Surgery for cervical intraepithelial neoplasia (Review)

Martin-Hirsch PL, Paraskevaidis E, Kitchener H

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

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This record should be cited as:
Martin-Hirsch PL, Paraskevaidis E, Kitchener H. Surgery for cervical intraepithelial neoplasia. *Cochrane Database of Systematic Reviews* 1999, Issue 3. Art. No.: CD001318. DOI: 10.1002/14651858.CD001318.

This version first published online: 26 July 1999 in Issue 3, 1999.
Date of most recent substantive amendment: 19 May 1999

ABSTRACT

Background
Cervical intra-epithelial neoplasia is treated by local ablation or lower morbidity excision techniques. Choice of treatment depends on the severity of the disease.

Objectives
The objective of this review was to assess the effects of alternative surgical treatments for cervical intra-epithelial neoplasia.

Search strategy
We searched the Cochrane Gynaecological Cancer Group trials register and MEDLINE up to July 1997. Update: in July 2004 a further search was conducted.

Selection criteria
Randomised and quasi-randomised trials of alternative surgical treatments in women with cervical intra-epithelial neoplasia.

Data collection and analysis
Trial quality was assessed and two reviewers abstracted data independently.

Main results
Twenty eight trials were included. Seven surgical techniques were tested in various comparisons. No significant difference in eradication of disease was shown, other than between laser ablation and loop excision. This was based on one trial where the quality of randomisation was doubtful. Large loop excision of the transformation zone appeared to provide the most reliable specimens for histology with the least morbidity. Morbidity was lower than with laser conisation, although all five trials did not provide data for every outcome. There were not enough data to assess the effect on morbidity compared with laser ablation.

Authors' conclusions
The evidence suggests that there is no obviously superior surgical technique for treating cervical intra-epithelial neoplasia.

PLAIN LANGUAGE SUMMARY

No clear evidence to show any optimal surgical technique is superior for treating pre-cancerous cervix abnormalities.

Cervical pre-cancer (cervical intraepithelial neoplasia) can be treated in different ways depending on the severity of the disease. Less invasive treatments not requiring a hospital stay may be used, but a general anaesthetic is occasionally needed, especially if the tumour has spread locally or previous out-patient treatment has failed. Surgery can be done with a knife, laser or cutting with a loop (an electrically charged wire). This review found there was not enough evidence to compare techniques and that more research is needed.

BACKGROUND

Current treatment for cervical intra-epithelial neoplasia (CIN) is by local ablative therapy or by excisional methods depending on the nature and extent of disease. Traditionally prior to colposcopy, all lesions were treated by knife excisional cone biopsy or by ablative radical point diathermy. Knife cone biopsy and radical point diathermy are usually performed under general anaesthesia and are now not the preferred treatment of choice as various more conservative local ablative and excisional therapies can be performed in an out-patient setting.

Patients are suitable for ablative therapy provided that:
(1) the entire Transformation Zone can be visualised (satisfactory colposcopy);
(2) there is no suggestion of micro-invasive or invasive disease;
(3) there is no suspicion of glandular disease;
(4) the cytology and histology correspond.

Excisional treatment is mandatory for a patient with an unsatisfactory colposcopy, suspicion of invasion or glandular abnormality. There is now a trend to utilise low morbidity excisional methods either laser conisation or Large Loop Excision of the Transformation Zone (LLETZ) in place of destructive ablative methods. Excisional methods offer advantages over destructive methods in that they can define the exact nature of disease and the completeness of excision/destruction of the transformation zone. Incomplete excision/destruction of the transformation zone is an important indicator of patients at risk of treatment failure or recurrence of disease .

The treatment modalities included in this review are described below:

Knife cone biopsy:
Traditionally broad deep cones were performed for most cases of CIN. Excision of a wide and deep cone of the cervix is associated with significant short and long term morbidity (peri-operative, primary and secondary haemorrhage, local and pelvic infection, cervical stenosis and mid-trimester pregnancy loss (Jordan 1984; Leiman 1980; Luesley 1985). A less radical approach is now generally adopted tailoring the width and depth of the cone according to colposcopic findings. The procedure is invariably performed under general anaesthesia. Peri-operative haemostasis can be difficult to achieve and various surgical techniques have been developed to reduce this. Routine ligation of the cervical vessels is commonly performed. This technique also allows manipulation of the cervix during surgery. Sturmdorf sutures have been advocated by some surgeons to promote haemostasis, others recommend circumferential locking sutures, electrocauterisation or cold coagulation or vaginal compression packing.
Treatment success (i.e. no residual disease on follow-up) of knife cone biopsy is reported as 90 to 94% (Bostofte 1986; Larson 1983; Tabor 1990) in non randomised studies.

Laser Conisation:
This procedure can be performed under general or local analgesia. A highly focused laser spot is used to make an ectocervical circumferential incision to a depth of 1 cm. Small hooks or retractors are then used to manipulate the cone to allow deeper incision to complete the endocervical incision. Haemostasis if required is generally achieved by laser coagulation by defocusing the beam. A disadvantage of laser conisation is that the cone biopsy specimen might suffer from thermal damage making histological evaluation of margins impossible.
Treatment success of laser cone biopsy is reported as 93 to 96% (Bostofte 1986; Tabor 1990) in non randomised studies. The major advantages are accurate tailoring of the size of the cone, low blood loss in most cases, and less cervical trauma than knife cut cones.

Loop Excision of The Transformation Zone:
Large Loop Excision of the Transformation Zone is often abbreviated to LLETZ in the UK or LEEP (Loop Electrosurgical Excisional Procedure) in the U.S.A. A wire loop electrode on the end of an insulated handle is powered by an electrosurgical unit. The current is designed to achieve a cutting and a coagulation effect simultaneously. Power should be sufficient to excise tissue without causing thermal artefact. The procedure can be performed under local analgesia.
Treatment success of LLETZ is reported as 97.4% (Murdoch 1984), 98% (Prendeville 1989), 95.9% (Bigrigg 1990), 95.9% (Luesley 1990), 94.9% (Whiteley 1990), 91%(Murdoch 1992) and 94% (Wright et al 1992) in non randomised studies.

Laser Ablation:
A laser beam is used to destroy the tissue of the transformation zone. Laser destruction of tissue can be controlled by the length of exposure. Defocusing the beam permits photocoagulation of bleeding vessels in the cervical wound.
Treatment success of laser ablation is reported as 95% (Wright 1984) and 96% (Jordan 1985).

Cryotherapy:
A circular metal probe is placed against the transformation zone. Hypothermia is produced by the evaporation of compressed refrigerant gas passing through the base of the probe. The cryonecrosis is achieved by crystallization of intracellular water. The effect tends to be patchy as sub-lethal tissue damage tends to occur at the periphery of the probe.
In non-controlled studies the success of treatment of CIN3 varied between 77% and 93%, 87% (Benedet 1981), 77% (Hatch 1981), 82% (Kaufman 1978), 84% (Ostergard 1980), and 93% (Popkin et al 1978).
Utilising a DOUBLE freeze-thaw-freeze technique improves the reliability in the observational study by Creasman 1984 .
Rapid ice-ball formation indicates that the depth of necrosis will extend to the periphery of the probe. The procedure can be asso-

ciated with unpleasant vasomotor symptoms.

This systematic review examines the efficacy and morbidity of local ablative and excisional therapies for eradicating disease. The effectiveness and morbidity of the various forms of treatment have been generally evaluated by uncontrolled observational studies. Hence direct comparison of treatment effects of alternative treatments is unreliable because of variable patient selection, treatment outcomes and follow-up criteria. We have therefore only included trials which appear to be randomised thus reducing selection bias and providing more reliable results. Randomised trials are the only reliable and valid method of generating truly comparable comparison groups.

OBJECTIVES

(1) To assess the efficacy of alternative surgical treatments for CIN at eradicating disease.

(2) To assess the characteristics and morbidity associated with different therapies with regards to:
(a) duration of treatment;
(b) peri-operative pain;
(c) peri-operative bleeding, primary and secondary haemorrhage;
(d) depth and presence of thermal artefact;
(e) adequate colposcopy at follow-up;
(f) cervical Stenosis at follow-up.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials (RCTs) using alternative surgical treatments of CIN were identified by a computerised literature search, tracing references listed in the relevant articles and a manual search of appropriate journals. A trial was eligible for inclusion if it dealt with the ability of a surgical treatment for CIN or investigated the morbidity associated with it, and contained a control group which the authors claimed was created by a randomised procedure. The computerised MEDLINE search was conducted to identify all registered randomised trials comparing alternative surgical treatments for CIN before July 1997. Update: in July 2004 a further search was undertaken.

Types of participants

Women with CIN confirmed by biopsy and undergoing surgical treatment.

Types of intervention

(1) Laser Ablation
(2) Laser Conisation
(3) LLETZ
(4) Knife Conisation
(5) Cryotherapy

Types of outcome measures

(1) Residual disease detected on follow-up examination

(2) Characteristics and Morbidity
(a) duration of treatment
(b) peri-operative severe pain
(c) peri-operative severe bleeding, primary and secondary haemorrhage
(d) Depth and presence of thermal artifact
(e) Adequate colposcopy at follow-up
(f) Cervical Stenosis at follow-up

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

A computerised MEDLINE search was conducted to identify all registered randomised trials comparing surgical treatments for CIN before July 1997. Update: in July 2004 a further search was undertaken.
The method for identifying trials was as follows:
1 RANDOMIZED-CONTROLLED TRIAL in PT
2 RANDOMIZED-CONTROLLED-TRIALS
3 RANDOM-ALLOCATION
4 DOUBLE-BLIND-METHOD
5 SINGLE-BLIND-METHOD
6 CLINICAL-TRIAL in PT
7 explode CLINICAL-TRIALS
8 (clin* near trial*) in TI
9 (clin* near trial*) in AB
10 (singl* or doubl* or trebl* or tripl*) near (blind* or mask*)
11 (#10 in TI) or (#10 in AB)
12 PLACEBOS
13 placebo* in TI
14 placebo* in AB
15 random* in TI
16 random* in AB
17 RESEARCH-DESIGN
18 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #11 or #12
or #13 or #14 or #15 or #16 or #17
19 explode GENITAL NEOPLASMS, FEMALE
20 #18 and #19
21 TG=ANIMAL not (TG=HUMAN and TG=ANIMAL)
22 #20 not #21
23 PT=CONTROLLED-CLINICAL-TRIAL
24 #18 or #23
25 #24 and #22
26 #25 not #21

Our search strategy was similar to the one that is advocated by the Cochrane Collaboration (Dickersin 1994)

Sixteen journals thought to be most likely to contain relevant publications were hand searched, (Acta Cytologica, Acta Obstetrica Gynecologica Scandanavia, Acta Oncologica, American Journal of Obstetrics and Gynaecology, British Journal of Cancer, British Journal of Obstetrics and Gynaecology, British Medical Journal, Cancer, Cytopathology, Diagnostic Cytopathology, Gynaecologic Oncology, International Journal of Cancer, International Journal of Gynaecological Cancer, Journal of Family Practice, Lancet, Obstetrics and Gynaecology).

METHODS OF THE REVIEW

RCTs were analysed for the method of randomisation, inclusion criteria, number of women included, treatment intervention (and variations in technique), duration of follow-up and out-comes residual disease and morbidity.

DESCRIPTION OF STUDIES

See Characteristics of Included Studies.

METHODOLOGICAL QUALITY

Twenty eight RCTs were identified:

The method of randomisation (an important source of bias) was not described in 11 studies (Berget 1987; Berget 1991; Bostofte 1986; Jobson 1984; Kirwan 1985; Kristensen 1990; Kwikkel 1985; Larsson 1982; Paraskevaidis 1994; Takac 1999;Townsend 1983). Twelve trials were truly randomised (Alvarez 1994; Crompton 1994; Duggan 1999, Giacalone 1999, Gilbert 1989; Healey 1996; Mathevet 1994; Mitchell 1998; Oyesanya 1993; Partington 1989; Santos 1996, Schantz 1984) using a genuine random method of treatment allocation and five trials were quasi-randomised (Ferenczy 1985; Girardi 1994; Gunasekera 1990, O'Shea 1986, Singh 1988). Quasi-randomisation was by alternate assignment, by birth date, or by file number.

Update: in July 2004 a further search did not identify any new RCTs.

RESULTS

Single Freeze compared to doube freeze cryotherapy
The study by Schantz 1984 demonstrated that the double freeze technique had a lower residual disease rate odds ratio (OR) 2.93 (95% confidence interval (CI) 2.93 to 8.60).

Laser ablation compared with cryotherapy

(1) Residual disease
Seven RCTs reported the incidence of residual disease. The study by Berget (Berget 1991) used the same group of patients as the study by (Berget 1987) hence the former publication was used in the analysis as it contained longer and more consistent follow-up data. None of the trials produced results that reached statistical significance. Meta-analysis failed to demonstrate a significant difference between the two treatments OR 0.96 (95% CI 0.67 to 1.36)

Stratification of disease revealed an apparent significant difference between the two treatment options when treating CIN1 OR 3.33 (95%CI 1.1 to 10.1), and a non-significant difference for CIN2 OR 1.58 (95% CI 0.69 to 3.2) and CIN3 OR 0.8 (95% CI 0.39 to 1.65).

(2) Peri-operative severe pain
Laser ablation was associated with a higher incidence of severe peri-operative severe pain OR 2.38 (95% CI 0.9 to 6.28).

(3) Peri-operative severe bleeding
Laser ablation was associated with significantly more peri-operative severe bleeding OR 7.45 (95% CI 1.68 to 33).

(4) Vaso-motor symptoms
One study (Townsend 1983) reported the incidence of vaso-motor symptoms (principally light headedness). Cryosurgery caused significantly more symptoms OR 0.11 (95% CI 0.04 to 0.28).

(5) Malodorous discharge
Two trials (Berget 1987; Townsend 1983) provided sufficient data to allow analysis of the incidence of malodorous vaginal discharge. Laser ablation caused significantly less symptoms OR 0.23 (95%CI 0.15 to 0.35)

(6) Adequate colposcopy
Three studies (Berget 1987; Jobson 1984; Ferenczy 1985) reported on adequate colposcopy at follow-up in the two treatment groups. Laser ablation was associated with a significantly higher adequate colposcopy rate compared to cryosurgery OR 4.64 (95% CI 2.98 to 7.27).

(7) Cervical stenosis
Berget (Berget 1987) reported on the incidence of cervical stenosis. Laser ablation was associated with a higher rate of cervical stenosis but not significantly so when compared to cryotherapy OR 1.96 (95% CI 0.52 to 7.44).

Laser conisation compared with knife conisation
(1) Residual disease (all grades)
In two trials (Bostofte 1986; Mathevet 1994), the direction of effect suggested that there was more residual disease in the knife cone group but no conclusions can be made as the CIs are wide OR 0.63 (95% CI 0.2 to 1.93).

(2) Primary haemorrhage
Two trials reported data on primary haemorrhage (Bostofte 1986; Kristensen 1990). The incidence of secondary haemorrhage in

cone biopsies performed with and without Sturmdorf sutures were combined. Laser conisation was associated with a lower incidence of primary haemorrhage OR 0.51 (95% CI 0.23 to 1.16).

(3) Secondary haemorrhage
Three trials (Kristensen 1990; Larsson 1982; Mathevet 1994) reported on secondary haemorrhage. They produced heterogeneous results. There was no significant difference OR 0.81 (95% CI 0.35 to 1.86).

(4) Satisfactory colposcopy at follow-up
Two trials (Bostofte 1986; Mathevet 1994) reported on satisfactory colposcopy at follow-up examination. Laser conisation produced a significantly higher adequate colposcopy rate OR 2.73 (95% CI 1.47 to 5.08).

(5) Cervical stenosis at follow-up
Four trials (Bostofte 1986; Kristensen 1990; Larsson 1982; Mathevet 1994) reported on cervical stenosis at follow-up. All trials demonstrated the same direction of effect. Laser conisation resulted in significantly less cervical stenosis at follow-up examination OR 0.39 (95% CI 0.25 to 0.61).

(6) Ectocervical and endocervical margins with disease
One trial (Mathevet 1994) reported on the presence of thermal artefact prohibiting interpretation of resection margins. As expected knife cone biopsy produced no such cases compared to 14 out of 37 laser cones OR 11.4 (95% CI 3.54 to 36).

Laser conisation compared with laser ablation
(1) Residual disease (all grades)
Only one trial (Partington 1989) reported on this outcome. There was no significant difference demonstrated OR 0.73 (95% CI 0.19 to 2.87).

(2) Significant peri-operative bleeding
Only one trial (Partington 1989) reported on this outcome. There was no significant difference demonstrated OR 1.55 (95% CI 0.42 to 5.7).

(3) Secondary haemorrhage
Only one trial (Partington 1989) reported on this outcome. There was no significant difference demonstrated OR 2.17 (95%CI 0.73 to 6.48).

(4) Adequate colposcopy at follow-up
Only one trial (Partington 1989) reported on this outcome. Laser ablation appeared to produce more adequate colposcopes at follow-up than laser conisation OR 0.25 (95% CI 0.06 to 1.27).

Laser conisation compared to LLETZ
(1) Residual disease
Three trials reported on residual disease at follow-up (Mathevet 1994; Oyesanya 1993; Santos 1996). They produced heterogeneous results. The largest trials by Oyesanya and Santos demonstrated more residual disease in the laser conisation group, but this just failed to achieve significance. The final meta-analysis was OR 1.22 (95% 0.71 to 2.12).

(2) Duration of procedure
Three studies measured the duration of treatment (Crompton 1994; Oyesanya 1993; Paraskevaidis 1994). All demonstrated a significant increased difference in operating time WMD 11.76 (95% CI 10.6 to 12.9).

(3) Peri-operative severe pain
Oyesanya (Oyesanya 1993) demonstrated that there were significantly more women complaining of severe pain during laser conisation OR 7.81 (95% 2.03 to 29.3). However the trial by Santos (Santos 1996) did not demonstrate any significant difference. There was insufficient data in the trial by Crompton (Crompton 1994) to include in the analysis, their assessment of pain by linear analogue scales did not demonstrate any difference in pain scores. The final meta-analysis was OR 5.36 (95%CI 1.02 to 17.2).

(4) Secondary haemorrhage
The trials did not demonstrate any significant difference OR 0.89 (95% CI 0.34 to 2.34).

(5) Significant thermal artefact
Mathevet and Oyesanya (Mathevet 1994; Oyesanya 1993) demonstrated significantly more thermal artefact in laser cone biopsy specimens OR 2.82 (95%CI 1.56 to 5.1).

(6) Depth of thermal artefact
Paraskevaidis (Paraskevaidis 1994) demonstrated a significant difference in depth of thermal artefact WMD 0.27 (95%CI 0.19 to 0.35).

(7) Adequate colposcopy at follow-up
Mathevet (Mathevet 1994) demonstrated that loop excision produced more adequate colposcopes at follow-up OR 0.27 (95% CI 0.08 to 0.89).
However, Santos (Santos 1996) did not a significant difference, the final meta-analysis being OR 0.94 (95% CI 0.59 to 1.54)

(8) Cervical stenosis at follow-up
Mathevet and Santos (Mathevet 1994; Santos 1996) did not demonstrate any significant difference OR 1.15 (95% CI 0.57 to 2.33).

Laser ablation compared to loop excision
(1) Residual disease
Three trials reported residual disease (Alvarez 1994; Gunasekera 1990; Mitchell 1998). There was no difference in residual disease rates OR 0.99 (95% CI 0.63 to 1.55).

(2) Severe peri-operative pain
Two trials reported on the incidence of severe peri-operative pain (Alvarez 1994; Gunasekera 1990). They produced heterogeneous results, the final meta-analysis demonstrating a higher incidence of women complaining of severe pain during laser ablation OR 4.4 (95% CI 1.86 to 10.4).

(3) Primary haemorrhage

The trials by Alvarez, Gunasekera and Mitchell (Alvarez 1994; Gunasekera 1990; Mitchell 1998) did not demonstrate any significant difference OR 1.56 (95% CI 0.35 to 7.00).

(4) Secondary haemorrhage
The trials by Alvarez, Gunasekera and Mitchell (Alvarez 1994; Gunasekera 1990; Mitchell 1998) did not demonstrate any significant difference OR 1.05 (95% CI 0.33 to 3.30)

Knife cone biopsy compared to loop excision
(1) Residual disease
Five randomised trials evaluated knife cone biopsy and loop excision. (Duggan 1999, Giacalone 1999, Girardi 1994, Mathevet 1994). The trials sugested that there might be a higher residual disease rate after loop excision but this was only just statistically significant OR 0.43 (95% CI 0.18 to 1.0).

(2) Primary haemorrhage
There was no clear evidence that there there was any difference in this outcome (Girardi 1994, Giacalone 1999, Takac 1999).

(3) Adequate colposcopy at follow-up
The studies by Giacalone 1999, Duggan 1999, Girardi 1994, Mathevet 1994, sugested that loop excision significantly had better adequate colposcopy rates OR 0.64 (95% CI 0.4 to 1.01). The study by Takac 1999 agreed with these findings but there was insufficient data to include their results in this analysis.

(4) Cervical stenosis.
There was no clear evidence that either method reduced the cervical stenosis rates.

Radical diathermy versus LLETZ
Only one trial compared these two treatments (Healey 1996). There was no significant difference with respect to duration of the following symptoms: blood loss , watery discharge, white or yellow discharge, upper or lower abdominal pain, deep pelvic pain. There was significantly more vaginal pain when using radical diathermy.

Radial diathermy compared to cryotherapy
(1) Residual disease
There was only one study O'Shea 1986 which compared these two treatment modalities. Cryotherapy appeared to be less effective compared to radial diathermy OR 0.33 (95%CI 0.09 to 1.16).

Cold coagulation compared to cryotherapy
(1) Residual disease
There was only one study Singh 1988 which compared these two treatment modalities. There appeared to be no significant difference in the two treatments OR 1.4 (95% CI 0.33 to 5.88).

Knife cone biopsy with or without haemostatic sutures
(1) Primary haemorrhage
Kristensen (Kristensen 1990) demonstrated that routine Sturmdorf sutures reduced the risk of primary haemorrhage OR 0.18 (95% CI 0.05 to 0.71), however this effect was not demonstrated by Gilbert (Gilbert 1989) OR 1.0 (95% CI 0.34 to 2.9).

(2) Secondary haemorrhage
Gilbert and Kristensen (Gilbert 1989; Kristensen 1990) demonstrated that routine sutures significantly increase the risk of secondary haemorrhage OR 3.81 (95%CI 1.11 to 13.15).

(3) Cervical stenosis at follow-up
Gilbert and Kristensen (Gilbert 1989; Kristensen 1990) demonstrated no difference in cervical stenosis OR 1.05 (95% CI 0.48 to 2.3).

(4) Adequate colposcopy at follow-up
Gilbert (Gilbert 1989) demonstrated that avoidance of routine suturing reduced inadequate colposcopy rates.

(5) Dysmenorrhoea
Gilbert and Kristensen (Gilbert 1989; Kristensen 1990) demonstrated that routine sutures increased the risk of dysmenorrhoea OR 2.42 (95%CI 0.95 to 6.15).

DISCUSSION

Reports of non randomised case series suffer from case selection bias and biases towards the operators' skills, hence direct comparisons of treatments from such data is not ideal.
The incidence of treatment failures following surgical treatment of CIN has been demonstrated by case series reports as illustrated in the Background section to be low. The vast majority of RCTs evaluating the differences in treatment success are grossly underpowered to demonstrate a significant difference between treatment techniques and no real conclusions can be drawn on differences of treatment effect. The reports from randomised and non-randomised studies suggest that most surgical treatments have around 90% success rate, in these circumstances several thousand women would have to be treated to demonstrate a signicant difference between two techniques. It might be the case that if a well conducted mega-trial was conducted no difference in treatment effect would be demonstrated.
The RCTs and meta-analyses have demonstrated some clear differences in morbidity and these should be considered as significant outcomes when deciding upon optimum management.

We have used a pragmatic approach to RCTs included in the comparisons. Slight variations of surgical technique occur in some of the comparisons which reflects the differences in clinical practice. If we considered that these differences did not seriously differ from other interventions in the comparison, then the trial was considered in the analysis. For example, when we compared laser ablation to cryotherapy, we included trials using single and double freeze technique.

(1) Double versus single freeze technique cryotherapy
The evidence suggests that cryotherapy should only be used with a double freeze technique to ensure higher success at treating disease.

(2) Laser ablation compared with cryotherapy demonstrated no overall difference in residual disease after treatment for CIN. Cryosurgery appears to have a lower success rate but the majority of authors used a single freeze thaw technique. Although Creasman (Creasman 1984) demonstrated that using a double freeze thaw freeze technique improves results towards those achieved by destructive and excisional methods.
However, analysis of results demonstrated that there was no significant difference for the treatment of CIN 1 and 2 but laser ablation appeared to be better but not significantly so at treating CIN3. We therefore cannot recommend cryosurgery for the treatment of high grade disease. The clinicians choice of treatment of low grade disease must therefore be influenced by the side effects related to the treatments.
Laser ablation was associated with significantly more per-operative and significant post operative bleeding and cryosurgery was associated with significantly more vaso-motor symptoms. Laser ablation produced significantly more adequate colposcopes (transformation zone seen in its entirety) at follow-up and cervical stenosis appeared to be less common after this treatment.

(3) Only one trial (Mathevet 1994) evaluated residual disease after laser conisation or knife conisation. There was no significant difference between the two groups. Primary haemorrhage appeared to be substantially less in the laser conisation but failed to reach significance, the direction of effect was similar with regards to secondary haemorrhage. Significant thermal artefact prevented interpretation of resection margins in 38% of laser cones compared to none in the knife cones. Laser conisation produced significantly more adequate colposcopes (transformation zone seen in its entirety) at follow-up and cervical stenosis was significantly less common after this treatment.

(4) Only one trial compared laser conisation with laser ablation for ectocervical lesions (Partington 1989). There was no significant difference with respect to residual disease at follow-up. Laser conisation appeared to increase peri-operative bleeding and secondary haemorrhage but neither outcome achieved significance. Laser conisation appeared to reduce adequate colposcopy at follow-up.

(5) Only four trials compared laser conisation with LLETZ (Crompton 1994; Mathevet 1994; Oyesanya 1993; Santos 1996). There was no significant difference with respect to residual disease at follow-up but the direction of effect suggested that LLETZ might have the advantage. Laser conisation takes significantly longer to perform, the depth of thermal artefact and incidence of significant thermal damage are all significantly increased.

(6) Laser ablation compared to LLETZ was evaluated by three trials. Alvarez 1994 was included in the comparison but its methodology differed from the trials by Gunasekera and Mitchell (Gunasekera 1990; Mitchell 1998). Alvarez performed LLETZ on all the patients randomised to that group whereas laser ablation was only performed if colposcopic directed biopsies were performed. There was no difference in residual disease rates between the two treatments.
There was no significant difference in primary or secondary haemorrhage but there appeared to be an increased chance of haemorrhage after laser ablation.

(7) Knife cone biopsy compared to Loop excision
(a) Four randomised trials evaluated knife cone biopsy and loop excision. (Duggan 1999, Giacalone 1999, Girardi 1994, Mathevet 1994). The trials sugested that there might be a higher residual disease rate after loop excision but this was only just statistically significant OR.
(b) Primary haemorrhage.
The studies by Giacalone 1999, Duggan 1999, Girardi 1994, Mathevet 1994 sugested that loop excision significantly had better adequate colposcopy rates OR 0.64 (95% CI 0.4 to 1.01). There was no clear evidence of that there was any difference in primary haemorrhage or cervical stenosis rates.

(8) Radical diathermy versus LLETZ
There was no significant difference in these two modalities with regards to the majority of side effects. Residual disease rates were not an outcome measure in the single trial identfied.

(9) Radial diathermy compared to cryotherapy
The residual disease rate was greater after cryotherapy.

(10) Cold coagulation compared to Cryotherapy
There was no significant difference with regards to persistence of disease.

(11) Haemostatic sutures
Haemostatic sutures significantly reduced the risk of primary haemorrhage but increased the risk of secondary haemorrhage, dysmenorrhoea, cervical stenosis and inadequate follow-up colposcopy in the study compared with no routine haemostatic sutures and vaginal packing.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence from the 28 RCTs identified suggests that there is no overwhelming superior surgical technique for eradicating CIN. Cryotherapy appears to be an effective treatment of low grade disease but not of high grade disease.
Choice of treatment of ectocervical situated lesions must therefore be based on cost, morbidity and whether excisional treatments provide more reliable biopsy specimens for assessment of disease compared to colposcopic directed specimens taken before ablative therapy. Colposcopic directed biopsies have been shown to underdiagnose micro-invasive disease compared with excisional biopsies performed by knife or loop excision, particularly if high grade disease is present (Anderson 1986; Chappatte 1991). However, the

accuracy of colposcopic directed biopsies compared to excisional biopsies is not the objective of this review.

Cryotherapy is easy to use, cheap and as demonstrated is associated with low morbidity and should be considered a viable alternative for the treatment of low grade disease particularly where resources are limited.

Laser Ablation appears to cause more peri-operative severe pain, and perhaps more primary and secondary haemorrhage compared to loop excision. The trials with adequate randomisation methods suggest that there is no difference in residual disease between the two treatments. It could be suggested that LLETZ is the superior as it is equipment is cheaper and it also permits confirmation of disease status by providing an excision biopsy.

Laser conisation takes longer to perform, requires greater operative training, more expensive investment in equipment, produces more peri-operative pain, greater depth and severe thermal artefact than loop excision. We would therefore recommend the use of LLETZ rather than laser excision unless the lesion is endocervical. In this situation, a narrow and deep cone biopsy can be performed reducing tissue trauma and providing a clear resection margin.

Knife cone biopsy still has a place if invasion or glandular disease is suspected. In both diseases adequate resection margins free of disease are important for prognosis and management. In such cases, LLETZ or laser conisation can induce thermal artefact so that accurate interpretation of margins is not possible.

Implications for research

We would advocate a large multi-centre trial of sufficient power to evaluate the role of primary 'see and treat' LLETZ treatment versus LLETZ or Laser Ablation after confirmation of disease by representative biopsy.

Many physicians now adopt a policy of performing a diagnostic colposcopy and LLETZ treatment at the same out-patient appointment. Unfortunately adopting this approach often results in a high false positive loop excision rate. In these circumstances, women would have had unnecessary treatment. Prior colposcopic directed biopsy reduces the false negative loop excision rate. This trial would evaluate patient satisfaction, cost implications of 'see and treat' versus deferred treatment and evaluate the efficacy of the two most widely used surgical techniques for CIN i.e. laser ablation or LLETZ.

POTENTIAL CONFLICT OF INTEREST

None

ACKNOWLEDGEMENTS

None

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

REFERENCES

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TABLES

Characteristics of included studies

Study	Alvarez 1994
Methods	True randomisation, allocation by computer generation (sealed envelopes)
Participants	375 women with cervical smears suggesting CIN 2 or 3, or 2 smears equivalent to CIN1 Women with adequte colposcopy included with entire lesion visible, not pregnant

Characteristics of included studies (*Continued*)

	Women with vaginitis, lesion extending to vagina, evidence of invasion excluded.
Interventions	Primary LLETZ Colposcopic directed biopsy and endocervical curettage, Only if positive Laser Ablation of Transformation Zone
Outcomes	Histological status of LLETZ or colposcopic specimens Operators impression of significant peri-operative bleeding Women's subjective opinion of peri-operative pain Women's subjective opinion of post-operative severe discomfort, heavy discharge, severe bleeding Residual disease (cytology) at 3 and 6 months
Notes	195 randomised to LLETZ, 180 to Laser All women had paracervical 1% lidocaine with 1:100,000 ephidrine LLETZ group: 6 treated by laser ablation due to technical problems, 4 failed to attend for treatment Laser group: 66 women did not require treatment, 114 required treatment 4 women were treated by LLETZ , 2 by cryosurgery due to technical problems
Allocation concealment	A – Adequate

Study	**Berget 1987**
Methods	Method of randomisation not stated
Participants	204 women with entire squamo-columnar junction visible CIN 1 on 2 biopsies 3-6 months apart, CIN 2 or 3 not extending 3 mm into crypts No extension onto vagina or lesion or 12.5 mm into canal
Interventions	Cryotherapy Laser Ablation
Outcomes	Operators impression of significant peri-operative bleeding >25cc Women's subjective opinion of peri-operative pain (mild, moderate severe, Severe being that the woman would not consider the treatment again) Women's subjective opinion of post-operative discomfort, heavy discharge, bleeding (None, Mild, Moderate, Severe) Post operative cervical stenosis Satisfactory folow-up colposcopy at 3 months Residual diseasse (histological) at 3 months (all women) Residual disease (histological) at 9 and 15 months (incomplete follow-up data)
Notes	103 randomised to Laser, 101 randomised to Cryotherapy Laser performed ablated 2 mm lateral to transformation zone to a depth of 5-7mm Cryo coagulation (DOUBLE freeze thaw freze technique) or more if the iceball did not exceed the probe (25mm) by 4 mm. Local analgesia was not routinely administered
Allocation concealment	B – Unclear

Study	**Berget 1991**
Methods	Method of randomisation not stated
Participants	204 women with entire squamo-columnar junction visible CIN 1 on 2 biopsies 3-6 months apart, CIN 2 or 3 not extending 3 mm into crypts No extension onto vagina or lesion or 12.5 mm into canal
Interventions	Cryotherapy Laser Ablation
Outcomes	Residual diseasse (histological) at 3, 9, 15, 21, 33, 45, 80 months
Notes	103 randomised to laser, 101 to cryotherapy

Characteristics of included studies (*Continued*)

	6 laser and 2 cryotherapy women refused to be followed up Women were offered repeat treatment with the same method of treatment as part of protocol. 3 laser and 6 cryotherapy women refused repeat treatment. Laser performed ablated 2 mm lateral to transformation zone to a depth of 5-7mm Cryo coagulation (DOUBLE freeze thaw freeze technique) or more if the iceball did not exceed the probe (25mm) by 4 mm. Local analgesia was not routinely administered
Allocation concealment	B – Unclear

Study	**Bostofte 1986**
Methods	Method of randomisation not stated
Participants	123 women with CIN1,2,3
Interventions	Laser Conisation Knife Conisation
Outcomes	Duration Peri-operative bleeding (quanity mls) Post-operative bleeding (primary requiring treatment and Secondary) Post-operative pain (use of analgesics) Adequate colposcopy Cervical stenosis (failure to pass cotton swab) Women complaining of dysmenorrhoea Residual disease (3-36 months)
Notes	All procedures performed under general anaesthesia Knife cone biopsy women had vaginal packing for 24 hours and 3 gms Tranexamic acid for 10 days. Sturmdorf sutures were not used, lateral cervical arteries used Laser conization women did not have vaginal packing or Tranexamic acid 59 women randomised to laser conisation, 64 to knife conisation
Allocation concealment	B – Unclear

Study	**Crompton 1994**
Methods	True randomisation, allocation by computer generation (sealed envelopes)
Participants	80 women recruited with CIN3 Women with a history of previous cervical surgery, peri- or post menopausal or whose lesion extends to vagina
Interventions	Laser Conisation LLETZ
Outcomes	Subjective scoring of pain by attendant nurse Subjective scoring of pain by women by linear analogue scale Peri-operative bleeding (none, spotting, requiring coagulation) Operative time
Notes	All women had intra-cervical 4mls 2% lignocaine with 0.3 IU /mls Octapressin prior to treatment (1 spoiled data sheet)
Allocation concealment	A – Adequate

Study	**Dey 2002**
Methods	True randomisation, allocation by computer
Participants	239 women with CIn I,II,III

Characteristics of included studies (*Continued*)

Interventions	Laser Ablation LLETZ
Outcomes	Residual / Recurent disease, Primary Haemorrhage duration of pregnancy
Notes	134 allocated to laser ablation. 120 received allocated treatment. 155 allocated to LLETZ 151 received allocated treatment
Allocation concealment	A – Adequate

Study	**Duggan 1999**
Methods	True randomisation, allocation by computer
Participants	180 women recruited with all grades of CIN with the following inclusion criteria 1) unsatisfactoery colposcopy with positive biopsy 2) endocervical curettage with positive biopsy 3) possible microinvasion on biopsy
Interventions	LLETZ Knife conisation
Outcomes	Adequate colposcopy. Cervical stenosis Incomplete resection margins Residual disease at 3 months
Notes	
Allocation concealment	A – Adequate

Study	**Ferenczy 1985**
Methods	Quasi-randomisation, allocation by alternate assignment
Participants	294 women with CIN 1,2,3 CIN present on ectocervix with or without marginal extension inrto cervical canal
Interventions	Cryotherapy Laser Ablation
Outcomes	Significant Peri-operative bleeding Adequate Colposcopy at Follow-up Residual Disease
Notes	147 randomised to laser, 147 to cryotherapy Women were offered repeat treatment with the same method of treatment as part of protocol. 3 laser and 6 cryotherapy women refused repeat treatment. Data included in comparison is for one treatment only Laser performed ablated 5 mm lateral to lesion to a depth of 5mm Cryo coagulation (SINGLE freeze thaw technique) iceball extending 5 mm lateral to lesion. Local analgesia was not routinely administered
Allocation concealment	A – Adequate

Study	**Giacalone 1999**
Methods	True randomisation, allocation by random number tables and sealed envelopes

Characteristics of included studies (*Continued*)

Participants	78 women with CIN 2,3
Interventions	Knife conisation LLETZ
Outcomes	Residual Disease Cervical stenosis Adequate Colposcopy
Notes	78 women randomised Only 66 available for follow-up 38 Knife Cone 28 Laser Excision
Allocation concealment	A – Adequate

Study	**Gilbert 1989**
Methods	True randomisation: sealed envelopes
Participants	200 women undergoing knife cone biopsy
Interventions	Lateral haemostatic sutures and interrupted sutures if indicated Vaginal pack with Monsels solution
Outcomes	Duration of surgical procedure Operative blood loss Primary haemorrhage Secondary haemorrhage
Notes	
Allocation concealment	A – Adequate

Study	**Girardi 1994**
Methods	Quasi-randomisation, allocation by odd/even birth dates
Participants	90 women with CIN 2 or 3 or persistant CIN1
Interventions	LLETZ Knife conisation
Outcomes	Incomplete resection margins (endocervical, ectocervical or both) Primary haemorrhage requiring treatment Residual disease at 3 months
Notes	38 women randomised to loop excision, 52 to knife conisation All women had pre-operative intracervical local analgesia and vasopressin 2 women with incomplete resection of endocervical disease had vaginal hysterectomy
Allocation concealment	A – Adequate

Study	**Gunasekera 1990**
Methods	Quasi-randomisation, allocation by unit number
Participants	199 women with CIN 2 or 3 Women with a history of previous cervical surgery or squamo-columnar junction not completely visible, suspicion of invasion or glandular disease excluded
Interventions	Laser ablation LLETZ
Outcomes	Duration of procedure (insuffient data for analysis) Peri-operative blood loss (subjective assessed by operator mild, moderate, severe)

Characteristics of included studies (*Continued*)

	Primary haemorrhage Secondary haemorrhage Acceptability of procedure/ pain (subjectively scored by womenn : not unpleasant, moderate, very unpleasant) Residual disease at 6 months
Notes	98 women randomised to LLETZ, 101 to laser ablation All women had paracervical 2% lignocaine with 1:100,000 adrenaline
Allocation concealment	A – Adequate

Study	**Healey 1996**
Methods	True randomisation, allocation by sealed envelopes
Participants	55 women with CIN
Interventions	Radical diathermy LLETZ
Outcomes	Duration of blood loss Duration of watery/ blood stained discharge Duration of yellow discharge Duration of upper abdominal pain Duration of lower abdominal pain Duration of deep pelvic pain Duration of vaginal pain
Notes	
Allocation concealment	A – Adequate

Study	**Jobson 1984**
Methods	Method of randomisation not stated
Participants	125 women with CIN 1,2,3 Women with satisfactory colposcopy, negative endocervical curettage, reproductive years
Interventions	Laser ablation Cryotherapy
Outcomes	Vasovagal reaction Patient acceptance (would patient have repeat treatment) Satisfactory colposcopy at 4 months Residual disease at 4 and 12 months
Notes	42 women were randomised to laser ablation, 39 to cryotherapy and completed protocol Laser performed ablated 2 mm lateral to transformation zone to a depth of 5-7mm. Women had pre-operative oral ibuprofen. Cryo coagulation (DOUBLE freeze thaw freeze technique) or more if the iceball did not exceed the probe (28mm) by 4-5mm. With or without analgesia
Allocation concealment	B – Unclear

Study	**Kirwan 1985**
Methods	Method of randomisation not stated
Participants	106 women with CIN 3 Adequate colposcopy and no extension to vagina
Interventions	Laser ablation Cryotherapy
Outcomes	Residual disease at 4 and 10 months

Characteristics of included studies (*Continued*)

Notes	71 women were randomised to laser ablation, 35 to cryotherapy Laser performed ablated transformation zone to a depth of 7mm Cryo coagulation (DOUBLE freeze thaw freeze technique) .
Allocation concealment	B – Unclear

Study	**Kristensen 1990**
Methods	Method of randomisation not stated
Participants	183 women with CIN2 or 3
Interventions	Knife cone with anterior+posterior Sturmdorf sutures Knife cone without haemostatic sutures but with vaginal packing for 6-8 hours Laser cone
Outcomes	Resection margins free of disease Primary haemorrhage Secondary haemorrhage Cervical stenosis Dysmenorrhoea
Notes	62 women randomised to knife cone with sutures, 60 women to knife cone with packing, 61 to laser cone All procedures performed under general anaesthesia All procedures performed with lateral sutures and intra-cervical vasopressin
Allocation concealment	B – Unclear

Study	**Kwikkel 1985**
Methods	Method of randomisation not stated
Participants	105 women with CIN1,2,3 Adquate colposcopy, no suspicion of invasion
Interventions	Laser Ablation Cryotherapy
Outcomes	Peri-operative pain Peri-operative bleeding Residual disease at 3-18 months
Notes	Laser performed ablating the transformation zone to a depth of 6-7mm Cryo coagulation (DOUBLE freeze thaw freeze technique) using a probe (18mm) 2 women in cryotherapy group, 2 women in laser group lost to follow-up
Allocation concealment	B – Unclear

Study	**Larsson 1982**
Methods	Method of randomisation not stated
Participants	110 women with CIN3
Interventions	Laser conisation Knife conisation
Outcomes	Peri-operative blood loss (insufficient data for analysis) Primary haemorrhage (bleeding requiring intervention in first 4 days) Secondary haemorrhage (bleeding after 4th day)
Notes	55 women were randomised to laser conisation, 55 to knife conisation All procedures performed under general anaesthesia Bood loss estimated by alkaline haematin extraction from swabs etc
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**Mathevet 1994**
Methods	True randomisation, allocation by sealed envelopes
Participants	110 women with CIN 1,2,3 Squamo-columnar junction NOT completely visible
Interventions	Knife cone Laser cone LLETZ
Outcomes	Ectocervical resection margin involved with disease Endocervical resection margin involved with disease Presence of thermal artifact not permitting evaluation of resection margins Peri-operative bleeding requiring haemostatic sutures (loop+laser only) Secondary haemorrhage Cervical stenosis Satisfactory colposcopy Residual disease at 6 months
Notes	37 women were randomised to knife conisation, 37 to laser conisation, 36 to loop All 3 treatments performed as an out-patient procedure with 10-20 mls 1% xylocaine with ephidrine. At knife conisation haemostasis was achieved by Sturmdorf sutures, laser cone by laser coagulation and Monsels solution, loop excision by coagulation and Monsels solution
Allocation concealment	A – Adequate

Study	**Mitchell 1998**
Methods	True randomisation, allocation by computer generation
Participants	498 women with CIN 1,2,3 Women over 18 yrs, using contraception, biopsy proven CIN, staisfactory colposcopy with lesion entirely visible
Interventions	Cryotherapy Laser ablation Loop Excision
Outcomes	Residual disease Primary haemorrhage Secondary haemorrhage
Notes	139 women were randomised to cryotherapy, 121 to laser ablation, 130 to loop excision
Allocation concealment	A – Adequate

Study	**O'Shea 1986**
Methods	Quasi-randomisation, allocation by odd/even birth dates
Participants	57 women with fuuly visible CIN 1 and 2 proven by biopsy
Interventions	Radial Diathermy Cryotherapy
Outcomes	Residual disease at 12 months
Notes	30 women randomised to Cryotherapy Some of these women had single , and some had double freeze technique 27 women to diathermy
Allocation concealment	C – Inadequate

Characteristics of included studies (*Continued*)

Study	**Oyesanya 1993**
Methods	True randomisation, allocation by sealed envelopes
Participants	300 women with CIN 1,2,3 Women with adequate colposcopy, no evidence of invasion
Interventions	Laser conisation LLETZ
Outcomes	Duration of treatment Patient subjective assesment of pain (none/minimal, moderate, severe) Peri-operative blood loss (difference in weight of blood stained / dry swabs) Secondary haemorrhage Presence of thermal artifact not permitting evaluation of resection margins Dysmenorrhoea Residual disease at 3-12 months
Notes	150 women randomised to laser conisation, 150 to loop excision Intra-cervical 6mls Citanest (0.5% prilocaine with Octapressin) used pre-operatively
Allocation concealment	A – Adequate

Study	**Paraskevaidis 1994**
Methods	Method of randomisation not stated
Participants	40 women undergoing elective hysterectomy
Interventions	Laser conisation LLETZ
Outcomes	Duration of procedure Depth of thermal injury
Notes	
Allocation concealment	B – Unclear

Study	**Partington 1989**
Methods	True randomisation, allocation by sealed envelopes
Participants	100 women with CIN 1,2,3 Women with adequate colposcopy , no evidence of invasion, lesion no more than 5mm into canal
Interventions	Laser conisation Laser ablation
Outcomes	Duration of treatment Significant peri-operative bleeding Women's subjective opinion of peri-operative pain (mild, moderate, severe) Secondary haemorrhage (seen in out-patients) Secondary haemorrhage (required admission) Adequate colposcopy Cervical stenosis Dysmennorrhoea Residual disease at 6, 12 , 24 months
Notes	50 women randomised to laser conisation, 50 women randomised to laser ablation Haemostasis achieved by pressure with a cotton swab or Monsel solution Laser Excision 2mm margin to lesion and to a depth of 2-3mm Laser ablation to a depth of 10mm Intra-cervical 3% prilocaine with Octapressin used pre-operatively

Characteristics of included studies (*Continued*)

Allocation concealment	A – Adequate

Study	**Santos 1996**
Methods	True randomisation, allocation by random tables
Participants	447 women with CIN 1,2,3 Women with suspicion of invasion, extensive lesion, pregnant were excluded
Interventions	LLETZ Laser conisation
Outcomes	Residual disease Significant peri-operative bleeding Secondary haemorrhage Cervical stenosis at follow-up Satisfactory colposcopy at follow-up
Notes	145 women randomised to laser conisation, 147 to loop Intra-cervical 6mls 2% lidocaine with 1:80,000 ephidrine used preoperatively
Allocation concealment	A – Adequate

Study	**Schantz 1984**
Methods	True randomisation, allocation by random tables
Participants	142 women with ectocervical CIN 1 and 2
Interventions	Single Freeze Double Freeze Cryotherapy
Outcomes	Residual Disease at 6 months
Notes	61 underwent single freeze, 81 underwent double freeze
Allocation concealment	A – Adequate

Study	**Singh 1988**
Methods	Quasi-randomisation, by alternate file number
Participants	161 women with CIN 1,2,3
Interventions	Cold Coagulation Cryotherapy
Outcomes	Residual disease at 24 months
Notes	92 randomised to cold coagulation 69 to cryotherapy Women with inadequate colposcopy or possibility of invasion excluded. Treatment repeated with modality that patient was randomised to, if initial treatment failed
Allocation concealment	C – Inadequate

Study	**Takac 1999**
Methods	Method of randomisation not stated
Participants	240 women with CIN 1,2,3. All procedues were done as in-patients
Interventions	Knife conisation

	LLETZ
Outcomes	completeness of excision (endo / ectocervial disease involvement) adequate colposcopy rates after treatment Primary haemorrhage
Notes	120 randomised to Knife cone 120 randomised to LLETZ
Allocation concealment	C – Inadequate

Study	**Townsend 1983**
Methods	Method of randomisation not stated
Participants	200 women with CIN 1,2,3 Adequate colposcopy, no evidence of invasion
Interventions	Laser ablation Cryotherapy
Outcomes	Severe cramps Vasomotor symptoms Residual disease at 6 months.
Notes	100 women randomised to laser ablation, 100 randomised to cryotherapy Cryo coagulation (SINGLE freeze thaw technique) using a probe (18mm) with iceball extending 5 mm beyond abnormal epithelium Laser ablation of all transformation zone
Allocation concealment	B – Unclear

CIN: cervical intraepithelial neoplasia
LLETZ: large loop excision of the transformation zone

ANALYSES

Comparison 01. Single Freeze Cryotherapy versus Double Freeze Cryotherapy

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Residual Disease within 12 months	1	142	Peto Odds Ratio 95% CI	2.93 [1.00, 8.60]

Comparison 02. Laser Ablation versus Cryotherapy

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Residual Disease (All Grades of CIN)	7	1229	Peto Odds Ratio 95% CI	0.96 [0.67, 1.36]
02 Residual Disease (CIN1)	5	207	Peto Odds Ratio 95% CI	3.33 [1.10, 10.11]
03 Residual Disease (CIN2)	5	387	Peto Odds Ratio 95% CI	1.49 [0.69, 3.20]
04 Residual Disease (CIN3)	5	267	Peto Odds Ratio 95% CI	0.80 [0.39, 1.65]
05 Peri-operative Severe Pain	3	493	Peto Odds Ratio 95% CI	2.38 [0.90, 6.28]
06 Peri-operative Severe Bleeding	3	599	Peto Odds Ratio 95% CI	7.45 [1.68, 33.05]
07 Vaso-motor Symptoms	1	200	Peto Odds Ratio 95% CI	0.11 [0.04, 0.28]
08 Malodorous Discharge	2	400	Peto Odds Ratio 95% CI	0.23 [0.15, 0.35]

09 Adequate Colposcopy at Follow-up	3	566	Peto Odds Ratio 95% CI	4.64 [2.98, 7.23]
10 Cervical Stenosis at Follow-up	2	464	Peto Odds Ratio 95% CI	1.44 [0.46, 4.55]

Comparison 03. Laser Conisation versus Knife Conisation

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Residual Disease (All Grades of CIN)	2	194	Peto Odds Ratio 95% CI	0.63 [0.20, 1.93]
02 Primary Haemorrhage	2	316	Peto Odds Ratio 95% CI	0.51 [0.23, 1.16]
03 Secondary Haemorrhage	3	359	Peto Odds Ratio 95% CI	0.81 [0.35, 1.86]
04 Adequate Colposcopy at Follow-up	2	160	Peto Odds Ratio 95% CI	2.73 [1.47, 5.08]
05 Cervical Stenosis at Follow-up	4	1009	Peto Odds Ratio 95% CI	0.39 [0.25, 0.61]
06 Significant Thermal Artifact Prohibiting Interpretation of Resection Margin	1	74	Peto Odds Ratio 95% CI	11.40 [3.59, 36.19]

Comparison 04. Laser Conisation versus Laser Ablation

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Residual Disease (All Grades of Disease)	1	93	Peto Odds Ratio 95% CI	0.73 [0.19, 2.87]
02 Peri-operative Severe Bleeding	1	100	Peto Odds Ratio 95% CI	1.55 [0.42, 5.70]
03 Secondary Haemorrhage	1	100	Peto Odds Ratio 95% CI	2.17 [0.73, 6.48]
04 Adequate Colposcopy at Follow-up	1	100	Peto Odds Ratio 95% CI	0.25 [0.05, 1.27]

Comparison 05. Laser Conisation versus Loop Excision

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Residual Disease	3	667	Peto Odds Ratio 95% CI	1.22 [0.71, 2.12]
02 Duration of Procedure	3	419	Weighted Mean Difference (Fixed) 95% CI	11.76 [10.60, 12.91]
03 Peri-operative Severe Pain	2	594	Peto Odds Ratio 95% CI	5.36 [1.62, 17.72]
04 Secondary Haemorrhage	3	667	Peto Odds Ratio 95% CI	0.89 [0.34, 2.34]
05 Significant Thermal Artefact on Biopsy	2	373	Peto Odds Ratio 95% CI	2.82 [1.56, 5.10]
06 Depth of Thermal Artifact	1	40	Weighted Mean Difference (Fixed) 95% CI	0.27 [0.19, 0.35]
07 Adequate Colposcopy	2	339	Peto Odds Ratio 95% CI	0.94 [0.59, 1.52]
08 Cervical Stenosis	2	338	Peto Odds Ratio 95% CI	1.15 [0.57, 2.33]

Comparison 06. Laser Ablation versus Loop Excision

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Residual Disease	4	1110	Peto Odds Ratio 95% CI	1.16 [0.76, 1.76]
02 Peri-operative Severe Pain	2	480	Peto Odds Ratio 95% CI	4.40 [1.86, 10.43]
03 Secondary Haemorrhage	3	759	Peto Odds Ratio 95% CI	1.05 [0.33, 3.30]

04 Primary Haemorrhage	3	759	Peto Odds Ratio 95% CI	1.56 [0.35, 7.00]

Comparison 07. Knife Conisation versus Loop Excision

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Residual Disease	4	369	Peto Odds Ratio 95% CI	0.43 [0.18, 1.00]
02 Primary Haemorrhage	3	396	Peto Odds Ratio 95% CI	1.05 [0.47, 2.33]
03 Adequate Colposcopy at Follow-up	4	381	Peto Odds Ratio 95% CI	0.64 [0.40, 1.01]
04 Cervical Stenosis	3	251	Peto Odds Ratio 95% CI	1.08 [0.38, 3.04]

Comparison 08. Radical Diathermy versus LLETZ

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Duration of blood loss	1	48	Weighted Mean Difference (Fixed) 95% CI	-1.20 [-5.20, 2.80]
02 Blood stained / watery discharge	1	48	Weighted Mean Difference (Fixed) 95% CI	0.80 [-3.84, 5.44]
03 Yellow discharge	1	48	Weighted Mean Difference (Fixed) 95% CI	-1.10 [-6.43, 4.23]
04 White discharge	1	48	Weighted Mean Difference (Fixed) 95% CI	-1.60 [-6.74, 3.54]
05 Upper Abdominal Pain	1	48	Weighted Mean Difference (Fixed) 95% CI	-0.30 [-1.86, 1.26]
06 Lower Abdominal Pain	1	48	Weighted Mean Difference (Fixed) 95% CI	0.50 [-5.84, 6.84]
07 Deep Pelvic Pain	1	48	Weighted Mean Difference (Fixed) 95% CI	1.00 [-2.49, 4.49]
08 Vaginal Pain	1	48	Weighted Mean Difference (Fixed) 95% CI	10.50 [5.37, 15.63]

Comparison 09. Radial Diathermy versus Cryotherapy

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Residual Disease at 12 months	1	57	Peto Odds Ratio 95% CI	0.33 [0.09, 1.16]

Comparison 10. Cold Coagulation versus Cryotherapy

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Residual Disease at 24 months	1	154	Peto Odds Ratio 95% CI	1.40 [0.33, 5.88]

Comparison 11. Knife Cone Biopsy: Haemostatic Sutures versus None

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Primary Haemorrhage	2	522	Peto Odds Ratio 95% CI	0.52 [0.23, 1.20]
02 Secondary Haemorrhage	2	515	Peto Odds Ratio 95% CI	2.69 [1.34, 5.39]
03 Cervical Stenosis	2	307	Peto Odds Ratio 95% CI	3.85 [2.45, 6.04]
04 Adequate Colposcopy at Follow-up	1	200	Peto Odds Ratio 95% CI	0.26 [0.15, 0.45]
05 Dysmenorrhoea	2	277	Peto Odds Ratio 95% CI	2.88 [1.55, 5.36]

INDEX TERMS

Medical Subject Headings (MeSH)

Cervical Intraepithelial Neoplasia [*surgery]; Conization; Cryosurgery; Laser Surgery; Uterine Cervical Neoplasms [*surgery]

MeSH check words

Female; Humans

COVER SHEET

Title	Surgery for cervical intraepithelial neoplasia
Authors	Martin-Hirsch PL, Paraskevaidis E, Kitchener H
Contribution of author(s)	Information not supplied by author
Issue protocol first published	/
Review first published	/
Date of most recent amendment	10 August 2004
Date of most recent SUBSTANTIVE amendment	19 May 1999
What's New	Update: in July 2004 a further search did not identify any new RCTs
Date new studies sought but none found	31 July 2004
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Mr Pierre Martin-Hirsch Consultant Gynaecologist Department of Obstetrics and Gynaecology Sharoe Green Hospital Sharoe Green Lane Preston Lancashire PR2 8DU UK E-mail: pierre.martinhirsch@btinternet.com Tel: + 44 1772716565 Fax: + 44 1772710162
DOI	10.1002/14651858.CD001318
Cochrane Library number	CD001318
Editorial group	Cochrane Gynaecological Cancer Group
Editorial group code	HM-GYNAECA

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Single Freeze Cryotherapy versus Double Freeze Cryotherapy, Outcome 01 Residual Disease within 12 months

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 01 Single Freeze Cryotherapy versus Double Freeze Cryotherapy

Outcome: 01 Residual Disease within 12 months

Study	Single Freeze n/N	Double Freeze n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Schantz 1984	10/61	5/81		100.0	2.93 [1.00, 8.60]
Total (95% CI)	61	81		100.0	2.93 [1.00, 8.60]
Total events: 10 (Single Freeze), 5 (Double Freeze)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.95 p=0.05					

Analysis 02.01. Comparison 02 Laser Ablation versus Cryotherapy, Outcome 01 Residual Disease (All Grades of CIN)

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 02 Laser Ablation versus Cryotherapy

Outcome: 01 Residual Disease (All Grades of CIN)

Study	n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Berget 1991	8/94	4/93		9.1	2.01 [0.63, 6.45]
Ferenczy 1985	6/147	13/147		14.4	0.46 [0.18, 1.15]
Jobson 1984	4/42	4/39		5.9	0.92 [0.22, 3.94]
Kirwan 1985	8/71	6/35		8.8	0.60 [0.18, 1.98]
Kwikkel 1985	15/51	7/50		14.0	2.45 [0.96, 6.27]
Mitchell 1998	21/121	33/139		34.5	0.68 [0.37, 1.24]
Townsend 1983	11/100	7/100		13.3	1.63 [0.62, 4.27]
Total (95% CI)	626	603		100.0	0.96 [0.67, 1.36]
Total events: 73 (), 74 (Control)					
Test for heterogeneity chi-square=10.83 df=6 p=0.09 I^2 =44.6%					
Test for overall effect z=0.23 p=0.8					

Analysis 02.02. Comparison 02 Laser Ablation versus Cryotherapy, Outcome 02 Residual Disease (CIN1)

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 02 Laser Ablation versus Cryotherapy

Outcome: 02 Residual Disease (CIN1)

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Berget 1991	1/9	1/11		15.1	1.24 [0.07, 21.66]
Ferenczy 1985	2/67	2/67		31.4	1.00 [0.14, 7.26]
Jobson 1984	1/3	0/1		6.0	3.79 [0.04, 350.61]
Kwikkel 1985	6/15	0/14		39.5	10.52 [1.80, 61.58]
Townsend 1983	1/10	0/10		8.0	7.39 [0.15, 372.38]
Total (95% CI)	104	103		100.0	3.33 [1.10, 10.11]
Total events: 11 (), 3 (Control)					
Test for heterogeneity chi-square=3.67 df=4 p=0.45 I^2 =0.0%					
Test for overall effect z=2.12 p=0.03					

Analysis 02.03. Comparison 02 Laser Ablation versus Cryotherapy, Outcome 03 Residual Disease (CIN2)

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 02 Laser Ablation versus Cryotherapy

Outcome: 03 Residual Disease (CIN2)

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Berget 1991	5/62	1/61		22.1	3.95 [0.77, 20.24]
Ferenczy 1985	2/49	2/49		14.9	1.00 [0.14, 7.32]
Jobson 1984	1/23	2/25		11.0	0.54 [0.05, 5.50]
Kwikkel 1985	6/20	6/24		34.0	1.28 [0.34, 4.78]
Townsend 1983	3/37	2/37		18.1	1.53 [0.25, 9.27]
Total (95% CI)	191	196		100.0	1.49 [0.69, 3.20]
Total events: 17 (), 13 (Control)					
Test for heterogeneity chi-square=2.30 df=4 p=0.68 I^2 =0.0%					
Test for overall effect z=1.01 p=0.3					

Analysis 02.04. Comparison 02 Laser Ablation versus Cryotherapy, Outcome 04 Residual Disease (CIN3)

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 02 Laser Ablation versus Cryotherapy

Outcome: 04 Residual Disease (CIN3)

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Berget 1991	2/23	2/19		12.3	0.81 [0.11, 6.28]
Ferenczy 1985	2/31	9/31		30.8	0.22 [0.06, 0.79]
Jobson 1984	2/16	1/13		9.2	1.65 [0.16, 17.49]
Kwikkel 1985	3/16	1/12		11.7	2.27 [0.28, 18.55]
Townsend 1983	7/53	5/53		36.0	1.45 [0.44, 4.80]
Total (95% CI)	139	128		100.0	0.80 [0.39, 1.65]
Total events: 16 (), 18 (Control)					
Test for heterogeneity chi-square=6.14 df=4 p=0.19 I² =34.9%					
Test for overall effect z=0.60 p=0.6					

Analysis 02.05. Comparison 02 Laser Ablation versus Cryotherapy, Outcome 05 Peri-operative Severe Pain

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 02 Laser Ablation versus Cryotherapy

Outcome: 05 Peri-operative Severe Pain

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Berget 1987	3/92	0/100		18.1	8.24 [0.85, 80.33]
Kwikkel 1985	3/51	0/50		18.0	7.54 [0.77, 74.22]
Townsend 1983	6/100	5/100		63.9	1.21 [0.36, 4.07]
Total (95% CI)	243	250		100.0	2.38 [0.90, 6.28]
Total events: 12 (), 5 (Control)					
Test for heterogeneity chi-square=3.31 df=2 p=0.19 I² =39.6%					
Test for overall effect z=1.75 p=0.08					

Analysis 02.06. Comparison 02 Laser Ablation versus Cryotherapy, Outcome 06 Peri-operative Severe Bleeding

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 02 Laser Ablation versus Cryotherapy

Outcome: 06 Peri-operative Severe Bleeding

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Berget 1987	2/103	0/101		28.7	7.32 [0.45, 117.82]
Ferenczy 1985	2/147	0/147		28.8	7.44 [0.46, 119.51]
Kwikkel 1985	3/51	0/50		42.5	7.54 [0.77, 74.22]
Total (95% CI)	301	298		100.0	7.45 [1.68, 33.05]

Total events: 7 (), 0 (Control)

Test for heterogeneity chi-square=0.00 df=2 p=1.00 I^2 =0.0%

Test for overall effect z=2.64 p=0.008

Analysis 02.07. Comparison 02 Laser Ablation versus Cryotherapy, Outcome 07 Vaso-motor Symptoms

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 02 Laser Ablation versus Cryotherapy

Outcome: 07 Vaso-motor Symptoms

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Townsend 1983	0/100	20/100		100.0	0.11 [0.04, 0.28]
Total (95% CI)	100	100		100.0	0.11 [0.04, 0.28]

Total events: 0 (), 20 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=4.70 p<0.00001

Analysis 02.08. Comparison 02 Laser Ablation versus Cryotherapy, Outcome 08 Malodorous Discharge

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 02 Laser Ablation versus Cryotherapy

Outcome: 08 Malodorous Discharge

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Berget 1987	17/100	36/100		48.4	0.38 [0.20, 0.71]
Townsend 1983	9/100	50/100		51.6	0.14 [0.08, 0.26]
Total (95% CI)	200	200		100.0	0.23 [0.15, 0.35]
Total events: 26 (), 86 (Control)					
Test for heterogeneity chi-square=4.96 df=1 p=0.03 I^2 =79.9%					
Test for overall effect z=6.67 p<0.00001					

Analysis 02.09. Comparison 02 Laser Ablation versus Cryotherapy, Outcome 09 Adequate Colposcopy at Follow-up

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 02 Laser Ablation versus Cryotherapy

Outcome: 09 Adequate Colposcopy at Follow-up

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Berget 1987	77/97	47/94		55.9	3.61 [1.99, 6.53]
Ferenczy 1985	147/147	129/147		21.7	8.36 [3.23, 21.65]
Jobson 1984	36/42	20/39		22.4	4.92 [1.93, 12.57]
Total (95% CI)	286	280		100.0	4.64 [2.98, 7.23]
Total events: 260 (), 196 (Control)					
Test for heterogeneity chi-square=2.17 df=2 p=0.34 I^2 =8.0%					
Test for overall effect z=6.78 p<0.00001					

Analysis 02.10. Comparison 02 Laser Ablation versus Cryotherapy, Outcome 10 Cervical Stenosis at Follow-up

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 02 Laser Ablation versus Cryotherapy

Outcome: 10 Cervical Stenosis at Follow-up

Study	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Berget 1987	6/103	3/101	74.5	1.96 [0.52, 7.44]
Mitchell 1998	1/121	2/139	25.5	0.59 [0.06, 5.71]
Total (95% CI)	224	240	100.0	1.44 [0.46, 4.55]

Total events: 7 (), 5 (Control)

Test for heterogeneity chi-square=0.81 df=1 p=0.37 I^2 =0.0%

Test for overall effect z=0.62 p=0.5

Analysis 03.01. Comparison 03 Laser Conisation versus Knife Conisation, Outcome 01 Residual Disease (All Grades of CIN)

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 03 Laser Conisation versus Knife Conisation

Outcome: 01 Residual Disease (All Grades of CIN)

Study	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Bostofte 1986	4/59	6/61	76.0	0.67 [0.19, 2.44]
Mathevet 1994	1/37	2/37	24.0	0.50 [0.05, 5.00]
Total (95% CI)	96	98	100.0	0.63 [0.20, 1.93]

Total events: 5 (), 8 (Control)

Test for heterogeneity chi-square=0.05 df=1 p=0.83 I^2 =0.0%

Test for overall effect z=0.81 p=0.4

Analysis 03.02. Comparison 03 Laser Conisation versus Knife Conisation, Outcome 02 Primary Haemorrhage

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 03 Laser Conisation versus Knife Conisation

Outcome: 02 Primary Haemorrhage

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Bostofte 1986	3/59	11/64		54.2	0.30 [0.10, 0.92]
Kristensen 1990	4/61	9/132		45.8	0.96 [0.29, 3.21]
Total (95% CI)	120	196		100.0	0.51 [0.23, 1.16]
Total events: 7 (), 20 (Control)					
Test for heterogeneity chi-square=1.89 df=1 p=0.17 I^2 =47.0%					
Test for overall effect z=1.59 p=0.1					

Analysis 03.03. Comparison 03 Laser Conisation versus Knife Conisation, Outcome 03 Secondary Haemorrhage

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 03 Laser Conisation versus Knife Conisation

Outcome: 03 Secondary Haemorrhage

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Kristensen 1990	7/60	11/115		65.5	1.25 [0.45, 3.49]
Larsson 1982	0/55	4/55		17.4	0.13 [0.02, 0.93]
Mathevet 1994	2/37	2/37		17.2	1.00 [0.14, 7.40]
Total (95% CI)	152	207		100.0	0.81 [0.35, 1.86]
Total events: 9 (), 17 (Control)					
Test for heterogeneity chi-square=4.06 df=2 p=0.13 I^2 =50.7%					
Test for overall effect z=0.50 p=0.6					

Analysis 03.04. Comparison 03 Laser Conisation versus Knife Conisation, Outcome 04 Adequate Colposcopy at Follow-up

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 03 Laser Conisation versus Knife Conisation

Outcome: 04 Adequate Colposcopy at Follow-up

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Bostofte 1986	37/56	22/57		71.1	2.98 [1.43, 6.21]
Mathevet 1994	16/23	12/24		28.9	2.21 [0.70, 7.01]
Total (95% CI)	79	81		100.0	2.73 [1.47, 5.08]
Total events: 53 (), 34 (Control)					
Test for heterogeneity chi-square=0.18 df=1 p=0.67 I^2 =0.0%					
Test for overall effect z=3.18 p=0.001					

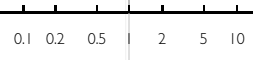
Analysis 03.05. Comparison 03 Laser Conisation versus Knife Conisation, Outcome 05 Cervical Stenosis at Follow-up

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 03 Laser Conisation versus Knife Conisation

Outcome: 05 Cervical Stenosis at Follow-up

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Bostofte 1986	4/56	15/57		21.0	0.26 [0.10, 0.69]
Kristensen 1990	14/56	39/109		42.8	0.61 [0.31, 1.22]
Larsson 1982	2/256	20/428		26.3	0.29 [0.12, 0.69]
Mathevet 1994	2/23	7/24		9.8	0.27 [0.07, 1.15]
Total (95% CI)	391	618		100.0	0.39 [0.25, 0.61]
Total events: 22 (), 81 (Control)					
Test for heterogeneity chi-square=3.04 df=3 p=0.39 I^2 =1.2%					
Test for overall effect z=4.14 p=0.00003					



Analysis 03.06. Comparison 03 Laser Conisation versus Knife Conisation, Outcome 06 Significant Thermal Artifact Prohibiting Interpretation of Resection Margin

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 03 Laser Conisation versus Knife Conisation

Outcome: 06 Significant Thermal Artifact Prohibiting Interpretation of Resection Margin

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Mathevet 1994	14/37	0/37		100.0	11.40 [3.59, 36.19]
Total (95% CI)	37	37		100.0	11.40 [3.59, 36.19]
Total events: 14 (), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.13 p=0.00004					

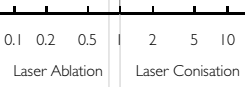
Analysis 04.01. Comparison 04 Laser Conisation versus Laser Ablation, Outcome 01 Residual Disease (All Grades of Disease)

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 04 Laser Conisation versus Laser Ablation

Outcome: 01 Residual Disease (All Grades of Disease)

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Partington 1989	4/48	5/45		100.0	0.73 [0.19, 2.87]
Total (95% CI)	48	45		100.0	0.73 [0.19, 2.87]
Total events: 4 (), 5 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.45 p=0.7					



Analysis 04.02. Comparison 04 Laser Conisation versus Laser Ablation, Outcome 02 Peri-operative Severe Bleeding

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 04 Laser Conisation versus Laser Ablation

Outcome: 02 Peri-operative Severe Bleeding

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Partington 1989	6/50	4/50		100.0	1.55 [0.42, 5.70]
Total (95% CI)	50	50		100.0	1.55 [0.42, 5.70]
Total events: 6 (), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.66 p=0.5					

Analysis 04.03. Comparison 04 Laser Conisation versus Laser Ablation, Outcome 03 Secondary Haemorrhage

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 04 Laser Conisation versus Laser Ablation

Outcome: 03 Secondary Haemorrhage

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Partington 1989	10/50	5/50		100.0	2.17 [0.73, 6.48]
Total (95% CI)	50	50		100.0	2.17 [0.73, 6.48]
Total events: 10 (), 5 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.39 p=0.2					

Analysis 04.04. Comparison 04 Laser Conisation versus Laser Ablation, Outcome 04 Adequate Colposcopy at Follow-up

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 04 Laser Conisation versus Laser Ablation

Outcome: 04 Adequate Colposcopy at Follow-up

Study	n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Partington 1989	45/50	49/50		100.0	0.25 [0.05, 1.27]
Total (95% CI)	50	50		100.0	0.25 [0.05, 1.27]
Total events: 45 (), 49 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.68 p=0.09					

Analysis 05.01. Comparison 05 Laser Conisation versus Loop Excision, Outcome 01 Residual Disease

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 05 Laser Conisation versus Loop Excision

Outcome: 01 Residual Disease

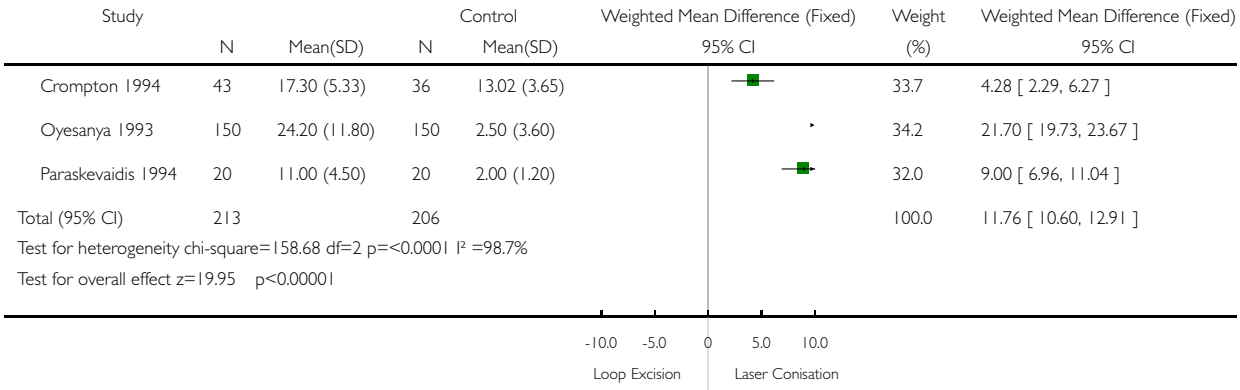
Study	n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Mathevet 1994	1/37	2/36		5.8	0.49 [0.05, 4.86]
Oyesanya 1993	25/150	17/150		71.5	1.56 [0.81, 2.98]
Santos 1996	5/145	7/149		22.8	0.73 [0.23, 2.31]
Total (95% CI)	332	335		100.0	1.22 [0.71, 2.12]
Total events: 31 (), 26 (Control)					
Test for heterogeneity chi-square=1.91 df=2 p=0.38 I^2 =0.0%					
Test for overall effect z=0.72 p=0.5					

Analysis 05.02. Comparison 05 Laser Conisation versus Loop Excision, Outcome 02 Duration of Procedure

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 05 Laser Conisation versus Loop Excision

Outcome: 02 Duration of Procedure

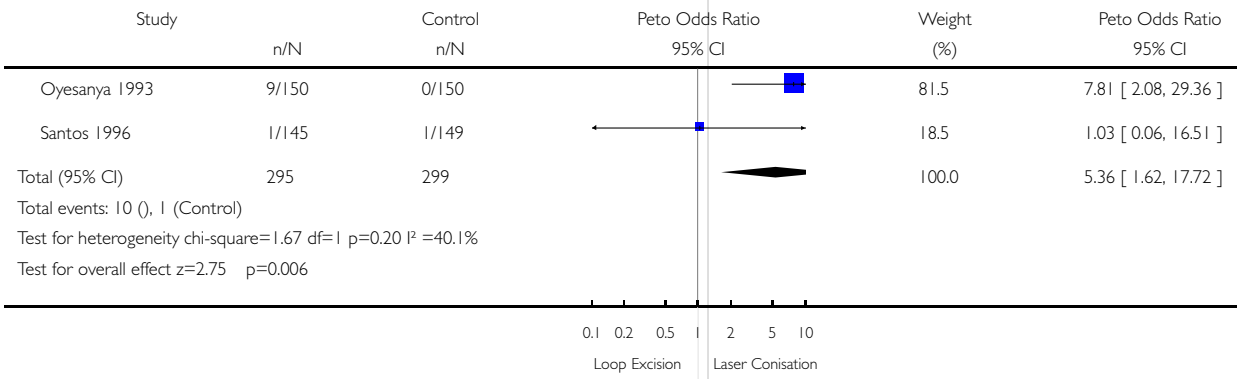


Analysis 05.03. Comparison 05 Laser Conisation versus Loop Excision, Outcome 03 Peri-operative Severe Pain

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 05 Laser Conisation versus Loop Excision

Outcome: 03 Peri-operative Severe Pain



Analysis 05.04. Comparison 05 Laser Conisation versus Loop Excision, Outcome 04 Secondary Haemorrhage

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 05 Laser Conisation versus Loop Excision

Outcome: 04 Secondary Haemorrhage

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Mathevet 1994	2/37	2/36		23.1	0.97 [0.13, 7.20]
Oyesanya 1993	3/150	2/150		29.8	1.50 [0.26, 8.76]
Santos 1996	3/145	5/149		47.1	0.62 [0.15, 2.51]
Total (95% CI)	332	335		100.0	0.89 [0.34, 2.34]
Total events: 8 (), 9 (Control)					
Test for heterogeneity chi-square=0.61 df=2 p=0.74 I^2 =0.0%					
Test for overall effect z=0.23 p=0.8					

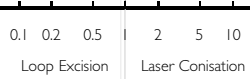
Analysis 05.05. Comparison 05 Laser Conisation versus Loop Excision, Outcome 05 Significant Thermal Artefact on Biopsy

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 05 Laser Conisation versus Loop Excision

Outcome: 05 Significant Thermal Artefact on Biopsy

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Mathevet 1994	14/37	11/36		38.1	1.38 [0.53, 3.59]
Oyesanya 1993	25/150	5/150		61.9	4.38 [2.06, 9.30]
Total (95% CI)	187	186		100.0	2.82 [1.56, 5.10]
Total events: 39 (), 16 (Control)					
Test for heterogeneity chi-square=3.46 df=1 p=0.06 I^2 =71.1%					
Test for overall effect z=3.43 p=0.0006					



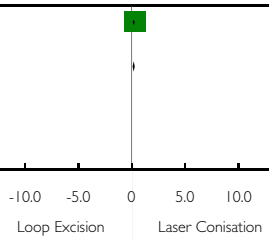
Analysis 05.06. Comparison 05 Laser Conisation versus Loop Excision, Outcome 06 Depth of Thermal Artifact

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 05 Laser Conisation versus Loop Excision

Outcome: 06 Depth of Thermal Artifact

Study			Control		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Paraskevaidis 1994	20	0.49 (0.16)	20	0.22 (0.09)		100.0	0.27 [0.19, 0.35]
Total (95% CI)	20		20			100.0	0.27 [0.19, 0.35]
Test for heterogeneity: not applicable							
Test for overall effect z=6.58 p<0.00001							



Analysis 05.07. Comparison 05 Laser Conisation versus Loop Excision, Outcome 07 Adequate Colposcopy

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 05 Laser Conisation versus Loop Excision

Outcome: 07 Adequate Colposcopy

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Mathevet 1994	12/24	17/21		15.4	0.27 [0.08, 0.89]
Santos 1996	109/145	107/149		84.6	1.19 [0.71, 1.99]
Total (95% CI)	169	170		100.0	0.94 [0.59, 1.52]
Total events: 121 (), 124 (Control)					
Test for heterogeneity chi-square=4.94 df=1 p=0.03 I^2 =79.8%					
Test for overall effect z=0.24 p=0.8					

Analysis 05.08. Comparison 05 Laser Conisation versus Loop Excision, Outcome 08 Cervical Stenosis

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 05 Laser Conisation versus Loop Excision

Outcome: 08 Cervical Stenosis

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Mathevet 1994	2/23	4/21		17.2	0.42 [0.08, 2.33]
Santos 1996	16/145	12/149		82.8	1.41 [0.65, 3.07]
Total (95% CI)	168	170		100.0	1.15 [0.57, 2.33]

Total events: 18 (), 16 (Control)

Test for heterogeneity chi-square=1.59 df=1 p=0.21 I^2 =37.0%

Test for overall effect z=0.38 p=0.7

Analysis 06.01. Comparison 06 Laser Ablation versus Loop Excision, Outcome 01 Residual Disease

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 06 Laser Ablation versus Loop Excision

Outcome: 01 Residual Disease

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Alvarez 1994	12/180	18/195		32.0	0.71 [0.34, 1.49]
Dey 2002	9/133	3/152		13.3	3.27 [1.03, 10.39]
Gunasekera 1990	8/101	5/98		14.1	1.58 [0.52, 4.86]
Mitchell 1998	21/121	21/130		40.6	1.09 [0.56, 2.11]
Total (95% CI)	535	575		100.0	1.16 [0.76, 1.76]

Total events: 50 (), 47 (Control)

Test for heterogeneity chi-square=5.11 df=3 p=0.16 I^2 =41.3%

Test for overall effect z=0.68 p=0.5

Analysis 06.02. Comparison 06 Laser Ablation versus Loop Excision, Outcome 02 Peri-operative Severe Pain

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 06 Laser Ablation versus Loop Excision

Outcome: 02 Peri-operative Severe Pain

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Alvarez 1994	0/96	2/185		8.7	0.22 [0.01, 4.07]
Gunasekera 1990	19/101	2/98		91.3	5.86 [2.38, 14.44]
Total (95% CI)	197	283		100.0	4.40 [1.86, 10.43]

Total events: 19 (), 4 (Control)

Test for heterogeneity chi-square=4.44 df=1 p=0.04 I^2 =77.5%

Test for overall effect z=3.37 p=0.0008

Analysis 06.03. Comparison 06 Laser Ablation versus Loop Excision, Outcome 03 Secondary Haemorrhage

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 06 Laser Ablation versus Loop Excision

Outcome: 03 Secondary Haemorrhage

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
× Alvarez 1994	0/114	0/195		0.0	Not estimable
Gunasekera 1990	3/101	0/98		25.4	7.32 [0.75, 71.19]
Mitchell 1998	3/121	6/130		74.6	0.54 [0.14, 2.04]
Total (95% CI)	336	423		100.0	1.05 [0.33, 3.30]

Total events: 6 (), 6 (Control)

Test for heterogeneity chi-square=3.76 df=1 p=0.05 I^2 =73.4%

Test for overall effect z=0.08 p=0.9

Analysis 06.04. Comparison 06 Laser Ablation versus Loop Excision, Outcome 04 Primary Haemorrhage

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 06 Laser Ablation versus Loop Excision

Outcome: 04 Primary Haemorrhage

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Alvarez 1994	0/114	2/195		27.3	0.20 [0.01, 3.62]
Gunasekera 1990	4/101	0/98		58.0	7.39 [1.03, 53.29]
Mitchell 1998	0/121	1/130		14.7	0.15 [0.00, 7.33]
Total (95% CI)	336	423		100.0	1.56 [0.35, 7.00]
Total events: 4 (), 3 (Control)					
Test for heterogeneity chi-square=5.71 df=2 p=0.06 I² =65.0%					
Test for overall effect z=0.58 p=0.6					

Analysis 07.01. Comparison 07 Knife Conisation versus Loop Excision, Outcome 01 Residual Disease

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 07 Knife Conisation versus Loop Excision

Outcome: 01 Residual Disease

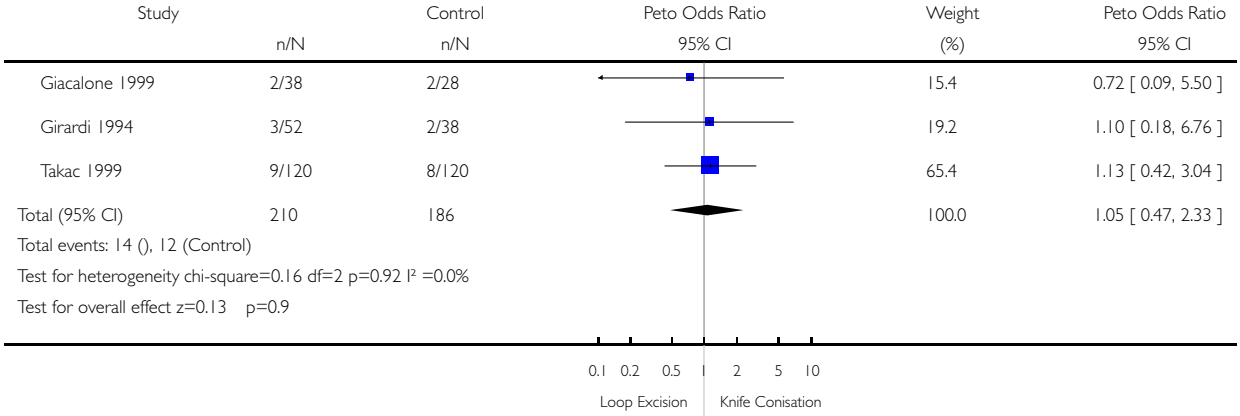
Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Duggan 1999	2/67	8/73		43.2	0.30 [0.08, 1.09]
Giacalone 1999	4/38	6/28		39.0	0.43 [0.11, 1.68]
× Girardi 1994	0/38	0/52		0.0	Not estimable
Mathevet 1994	2/37	2/36		17.8	0.97 [0.13, 7.20]
Total (95% CI)	180	189		100.0	0.43 [0.18, 1.00]
Total events: 8 (), 16 (Control)					
Test for heterogeneity chi-square=0.92 df=2 p=0.63 I² =0.0%					
Test for overall effect z=1.97 p=0.05					

Analysis 07.02. Comparison 07 Knife Conisation versus Loop Excision, Outcome 02 Primary Haemorrhage

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 07 Knife Conisation versus Loop Excision

Outcome: 02 Primary Haemorrhage

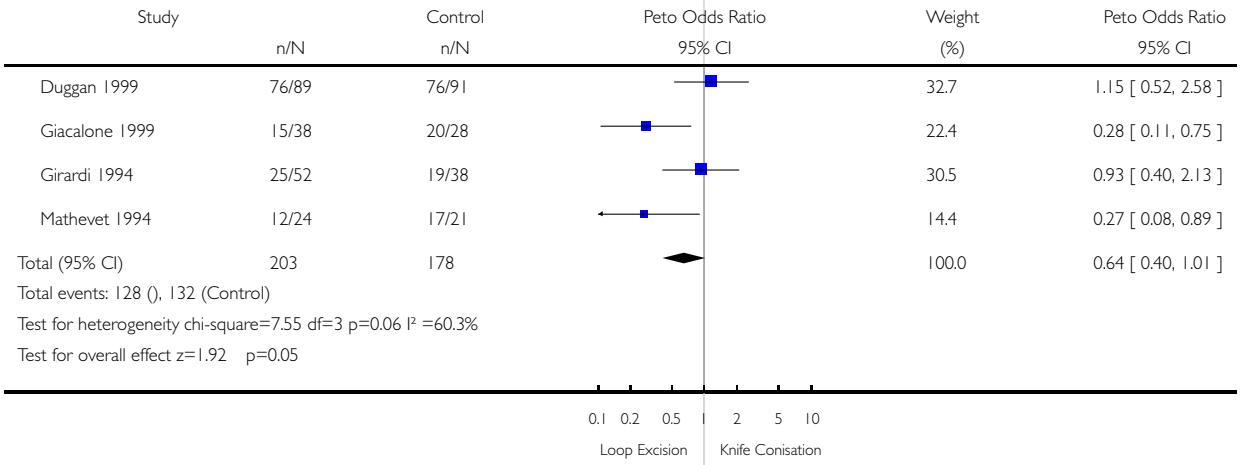


Analysis 07.03. Comparison 07 Knife Conisation versus Loop Excision, Outcome 03 Adequate Colposcopy at Follow-up

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 07 Knife Conisation versus Loop Excision

Outcome: 03 Adequate Colposcopy at Follow-up



Analysis 07.04. Comparison 07 Knife Conisation versus Loop Excision, Outcome 04 Cervical Stenosis

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 07 Knife Conisation versus Loop Excision

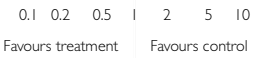
Outcome: 04 Cervical Stenosis

Study	Knife Cone n/N	LLETZ n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Duggan 1999	2/67	4/73		40.6	0.55 [0.11, 2.79]
× Giacalone 1999	0/38	0/28		0.0	Not estimable
Mathevet 1994	7/24	4/21		59.4	1.71 [0.44, 6.57]
Total (95% CI)	129	122		100.0	1.08 [0.38, 3.04]

Total events: 9 (Knife Cone), 8 (LLETZ)

Test for heterogeneity chi-square=1.11 df=1 p=0.29 I^2 =10.2%

Test for overall effect z=0.14 p=0.9



Analysis 08.01. Comparison 08 Radical Diathermy versus LLETZ, Outcome 01 Duration of blood loss

Review: Surgery for cervical intraepithelial neoplasia

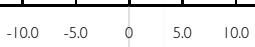
Comparison: 08 Radical Diathermy versus LLETZ

Outcome: 01 Duration of blood loss

Study	Treatment N	Mean(SD)	Control N	Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Healey 1996	24	7.50 (6.60)	24	8.70 (7.50)		100.0	-1.20 [-5.20, 2.80]
Total (95% CI)	24		24			100.0	-1.20 [-5.20, 2.80]

Test for heterogeneity: not applicable

Test for overall effect z=0.59 p=0.6



Analysis 08.02. Comparison 08 Radical Diathermy versus LLETZ, Outcome 02 Blood stained / watery discharge

Review: Surgery for cervical intraepithelial neoplasia
Comparison: 08 Radical Diathermy versus LLETZ
Outcome: 02 Blood stained / watery discharge

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Healey 1996	24	13.20 (8.10)	24	12.40 (8.30)		100.0	0.80 [-3.84, 5.44]
Total (95% CI)	24		24			100.0	0.80 [-3.84, 5.44]
Test for heterogeneity: not applicable							
Test for overall effect z=0.34 p=0.7							

Analysis 08.03. Comparison 08 Radical Diathermy versus LLETZ, Outcome 03 Yellow discharge

Review: Surgery for cervical intraepithelial neoplasia
Comparison: 08 Radical Diathermy versus LLETZ
Outcome: 03 Yellow discharge

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Healey 1996	24	7.80 (5.80)	24	8.90 (12.00)		100.0	-1.10 [-6.43, 4.23]
Total (95% CI)	24		24			100.0	-1.10 [-6.43, 4.23]
Test for heterogeneity: not applicable							
Test for overall effect z=0.40 p=0.7							

Analysis 08.04. Comparison 08 Radical Diathermy versus LLETZ, Outcome 04 White discharge

Review: Surgery for cervical intraepithelial neoplasia
Comparison: 08 Radical Diathermy versus LLETZ
Outcome: 04 White discharge

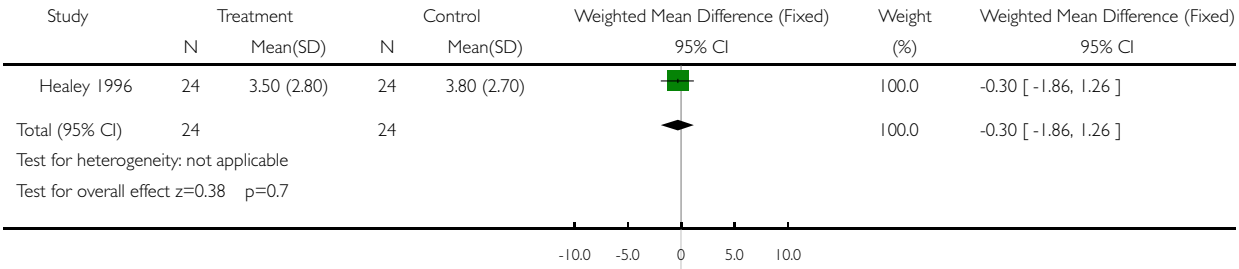
Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Healey 1996	24	7.30 (4.60)	24	8.90 (12.00)		100.0	-1.60 [-6.74, 3.54]
Total (95% CI)	24		24			100.0	-1.60 [-6.74, 3.54]
Test for heterogeneity: not applicable							
Test for overall effect z=0.61 p=0.5							

Analysis 08.05. Comparison 08 Radical Diathermy versus LLETZ, Outcome 05 Upper Abdominal Pain

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 08 Radical Diathermy versus LLETZ

Outcome: 05 Upper Abdominal Pain

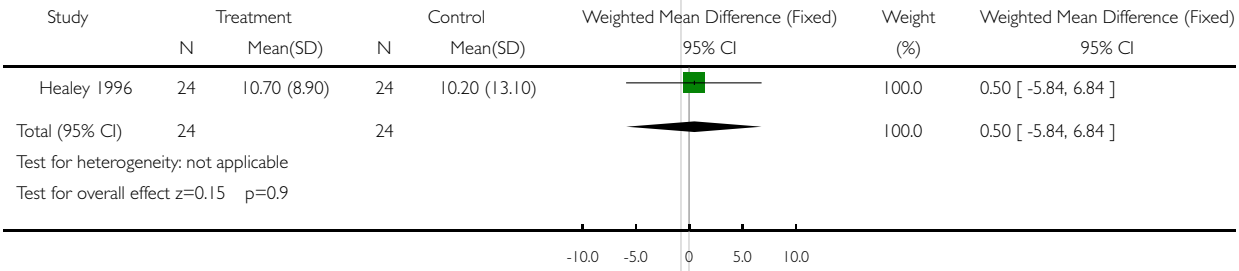


Analysis 08.06. Comparison 08 Radical Diathermy versus LLETZ, Outcome 06 Lower Abdominal Pain

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 08 Radical Diathermy versus LLETZ

Outcome: 06 Lower Abdominal Pain

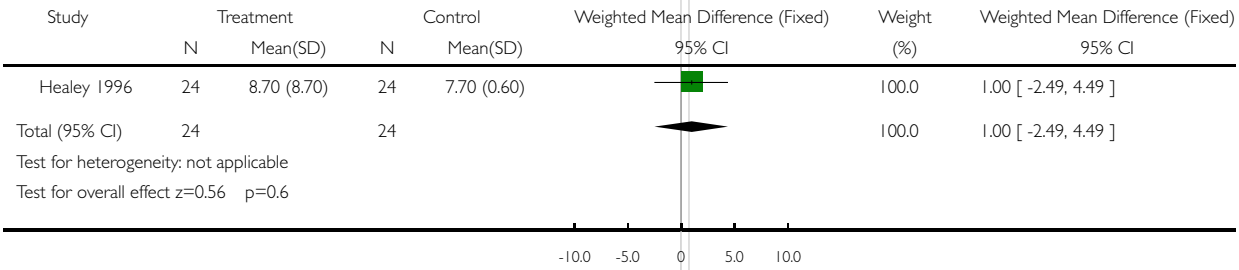


Analysis 08.07. Comparison 08 Radical Diathermy versus LLETZ, Outcome 07 Deep Pelvic Pain

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 08 Radical Diathermy versus LLETZ

Outcome: 07 Deep Pelvic Pain



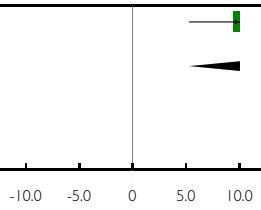
Analysis 08.08. Comparison 08 Radical Diathermy versus LLETZ, Outcome 08 Vaginal Pain

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 08 Radical Diathermy versus LLETZ

Outcome: 08 Vaginal Pain

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Healey 1996	24	12.00 (12.80)	24	1.50 (0.60)		100.0	10.50 [5.37, 15.63]
Total (95% CI)	24		24			100.0	10.50 [5.37, 15.63]
Test for heterogeneity: not applicable							
Test for overall effect z=4.01 p=0.00006							



Analysis 09.01. Comparison 09 Radial Diathermy versus Cryotherapy, Outcome 01 Residual Disease at 12 months

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 09 Radial Diathermy versus Cryotherapy

Outcome: 01 Residual Disease at 12 months

Study	Radial Diathermy n/N	Cryotherapy n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
O'Shea 1986	3/27	9/30		100.0	0.33 [0.09, 1.16]
Total (95% CI)	27	30		100.0	0.33 [0.09, 1.16]
Total events: 3 (Radial Diathermy), 9 (Cryotherapy)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.73 p=0.08					

Analysis 10.01. Comparison 10 Cold Coagulation versus Cryotherapy, Outcome 01 Residual Disease at 24 months

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 10 Cold Coagulation versus Cryotherapy

Outcome: 01 Residual Disease at 24 months

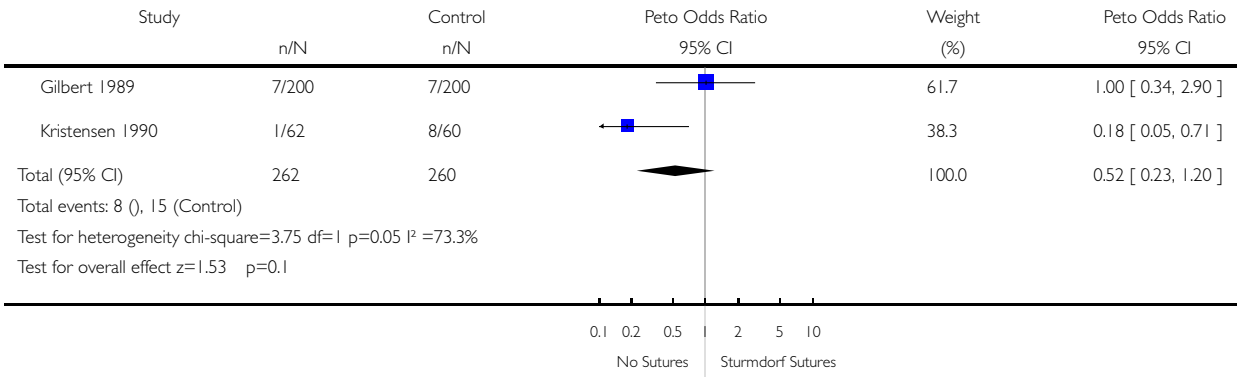
Study	Cold Coagulation n/N	Cryotherapy n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Singh 1988	85/89	61/65		100.0	1.40 [0.33, 5.88]
Total (95% CI)	89	65		100.0	1.40 [0.33, 5.88]
Total events: 85 (Cold Coagulation), 61 (Cryotherapy)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.46 p=0.6					

Analysis 11.01. Comparison 11 Knife Cone Biopsy: Haemostatic Sutures versus None, Outcome 01 Primary Haemorrhage

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 11 Knife Cone Biopsy: Haemostatic Sutures versus None

Outcome: 01 Primary Haemorrhage

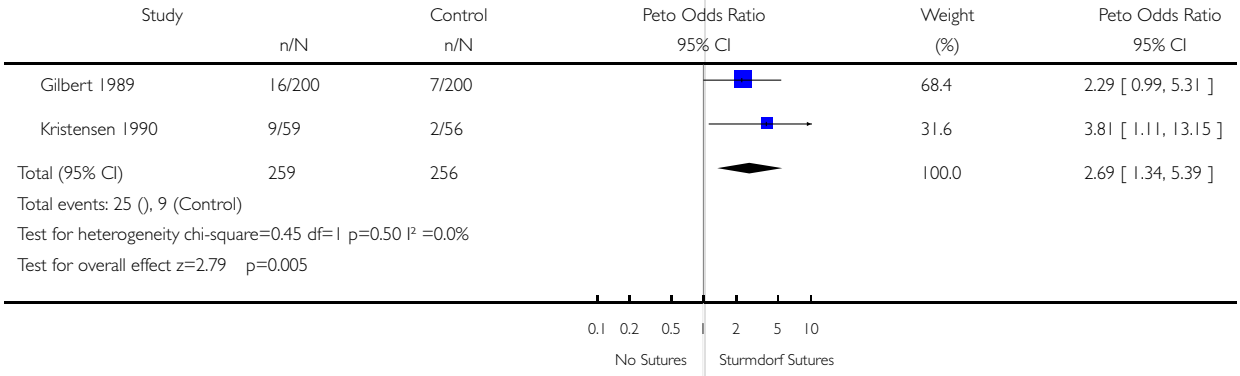


Analysis 11.02. Comparison 11 Knife Cone Biopsy: Haemostatic Sutures versus None, Outcome 02 Secondary Haemorrhage

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 11 Knife Cone Biopsy: Haemostatic Sutures versus None

Outcome: 02 Secondary Haemorrhage



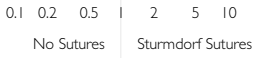
Analysis 11.03. Comparison 11 Knife Cone Biopsy: Haemostatic Sutures versus None, Outcome 03 Cervical Stenosis

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 11 Knife Cone Biopsy: Haemostatic Sutures versus None

Outcome: 03 Cervical Stenosis

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Gilbert 1989	77/100	27/100		66.7	7.34 [4.22, 12.76]
Kristensen 1990	20/54	19/53		33.3	1.05 [0.48, 2.30]
Total (95% CI)	154	153		100.0	3.85 [2.45, 6.04]
Total events: 97 (), 46 (Control)					
Test for heterogeneity chi-square=15.75 df=1 p=<0.0001 I^2 =93.6%					
Test for overall effect z=5.84 p<0.00001					



Analysis 11.04. Comparison 11 Knife Cone Biopsy: Haemostatic Sutures versus None, Outcome 04 Adequate Colposcopy at Follow-up

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 11 Knife Cone Biopsy: Haemostatic Sutures versus None

Outcome: 04 Adequate Colposcopy at Follow-up

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Gilbert 1989	42/100	75/100		100.0	0.26 [0.15, 0.45]
Total (95% CI)	100	100		100.0	0.26 [0.15, 0.45]
Total events: 42 (), 75 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.72 p<0.00001					

Analysis 11.05. Comparison 11 Knife Cone Biopsy: Haemostatic Sutures versus None, Outcome 05 Dysmenorrhoea

Review: Surgery for cervical intraepithelial neoplasia

Comparison: 11 Knife Cone Biopsy: Haemostatic Sutures versus None

Outcome: 05 Dysmenorrhoea

Study		Control	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	95% CI	(%)	95% CI
Gilbert 1989	19/81	7/89		55.6	3.31 [1.44, 7.62]
Kristensen 1990	15/54	7/53		44.4	2.42 [0.95, 6.15]
Total (95% CI)	135	142		100.0	2.88 [1.55, 5.36]
Total events: 34 (), 14 (Control)					
Test for heterogeneity chi-square=0.24 df=1 p=0.62 I^2 =0.0%					
Test for overall effect z=3.33 p=0.0009