnaires were sent at three and six months following hysterectomy. For a detailed description of the trial interventions and the follow-up visits we refer to the published study protocol.[4] The HALON trial was registered as NCT 02631837 in ClinicalTrials.gov.

Outcome measurements

The primary outcome was removal of the uterus according to the allocated technique. Secondary outcomes were duration of the surgical procedure, the proportion of women leaving the hospital within 12 hours after surgery, length of hospital stay, total amount of analgesics used and the VAS pain scores measured twice daily during the first week following surgery. We searched the CROWN database (http://www.crown-initiative.org) for a core outcome set on hysterectomy for benign disease and found no match. We therefore decided to contact ten women treated by total vaginal NOTES hysterectomy in an observational study published by our group for a short interview by telephone[5]. We asked women if they would have preferred leaving the hospital on the day of the hysterectomy and the risk of conversion of a new surgical technique they would accept if this new technique

could avoid visible surgical scars. We used these patient reported outcomes as a basis for the sample size calculation.

Direct health-related costs were measured using the total hospital bill for all costs incurred up to six weeks as a parameter. Occurrence and severity of dyspareunia before surgery and at three and six months after hysterectomy were assessed using a simple questionnaire and VAS score. Quality of life was measured at baseline and at three and six months after hysterectomy using the two part EQ-5D-3L questionnaire (VAS and descriptive system) with permission of the EuroQol Research Foundation.

We measured the following adverse events: postoperative infection, complications during surgery and in the first six weeks after hysterectomy and hospital readmission within six weeks after surgery. We used the 2004 modified Clavien-Dindo classification of surgical complications[6]. Any deviation -even asymptomatic- from the normal postoperative course constitutes a surgical complication.

Sample size calculation

The study was designed as a non-inferiority study. Our hypothesis was that women would accept a higher conversion rate of 15% for vNOTES driven by their preference to avoid visible scars. We refer to the telephone interview of ten women treated by total vaginal NOTES hysterectomy[5]. Women were asked to choose among five cut-off rates (5%, 10%, 15%, 20% or 25%). Most women indicated 15%. We had informed women that the mean conversion rate from LH to AH was 5% (range 0% to 19%), reported in the literature [7]. We would conclude non-inferiority when the upper limit of the one-sided 95% confidence interval for the difference in the proportions of women who had the uterus removed by the

allocated technique would be below 15%. Before starting the trial, we calculated that we needed to include 54 women to demonstrate non-inferiority of vNOTES compared to TLH for the primary outcome (power 80%, alpha error of 5%). To account for a potential drop-out of 15%, the final sample size was set at 64 participants (32 women per group).

Randomisation, blinding and treatment allocation

Eligible women were informed about the trial by a gynaecologist working at the department. After written informed consent, all women were randomised for vNOTES or TLH using computer generated random number lists. Randomisation was stratified for the clinically estimated uterine volume into category A (uterine size < 10 weeks), category B (uterine weight 10 to 16 weeks) or category C (uterine size > 16 weeks), and performed by an officer, who was otherwise not involved in the trial, using a list of random numbers (0 or 1) generated using free online software (https://www.randomizer.org). Allocation was concealed by sequentially numbered, opaque sealed envelopes. The day before surgery, participants were randomly allocated to the intervention (vNOTES) or control (TLH) group.

All procedures in the study (vNOTES and TLH group) were performed by one surgeon (JFB). To assure blinding of participants, personnel of the day- care unit and the outcome assessor, four superficial non therapeutic skin incisions were made in all women of the vNOTES group, identical to those in the TLH group. Intra- and postoperative care was standardized to minimize the risk of performance bias. Post-operative assessment of all participants and data collection were done by a second surgeon (JJAB) who was blinded for the type of procedure performed. When writing the study protocol we decided not t do a formal evaluation of the success of blinding in the HALON trial: at the present, none of the

methods of formal assessment of blinding in clinical trials are commonly used or regarded as standard.[8]

Statistical analysis

We refer to the statistical analysis plan (Appendix S2). All analyses were performed by the intention-to-treat principle. Data analysis was done by a biostatistician who was otherwise not involved in the daily conduct of the trial or data collection. A non-inferiority analysis was performed for the primary endpoint by estimating the one-sided 95% upper confidence limit for the difference in conversion rate between vNOTES and TLH. Superiority analysis and two-sided tests were applied for all secondary endpoints. For dichotomous secondary outcome measures, comparisons between the two arms were performed by applying Fisher exact test or Chi-square test, as appropriate. Cross-sectionally measured continuous secondary outcomes were analysed using an independent T-test or Mann–Whitney U- Test, as appropriate. Longitudinally measured continuous secondary outcomes were analysed using multilevel modelling. A sensitivity analysis was performed using multiple imputation for missing values. P-values of less than 0.05 were considered to indicate statistical significance. Data analysis was performed by A.L. using SAS software (version 9.4 SAS® System for Windows, SAS Belgium, Tervuren, Belgium).

Role of the funding source

The HALON trial was an investigator-driven trial. All the costs of the design and the conduct of the trial were paid by the investigators without funding by a pharmaceutical company or any other third party.

RESULTS

Figure 1 shows the CONSORT flow chart of the trial. Between December 9, 2015, and February 23, 2017, 194 women were screened for eligibility: 108 preferred hysterectomy by vNOTES outside the trial to avoid visible scars, nine 9had a strong preference for a specific technique and sevendeclined to participate in a clinical trial. The 70 women who provided written informed consent were randomly allocated to vNOTES (n=35) or TLH (n=35). Data on the primary outcome were available for all women.

Baseline characteristics were comparable between the two groups except for a lower proportion of dyspareunia at baseline in the TLH group (OR 0.29, 95% CI 0.09 to 0.86, P = 0.03). The baseline characteristics of women in the HALON trial were comparable with those of 124 women who were eligible for inclusion but declined to provide written informed consent (Table 1).

Primary outcome

. . In both groups, the uterus was removed by the allocated technique in all women (Table 2). There were no conversions, hence the confidence interval for the difference between both comparison groups cannot be determined. We performed a sensitivity analysis for the primary outcome while assuming one case of conversion in the vNOTES group and no conversions in the control group: the one-sided 95% upper confidence limit for the differences in proportions was estimated as 7.5%. This upper limit is below the predefined 15% non-inferiority margin.

Secondary outcomes

We refer to Table 2 for the findings of the main secondary outcomes of the HALON trial. The duration of a vNOTES hysterectomy was shorter compared to TLH (41 versus 75 minutes; MD, -34 minutes; 95% CI, -46 to -22 minutes; P<0.001). More women left the hospital within 12 hours of hysterectomy after a vNOTES procedure versus TLH (77% versus 43%; difference, 34%; 95% CI, 13% to 56%; P=0.007). Hysterectomy by vNOTES was associated with a shorter length of hospital stay compared to TLH (0.8 versus 1.3 days; MD, -0.50; 95% CI, -0.98 to -0.02 days; P=0.004). The total amount of analgesics used during the first seven days following surgical treatment was less in the vNOTES group (8 versus 14 units; MD, - 6 units; 95% CI, -10 to -2 units; P=0.006), where women also self-reported lower VAS pain scores (P=0.003) (Fig. 2).

There were less postoperative complications in women treated by vNOTES (9.0 % versus 37 %; RD, -28 %; 95% CI, -47 to -10%; P = 0.009). There were no differences between vNOTES hysterectomy and TLH for the occurrence of postoperative infection, intra-operative complications or hospital readmission within six weeks .

There were no differences between both comparison arms for the other predefined secondary outcomes (direct health-related costs incurred up to six weeks after hysterectomy based on the hospital bill, occurrence and severity of pain on sexual intercourse at three and six months and health-related quality of life at three and six months). These findings are presented online as Table S1. Finally table S2 presents an overview of the types of surgical complications and the reasons for hospital readmission in both treatment arms.

The majority of all surgical complications (14/17 or 82%) were grade I-II according to the Clavien-Dindo classification: these are minor events. There were three grade III-IV complications (3/17 or 18%): these are major events. There were no deaths or lasting disabilities caused by surgery in the trial.

There were no deaths or lasting disabilities caused by surgery in the trial.

DISCUSSION

Main findings

In this first ever-reported randomised trial comparing vNOTES and TLH we found that vNOTES was non-inferior to TLH for doing hysterectomy by the allocated technique without conversion: based on the findings of a sensitivity analysis we can state with confidence that non-inferiority of vNOTES has been demonstrated in the more disadvantageous situation of one conversion for the experimental treatment (vNOTES) compared to no conversions in the control group (TLH). vNOTES was associated with a shorter length of hospital stay and more women leaving the day-care unit within 12 hours after the intervention.There was no evidence of differences between both techniques for postoperative infection or hospital readmission rates at 6 weeks after surgery.

Strengths and limitations

This is the first ever randomised controlled trial studying the efficacy and short term safety of vNOTES. We assessed several patient-reported outcomes. Recordings of patient-reported outcome measures (PROMs), such as pain and quality of life reflect, even in this small study, the benefits of vNOTES. PROMs are important to measure the impact of surgery on the daily life of women; in our opinion these should be included in all trials evaluating novel surgical

techniques.[9] The secondary outcomes measured in the HALON study can be used to develop a core outcome set (COS) for hysterectomy in women with benign disease.

Besides these strengths our pilot study has several limitations. HALON is a single-centre trial and all procedures were done by one expert surgeon (no conversions in both groups), which limits the generalisability of the study findings.. We intended to blind personnel, participants and the outcome assessorfor not compromising the internal validity of the HALON trial.[10] To this aim, we uses similarly lookingincisions in all participants: this "sham" surgery was approved by the ethics board.[11] To our judgement this seemed to us a more reliable method of blinding: "sham" abdominal dressings or identically sized plasters still leave room for bias.[12, 13] We cannot exclude that some women may have been able to guess the allocated technique since the use of a transabdominal approach in the TLH group must inevitably cause more pain around the umbilicus as opposed to the vNOTES technique. Blinding in surgical trials remains very difficult, if not impossible.

Being a small single-centre study, the HALON trial is but a first step in a long process of rigorous evaluation of the effectiveness and safety of vNOTES, as outlined by the IDEAL Collaborative Group, an international cooperation between biostatisticians, clinical trial specialists and surgeons.[14-16] We are fully aware that our study findings may raise some controversy due to the perception of a thin line between vaginal hysterectomy and vNOTES hysterectomy. The HALON trial's intention was to compare vNOTES versus laparoscopy for doing a hysterectomy when VH is not an option. This was based on clinical judgment rather than using the Pelvic Organ Prolapse Quantification system (POP–Q) system in the eligibility criteria. This methodological weakness adds further to the limitations on the generalisability.

Interpretation (in light of other evidence)

The findings of a shorter length of hospital stay with vNOTES are consistent with the findings of a systematic review and meta-analysis including two observational studies.[17, 18] Based on the findings of this systematic review length of hospital stay was shorter with vNOTES compared to LAVH. There were no differences between both techniques for complications, Visual Analogue Scores (VAS) pain scores at 12 hours or additional analgesic dose request. There were no data on quality of life, sexual wellbeing or dyspareunia.[19]

The findings of the HALON trial demonstrating less postoperative pain after vNOTES are consistent with the results of a recently reported systematic review including six RCTs and 21 non-randomized trials in 2186 patients undergoing abdominal surgery.[20]

Less postoperative pain, a criterion for discharge from the day-care unit, allowed more women to return home within 12 hours of surgery.

CONCLUSION

Besides avoiding visible scars and while being non-inferior to TLH, vNOTES allows more women to undergo hysterectomy as a day-care surgical procedure. The promising findings of our single-centre pilot RCT constitute a basis on which to design and conduct pragmatic multi-centre trials involving several surgeons beyond their surgical learning curve on the cost-effectiveness of vNOTES. A randomised comparison between vNOTES and VH is equally needed to assess the comparative cost-effectiveness of both techniques. Prospective complication registries should be used to monitor the long term safety of this new technique.

Disclosure of interests

BWJM is supported by a NHMRC Practitioner Fellowship (GNT1082548). BWJM reports consultancy for ObsEva, Merck and Guerbet. JFB reports other from Applied Medical, the authorisation holder of the GelPOINT® Advanced Access Platform, outside the submitted work: he is a paid consultant for Applied Medical (starting December 14th 2016). Applied Medical was not involved in the design, daily conduct or final data analysis of the HALON trial. The remaining authors have no disclosures. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

JFB was the gynaecologist performing all surgical procedures and was involved in the writing of the drafts of the study protocol/ manuscript, JJAB was the outcome assessor, was involved in the writing of the drafts of the study protocol/ manuscript and the data collection, PADM and ILR were responsible for the anaesthesiology of the study participants and the standardisation of peri- and postoperative pain treatment, CM reviewed the manuscript, AL reviewed the draft of the statistical analysis plan written by JJAB and did the final data analysis, PE provided information for the protocol on the assessment of pain during sexual intercourse and sexual well-being and reviewed the manuscript, SW reviewed the manuscript, BWJM reviewed the study protocol and the manuscript.

Details of ethics approval

Approval from the ethics board of the Imelda hospital Bonheiden (date of approval: 01-12-2015; reference number B689201526261). All participants provided written informed consent.

Funding

The HALON study was an investigator-driven non-commercial trial. All costs linked to the design and the daily conduct of the trial were paid by the investigators without any financial support by a pharmaceutical company or any other third party.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1: the full study protocol

Appendix S2: the statistical analysis plan (SAP)

Table S1. HALON trial secondary outcomes.

Table S2. HALON trial types of complications and reasons for readmission.

Video S1. vNOTES hysterectomy surgical video

	TLH (N=35)	vNOTES (N=35)	Non-randomised (N=124)
Age (y) ((range)	49 (34 to 68)	46 (24 to 65)	49 (24 to 68)
BMI (kg/m²) (range)	26 (19 to 43)	27 (18 to 44)	26 (18 to 44)
N vaginal births (range)	1.3 (0 to 3)	1.4 (0 to 4)	1.5 (0 to 4)
Prior surgery (n, %)	16 (46 %)	20 (57 %)	50 (40 %)
Prior Caesarean section (n, %)	5 (14 %)	..8 (23 %)	12 (10 %)
Uterine weight (g)† (range)	177 (28 to 590)	206 (44 to 788)	206 (28 to 788)
Indication for surgery (n, %)			
- **myomatous uterus**	16 (45%)	17 (49%)	51 (41%)
- **adenomyosis**	6 (17%)	6 (17%)	16 (13%)
- **cervical dysplasia**	7 (20%)	4 (11%)	24 (19%)
- **treatment resistant DUB**	2 (6%)	5 (14%)	17 (14%)
- **atypical endometrial hyperplasia**	2 (6%)	2 (6%)	10 (8%)
- **BRCA positive breast cancer**	2 (6%)	1 (3%)	3 (2%)
Pain vagina (n, %) ∫	6 (17%)	15 (43%)	Not available
VAS pain vagina (median ±IQR)	0 (0 - 0)	0 (0 – 4))	Not available
Pain pelvis (n, %)	8 (23%)	12 (34%)	Not available
VAS pain pelvis (median ±IQR)	0 (0 -0)	0 (0 – 4)	Not available
Quality of life (mean ±SD)	77 (18)	75 (18)	Not available

Table 1. Baseline characteristics of the intention-to-treat population*

* There were no significant differences (P<0.05) between the two groups in the baseline characteristics except for pain in the vagina at baseline (∫ P = 0.03 - logistic regression analysis)

† Uterine weight was not measured in two women (one from each group).

DUB: dysfunctional uterine bleeding

IQR: interquartile range

SD: standard deviation

TLH: Total Laparoscopic Hysterectomy

VAS: Visual Analogue Scale

	TLH (N=35)	**vNOTES (N=35)**	**Effect size (95%CI)**
Conversions	0	0	Not estimable
Duration of surgery (minutes) (mean ±SD)	75 (27)	41 (22)	MD -34 (- 46 to - 22) ∫
Discharge day 0 (n, %)	15 (43%)	27 (77%)	RD + 0.34 (+ 0.13 to + 0.56) †
Length of hospital stay (days) (mean ±SD)	1.3 (1.2)	0.8 (0.77)	MD – 0.50 (- 0.98 to – 0.02)§
Total use analgesics (units) (mean ±SD)	14 (11)	8 (6.5)	MD -5.9 (- 10 to - 1.8) ‡
Complications:			
- Intra-operative (n, %)	0 (0 %)	1 (3 %) bladder trauma : n=1	*
- Postoperative (n, %)	13 (37 %) Type I: 2 Type II: 9 Type III: 1 Type IV: 1	3 (9 %) Type I: 1 Type II: 2 Type III: 0 Type IV: 0	RD - 0.29 (- 0.47 to - 0.10) Δ
Postoperative infection (n, %)	2 (6 %)	1 (3 %)	*
Readmission < 6 weeks (n, %)	6 (17 %)	1 (3 %)	*

Table 2. HALON trial main outcomes

CI: confidence interval

MD: mean difference

RD: risk difference

SD: standard deviation

∫ P < 0.001 (Mann-Whitney U test)

† P = 0.007 (Fishers Exact test)

§ P = 0.004 (Mann-Whitney U test)

‡ P = 0.006 (Mann-Whitney U test)

Δ P = 0.009 (Fishers Exact test)

* There were no significant differences (P<0.05) between the two groups (Fishers Exact test)

CONSORT 2010 Flow Diagram

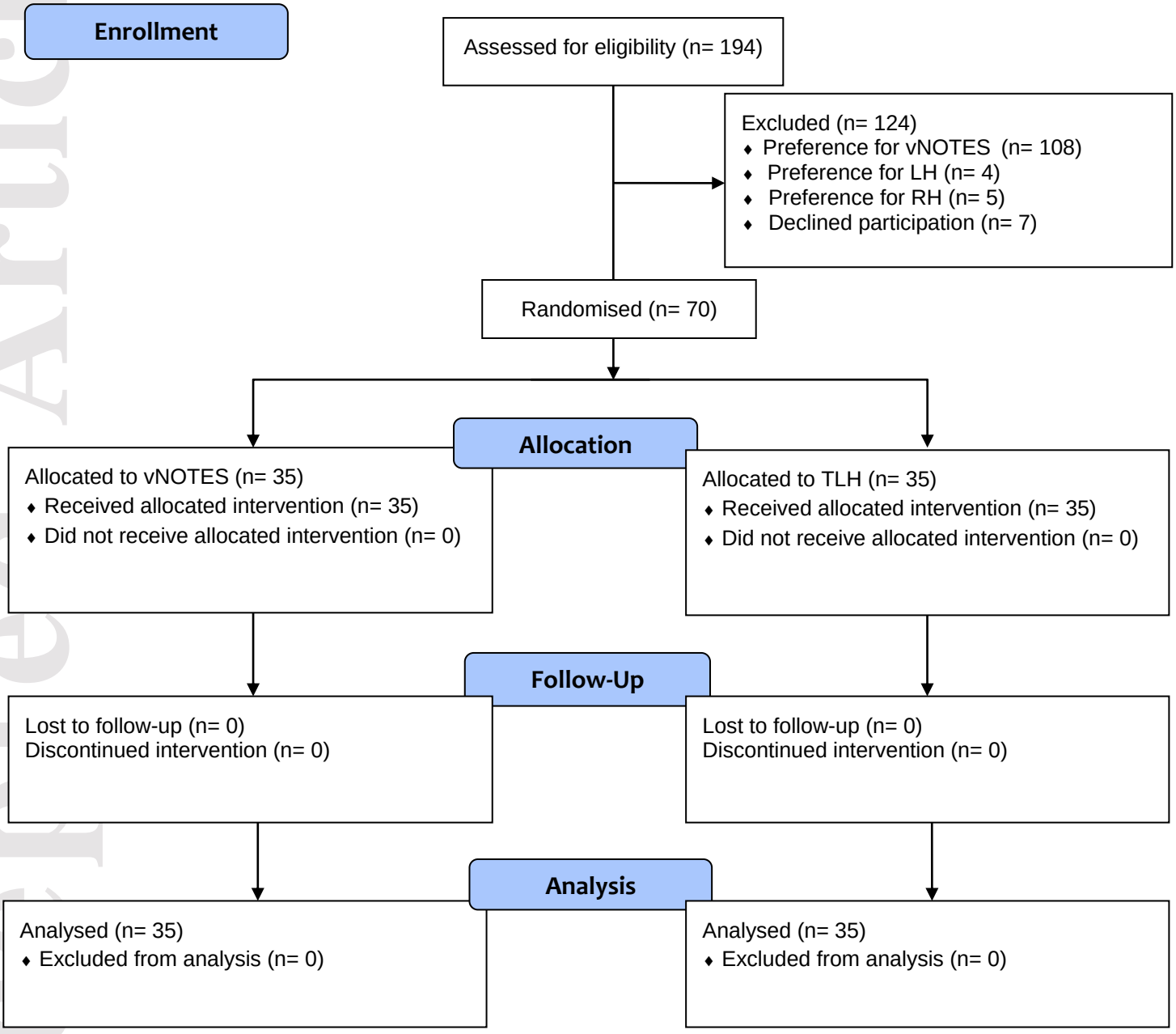

Figure 1. Trial profile

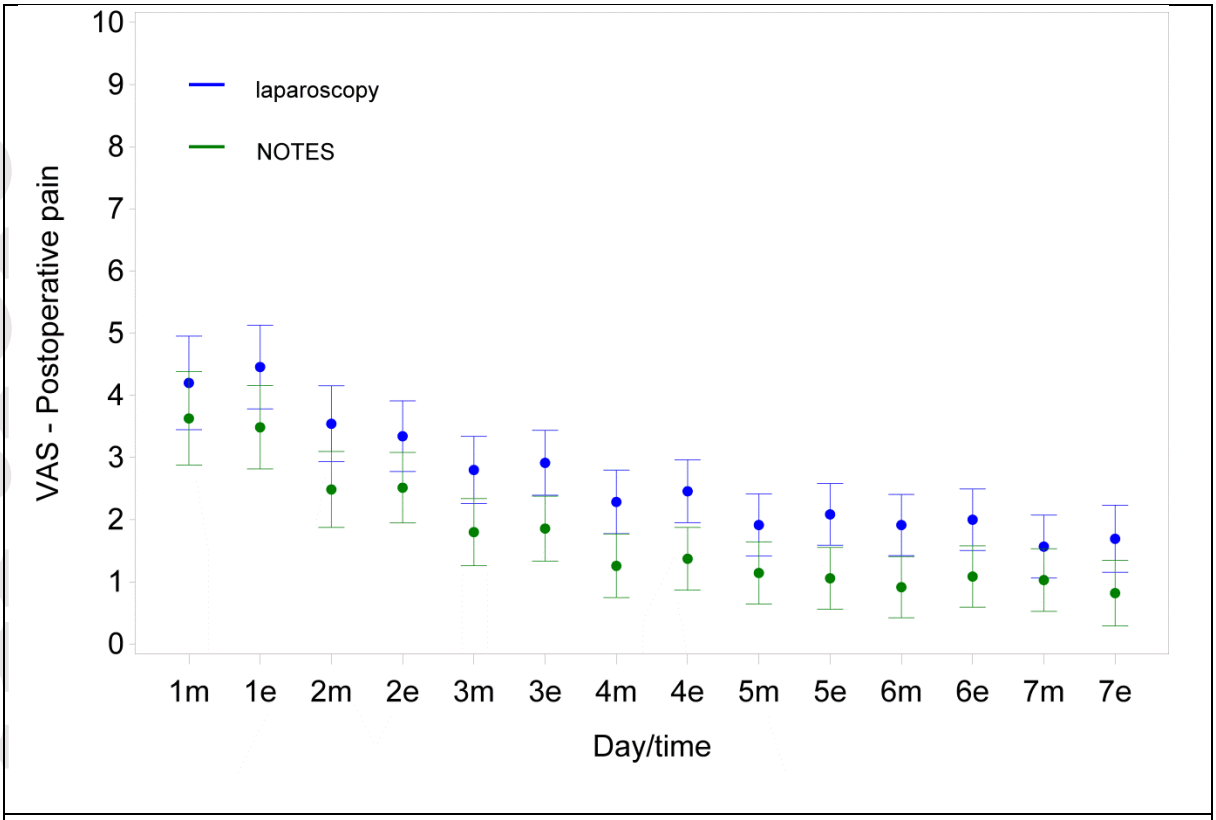

Figure 2. VAS Pain scores.

VAS scores during the first postoperative week by treatment arm and time (+95% CI). The blue dots/ whiskers represent TLH and the green represent vNOTES.

Mean difference, MD; - 0.89; 95% CI, - 0.31 to - 1.5; P = 0.003.

Number 1-7: postoperative day 1-7 m: morning e: evening