

Laparoscopic Uterosacral Nerve Ablation for Alleviating Chronic Pelvic Pain

A Randomized Controlled Trial

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CHRONIC PELVIC PAIN IN women is as common as asthma and chronic back pain,^{1,2} is one of the most difficult and perplexing of women's health problems, and has a multifactorial etiology.³ Chronic pelvic pain has a major effect on health-related quality of life, work attendance and productivity,⁴ and health care use, accounting for 40% of referrals for diagnostic laparoscopy,⁵ and is an important contributor to health care expenditures.⁶

Treatments for chronic pelvic pain are often unsatisfactory.⁷ As part of the evaluation and management phase, patients often undergo diagnostic laparoscopy⁸ but actionable pathology is found only occasionally.^{9,10} Negative findings at laparoscopy and during follow-up with ultrasound may provide re-

Context Chronic pelvic pain is a common condition with a major effect on health-related quality of life, work productivity, and health care use. Operative interruption of nerve trunks in the uterosacral ligaments by laparoscopic uterosacral nerve ablation (LUNA) is a treatment option for patients with chronic pelvic pain.

Objective To assess the effectiveness of LUNA in patients with chronic pelvic pain.

Design, Setting, and Participants Randomized controlled trial of 487 women with chronic pelvic pain lasting longer than 6 months without or with minimal endometriosis, adhesions, or pelvic inflammatory disease, who were recruited to the study by consultant gynecological surgeons from 18 UK hospitals between February 1998 and December 2005. Follow-up was conducted by questionnaires mailed at 3 and 6 months and at 1, 2, 3, and 5 years.

Intervention Bilateral LUNA or laparoscopy without pelvic denervation (no LUNA); participants were blinded to the treatment allocation.

Main Outcome Measures The primary outcome was pain, which was assessed by a visual analogue scale. Data concerning the 3 types of pain (noncyclical pain, dysmenorrhea, and dyspareunia) were analyzed separately as was the worst pain level experienced from any of these 3 types of pain. The secondary outcome was health-related quality of life, which was measured using a generic instrument (EuroQoL EQ-5D and EQ-VAS).

Results After a median follow-up of 69 months, there were no significant differences reported on the visual analogue pain scales for the worst pain (mean difference between the LUNA group and the no LUNA group, -0.04 cm [95% confidence interval {CI}, -0.33 to 0.25 cm]; $P = .80$), noncyclical pain (-0.11 cm [95% CI, -0.50 to 0.29 cm]; $P = .60$), dysmenorrhea (-0.09 cm [95% CI, -0.49 to 0.30 cm]; $P = .60$), or dyspareunia (0.18 cm [95% CI, -0.22 to 0.62 cm]; $P = .40$). No differences were observed between the LUNA group and the no LUNA group for quality of life.

Conclusion Among women with chronic pelvic pain, LUNA did not result in improvements in pain, dysmenorrhea, dyspareunia, or quality of life compared with laparoscopy without pelvic denervation.

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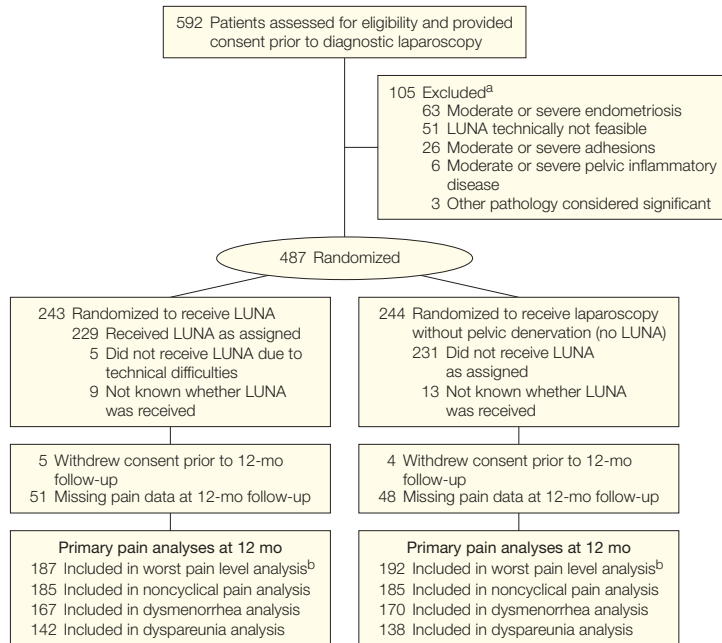
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Figure 1. Selection of Participants for the Laparoscopic Uterosacral Nerve Ablation (LUNA) Trial

^aTwenty-six patients had more than 1 reason for exclusion.

^bIndicates worst pain level experienced from any of the 3 types of pain analyzed (noncyclical pain, dysmenorrhea, and dyspareunia).

assurance and relief to some patients¹¹ but in the absence of underlying pathology, no established gynecological treatments are available.

Nerve plexuses and parasympathetic ganglia in the uterosacral ligaments^{12,13} are thought to carry pain signals from the uterus, cervix, and other pelvic structures. Conventional open vaginal and abdominal procedures have been used to interrupt these nerve trunks by dividing the attachments of the uterosacral ligaments to the cervix in women with dysmenorrhea.^{14,15} In part because these procedures are invasive and carry risk and their efficacy has not been established, they have not been widely adopted. Laparoscopic uterosacral nerve ablation (LUNA) is performed after diagnostic laparoscopy and can be completed using lasers or electrodiathermy and has become increasingly used.^{16,17} Systematic reviews of the current research evidence on LUNA's efficacy are inconclusive.^{18,19} A National Institute of Clinical Excellence report suggested that

there was not sufficient evidence of its value.²⁰ Clinicians' beliefs about LUNA's effectiveness vary widely²¹ and LUNA remains a controversial procedure. We conducted a single-blind, randomized controlled trial comparing LUNA with laparoscopy without pelvic denervation.

METHODS

The LUNA trial was a multicenter, prospective, randomized intervention trial with patient-blinded, patient-rated assessment of outcomes to evaluate LUNA.^{22,23} Ethics committee approval was obtained from the West Midlands Multicenter Research Ethics Committee (reference No. 99/7/03). Patients presenting to gynecology outpatient clinics with chronic pelvic pain (noncyclical pain, dysmenorrhea, or dyspareunia) lasting longer than 6 months, located within and below the anterior iliac crests, and who were undergoing diagnostic laparoscopy for differential diagnosis of chronic pelvic pain were invited to participate in our study.

Women were ineligible if they had previous LUNA, hysterectomy, or therapeutic procedures for, or diagnosis of, moderate to severe endometriosis or major pelvic inflammatory disease. Written informed consent was obtained before surgery. At laparoscopy, women were excluded if they were found to have more than minimal pathology (ie, American Fertility Society endometriosis score >5 or significant adhesions or serious adnexal pathology) or if bilateral LUNA was technically unfeasible. Intraoperatively, eligible patients were randomized via a telephone call to the Birmingham University Clinical Trials Unit, or through its Internet-based randomization service, to the LUNA group or the no LUNA group.

Randomization involved a computer minimization program to balance group allocations for site of pain, parity, self-reported sexual activity status, and presence or absence of minimal pathology. To avoid eligibility classification bias, treatment allocation was issued only after the surgeon had inspected the pelvis and ensured that the patient fulfilled all of the inclusion criteria and did not have any of the exclusion criteria.

Those allocated to the LUNA group had the procedure performed immediately by the same laparoscopic surgeon who had prior experience of the technique and who followed a common protocol.²⁴ In a typical case, after inspection of the posterior leaf of the broad ligament to identify ureters and any pelvic venous congestion, the ablation was performed as close to the posterior aspect of the cervix as possible and continued for a minimum of 1 cm posterolaterally on either side with the intended aim of destroying the sensory nerve fibers and the secondary ganglia as they left the uterus and lie within the uterosacral ligaments.

Full or partial transaction of the ligaments was achieved bilaterally with laser or electrodiathermy, according to the surgeons' preference. In centers in which surgeons used 2 additional ports to perform LUNA, a second 5-mm in-

cision was made in the patients in the no LUNA group through the skin in an area corresponding to where an additional port site was made. This approach of sham incisions has been used in a previous trial²⁵ and was ethically justified to help avoid bias in the patient-rated assessment of a subjective outcome like pain.²⁶ All women were asked at least 12 months after randomization whether they believed they had LUNA or no LUNA.

Baseline data were collected following consent and prior to laparoscopy. At 3 and 6 months following randomization and at 1, 2, 3 and 5 years, the same questionnaires were mailed to patients with a prepaid return envelope. Nonresponders were followed up through postal and/or telephone reminders or, if this failed, via their general practitioners.

The primary outcome of pain was rated using a 10-cm visual analogue scale (VAS),²⁷ anchored at one end as no pain at all and at the other as the worst imaginable pain. The VAS ratings were obtained at 12 months for each of the 3 types of pain: noncyclical pain (pain at any other times other than during periods or during intercourse), dysmenorrhea (pain during periods), and dyspareunia (pain during intercourse). Women rated the degree of pain by placing a mark on the line and scale values were obtained by measuring the distance from zero to that mark. This measurement is validated as a sensitive measure for large group comparisons.²⁸

The secondary outcome was health-related quality of life, which was measured using a generic instrument (EuroQoL EQ-5D [measured on a scale of -0.59 to 1 based on responses to 5 questions about life quality] and the EQ-VAS [measured on a 0-100 scale]).²⁹ The need for additional treatments, resource usage, days off work, and complications of surgery were also recorded.

The sample size was powered to detect a small to medium effect of LUNA in alleviating pain symptoms compared with laparoscopy without pelvic denervation. To confirm or refute

a 0.3 SD effect size,³⁰ equivalent to a difference between groups of 1.2 cm on the VAS, at a 2-sided α level of .05 and a β level of .20 (80% power), 175 women in each group (ie, 350 in total) were required. Allowing for a 20% loss to follow-up, the recruitment target was inflated to 420. Considering that existing research for chronic pelvic pain has shown substantial rates of loss to follow-up, recruitment continued until the end of the funding period when 487 women were included.

An independent data and safety monitoring board reviewed confidential interim analyses annually and rec-

ommended at each meeting continuing recruitment because the data were inconclusive.

All participants were analyzed in the group to which they were allocated using all available data and SAS statistical software version 9 (SAS Institute Inc, Cary, North Carolina). Baseline characteristics of the patients enrolled in the 2 groups were compared to ensure that randomization has produced comparable groups. Data for the various outcome measures were presented as means and mean differences over time with 95% confidence intervals (CIs).

Table 1. Baseline Characteristics of Participants in the Laparoscopic Uterosacral Nerve Ablation (LUNA) Trial^a

	LUNA (n = 243)	No LUNA (n = 244)
Age, mean (SD) [range], y	30.6 (7.53) [17-64]	30.5 (7.48) [17-57]
Clinical presentation		
Nulliparous	87 (36)	92 (38)
Sexually active	195 (80)	193 (79)
Type of pain		
Dysmenorrhea only	184 (76)	179 (73)
Noncyclical pain only	159 (65)	153 (63)
Dyspareunia only ^b	158 (65)	149 (61)
All 3 types of pain	89 (37)	79 (32)
Central location of pain	168 (69)	167 (68)
Laparoscopic findings		
Any visible pathology	110 (45)	111 (45)
Adhesions	49 (20)	37 (15)
Pelvic inflammatory disease	4 (2)	9 (4)
Endometriosis		
None	177 (73)	164 (67)
Minimal	41 (17)	52 (21)
Minimal, ablated	25 (10)	28 (11)
Pain medication		
Analgesics ^c	155 (64)	156 (64)
Antidepressants ^d	16 (7)	28 (11)
Type of contraceptive		
Combined oral	33 (14)	33 (14)
Mini-pill	4 (2)	5 (2)
Mirena coil	1 (<1)	0
Not specified	30 (12)	24 (10)
Indication for other medication		
Irritable bowel syndrome	2 (<1)	1 (<1)
Bladder pain	0	1 (<1)
Urinary tract infection	2 (<1)	1 (<1)
Migraine	5 (2)	2 (1)
Asthma	19 (8)	15 (6)
Blood pressure	4 (2)	4 (2)

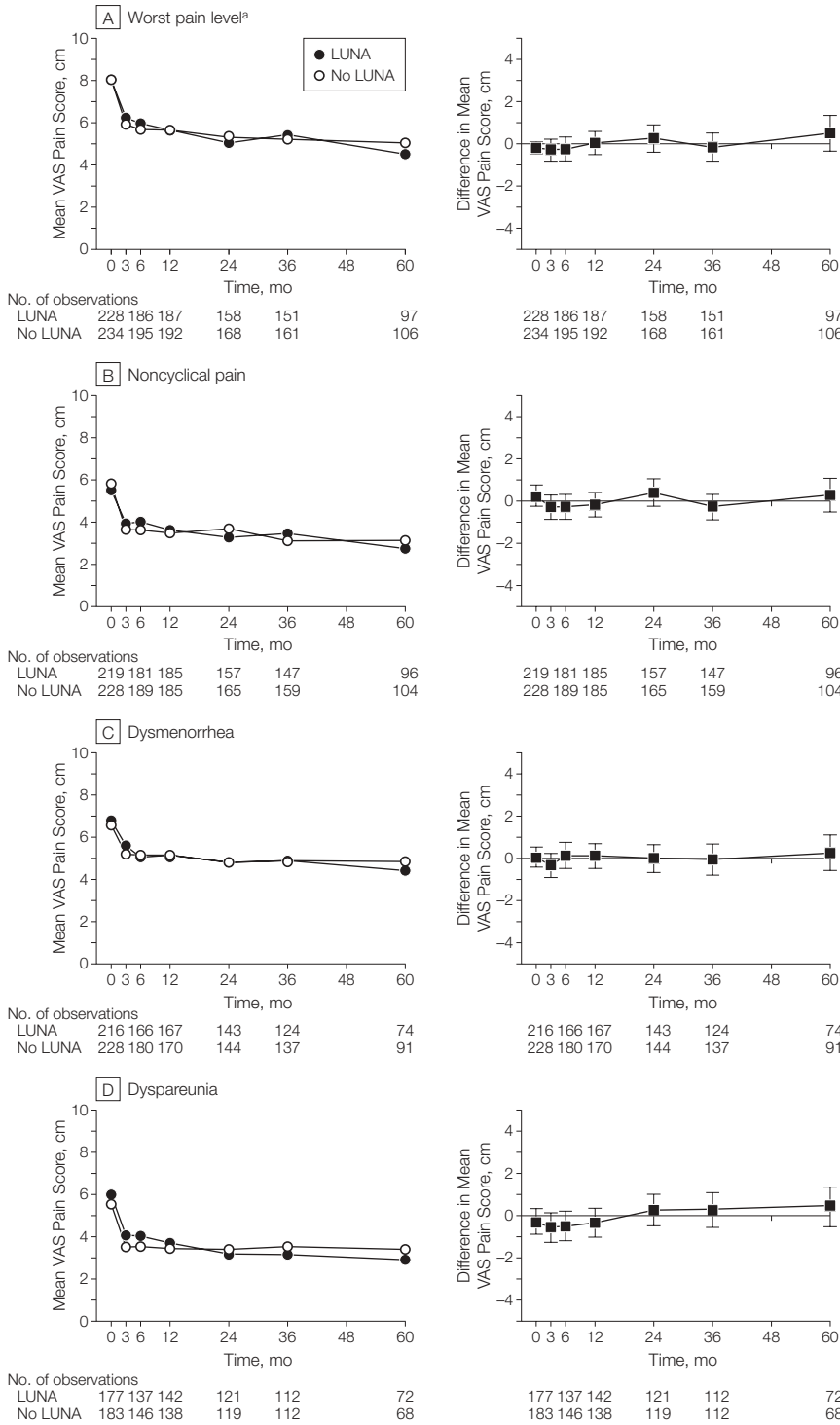
^aValues are expressed as number (percentage) unless otherwise indicated.

^bRepresents sexually active women only.

^cThere were missing data for 13 participants in the LUNA group and for 8 participants in the no LUNA group.

^dThere were missing data for 20 participants in the LUNA group and for 20 participants in the no LUNA group.

Figure 2. Effect of Laparoscopic Uterosacral Nerve Ablation (LUNA) at 12 Months and at Each Time Point



The graph on the right in each lettered part of the figure shows the difference in mean visual analogue scale (VAS) pain scores and 95% confidence intervals; values greater than 0 indicate that LUNA is a better therapy than no LUNA. The error bars indicate 95% confidence intervals.

^aIndicates worst pain level experienced from any of the 3 types of pain analyzed (noncyclical pain, dysmenorrhea, and dyspareunia).

For the primary outcome, we analyzed data separately concerning the 3 types of pain (noncyclical pain, dysmenorrhea, and dyspareunia) and performed an analysis of the worst pain level experienced from any of these 3 types of pain. Comparisons between groups over time were undertaken using repeated-measures analyses,³¹ a statistically efficient approach that includes all of the follow-up data collated during the study, increasing power over analysis of data at individual time points. Pain scores at 12 months were compared using standard 2-sample *t* tests.

The principal analysis for the worst pain level experienced from any of the 3 types of pain was an intention-to-treat analysis using multiple imputation.³¹⁻³³ To investigate the effect of missing data, the analyses of the individual types of pain at 12 months were repeated using the last observation carried forward method of imputation. All comparisons were 2-sided and were considered statistically significant if *P* < .05.

Subgroup analyses were chosen on the basis of anticipated variations in pain and potential benefit from LUNA, but were considered hypothesis generating. Pre-specified subgroups were those used to stratify the randomization, namely site of pain (central, not central), presence or absence of minimal pathology for all types of pain, parity (nulliparous, multiparous), and whether women were sexually active or not.

RESULTS

Between February 1998 and December 2005, 487 women were randomized into the LUNA trial from 18 UK hospitals. A further 105 patients provided consent but were found at laparoscopy to have pathology that made them ineligible for randomization, or anatomy that precluded LUNA from being performed. No women in the control (no LUNA) group received LUNA, whereas 5 women in the LUNA group ultimately did not have LUNA performed bilaterally due to technical difficulties, but were analyzed in the LUNA group. FIGURE 1 shows the trial profile. Baseline pain data were miss-

Table 2. Prespecified Subgroup Analyses Using Repeated-Measures Analysis

Subgroup	Worst Pain Level ^a		Noncyclical Pain		Dysmenorrhea		Dyspareunia	
	Treatment Effect (95% CI), cm	P Value	Treatment Effect (95% CI), cm	P Value	Treatment Effect (95% CI), cm	P Value	Treatment Effect (95% CI), cm	P Value
Parity								
Nulliparous	0.34 (-0.06 to 0.74)	.50	-0.02 (-0.41 to 0.37)	.60	0.14 (-0.28 to 0.54)	.40	0.44 (-0.04 to 0.92)	.10
Parous	-0.08 (-0.41 to 0.24)		-0.13 (-0.47 to 0.20)		-0.20 (-0.55 to 0.15)		-0.32 (-0.68 to 0.05)	
Pathology								
None	0.10 (-0.16 to 0.36)	.20	-0.08 (-0.34 to 0.18)	.20	-0.11 (-0.39 to 0.17)	.30	0.08 (-0.22 to 0.39)	.02
Any minimal	0.19 (-0.81 to 1.18)		0.64 (-0.68 to 1.39)		0.64 (-0.29 to 1.56)		-0.54 (-1.04 to 0.12)	
Mild or minimal endometriosis							0.20 (-0.59 to 0.62)	.80
Site of pain								
Central	-0.03 (0.31 to 0.30)	.20	-0.15 (-0.46 to 0.16)	.30	-0.15 (-0.46 to 0.16)	.20	-0.06 (-0.41 to 0.30)	.10
Not central	0.10 (-0.49 to 0.49)		0.01 (-0.50 to 0.51)		-0.19 (-0.74 to 0.36)		0.21 (-0.33 to 0.76)	

Abbreviation: CI, confidence interval.

^aIndicates worst pain level experienced from any of the 3 types of pain analyzed (noncyclical pain, dysmenorrhea, and dyspareunia).

ing for 26 participants (5%), including 10 participants from 1 center in which a batch of baseline data was lost.

Baseline characteristics of the women did not differ between the 2 groups (TABLE 1) and there were not any differences in cointerventions between the groups. Blinding was maintained, apart from 13 women who asked to be informed of their allocation. In a subsample of 211 women who had been blinded to their treatment allocation, 122 correctly guessed their allocation (58%).

The majority of women had multiple types of pain. A total of 168 participants reported noncyclical pain, dysmenorrhea, and dyspareunia (36%) and 113 reported dysmenorrhea and dyspareunia (24%). In 266 women (54%), there was no obvious pathology identified, suggestive of primary dysmenorrhea. A further 146 had minimal to mild endometriosis (30%), 86 had adhesions (18%), 13 had pelvic inflammatory disease (3%), and 35 had other visible pathologies (7%), the majority being subserosal fibroids and small ovarian cysts.

Median time in the study was 69 months with 72% of participants having reached 5 years of follow-up. The differences in pain are shown in FIGURE 2. The results are presented as the mean pain scores from the VAS for each randomized group in the left graph and as the difference between the 2

groups in the right graph, in which a positive value indicates better pain relief with LUNA than without LUNA. There was no difference reported for the worst pain level experienced from any of the 3 types of pain (mean difference between the LUNA group vs the no LUNA group, -0.02 cm [95% CI, -0.61 to 0.65 cm]; $P = .90$ at 12 months; -0.04 cm [95% CI, -0.33 to 0.25 cm]; $P = .80$ over all time points), noncyclical pain (0.17 cm [95% CI, -0.40 to 0.74 cm]; $P = .50$ at 12 months; -0.11 cm [95% CI, -0.50 to 0.29 cm]; $P = .60$ over all time points), dysmenorrhea (-0.10 cm [95% CI, -0.70 to 0.50 cm]; $P = .70$ at 12 months; -0.09 cm [95% CI, -0.49 to 0.30 cm]; $P = .60$ over all time points), or dyspareunia (0.34 cm [95% CI, -0.34 to 1.02 cm]; $P = .30$ at 12 months; 0.18 cm [95% CI, -0.22 to 0.62 cm]; $P = .40$ over all time points).

Using last observation carried forward for imputation of missing observations at 12 months, we found no significant difference between the LUNA group and the no LUNA group for noncyclical pain (0.35 cm [95% CI, -0.19 to 0.88 cm]; $P = .20$), dysmenorrhea (-0.16 cm [95% CI, -0.73 to 0.40 cm]; $P = .60$), or dyspareunia (0.26 cm [95% CI, -0.39 to 0.92 cm]; $P = .40$). A similar lack of efficacy was observed for the outcome measures concerning health-related quality of life with the mean difference in the EuroQoL EQ-5D being 0.03 cm (95% CI, -0.03 to 0.09 cm);

$P = .30$) and that in EQ-VAS being -0.78 cm (95% CI, -3.9 to 5.4 cm; $P = .30$) at 12 months. Between 9 and 12 months, no differences were found between the LUNA group and the no LUNA group in terms of days off work (27% vs 22%, respectively, took at least 1 day off work; $P = .20$) or in the number of general practitioner surgery visits (mean [SD] number of visits, 1.9 [1.1] vs 2.5 [2.0], respectively; $P = .08$). The prespecified subgroup analyses using repeated-measures analysis appears in TABLE 2.

There were 8 cases of minor hemorrhaging while performing the LUNA procedure and 1 case that converted to an open procedure. One participant not allocated to the LUNA group experienced ureteric damage.

COMMENT

The LUNA trial was designed to assess the effects of LUNA compared with no denervation among women undergoing diagnostic laparoscopy for chronic pelvic pain. LUNA did not alleviate any type of pain—noncyclical pain, dysmenorrhea, or dyspareunia—or improve quality of life, irrespective of the presence or absence of mild endometriosis. A Cochrane review¹⁹ did suggest a subgroup benefit for patients with dysmenorrhea that our study did not find. This finding came from 2 small studies^{34,35} totaling 68 randomized participants; one³⁴ of these

studies did not have strictly concealed randomization.

The LUNA trial is 4 times larger than any previously published trial evaluating neuroablation for chronic pelvic pain. It may be more reliable than any previous study of LUNA and also was designed to minimize bias, with concealment of allocation before randomization and blinded outcome assessment. Women were not told whether they received LUNA or not. Although the majority of women were not informed of their allocation, there is a suggestion that a small proportion were able to guess it correctly. If anything, however, this would likely enhance the apparent value of LUNA.

LUNA was adopted by many practitioners because afferent nerves from pelvic organs pass through the uterosacral ligament and it was thought that disruption of these would reduce the perceived pain. Lack of efficacy in our study and in prior studies provide evidence that the anatomical and physiological picture of chronic pelvic pain is more complicated. Anatomically, at least 5 pathways transmit signals from noxious stimuli in the pelvis. These nerve trunks vary in location and can intersect, with the potential for neuronal cross-talk. LUNA may obliterate some of the nerve fibers, but others are interwoven with the pelvic arteries and ureters.

Aggressive ablation more laterally risks damaging the ureter, so most procedures are compromised in their ability to achieve complete neurodestruction.

We followed up participants for longer than 6 months because laparoscopy may have a placebo effect for up to 3 to 6 months.^{36,37} We found no benefit for LUNA at any time point but found improvement in pain at 3 months for patients in both the LUNA group and the no LUNA group. This early pain reduction may be a placebo effect and attributable to the reassurance provided by the laparoscopic examination that there was no serious pathology. A comparison of diagnostic laparoscopy against no laparoscopy would be required to es-

tablish benefit. Alternatively, it could be a regression to the mean effect, with women more likely to undergo laparoscopy when their pain is at its worst, rather than at its average level.

This study has several limitations. We did not obtain follow-up data on all women but dropout rates were similar in each group and multiple imputation and last observation carried forward analyses produced near identical findings to those of the observed data. Given that we observed no effect of LUNA, the question arises whether this might be due to type II error (ie, inadequate statistical power). A clinically significant difference in pain has been defined as 2 points on a 10-point (cm) VAS for chronic pelvic pain^{36,38} and also for other types of pain,³⁹ whereas our trial had the power to detect a 1.2-point difference at 12 months and even smaller differences over time. In every comparison, the 95% CIs around the mean difference in VAS scores between the groups were less than 1.2 points. Taking worst pain level experienced at 12 months as an example, the pain score was 0.02 cm lower in the LUNA group than in the no LUNA group and the 95% CI was 0.61 cm lower to 0.65 cm higher (ie, well below the level for clinically significant improvement).

In conclusion, among women with chronic pelvic pain, LUNA did not result in improvements in pain, dysmenorrhea, dyspareunia, pelvic pain or quality of life compared with laparoscopy without pelvic denervation.

Author Contributions: Ms Daniels had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors listed in the byline constitute the Trial Management Group who managed the day to day conduct of the trial.

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Study supervision: Daniels, Gray, Gupta, Lilford, Khan.

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Data and Safety Monitoring Board: Peter Brocklehurst, MSc, FRCOG (chair, University of Oxford), Joe Jordan, MD, FRCOG (retired), Peter Braunholtz, PhD (University of Aberdeen), Josie Sandercock, PhD (University of Birmingham).

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