Chronic pelvic pain and menorrhagia: Assessing treatment effectiveness

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Chapter 5

Laparoscopic Uterosacral Nerve Ablation (LUNA) for alleviating Chronic Pelvic Pain: a Randomized Trial
Chapter 5

Abstract

Context
Chronic pelvic pain (CPP) is a common condition with a major impact on health-related quality of life, work productivity and health care use. Operative interruption of nerve trunks in the utero-sacral ligaments, believed to carry pain from the uterus and cervix, 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 by postal questionnaires at 3 and 6 months, 1, 2, 3 and 5 years.

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

Main outcome measures
The primary outcome was pain, assessed by a visual analogue scale. Data concerning the 3 types of pain (non-cyclical, dysmenorrheal, and dyspareunia) were analyzed separately as was the worst pain level experienced from any of these 3 types of pain. Secondary outcomes were quality of life (EuroQoL EQ-5D and EQ-VAS).

Results
After a median follow up of 69 months, there were no significant differences between the visual analogue pain scales for for the worst pain reported (mean difference between LUNA group and No LUNA group: -0.04cm, 95% confidence interval (CI), -0.33 to 0.25cm; p=0.80), non-cyclical pain (-0.11cm, 95%CI -0.50 to 0.29cm; p=0.60) dysmenorrhoea (-0.09cm, 95%CI -0.49 to 0.30cm; p=0.60), or dyspareunia (-0.18cm, 95%CI -0.22 to 0.62cm; p=0.40). No differences were observed between the LUNA group and the no LUNA group for quality of life.
Conclusions
Among women with chronic pelvic pain, LUNA did not result in improvements in pain, dysmenorrheal, dyspareunia or quality of life, compared to laparoscopy without pelvic denervation.

Trial Registration
Controlled-trials.com identifier ISRCTN number: 41196151

Introduction
Chronic pelvic pain (CPP) in women is as common as asthma and chronic back pain in primary care\(^1,2\) CPP continues to be one of the most difficult and perplexing of women’s health problems with a multifactorial etiology.\(^3\) Chronic pelvic pain has a major impact on health-related quality of life, work attendance and productivity\(^4\) and health care utilization, accounting for 40% of referrals for diagnostic laparoscopy,\(^5\) and is an important contributor to health care expenditures.\(^6\)

Treatments for CPP are often unsatisfactory.\(^7\) As part of the evaluation and management phase, patients often undergo diagnostic laparoscopy,\(^8\) but actionable pathology is found only occasionally identified.\(^9,10\) Negative findings at laparoscopy, and follow up with ultrasound, may provide reassurance and relief to some patients,\(^11\) but in the absence of underlying pathology no established gynaecological 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 they have not been widely adopted. Laparoscopic uterosacral nerve ablation (LUNA) is performed after diagnostic laparoscopy and can be completed using lasers or electro-diathermy, and has become increasingly used.\(^16,17\) Systematic reviews of the current research evidence on LUNA’s efficacy are inconclusive.\(^18,19\) and 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 widely\(^21\) 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 Multi-centre Research Ethics Committee (reference number
Patients presenting to gynaecology outpatient clinics with CPP (dysmenorrhea, non-cyclical pain or dyspareunia) of longer than 6-month duration located within between and below the anterior iliac crests, and who were undergoing diagnostic laparoscopy for differential diagnosis of CPP, 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 consent was obtained before surgery. At laparoscopy, women were excluded if they were found to have more than minimal pathology (i.e. 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 by telephone call to the Birmingham University Clinical Trials Unit, or through its Internet based randomization service, to LUNA or no denervation.

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 LUNA had the procedure performed immediately by the same laparoscopic surgeon, who had prior experience of the technique and who followed a common protocol. 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 fibres 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 electro-diathermy, according to the surgeons’ preference. In centers where surgeons used 2 secondary ports to perform LUNA, a second 5 mm incision 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 trial and was ethically justified to help avoid bias in the patient rated assessment of a subjective outcome like pain. 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 pre-paid return envelope. Non responders 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), anchored at one end as no pain at all and the other as worst imaginable pain. The VAS ratings were obtained for each of the 3 types of pain: non-cyclical pain (pain at any other times, other than during periods or during intercourse), dysmenorrhoea (pain during your 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.

The secondary outcomes were health-related quality of life measured using a generic instrument (EuroQOL EQ-5D and EQ-VAS), and a proforma recording the need for additional treatments, resource usage, days off work and complications of surgery. The EQ-5D is measured on a 0-1 scale based on responses to five questions about life quality and the EQ-VAS is measured on a 0 - 100 scale.

The sample size was powered to detect a small to medium effect of LUNA in alleviating pain symptoms compared to laparoscopy without pelvic denervation. To confirm or refute a 0·3 standard deviation effect size, equivalent to a difference between groups of 1.2cm on the visual analogue scale, at a two-sided α=0·05 and β=0·2 (80% power), 175 women in each group (i.e. 350 in total) were required. Allowing for a 20% loss to follow-up, the recruitment target was inflated to 420. Considering that existing research in this condition 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 monitoring committee reviewed confidential interim analyses annually and, recommended 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, Cary, North Carolina). Baseline characteristics of the patients enrolled in the two 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).

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

The principal analysis for the worst pain experienced from any of the three types of pain was an
intention to treat analysis using multiple imputation. To investigate the impact of missing data,
the analyses of the individual types of pain at 12 months were repeated using the last observa-
tion carried forward method of imputation. All comparisons were two-sided and were considered
statistically significant if p<0.05.

Sub group analyses were chosen on the basis of anticipated variations in pain and potential
benefit from LUNA, but were considered hypothesis generating. Pre-specified sub-groups were
those used to stratify the randomization, namely site of pain (central, not central) and presence
or absence of some 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 centers. A further 105 were consented but were found at laparoscopy to have pathol-
ogy that made them ineligible for randomization, or anatomy that precluded LUNA from being
performed. No women in the control group received LUNA, whereas five women allocated LUNA
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 missing on 26 (5%) par-
ticipants, including 10 participants from one centre where a batch of baseline data was lost.

Baseline characteristics of the women did not differ between the two 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, although in a sub-sample of 211
who had been blinded to their allocation, 122 correctly guessed their allocation (58%).

The majority of women had multiple types of pain. A total of 168 participants reporting non-
cyclical pain dysmenorrhoea, and dyspareunia (36%), and 113 reporting dysmenorrhoea and
dyspareunia (24%). In 266 (54%) women, there was no obvious pathology identified, suggestive
of primary dysmenorrhoea. A further 146 had minimal to mild endometriosis (30%), 86 had adhe-
sions (18%), 13 had pelvic inflammatory disease (3%), and 35 had other visible pathologies (7%),
the majority being subserosal fibroids and small ovarian cysts.
Figure 1: Selection of participants for the Laparoscopic Uterosacral Nerve Ablation (LUNA) Trial

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 upper graph, and as the difference between the two groups in the lower graph, where 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=0.90 at 12 months; −0.04 cm, 95% CI, −0.33 to 0.25 cm; p =0.80 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 =0.60 over all time points), dysmenorrhea (−0.10 cm, 95% CI −0.70 to 0.50 cm; p =0.70 at 12 months; −0.09 cm, 95% CI −0.49 to 0.30 cm; p =0.60 over all time points), or dyspareunia (0.34 cm, 95% CI −0.34 to 1.02 cm; p =0.30 at 12 months; 0.18 cm, 95% CI −0.22 to 0.62 cm; p =0.40 over all time points).
Table 1: Baseline characteristics of participants in the Laparoscopic Uterosacral Nerve Ablation (LUNA) trial

<table>
<thead>
<tr>
<th></th>
<th>LUNA n (%) total=243</th>
<th>No LUNA n (%) total=244</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age¹</td>
<td>30·6 (7·53; 17-64)</td>
<td>30.5 (7·48; 17-57)</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>87 (36)</td>
<td>92 (38)</td>
</tr>
<tr>
<td>Sexually active</td>
<td>195 (80)</td>
<td>193 (79)</td>
</tr>
<tr>
<td><strong>Type of pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>184 (76)</td>
<td>179 (73)</td>
</tr>
<tr>
<td>Dyspareunia²</td>
<td>158 (65)</td>
<td>149 (61)</td>
</tr>
<tr>
<td>Non-cyclical pain</td>
<td>159 (65)</td>
<td>153 (63)</td>
</tr>
<tr>
<td>All three types of pain</td>
<td>89 (37)</td>
<td>79 (32)</td>
</tr>
<tr>
<td><strong>Location of pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>168 (69)</td>
<td>167 (68)</td>
</tr>
<tr>
<td><strong>Laparoscopic findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any visible pathology</td>
<td>110 (45)</td>
<td>111 (45)</td>
</tr>
<tr>
<td>Adhesions</td>
<td>49 (20)</td>
<td>37 (15)</td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td>4 (2)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>None 177 (73)</td>
<td>164 (67)</td>
</tr>
<tr>
<td>Minimal</td>
<td>41 (17)</td>
<td>52 (21)</td>
</tr>
<tr>
<td>Minimal, ablated</td>
<td>25 (10)</td>
<td>28 (11)</td>
</tr>
<tr>
<td><strong>Pain medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painkillers³</td>
<td>155 (64)</td>
<td>156 (64)</td>
</tr>
<tr>
<td>Anti-depressants⁴</td>
<td>16 (7)</td>
<td>28 (11)</td>
</tr>
<tr>
<td>Hormonal contraceptives</td>
<td>33 (14)</td>
<td>33 (13)</td>
</tr>
<tr>
<td>Combined oral contraceptive</td>
<td>4 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Mini-pill</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mirena coil</td>
<td>30 (12)</td>
<td>24 (10)</td>
</tr>
<tr>
<td>Contraception (not specified)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>2 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Bladder pain</td>
<td>0 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Migraine</td>
<td>5 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Asthma</td>
<td>19 (8)</td>
<td>15 (6)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>4 (2)</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

¹ Mean (standard deviation; range)
² % of sexually active women only
³ 13 and 8 missing data items for LUNA and no LUNA respectively
⁴ 20 and 20 missing data items
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 non-cyclical pain (0.35 cm, 95% CI -0.19 to 0.88 cm; \(p=0.2\)), dysmenorrhea (-0.16 cm, 95% CI -0.73 to 0.40 cm; \(p=0.6\)), or dyspareunia (0.26 cm, 95% CI -0.39 to 0.92 cm; \(p=0.4\)). A similar lack of efficacy was observed for the outcome measures concerning health-related quality of life with the mean difference in the EQ-5D being 0.03 (95% CI -0.03 to 0.09; \(p=0.3\)) and that in EQ-VAS being -0.78 cm (95% CI, -3.9 to 5.4; \(p=0.3\)) 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; \(p=0.20\)) or in the number of general practitioner surgery visits (mean [SD] number of visits, 1.9 [1.1] vs 2.5 [2.0], respectively; \(p=0.08\)). The pre-specified subgroup analyses using repeated-measures analysis appears in Table 2.

There were 8 cases of minor haemorrhaging while performing the LUNA procedure and one case that converted to an open procedure. One participant not allocated LUNA suffered ureteric damage.

**Comment**

The LUNA trial was designed to assess the effects of LUNA, compared to no denervation, among women undergoing diagnostic laparoscopy for chronic pelvic pain. LUNA did not alleviate pain - non-cyclical pain, dysmenorrhea, or dyspareunia - or improve life quality, irrespective of the presence or absence of mild endometriosis. A Cochrane review\(^\text{19}\) did suggest a subgroup benefit for patients with dysmenorrhea that our study did not find. This finding came from two small studies\(^\text{34, 35}\) totaling 68 randomised participants, one of which\(^\text{34}\) did not have strictly concealed randomization.

**Table 2:** Pre-specified sub-group analyses using repeated measures analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Worst pain Treatment effect (95% CI)</th>
<th>p value</th>
<th>Dysmenorrhea Treatment effect (95% CI)</th>
<th>p value</th>
<th>Dyspareunia Treatment effect (95% CI)</th>
<th>p value</th>
<th>Non-cyclical pain Treatment effect (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous</td>
<td>0.34 (-0.06-0.74)</td>
<td>0.05</td>
<td>0.14 (-0.28-0.54)</td>
<td>0.04</td>
<td>0.44 (-0.04-0.92)</td>
<td>0.01</td>
<td>-0.02 (-0.41-0.37)</td>
<td>0.06</td>
</tr>
<tr>
<td>Parous</td>
<td>-0.08 (-0.41-0.24)</td>
<td></td>
<td>-0.20 (-0.55-0.15)</td>
<td></td>
<td>-0.32 (-0.68-0.05)</td>
<td></td>
<td>-0.13 (-0.47-0.20)</td>
<td></td>
</tr>
<tr>
<td>No pathology</td>
<td>0.10 (-0.16-0.36)</td>
<td>0.02</td>
<td>-0.11 (-0.39-0.17)</td>
<td>0.03</td>
<td>0.08 (-0.22-0.39)</td>
<td></td>
<td>-0.08 (-0.34-0.18)</td>
<td></td>
</tr>
<tr>
<td>Any minimal pathology</td>
<td>0.19 (-0.81-1.18)</td>
<td>0.2</td>
<td>0.64 (-0.29-1.56)</td>
<td>0.01</td>
<td>-0.54 (-1.04-0.12)</td>
<td>0.02</td>
<td>0.64 (-0.68-1.39)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mild/minimal endometriosis</td>
<td>0.2 (-0.59-0.62)</td>
<td>0.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central pain</td>
<td>-0.03 (0.31-0.30)</td>
<td>0.02</td>
<td>-0.15 (-0.46-0.16)</td>
<td>0.01</td>
<td>-0.06 (-0.41-0.30)</td>
<td>0.01</td>
<td>-0.15 (-0.46-0.16)</td>
<td>0.01</td>
</tr>
<tr>
<td>No central pain</td>
<td>0.10 (-0.49-0.49)</td>
<td></td>
<td>-0.19 (-0.74-0.36)</td>
<td></td>
<td>0.21 (-0.33-0.76)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Each Time Point

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.

*Indicates worst pain level experienced from any of the 3 types of pain analyzed (noncyclical pain, dysmenorrhea, and dyspareunia).
The LUNA trial is 4 times larger than any previously published trial evaluating neuroablation in chronic pelvic pain. It may be more reliable than any previous study of LUNA and was also 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 were not informed of their allocation, there is a suggestion that a small proportion were able to guess correctly. If anything, however, this would be likely to enhance the apparent value of LUNA.

LUNA was adopted by many practitioners because afferent nerves from pelvic organs passed through the uterosacral ligament and it was believed that disruption of these would reduce the perceived pain. Lack of efficacy in this study, and in prior studies, provide evidence that the anatomical and physiological picture of chronic pelvic pain is more complicated. Anatomically, there are at least five pathways that 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.

Furthermore, it is conceivable that nerves regenerate, or there may be a retrograde rerouting of nerve pathways.

We followed participants for longer than 6 months because laparoscopy may have a placebo effect for up to 3-6 months. We found no benefit for LUNA at any time point, but found improvement in pain at 3 months in both the LUNA group and the No LUNA group. This early pain reduction may be a placebo effect; attributable to the reassurance provided by the laparoscopy that there was no serious pathology. A comparison of diagnostic laparoscopy against no laparoscopic investigation would be required to establish benefit. Alternatively, it could be a regression to the mean effect, with women more likely to undergo laparoscopic investigation when their pain is at its worst, rather than average level.

This study has several limitations. We did not obtain follow-up data on all women but drop out 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 (i.e. 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 and also for other types of pain 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 confidence intervals around the mean difference in VAS scores between the groups were less than ±1.2 points. Taking worst pain experienced at 12 months as an example, the pain score was 0.02 cm lower in the LUNA group than no LUNA group and the 95% confidence interval was 0.61 cm lower to 0.65 cm higher (i.e. well below the clinically significant improvement).

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


