Title page

Title – Laparoscopic excision versus ablation for endometriosis-associated pain – Updated systematic review and meta-analysis

Running title - Excision vs ablation for endometriosis-associated pain

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Abstract

The aim of the study is to update the evidence on surgical management of endometriosis associated pain - does laparoscopic excision offers any benefits over laparoscopic ablation? This is a systematic review and meta-analysis, where we searched MEDLINE, EMBASE, ISI conference proceedings, ISRCTN, Register and Meta-register for RCTs, WHO trials search portal, Cochrane Library and the 'British Library of electronic theses'. Three RCTs were included which enrolled 335 participants with a sample size per study ranging from 24 to 178 participants. Out of these three studies, data from two could be pooled for meta-analysis. Primary outcome measure was reduction in VAS score for dysmenorrhea. Secondary outcome measures included reduction in VAS score for dyspareunia, dyschezia, chronic pelvic pain and reduction in EHP30 Core pain scores.

Meta-analysis showed that the excision group had a significantly greater reduction in symptoms of dysmenorrhea (MD 0.99; 95% CI -0.02, 2.00; p = 0.05), and dyschezia (MD 1.31; 95% CI 0.33, 2.29; p = 0.009) compared with ablation. The symptoms of dyspareunia showed non-significant benefit with excision (MD 0.96; 95% CI -0.07, 1.99; p = 0.07). Data from one study showed a significant reduction in chronic pelvic pain (MD 2.57; 95% CI 1.27, 3.87; p = 0.0001) and EHP30 Core pain scores (MD 13.20; 95% CI 3.70, 22.70; p = 0.006) with the excision group as compared with the ablation group.

The limited available evidence shows that at twelve months post-surgery, symptoms of dysmenorrhea, dyschezia and chronic pelvic pain secondary to endometriosis showed significantly greater improvement with laparoscopic excision compared with ablation.

Key words: Laparoscopic, excision, ablation, vaporization, endometriosis, pain

Introduction

The evaluation and treatment of endometriosis has evolved alongside the development of minimally invasive surgery in recent decades. This is a direct result of having a relatively simple, low morbidity means of assessing the female pelvis by diagnostic laparoscopy. Although recently we have developed the ability to accurately diagnose and map the presence of deep infiltrating endometriosis in specialist centers with readily accessible transvaginal or transrectal ultrasound (1, 2). we still lack the ability to diagnose early stage disease without diagnostic laparoscopy. Once it has been found it is recommended in ESHRE Guidelines to see and treat the lesions where possible (3) as there is evidence that their removal reduces endometriosis associated pelvic pain and improves spontaneous fertility rates (4, 5, 6).

The technique used during laparoscopy for achieving this remains a contentious issue with many general gynaecologists not see-and-treating or applying only superficial electrosurgical ablation. Those with an interest in endometriosis are more likely to employ more comprehensive vaporization techniques with laser, helium gas or argon plasma therapy through to full surgical excision of lesions.

A recent Cochrane review concluded that there was low quality evidence that laparoscopic excision and ablation were similarly effective in relieving pain (7). However, this review only included one trial from the medical literature. This data has been used in ESHRE Guidelines for endometriosis as grade C evidence advising that clinicians may consider both ablation and excision of peritoneal endometriosis to reduce endometriosis-associated pain (3). As there have been more studies identified on this subject, our study sought to systematically re-review and update existing evidence related to the impact of laparoscopic excision on endometriosis-associated

pelvic pain compared with laparoscopic ablation or vaporisation to further guide clinical practice.

Materials and Methods

Literature search methodology

We searched MEDLINE (1950 to Oct 2014), EMBASE (1980 to Oct 2014). The search also included ISI conference proceedings as well as databases for registration of ongoing and archived randomised controlled trials (RCTs), namely International Standard Randomised Controlled Trial Number (ISRCTN), Register and Meta-register for RCTs (http://www.controlled-trials.com), WHO trials search portal (ICTRP, apps.who.int/trialsearch/Trial). A combination of Medical Subject Headings (MeSH) and text words were used to generate two subsets of citations, one including studies of 'endometriosis' and the second 'excision, ablation, diathermy, vaporisation, vaporization'. These subsets were combined using 'AND' to generate a subset of citations relevant to our research question. We also searched the Cochrane Library for RCTs and the 'British Library of electronic theses' online service (http://ethos.bl.uk) with the search term of "endometriosis". The reference lists of all known primary and review articles were examined to identify cited articles not captured by the electronic searches. No language restrictions were placed on any of our searches. The searches were conducted independently by JP and VP.

Study selection

PICOS Study protocol for the review was followed. Studies were selected if the target population (P) were women undergoing laparoscopic surgery for endometriosis with any excision technique and were compared with women with any ablative or

vaporisation technique. The primary outcome measure was reduction in dysmenorrhea and secondary outcome measures were reduction in dyspareunia, dyschezia, pelvic pain, chronic pelvic pain and QoL EHP 30 pain scores. We included all randomised and non-randomised trials ~~Only RCTs were included in~~ this systematic review. Studies were selected in a two-stage process. Firstly, the titles and abstracts from the electronic searches were scrutinised by two reviewers independently (JP and VP) and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. We wrote to the corresponding authors in the case where data was not clear nor reported, or a full manuscript was not available for the details. Secondly, final inclusion or exclusion decisions were made on examination of the full manuscripts. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer (EK).

Assessment of methodological quality and data extraction

Each study included was assessed for sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. The selected studies were assessed for methodological quality by using the components of study design that are related to internal validity. The assessment of methodological quality was based on the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions v 5.1.0. The selected studies were assessed for methodological quality by using the components of study design that are related to internal validity (8). Two reviewers (VP and KO) completed data extraction and quality assessment (9). The information on the method of randomisation, allocation concealment, blinding, intention-to-treat analysis and follow-up rates was sought by examining the full text articles. Study characteristics

and participant features were extracted from each study.

Statistical analysis

From each study, outcome data were extracted by two reviewers (JP, KO). For continuous estimates, the mean difference (MD) with 95% CI was calculated using the inverse-variance method. We considered $p \leq 0.05$ to be statistically significant. The results from individual studies were pooled using random-effects models because we assumed that the observed estimates of treatment effect would vary across studies because of real differences in the treatment effect in each study due to study characteristics (as well as sampling variability) (10). Heterogeneity of the exposure effects was evaluated graphically using forest plots (11) and statistically using the I^2 statistic (12). A chi-squared test for heterogeneity was also performed and the 'p' values are presented. Exploration of causes of heterogeneity was planned using variations in features of population, exposure and study quality. We adhered to published guidance for conducting systematic reviews throughout (i.e. The Cochrane Handbook). Statistical analyses were performed using RevMan 5.2.7 software (Cochrane Collaboration, Oxford, UK).

Results

Literature search

The process of literature identification and selection is summarised in Figure 1. Of the 502 publications identified by the search, 13 were selected during the initial screening. After examination of the full manuscripts, 10 were excluded (Table 3) (5-7, 13-19). Therefore, three studies satisfied the selection criteria and were included in this review (20, 21, 22). All these three studies were randomised trials. We did not find any non-randomised trials addressing this subject.

Study characteristics

The three included RCTs enrolled 335 participants. In total, 167 women were randomised to treatment with excision and 168 women were randomised to ablation. Overall, 222 (66.3%) women completed the follow-up of the study protocol, 114 (68.2%) in excision arm and 108 women in ablation arm (64.3%), with a similar rate of follow-up in both arms. The sample size per study varied across the trials and ranged from 24 to 178 participants. Out of these three studies, two were published as full manuscripts (20, 21) and one was a Doctoral thesis dissertation examined and accepted at the University of Surrey (22).

The characteristics and methodological quality of the included trials are summarised in Table 1 and Table 2 respectively. Inclusion and exclusion criteria, sample size, treatment protocol and all outcomes reported are included. Risk of bias from included studies is represented in Figures 2 and 3. Our judgments about each risk of bias item, presented as percentages across all included studies, are shown in Figure 2, and for each risk of bias item for each included study in Figure 3. All three studies had a parallel design. The method of randomisation was by computer-generated random numbers in one study (21) and by random sequence generation in blocks of 10 in two studies (20, 22). Allocation concealment was in place in two studies (21, 22). All studies claimed they were double-blinded, however it was not clear in the methodology of the study of Wright et al. All trials addressed incomplete outcome data. The follow-up duration was 6 months in one study (20) and 12 months in the remaining two studies (21, 22). The follow-up rate varied between 58% and 100%. All studies performed a priori power calculation to determine the sample size needed for the outcome of pelvic pain.

Description of studies

The study of Wright and colleagues included 24 women (20). It compared excisional with ablative treatment for rASRM stage 1 (mild endometriosis) (23) endometriosis in the management of chronic pelvic pain. Participants completed a questionnaire detailing symptoms related to chronic pelvic pain (pelvic pain, dysmenorrhea, dyspareunia, dyschezia, constipation, diarrhoea, cramps exercise pain, back pain, fatigue) and rated their pain on a ranked ordinal scale, pre-operatively and after 6 months following surgery. Signs were assessed by the patient rating the amount of discomfort felt during palpation (uterine mobility, tenderness, adnexal pain, ultrasound scan, Pouch of Douglas). The group used 3 mm monopolar diathermy scissors with a combination of 90 watts pure cut and 50 watts coagulation for excision and a coagulation current of 50 watts with the closed end of a pair of 3 to mm monopolar laparoscopic scissors for ablation. The study reported that both treatment modalities produced good symptomatic relief and reduction in pelvic tenderness (67%). There was no significant difference between the two procedures for any of the individual questionnaire items. A high pain score before treatment was suggested to be a good predictor of appreciable improvement following surgery.

The study of Healey and colleagues (21) randomised 178 women of reproductive age presenting with pelvic pain and visually proven endometriosis. Women with rASRM endometriosis stage 1-3 were included. The study recruited 89 women in each arm of excision and ablation. Out of these 95 women completed study at 12 months, 54 women in excision and 49 women in ablation arm. Each subject’s endometriosis was scored and staged with use of the rASRM system and also using the superficial/deep categorization (24) at the end of the operation. Both groups were comparable

regarding baseline patient characteristics. Women completed a questionnaire rating their various pains using visual analogue scales (VAS) pre-operatively and at 3, 6, 9, and 12 months following surgery. The study did not specify the method of excision and ablation as they allowed individual consultants to use their preferred method. Of the excision group 87% subjects had positive histology for endometriosis. The study reported no significant difference in reduction in overall VAS pain scores at 12 months following surgery between ablation and excision. They suggested that due to the non-significant trends seen in this study, a larger study may find a difference in outcomes looking at dyspareunia, rectal pain or dyschezia. Subjects were also stratified on the basis of the superficial and deep endometriosis. No significant differences were found in changes in VAS score amongst women with deep endometriosis undergoing excision or ablation.

The Doctoral thesis of Barton-Smith (22) was a randomized blinded trial of CO_2 laser vaporization versus harmonic scalpel excision of rASRM stage 1-3 stage 1-3 i.e. superficial and deep infiltrating endometriosis and excluded rASRM stage 4 or severe disease. The for pelvic pain recorded pre-operatively and at 3, 6 and 12 months following surgery. The hypothesis was that thorough vaporization should not be inferior to excision. The study recruited 133 women and randomised 66 to excision and 67 to ablation. 95 women completing study at 12 months, 48 in excision and 47 in ablation group. Histology was taken in 65 of 133 cases (49%), 49 from the excision group and 16 from the vaporisation group. Overall 54 of the 65 cases had histology positive for endometriosis, showing a successful correlation between visual inspection and histological analysis in 83% of cases. The proportion of women showing pain improvement was not statistically significant between the two groups though, there

was a trend towards excision being superior (85.4% excision, 72.9% vaporization). However, the *extent* of pain improvement in reduction of EHP30 Pain Scores was significantly better for excision compared with vaporisation at 12 months for both superficial and deep disease. VAS scores were significantly improved at 12 months in all pain domains for excision whereas vaporization showed significant improvements for dysmenorrhea and dyspareunia but not for dyschezia. Improvement in chronic pelvic pain was significantly better in excision compared with vaporisation. Analysis of deep disease alone revealed that, unlike excision, vaporization did not show a significant improvement in EHP30 Pain scores at 12 months.

We could not include results from Wright et al. 2005 in this meta-analysis due to incomplete data. We pooled the data from the remaining two studies in this meta-analysis where possible (21, 22).

Primary outcome measure

Reduction in VAS score for dysmenorrhea

Pooling of the results of the two studies (21, 22) showed that the excision group had a significantly greater reduction in VAS scores of dysmenorrhea compared with ablation (MD 0.99; 95% CI -0.02, 2.00; p = 0.05; Figure 4). There was no significant heterogeneity between the studies (I^2 = 4%; x^2 = 1.04, p = 0.31).

Secondary outcome measures

Reduction in VAS score for dyspareunia

Pooling of the results of these two studies (21, 22) showed that the excision group had a significantly greater reduction in VAS scores of dyspareunia compared with ablation

(MD 0.96; 95% CI -0.07, 1.99; p = 0.07; Figure 5.1). There was no significant heterogeneity between the studies (I^2 = 0%; x^2 = 0.31, p = 0.58).

Reduction in VAS score for dyschezia

Pooling of the results of these two studies (21, 22) showed that the excision group had significantly greater reduction in VAS scores of dyschezia compared with ablation (MD 1.31; 95% CI 0.33, 2.29; p = 0.009; Figure 5.2). There was no significant heterogeneity between the studies (I^2 = 0%; x^2=0.26, p 0.61).

Reduction in VAS score for chronic pelvic pain

One study reported on chronic pelvic pain (22), which showed a significant reduction in chronic pelvic pain with the excision group as compared with the ablation group (MD 2.57; 95% CI 1.47, 3.67; p < 0.00001, Figure 5.3).

Reduction in VAS score for pelvic pain

One study reported on pelvic pain (21), which showed no significant difference between the excision and ablation groups (MD -0.10; 95% CI -1.30, 1.10; p = 0.87, Figure 5.4).

Reduction in EHP30 Core pain score

Only one study reported on this outcome (22) This study showed that the excision group had significantly more reduction in EHP30 Core pain scores compared with ablation (MD 13.20; 95% CI 5.15, 22.25; p = 0.001; Figure 5.5).

Discussion

Our systematic review identified and included three RCTs and pooled the data from two RCTs with a comparative meta-analysis of laparoscopic excision versus ablation in alleviating endometriosis associated pain symptoms. We could not include results from Wright et al. 2005 in the meta-analysis due to incomplete data (20) We pooled the data from the remaining two studies in this meta-analysis where possible (21, 22). The current Cochrane review (7) also excluded the study of Wright et al., 2005 from meta-analysis due to incomplete data and pooled data from only one RCT (21).

Both the excision and ablation of endometriosis have been shown to improve pain symptoms versus controls in randomised studies at 12 months post-surgery (4,13). The main symptom of endometriosis is dysmenorrhoea which Sutton et al., reported as the worst pain symptom women complained of, and Abbott et al., reported as the most common symptom on follow up in their respective RCTs. Therefore, dysmenorrhoea was selected as the primary outcome. In this meta-analysis dysmenorrhea, dyschezia and chronic pelvic pain, all important symptoms of endometriosis, have shown significantly greater improvement from excision compared with ablation at 12 months post-surgery. The symptom of dyspareunia showed a trend towards benefit, though did not reach statistical significance. Healey et al., gave no definition for pelvic pain in his paper whereas Barton-Smith defined chronic pelvic pain as pelvic pain lasting for greater than 6 months not related to menstruation in order to differentiate it from dysmenorrhoea. Many definitions define chronic pelvic pain as including cyclical pain and, if Healey and colleagues' definition also included cyclical menstruation pain, then the definitions are heterogeneous and are not comparable in a meta-analysis. Therefore, we did not pool these data and reported them separately. Healey et al., showed no significant improvement in any

area between the two modalities although it did show a trend towards a greater reduction in dyspareunia, rectal pain and defecation pain in the excision group compared with ablation.

Strengths and limitations

In general, both trials were sufficiently powered, well designed and had acceptable risk of bias summaries. Both included investigation of dysmenorrhoea, the most common symptom of endometriosis, and measured it in the same way, as well as for the secondary outcome measures of dyspareunia and dyschezia, resulting in a more than reasonable number of outcomes to compare. Both groups had more deep infiltrating disease cases in their excision groups compared with their ablation groups thus reducing the risk of bias in comparing the two trials.

This meta-analysis could only pool data for Visual Analogue Scale scores for pain symptoms of dysmenorrhoea dyspareunia and dyschezia. It included quality of life data from only one study (22) that revealed significantly greater improvements in quality of life for excision compared with ablation in all EHP30 domains at 12 months.

The main limitation of this review remains inclusion of only three studies from the systematic review and two studies for pooling the results for meta-analysis. Some outcomes were reported in only one study. The existing meta-analysis carried out by the Cochrane group on which major national and international guidelines for management of endometriosis associated pain are based, includes only study. The reason for doing this updated review paper was therefore to provide better evidence

than that currently available as one study meta-analyses are not only pointless but can be misleading. Inclusion of two studies for meta-analysis is also not ideal but it is the best evidence we have for this important aspect of endometriosis. Furthermore, this updated review changes the results and conclusion of the previous Cochrane review and therefore will provide valuable information to update the evidence based guidelines. This will lead to change in practice and therefore more effective management of endometriosis associated pain which has been a long awaited outcome for clinicians. There is a precedent since we have all practiced for many years according to the two study meta-analysis on management of endometrioma published by the Cochrane group. We attempted to include both randomised and non-randomised studies with a hope to include more studies, but we found no such studies in the literature. This highlights the difficulty in conducting such surgical trials addressing the research question and the dilemma faced by the clinicians who practise evidence based medicine, who are currently forced to adopt practice based on the current Cochrane review including one study. This updated review will provide further information on this difficult research question which is a very common clinical situation faced by many gynaecologists.

The other main weakness in terms of interpreting pain in these two trials is a lack of information on co-existing adenomyosis. The presence of co-existing adenomyosis is not recorded in either paper and is likely to be a major factor affecting pain score improvements. At the time of both studies the diagnosis of adenomyosis was generally retrospective in hysterectomy specimens and not by ultrasound. Adenomyosis is now routinely diagnosed on transvaginal ultrasound and even graded

on severity of appearance (25), although this grading is only just beginning to be validated as a prognostic indicator for pain (26).

For most surgeons treating endometriosis of all severities and depths, the preferred technique to be used is excision. This approach is logical as damage-prone adjacent structures like ureters, blood vessels, nerves and bowel can be dissected free by skilled surgeons to reduce the risk of complications. Furthermore, the depth of disease can be fully assessed by excising around the disease till normal tissue is seen thus achieving adequate clearance. In other words, the more complex the case, greater is the rationale for using excision as the chosen method. We may also bear in mind that the two RCTs for ablation and excision of endometriosis versus no treatment also suggested a possible advantage to excision by showing 80% versus 62.5% with ablation in women showing pain improvement at 6 months (4, 13).

The case for excision would undoubtedly be more powerful if both studies were significantly in favour of excision especially as both trials were sufficiently powered, unlike in the Cochrane endometrioma review where the ambivalent result between excision and ablation came from an underpowered trial (27) That being said, our meta-analysis suggests that laparoscopic excision significantly reduces dysmenorrhoea, dyschezia and chronic pelvic pain, along with a non-significant reduction in dyspareunia, which are the most common symptom of endometriosis.

Conclusion

With only two trials able to be included in this meta-analysis, and one of those trials showing no statistically significant benefit for excision over ablation in any of the

outcomes, the evidence cannot be deemed as conclusive. Also, comparative data on outcomes greater than twelve months is lacking. However, at twelve months post-surgery, beyond the time period of the well documented placebo effect, all the major symptoms of endometriosis of dysmenorrhea, dyschezia and chronic pelvic pain showed significantly greater improvement and a non-significant improvement in dyspareunia, with laparoscopic excision compared with ablation in this comprehensive updated systematic review. Further well-designed and well-conducted multicenter trials with long term follow-up are warranted to address this issue.

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