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Randomised Controlled Trial

Laparoscopic ablation or excision with helium thermal coagulator versus electrodiathermy for the treatment of mild-to-moderate endometriosis: randomised controlled trial

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Objective To compare electrodiathermy with helium thermal coagulation in laparoscopic treatment of mild-to-moderate endometriosis.

Design Parallel-group randomised controlled trial.

Setting A UK endometriosis centre.

Population Non-pregnant women aged 16–50 years with a clinical diagnosis of mild-to-moderate endometriosis.

Methods If mild or moderate endometriosis was confirmed at laparoscopy, women were randomised to laparoscopic treatment with electrodiathermy or helium thermal coagulator.

Main outcome measures Cyclical pain and dyspareunia (rated on a 100-mm visual analogue scale, VAS), quality of life at baseline and at 6, 12 and 36 weeks following surgery, operative blood loss and surgical complications.

Results A total of 192 women were randomised. Of these, 155 (81%) completed the primary outcome point at 12 weeks. In an intention-to-treat analysis, VAS scores for cyclical pain were significantly lower in the electrodiathermy group compared with the helium group at 12 weeks (mean difference, 9.43 mm; 95% CI 0.46, 18.40 mm; $P = 0.039$) and across all time points (mean difference, 10.13 mm; 95% CI 3.48, 16.78 mm; $P = 0.003$). A significant difference in dyspareunia also favoured electrodiathermy at 12 weeks (mean difference, 11.66 mm; 95% CI 1.39, 21.93 mm; $P = 0.026$). These effects were smaller than the proposed minimum important difference of 18.00 mm, however. Differences in some aspects of quality of life favoured electrodiathermy. There was no significant difference in operative blood loss (fold-change with helium as reference, 1.43; 95% CI 0.96, 2.15; $P = 0.081$).

Conclusions Although electrodiathermy was statistically superior to helium ablation in reducing cyclical pain and dyspareunia, these effects may be too small to be clinically significant.

Keywords Endometriosis, laparoscopic surgery, pelvic pain.

Tweetable abstract Helium coagulation is not superior to electrodiathermy in laparoscopic treatment of mild-to-moderate endometriosis.

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Introduction

Endometriosis is described as the presence of endometrium or endometrium-like tissue at sites other than the uterine cavity.[1] This chronic and benign gynaecological condition has a prevalence of approximately 5–10% in women of reproductive age, increasing to 30–50% in cases of infertility.[1,2] Prevalence peaks between 25 and 35 years of age.[1] Symptoms include abdominopelvic pain, dyspareunia and infertility,[3] all of which can decrease quality of life.[4]

Endometriosis is challenging to treat owing to the chronic and recurrent nature of the symptoms, the severity

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of which does not correlate with the extent of disease visualised at laparoscopy, which is the gold standard for diagnosis.[3] There is frequently a significant delay from the onset of symptoms to final diagnosis, leading to further morbidity.[5] The problem is compounded by a lack of objectivity in assessing clinical features, relying upon the subjective perception of pain severity, which shows interindividual variation.

Treatment aims for endometriosis include relieving pain and improving fertility. Analgesia, with or without hormonal therapies, may be used on an empirical basis before a formal diagnosis is made.[6] If symptoms persist despite medical treatment, a 'see-and-treat' approach may be undertaken whereby endometriosis is treated with excision and/or ablation at the initial diagnostic laparoscopy.[6]

A meta-analysis has demonstrated that laparoscopic surgery can improve symptoms of endometriosis.[7] Typically, endometriosis is treated with electrodiathermy; however, there are limitations as to where electrodiathermy can be safely used, for example when close to the bowel or the bladder. An alternative procedure, the helium thermal coagulator, uses a combination of helium gas and very low electrical power (2–8 W) to deliver an inert plasma of gas to the affected tissue. The probe is directed laparoscopically to the affected area and has no physical contact with the tissue when activated. Careful control of power levels allows extremely precise degrees of cauterisation to be applied. Because the interaction between electrons and tissue occurs in helium, no smoke is generated. The low thermal spread potentially allows for the safe ablation of endometriosis over usually inoperable areas that could be injured with the increased penetration of electrodiathermy, such as tissue overlying the bladder, bowel and diaphragm. The National Institute for Health and Care Excellence (NICE) cites evidence relating to the safety of the technique from case series but recognises a lack of evidence relating to efficacy.[8]

The objective of this study was to determine whether laparoscopic treatment of mild-to-moderate endometriosis with a helium thermal coagulator is associated with superior symptom relief and reduced morbidity, compared with treatment using electrodiathermy.

Methods

We conducted a randomised parallel-group controlled trial, with equal allocation, in which patients with mild-to-moderate endometriosis underwent laparoscopic excision and/or ablation of endometriosis with either helium thermal coagulator or hook electrodiathermy.

Participants and recruitment

Women between the ages of 16 and 50 years presenting with pelvic pain and a clinical diagnosis of mild or moderate endometriosis, between January 2014 and September 2017, in a UK gynaecology outpatient clinic, were offered recruitment into the trial following a full explanation. We excluded women with possible gynaecological cancer, women with advanced endometriosis and women who were currently pregnant. The patient then gave written consent and baseline data on outcome measures were recorded prior to surgery. A translator was provided where necessary.

Sample size

To detect a 12-week mean difference in visual analogue scale (VAS) scores for cyclical pain of 18 mm with a standard deviation (SD) of 40 mm (assuming equal allocation, 80% power and a 5% two-tailed significance level), data from a minimum of 79 women in each arm were required. Assuming a maximum of 15% loss to follow up, at least 93 women needed to be recruited to each arm. The SD was set at the highest relevant estimate found in the literature,[9–12] and 18 mm was taken as the minimum important between-group difference (MID), based on information from this literature.[11]

Randomisation

Participants were randomised to laparoscopic ablation and/or excision with either helium thermal coagulator or electrodiathermy. A randomisation list, using random permuted blocks of sizes between 2 and 8, was drawn up by an independent statistician and incorporated in a password-protected database constructed by an information technology specialist who had no other role in the study.

Blinding

The study was double-blinded, whereby participants, assessors and the trial statistician were not aware of the intervention received. Of necessity, the surgeon was not blind to the intervention. As both groups of patients had laparoscopic treatment, there were no indicators to the patients, nursing staff or other clinicians to suggest which intervention had been performed. Postoperative management did not indicate to the women the procedure received, and steps were taken to ensure that this was not revealed by their treating surgeon during postoperative recovery, prior to discharge (approximately 4 hours). An emergency unblinding procedure was in place in the event of readmission with significant postoperative complications.

Procedure

Laparoscopy was performed to either confirm or exclude the diagnosis of endometriosis. If endometriosis was present, staging was performed using the Revised American Society for Reproductive Medicine (RASRM) classification of endometriosis.[13] If no endometriosis was present, or the

extent of the disease was greater than mild to moderate, the patient was not randomised and was excluded from the trial. In cases where endometriosis was confirmed, the surgeon then logged into the randomisation database and was provided with the code for the procedure to be performed (helium thermal coagulator or hook electrodiathermy). In relation to both procedures, the surgeon performed ablation and/or excision, depending upon clinical judgment as to the severity and depth of the disease, and with regard to delicate underlying structures. Intraoperative blood loss and any complications were recorded. The patient was discharged home after approximately 4 hours.

Data collection and outcome measures

Although recently published,[14] no core outcome set for endometriosis was available when the trial was designed to guide the selection of outcome measures. Baseline data on demographics, clinical history and outcome measures were collected prior to surgery. The primary outcome measure was cyclical pain. Secondary outcome measures were dyspareunia, quality of life, operative duration, intraoperative blood loss, intraoperative visceral complications, postoperative complications, and conception rates among those seeking to become pregnant.

Participants were invited to attend a dedicated outpatient follow-up clinic to be assessed by an independent practitioner (research nurse), blind to the procedure that the patient had received. Clinics were conducted at 6, 12 and 36 weeks following surgery. At each visit an assessment of the worst intensity for both cyclical pain and dyspareunia over the previous 4 weeks was performed using a 100-mm VAS, commonly used for endometriosis-related symptoms.[1,9,10,12,15,16] Quality of life was also assessed at these time points using the Endometriosis Health Profile (EHP-30) questionnaire.[17,18] This measure has five 0–100 subscales: pain, control and powerlessness, emotional wellbeing, social support, and self-image. Lower scores indicate a better quality of life.

Postoperative complications were assessed at the 6- and 12-week time points. Any participant who successfully conceived, or attempted to do so, during the 36-week follow up was also noted. Women failing to attend follow up were sent a self-assessment form on the primary outcome (cyclical pain intensity at 12 weeks) and asked to return this by post.

Statistical analysis

Data analysis was blind to group allocation on an intention-to-treat basis. The primary outcome, between-group differences in VAS scores for cyclical pain, was analysed at 12 weeks and also across the full follow-up period, with a linear mixed model (with repeated observations clustered within participants). Using maximum-likelihood estimation, and assuming that values are missing at random, this analysis accommodates missing data and thus includes all randomised participants.[19] Covariates in the model, selected a priori, were baseline VAS scores, age, surgeon (surgeon A or surgeon B), staging on the RASRM classification (mild, moderate or severe) and history of previous pelvic surgery (yes or no). For secondary outcomes, a similar analysis was performed. Pregnancy rates were compared using logistic regression, with maximum-likelihood estimation. A secondary unadjusted analysis was performed on the primary outcome measure, but an intended per-protocol sensitivity analysis was not performed, as all but one participant received the randomised intervention.[20] Statistical significance was set at $P \leq 0.05$ (two-tailed) and 95% confidence intervals (95% CIs) were calculated for all estimates. The assumptions of all statistical models were checked, and data were analysed with SPSS 25 (IBM, Armonk, NY, USA).

Patient involvement

We held a focus group of patients prior to the study to explore the perceived importance of the research, the procedures to be tested, the choice of outcome measures and the timing of their administration. The views expressed in the focus group informed the design of these aspects of the

Table 1. Baseline characteristics (n = 192)

		Diathermy (n = 96)	Helium (n = 96)
Age (years)		28.99 (6.99)	29.03 (7.11)
VAS score for cyclical pain (mm)*		76.52 (19.65)	72.14 (20.68)
VAS score for dyspareunia (mm)**		62.79 (30.49)	66.49 (27.53)
EHP-30 pain		59.00 (20.04)	56.46 (19.74)
EHP30 control and powerlessness		71.35 (22.95)	69.03 (22.93)
EHP-30 emotional wellbeing		55.86 (21.33)	56.79 (22.30)
EHP-30 social support		61.65 (25.11)	57.68 (27.48)
EHP-30 self-image		59.72 (27.30)	57.60 (30.85)
Surgeon: n (%)	A	64 (66.7)	72 (75.0)
	B	32 (33.3)	24 (25.0)
RASRM grade: n (%)***	1	39 (41.5)	37 (41.6)
	2	49 (52.1)	50 (56.2)
	3	6 (6.4)	2 (2.2)
Previous laparotomy or laparoscopy: n (%)****	Yes	46 (48.9)	42 (46.7)
	No	48 (51.1)	48 (53.3)

Values are means (standard deviations), unless otherwise indicated. EHP-30, Endometriosis Health Profile (each dimension scored 0–100; lower scores indicate better quality of life); RASRM grade, Revised American Society for Reproductive Medicine endometriosis classification; VAS, visual analogue scale.
*Four missing values, n_1 = 93, n_2 = 95.
**Six missing values, n_1 = 92, n_2 = 94.
***Nine missing values, n_1 = 94, n_2 = 89.
****Eight missing values, n_1 = 94, n_2 = 90.

study. Two patient representatives were co-applicants on the funding proposal and subsequently became members of the trial steering committee, and these and one other patient representative reviewed the paper prior to submission.

Funding

This study was funded by the National Institute for Health Research under its Research for Patient Benefit Programme (project number PB-PG-0212-27072).

Results

One hundred and ninety-two women were randomised to the two interventions between January 2014 and September 2017. In total, 274 women were excluded from the study, 106 of whom were rejected once in theatre, predominantly because no endometriosis was identified at laparoscopy. Baseline characteristics of randomised participants are shown in Table 1; variables were well balanced across the trial arms. Progress through the trial is shown in the Consolidated Standards of Reporting Trials (CONSORT) diagram (Figure 1). There was one protocol deviation: a woman randomised to treatment with electrodiathermy received treatment with a helium thermal coagulator.

Among participants treated with helium thermal coagulator, ablation was performed on 36 women (40%) and excision was performed on seven women (8%); 47 women (52%) received both ablation and excision. The corresponding figures for electrodiathermy were one (1%), 20 (21%) and 73 (78%). Information was missing for eight participants.

Table 2 shows the values of outcome variables at follow up. For the primary outcome of cyclical pain, at the 12-week follow up the covariate-adjusted VAS scores were significantly lower in the electrodiathermy group compared with the helium group (adjusted mean difference, 9.43 mm; 95% CI 0.46, 18.40 mm; $P = 0.039$). Across all time points, there was also a significant difference in cyclical pain favouring the electrodiathermy group (adjusted mean difference, 10.13 mm; 95% CI 3.48, 16.78; $P = 0.003$). Crucially, neither of these effects attained the prespecified MID of 18.00 mm.

There was a significant difference at 12 weeks in dyspareunia in favour of the electrodiathermy group, although of smaller magnitude than the MID (adjusted mean difference, 11.66 mm; 95% CI 1.39, 21.93 mm; $P = 0.026$), but differences in other secondary outcomes at 12 weeks were nonsignificant (Table 3). Profile plots for cyclical pain and dyspareunia (adjusted mean values) are shown in Figure 2,

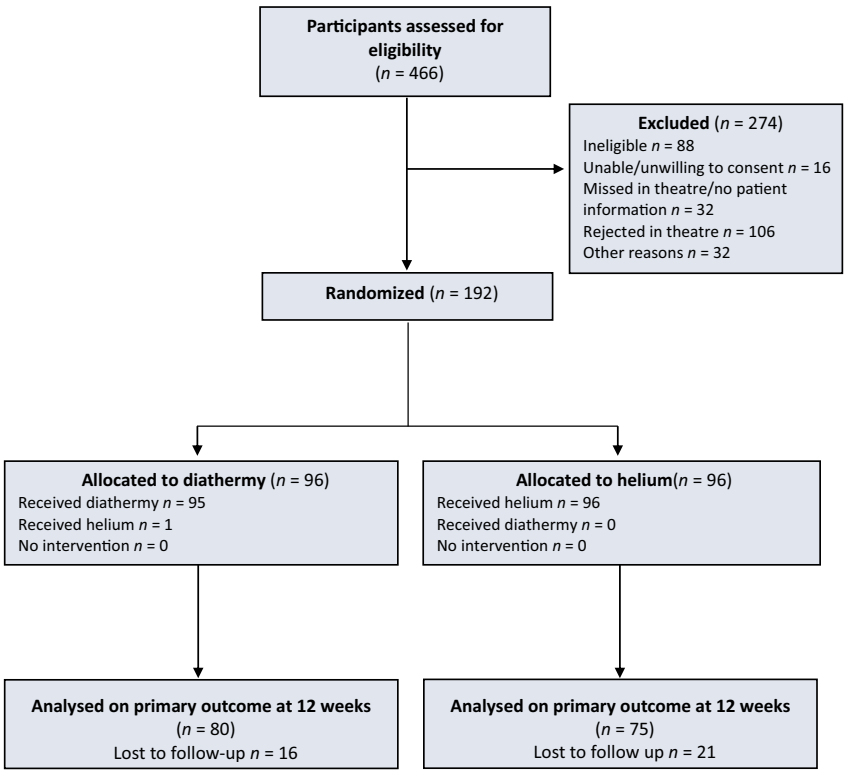

Figure 1. HYPERLINK "sps:id::fig1||locator::gr1" CONSORT diagram.

Table 2. Values of outcome variables at follow up

	6 weeks			12 weeks			36 weeks		
	Diathermy	Helium	*n*1, *n*2	Diathermy	Helium	*n*1, *n*2	Diathermy	Helium	*n*1, *n*2
VAS score for cyclical pain (mm)	48.01 (28.15)	50.64 (30.20)	82, 75	45.56 (28.80)	52.68 (31.60)	80, 75	41.88 (33.03)	58.47 (29.35)	58, 59
VAS score for dyspareunia (mm)	33.54 (32.25)	40.69 (36.44)	79, 71	38.67 (32.10)	52.23 (37.42)	72, 70	38.20 (36.66)	49.43 (38.53)	55, 56
EHP-30 pain	34.50 (23.03)	39.81 (25.69)	88, 83	32.44 (26.61)	37.22 (27.17)	81, 77	35.19 (28.05)	41.87 (26.17)	60, 59
EHP-30 control & powerlessness	40.62 (27.58)	47.39 (30.88)	88, 83	41.05 (32.64)	45.18 (34.24)	81, 77	44.79 (32.67)	49.58 (32.48)	60, 59
EHP-30 emotional wellbeing	35.75 (23.79)	44.02 (25.55)	88, 83	35.19 (26.96)	41.72 (28.97)	81, 77	39.10 (28.49)	45.27 (27.86)	60, 59
EHP-30 social support	42.26 (29.07)	46.16 (30.69)	88, 83	45.83 (34.29)	46.51 (34.20)	81, 77	44.27 (35.06)	49.89 (30.65)	60, 59
EHP-30 self-image	40.53 (31.01)	46.49 (31.43)	88, 83	44.86 (35.42)	45.13 (35.16)	81, 77	43.47 (32.98)	47.03 (35.14)	60, 59

Values are means (standard deviations).
EHP-30, Endometriosis Health Profile (each dimension scored 0–100; lower scores indicate better quality of life); VAS, visual analogue scale.

showing a somewhat greater difference towards the end of the follow-up period for cyclical pain, but a fairly consistent effect over time in relation to dyspareunia.

Averaging across time points, there were significant differences in favour of the electrodiathermy group in respect of three subscales of the EHP-30: pain, emotional wellbeing and self-image (Table 3).

Mean (SD) intraoperative blood loss was 24 ml (29 ml) (range 0–200 ml) in the electrodiathermy group and 15 ml (17 ml) (range 0–100 ml) in the helium group. Following a natural-logarithm transformation of the data (owing to violation of the assumptions of normality and homogeneity of variance of the residuals), this difference was tested through a Student's *t*-test; the back-transformed data are expressed as a fold change. Compared with the helium group, blood loss in the electrodiathermy group was 1.43 times greater (95% CI 0.96, 2.15), but this effect was not statistically significant ($t = 1.757$; $P = 0.081$). No visceral complications were noted, nor any postoperative complications.

The operative duration was slightly longer in the electrodiathermy group (mean 37.66 minutes, SD 12.56 minutes; two missing values) than in the helium group (mean 36.02 minutes, SD 11.89 minutes; six missing values). This difference of 1.64 minutes was not significant ($t = 0.907$; $P = 0.365$). Among women who had tried to become pregnant following surgery ($n = 81$), 17/44 (38.6%; 11 missing values) in the electrodiathermy and 9/37 (24.3%; 14 missing values) in the helium group had succeeded in doing so. This difference was not significant (odds ratio with electrodiathermy as reference category, 0.554, 95% CI 0.200, 1.481; $P = 0.234$). Given the maximum-likelihood estimation, the 25 missing values in this analysis were not imputed.

A secondary unadjusted analysis on the primary outcome measure yielded a significant, but smaller, effect across all time points (mean difference, 7.90 mm; 95% CI 0.60, 15.20; $P = 0.034$). The effect at 12 weeks was non-significant (mean difference, 6.42 mm; 95% CI −2.93, 15.77; $P = 0.177$).

Discussion

Main findings

In this randomised controlled trial comparing the effect of the treatment of mild-to-moderate endometriosis with electrodiathermy or helium thermal coagulator, a statistically significant difference in cyclical pain scores was detected at 12 weeks in favour of electrodiathermy. Across all time points there was also a statistically significant difference in cyclical pain in favour of the electrodiathermy group. For the secondary outcome measures, statistically significant differences favoured electrodiathermy for dyspareunia at

Table 3. Estimates of mean differences in secondary outcome variables at 12-week follow up and averaged across all follow-up time points (differences are helium group minus electrodiathermy group)

	12-week follow-up: difference (95% CI); *P* value	All follow-up time points: difference (95% CI); *P* value
VAS score for dyspareunia (mm)	11.66 (1.39, 21.93); 0.026	8.13 (−0.08, 16.34); 0.052
EHP-30 pain	6.38 (−0.88, 13.64); 0.085	6.32 (0.49, 12.15); 0.034
EHP-30 control and powerlessness	4.94 (−3.68, 13.56); 0.259	5.47 (−1.65, 12.58); 0.131
EHP-30 emotional wellbeing	6.47 (−0.13, 13.08); 0.055	5.54 (0.00, 11.08); 0.050
EHP-30 social support	5.05 (−3.59, 13.68); 0.250	5.60 (−1.10, 12.31); 0.101
EHP-30 self-image	5.79 (−2.33, 13.91); 0.161	7.16 (0.10, 14.22); 0.047

Values are derived from linear mixed models (including all randomised participants) adjusted for baseline value, age, surgeon, Revised American Society of Reproductive Medicine classification and previous abdominal surgery.
EHP-30, Endometriosis Health Profile (each dimension scored 0–100; positive differences indicate better quality of life in the electrodiathermy group). VAS, visual analogue scale (positive differences indicate less dyspareunia in the electrodiathermy group).

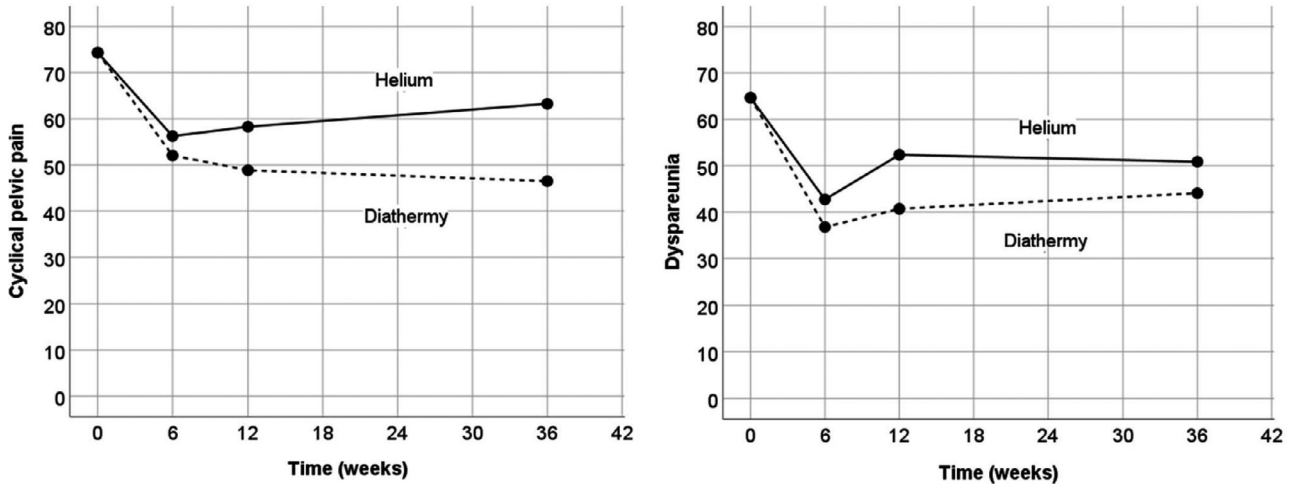

Figure 2. Profile plots for cyclical pain and dyspareunia (covariate-adjusted mean values).

12 weeks. The effects seen on cyclical pain and dyspareunia were, however, both smaller than the proposed MID and therefore cannot be assumed to be clinically important. Small but statistically significant differences in some quality-of-life measures (pain, emotional wellbeing and self-image) also favoured the use of electrodiathermy.

Strengths and limitations

This trial provides high-quality evidence comparing the use of a helium thermal coagulator to electrodiathermy in the treatment of mild-to-moderate endometriosis. Its design was informed by the perspectives of patients, and their views on outcome measures and timing of follow-up were particularly helpful. The study was double-blinded, except for the surgeon, who of necessity was not blind to the intervention. Only one woman failed to receive the assigned intervention. Analysis was performed on an intention-to-treat basis and steps were put in place to minimise loss to follow up.

Over-recruitment to meet the desired sample size was needed because of the larger than expected number of participants being rejected in theatre prior to randomisation (n = 106). This was either because of an absence of disease or because the disease was classified as more severe than mild to moderate, and suggests the need for a more effective way to determine which patients will benefit from laparoscopic surgery.

Interpretation

Meta-analysis of laparoscopic treatment of endometriosis has shown a superior reduction in symptoms compared with diagnostic laparoscopy alone.[7] Defining which laparoscopic technique yields the best results has been the focus of much debate and research. In our trial, participants in

both treatment arms could receive ablation and/or excision, according to clinical judgment. Other trials that have specifically compared ablation with excision of endometriosis have demonstrated comparable reductions in the severity of symptoms.[12,21,22] Meta-analysis, however, has shown a greater improvement in symptoms of endometriosis at 12 months with excision than with ablation.[23]

It has been suggested that the benefit of excision is the removal of deep disease, conferring better symptomatic relief than ablation, which may just treat superficial disease, leaving deeper disease behind. We theorise that this is the likely mechanism by which electrodiathermy showed statistically superior results in this trial – albeit not of clinical significance – as excision was much more commonly performed with this technique than with the helium thermal coagulator. As traditional electrodiathermy allows for the excision of deeper endometriotic tissues, it may therefore provide a greater degree of reduction in symptoms such as pain and dyspareunia, which are considered to be associated with deeper disease.

In this study, helium coagulation was not shown to be clinically superior to electrodiathermy in the laparoscopic treatment of mild-to-moderate endometriosis. Surgeons may therefore choose to base their choice of intervention on other considerations. Faced with disease overlying delicate structures, such as the bladder, bowel and diaphragm, they may favour the use of helium coagulation, owing to its low thermal spread. Conversely, a desire to achieve deeper excision may prompt them to use electrodiathermy.

The interventions performed in this study were undertaken by surgeons working in an accredited endometriosis centre and the results obtained may not reflect those achieved by a general gynaecologist. For example, the excision performed through electrodiathermy may have been fuller and deeper than that undertaken by a generalist.

Conclusion

In conclusion, although laparoscopic treatment of mild-to-moderate endometriosis with electrodiathermy showed statistically significant superior improvement in symptoms of cyclical pain, dyspareunia and some quality-of-life measures, when compared with treatment with a helium thermal coagulator, the magnitude of these effects was generally too small to infer that they are clinically important. Further research, including health economics evaluation, is needed before clear recommendations can be made for clinical practice.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

GM, JS, ZEG, SOB and KW contributed to the conception and design of the study. GM and ZEG performed the clinical interventions. SJ managed the outcome assessments. JS analysed the data. JS, GM, TC and JR drafted the paper. All authors reviewed the article and approved the final version for publication.

Details of ethical approval

The study was approved on 3 October 2013 by the NRES East Midlands – Leicester Ethics Committee (13/EM/0354) and was registered in December 2013 (ISRCTN 50928834).

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