Chronic pelvic pain and menorrhagia: Assessing treatment effectiveness
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Chapter 6

Meta-analysis using individual patient data from randomised trials to assess the effectiveness of laparoscopic uterosacral nerve ablation in the treatment of chronic pelvic pain: a proposed protocol
Chapter 6

Abstract

Background: Currently, there are a number of clinical trials, but no international collaboration for collating research on effectiveness of laparoscopic uterosacral nerve ablation (LUNA) for alleviating chronic pelvic pain.

Objective: Meta-analysis was used by collecting individual patient data (IPD) from the existing trials, to provide a comprehensive assessment of the effectiveness of LUNA that will be generalisable in various clinical contexts.

Methods: IPD will be sought and collected from all relevant (both already finished and continuing) randomised trials identified through previous systematic reviews. After obtaining raw data and cleaning the database, analysis will be of all patients ever randomised based on the intention-to-treat principle using endpoints measured at 12 months following randomisation.

Proposal: We will update searches, contact all authors, obtain data in whatever form it can be provided, build a single database, produce results for individual studies, have them verified by original authors, explore of any heterogeneity and reasons behind it and finally pool all raw data in to a meta-analysis using appropriate statistical methods. The project will test the effectiveness of LUNA for women with chronic pelvic pain. It will also motivate collaborating primary investigators to undertake new primary studies to corroborate or improve upon the conclusions derived from the retrospective analysis.

Introduction

Chronic pelvic pain is a common condition with a major impact on health-related quality of life, work productivity and health care utilisation,\textsuperscript{1-3} costing an estimated £158 million per year to the NHS.\textsuperscript{4} An effective treatment for this condition has evaded the medical profession for centuries. Even today only 20-25\% patients respond to conservative management.\textsuperscript{5} When such treatment fails, a diagnostic laparoscopy is performed.\textsuperscript{1;3;6} The cause of the pain is not always obvious as no pathology is seen in 40-60\% of the cases.\textsuperscript{1} In the absence of pathology there is no established treatment. The Lee-Frankenhauser sensory nerve plexuses and parasympathetic ganglia in the uterosacral ligaments carry pain from the uterus, cervix and other pelvic structures.\textsuperscript{7-10} Interruption of these nerve trunks by laparoscopic uterosacral nerve ablation (LUNA) may alleviate pain.\textsuperscript{11} However, the balance of benefits and risks of this intervention have not been reliably assessed.
LUNA has, nevertheless, been introduced into practice, although there remains controversy regarding indications for LUNA.

We carried out a comprehensive systematic review of observational and randomised evidence on the efficacy of LUNA in the treatment of chronic pelvic pain. For the treatment of primary dysmenorrhoea there was some evidence of the effectiveness of LUNA when compared to a control or no treatment. The comparison between LUNA and laparoscopic presacral neurectomy (LPSN) for primary dysmenorrhoea showed no significant difference in pain relief in the short term; however, long-term LPSN was shown to be significantly more effective than LUNA. For the treatment of secondary dysmenorrhoea six identified randomised controlled trials (RCT) addressed endometriosis and one included women with uterine myomas. The treatment of LUNA combined with surgical treatment of endometrial implants versus surgical treatment of endometriosis alone showed that the addition of LUNA did not aid pain relief. For presacral neurectomy (PSN) combined with endometriosis treatment versus endometriosis treatment alone there was an overall difference in pain relief, although the data suggests this may be specific to laparoscopy and for midline abdominal pain only. Adverse events were significantly more common for presacral neurectomy; however, the majority were complications such as constipation, which may spontaneously improve. This systematic review concluded that there is insufficient evidence to recommend the use of nerve interruption in the management of dysmenorrhoea, regardless of cause.

Hence, there is an urgent need for a methodologically sound and sufficiently powered analytic research to be undertaken, to confirm, or refute, any worthwhile effectiveness. A more realistic and unbiased assessment for the effectiveness of LUNA might be obtained via multivariable analyses that incorporate the clinical context in which investigations are carried out. Systematic reviews and conventional meta-analyses of such data increase the number of outcome events but do not permit the clinical context to be taken into account.

Meta-analysis using individual patient data (IPD) from primary studies has the potential to estimate informativeness of the investigations in context, which has been introduced as the gold standard analytic approach in reviews of randomised controlled trials, however no such analyses appear to exist in the current literature. This project will undertake IPD meta-analysis including all relevant studies identified in previously published systematic reviews. In this way it will provide the most comprehensive and reliable means of assessing the effectiveness of LUNA in a clinical setting considering various clinical context.

We aim to answer the following purposes through this IPD meta-analysis. Firstly, to test the hypothesis that in women with chronic pelvic pain in whom diagnostic laparoscopy reveals either no pathology or stage I-II endometriosis LUNA alleviates pain and improves life quality at 12
months, using raw data collated from studies included in systematic review. Secondly, to test the hypothesis that response to LUNA differs according to the site and cause of the pain by two secondary analyses – women with central pain and women with no visible pathology. Thirdly, to motivate collaborating primary investigators to undertake new, mutually planned, primary studies to corroborate or improve upon the conclusions derived from the retrospective analysis above, e.g. long term follow-up of randomised trials. Lastly, to initiate and advocate the execution of IPD meta-analysis in clinical research and to motivate others to experiment with it in other fields of medicine – if it were proven to be of value.

**Methods**

**Identification Of Randomised Trials And Investigators**

Individual patient (raw) data will be sought from all currently existent and relevant studies of randomised trials identified in the previously published systematic review, including both already finished and continuing trials.

All authors of included studies of randomised trials were invited formally or personally by the initiator of this study for collaboration in the spring of 2006 (a related website has been developed). An e-mail system based team building exercise will be undertaken by bringing authors’ viewpoints together to an electronic forum. This forum will: examine the protocol for refinements; discuss the variables on which the data are to be collected, the data checking procedures and the main analyses to be performed; and agree on a timetable and a publication policy (a collaborative/group authorship will be proposed).

**Data Collection And Administration**

The Birmingham Clinical Trials Unit (BCTU) will act as the group’s secretariat and will hold the main database (International LUNA IPD Meta-analysis Collaborative Group, Birmingham, United Kingdom. Email bctu@bham.ac.uk, website: birmingham.ac.uk/bctu). All data, updates and corrections should be sent to BCTU in whatever format is most convenient for each group and will be stored in an Access database. All data will be held securely and treated in the strictest confidence. The data will not be used in any publication without the permission of the responsible trialists.

Additional items may be collected if they are of interest to the Group and are available. In addition, we invite the principal investigators of included studies to send us their study protocol and details about study execution. We expect that many of these protocols will give us details that cannot be taken from the publications. Furthermore, the current project will ensure checks on consistency and ranges of the data. The original investigators will be contacted to supply missing data or to check values of doubtful validity.
Statistical Analysis Plan

Analysis will be of all patients ever randomised and will be based on the intention to treat principle. Visual analogue scale scores [on the scale 0 (no pain) to 10 (worst pain)] within the first 12 months of treatment will be combined and considered in a repeated measures analysis, giving us the advantage of being able to estimate overall effects over time utilising all available information. Multilevel modelling techniques in SAS PROC MIXED will be used, adjusting for baseline score and allowing for treatment type and study of origin using fixed or random effects as deemed appropriate. Confidence intervals for overall treatment effects will then be estimated from the model.

Pre-specified subgroup analyses will be performed by:

1. Presence or absence of some coexisting pathology (endometriosis ± ablation; adhesions requiring adhesiolysis only; minimal pelvic inflammatory disease)
2. Site of pain (presence of central pain or not)
3. Age group
4. Parity (presence/absence of children)

We will also perform stratified analysis at study level depending on the control arm – diagnostic laparoscopy versus other intervention.

By collecting IPD, investigation of heterogeneity between these subgroups and estimation of possible difference between will be possible, which is a clear advantage over using summary data from published reports. Furthermore, the collection of updated data, with longer follow up than in many of the individual trial reports, will enable reliable evaluation of treatment effects over time.

Future Publications

The results of the IPD meta-analysis will be presented and discussed at a meeting of the collaborating trialists. Any subsequent report of the meta-analysis results will be published in the name of the collaborative group – the International LUNA IPD Meta-analysis Collaborative Group – and will be circulated to the collaborators for comment, amendment and approval before submission. In case of any disagreement, the fundamental principle that will be applied is that the report should provide the meta-analysis results, presenting the totality of the available evidence, but will not include any interpretations of the data, except for those that are unanimously agreed by all collaborators. Any group will be free to withdraw its data from the collaboration at any time.
Conclusion

This proposed international collaboration will provide the opportunity to achieve a new methodology of IPD meta-analysis in a field requiring urgent high quality research. It will also facilitate international collaboration in medical research while allowing individual investigators to maintain autonomy. The proposed analyses also provide the potential to provide high-level evidence on methods of pain management in a timely manner.
References


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