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Individual patient data meta-analysis of randomized evidence to assess the effectiveness of laparoscopic uterosacral nerve ablation in chronic pelvic pain

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BACKGROUND: There have been conflicting results in randomized trials of the effects of laparoscopic uterosacral nerve ablation (LUNA) in chronic pelvic pain. Our objective was to perform a meta-analysis using individual patient data (IPD) to provide the most comprehensive and reliable assessment of the effectiveness of LUNA.

METHODS: Electronic searches were conducted in the Medline, Embase, PsycInfo and Cochrane Library databases from database inception to August 2009. The reference lists of known relevant papers were searched for any further articles. Randomized trials comparing LUNA with no additional intervention were selected and authors contacted for IPD. Raw data were available from 862 women randomized into five trials. Pain scores were calibrated to a 10-point scale and were analysed using a multilevel model allowing for repeated measures.

RESULTS: There was no significant difference between LUNA and No LUNA for the worst pain recorded over a 12 month time period (mean difference 0.25 points in favour of No LUNA on a 0–10 point scale, 95% confidence interval: −0.08 to 0.58; $P = 0.1$).

CONCLUSIONS: LUNA does not result in improved chronic pelvic pain.

Key words: individual patient data / meta-analysis / chronic pelvic pain / dysmenorrhoea / neuroablation

Introduction

Chronic pelvic pain, defined as lower abdominal pain or pelvic pain of longer than 6 months' duration, is a common condition (Zondervan *et al*., 1999). It has multiple causes (Latthe *et al*., 2006a), and prevalence varies widely globally (Latthe *et al*., 2006b). It remains one of the most challenging of women's health problems with a major impact on health-related quality of life, productivity (Sundell *et al*., 1990) and health care utilization, costing an estimated £250 million (at 2005/2006 prices) on its management in the UK (Davies *et al*., 1992). Only 20–25% patients respond to initial conservative management (Henzl, 1985). When such treatment fails, a diagnostic laparoscopy is frequently performed (Royal College of Obstetricians and Gynaecologists, 2005). The cause of the pain is not always obvious as no pathology is seen in 35% (range 3–92%) of the cases (Porpora and Gomel, 1997; Howard, 2000). In the absence of pathology there is no established gynaecological treatment.

Interruption of the Lee-Frankenhauser sensory nerve plexuses by laparoscopic uterosacral nerve ablation (LUNA) may alleviate pain (Doyle, 1955; Doyle and Des Rosiers, 1963). LUNA can be carried out quickly and simply alongside diagnostic laparoscopy using lasers or electro-diathermy and has become widely practised (Daniels *et al*., 2000; Latthe *et al*., 2004), although clinicians' beliefs about its effectiveness vary widely (Latthe *et al*., 2005). The effects of this intervention have been assessed in randomized controlled trials (Lichten and Bombard, 1987; Sutton *et al*., 2001; Vercellini *et al*., 2003; Johnson *et al*., 2004; Daniels *et al*., 2009) and summarized in published data systematic reviews (Khan *et al*., 1999; Stones and Mountfield, 2000; Proctor *et al*., 2005). In a Cochrane review of surgical interruption for primary and secondary dysmenorrhoea (Proctor *et al*., 2005), there was some evidence of the effectiveness of LUNA when compared with a control or no treatment in the absence of endometriosis [odds ratio 6.1, 95% confidence interval (CI) 1.8–21.0], but not for secondary dysmenorrhoea (0.8, 95% CI −0.4 to 1.4). These reviews concluded that there is insufficient evidence to recommend the use of nerve interruption in the management of dysmenorrhoea, regardless of cause, which was reiterated by the UK National Institute of Health and Clinical Excellence (NICE, 2007).

Meta-analysis using individual patient data (IPD) from primary studies has the potential to produce a more reliable estimate of treatment effect than from meta-analysis of aggregate data and also to allow exploration of subgroups (Stewart and Clarke, 1995; Stewart and Tierney, 2002). The LUNA IPD Meta-analysis Collaborative Group, a consortium of authors of all primary studies involving LUNA, was established to use these advanced analytic techniques to evaluate the effectiveness of LUNA in reducing chronic pelvic pain.

Methods

We undertook an IPD meta-analysis to examine the effectiveness of LUNA in reducing chronic pelvic pain according to a pre-specified protocol (Xiong *et al*., 2007), developed using recommended methods (Stewart *et al*., 2008).

Search strategy

The search methods previously described (Proctor *et al*., 2005) were updated in August 2009 (from 2003 to current) to identify any trials published since the last search and to identify ongoing trials to seek unpublished data. A comprehensive database was constructed using Reference Manager 12.0 to store all identified references. No language restrictions were applied.

Study inclusion and data collection

Studies were considered for inclusion if LUNA, as an intervention for women of reproductive age with CPP, primary or secondary dysmenorrhoea, was compared against diagnostic laparoscopy in a randomized controlled trial. Trials with concomitant ablation of endometrial lesions were included provided ablation was an option in both study groups. Two reviewers (J.P.D., R.C.) independently assessed trials for inclusion and quality, with queries resolved by a third reviewer (K.S.K.). Criteria for quality assessment were based initially on the reported characteristics and included adequacy of sequence generation and allocation concealment; blinding of participants, and assessors where used, to treatment allocation; intention to treat analysis performed and potential impact of losses of follow-up data.

Primary authors of included randomized trials were invited to join the collaborative group and to provide anonymized raw data on visual analogue score (VAS) pain ratings, the presence or absence of visual pathology, age at randomization and parity. Further assessment of data quality on receipt of the data set included the ability to reproduce the published results and discrepant patterns of data. Where discrepancies existed authors were contacted for clarification.

Statistical analysis

The primary outcome was a derived measure of the worst pain level experienced if data were received on different pain symptoms (e.g. dysmenorrhoea, non-cyclical pain and dyspareunia). Pain scores using a VAS were rescaled where necessary, to anchor the scale between 0 (no pain) and 10 (worst pain imaginable). Rather than dichotomising the data at an arbitrary threshold, as was the case in two of the included

studies (Vercellini et al., 2003; Johnson et al., 2004), scores were evaluated as a continuous measurement, thus improving the precision of the analysis (Altman and Royston, 2006). A clinically significant difference in pain has been defined as 2 points on a 10-point VAS for chronic pelvic pain (Baker and Symonds, 1992) and elsewhere, moderately important difference equates to at least a 30% reduction of the 10-point VAS for pain (Dworkin et al., 2008).

Where study information was available on allocated and received treatments, the intention to treat principle was used to analyse the data. Comparisons between allocation groups, using data up to and including 12 months, were performed using multilevel modelling techniques in SAS PROC MIXED, using all available data to estimate treatment effects over time (Higgins et al., 2001). The primary analysis model included covariate parameters for trial (to take account of differing sized trials), allocation group, baseline score and time, the latter nested within patient and trial. (Brown and Prescott, 2006; Jones et al., 2009). Heterogeneity of treatment effects across trials was investigated by including a trial by treatment interaction term in the model (Whitehead, 2002). Where this test was statistically significant (a value of $P < 0.05$ used here), sensitivity analysis were undertaken to investigate any existing inconsistency in the data. Secondary analyses incorporating the allocation group as a random effect were also undertaken for the primary analysis. Restricted maximum likelihood estimates of the overall treatment effect were calculated along with 95% CIs.

Subgroup analysis, including any differential treatment effect over time, was explored in a similar fashion by adding the relevant parameter by treatment interaction term to the basic model. Predefined subgroup analyses were the presence or absence of visual pathology (endometriosis, adhesions, pelvic inflammatory disease) and site of pain (central versus peripheral), as some trials reported differential effects (Tjaden et al., 1990; Johnson et al., 2004). Additional subgroups that could feasibly impact on treatment effects and for which data were available were age group (<30 years, ≥30 years at randomization) and parity (nulliparous, parous). Treatment effect estimates within subgroups were further investigated, alone, and where necessary in combination, if the relevant interaction terms were statistically important at $P < 0.05$.

Results

Trials and patients

A total of 56 citations were identified by electronic searches (Fig. 1). After detailed evaluation of the papers and removal of four duplicates, five primary articles met the selection criteria and were included (Lichten and Bombard, 1987; Sutton et al., 2001; Vercellini et al., 2003; Johnson et al., 2004; Daniels et al., 2009). Trials were excluded due to a lack of an adequate method for generating allocation sequence for randomization (Moon, 2001), if they used an intervention not within the scope of this meta-analysis (Tjaden et al., 1990; Candiani et al., 1992; Zullo et al., 2003), did not have a non-interventional control (Chen et al., 1996; Yen, 2001; Garcia et al., 2003; Juang et al., 2007) or could not assess the individual contribution of LUNA (Sutton et al., 1994). The characteristics of all included studies in the analysis are summarized in Table 1. The interventions in experimental and control arms were comparable across all trials. Trial populations comprised women with CPP with or without visible pathology, apart from one (Lichten and Bombard, 1987), which only assessed LUNA for primary dysmenorrhoea. IPD was received for all five (100%) of the included trials, which involved 862 randomized women.

The methodological quality of the included studies was generally good, with adequate randomization and blinding of the participants

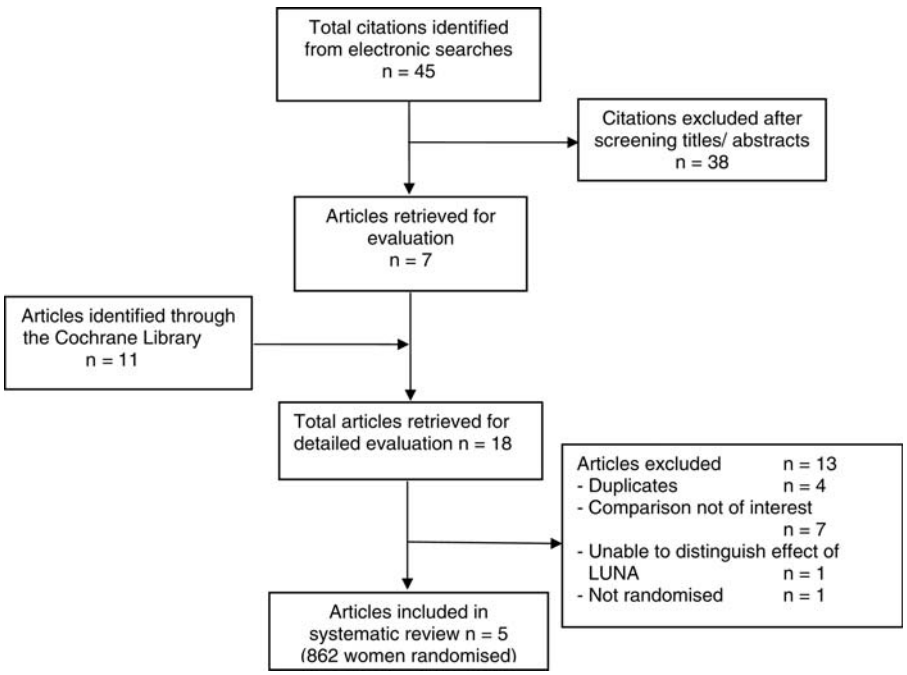

Figure 1 Study selection process for the individual patient data meta-analysis to assess the effectiveness of laparoscopic uterosacral nerve ablation (LUNA) in chronic pelvic pain.

Table I Table of characteristics of included studies in the individual patient data meta-analysis to assess the effectiveness of laparoscopic uterosacral nerve ablation in chronic pelvic pain.

Studies		Lichten and Bombard (1987)	Sutton *et al.* (2001)	Vercellini *et al.* (2003)	Johnson *et al.* (2004)	Daniels *et al.* (2009)
Methods						
	Allocation concealment	Inadequate	Adequate, sealed envelopes	Adequate, sealed envelopes	Adequate, sealed envelopes	Adequate, third-party randomization
	Randomization	Randomized by last digit of medical case number on day of surgery	Computer-generated randomization sequence	Computer-generated randomization sequence	Computer-generated randomization sequence	Computer-generated randomization sequence using minimization
	Blinding	Double blinding: participant and clinical psychologist	Double blinding; participant and research nurse	Open	Double blinding; participant and investigator	Single blinding; only patient blinded, no evaluator in this trial
	Follow-up	3 and 12 months		6 and 12 months	24 h, 3 and 12 months	3, 6 and 12 months and 2, 5 and 10 years
	Number of women randomized	21	51	180	123 (56 with no endometriosis)	487 (266 with no pathology)
	Number of women in primary analysis	21 at 12 months	46 at 6 months	116 at 12 months	106 at 12 months	378 at 12 months
	Drop-outs/ withdrawals	None	5 (1 became pregnant and 4 were lost to follow up) However, data points for 14 women were missing for some analyses	29 pregnant, 14 used oral contraception, 15 lost to follow-up, 6 miscellaneous reasons	14 were excluded based on laparoscopic findings. Loss to follow up: 3 months: 3 (2 LUNA and 0 No LUNA in the population with no endometriosis; 0 LUNA and 1 No LUNA in the endometriosis population) 12 months: 17 (4 LUNA and 2 No LUNA in the population with no endometriosis; 6 LUNA and 5 No LUNA in the endometriosis population)	Withdrawals: 6 (3 LUNA 3 No LUNA) before 12 months; Lost to follow-up: 18 (11 LUNA 8 No LUNA) provided no data up and including 12 months
Quality	Compliance with quality criteria (out of 5)	2	4	3	4	4

Continued

Table I *Continued*

Studies		Lichten and Bombard (1987)	Sutton *et al.* (2001)	Vercellini *et al.* (2003)	Johnson *et al.* (2004)	Daniels *et al.* (2009)
	Inclusion criteria	Women with severe dysmenorrhoea. No improvement during run-in phase on medication or oral contraceptive	Women with history and physical or laparoscopic examination suggestive of endometriosis who had not received medical treatment for endometriosis within the last 6 months, and had not previously undergone surgical treatment of their disease	Women aged 18 to 40, who reported pelvic pain of more than 6 months duration; undergoing operative laparoscopy for symptomatic minimal to severe endometriosis	Women aged 18 to 45 years, who reported pelvic pain of more than 6 months duration; no change in medication in previous 3 months	Women who reported pelvic pain of 6 months or longer in duration, located within the true pelvis or between and below the anterior iliac crests; associated functional disability; lack of response to medical treatment; undergoing diagnostic laparoscopy
	Exclusion criteria	History of psychotherapy, major abdominal procedures, drug abuse; demonstrable pelvic pathology at diagnostic laparoscopy	Severe endometriosis, any other pathology that may have been responsible for their pain symptoms; currently pregnant or intending to get pregnant; medical treatment for endometriosis within last 6 months; previous surgery for endometriosis	Previous diagnosis of endometriosis; any other pathology that may have been responsible for their pain symptoms, presence of vaginal endometriosis; treatment for endometriosis other than non-steroid anti-inflammatory drugs up to 6 months before entry in the study; previous diagnosis of gastrointestinal, urologic and orthopedic diseases in which pain may radiate to the pelvic area; known psychiatric disturbances	Previous hysterectomy or pelvic malignancy; previous LUNA; known ovarian cysts; pelvic adhesions which did not appear to be due to endometriosis; plan for a pregnancy within 12 months; intention to change other medical treatment which could influence pelvic pain scores within 12 months; LUNA technically not possible	Previous hysterectomy; previous LUNA; moderate and severe endometriosis; previous surgery for endometriosis or pelvic inflammatory disease; adnexal pathology; LUNA technically not possible
		Primary dysmenorrhoea	CPP with minimal to moderate pelvic endometriosis	Secondary dysmenorrhoea (minimal to severe endometriosis)	CPP with no visible pathology or with minimal to severe endometriosis	CPP with no visible pathology or minimal to mild endometriosis, mild pelvic inflammatory disease, minimal adhesions
	Age	Range 18–34. Mean for each group not given	Mean 28 (range 20–41). Mean for each group not given, but stated no difference	Range 18–40. Mean for each group not given	Mean (SD) No endometriosis group LUNA 29 (5.83) No LUNA 29 (6.49) with endometriosis group LUNA 30 (6.71) No LUNA 29 (5.31)	Mean (SD) LUNA 30.6 (7.53) No LUNA 30.5 (7.48)
	Location	Detroit, USA	Surrey, UK	Milan, Italy	Auckland, New Zealand	Multicentre, UK
	Treatment	LUNA	LUNA with laparoscopic excision or ablation of all visible endometriosis	LUNA with laparoscopic excision or ablation of all visible endometriosis	Group with endometriosis: LUNA with laparoscopic excision or ablation of all visible endometriosis; Group without endometriosis: LUNA	Group with pathology: LUNA with laparoscopic excision or ablation of all visible endometriosis and/or adhesionolysis. Group without pathology: LUNA
	Control	Diagnostic laparoscopic surgery only	Laparoscopic excision or ablation of visible endometriosis	Laparoscopic excision or ablation of visible endometriosis	Group with endometriosis: laparoscopic excision or ablation of visible endometriosis; Group without endometriosis: diagnostic laparoscopic surgery only	Group with pathology: laparoscopic excision or ablation of visible endometriosis and/or adhesionolysis. Group without pathology: diagnostic laparoscopic surgery only

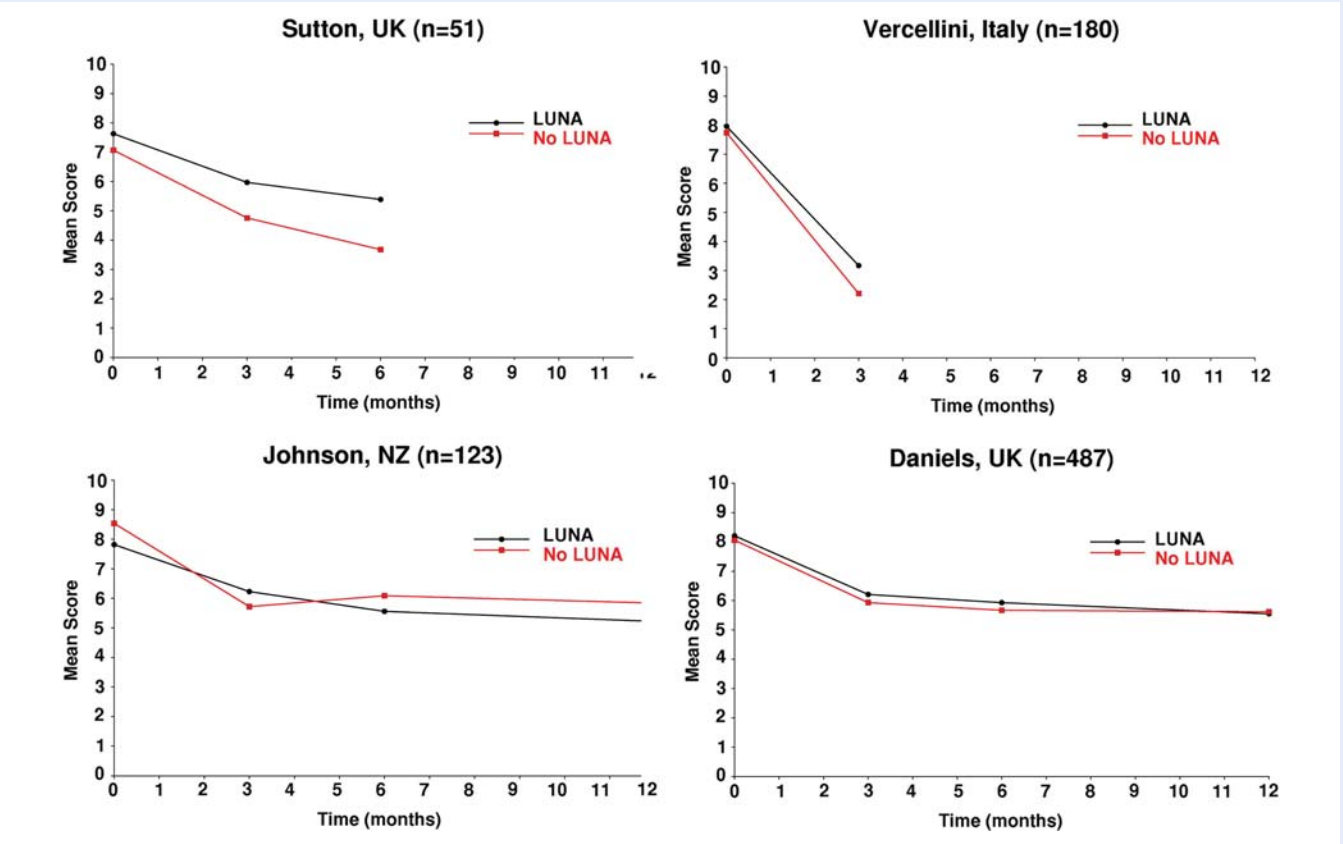

Figure 2 Mean pain scores over time for trials included in the analysis. Lower score indicates less pain.

and assessors, where employed. In one trial (Lichten and Bombard, 1987) randomization was inadequately concealed so it was excluded from the primary analysis, although a sensitivity analyses including these data was conducted. On receipt of raw data, it was not possible to guarantee an intention-to-treat analysis for two studies (Sutton *et al.*, 2001; Vercellini *et al.*, 2003), as provided data did not give details on allocated and received procedures. In one of these studies, a problem with the database precluded use of all but the baseline and 3 months data.

Effectiveness of LUNA on relieving pain

In all trials, a marked improved in pain scores was seen in both LUNA and No LUNA groups following laparoscopy. Dysmenorrhoea was invariably the worst pain reported. In the primary analysis, the No LUNA group demonstrated a non-significant greater improvement in their worst pain score than the LUNA group when a constant treatment effect over time was assumed (0.25 points on a 10-point scale, 95% CI: −0.08, 0.58; $P = 0.1$). This result was consistent over the four high quality trials (test for trial by treatment interaction: $P = 0.2$) (Fig. 2). A similar difference was seen when the treatment effect was allowed to vary randomly over the trials (0.32 points, 95% CI: −0.40, 1.05; $P = 0.3$). Likewise, including the inadequately concealed trial as a sensitivity analysis did not change the overall result (0.1 points, 95% CI: −0.23, 0.44; $P = 0.5$), but significant heterogeneity between trials was introduced ($P < 0.0001$) and so no further examination of the data including this trial was undertaken.

The observed treatment effect was demonstrated to change over time (test for time by treatment interaction $P = 0.004$); a difference in pain improvement in favour of No LUNA was seen at 3 months (0.49 points, 95% CI: 0.12, 0.86; $P = 0.009$), but not at 6 months (0.25 points, 95% CI: −0.09, 0.58; $P = 0.1$) or 1 year (−0.25 points, 95% CI: −0.72, 0.23; $P = 0.3$) (Fig. 3).

There was some evidence that the presence of visible pathology altered the effectiveness of LUNA ($P = 0.01$) (Table II).Where pathology was present, the No LUNA group had greater improvement in pain at 3 months (0.81 points, 95% CI: 0.36, 1.26; $P = 0.0004$) and 6 months (0.61 points, 95% CI: 0.19, 1.04; $P = 0.005$), whereas those without visible pathology benefited more from LUNA at 1 year (−0.68 points, 95% CI: −1.29, 0.07; $P = 0.03$), but not at 3 or 6 months. There was no evidence that age ($P = 0.1$) or parity ($P = 0.7$) had any differential effect on the treatment effect when these parameters were assessed in the model, so combinations of subgroups were not investigated further. Only one trial provided data on the site of pain, so this subgroup analysis was not attempted. There were no reports of serious perioperative or subsequent adverse events.

Discussion

Main findings

Our review provides the most comprehensive and reliable means of assessing the effectiveness of LUNA in women with CPP in whom

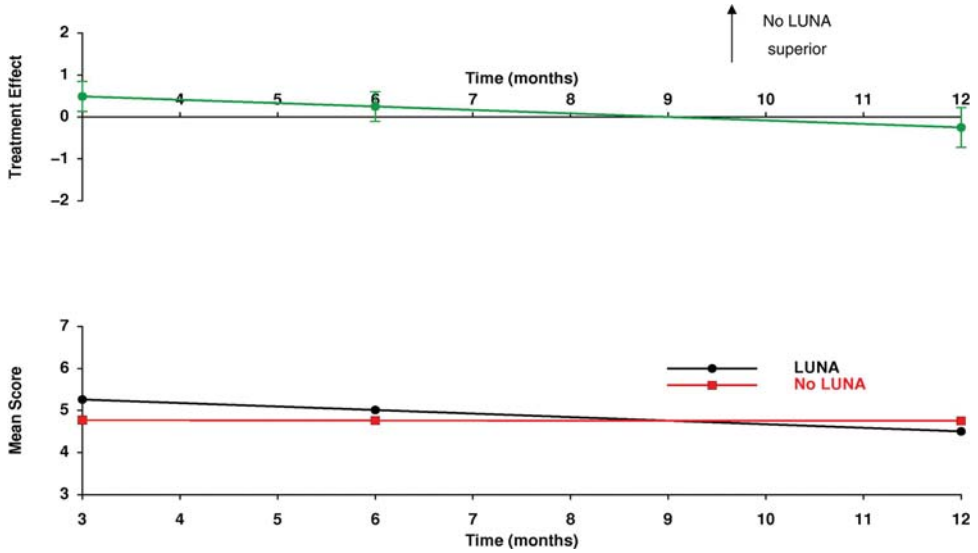

Figure 3 The bottom graph shows the maximum likelihood estimates of visual analogue pain scores from a multilevel model with timepoint nested within patient, within trial and with baseline score as a covariate and treatment effect allowed to vary over time. Mean pain score are measured on a visual analogue scale of 0 (no pain) to 10 (worst imaginable pain). The top graph shows the difference in mean visual analogue scale (VAS) pain scores, with error bars indicating 95% CIs.

Table II Subgroup analysis of presence or absence of pathology on the effect of LUNA in alleviating pain.

Timepoint	Pathology present mean VAS difference (95% confidence interval), *P*-value for difference	Pathology absent mean VAS difference (95% confidence interval), *P*-value for difference
3 months	0.81 (0.36,1.26) $P = 0.0004$	−0.08 (−0.66,0.50) $P = 0.8$
6 months	0.61 (0.19,1.04) $P = 0.005$	−0.28 (−0.82,0.26) $P = 0.3$
12 months	0.21 (−0.35,0.78) $P = 0.5$	−0.68 (−1.29, − 0.07) $P = 0.03$

Test for heterogenetity between subgroups $P = 0.01$ mean VAS difference of worst pain score between LUNA and No LUNA groups. Positive number indicates greater improvement in No LUNA group.

diagnostic laparoscopy reveals either no or minimal pathology. LUNA did not alleviate pain compared with the No LUNA group, indeed there was some evidence that women who have the LUNA procedure may suffer from more pain in the short term than those who do not. Contradictory treatment effects were seen in the presence and absence of pathology, but were not consistent at every timepoint, whereas age and parity did not influence the treatment effect.

Strengths and limitations of the review

The availability of IPD from all included studies enabled a more thorough investigation of overall and subgroup treatment effects than previous meta-analyses have achieved. Problems with database relational integrity prompted us to exclude some data from the meta-analysis. One lower-quality study, which was clinically and statistically heterogeneous to the other studies was excluded from the primary analyses, although sensitivity analysis indicated this had no effect on the overall treatment effect. The multilevel model accounting for repeated measures increased the accuracy of estimates by using continuous pain scores, rather than dichotomized measures of success used in some trials (Vercellini *et al.*, 2003; Johnson *et al.*, 2004). With IPD, we were able to explore the variation between subgroups and treatment effects within subgroups, using similar statistical models. Unlike previous meta-analyses (Proctor *et al.*, 2005), we chose to exclude trials with interventional controls in order to assess LUNA's efficacy in pain relief, therefore we cannot comment on its effectiveness compared with presacral neurectomy. There were no other outcome measures common to included studies, so analyses were restricted to pain reduction.

Interpretation

This IPD meta-analysis reinforces the conclusions drawn from the largest trial of LUNA (Daniels *et al.*, 2009) that the procedure is not effective in alleviating pain within 1 year of treatment. Although a long-term assessment of LUNA was not possible here due to lack of data beyond 12 months from most primary studies, the UK LUNA trial does not suggest any delayed effect of LUNA. Subgroup

analysis did suggest a benefit of LUNA in those without visible pathology, consistent with the Cochrane review, although this effect was only seen at 12 months and was of borderline statistical significance (Proctor *et al*., 2005). Conversely, the IPD meta-analysis of those with visible pathology showed greater decrease in pain in the No LUNA group, contradicting the Cochrane review. These subgroup effects lack biological plausibility and are likely to have arisen by chance. Moreover, given that a clinically significant difference in pain has been defined as 2 points on a 10-point visual analogue scale for chronic pelvic pain (Baker and Symonds, 1992; Dworkin *et al*., 2008), and also for other types of pain (Biljsma, 2007), it seems implausible that LUNA could produce a clinically relevant effect in women with minimal gynaecological pathology. In every comparison, the CIs around the mean difference in pain scores between the groups were less than ± 0.7 points: in our statistically significant subgroup analysis, at 12 months in the absence of pathology, the pain score was 0.68 points lower with LUNA and the upper 95% CI was 1.29 points lower, well below a clinically significant improvement.

The meta-analysis conclusively dismisses the use of LUNA for all women with pelvic pain in the presence of visible pathology, and strongly suggests that LUNA does not provide any benefit of clinical importance for women without recognizable pathology, due to lack of efficacy. National guidelines should be updated and brought in line with that of the UK (National Institute for Health and Clinical Excellence, 2007). There is no need for any further randomized controlled trials of LUNA and future research should focus on further investigation of the causes of chronic pelvic with a view to identifying novel treatments or refining existing therapies and assessing their effectiveness in large, well designed randomized trials.

Lack of efficacy in this study and others (Personal communication E. Lichten), provides strong evidence that the pathophysiology of chronic pelvic pain is complicated, and a greater understanding of the interaction of neural pathways and uterine physiology is needed to direct the research of further interventions.

An additional aim was to motivate the collaborating primary investigators to undertake new, mutually planned, primary studies in this field. Few IPD meta-analysis have been published in gynaecological research to date and it is hoped this paper, alongside other international initiatives (www.ipd-meta-analysis.com) will motivate others to adopt this technique when uncertainty remains despite published data meta-analysis.

Authors' roles

K.S.K. conceived the idea for undertaking the IPD meta-analysis, provided clinical advice and supervised all aspects of the review. J.P.D. prepared the protocol, assessed eligibility and methodological quality of the trials and wrote the first draft of the manuscript. R.C. updated the searches, assessed quality and prepared the tables and figures. L.M. cleaned and checked the individual patient data sets, contacted the authors with queries, wrote the statistical analysis plan, performed data validation checks and statistical analyses. T.X. assessed eligibility and liaised with individual trialists. R.G. and R.K.H. provided advice on the statistical analysis plan and the statistical analyses. All members of the collaborative group provided comments on the manuscript and approved the final draft.

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Conflicts of interest: K.S.K. and N.P.J. were authors of the Cochrane systematic review on this topic (Proctor *et al*., 2005). The authors declare that they do not have any other competing interests.

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