Does the modality of surgical treatment of cervical intra-epithelial neoplasia effect outcomes?

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Authors' objectives
To assess the efficacy and morbidity of local ablative and excisional surgical treatments for cervical intra-epithelial neoplasia (CIN).

Searching
MEDLINE was searched up to December 1998. Sixteen named journals were handsearched and the reference lists of relevant articles were checked.

Study selection
Study designs of evaluations included in the review
Studies that were described as randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared alternative surgical treatments were eligible for inclusion. These could be local ablative (laser ablation, cryotherapy, radical diathermy) or excisional (laser conisation, knife conisation with and without haemostatic sutures, and loop excision of the transformation zone (LLETZ)) surgery.

Participants included in the review
Studies of women with CIN were eligible for inclusion.

Outcomes assessed in the review
Studies that assessed morbidity were eligible for inclusion. The review assessed peri-operative pain, peri-operative bleeding, malodorous discharge, adequate colposcopy and cervical stenosis at follow-up, residual disease of all grades, primary and secondary haemorrhage, depth of thermal artifact and significant thermal artifact on biopsy, duration of the procedure and dysmenorrhoea.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The studies were assessed for method of randomisation only. The authors did not state who performed the assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For binary outcomes, the number of patients with each outcome was extracted for each treatment arm and the odds ratio (OR), with 95% confidence interval (CI), was calculated. For continuous outcomes, the mean and standard deviation were extracted.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis using the Mantel-Haenszel fixed-effect model. A pooled OR and 95% CI were calculated separately for each binary outcome for the different treatment comparisons. For continuous outcomes, a weighted mean difference (WMD) and 95% CI were calculated.
How were differences between studies investigated?

For studies that compared laser ablation with cryotherapy, data were analysed separately for all grades of CIN and for CIN 1. For studies that compared laser ablation with LLETZ, the analysis was repeated by excluding the one study showing a marked increase in success with LLETZ.

Results of the review

Twenty-three RCTs or quasi-RCTs were included. It was unclear how many participants were included in each study.

Eleven studies did not describe the method of randomisation. Seven studies used adequate randomisation methods. Three studies were quasi-randomised.

Laser ablation versus cryotherapy.

Seven studies (n not reported) evaluated residual disease and found no statistically significant difference between surgical treatments when all grades of CIN were considered, but laser ablation was significantly more effective than cryotherapy for CIN 1 (the results were only presented graphically). The results for high-grade CIN were not reported.

Laser ablation was associated with a statistically significant increase in the likelihood of peri-operative severe bleeding (OR 7.45, 95% CI: 1.68, 33.05; based on 599 patients in 3 RCTs) and adequate colposcopy at follow-up (OR 4.64, 95% CI: 2.98, 7.23; based on 536 patients in 3 RCTs).

Cryotherapy was associated with a statistically significant increase in the likelihood of vaso-motor symptoms (OR 0.11, 95% CI: 0.04, 0.28; based on 1 RCT) and malodorous discharge (OR 0.23, 95% CI: 0.15, 0.35; based on 400 patients in 2 RCTs). No statistically significant difference was observed between treatments in the likelihood of peri-operative pain (OR 2.38, 95% CI: 0.90, 6.26; based on 493 patients in 3 RCTs), cervical stenosis at follow-up (OR 1.44, 95% CI: 0.46, 4.55; based on 464 patients in 2 RCTs).

Laser conisation versus knife conisation.

No statistically significant difference was observed between surgical treatments in the likelihood of residual disease (OR 0.63, 95% CI: 0.20, 1.93; based on 134 patients in 2 RCTs), primary haemorrhage (OR 0.51, 95% CI: 0.23, 1.16; based on 256 patients in 2 RCTs) or secondary haemorrhage (OR 0.81, 95% CI: 0.35, 1.86; based on 199 patients in 3 RCTs).

Laser conisation significantly increased the likelihood of adequate coloscopy at follow-up (OR 2.73, 95% CI: 1.47, 5.08; based on 160 patients in 2 RCTs).

Knife conisation was associated with a slight significant likelihood of cervical stenosis at follow-up (OR 0.39, 95% CI: 0.25, 0.61; based on 1,019 patients in 4 RCTs). Laser conisation versus LLETZ.

No statistically significant difference was observed between surgical treatments in the likelihood of residual disease (OR 1.22, 95% CI: 0.71, 2.12; based on 667 patients in 3 RCTs), secondary haemorrhage (OR 0.89, 95% CI: 0.34, 2.34; based on 667 patients in 3 RCTs), adequate colposcopy at follow-up (OR 0.94, 95% CI: 0.59, 1.52; based on 339 patients in 2 RCTs) or cervical stenosis at follow-up (OR 1.15, 95% CI: 0.57, 2.33; based on 338 patients in 2 RCTs).

Laser conisation took significantly longer to perform (WMD 12.9, 95% CI: 10.60, 12.91; based on 419 patients in 3 RCTs), and significantly increased the likelihood of significant thermal damage (OR 2.82, 95% CI: 1.56, 5.10; based on 373 patients in 2 RCTs) and peri-operative severe pain (OR 5.36, 95% CI: 1.62, 17.72; based on 594 patients in 2 RCTs).

LLETZ was associated with a significantly greater depth of thermal artifact (WMD 0.27, 95% CI: 0.19, 0.35; based on 40 patients in 1 RCT).

Laser ablation versus LLETZ.
Laser ablation was associated with a significantly increased likelihood of residual disease compared with LLETZ (OR 2.57, 95% CI: 1.93, 3.43; based on 1,463 patients in 4 RCTs). Reanalysis excluding the one study showing a marked increase in success with LLETZ showed no significant difference between treatments (OR 0.90, 95% CI: 0.49, 1.68). The authors could identify no reason for the difference between the studies.

Laser ablation was associated with a significantly increased likelihood of residual disease compared with LLETZ (OR 4.40, 95% CI: 1.86, 10.43; based on 480 patients in 2 RCTs).

No statistically significant difference was observed between surgical treatments for the likelihood of primary haemorrhage (OR 1.56, 95% CI: 0.35, 7.0) or secondary haemorrhage (OR 1.08, 95% CI: 0.33, 3.30), based on 759 patients in 3 RCTs.

Knife conisation with versus without haemostatic sutures.

Haemostatic sutures significantly reduced the likelihood of secondary haemorrhage (OR 2.69, 95% CI: 1.34, 5.39; based on 515 patients in 2 RCTs), dysmenorrhoea (OR 2.88, 95% CI: 1.55, 5.36; based on 277 patients in 2 RCTs), cervical stenosis (3.85, 95% CI: 2.45, 6.04; based on 307 patients in 2 RCTs) and adequate colposcopy at follow-up (0.26, 95% CI: 0.15, 0.45 based on 200 patients in 1 RCT).

No statistically significant difference was observed in the likelihood of primary haemorrhage (OR 0.52, 95% CI: 0.23, 1.20; based on 522 patients in 2 RCTs).

A single trial compared different surgical techniques and found no consistent differences between laser conisation versus laser ablation (1 RCT), knife conisation versus LLETZ (1 RCT), or radical diathermy versus LLETZ (1 RCT).

Authors’ conclusions

No single surgical technique appeared to be superior. Cryotherapy appeared effective for low-grade but not high-grade disease. Treatment selection should be based on costs, morbidity and the adequacy of biopsy specimens post-treatment.

CRD commentary

The review question was clear in terms of the study design, participants, intervention and outcomes. Only one electronic database was searched up to 1998, although this was supplemented by handsearches of relevant journals. However, the dates searched were not reported, so the adequacy of the search could not be assessed. The possibility of publication bias cannot, therefore, be ruled out. In addition, since it was not stated whether any language restrictions were applied, the potential for language bias could not be assessed. The methods used to select studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer errors and bias. The validity assessment was inadequate, as it was limited to an assessment of the appropriateness of the randomisation method, thus it is not possible to confirm the reliability of evidence presented in the studies included in the review.

There was no information on the participants included in the individual studies, which means that it is not possible to determine which populations the results were applicable to. In addition, it was not explicitly clear how many participants were included in each study. The studies were combined using a fixed-effect meta-analysis without any assessment of statistical heterogeneity, and an examination of potential differences was only possible for the two meta-analyses with accompanying graphs. In the absence of study characteristics it is difficult to determine whether the studies were combined using an appropriate method. It was unclear whether differences explored between studies were defined a priori, and no results were presented for the use of cryosurgery in high-grade CIN. This casts doubt on the authors’ conclusion regarding cryotherapy. In summary, the reliability of the authors’ conclusion is unclear based on the incomplete reporting of study characteristics and limitations in the reporting and conduct of the review.

Implications of the review for practice and research

Practice: The authors stated that cryotherapy should not be used for high-grade disease but should be considered for low-grade disease, particularly where resources are limited. They recommended the use of LLETZ rather than laser excision unless lesions are endocervical.
Research: The authors did not state any implications for further research.

**Bibliographic details**


**Indexing Status**

Subject indexing assigned by CRD

**MeSH**

Adult; Cervical Intraepithelial Neoplasia /surgery; Disease Progression; Female; Treatment Outcome

**AccessionNumber**

12005009773

**Date bibliographic record published**

31/05/2006

**Date abstract record published**

31/05/2006

**Record Status**

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.