Laparoscopic supracervical hysterectomy compared with second-generation endometrial ablation for heavy menstrual bleeding: the HEALTH RCT

Kevin Cooper,[1]* Suzanne Breeman,[2] Neil W Scott,[3] Graham Scotland,[2,4] Rodolfo Hernández,[4] T Justin Clark,[5] Jed Hawe,[6] Robert Hawthorn,[7] Kevin Phillips,[8] Samantha Wileman,[2] Kirsty McCormack,[2] John Norrie[9] and Siladitya Bhattacharya[1,10] on behalf of the HEALTH Study Group

[1]NHS Grampian, Aberdeen Royal Infirmary, Aberdeen, UK
[2]Health Services Research Unit, University of Aberdeen, Aberdeen, UK
[3]Medical Statistics Team, University of Aberdeen, Aberdeen, UK
[4]Health Economics Research Unit, University of Aberdeen, Aberdeen, UK
[5]Birmingham Women's NHS Foundation Trust, Birmingham Women's Hospital, Birmingham, UK
[6]Countess of Chester Hospital NHS Foundation Trust, Chester, UK
[7]NHS Greater Glasgow and Clyde, Southern General Hospital, Glasgow, UK
[8]Hull and East Yorkshire Hospitals NHS Trust, Castle Hill Hospital, Cottingham, UK
[9]Usher Institute of Population Health Sciences & Informatics, University of Edinburgh, Edinburgh, UK
[10]Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK

*Corresponding author kevincooper@nhs.net

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Scientific summary

The HEALTH RCT

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Scientific summary

Background

Heavy menstrual bleeding (HMB) is a common problem that has a major impact on women's physical, emotional, social and material quality of life. The condition is initially treated in primary care by either oral medication or insertion of the levonorgestrel-releasing intrauterine system (Mirena®, Bayer, Whippany, NJ, USA). If medical therapy fails or is deemed unsuitable, surgical treatment can be offered: either endometrial ablation (EA), which destroys the lining of the uterine cavity (endometrium), or hysterectomy (removal of the uterus). Neither medical treatment nor EA can guarantee complete resolution of symptoms and up to 59% of women on oral drugs and 13.5% of those using the levonorgestrel-releasing intrauterine system (Mirena) need surgery within 2 years. Following initial treatment with EA, 19% of women require hysterectomy for relief of their symptoms.

Although clinically and economically more effective than EA, a conventional total hysterectomy is more invasive, poses a higher risk of injury to surrounding organs, involves a longer hospital stay and requires a longer postoperative recovery period. The advantages of total hysterectomy could be maintained, and the risk of complications reduced, by undertaking a laparoscopic supracervical hysterectomy (LASH), in which only the body of the uterus is removed and the cervix is preserved.

Objectives

To compare the clinical effectiveness and cost-effectiveness of LASH with second-generation EA in women with HMB.

Methods

The Hysterectomy or Endometrial AbLation Trial for Heavy menstrual bleeding (HEALTH) was a parallel-group, multicentre, randomised controlled trial involving 31 UK secondary and tertiary hospitals. Women aged < 50 years with HMB who wanted surgical treatment, and had no plans to conceive, were invited to participate. Women were excluded if they met any of the following exclusion criteria: endometrial atypia; abnormal cytology; uterine cavity size > 11 cm; any fibroids > 3 cm; contraindications to laparoscopic surgery; previous EA; and inability to give informed consent or complete trial paperwork.

Interventions and randomisation

Eligible and consenting women were randomised to one of the following two treatment arms in a 1 : 1 allocation ratio using a remote web-based randomisation service:

1. LASH (removal of the body of the uterus by means of keyhole surgery)
2. second-generation EA (destroying the endometrium by means of a silicone balloon containing hot fluid or radiofrequency energy).

The minimisation algorithm was based on centre and age group (< 40 years vs. ≥ 40 years).

Outcome measures

The co-primary clinical outcome measures were (1) patient satisfaction at 15 months post randomisation and (2) the Menorrhagia Multi-Attribute Quality-of-Life Scale (MMAS) score at 15 months post randomisation. The primary economic outcome was incremental cost per quality-adjusted life-year (QALY) gained.

Secondary outcome measures included pain score at days 1–14 and 6 weeks post surgery; acceptability of treatment at 6 weeks post surgery; satisfaction with treatment and MMAS score at 6 months post surgery; menstrual outcomes at 6 months post surgery and 15 months post randomisation; generic health-related quality of life [Short Form questionnaire-12 items (SF-12) and EuroQol-5 Dimensions, three-level version (EQ-5D-3L)] at 6 weeks and 6 months post surgery and 15 months post randomisation; perioperative complications, including recovery details and need for additional gynaecological surgery; cost; and cost-effectiveness.

Blinding

Surgeons and participants could not be blinded to the allocated procedure.

Delivery of the intervention

Randomised participants were placed on the waiting list for the allocated treatment with the anticipation that treatment would occur within 12–18 weeks of randomisation, as per the Scottish and UK government guidelines. Operative techniques were not modified for the purposes of the trial.

Data collection during follow-up

Participant-reported outcomes were assessed by self-completed questionnaires at baseline (before surgery), 6 weeks and 6 months post surgery, and 15 months post randomisation. A self-completed 14-day diary was also collected.

Sample size

It was originally anticipated that 292 participants per group would provide 90% power to detect a difference in satisfaction rates of 8%, and 95% power to detect a 10-point difference in MMAS score [assuming a standard deviation (SD) of 33 units]. Based on an expected 10% drop-out rate, the recruitment target was 648 participants in total (324 participants per group).

Statistical analysis

Stata® version 15 (StataCorp LP, College Station, TX, USA) was used to conduct analyses in accordance with the intention-to-treat principle. Analyses used a two-sided 5% significance level with corresponding 95% confidence intervals (CIs) generated as appropriate. Analysis of the two co-primary outcomes (patient satisfaction and MMAS score at 15 months post randomisation) was conducted in a hierarchy such that MMAS score was considered only if the difference in patient satisfaction was shown to be statistically significant. Secondary outcomes were compared by randomised groups. These analyses were regarded as hypothesis-generating and no adjustment was made for multiple statistical testing.

Economic evaluation

The economic analysis consisted of a trial-based analysis of individual patient-level cost and effect (QALY) data and a Markov modelling component to inform cost-effectiveness in the longer term. Given the limitations of the follow-up period for economic evaluation, the model-based approach forms the primary economic analysis. Costs and outcomes were assessed via the trial case report forms, patient diary of pain symptoms post surgery and postal questionnaires. The EQ-5D-3L scores were used to estimate QALYs.
To estimate longer-term economic differences, a simple Markov decision-analytic model was developed to extrapolate the estimated 15-month difference in utility and simulate the incidence of further gynaecological surgery over time. The key objective of the analysis was to inform the long-term cost-effectiveness of LASH compared with EA.

Management of the study

The study was supervised by the Project Management Group, which consisted of representatives from the study office and grant holders. The study was further overseen by a Trial Steering Committee, which comprised four independent members, and an independent Data Monitoring Committee.

Results

Recruitment

Between May 2014 and March 2017, 2552 potentially eligible patients were screened; 1351 (52.9%) were confirmed as eligible, of whom 664 (49.1%) gave their consent and were randomised. Following randomisation, four women were considered ineligible and treated as post-randomisation exclusions. Therefore, 660 women (330 in each group) were included in the main trial.

Clinical results

Women randomised to LASH or to EA were comparable at baseline in terms of mean age [42.2 (SD 4.89) years vs. 42.1 (SD 4.96) years], body mass index [29.1 kg/m^2 (SD 5.55 kg/m^2) vs. 29.0 kg/m^2 (SD 5.34 kg/m^2)], preoperative haemoglobin levels [131.0 g/l (SD 13.1 g/l) vs. 130.1 g/l (SD 12.6 g/l)] and duration of symptoms [227 (69.4%) participants in the LASH group vs. 216 (66.1%) participants in the EA group for symptoms in excess of 3 years].

There were also no differences between the LASH and EA groups at baseline in the mean values for the MMAS total score [30.5 (SD 19.0) vs. 32.3 (SD 20.0)], EQ-5D-3L utility score [0.71 (SD 0.30) vs. 0.70 (SD 0.31)] and SF-12 physical component score [45.0 (SD 9.0) vs. 44.9 (SD 9.7)] or mental component score [37.2 (SD 11.0) vs. 38.7 (SD 11.6)]. There were no clear differences between the randomised groups with respect to any of the baseline outcomes, including mean bleeding score and mean pain score.

A total of 44 participants who were randomised to either LASH (21/330, 6.4%) or EA (23/330, 7.0%) did not undergo an operation but were sent the final questionnaire at 15 months post randomisation.

The median number of days between randomisation and treatment was higher for those randomised to LASH [84 days, interquartile range (IQR) 57–127 days] than for those randomised to EA (63 days, IQR 41–97 days).

Of those undergoing treatment, 291 out of 309 (94.2%) women randomised to LASH and 297 out of 307 (96.7%) women randomised to EA received the allocated procedure. Women undergoing LASH were more likely to be operated on by a consultant [239 (77.3%) vs. 176 (57.3%)] and required more postoperative opiate injections [94/309 (30.4%) vs. 46/307 (15.0%)]. More women in the LASH arm stayed in hospital for over 24 hours post procedure [99/306 (32.4%) vs. 16/303 (5.3%)].

Primary outcomes at 15 months post randomisation

Based on responses from 278 out of 330 (84.2%) women randomised to the LASH group and 280 out of 330 (84.8%) women randomised to the EA group, women randomised to LASH were more likely to be satisfied with their treatment than those randomised to EA (97.1% vs. 87.1%) [adjusted difference in proportions 0.10, 95% CI 0.05 to 0.15; adjusted odds ratio (OR) from ordinal logistic regression (OLR) 2.53, 95% CI 1.83 to 3.48; $p < 0.001$].

Total MMAS scores, based on responses from 262 out of 330 (79.4%) women in the LASH group and 268 out of 330 (81.2%) women in the EA group, indicate that women randomised to receive LASH were more likely to have the best possible MMAS score of 100 (68.7% vs. 54.5%) (adjusted difference in proportions 0.13, 95% CI 0.04 to 0.23; adjusted OR from OLR 1.87, 95% CI 1.31 to 2.67; $p = 0.001$). They had almost twice the odds of being in a more favourable MMAS category than those allocated to EA (adjusted OR 1.87, 95% CI 1.31 to 2.67; $p = 0.001$).

Twenty-five women experienced a total of 26 serious adverse events (SAEs) (LASH, $n = 15$; EA, $n = 11$). There were no statistically or clinically significant differences between the randomised groups in the proportions having a SAE (adjusted OR 1.30, 95% CI 0.56 to 3.02; $p = 0.54$).

A total of 32 women experienced a complication following surgery. These included voiding dysfunction (LASH, $n = 14$; EA, $n = 2$), consultation for pain (LASH, $n = 1$; EA, $n = 1$), haematoma (LASH, $n = 1$; EA $n = 1$), blood loss > 500 ml (LASH, $n = 1$; EA, $n = 1$), inactive/blunt uterine perforation (LASH, $n = 1$; EA, $n = 3$), pyrexia requiring antibiotics (LASH, $n = 3$; EA, $n = 2$) and blood transfusion (LASH, $n = 0$; EA, $n = 1$).

Eighteen women randomised to EA and two women randomised to LASH received further treatment for HMB during the follow-up period. The most common reason was that the index EA procedure produced an unsatisfactory reduction in HMB ($n = 12$). A further seven women required unplanned further surgery because the index EA procedure could not be completed on first admission; this included one woman who was randomised to LASH but for whom an EA procedure was attempted. On five occasions, a hysterectomy was performed on the second admission.

Postoperative recovery

In the first 14 days following surgery, those in the LASH group had pain scores that were almost 1 point higher than those reported by the EA group (mean difference 0.92, 95% CI 0.59 to 1.24; $p < 0.001$).

By 6 weeks post surgery, over half of the women in both groups reported no pain on a 10-point scale. Those in the LASH group had higher odds of pain at 6 weeks than those in the EA group (adjusted OR 1.43, 95% CI 1.05 to 1.96; $p = 0.03$).

Women in the EA group returned to paid work sooner than those randomised to LASH (median time 10 days vs. 42 days; adjusted hazard ratio 0.23, 95% CI 0.18 to 0.30; $p < 0.001$).

Menstrual outcomes

Fewer women continued to have periods after receiving LASH than after receiving EA [6 months: LASH, 39/253 (15.4%); EA, 111/246 (45.7%) (adjusted OR 0.22, 95% CI 0.15 to 0.32; $p < 0.001$); 15 months: LASH, 52/277 (18.8%); EA, 117/278 (42.1%) (adjusted OR 0.32, 95% CI 0.21 to 0.48; $p < 0.001$)].

A higher proportion of all women (including those with no periods) experienced cyclical pain following EA [6 months: LASH, 68/236 (28.8%); EA, 108/199 (54.3%); 15 months: LASH, 71/224 (31.7%); EA, 118/196 (60.2%)].

Quality of life

At 6 weeks post surgery, those in the EA group had higher EQ-5D-3L utility scores than those in the LASH group (adjusted OR 0.66, 95% CI 0.48 to 0.90; $p = 0.009$). However, at 6 months post surgery and 15 months post randomisation, the point estimates favoured LASH, although the results were not statistically significant (6 months: adjusted OR 1.15, 95% CI 0.84 to 1.57, $p = 0.38$; 15 months: adjusted OR 1.21, 95% CI 0.89 to 1.64, $p = 0.23$).

The results for the visual analogue scale of the EQ-5D-3L tended to favour the LASH group, and this finding was statistically significant at 6 months post surgery and at 15 months post randomisation (6 weeks: adjusted OR 1.12, 95% CI 0.80 to 1.58, $p = 0.51$; 6 months: adjusted OR 1.53, 95% CI 1.08 to 2.17, $p = 0.02$; 15 months: adjusted OR 1.50, 95% CI 1.12 to 1.99, $p = 0.006$).

Health economic results

The mean initial episode costs for LASH and EA were £2757 and £1071, respectively. LASH was more costly than EA because surgical costs were higher, time spent in the anaesthetic room, theatre and in recovery was longer (178 minutes vs. 90 minutes) and discharge from hospital occurred later (23 hours vs. 6 hours). Taking all relevant NHS resource use into account over 15 months, unadjusted mean health service costs were £3004 for LASH compared with £1281 for EA.

Societal costs were also increased following LASH because women who received LASH took longer to return to paid and unpaid productive activities than than who received EA (£2586 vs. £990). Mean out-of-pocket expenses (£9 vs. £7) and the cost of time lost to attend outpatient appointments (£26 and £22) were slightly higher in the LASH group.

The mean EQ-5D-3L scores in the LASH group at baseline, 6 weeks and 6 months post surgery and 15 months post randomisation were 0.7065 (SD 0.30), 0.8279 (SD 0.22), 0.8315 (SD 0.27) and 0.8357 (SD 0.24), respectively. The corresponding mean scores in the EA group were 0.6983 (SD 0.31), 0.8282 (SD 0.28), 0.8269 (SD 0.25) and 0.8005 (SD 0.28), respectively. By 15 months, the EQ-5D-3L score was higher in the LASH group than in the EA group (unadjusted difference = 0.035), although the difference was not statistically significant. At 15 months post randomisation (12 months post surgery), the mean adjusted QALY gain was 0.978 and 0.974, whereas the mean adjusted costs were £2886 and £1282 for LASH and EA, respectively, producing adjusted differences of 0.004 QALYs and £1604. The incremental cost-effectiveness ratio (ICER) for LASH compared with EA was £458,334 per QALY gained at 15 months post randomisation.

Over a modelled 10-year time horizon, in comparison with EA, the intention to treat with LASH resulted in an increased cost to the health service of £1362 per woman, for an expected QALY gain of 0.111 per woman. The corresponding ICER was £12,314 per QALY gained for LASH compared with EA. The chance of LASH being cost-effective ranged from 53% to 80% at cost-effectiveness thresholds of £13,000 and £30,000, respectively. Extending the time horizon of the model from 1 to 10 years reduced the incremental cost of LASH by £242 (from £1604 to £1362), owing to incorporation of the expected costs of further gynaecological surgery.

Conclusion

Laparoscopic supracervical hysterectomy is superior to EA in terms of clinical effectiveness. As EA is quicker, cheaper and associated with an earlier discharge, it is less costly in the short term, but its expected higher failure rate means that LASH could be considered cost-effective by 10 years post procedure. Long-term follow-up is required to verify retreatment rates and their impact on cost-effectiveness.

Trial registration

This trial is registered as ISRCTN49013893.

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This report

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