Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment (Review)

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[Intervention Review]

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ABSTRACT

Background

Pre-cancerous lesions of cervix (cervical intraepithelial neoplasia (CIN)) are usually treated with excisional or ablative procedures. In the UK, the NHS cervical screening guidelines suggest that over 80% of treatments should be performed in an outpatient setting (colposcopy clinics). Furthermore, these guidelines suggest that analgesia should always be given prior to laser or excisional treatments. Currently various pain relief strategies are employed that may reduce pain during these procedures.

Objectives

The aim of this review was to assess whether the administration of pain relief reduced pain during colposcopy treatment and in the postoperative period.

Search methods

We searched the Cochrane Gynaecological Cancer Review Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL - May 2011) (2011, Issue 2), MEDLINE (1950 to May week 2, 2011), EMBASE (1980 to week 20, 2011) for studies of any design relating to analgesia for colposcopic management. We also searched registers of clinical trials, abstracts of scientific meetings, reference lists of included studies and contacted experts in the field.

Selection criteria

Randomised controlled trials (RCTs) that compared all types of pain relief before, during or after outpatient treatment to the cervix, in adult women with CIN undergoing loop excision, laser ablation, laser excision or cryosurgery in an outpatient colposcopy clinic setting.

Data collection and analysis

We independently assessed study eligibility, extracted data and assessed risk of bias. We entered data into RevMan and double checked it for accuracy. Where possible, the results were expressed as mean pain score and standard error of the mean with 95% confidence intervals (CI) and the data were synthesised in a meta-analysis.

Main results

We included 17 RCTs (1567 women) of varying methodological quality in the review. These trials compared a variety of interventions aimed at reducing pain in women who underwent treatment for CIN, including cervical injection with lignocaine alone, lignocaine with adrenaline, prilocaine with felypressin, oral analgesics (non-steroidal anti-inflammatory drugs (NSAIDs)), inhalation analgesia (gas mixture of isoflurane and desflurane), lignocaine spray, cocaine spray, local application of benzocaine gel, lignocaine-prilocaine cream (EMLA cream) and transcutaneous electrical nerve stimulation (TENS).

Most comparisons were restricted to single trial analyses and were under-powered to detect differences in pain scores between treatments that may or may not have been present. There was no significant difference in pain relief between women who received local anaesthetic infiltration (lignocaine 2%; administered as a paracervical or direct cervical injection) and a saline placebo (2 trials; 130 women; MD -13.74; 95% CI -34.32 to 6.83). However, when local anaesthetic was combined with a vasoconstrictor agent (one trial used lignocaine combined with adrenaline while the second trial used prilocaine combined with felypressin), significantly less pain (on visual analogue scores) occurred compared with no treatment (2 trials; 95 women; MD -23.73; 95% CI -37.53 to -9.93). Comparing two preparations of local anaesthetic plus vasoconstrictor, prilocaine combined with felypressin did not differ from lignocaine combined with adrenaline for its effect on pain control (1 trial; 200 women; MD -0.05; 95% CI -0.26 to 0.16). Although the mean observed blood loss score was less with lignocaine plus adrenaline (1.33 ± 1.05) as compared with prilocaine plus felypressin (1.74 ± 0.98), the difference was not clinically significant as the overall scores in both groups were low (1 trial; 200 women; MD 0.41; 95% CI 0.13 to 0.69). Inhalation of gas mixture (isoflurane and desflurane) in addition to standard cervical injection with prilocaine plus felypressin resulted in significantly less pain during the LLETZ (loop excision of the transformation zone) procedure (1 trial; 389 women; MD -7.20; 95% CI -12.45 to -1.95). Lignocaine plus ornipressin resulted in significantly less measured blood loss (1 trial; 100 women; MD -8.75; 95% CI -10.43 to -7.07) and a shorter duration of treatment (1 trial; 100 women; MD -7.72; 95% CI -8.49 to -6.95) than cervical infiltration with lignocaine alone.

One meta-analysis found no statistically significant difference in pain using visual analogue scores between women who received oral analgesic and those who received placebo (2 trials; 129 women; MD -3.51; 95% CI -10.03 to 3.01; Analysis 6.1).

Cocaine spray was associated with significantly less pain (1 trial; 50 women; MD -28; 95% CI -37.86 to -18.14) and blood loss (1 trial; 50 women; MD 0.04; 95% CI 0 to 0.70) than placebo.

No serious adverse events were reported in any of the trials and majority of trials were at moderate or high risk of bias (n = 12).

Authors' conclusions

Based on two small trials, there was no significant difference in pain relief in women receiving oral analgesics compared with placebo or no treatment (129 women; MD -3.51; 95% CI -10.03 to 3.01). We consider this evidence to be of a low to moderate quality. In routine clinical practice, intracervical injection of local anaesthetic with a vasoconstrictor (lignocaine plus adrenaline or prilocaine plus felypressin) appears to be the optimum analgesia for treatment. However, further high-quality, adequately powered trials should be undertaken in order to provide the data necessary to estimate the efficacy of oral analgesics, the optimal route of administration and dose of local anaesthetics.

PLAIN LANGUAGE SUMMARY

Pain relief for women with pre-cancerous changes of the cervix (cervical intraepithelial neoplasia (CIN)) undergoing outpatient treatment

Treatment for CIN is usually undertaken in an outpatient colposcopy clinic to remove the pre-cancerous cells from the cervix. It commonly involves lifting the cells off the cervix with electrically heated wire (diathermy) or laser, or destroying the abnormal cells with freezing methods (cryotherapy). This is potentially a painful procedure. The purpose of this review is to determine which, if any, pain relief should be used during cervical colposcopy treatment. We identified 17 trials and these reported different forms of pain relief before, during and after colposcopy. Evidence from two small trials showed that women having a colposcopy treatment had less pain and blood loss if the cervix was injected with a combination of a local anaesthetic drug and a drug that causes blood vessels to constrict (narrow), compared with placebo. Although taking oral pain-relieving drugs (e.g. ibuprofen) before treatment on the cervix in the colposcopy clinic is recommended by most guidelines, evidence from two small trials did not show that this practice reduced pain during the procedure. Most of the evidence in this field is of a low to moderate quality and further research may change these findings.

Additionally, we were unable to obtain evidence with regards to dosage of the local anaesthetic drug or method of administering local anaesthetic into the cervix. There is need for high-quality trials with sufficient numbers of participants in order to provide the data necessary to estimate these effects.

BACKGROUND

Description of the condition

Cervical cancer is the second most common cancer among women up to 65 years of age and is the most frequent cause of death from gynaecological cancers worldwide. A woman's risk of developing cervical cancer by the age of 65 years ranges from 0.69% in developed countries to 1.38% in developing countries (GLOBOCAN 2008). In Europe, about 60% of women with cervical cancer are alive five years after diagnosis (EUROCARE 2003). Cervical screening has all the characteristics of a good screening programme. There are effective screening tests, such as the traditional cytological approach (Pap smear) for diagnosing pre-invasive and early invasive disease, or new methodologies, such as human papillomavirus (HPV) testing, which try to improve sensitivity and specificity. Also there are effective surgical treatments for pre-invasive and early invasive disease, which dramatically alter the prognosis. As cervical screening is relatively inexpensive, non-invasive and treatment of pre-invasive disease requires only simple surgical techniques, screening is cost-effective and has been clearly demonstrated to reduce mortality in countries with well-organised screening programmes (Peto 2004).

The effectiveness of different modalities of treatment for pre-invasive disease has been the subject of a previous Cochrane review (Martin-Hirsch 2010). In this review, each modality of treatment was assessed for its ability to eradicate disease and associated morbidity. Current treatment for cervical intraepithelial neoplasia (CIN) is by local ablative therapy or by excisional methods, depending on the nature and extent of the disease. There is an international consensus that the majority of these procedures can be performed within the colposcopy clinic in an outpatient setting. In the UK, the National Health Service (NHS) cervical screening guidelines suggest that over 80% of treatments should be performed in a clinic setting (NHSCSP 2004; NHSCSP 2010). Furthermore, these guidelines also suggest that analgesia should always be given prior to laser or excisional treatments.

Description of the intervention

Therapies that are available to treat pre-malignant lesions of the cervix in outpatient settings include loop diathermy excision, laser ablation or excision and cryotherapy (Martin-Hirsch 2010). Studies have reported variable outcomes with different types of pain relief for these procedures. The choice of pain relief in these studies varies from no analgesia to intracervical infiltration with anaesthetic agent (e.g. lignocaine or prilocaine) with or without vasopressor agents (e.g. adrenaline or felypressin) (Lee 1986; Johnson 1989). Other methods studied are oral therapy with non-steroidal anti-inflammatory drugs (NSAIDs) (Frega 1994), local spray with cocaine (Mikhail 1988), topical benzocaine gel (Lipscomb 1995), inhalation of gas mixture of isoflurane and desflurane (Cruickshank 2005), local anaesthetic cream (EMLA cream) (Sarkar 1993) and transcutaneous electrical nerve stimulation (TENS) (Crompton 1992).

How the intervention might work

The possible mechanisms proposed in the literature to explain pain during cervical laser vaporisation includes pain mediated through peripheral pain fibres in the cervix, stimulated by heat energy, with or without pain caused by increased uterine contractions, probably because of the release of prostaglandins. The interventions may work by blocking the pain pathways. The nerve supply to the cervix is unclear, but the richest supply appears to be at the level of internal os. The ectocervix appears to be relatively insensitive to extremes of temperature with few specialised nerve fibres (Jordan 1976). Pain stimuli from the cervix and vagina are conducted by visceral afferent fibres to the S2 to S4 spinal ganglia via the pudendal and pelvic splanchnic nerves, along with parasympathetic fibres (Moore 2006).

Why it is important to do this review

There now appears to be a consensus that analgesia should be administered before treatment to the cervix. Currently, there is no systematic review or meta-analysis evaluating whether administering analgesia reduces the pain experienced by patients undergoing outpatient treatment. Most guidelines are also not explicit on the nature of optimum analgesia for intra- and postoperative pain relief. Analgesia is commonly administered intra- or para-cervically using fine dental needles. Other routes of administering analgesics evaluated are TENS, peri-operative NSAIDs and inhalation analgesia.

OBJECTIVES

To assess whether the administration of anaesthesia reduces pain during colposcopy treatment and in the postoperative period.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs)

Types of participants

Women with CIN undergoing loop excision, laser ablation, laser excision or cryosurgery treatment of the cervix in an outpatient colposcopy clinic setting.

Types of interventions

All types of pain relief before, during or after outpatient treatment to the cervix, compared with no pain relief or another type of pain relief. Any studies that included treatment performed under general anaesthetic were excluded.

Types of outcome measures

Primary outcomes

Presence or absence of pain, as a dichotomous outcome, or the degree of pain, measured by visual analogue scores or categorical scales.

Secondary outcomes

1. Speed of procedure (in minutes).
2. Blood loss (either in mL or categorical scale as none, mild or minimal, heavy, troublesome or as dichotomous data).
3. Any moderate or severe adverse effects (dizziness, fainting, shaking, delayed discharge, etc.).

Search methods for identification of studies

We searched for papers in all languages and translations were undertaken, if necessary.

Electronic searches

A search strategy was used to identify relevant RCTs.
We searched the Cochrane Gynaecological Cancer Review Group Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL) (2011, Issue 2), MEDLINE (1950 to May week 2, 2011), EMBASE (1980 to week 20, 2011) for studies of any design relating to analgesia for colposcopic management. The electronic literature search strategies for CENTRAL, MEDLINE and EMBASE are summarised in Appendix 1, Appendix 2 and Appendix 3, respectively.
All relevant articles found were identified on PubMed and using the 'related articles' feature, further searches were carried out for newly published articles.

Searching other resources

Registries of randomised trials

We searched the following registries for ongoing trials: Metaregister (www.controlled-trials.com/mrct/), Physicians Data Query (www.ncbi.nlm.nih.gov/), www.clinicaltrials.gov and www.cancer.gov/clinicaltrials.
Conference proceedings and abstracts were searched through ZETOC (http://zetoc.mimas.ac.uk).

Handsearching

The citation lists of included studies, key textbooks and previous systematic reviews were handsearched.
Reports of conferences were handsearched in the following sources:

- Gynecologic Oncology (Annual Meeting of the American Society of Gynecologic Oncologist);
- International Journal of Gynecological Cancer (Annual Meeting of the International Gynecologic Cancer Society);
- British Society for Colposcopy and Cervical Cytology (BSCCP) Annual Meeting.

Data collection and analysis

Selection of studies

Two review authors (KG, AB) scanned the titles and abstracts (when available) of all reports identified through the electronic searches. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained. Two review authors (KG, AB) assessed the full reports obtained from all the electronic and other methods of searching were assessed independently to establish whether the studies met the inclusion criteria or not. Disagreements were resolved by discussion. Where resolution

was not possible, a third review author (PM-H) was consulted. All studies meeting the inclusion criteria underwent validity assessment and data extraction using a standardised proforma. Studies rejected at this or subsequent stages were recorded in the table of excluded studies, and reasons for exclusion recorded.

Data extraction and management

Two review authors (KG, AB) extracted the data independently using specially designed data extraction forms. The data extraction forms were piloted on several papers and modified as required before use. Any disagreements were discussed and a third review author (PM-H) consulted when necessary. Study authors were contacted for clarification or missing information if necessary. Data were excluded until further clarification was available or if agreement could not be reached.

For included studies, data were abstracted as recommended in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This included data on the following:

- author, year of publication, country of origin, source of study funding and journal citation (including language);
- setting;
- details of the participants including demographic characteristics (e.g. age, co-morbidities, etc.), total number enrolled and criteria for inclusion and exclusion;
- CIN details at diagnosis;
- details of the type of intervention;
- risk of bias in study (see below);
- duration of follow-up;
- details of the outcomes reported (pain, blood loss, adverse events), including method of assessment, and time intervals (see below):
    - for each outcome: outcome definition (with diagnostic criteria if relevant);
    - unit of measurement (if relevant);
    - for scales: upper and lower limits, and whether high or low score is good;
    - results: number of participants allocated to each intervention group;
    - for each outcome of interest: sample size; missing participants;
    - the time points at which outcomes were collected and reported were noted.

Data on outcomes were extracted as below:

- for dichotomous outcomes (e.g. pain, adverse events), we extracted the number of women in each treatment arm who experienced the outcome of interest and the number of women assessed at endpoint, in order to estimate a risk ratio (RR);
- for continuous outcomes (e.g. blood loss), we extracted the final value and standard deviation (SD) of the outcome of interest and the number of women assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (MD) (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales) between treatment arms and its standard error.

Where possible, all data extracted were those relevant to an intention-to-treat (ITT) analysis, in which participants are analysed in groups to which they were assigned.

Assessment of risk of bias in included studies

The risk of bias in included RCTs was assessed in accordance with guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* using the Cochrane Collaboration's tool and the criteria specified in Chapter 8 (Higgins 2011). This included assessment of:

- sequence generation;
- allocation concealment;
- blinding (of participants, healthcare providers and outcome assessors);
- incomplete outcome data:
    - we recorded the proportion of women whose outcomes were not reported at the end of the study. We coded the satisfactory level of loss to follow-up for each outcome as:
        - low risk of bias, if fewer than 20% of women were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms;
        - high risk of bias, if more than 20% of women were lost to follow-up or reasons for loss to follow-up were different between treatment arms;
        - unclear risk of bias, if loss to follow-up was not reported;
- selective reporting of outcomes;
- other possible sources of bias.

Two review authors (KG, AB) applied the 'Risk of bias' tool independently and differences were resolved by discussion or by appeal to a third review author (PM-H). Results were summarised in both a 'Risk of bias' graph and a 'Risk of bias' summary. Results of meta-analyses were interpreted with consideration of the findings with respect to risk of bias.

Measures of treatment effect

We used the following measures of the effect of treatment:

- for dichotomous outcomes, we used the RR;
- for continuous outcomes, we used the MD between treatment arms.

Unit of analysis issues

Two review authors (KG, AB) reviewed any unit of analysis issues according to Higgins 2011 and differences were resolved by discussion.

Dealing with missing data

We did not impute missing outcome data for the primary outcome. If data were missing or only imputed data were reported we contacted trial authors to request data on the outcomes only among women who were assessed.

Assessment of heterogeneity

We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials that could not be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, when possible, by subgroup analyses. If there was evidence of substantial heterogeneity, we investigated and reported the possible reasons.

Data synthesis

Each trial was characterised by its type of analgesia and route of administration. Furthermore, the assessment of pain or any other outcomes were classified on whether dichotomous or continuous outcomes were used. Meta-analysis was only performed, when the interventions, route of administration and outcome measures were clinically similar.

- For any dichotomous outcomes, the RR was calculated for each trial and these were then pooled.
- For continuous outcomes, the MDs between the treatment arms at the end of follow-up were pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences were pooled.

If any trials had multiple treatment groups, the 'shared' comparison group was divided into the number of treatment groups and comparisons between each treatment group and the split comparison group was treated as independent comparisons.
Random-effects models with inverse variance weighting were used for all meta-analyses (DerSimonian 1986).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The search strategy identified 232 unique references. Two review authors (KG, AB) read the abstracts of these and articles that obviously did not meet the inclusion criteria were excluded at this stage. Twenty articles were retrieved in full and translated into English where appropriate and updated versions of relevant studies were identified. The full-text screening of these 20 references excluded a further two references for the reasons described in the table Characteristics of excluded studies. However, 18 references reporting on 17 completed RCTs were identified that met our inclusion criteria and are described in the table Characteristics of included studies.
Searches of the grey literature did not identify any additional trials.

Included studies

The 17 included trials (Al Kurdi 1985; Connell 2000; Crompton 1992; Cruickshank 2005; Diakomanolis 1997; Duncan 2005; Frega 1994; Howells 2000; Johnson 1989; Johnson 1996; Lee 1986; Lipscomb 1995; Mikhail 1988; Rogstad 1992; Sammarco 1993; Sarkar 1993; Winters 2009) randomised 1600 eligible women, of whom 1567 were assessed at the end of the trials (Characteristics of included studies; Table 1)

Design

All trials were conducted as single centre trials in a colposcopy clinic setting. Various pain relief interventions were reported in the 17 included trials. Two trials (Johnson 1989; Rogstad 1992) investigated cervical injection (intracervical and paracervical block, respectively) with anaesthetic agent (lignocaine 2%) compared with saline. Three trials (Duncan 2005; Lee 1986; Sammarco 1993) used preparations made up of local anaesthetic plus vasoconstrictor. One of these three trials used cervical injection with lignocaine 1% mixed with 1:100,000 dilution of adrenaline given submucosally and compared it with no treatment (Sammarco 1993), while two other trials (Duncan 2005; Lee 1986) reported cervical injection with a different anaesthetic agent (prilocaine 30 mg/mL) mixed with vasoconstrictor (felypressin 0.03 IU/mL) compared with no treatment or placebo. Lignocaine 1% with vasoconstrictor (1:30 of ornipressin in lignocaine 1% solution) compared to lignocaine 1% alone was investigated in one trial (Diakomanolis 1997) to evaluate the effects on the blood loss during the procedure.
Three trials investigated the method of cervical injection. In one trial local anaesthetic combined with vasoconstrictor (prilocaine 3% plus felypressin) administered by deep and superficial injection was compared with deep injection alone (Winters 2009), while in another trial paracervical injection of lignocaine 2% was compared with direct injection (Johnson 1996). Two different preparations of anaesthetic agent with vasoconstrictor (prilocaine 30 mg/mL plus felypressin 0.03 IU/mL compared with lignocaine 2% plus adrenaline 1:80,000) was investigated in a third trial (Howells 2000).
The use of oral analgesia with NSAID (naproxen sodium, dose 550 mg), given half an hour to one hour before treatment, compared

to placebo or no treatment was reported in two trials (Al Kurdi 1985; Frega 1994) with one trial (Frega 1994) using a single dose of naproxen sodium 550 mg while the other trial (Al Kurdi 1985) used double the dose (1100 mg).

One trial (Cruickshank 2005) used a gas mixture (isoflurane 0.3% and desflurane 1%) as inhalation agent, in addition to standard cervical injection of local anaesthetic plus vasoconstrictor (prilocaine 30 mg/mL plus felypressin 0.03 IU/mL, also known as octapressin).

A further four trials (Connell 2000; Lipscomb 1995; Mikhail 1988; Sarkar 1993) used topical application of gel, cream and sprays for their anaesthetic effects during the treatment on cervix. One trial looked at the effects of benzocaine 20% gel (Lipscomb 1995) compared to placebo gel and the other trial compared EMLA cream, which is a local anaesthetic cream consisting of a mixture of lignocaine 2.5% and prilocaine 2.5% (Sarkar 1993) to a placebo cream. Mikhail 1988 compared 3 to 4 mL of a cocaine 10% spray as a surface anaesthesia to a placebo solution (preservative) for its effects on pain relief. In the trial of Connell 2000, women were randomised to receive either lignocaine hydrochloride 10% spray or saline in addition to standard cervical infiltration using prilocaine 30 mg/mL plus felypressin 0.03 IU/mL. TENS, a non-invasive method, was also investigated (Crompton 1992).

Participant characteristics

The age of the women in the included trials ranged from 17 to 60 years; the mean age across the trials ranged from 27 to 35 years. Both pre- and postmenopausal women were included in the majority of the studies, although two trials (Crompton 1992; Johnson 1989) excluded perimenopausal, postmenopausal women, or both. Other common exclusion criteria were: various allergies, pregnancy and previous treatment to the cervix. Concomitant use of highly protein-bound drug was an exclusion criteria in one trial (Al Kurdi 1985) with oral analgesia using NSAID, while another trial using a gas mixture of isoflurane and desflurane (Cruickshank 2005) excluded women on monoamine-oxidase inhibitors or women driving themselves home from the clinic. Pelvic inflammatory disease, cardiac pacemaker (Crompton 1992), bronchial asthma (Al Kurdi 1985), cardiac conditions, hypertension and epilepsy (Diakomanolis 1997) were other reasons for excluding patients from trials.

Parity was described in patient characteristics for intervention and control group in the Crompton 1992; Cruickshank 2005; Duncan 2005: Howells 2000; Lipscomb 1995 and Johnson 1989 trials. Number of nulliparous women recruited in these trials ranged from 18% to 48%. Two trials (Lipscomb 1995; Mikhail 1988) reported the number of children, which ranged from no children up to five. Marital status was provided in Duncan 2005, Mikhail 1988 and Sarkar 1993 trials; whereas the usage of contraception was provided in Howells 2000 and Johnson 1989. Sixty-five per cent of women in the intervention group and 72% in the control group used contraception in the trial of Howells 2000. The use of oral contraceptive pills in Johnson 1989 was 47% in the intervention group compared to 53% in the control group.

Cruickshank 2005 used depravation scores, while median anxiety Hospital Anxiety and Depression (HAD) score (Zigmond 1983) and median depression HAD score (Zigmond 1983) was used to compare the characteristics of intervention and control groups in the Crompton 1992 and Johnson 1989 trials. The Johnson 1989 trial also used anxiety visual analogue score (Zigmond 1983) and premenstrual syndrome scores (no reference provided). Anxiety score (Spielberger 1970) was also used in the trial of Lee 1986. Only one trial (Howells 2000) compared the groups for smoking status.

Two trials (Howells 2000; Winters 2009) reported smear grades as well as final histology with CIN grades. Lipscomb 1995 and Winters 2009 reported positive margins of excised cervical specimen after treatment. The size of the cervical pre-invasive lesion was reported in patients' characteristics by Crompton 1992, while Howells 2000 reported the size of the loop excised. Passes of loop diathermy were provided by Howells 2000 with 76% in the intervention group and 75% in the control group having one pass of the loop. Lipscomb 1995 reported average number of loop passes per person in trial and control group.

In nine of the 17 trials, women underwent laser ablation of cervix (Al Kurdi 1985; Crompton 1992; Diakomanolis 1997; Frega 1994; Johnson 1989; Johnson 1996; Lee 1986; Mikhail 1988; Sarkar 1993), in five trials LLETZ was used (Cruickshank 2005; Howells 2000; Lipscomb 1995; Winters 2009; Connell 2000), cryotherapy in one trial (Sammarco 1993) and in two trials cold coagulation with Semm Coagulator was used to treat the cervix (Duncan 2005; Rogstad 1992).

Outcomes

The diverse nature of the interventions in the trials precluded direct comparison apart from two trials (Al Kurdi 1985; Frega 1994) comparing oral analgesia versus control, it was possible to combine the pain relief outcome reported on visual analogue scale (VAS).

Pain relief reported on visual analogue scale (VAS)

For the included studies, the degree of pain relief during the procedure was reported as VAS in 13 trials (Al Kurdi 1985; Connell 2000; Cruickshank 2005; Frega 1994; Johnson 1989; Johnson 1996; Lee 1986; Lipscomb 1995; Mikhail 1988; Rogstad 1992; Sammarco 1993; Sarkar 1993; Winters 2009). In all trials VAS scores were assessed immediately after the procedure. Five trials (Al Kurdi 1985; Cruickshank 2005; Lipscomb 1995; Sarkar 1993; Winters 2009) used a 100-mm or 10-cm linear analogue scale, where 0 was no pain at all and 100 (or 10 in the 10-cm scale) was

worst pain imaginable. One trial (Johnson 1989) reported pain relief on 120-mm visual linear analogue scale, which was converted to percentages. Johnson 1996 and Connell 2000 reported pain relief as VAS; however, the values were median and interquartile range, rather than mean and SD. Sammarco 1993 reported VAS on an 11-point scale (0 to 10) where 0 was no pain and 10 was severe pain.

Pain relief reported on verbal rating scores (VRS)

In five trials (Al Kurdi 1985; Diakomanolis 1997; Duncan 2005; Lee 1986; Mikhail 1988), pain relief was reported on VRS categorised as none, mild, moderate or severe.

Pain relief reported on other categorical scales

In addition to VAS, Johnson 1989 and Johnson 1996 also reported pain relief as an objective score, given by the attending nurse and laser operator on a categorical scale of 0 to 2. In another trial (Howells 2000), pain was scored by the attending colposcopist on a categorical scale (0 = none to 4 = severe) as well as by women undergoing treatment (0 = none to 5 = unbearable). In the Sarkar 1993 trial, pain scores were measured for pain relief after treatment and not just during treatment. However, the time scale for carrying out the pain score was not specified. In the trial of Al Kurdi 1985, women were asked whether additional pain killers were required within the first 24 hours. In Cruickshank 2005 trial, women were asked whether additional pain relief was required after treatment. It would appear that this was asked at six months' follow-up, which carries a risk of recall bias. Owing to this risk, these data were not included in the analysis.

Blood loss during treatment

Blood loss was reported as none, mild, moderate and troublesome in seven trials (Crompton 1992; Cruickshank 2005; Diakomanolis 1997; Howells 2000; Lee 1986; Mikhail 1988; Sarkar 1993). In the Diakomanolis 1997 trial, the method of measuring blood loss was explicitly specified, while other trials (Crompton 1992; Cruickshank 2005; Howells 2000; Lee 1986; Mikhail 1988; Sarkar 1993) reported blood loss subjectively as scored by the operator on a categorical scale (0 = none to 5 = heavy/troublesome).

Speed of procedure (or duration of treatment)

Speed of procedure was reported in four trials (Diakomanolis 1997; Howells 2000; Lee 1986; Sarkar 1993).

Anxiety

Preoperative anxiety is one of the most significant risk factors for experiencing pain during cervical colposcopy treatment (Johnson 1994). In four trials anxiety levels were measured preoperatively in both arms. Anxiety was measured using HAD scores in three trials (Crompton 1992; Cruickshank 2005; Johnson 1989), while a fourth trial (Lee 1986) used a different scale (Spielberger State Anxiety Inventory) (Spielberger 1970).

Excluded studies

Two references were excluded, after obtaining the full text, for the following reasons:

- The trial of Sarkar 1990 was excluded as it was not an RCT and it was not controlled for placebo effects. This trial reported use of EMLA cream (lignocaine-prilocaine cream) for pain relief during cervical laser treatment;
- Sharp 2009 was excluded because this study did not compare pain relief interventions. This was an observational study nested within an RCT in which women completed questionnaire about their experiences at colposcopy, colposcopy and biopsy, and colposcopy and LLETZ treatment.

For further details of all the excluded studies see the Characteristics of excluded studies table.

Risk of bias in included studies

Five trials (Connell 2000; Cruickshank 2005; Johnson 1989; Johnson 1996; Mikhail 1988) were at low risk of bias, as they satisfied at least five of the criteria that we used to assess risk of bias. Eight trials (Al Kurdi 1985; Diakomanolis 1997; Duncan 2005; Howells 2000; Lee 1986; Lipscomb 1995; Sarkar 1993; Winters 2009) were at moderate risk of bias as they satisfied three or four of the criteria. The trial of Rogstad 1992 was at high risk of bias as it only satisfied two of the criteria and a further three trials (Crompton 1992; Frega 1994; Sammarco 1993) were also at high risk of bias as they only satisfied one criterion (see Figure 1; Figure 2).

Figure 1. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.

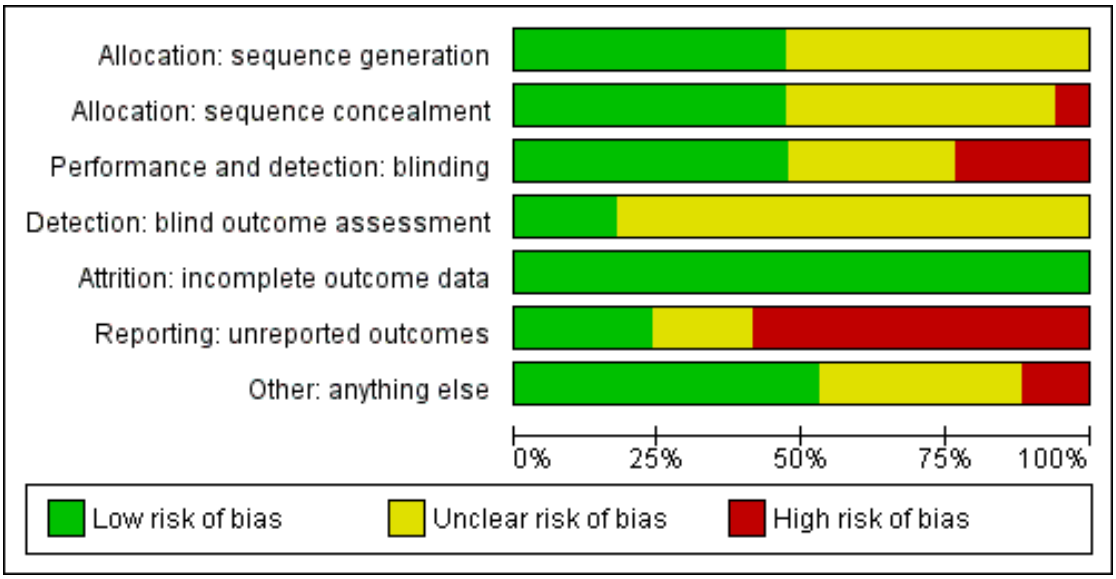
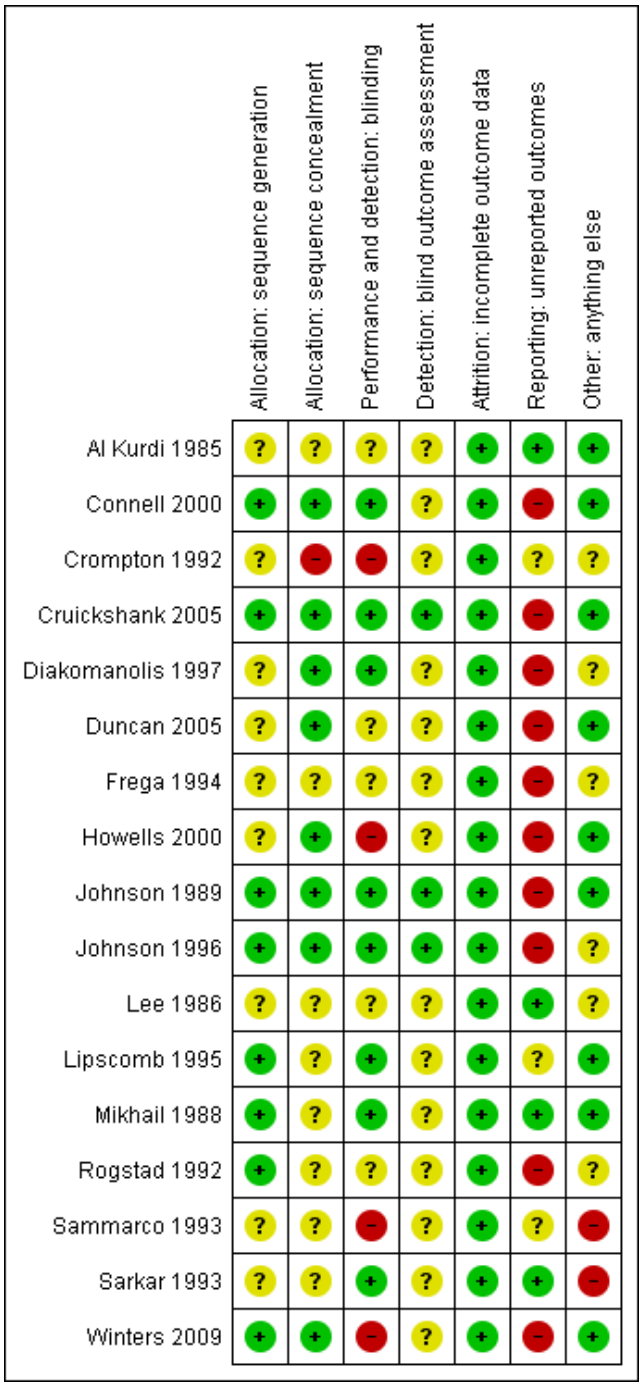


Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.



Eight trials (Connell 2000; Cruickshank 2005; Johnson 1989; Johnson 1996; Lipscomb 1995; Mikhail 1988; Rogstad 1992; Winters 2009) reported the method of generation of the sequence of random numbers used to allocate women to treatment arms, but three of these trials (Lipscomb 1995; Mikhail 1988; Rogstad 1992) did not report concealment of this allocation sequence from patients and healthcare professionals involved in the trial. Five trials (Al Kurdi 1985; Connell 2000; Frega 1994; Lee 1986; Sammarco 1993; Sarkar 1993) did not report on either the method of sequence generation or concealment of allocation. In the trials of Duncan 2005 and Howells 2000 it was unclear whether the method of assigning women to treatment groups was carried out using an adequate method of sequence generation, but the allocation was adequately concealed. The trial of Crompton 1992 did not report sequence generation details but did state that the allocation was not concealed. Three trials (Cruickshank 2005; Johnson 1989; Johnson 1996) reported blinding of patients, healthcare professionals and outcome assessors, whereas this information was not reported in five trials (Al Kurdi 1985; Duncan 2005; Frega 1994; Lee 1986; Rogstad 1992). Five trials (Connell 2000; Diakomanolis 1997; Lipscomb 1995; Mikhail 1988; Sarkar 1993) confirmed blinding of patients and healthcare professionals, but it was unclear whether the outcome assessor was blinded and a further four trials (Crompton 1992; Howells 2000; Sammarco 1993; Winters 2009) confirmed that at least one of patients and health care professionals were not blinded but did not report whether the outcome assessor was blinded or not. It was not certain whether three trials (Crompton 1992; Lipscomb 1995; Sammarco 1993) reported all the outcomes that they assessed, but in 10 trials (Connell 2000; Cruickshank 2005; Diakomanolis 1997; Duncan 2005; Frega 1994; Howells 2000; Johnson 1989; Johnson 1996; Rogstad 1992; Winters 2009) it appeared that additional pertinent outcomes should have been reported and their omission left a gap in the evidence. The remaining four trials seemed to report all relevant outcomes related to the subject matter. No other form of bias appeared likely in 10 trials (Al Kurdi 1985; Connell 2000; Cruickshank 2005; Duncan 2005; Howells 2000; Johnson 1989; Lee 1986; Lipscomb 1995; Mikhail 1988; Winters 2009). Additional forms of bias seemed a possibility in the trials of Sammarco 1993 and Sarkar 1993 in the way some analyses were undertaken, but it was unclear whether this was the case in the remaining five trials. At least 80% of women who were enrolled were assessed at endpoint in all 17 trials.

Effects of interventions

Local anaesthetic (lignocaine 2%) versus placebo (saline injection)

Pain scores during procedure (VAS)

Two trials (Johnson 1989; Rogstad 1992) compared the effects of local anaesthetic lignocaine 2% without a vasoconstrictor to placebo (saline injection). The trial of Johnson 1989 used lignocaine 2% injection for paracervical block while the trial of Rogstad 1992 used lignocaine 2% for direct injection in the cervix. The trial of Rogstad 1992 found that women who received local anaesthetic had significantly less pain during treatment than women who received saline injection (60 women; MD -24.00; 95% CI -35.44 to -12.56), whereas the Johnson 1989 trial found no statistically significant difference between the same groups (70 women; MD -3.00; 95% CI -16.03 to 10.03) (Analysis 1.1).

Moderate to severe pain during procedure

The trial of Rogstad 1992 found that women who received local anaesthetic reported significantly less moderate or severe pain during treatment than women who received control (RR 0.36; 95% CI 0.18 to 0.71) (Analysis 1.2).

Local anaesthetic plus vasoconstrictor versus control

Three trials (Duncan 2005; Lee 1986; Sammarco 1993) reported comparisons of local anaesthetic with vasoconstrictor versus control, but variations in both the interventions or control groups, or both, meant that the trials were unable to be pooled in a meta-analysis.

Pain scores during procedure

Meta-analysis of two trials (Lee 1986; Sammarco 1993), assessing 95 women, found that women who received local anaesthetic with vasoconstrictor (prilocaine 3% with felypressin 0.03 IU/mL and lignocaine 1% with adrenaline 1:100,000 dilution in the trials of Lee 1986 and Sammarco 1993, respectively) had significantly less pain during treatment than women who received no treatment (MD -23.73; 95% CI -37.53 to -9.93) (Analysis 2.1). The percentage of the variability in effect estimates that is because of heterogeneity rather than chance may represent substantial heterogeneity (I^2 = 63%). In trial of Sammarco 1993 women in both intervention arm and control arm received oral analgesic ketoprofen 75 mg single dose within one hour of receiving treatment.

Moderate or severe pain during procedure

Two trials (Duncan 2005; Lee 1986) reporting pain relief with local anaesthetic plus vasoconstrictor versus control using VRS showed contrasting results. The trial of Duncan 2005 found that women who received local anaesthetic with vasoconstrictor (5-mL

vials of prilocaine 3% (30 mg/mL) with felypressin 0.03 IU/mL) reported significantly less moderate or severe pain during treatment than women who received placebo. The Lee 1986 trial found no statistically significant difference in the same outcome between women who received vasoconstrictor with local anaesthetic (2 mL of prilocaine 3% with felypressin 0.03 IU/mL) and those who received no treatment (RR 0.12; 95% CI 0.04 to 0.37 and RR 0.73; 95% CI 0.42 to 1.27 (Analysis 2.2) for local anaesthetic with vasoconstrictor versus placebo or no treatment, respectively). Whether the difference could be attributable to varying dosage of anaesthetic agents (5 mL in Duncan 2005 trial versus 2 mL in Lee 1986 trial) is worth considering. No other trials on optimal dosage have been identified to address this issue. Also of note, the method of cervical treatment differed in these two trials. Women in Lee 1986 received cervical treatment with laser vaporisation while in Duncan 2005 trial the women received treatment with Semm coagulator (high-temperature electro-cautery).

Haemorrhage (subjective blood loss) during procedure

The trial of Lee 1986 found no statistically significant difference in the risk of troublesome bleeding between women who received local anaesthetic with vasoconstrictor (2 mL of prilocaine 3% with 0.03 IU/mL of felypressin 0.03 IU/mL) and those who received no treatment (RR 0.40; 95% CI 0.09 to 1.87) (Analysis 2.3). However, the blood loss was not measured and was a subjective impression by the operator.

Local anaesthetic plus vasoconstrictor versus local anaesthetic injection alone

Moderate or severe pain during procedure

The trial of Diakomanolis 1997 found no statistically significant difference in the risk of moderate or severe pain between women who received local anaesthetic with vasoconstrictor (30 mL of a 1:30 ornipressin-lignocaine 1% solution) and those who received local anaesthetic (30 mL of lignocaine 1% solution) alone (RR 1.20; 95% CI 0.57 to 2.52) (Analysis 3.1).

Haemorrhage (measured blood loss) during procedure

The trial of Diakomanolis 1997 found that women who received vasoconstrictor (ornipressin 1:30) with local anaesthetic (30 mL of lignocaine 1%) had significantly less measured blood loss during treatment than women who received local anaesthetic (30 mL of lignocaine 1%) alone (MD -8.75; 95% CI -10.43 to -7.07) (Analysis 3.2). In this trial the amount of solution used for cervical injection of 30 mL is higher than what is generally used. Unlike the subjective evaluation of blood loss in other trials by the operator, trial of Diakomanolis 1997 reported the actual measured volume of blood loss.

Speed of procedure (duration of treatment)

The trial of Diakomanolis 1997 found that duration of treatment was significantly less in women who received vasoconstrictor with local anaesthetic (30 mL of a 1:30 ornipressin with lignocaine 1%) than women who received control (30 mL of lignocaine 1%) (MD -7.72; 95% CI -8.49 to -6.95) (Analysis 3.3).

Local anaesthetic plus vasoconstrictor (prilocaine (local anaesthetic) with felypressin (vasoconstrictor) versus lignocaine (local anaesthetic) with adrenaline (vasoconstrictor))

The trial of Howells 2000 compared two types of local anaesthetic with vasoconstrictor. More specifically, it reported a comparison of prilocaine 3% with felypressin 0.03 IU/mL versus lignocaine 2% with adrenaline 1:80,000.

Pain scores during procedure (using 6-point categorical scale)

The trial found no statistically significant difference in pain scores when measured using a 6-point categorical scale between women who received prilocaine and felypressin and those who received lignocaine and adrenaline (MD -0.05; 95% CI -0.26 to 0.16) (Analysis 4.1).

Blood loss during procedure

The trial found that women who received prilocaine and felypressin had more mean blood loss during treatment than women who received lignocaine and adrenaline (MD 0.41; 95% CI 0.13 to 0.69) (Analysis 4.2). However, the observed difference is unlikely to be clinically significant and the assessment of blood loss was by subjective scoring and not the actual measured loss.

Deep plus superficial versus deep cervical injection

Pain scores during procedure (VAS: 0 to 100)

The trial of Winters 2009 found no statistically significant difference in pain scores when measured using a VAS between women who received deep and superficial injection and those who received deep cervical injection (MD -4.90; 95% CI -11.51 to 1.71) (Analysis 5.1).

Oral analgesic versus placebo or no treatment

Two trials (Al Kurdi 1985; Frega 1994) reported a comparison of naproxen sodium 550 mg tablets given at least 30 minutes before treatment (oral analgesic) versus placebo. The trial of Frega 1994 also included a third arm, which had randomised women to no drug.

Pain scores during procedure

Meta-analysis of the two trials (Al Kurdi 1985; Frega 1994), assessing 129 women, found no statistically significant difference in pain scores when measured using a VAS between women who received oral analgesic and those who received placebo (MD -3.51; 95% CI -10.03 to 3.01 (Analysis 6.1). The percentage of the variability in effect estimates that is because of heterogeneity rather than sampling error (chance) was not important (I^2 = 0%). The trial of Frega 1994 also found no significant difference in pain scores between oral analgesic versus no treatment (MD -4.00; 95% CI -13.69 to 5.69 (Analysis 6.1).

Moderate to severe pain during procedure

The trial of Al Kurdi 1985 found no statistically significant difference in the moderate or severe pain experienced during treatment between women who received oral analgesic and those who received placebo (RR 0.82; 95% CI 0.60 to 1.13) (Analysis 6.2).

Pain relief required in first 24 hours

The trial of Al Kurdi 1985 found that women who received oral analgesic for pain relief during colposcopy were significantly less likely to use additional pain relief within the first 24 hours following treatment than women who received placebo (RR 0.12; 95% CI 0.03 to 0.47) (Analysis 6.3).

Inhalation analgesia versus placebo or no treatment

The trial of Cruickshank 2005 reported a comparison of a gas mixture (isoflurane and desflurane) as inhalation analgesia versus placebo (air).

Pain scores during procedure

Cruickshank 2005 found that women who received trial gas mixture for pain relief (in addition to standard cervical injection with prilocaine 30 mg/mL plus felypressin 0.03 IU/mL) had significantly less pain during treatment than women who received placebo (MD -7.20; 95% CI -12.45 to -1.95) (Analysis 7.1).

Haemorrhage during procedure

Cruickshank 2005 found no statistically significant difference in the risk of heavy vaginal bleeding between women who received gas mixture and those who received placebo (RR 1.17; 95% CI 0.83 to 1.64) (Analysis 7.2).

Anxiety (HAD score) during procedure

Cruickshank 2005l found no statistically significant difference in anxiety scores between women who received gas mixture and those who received placebo (MD 0.01; 95% CI -0.80 to 0.82) (Analysis 7.3).

Topical application versus placebo

Four trials (Connell 2000; Lipscomb 1995; Mikhail 1988; Sarkar 1993) reported comparisons of anaesthetic topical application versus placebo, but variations in the interventions meant that the trials were unable to be pooled in meta-analysis.

Pain scores during procedure

The trial of Lipscomb 1995 found no statistically significant difference in pain scores when measured using a VAS between women who received anaesthetic topical application (20% benzocaine gel) and those who received placebo (MD -9.00; 95% CI -68.59 to 50.59) (Analysis 8.1). Women in both intervention and placebo arm received preprocedure oral analgesia in addition to injecting a total of 4 mL of lignocaine 1% (mixed with adrenaline 1:100,000) in four quadrants of the cervix.

Speed of procedure (duration of treatment)

The trial of Sarkar 1993 found no statistically significant difference in the duration of treatment between women who received anaesthetic topical application (EMLA cream - mixture of lignocaine 2.5% and prilocaine 2.5%) and those who received placebo (MD 0.10; 95% CI -1.38 to 1.58) (Analysis 8.2).

Cocaine spray versus placebo

The trial of Mikhail 1988 reported a comparison of cocaine spray versus placebo.

Pain scores during procedure (VAS: 0 to 100)

The Mikhail 1988 trial found that women who received cocaine spray for pain relief had significantly less pain during treatment than women who received placebo (MD -28.00; 95% CI -37.86 to -18.14) (Analysis 9.1).

Moderate to severe pain during procedure

The Mikhail 1988 trial found that women who received cocaine spray experienced significantly less moderate or severe pain during treatment than women who received placebo (RR 0.57; 95% CI 0.37 to 0.89) (Analysis 9.2).

Haemorrhage during procedure (troublesome bleeding)

The Mikhail 1988 trial found that women who received cocaine spray had significantly less risk of troublesome bleeding following treatment than women who received placebo. No women in the cocaine spray arm and 11 out of 25 in the placebo arm had troublesome bleeding. We did not calculate the RR; the default zero-cell correction within RevMan would bias the result of the meta-analysis towards no difference between cocaine spray and placebo (Analysis 9.3).

TENS, local anaesthetic and TENS plus local anaesthetic injection

The trial of Crompton 1992 reported comparison of TENS, TENS plus cervical infiltration with local anaesthetic with a vasoconstrictor (2 mL of lignocaine 2% plus octapressin) injection and local anaesthetic injection alone. As results of pain relief were reported as median with interquartile range, they were not included in analysis but were summarised separately.

Troublesome blood loss during procedure

The Crompton 1992 trial found no statistically significant difference in the risk of troublesome vaginal bleeding between women who received TENS, TENS plus local anaesthetic and local anaesthetic alone (RR 2.56; 95% CI 0.28 to 23.29; RR 0.77; 95% CI 0.19 to 3.20 and RR 0.30; 95% CI 0.04 to 2.55 for comparisons of TENS versus TENS plus local anaesthetic, TENS versus local anaesthetic alone and TENS plus local anaesthetic versus local anaesthetic alone, respectively) (Analysis 10.1; Analysis 11.1; Analysis 12.1).

Studies and analyses included within the review but not in the forest plots

Pain scores (VAS and objective pain scores)

The trials of Connell 2000; Crompton 1992; and Johnson 1996 reported pain scores on VAS scales using median and interquartile range. The trial of Johnson 1996 also reported objective pain scores by attending nurse and colposcopist.

Lignocaine spray versus placebo

The trial of Connell 2000 comparing 0.5 mL of lignocaine 10% spray in addition to standard cervical infiltration with prilocaine 30 mg/mL plus felypressin 0.03 IU/mL versus placebo. The trial reported the results of pain relief using a VAS scale as median and interquartile range. The results showed that application of lignocaine spray had no significant effect on pain scores (P = 0.38). The medians with interquartile range of the VAS scale for lignocaine spray versus placebo were 40.0 (21.25 to 63.25) and 36.0 (17.5 to 49.5), respectively.

TENS, local anaesthetic injection and TENS plus local anaesthetic injection

The trial of Crompton 1992 reported comparison of TENS, TENS plus cervical infiltration with 2 mL of lignocaine 2% plus octapressin and cervical infiltration with cervical infiltration with 2 mL of lignocaine 2% plus octapressin alone.

The results of pain relief using VAS were reported as median pain scores and interquartile range (24 (10 to 42), 17 (7 to 30) and 18(8 to 31) for TENS, local anaesthetic and TENS plus local anaesthetic, respectively). The median pain score for the group assigned TENS only was higher than the median score for the group given direct infiltration of local anaesthetic (U = -1.57; P = 0.12).

Paracervical versus intracervical injection in the transformation zone (TZ) of cervix with lignocaine

The trial of Johnson 1996 compared direct infiltration in the TZ with 2 mL of lignocaine 2% versus paracervical block with lignocaine 2% using 5 mL on each side of the cervix. This trial reported pain relief on a VAS expressing in median and interquartile ranges. The median linear analogue pain scores (interquartile range) for direct infiltration and paracervical blocks were 14% (6% to 29%) and 30% (21% to 47%), respectively (Mann-Whitney Z = 2.79; P = 0.005) suggesting direct infiltration was associated with lower pain scores. The trial also reported objective pain scores as scored by attending nurse and colposcopist. The objective pain score for direct injection with local anaesthetic was slightly lower (23 women; 0 (0 to 0.25)) than the score associated with paracervical lignocaine injection (21 women; 0 (0 to -0.75); Mann-Whitney test Z = 0.23; P = 0.8).

DISCUSSION

Summary of main results

Seventeen RCTs (1567 women) met the inclusion criteria and were assessed in the review. These trials compared a variety of interventions aimed at reducing pain in women who underwent treatment for CIN in colposcopy clinic settings, including cervical injection with lignocaine alone, lignocaine with adrenaline, prilocaine with felypressin, oral analgesics (NSAID), inhalation analgesia (gas mixture of isoflurane and desflurane), lignocaine spray, cocaine spray, local application of benzocaine 20% gel, EMLA cream and TENS.

Use of lignocaine 2% for cervical injection (as direct injection or paracervical block) showed no overall benefit in pain relief as compared to placebo, with one trial (Rogstad 1992) showing a beneficial effect while another trial (Johnson 1989) found no benefit. Use of the local anaesthetic prilocaine with a vasoconstrictor (felypressin) showed significant reduction in pain on VAS (Duncan 2005; Lee 1986). However, one trial (Lee 1986) found no benefit when the pain was assessed with VRS. This trial also reported no reduction in blood loss with prilocaine plus felypressin. However, the blood loss was not measured and it was the subjective impression of the operator. It is also worth noting that this trial (Lee 1986), though randomised, was not a double-blind controlled trial and only had a small sample size (25 in the intervention arm and 25 in the placebo arm). The addition of a vasoconstrictor agent (ornipressin) to anaesthetic agent (lignocaine 1%) resulted in significantly less measured blood loss and reduction of the duration of procedure (Diakomanolis 1997). Direct cervical injection with local anaesthetic (lignocaine 2%) resulted in better pain relief than placebo (Rogstad 1992) and paracervical block (Johnson 1996). Superficial injection of local anaesthetic in the cervix before deep injection did not result in any better pain relief (Winters 2009).

Oral analgesia with an NSAID before the procedure did not result in better pain relief, although one trial (Al Kurdi 1985) reported that the women were significantly less likely to use oral analgesics at home within the first 24 hours of treatment.

Inhalation of gas mixture (isoflurane and desflurane) in addition to standard cervical injection with prilocaine 30 mg/mL plus felypressin 0.03 IU/mL resulted in significantly less pain during the LLETZ procedure with no effect on blood loss or HAD anxiety scores (Cruickshank 2005).

EMLA local anaesthetic cream did not result in better pain relief compared to placebo (Sarkar 1993). Spraying of the cervix with cocaine spray before treatment resulted in better pain relief and less troublesome bleeding (Mikhail 1988). Use of topical gel (benzocaine 20%) (Lipscomb 1995) or lignocaine spray in addition to standard cervical injection prilocaine 30 mg/mL plus felypressin 0.03 IU/mL did not result in any benefit (Connell 2000).

On comparison of different preparations of local anaesthetic mixed with vasoconstrictor, prilocaine with felypressin did not differ from lignocaine with adrenaline for its effect on pain control (Howells 2000). Mean observed blood loss was less in the lignocaine with adrenaline group compared with prilocaine with felypressin group, although the difference was not clinically significant.

The use of TENS on its own or combined with local anaesthetic injection during cervical laser therapy did not appear to be of any benefit (Crompton 1992).

No serious side effects were noticed in the trials reporting these outcomes. The reported side effects were feeling faint, shaking, dizziness, abdominal cramps, sweating, feeling hot, weakness, and moderate, transient hypertension. Prilocaine with felypressin caused fewer side effects (mainly shaking and fainting) than lignocaine with adrenaline in one trial (Howells 2000).

Overall completeness and applicability of evidence

This review consists of many single trial analyses of small numbers of women, which limits the conclusions that can be drawn. Some of the trials included use of more than one type of pain relief intervention such as preoperative oral analgesics in addition to cervical infiltration. In modern day colposcopy practice, commonly used interventions for pain relief are local anaesthetic infiltration with vasopressin followed by large loop excision of the cervix, cryotherapy, laser ablation or conisation with a knife. In order to improve quantification of the benefits of these interventions in relief of pain and other symptoms (blood loss, etc.) without significant side effects, larger RCTs are required.

Measurement of pain

Several validated scales were used for the measurement of pain in the trials included within the review, which may influence the accuracy of the outcome as complexity of the rating task for the measure influences the sensitivity and specificity. It is thought that a VAS reflects pain experienced during operative procedures more accurately (Huskisson 1983). VAS were used to report pain relief in 13 of the included trials (Al Kurdi 1985; Connell 2000; Cruickshank 2005; Frega 1994; Johnson 1989; Johnson 1996; Lee 1986; Lipscomb 1995; Mikhail 1988; Rogstad 1992; Sammarco 1993; Sarkar 1993; Winters 2009). Sammarco 1993 reported VAS using an 11-point scale. In addition to VAS, two trials (Johnson 1989; Johnson 1996) also reported pain relief as an objective score given by the attending nurse and laser operator on a categorical scale of 0 to 2. In the other trial (Howells 2000), pain was scored by the attending colposcopist on a categorical scale (0 to 4) as well as by women undergoing treatment (0 to 5). Sarkar 1993 reported pain utilising McGill's pain questionnaire, on a categorical scale to grade pain, cramp and backache caused by the laser treatment. In five trials (Al Kurdi 1985; Diakomanolis 1997; Duncan 2005; Lee 1986; Mikhail 1988) pain relief was reported on VRS categorised as none, mild, moderate or severe.

An element of under reporting has been demonstrated, especially where specific mean and SDs have not been stated. Several trials reported pain as a graphical representation without numerical values, which is a form of under reporting. Such selective outcome reporting must be taken into consideration when interpreting the results. The trials of Johnson 1996, Connell 2000 and Sarkar 1993 reported pain relief as VAS, but the values were median and interquartile range rather than mean and SD and therefore these data could not be converted to mean pain scores. In four trials (Frega 1994; Lee 1986; Mikhail 1988; Rogstad 1992), pain relief outcomes were reported as a graphical representation that required calculation of mean and SD. In three trials (Frega 1994; Mikhail 1988; Lee 1986), graphical representation of data was without numerical values. The major limitation of the review and interpretation of the results is the presence of selective outcome reporting.

Quality of the evidence

This review incorporates evidence from 17 RCTs that assessed 1567 women in total. Effective pain relief from local anaesthesia is dependent on various factors, including route of administration, concentration and classification of drug, and the time interval between the administration of the analgesic and start of the procedure. These factors differed between the trials. This review was unable to establish the time interval between administration of injection and start of the procedure from the trial data.

Owing to the heterogeneity of the outcomes and treatments considered, there are many single trial analyses and limited consistent data available to carry out comparisons between trials. The majority of the included trials were underpowered to demonstrate a significant effect and some trials did not include a power calculation in their methodologies. As the majority of comparisons relied on single trials that were underpowered, the treatment effects should ideally be examined by conducting further studies.

Potential biases in the review process

A comprehensive search was performed, including electronic databases and a thorough search of the grey literature. All references were sifted and data extracted by two review authors independently. We restricted the included studies to RCTs as they provide the strongest level of evidence available. Hence, we have attempted to reduce bias in the review process.

The greatest threat to the validity of the review is likely to be the possibility of publication bias (i.e. studies that did not find the treatments to have been effective may not have been published). We were unable to assess this possibility as the meta-analyses included a limited number of the included trials (two out of 17 included trials).

Agreements and disagreements with other studies or reviews

These found no other systematic reviews in this field and we did not identify any other retrospective controlled studies using these outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Oral analgesia, EMLA cream, TENS, lignocaine spray or benzocaine gel did not provide any benefit in pain relief during cervical colposcopy treatment. Spraying of cervix with cocaine spray before treatment resulted in better pain relief and also less troublesome bleeding. Local anaesthetic agent combined with a vasoconstrictor agent resulted in better pain control compared with placebo and was associated with significantly less blood loss. Mean observed blood loss score was less with lignocaine plus adrenaline as compared with prilocaine plus felypressin, although the difference was not clinically significant. Direct cervical injection of local anaesthetic with a vasoconstrictor agent resulted in reduction in pain scores during treatment and should be considered for all cervical colposcopy treatment for CIN. However, no conclusions can be drawn with regards to optimum number of sites to inject in the cervix, depth of injection in the cervix (superficial, deep, or both) and dosage of the agent used. In terms of side effects, combination of prilocaine with felypressin caused fewer side effects than lignocaine with adrenaline. Inhalation of gas mixture in addition to standard pain relief injection appears to have additional pain relief benefit. In routine clinical practice, intracervical injection of analgesic with a vasoconstrictor, particularly those related to vasopressin, appeared to be the optimum analgesia for treatment.

Implications for research

Oral analgesia and the individual topical agents such as EMLA cream, lignocaine spray or benzocaine gel appeared to provide little benefit over placebo or no treatment for pain relief during colposcopy. However, this evidence comes from small trials with methodological shortcomings, therefore we consider this evidence to be of a low quality.

Further available evidence suggests that a local anaesthetic combined with a vasoconstrictor agent significantly reduces pain and measured blood loss, therefore this treatment should be offered to women undergoing colposcopy. This evidence is of moderate quality and further research will have an important impact on our confidence in these findings.

Further high-quality, adequately powered trials should be undertaken in order to provide the data necessary to estimate the optimal route of administration and dose of local anaesthetics.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Al Kurdi 1985

Methods	Prospective randomised double-blind trial Single centre
Participants	97 women satisfied the inclusion criteria and were entered into the study. 50 were allotted naproxen sodium treatment and 47 were given a placebo. Women were generally healthy and undergoing CO_2 laser treatment for CIN for the first time. Pregnancy, lactation, a history of bronchial asthma or allergic diathesis, and concomitant use of highly protein bound drugs excluded women from entry to the trial. All women were assessed following laser treatment but 2 women from the naproxen sodium group failed to return their 24-hour questionnaire Age 18 to 50 years 3 women from each group failed to complete their laser treatment because of pain and were subsequently given local or general anaesthetics. Their response to the laser treatment was recorded and included in the analysis
Interventions	2 naproxen sodium 550 mg or 2 placebo tablets were given not less than 30 minutes before the CO_2 laser treatment of the cervix was performed. Almost always the procedure started within 60 minutes of taking the tablets. Laser treatment was performed as previously described (Lowles 1983) and the duration of laser treatment and laser working time were recorded
Outcomes	VAS: a 10-cm VAS, which ranged from no pain to the worst pain ever experienced by the patient Pain intensity was measured using both a VAS and VRS (none, very slight, mild, moderate, severe) Speed of procedure reported as total treatment time Various other outcomes not specified in our protocol
Notes	Analgesic use following treatment (in the naproxen sodium group only 2 out of 48 women used analgesics compared to 17 out of 47 women in the placebo group) Self-reported side effects were very minor (aches and pains at 24 hours) and not included in analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation: sequence generation	Unclear risk	Not reported
Allocation: sequence concealment	Unclear risk	Not reported
Performance and detection: blinding All outcomes	Unclear risk	Not reported

Al Kurdi 1985 (*Continued*)

Detection: blind outcome assessment All outcomes	Unclear risk	Not reported
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 97/97 (100%) women were analysed for pain. 2 women in treatment arm did not reply to 24-hour questionnaire, but we assessed women immediately after treatment to eliminate recall bias
Reporting: unreported outcomes	Low risk	Pertinent outcomes were reported in the trial
Other: anything else	Low risk	No additional form of bias was likely

Connell 2000

Methods	Prospective, randomised, double-blind, placebo-controlled study Setting: colposcopy clinics at teaching hospital
Participants	Women aged 20 to 64 years who were undergoing biopsy or loop excision under local anaesthetic for cytological abnormalities were recruited to the study. Of the 51 women entered into the study, 19 had a biopsy performed and were excluded from analysis. 32 had a LLETZ and were included for analysis. 16 were randomised to receive solution A (lignocaine spray) and 16 had solution B (saline). 2 women in group failed to complete the second VAS so effectively 30 women were included in the final analysis - 15 in each of 2 groups
Interventions	Women were randomised to receive either the lignocaine hydrochloride 10% spray or saline. Multiple atomiser bottles were made up with solution and were labelled 'A' or 'B'. The spray was primed and the operator depressed the spray 4 times applying approximately 0.5 mL of solution to the cervix. At least 1 minute later 1.1 mL of local anaesthetic (prilocaine hydrochloride 30 mg/mL with felypressin 0.54 μg/mL) was injected with a dental syringe and needle. In the LLETZ group injection was into 4 quadrants, the total volume being 4.4 mL
Outcomes	Pain was measured using 100-mm VAS score. The woman was asked to mark the line with a cross as soon as the injections had been performed. Pain was also assessed with a 4-point categorical scale: 1 = not painful; 2 = slightly painful; 3 = moderately painful; 4 = severely painful
Notes	Pain was only reported on VAS. The outcome reported on categorical scale was not included in the analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Connell 2000 (*Continued*)

Allocation: sequence generation	Low risk	"Randomisation was by stratified computer-generated numbers"
Allocation: sequence concealment	Low risk	To ensure blinding, the bottles were made up in the pharmacy department who also sealed the code in an envelope
Performance and detection: blinding All outcomes	Low risk	The attending doctor, the nursing staff, the woman and the investigator were all blinded to the identification of the solution used
Detection: blind outcome assessment All outcomes	Unclear risk	Not reported
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 94% (30/32) analysed for all outcomes
Reporting: unreported outcomes	High risk	Blood loss and duration of procedure was not reported. The outcome for categorical scale of pain relief was not available to carry out comparison
Other: anything else	Low risk	No additional risk of bias was likely

Crompton 1992

Methods	Prospective randomised 3-arm controlled clinical trial Setting: colposcopy unit adapted to run randomised trials
Participants	100 women with a colposcopic diagnosis of CIN were recruited. They had a gynaecological interview, colposcopy and a colposcopically directed biopsy. Linear analogue anxiety and HAD anxiety/depression personality trait scores (Zigmond 1983), age and number of vaginal deliveries were recorded to assess group comparability. Women who had a past history of treatment for CIN, other cervical surgery or pelvic inflammatory disease, postmenopausal women and women with cardiac pacemakers were excluded. 2 other women refused to enter the trial Mean (SD) age at trial entry: TENS only: N = 34, 31.8 years (SD = 9); local anaesthetic: N = 35, 32.6 years (SD = 9); TENS and local anaesthetic: N = 29, 30.1 years (SD = 8) % of women who were nullipara: TENS only: 48%; local anaesthetic: 44%; TENS plus local anaesthetic: 35% Median anxiety HAD score (interquartile range): TENS only: 6 (5 to 11), local anaesthetic: 7 (4 to 9), TENS plus local anaesthetic: 6.5 (4 to 8) Median depression HAD score (interquartile range): TENS only: 3 (1 to 4), local anaesthetic: 2 (1 to 4), TENS plus local anaesthetic: 3 (1 to 3)

Crompton 1992 (*Continued*)

Interventions	Subjects were allocated to 1 of 3 groups: (1) TENS (N = 34), (2) TENS plus direct infiltration of 2 mL lignocaine 2% plus octapressin 1:10,000 (0.03 IU/mL) (N = 29) and (3) direct infiltration of 2 mL 2% lignocaine plus octapressin (N = 35). A total of 2 mL of lignocaine 2% + octapressin was injected from a dental syringe via a 30-gauge needle into 4 points on the TZ to a depth of 3 to 5 mm. Microtens TENS pads (Neen Pain Management Systems, Norfolk, UK) were applied 20 minutes before treatment. 4 conductive silicone polymer electrodes were applied using conducting gel and tape fixative; 2 anterior to the abdominal wall just above the symphysis pubis and 1 on each side of the sacrum. The electrodes were connected to an 80-Hz nerve stimulator (pulse width 210 μs) by a cable. The single channel amplitude control was activated by the patients under instruction. Initially they were encouraged to experience a tingling sensation and then they increased the amplitude until it became uncomfortable. They were given approximately 20 minutes to experiment with the device until they were called into the second room for laser treatment. All the treatments were carried out in this second room by a second operator. The entire ectocervical TZ was either ablated to a depth of approximately 7 mm or excised with the aid of skin hooks using a 35-W CO_2 laser (spot size 1.5 mm)
Outcomes	At the end of the procedure the surgeon gave a further explanation of the treatment and scored the pain experienced by the patient using 120-mm visual linear analogue scores. The scores were converted into percentages At the end of the procedure the women offered TENS were given a simple questionnaire. They were asked to answer 'Yes' or 'No' to indicate whether or not they found the TENS each of the following: (1) comfortable, (2) unpleasant, (3) helpful, (4) frightening, (5) soothing or (6) pain relieving
Notes	Median pain score was on 120-mm VAS; however, authors converted it to percentage for reporting

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation: sequence generation	Unclear risk	Not reported
Allocation: sequence concealment	High risk	"The block randomisation code was held by one investigator who then allocated treatment"
Performance and detection: blinding All outcomes	High risk	"It was impossible to conceal the use of TENS from the surgeon and patients but we had intended to 'blind' the attendants to the use of local anaesthesia. Injections of lignocaine were given in a separate room before the laser surgery was carried out by a different attendant but the surgeon was able to identify points where local anaesthetic had been given"

Crompton 1992 (*Continued*)

Detection: blind outcome assessment All outcomes	Unclear risk	Not reported
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 98% (98/100) analysed for all outcomes
Reporting: unreported outcomes	Unclear risk	Median pain scores reported rather than mean and adverse events were not reported
Other: anything else	Unclear risk	Insufficient information to permit judgement

Cruickshank 2005

Methods	Prospective double-blind RCT A colposcopy clinic serving a regional population in single-centre setting
Participants	396 women scheduled for treatment of CIN by LLETZ. All women attending for investigation of an abnormal smear were screened and women suitable for treatment at their first visit ('see and treat'). Most women were seen for initial colposcopic assessment with directed punch biopsies only and treatment at a later appointment if necessary. Women were excluded if treatment was deferred because of pregnancy, if they were currently taking a monoamine oxidase inhibitor or if they had to drive home from the clinic themselves Mean age at trial entry was 32.7 years (SD 9.8) and 31.5 (SD 9.1) in the isoflurane plus desflurane and placebo arms, respectively Deprivation score details were as follows: Class 1 (least deprived): 82 (82/395, 20.7%); Class 2: 72 (18.2%); Class 3: 53 (13.4%) ; Class 4: 37 (9.4%); Class 5: 36 (9.1%); Class 6: 16 (4.0%); Class 7: 46 (11.6%); not classified: 53 (13.4%) Parity details were as follows: no children: 158 (40.3%), 1 to 5 children: 234 (59.7%)
Interventions	The intervention was a mixture of isoflurane and desflurane gases (N = 195) versus placebo (air) (N = 194). Both gases were self-administered by the women using a demand valve regulator (Ohmeda) as is used for Entonox. The slight odour of the trial gas was masked by a small amount of peppermint oil smeared inside the facemask for trial and control gas administration. The women were instructed to use the gas before the procedure began and to continue to use the gas according to their own requirements. Exhaled gas was scavenged using standard equipment (Ohmeda). Infiltration of the cervix with prilocaine hydrochloride (30 mg/mL) and octapressin (0.54 mg/mL) was started approximately 2 minutes after the start of inhalation. 2 to 3 ampoules were used at the clinical discretion of the colposcopist depending on the size of the cervical lesion. A number of different colposcopists performed treatment and were evenly distributed between the 2 arms
Outcomes	Pain measured using VAS (0 to 100 where 100 was worst pain imaginable) Heavy vaginal bleeding Anxiety using HAD

Cruickshank 2005 (*Continued*)

	Various other outcomes not specified in our protocol
Notes	Women were followed up immediately after colposcopy and at 6 months after. We did not report 6 month data as recall bias was likely to be a problem "Took pain killer for stomach pain" - this outcome did not mention the time limit from procedure and so it was excluded from analysis (intervention group: 66/175; comparison group: 66/173) 9/175 and 7/173 women had difficulty returning to normal activity after colposcopy in intervention and placebo groups, respectively 14/175 and 15/173 women contacted on-call service with problem related to treatment in intervention and placebo groups, respectively These 2 outcomes were not included in forest plots since descriptions were vague and full details were not provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation: sequence generation	Low risk	"The random allocation of women to the cylinder code used computer-generated random numbers"
Allocation: sequence concealment	Low risk	"The random allocation of women ... used ... a series of opaque sequentially numbered envelopes"
Performance and detection: blinding All outcomes	Low risk	"The trial and clinic staff and trial participants were blinded to the contents of the cylinders, and peppermint oil was applied to the facemask prior to use"
Detection: blind outcome assessment All outcomes	Low risk	"The subject matter was tabulated by an assessor blinded to the randomisation of each individual"
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 348/395 (88%) for heavy vaginal bleeding outcome. Other outcomes assessed more than 88% of women in the trial
Reporting: unreported outcomes	High risk	Adverse events of gas were not reported
Other: anything else	Low risk	No additional form of bias was likely

Diakomanolis 1997

Methods	Randomised double-blind study Single centre
Participants	100 women were randomly allocated to 1 of 2 groups. All underwent laser excision of TZ for CIN. All women included in the study had abnormal Pap smears. Abnormal colposcopic findings, histologically confirmed CIN and were premenopausal. All women with history of coronary disease, epilepsy and chronic hypertension were excluded from the study Median age of patient in Group A (vasoconstrictor + lignocaine) 28 years (range 17 to 50) Median age of patient in Group B (lignocaine only) 28.5 years (range 19 to 51)
Interventions	Group A vasoconstrictor + lignocaine) consisted of 50 women who underwent laser excision using 30 mL of a 1:30 POR8 (vasoconstrictor) + lignocaine 1% solution The ectocervix was infiltrated with solution just before the start of procedure using a 30-gauge dental needle on a dental syringe to a depth of 3 to 4 cm Group B (lignocaine only) consisted of 50 women who underwent laser excision received 30 mL of lignocaine 1% solution without POR8 - vasoconstrictor
Outcomes	The intraoperative blood loss was measured with a glass blood measure (maximum volume 60 mL) (used in paediatric surgery) set in the suction apparatus Postoperative haemorrhage was measured with weighing the blood that soaked the pads Early haemorrhage was defined as bleeding occurring within 4 days of operation that requires intervention to stop bleeding. Late haemorrhage was after 4 days Pain relief was recorded as VRS (none, moderate and severe) postoperatively The operative time of each procedure was recorded. After the procedure, all women were contacted by telephone 1 week later
Notes	Other outcomes were not included in analysis like hypertension. Hypertension was seen in 7 women in Group A (vasoconstrictor + lignocaine) while in 2 women in Group B (lignocaine only) Note: the 30 mL of local anaesthetic with vasoconstrictor or local anaesthetic alone is considered a higher than average amount used to infiltrate cervix in pain relief for colposcopic management

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation: sequence generation	Unclear risk	Not reported
Allocation: sequence concealment	Low risk	"The randomization was performed as the central pharmacy of the hospital during the preparation and distribution of both medications used"
Performance and detection: blinding All outcomes	Low risk	"The surgeon was not aware of the medication that was used"

Diakomanolis 1997 (*Continued*)

Detection: blind outcome assessment All outcomes	Unclear risk	Not reported
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 100/100 (100%) analysed for all outcomes
Reporting: unreported outcomes	High risk	Pain was not analysed using VAS
Other: anything else	Unclear risk	An additional form of bias was unlikely

Duncan 2005

Methods	Double-blind randomised prospective placebo-controlled trial Single centre
Participants	Out of 100 women who met the criteria and approached 93 were enrolled in the study. The numbers of women studied were 46 in intervention arm and 47 in comparison arm. 100 consecutive women attending the colposcopy clinic and expected to undergo colposcopically directed biopsy and treatment with Semm coagulator were approached. 7 did not meet the eligibility criteria. Women with a history of allergy to local anaesthetic, who are unsuitable for treatment at first colposcopy examination, who had previous treatment to cervix or were pregnant were excluded Mean (SD) and/or median (and range) age at trial entry: intervention: N = 46, mean age = 31.3 years (SD 8.4); comparison: N = 47, mean age = 32.6 years (SD 8.0) Nullipara: intervention: 14 women (30.4%); comparison: 10 women (21.3%) Married/cohabiting: intervention: 20 women (43.5%); comparison: 22 women (46.8%) CIN (1/2/3/unspecified) details (number (%)): • intervention: HPV/CIN1 = 17/46 (37%), CIN2,3 = 29/46 (63%), microinvasion = 0/46 (0%) • comparison: HPV/CIN1 = 17/47 (36.2%), CIN2,3 = 29/47 (61.7%), microinvasion = 1/47 (2.1%)
Interventions	Externally identical numbered 5-mL vials of prilocaine 3% (30 mg/mL) with felypressin 0.03 IU/mL or normal saline were prepared in-house in pharmacy department along with randomised opaque sealed envelopes each containing number of vial. Colposcopic examinations were performed by 1 of the authors. Once treatment decision was taken vial was opened from sealed envelope and injected circumferentially in TZ of cervix. Volume was noted. Treatment was performed with SEMM coagulator
Outcomes	Pain was recorded on 11-point analogue scale where 0 was no pain at all and 10 indicated the worst pain imaginable. Each patient was asked to complete 4 such scales: expected and actual sensation for biopsy and treatment. Pain scores of 1 to 3 were classified as mild, 4 to 7 as moderate and 8 to 10 as severe
Notes	Details of anticipated pain was excluded from the analysis
Risk of bias	

Duncan 2005 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation: sequence generation	Unclear risk	Not reported
Allocation: sequence concealment	Low risk	"Externally identical, numbered vials of active medications or normal saline were prepared by the in house pharmacy department along with randomised opaque sealed envelopes, each containing the number of a vial. Pharmacy retained the key to the vial contents until the end of the trial"
Performance and detection: blinding All outcomes	Unclear risk	Labelled as double blind placebo controlled trial, but details are not documented in materials and methods section
Detection: blind outcome assessment All outcomes	Unclear risk	See above
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 92/93 (99%) of the women were analysed for pain related to treatment. Data from 1 patient were missing in the active drug group
Reporting: unreported outcomes	High risk	Adverse event were not reported
Other: anything else	Low risk	An additional form of bias was unlikely

Frega 1994

Methods	Randomised study
Participants	63 women affected by CIN of various degrees were randomly divided into 3 groups in order to evaluate the pain experienced during laser vaporisation of the lesion. All women were premenopausal and ages ranged between 19 and 39 years. Each group consisted of 21 women
Interventions	The first group received naproxen sodium 550 mg 30 minutes before treatment; the second group received placebo 30 minutes before treatment and the third no drug (21 women in each group)
Outcomes	At the end of the procedure, the severity of pain was assessed using 0- to 100-mm VAS
Notes	Mean and SD for each group was calculated from figure 1 on page 189 of the publication, using GraphPad Prism software package, where the graphs were enlarged allowing an accurate estimate of each individuals pain score Since the trial included 3 arms, the shared intervention group was divided out approximately evenly among the comparisons. Hence for pain outcome on VAS, the total num-

Frega 1994 (*Continued*)

	ber of women in the drug group was divided up into 2 (the total number of 21 in the group was halved and rounded up to 11) and the means and SDs were left unchanged (see Higgins 2011, chapter 16.5.4)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation: sequence generation	Unclear risk	Not reported
Allocation: sequence concealment	Unclear risk	Not reported
Performance and detection: blinding All outcomes	Unclear risk	Not reported
Detection: blind outcome assessment All outcomes	Unclear risk	Not reported
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 63/63 (100%) analysed for all outcomes
Reporting: unreported outcomes	High risk	Median rather than mean used for pain and adverse events were not reported
Other: anything else	Unclear risk	Insufficient information to permit judgement

Howells 2000

Methods	Prospective RCT Setting: colposcopy clinic
Participants	200 consecutive women referred by general practitioners with abnormal cervical cytology (N = 180) or clinically suspicious abnormality (n = 20) were enrolled Inclusion criteria for the study were: women aged 20 and 60 years; who had received no previous treatment to the cervix who require treatment Mean age (SD) (prilocaine plus felypressin vs. lignocaine plus adrenaline): 94 women; 36.6 years (10.3) vs. 106 women; 34.6 years (9.7) Menopausal status (prilocaine plus felypressin vs. lignocaine plus adrenaline): premenopausal: 81 (86%) vs. 96 (91%); postmenopausal: 12 (13%) vs. 9 (8%); missing data: 1 (1%) vs. 1 (1%) Contraception (prilocaine plus felypressin vs. lignocaine plus adrenaline): no: 37 (39%) vs. 44 (42%); yes: 61 (65%) vs. 76 (72%); missing data: 0 vs. 1 (1%) Smear grade (prilocaine plus felypressin vs. lignocaine plus adrenaline): • low grade/negative: 35 (37%) vs. 49 (46%) • high grade: 53 (57%) vs. 51 (48%) • other grades: 5 (5%) vs. 4 (4%) Nullipara (prilocaine plus felypressin vs. lignocaine plus adrenaline): 17 (18%) vs. 24 (23%)

	Colposcopic findings (prilocaine plus felypressin vs. lignocaine plus adrenaline): normal: 13 (14%) vs. 15 (14%); low grade: 25 (27%) vs. 29 (27%); high grade: 49 (52%) vs. 53 (50%); uncertain: 5 (5%) vs. 7 (7%); ? invasion: 1 (1%) vs. 1 (1%); missing data: 1 (1%) vs. 1 (1%) Final histology (prilocaine plus felypressin vs. lignocaine plus adrenaline): normal: 4 (4%) vs. 8 (8%); low grade: 36 (38%) vs. 31 (29%); high grade: 51 (55%) vs. 63 (59%) ; others: 3 (3%) vs. 2 (2%); missing data: 0 vs. 2 (2%) Final histology was negative for (prilocaine plus felypressin vs. lignocaine plus adrenaline) : 4/94 (4%) vs. 8/106 (8%); exclusion from analysis not possible so included in analysis Local anaesthetic volume (mL) (prilocaine plus felypressin vs. lignocaine plus adrenaline) : 5.02 mL vs. 4.83 mL Loop passes (prilocaine plus felypressin vs. lignocaine plus adrenaline): 1 pass: 71 (76%) vs. 80 (75%); 2 passes: 19 (20%) vs. 18 (17%); 3 passes: 2 (%) vs. 4 (4%) Loop size (prilocaine plus felypressin vs. lignocaine plus adrenaline): small: 10 (11%) vs. 14 (13%); medium: 80 (85%) vs. 87 (82%); large: 3 (3%) vs. 1 (1%); Missing data (prilocaine plus felypressin vs. lignocaine plus adrenaline): 1 (1%) vs. 4 (4%)
Interventions	Intervention group (N = 94) received prilocaine 3% (30 mg/mL) with felypressin 0.03 IU/mL. Comparison group (N = 106) received lignocaine 2% with adrenaline 1:80,000 (xylocaine)
Outcomes	The duration of the treatment was calculated from the start of the loop excision to the end of ball diathermy used to achieve haemostasis The colposcopist scored his or her perception of the discomfort experienced by the women in a scale of ordered categories (0 = 'none'; 4 = 'severe') and also the degree of bleeding caused by the procedure (0 = 'none'; 5 = 'heavy') Following treatment, the women answered a questionnaire on their perception of pain during the administration of the local anaesthetic and during their treatment in a scale of ordered categories (0 = 'none'; 5 = 'unbearable') Other side effects, such as feeling faint, nausea and shaking, were also scored in a similar fashion (0 = 'none'; 5 = 'a great deal'). The scores were then added to derive an overall score
Notes	Missing data (prilocaine plus felypressin vs. lignocaine plus adrenaline): 1 (1%)vs. 2 (2%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation: sequence generation	Unclear risk	"The women were randomised by an independent observer using simple randomisation"
Allocation: sequence concealment	Low risk	"The women were randomised ... using simple randomisation with opaque sealed envelopes"

Howells 2000 (*Continued*)

Performance and detection: blinding All outcomes	High risk	"The colposcopists were aware of the identity of the local anaesthetic solutions"
Detection: blind outcome assessment All outcomes	Unclear risk	Not reported
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 200/200 (100%)
Reporting: unreported outcomes	High risk	Important outcomes were reported by the trial authors but these could have been reported using more appropriate methods (e.g. continuous data for pain and blood loss, rather than using logistic regression for non-parametric data)
Other: anything else	Low risk	No additional form of bias was likely

Johnson 1989

Methods	Prospective double-blind randomised placebo-controlled clinical trial
Participants	70 women with a new colposcopic and histological diagnosis of a cervical dysplastic lesion suitable for laser ablation. The following prospective exclusion criteria were used: previous cervical surgery, more than 1 colposcopic examination, menopausal or perimenopausal status, sensitivity to lignocaine, patient refusing paracervical injection or refusing to be recruited into the trial, or vaginal involvement of the lesion
Interventions	Women were randomised to receive either lignocaine 2% or normal saline from a numbered vial. A bilateral paracervical block was delivered by injecting 10 mL into the paracervical tissues
Outcomes	At the end of the procedure and after a further explanation, the women scored their pain on a 120-mm visual linear analogue scale. Pain was also objectively scored by the attending nurse who assessed the woman's level of vocalisation (2 = moan/cry; 1 = gasp; 0 = no vocalisation), muscle tension of the upper limbs (2 = the clenching the bed etc.; 1 = making a fist; 0 = relaxed), thigh movements (2 = adduction; 1 = twitchy; 0 = relaxed) . The laser operator independently scored movements of the thigh as well as perineal movement (2 = bottom movement up the bed; 1 = speculum twitches; 0 = no movement/ relaxed). The size of the TZ and blood loss were recorded. Anxiety and depression HAD scores and premenstrual syndrome scores were also recorded
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Johnson 1989 (*Continued*)

Allocation: sequence generation	Low risk	"Consenting patients were then randomised to receive either 2% lignocaine or normal saline from a numbered vial. Each vial could only be identified at the end of the study by its number which was allocated prospectively according to a block randomised code"
Allocation: sequence concealment	Low risk	"Each vial could only be identified at the end of the study by its number which was allocated prospectively"
Performance and detection: blinding All outcomes	Low risk	Trial was labelled as a placebo-controlled double-blind trial. "Laser ablation of the entire transformation zone to a depth of approximately 7 mm was performed with a continuous fine beam (spot size 1.5 mm) 35-W CO, laser by a separate surgeon in a second suite"
Detection: blind outcome assessment All outcomes	Low risk	"Pain was objectively scored by the attending nurse who assessed the woman's level of vocalization ... muscle tension of the upper limbs, thigh movements ... The laser operator independently scored movements of the thigh as well as perineal movement"
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 70/70 (100%)
Reporting: unreported outcomes	High risk	Adverse events of paracervical injections were not reported and pain was inadequately reported
Other: anything else	Low risk	No additional form of bias was likely

Johnson 1996

Methods	Double-blind randomised clinical trial Colposcopic clinic specifically adapted to run clinical trials
Participants	44 (23 in intervention group and 21 in comparison group) women were recruited from a laser colposcopy clinic. They were referred following abnormal smear and underwent colposcopic examination and biopsy before being recruited. No participant refused entry in the trial but the trial was terminated prematurely when the laser surgeon realised that he could identify women given direct infiltration by looking for the injection mark. Following exclusion criteria were applied: past cervical surgery, past cervical atypia, vaginal involvement with lesion, the menopause, reluctance to take part in trial

Johnson 1996 (*Continued*)

Interventions	This study compared site of injection of the pain relief. Intervention group received 10 mL of paracervical lignocaine 2% while the comparison group received 2 mL of lignocaine 2% directly into the TZ
Outcomes	Pain was scored on VAS at the end of the procedure by the patients. Pain was objectively scored by the attending nurse and the laser operator independently
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation: sequence generation	Low risk	"Consenting women were block randomised to receive either 10ml of paracervical 2% lignocaine or 2ml of 2% lignocaine injected directly into the transformation zone"
Allocation: sequence concealment	Low risk	"Neither nurses, clerical officers responsible for appointments, nor the laser surgeon had access to this code. The worker responsible for randomisation obtained consent, drew the allocation code from a box"
Performance and detection: blinding All outcomes	Low risk	"The worker responsible for randomisation ... gave the local anaesthetic in a room separate from the laser suite"
Detection: blind outcome assessment All outcomes	Low risk	"Pain was objectively scored by the attending nurse who assessed the woman's level of vocalization ... muscle tension of the upper limbs and thigh movements. The laser operator independently scored movements of the thigh as well as perineal movement"
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 44/44 (100%)
Reporting: unreported outcomes	High risk	Adverse events of paracervical injections were not reported and pain was inadequately reported
Other: anything else	Unclear risk	No woman refused entry to the trial, but the study was terminated prematurely when the laser surgeon realised that he could identify women given direct infiltration by looking for the injection marks. Up to this point, the study was a true double-

Johnson 1996 (*Continued*)

		blind, randomised trial. This is not necessarily a source of bias but we were unsure whether any additional source of bias may have been present

Lee 1986

Methods	RCT
Participants	50 women undergoing laser vaporisation of cervix for CIN were recruited to 1 of the 2 groups. All women were premenopausal and aged 19 to 39 years
Interventions	In the intervention group (N = 25), the ectocervix was infiltrated with 2 mL prilocaine 3% with felypressin 0.03 IU/mL immediately before the procedure, while in the comparison group (N = 25) women received no analgesia or anaesthesia. Using a 30-gauge dental needle on a dental syringe, Infiltration around the periphery of the TZ was performed immediately before the procedure. Local anaesthetic was employed in the control group only when significant pain was experienced
Outcomes	The severity of the pain was assessed at the end of the procedure using VAS and VRS. The VAS consisted of a 100-mm line drawn on plain paper representing pain ranging from 'no pain at all' to 'pain as much as you can imagine'. Patients marked a point on the line at the end of the procedure which they felt corresponded to the pain they experienced. The VRS consisted of a choice of 4 descriptions, none, mild, moderate or severe. Blood loss during the procedure was recorded as none, slight, moderate and troublesome
Notes	Other outcome measures included pain while receiving the injection and the level of anxiety before the procedure was measured before the patient undressed using the Spielberger state anxiety inventory. Side effects such as sweating, nausea, dizziness and cramps were also reported. This was not included in the analysis Mean and SD for each group was calculated from figure 1 on page 968 of the publication, using GraphPad Prism software package, where the graph was enlarged allowing an accurate estimate of each individuals pain score

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation: sequence generation	Unclear risk	Not reported
Allocation: sequence concealment	Unclear risk	Not reported
Performance and detection: blinding All outcomes	Unclear risk	Not reported
Detection: blind outcome assessment All outcomes	Unclear risk	Not reported

Lee 1986 (*Continued*)

Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 50/50 (100%)
Reporting: unreported outcomes	Low risk	Pertinent outcomes were reported in the trial
Other: anything else	Unclear risk	No additional form of bias was likely

Lipscomb 1995

Methods	Prospective double-blind RCT
Participants	50 women scheduled for the loop excision for treatment of cervical dysplasia were asked to participate in the study. All agreed to take part. Age and parity was comparable in both groups Age: mean (SD) (intervention vs. comparison): 29.5 years (10.5) vs. 28.4 years (8.9) Parity: mean (SD) (intervention vs. comparison): 2.1 (2.1) vs. 2.3 (1.6) Loop passes: mean (SD) (intervention vs. comparison): 1.2 (0.4) vs. 1.3 (0.6) Positive margins: mean (SD) (intervention vs. comparison): 2/25 vs. 3/25
Interventions	In the intervention arm, 25 women received cervical application of benzocaine 20% gel and in comparison arm women received a placebo gel before the procedure. In addition, all women also received preprocedural oral analgesia ketorolac tromethamine 10 mg orally 30 minutes before procedure. After 1 minute of gel application, 1 mL of lignocaine 1% with adrenaline 1:100,000 was injected in 1 mL doses into the cervical stroma at the 12, 3, 6 and 9 o'clock positions (total 4 mL) with 25-gauge needle on a needle extender
Outcomes	Immediately after the procedure the women were asked to rate on a standard VAS the pain from injection as well as pain from loop excision procedure. The scale consisted of 10-cm horizontal line with vertical cross bars at each endpoint. The endpoints were labelled 'no pain' and 'worst pain possible'
Notes	Other outcomes such as number of passes of the loop or details of margins of the loop were not included for the analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation: sequence generation	Low risk	"By use of computer-generated numbers, patients were randomized to one of two groups"
Allocation: sequence concealment	Unclear risk	Not reported
Performance and detection: blinding All outcomes	Low risk	"Both patient and physician were unaware which gel the syringe contained"

Lipscomb 1995 (*Continued*)

Detection: blind outcome assessment All outcomes	Unclear risk	Not reported
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 50/50 (100%)
Reporting: unreported outcomes	Unclear risk	Adverse events of gel were not reported
Other: anything else	Low risk	No additional form of bias was likely

Mikhail 1988

Methods	A randomised prospective double-blind placebo controlled trial
Participants	50 women undergoing laser vaporisation of the cervix for CIN were allocated to 1 of the 2 groups. There were 25 women in each group. Characteristics of the 2 groups were recorded Age: mean (SD) (intervention vs. comparison): 27.4 years (3.9) vs. 26.7 years (4.57) Parity: mean (SD): (intervention vs. comparison): 0.9 (1.24) vs. 1 (1)
Interventions	In the intervention group (N = 25) the cervix was sprayed with 3-4 mL of a cocaine 10% solution preserved in nipasept (a mixture of the methyl, ethyl and propyl esters of *p*-hydroxybenzoic acid). The comparison group (N = 25) was sprayed with a similar quantity of the preservative alone. There was no indication on the spray to identify the solution. When necessary, additional pain relief was given by the local infiltration of prilocaine by hypodermic injection. 1 to 2 mL of the solution were sprayed on the cervix and repeated as necessary through the procedure
Outcomes	The time taken to complete the treatment and assessment of the blood loss were noted. The severity of the pain experienced was assessed at the end of the procedure using standard 10-mm VAS (Huskisson 1983) and VRS. The VRS consisted of 4 categories - none, mild, moderate or severe. Blood loss was assessed subjectively by the operator as minimal, moderate and severe
Notes	Mean and SD for each group was calculated from figure 1 on page 471 of the publication, using GraphPad Prism software package, where the graph was enlarged allowing an accurate estimate of each individuals pain score

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation: sequence generation	Low risk	"The patients were allocated to their groups by a computer-generated random list"
Allocation: sequence concealment	Unclear risk	Not reported

Mikhail 1988 (*Continued*)

Performance and detection: blinding All outcomes	Low risk	"There was no indication on the spray to identify the solution ... The randomized and double-blind nature of the trial eliminated observer bias"
Detection: blind outcome assessment All outcomes	Unclear risk	Not reported
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 50/50 (100%)
Reporting: unreported outcomes	Low risk	There reason to suspect outcomes were selectively reported
Other: anything else	Low risk	No additional form of bias was likely

Rogstad 1992

Methods	Randomised placebo-controlled double-blind trial
Participants	60 women who were scheduled to undergo cold coagulation for cervical abnormalities
Interventions	21 received lignocaine (intervention) and 31 received normal saline (comparison). Cervix was infiltrated with 2 mL of lignocaine 2% or 2 mL of normal saline before cold coagulation
Outcomes	The degree of pain felt was measured by VRS and VAS
Notes	Other outcomes like pain of injection and 3 to 6 weeks' follow-up questionnaire of pain and bleeding were excluded from the analysis Mean and SD for each group was calculated from figure on page 942 of the publication, using GraphPad Prism software package, where the graph was enlarged allowing an accurate estimate of each individuals pain score

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation: sequence generation	Low risk	"The trial was randomised, placebo controlled and double-blind. Randomisation was by computerised generation of random numbers"
Allocation: sequence concealment	Unclear risk	Not reported
Performance and detection: blinding All outcomes	Unclear risk	Labelled as double-blind placebo-controlled trial, but details are not documented in paper

Rogstad 1992 (*Continued*)

Detection: blind outcome assessment All outcomes	Unclear risk	Not reported
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 60/60 (100%) for pain outcome
Reporting: unreported outcomes	High risk	Adverse events were not reported
Other: anything else	Unclear risk	Insufficient information to permit judgement

Sammarco 1993

Methods	A prospective RCT
Participants	Each patient was evaluated by colposcopy with biopsy and had a histological diagnosis of cervical dysplasia. They were scheduled to undergo cryosurgery. Cryosurgery was carried out with liquid nitrogen using Cryo-2000 (Valleylab, Boulder, Colorado) by double freeze technique with a 3-minute freeze and 5-minutes thaw cycle. Nulliparous women, those under 16 years of age and those with allergies were excluded. Women with no endocervical disease and lesions of less than 3 cm were eligible
Interventions	Both control and intervention group received a single dose of ketoprofen 75 mg (a non-steroidal anti-inflammatory drug) within 1 hour of procedure, 2 women received naproxen sodium 550 mg. The control group received no further analgesia. The intervention women received an injection of 2 to 3 mL of lignocaine with a 1:100,000 dilution of adrenaline, which was administered submucosally at the 2 and 10 o'clock positions with 25-gauge needle 1 minute prior to the cryosurgery
Outcomes	A VAS with 0 representing no pain and 10 representing severe pain, was used to evaluate the amount of pain experienced by the patient
Notes	Mean VAS score recorded by nurses was not included in analysis owing to high risk of bias

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation: sequence generation	Unclear risk	Not reported
Allocation: sequence concealment	Unclear risk	Not reported
Performance and detection: blinding All outcomes	High risk	"The study was limited since neither the nurse nor the patient was blinded"

Sammarco 1993 (*Continued*)

Detection: blind outcome assessment All outcomes	Unclear risk	Not reported
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 45/49 (92%) for pain outcomes
Reporting: unreported outcomes	Unclear risk	Adverse events were not reported
Other: anything else	High risk	Nulliparous women were excluded from the study. Women with no endocervical disease and lesions of less than 3 cm were eligible "Four of the original 49 study patients were excluded from the final data analysis since they recorded a higher pain score prior to the procedure than after the procedure and therefore recorded a negative pain score for unexplained reasons. This included 2 patients in the control group and 2 patients in the study group"

Sarkar 1993

Methods	Prospective, random allocation, double-blind, placebo-controlled trial
Participants	Women were undergoing laser treatment for CIN in the colposcopy and laser clinic. 35 women were allocated to receive EMLA cream (intervention group) and 35 to receive placebo cream (comparison group). The following exclusion criteria were used: known or suspected hypersensitivity to local anaesthetics of amide type, concomitant treatment with analgesic medication, inability to complete assessment forms and patient's refusal to be recruited into the trial Age: mean (SD) (intervention vs. comparison): 27.8 years (6.3) vs. 28 years (5.4)
Interventions	The EMLA and placebo creams were supplied in visually identical metal tubes that were identified by patient number. 10 minutes before the start of the laser treatment, 10 mL of cream was applied to the cervix and surrounding area
Outcomes	The severity of the pain experienced during the treatment was assessed at the end of the treatment, using McGill's pain questionnaire (Melzack 1975), and the VAS (Huskisson 1983). Blood loss during the procedure was reported as none, mild, moderate and troublesome
Notes	Minor adverse experiences during treatment such as feeling hot, sweating, dizziness, fainting and sickness were not included in analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation: sequence generation	Unclear risk	Not reported
Allocation: sequence concealment	Unclear risk	Not reported

Sarkar 1993 (*Continued*)

Performance and detection: blinding All outcomes	Low risk	"The EMLA and the placebo cream were supplied in visually identical metal tubes which were identified by patient number"
Detection: blind outcome assessment All outcomes	Unclear risk	Not reported
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 68/70 (97%) for pattern of pain outcome
Reporting: unreported outcomes	Low risk	Pertinent outcomes were reported in the trial
Other: anything else	High risk	"When expressing the 'present pain intensity', some patients indicated a score between categories, so extra categories were created, such as 1-5, 2.5 etc". Such analyses are therefore dubious. Furthermore, "When patients were asked to describe their present pain by choosing specific words from McGill's pain questionnaire (Melzack, 1975), the EMLA treated group tended to select words from fewer categories. The average number of words selected by the EMLA group was 3.83, compared with 5. 06 for the placebo group ($P < 0.05$)". This probably applies to an average ordinal score rating rather than average number of words chosen, but this was unclear

Winters 2009

Methods	RCT Setting: colposcopy clinic
Participants	60 women scheduled to have LLETZ carried out for CIN were recruited to have the anaesthetic injection in the cervix before procedure by 2 different techniques Referral smear (intervention vs. control): mild: 8/32 vs. 5/32; moderate: 12/32 vs. 10/32; severe: 8/32 vs. 7/32; borderline: 2/32 vs. 3/32; inadequate: 2/32 vs. 0/32; glandular abnormality: 0/32 vs. 1/32 LLETZ histology: CIN 1: 5/32 vs. 1/32; CIN 2: 7/32 vs. 7/32; CIN 3: 15/32 vs. 17/32; inflammation: 3/32 vs. 0/32; CGIN: 2/32 vs. 0/32; adenocarcinoma: 0/32 vs. 1/32 Margins: both negative: 24/32 (75%) vs. 17/32 (65%); positive endocervical margin: 0/32 vs. 2/32; positive ectocervical margin: 5/32 vs. 6/32 Both positive: 1/32 vs. 0/32 Uncertain: 2/32 vs. 1/32

Interventions	Both groups received a total of 8.8 mL (4 ampoules) of prilocaine 3% with felypressin (Citanest, AstraZeneca, UK). The control group received four 2.2 mL ampoules of prilocaine with felypressin injected deep into the cervical stroma at 8 equally spaced points around the circumference of the cervical TZ, using a 35-mm 27-gauge dental needle. In the intervention group the injection technique differed in that one 2.2 mL ampoule of prilocaine with felypressin was injected just under the epithelium, in 4 areas circumferentially, in order to raise a blanch. Then three 2.2 mL ampoules were injected in 8 places circumferentially deep into the cervical stroma
Outcomes	Following completion of treatment, women were asked to indicate on separate 100-mm VAS the pain they experienced during administration of local anaesthetic and then during the actual LLETZ procedure
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation: sequence generation	Low risk	"The block randomisation code was computer generated"
Allocation: sequence concealment	Low risk	"Randomisation was performed by opening sequentially numbered, sealed envelopes in order of recruitment"
Performance and detection: blinding All outcomes	High risk	"Participants were blinded to the technique of administration of local anaesthetic, by necessity the colposcopist could not be blinded to this"
Detection: blind outcome assessment All outcomes	Unclear risk	Not reported
Attrition: incomplete outcome data All outcomes	Low risk	% analysed: 58/60 (%)
Reporting: unreported outcomes	High risk	Adverse events of injections were not reported
Other: anything else	Low risk	No additional form of bias was likely

CGIN: cervical glandular intraepithelial neoplasia; CIN: cervical intraepithelial neoplasia; HAD: Hospital Anxiety and Depression scale; HPV: human papillomavirus; LLETZ: large loop excision of the transformation zone; RCT: randomised controlled trial; SD: standard deviation; TENS: transcutaneous electric nerve stimulation; TZ: transformation zone; VAS: visual analogue scale; VRS: verbal rating score.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Sarkar 1990	Not an RCT
Sharp 2009	Pain relief interventions were not part of trial scope

RCT: randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Local anaesthetic (lignocaine 2%) injection versus control (saline injection)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain scores during procedure (VAS)	2	130	Mean Difference (IV, Random, 95% CI)	-13.74 [-34.32, 6.83]
1.1 Paracervical block versus placebo	1	70	Mean Difference (IV, Random, 95% CI)	-3.0 [-16.03, 10.03]
1.2 Direct cervical infiltration versus placebo	1	60	Mean Difference (IV, Random, 95% CI)	-24.0 [-35.44, -12.56]
2 Moderate to severe pain	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 2. Local anaesthetic plus vasoconstrictor versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain scores during procedure (VAS: 0-100)	2	95	Mean Difference (IV, Random, 95% CI)	-23.73 [-37.53, -9.93]
1.1 Lignocaine plus adrenaline	1	45	Mean Difference (IV, Random, 95% CI)	-31.10 [-43.74, -18.46]
1.2 Prilocaine plus felypressin	1	50	Mean Difference (IV, Random, 95% CI)	-17.0 [-28.19, -5.81]
2 Moderate or severe pain	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.1 versus placebo	1	92	Risk Ratio (IV, Random, 95% CI)	0.12 [0.04, 0.37]
2.2 versus no treatment	1	50	Risk Ratio (IV, Random, 95% CI)	0.73 [0.42, 1.27]
3 Troublesome bleeding	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 3. Local anaesthetic plus vasoconstrictor versus local anaesthetic injection alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Moderate or severe pain	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2 Blood loss (volume)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3 Duration of treatment	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 4. Prilocaine plus felypressin versus lignocaine plus adrenaline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (using 6 category scale)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2 Blood loss (0-5 scale)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 5. Deep plus superficial versus deep cervical injection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain scores during procedure (VAS: 0-100)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 6. Oral analgesic versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain scores (VAS: 0-100)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 versus placebo	2	129	Mean Difference (IV, Random, 95% CI)	-3.51 [-10.03, 3.01]
1.2 versus no treatment	1	32	Mean Difference (IV, Random, 95% CI)	-4.0 [-13.69, 5.69]
2 Moderate to severe pain	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3 Pain relief required in first 24 hours	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 7. Inhalation analgesia versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain scores (VAS: 0-100)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2 Heavy vaginal bleeding	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3 Anxiety - HAD score	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 8. Topical application versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain scores during procedure (VAS: 0-100)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2 Duration of treatment	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 9. Cocaine spray versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain scores during procedure (VAS: 0-100)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2 Moderate to severe pain	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3 Troublesome bleeding	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 10. TENS versus TENS plus local anaesthetic injection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Troublesome blood loss	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 11. TENS versus local anaesthetic injection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Troublesome blood loss	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Comparison 12. TENS plus local versus local anaesthetic injection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Troublesome blood loss	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Local anaesthetic (lignocaine 2%) injection versus control (saline injection), Outcome 1 Pain scores during procedure (VAS).

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 1 Local anaesthetic (lignocaine 2%) injection versus control (saline injection)

Outcome: 1 Pain scores during procedure (VAS)

Study or subgroup	Local anaesthetic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Paracervical block versus placebo							
Johnson 1989	35	27 (30.6)	35	30 (24.7)		48.9 %	-3.00 [-16.03, 10.03]
Subtotal (95% CI)	**35**		**35**			**48.9 %**	**-3.00 [-16.03, 10.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.45 (P = 0.65)							
2 Direct cervical infiltration versus placebo							
Rogstad 1992	29	29 (22.1)	31	53 (23.1)		51.1 %	-24.00 [-35.44, -12.56]
Subtotal (95% CI)	**29**		**31**			**51.1 %**	**-24.00 [-35.44, -12.56]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.11 (P = 0.000039)							
Total (95% CI)	**64**		**66**			**100.0 %**	**-13.74 [-34.32, 6.83]**
Heterogeneity: Tau^2 = 181.38; Chi^2 = 5.64, df = 1 (P = 0.02); I^2 =82%							
Test for overall effect: Z = 1.31 (P = 0.19)							
Test for subgroup differences: Chi^2 = 5.64, df = 1 (P = 0.02), I^2 =82%							

Analysis 1.2. Comparison 1 Local anaesthetic (lignocaine 2%) injection versus control (saline injection), Outcome 2 Moderate to severe pain.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 1 Local anaesthetic (lignocaine 2%) injection versus control (saline injection)

Outcome: 2 Moderate to severe pain

Study or subgroup	Local anaesthetic n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Rogstad 1992	7/29	21/31		0.36 [0.18, 0.71]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 7 (Local anaesthetic), 21 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

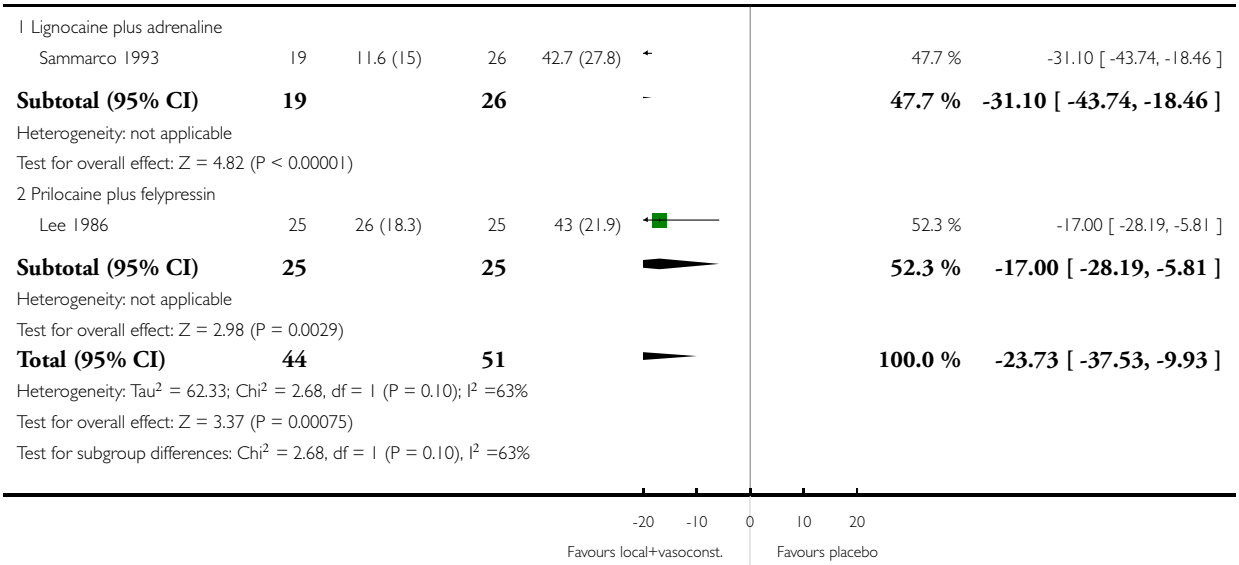
Analysis 2.1. Comparison 2 Local anaesthetic plus vasoconstrictor versus control, Outcome 1 Pain scores during procedure (VAS: 0-100).

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 2 Local anaesthetic plus vasoconstrictor versus control

Outcome: 1 Pain scores during procedure (VAS: 0-100)

Study or subgroup	Local + vasocon-strictor N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Lignocaine plus adrenaline							
Sammarco 1993	19	11.6 (15)	26	42.7 (27.8)		47.7 %	-31.10 [-43.74, -18.46]
Subtotal (95% CI)	**19**		**26**			**47.7 %**	**-31.10 [-43.74, -18.46]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.82 (P < 0.00001)							
2 Prilocaine plus felypressin							
Lee 1986	25	26 (18.3)	25	43 (21.9)		52.3 %	-17.00 [-28.19, -5.81]
Subtotal (95% CI)	**25**		**25**			**52.3 %**	**-17.00 [-28.19, -5.81]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.98 (P = 0.0029)							
Total (95% CI)	**44**		**51**			**100.0 %**	**-23.73 [-37.53, -9.93]**
Heterogeneity: Tau^2 = 62.33; Chi^2 = 2.68, df = 1 (P = 0.10); I^2 =63%							
Test for overall effect: Z = 3.37 (P = 0.00075)							
Test for subgroup differences: Chi^2 = 2.68, df = 1 (P = 0.10), I^2 =63%							



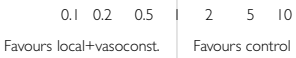
Analysis 2.2. Comparison 2 Local anaesthetic plus vasoconstrictor versus control, Outcome 2 Moderate or severe pain.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 2 Local anaesthetic plus vasoconstrictor versus control

Outcome: 2 Moderate or severe pain

Study or subgroup	Local + vasocon-strictor n/N	Control n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 versus placebo					
Duncan 2005	3/45	26/47		100.0 %	0.12 [0.04, 0.37]
Subtotal (95% CI)	**45**	**47**		**100.0 %**	**0.12 [0.04, 0.37]**
Total events: 3 (Local + vasoconstrictor), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.69 (P = 0.00022)					
2 versus no treatment					
Lee 1986	11/25	15/25		100.0 %	0.73 [0.42, 1.27]
Subtotal (95% CI)	**25**	**25**		**100.0 %**	**0.73 [0.42, 1.27]**
Total events: 11 (Local + vasoconstrictor), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.11 (P = 0.27)					
Test for subgroup differences: Chi^2 = 8.03, df = 1 (P = 0.00), I^2 =88%					



Analysis 2.3. Comparison 2 Local anaesthetic plus vasoconstrictor versus control, Outcome 3 Troublesome bleeding.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 2 Local anaesthetic plus vasoconstrictor versus control

Outcome: 3 Troublesome bleeding

Study or subgroup	Local + vasocon-strictor n/N	Control n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Lee 1986	2/25	5/25		0.40 [0.09, 1.87]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 2 (Local + vasoconstrictor), 5 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

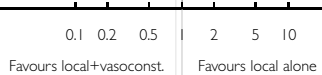
Analysis 3.1. Comparison 3 Local anaesthetic plus vasoconstrictor versus local anaesthetic injection alone, Outcome 1 Moderate or severe pain.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 3 Local anaesthetic plus vasoconstrictor versus local anaesthetic injection alone

Outcome: 1 Moderate or severe pain

Study or subgroup	Local +vasocon-strictor n/N	Local alone n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Diakomanolis 1997	12/50	10/50		1.20 [0.57, 2.52]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 12 (Local +vasoconstrictor), 10 (Local alone)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				



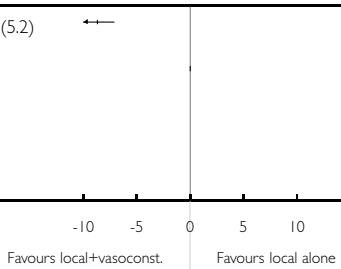
Analysis 3.2. Comparison 3 Local anaesthetic plus vasoconstrictor versus local anaesthetic injection alone, Outcome 2 Blood loss (volume).

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 3 Local anaesthetic plus vasoconstrictor versus local anaesthetic injection alone

Outcome: 2 Blood loss (volume)

Study or subgroup	Local + vasocon-strictor		Local alone		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
Diakomanolis 1997	50	30.25 (3.1)	50	39 (5.2)		-8.75 [-10.43, -7.07]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Analysis 3.3. Comparison 3 Local anaesthetic plus vasoconstrictor versus local anaesthetic injection alone, Outcome 3 Duration of treatment.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 3 Local anaesthetic plus vasoconstrictor versus local anaesthetic injection alone

Outcome: 3 Duration of treatment

Study or subgroup	Local + vasocon-strictor N	Mean(SD)	Local alone N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Diakomanolis 1997	50	17.53 (1.2)	50	25.25 (2.5)		-7.72 [-8.49, -6.95]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Test for subgroup differences: Not applicable						

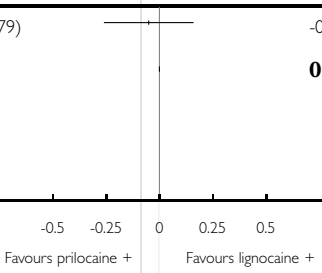
Analysis 4.1. Comparison 4 Prilocaine plus felypressin versus lignocaine plus adrenaline, Outcome 1 Pain (using 6 category scale).

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 4 Prilocaine plus felypressin versus lignocaine plus adrenaline

Outcome: 1 Pain (using 6 category scale)

Study or subgroup	Prilocaine + group N	Mean(SD)	Lignocaine + group N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Howells 2000	94	0.45 (0.73)	106	0.5 (0.79)		-0.05 [-0.26, 0.16]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Analysis 4.2. Comparison 4 Prilocaine plus felypressin versus lignocaine plus adrenaline, Outcome 2 Blood loss (0-5 scale).

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 4 Prilocaine plus felypressin versus lignocaine plus adrenaline

Outcome: 2 Blood loss (0-5 scale)

Study or subgroup	Prilocaine + group N	Mean(SD)	Lignocaine + group N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Howells 2000	94	1.74 (0.98)	106	1.33 (1.05)		0.41 [0.13, 0.69]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Test for subgroup differences: Not applicable						

Analysis 5.1. Comparison 5 Deep plus superficial versus deep cervical injection, Outcome 1 Pain scores during procedure (VAS: 0-100).

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 5 Deep plus superficial versus deep cervical injection

Outcome: 1 Pain scores during procedure (VAS: 0-100)

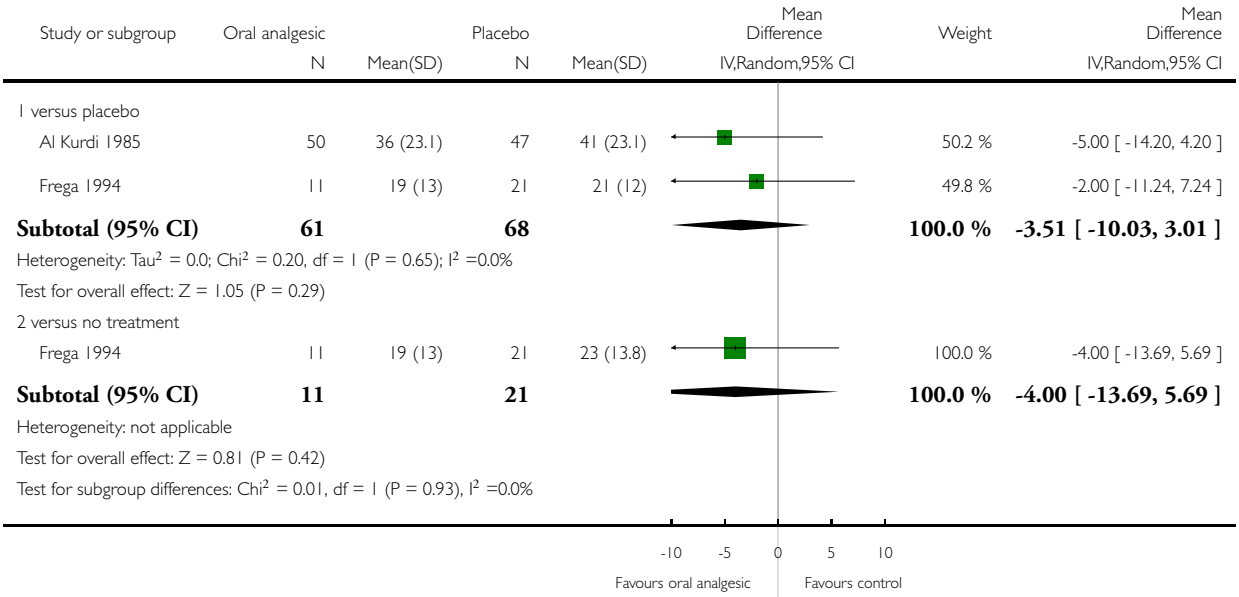
Study or subgroup	Deep + superficial N	Mean(SD)	Deep cervical N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Winters 2009	32	7.7 (9.1)	26	12.6 (15.1)		-4.90 [-11.51, 1.71]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Test for subgroup differences: Not applicable						

Analysis 6.1. Comparison 6 Oral analgesic versus control, Outcome 1 Pain scores (VAS: 0-100).

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 6 Oral analgesic versus control

Outcome: 1 Pain scores (VAS: 0-100)



Analysis 6.2. Comparison 6 Oral analgesic versus control, Outcome 2 Moderate to severe pain.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 6 Oral analgesic versus control

Outcome: 2 Moderate to severe pain

Study or subgroup	Oral analgesic n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Al Kurdi 1985	28/50	32/47		0.82 [0.60, 1.13]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 28 (Oral analgesic), 32 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

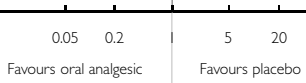
Analysis 6.3. Comparison 6 Oral analgesic versus control, Outcome 3 Pain relief required in first 24 hours.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 6 Oral analgesic versus control

Outcome: 3 Pain relief required in first 24 hours

Study or subgroup	Oral analgesic n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Al Kurdi 1985	2/48	17/47		0.12 [0.03, 0.47]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 2 (Oral analgesic), 17 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				



Analysis 7.1. Comparison 7 Inhalation analgesia versus placebo, Outcome 1 Pain scores (VAS: 0-100).

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 7 Inhalation analgesia versus placebo

Outcome: 1 Pain scores (VAS: 0-100)

Study or subgroup	Gas N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Cruickshank 2005	194	22.4 (25.1)	195	29.6 (27.7)		-7.20 [-12.45, -1.95]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 7.2. Comparison 7 Inhalation analgesia versus placebo, Outcome 2 Heavy vaginal bleeding.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 7 Inhalation analgesia versus placebo

Outcome: 2 Heavy vaginal bleeding

Study or subgroup	Gas n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Cruickshank 2005	52/175	44/173		1.17 [0.83, 1.64]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**

Total events: 52 (Gas), 44 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 7.3. Comparison 7 Inhalation analgesia versus placebo, Outcome 3 Anxiety - HAD score.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 7 Inhalation analgesia versus placebo

Outcome: 3 Anxiety - HAD score

Study or subgroup	Gas N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Cruickshank 2005	191	7.3 (4.11)	196	7.29 (4.06)		0.01 [-0.80, 0.82]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 8.1. Comparison 8 Topical application versus placebo, Outcome 1 Pain scores during procedure (VAS: 0-100).

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 8 Topical application versus placebo

Outcome: 1 Pain scores during procedure (VAS: 0-100)

Study or subgroup	Anaesthetic gel N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Lipscomb 1995	25	62 (82)	25	71 (128)		-9.00 [-68.59, 50.59]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

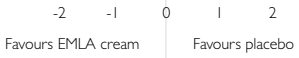
Analysis 8.2. Comparison 8 Topical application versus placebo, Outcome 2 Duration of treatment.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 8 Topical application versus placebo

Outcome: 2 Duration of treatment

Study or subgroup	Anaesthetic cream N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Sarkar 1993	35	6.1 (3.4)	35	6 (2.9)		0.10 [-1.38, 1.58]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Test for subgroup differences: Not applicable						



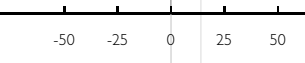
Analysis 9.1. Comparison 9 Cocaine spray versus placebo, Outcome 1 Pain scores during procedure (VAS: 0-100).

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 9 Cocaine spray versus placebo

Outcome: 1 Pain scores during procedure (VAS: 0-100)

Study or subgroup	Cocaine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Mikhail 1988	25	28 (15.9)	25	56 (19.5)		-28.00 [-37.86, -18.14]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Test for subgroup differences: Not applicable						



Analysis 9.2. Comparison 9 Cocaine spray versus placebo, Outcome 2 Moderate to severe pain.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 9 Cocaine spray versus placebo

Outcome: 2 Moderate to severe pain

Study or subgroup	Cocaine n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Mikhail 1988	12/25	21/25		0.57 [0.37, 0.89]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 12 (Cocaine), 21 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

Analysis 9.3. Comparison 9 Cocaine spray versus placebo, Outcome 3 Troublesome bleeding.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 9 Cocaine spray versus placebo

Outcome: 3 Troublesome bleeding

Study or subgroup	Cocaine n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Mikhail 1988	0/25	11/25		0.04 [0.00, 0.70]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Cocaine), 11 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

Analysis 10.1. Comparison 10 TENS versus TENS plus local anaesthetic injection, Outcome 1 Troublesome blood loss.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 10 TENS versus TENS plus local anaesthetic injection

Outcome: 1 Troublesome blood loss

Study or subgroup	TENS n/N	TENS plus local anaesthetic n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Crompton 1992	3/34	1/29		2.56 [0.28, 23.29]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 3 (TENS), 1 (TENS plus local anaesthetic)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

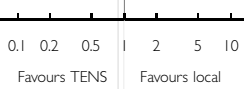
Analysis 11.1. Comparison 11 TENS versus local anaesthetic injection, Outcome 1 Troublesome blood loss.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 11 TENS versus local anaesthetic injection

Outcome: 1 Troublesome blood loss

Study or subgroup	TENS n/N	Local anaesthetic n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Crompton 1992	3/34	4/35		0.77 [0.19, 3.20]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 3 (TENS), 4 (Local anaesthetic)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

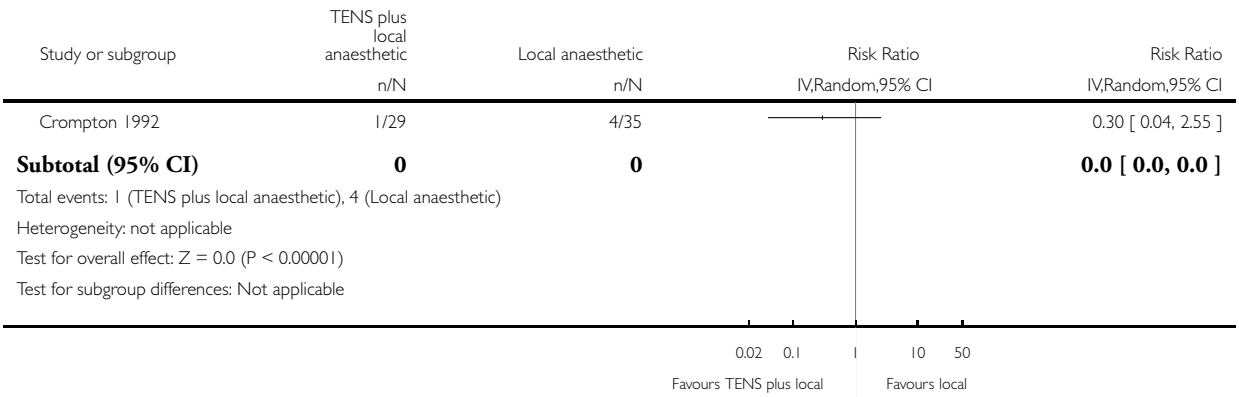


Analysis 12.1. Comparison 12 TENS plus local versus local anaesthetic injection, Outcome 1 Troublesome blood loss.

Review: Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment

Comparison: 12 TENS plus local versus local anaesthetic injection

Outcome: 1 Troublesome blood loss



ADDITIONAL TABLES

Table 1. Overview of included studies

Study	Participants' characteristics	Interventions	Outcomes	Notes
Al Kurdi 1985	97 women, undergoing CO_2 laser treatment for CIN Aged 18 to 50 years	Intervention group: (N = 50) 2 tablets naproxen sodium 550 mg Comparison group: (N = 47) 2 placebo tablets Given no less than 30 minutes before procedure	Pain relief: VAS on 10-cm scale VRS: (none, very slight, mild, moderate, severe) Speed of procedure Use of analgesia in first 24 hours	Self-reported side effects were very minor (aches and pains at 24 hours) and not included in analysis
Connell 2000	30 women undergoing LLETZ Aged 20 to 64 years	Intervention group: (N = 15) lignocaine hydrochloride 10% spray Comparison group: (N = 15) saline spray Both group received 4.4	Pain relief: VAS on 100-mm scale and 4-point categorical scale 1-4; 1 = not painful; 2 = slightly painful; 3 = moderately painful; 4 = severely painful	The outcome reported on categorical scale was not included in the analysis

Table 1. Overview of included studies (*Continued*)

		mL of local anaesthetic (prilocaine hydrochloride 30 mg/mL with felypressin 0.54 µg/mL) in the cervix		
Crompton 1992	98 women undergoing CO_2 laser treatment for CIN Linear analogue anxiety and HAD anxiety/depression personality trait scores (Zigmond 1983) , age and parity were recorded to assess group comparability 3-arm trial	(1) TENS (N = 34) vs. (2) TENS plus direct infiltration of 2 mL lignocaine 2% plus octapressin 1:10,000 (0.03 IU/mL) (N = 29) (3) Direct infiltration of 2 mL lignocaine 2% plus octapressin (N = 35)	Pain relief: VAS on 120-mm scale	Median pain score was on 120-mm VAS; however, authors converted it to percentage for reporting
Cruickshank 2005	389 women undergoing LLETZ treatment for CIN Mean age for intervention group 32.7 years and for control 31.5 years	Intervention group: (N = 195) isoflurane and desflurane gases Comparison group: (N = 194) placebo (air) Both groups also received infiltration of the cervix with prilocaine hydrochloride (30 mg/mL) and octapressin (0.54 mg/mL)	Pain relief: VAS on 100-mm scale Heavy vaginal bleeding (yes/no) Anxiety using HAD scale	Acceptability, satisfaction, helpfulness and willingness to undergo procedures in future - not included in analysis
Diakomanolis 1997	100 women undergoing CO_2 laser for CIN. Median age for intervention group 28 years and for comparison group 28. 5 years	Intervention group: (N = 50) 30 mL of a 1:30 POR8 (vasoconstrictor) + lignocaine 1% solution Comparison group (lignocaine only): (N = 50) 30 mL of lignocaine 1% solution	Pain relief: VRS (none, moderate, severe) Intra-operative blood loss Duration of procedure	Side effects - transient hypertension and sweating
Duncan 2005	97 women undergoing treatment with Semm coagulator Intervention: N = 46, mean age 31.3 (SD 8.4) Comparison: N = 47, mean age 32.6 (SD 8.0) Nullipara: intervention:	Intervention group: (N = 46) 5-mL vials of prilocaine 3% (30 mg/mL) with felypressin 0.03 IU/mL Comparison group: (N = 47) normal saline	Pain relief: 11-point analogue scale, 1-3, mild; 4-7, moderate; 8-10, severe pain	Details of anticipated pain were excluded from the analysis

Table 1. Overview of included studies (*Continued*)

	14 (30.4%); comparison: 10 (21.3%) Married/cohabiting: intervention: 20 (43.5%); comparison: 22 (46.8%) CIN (1/2/3/unspecified) details (number (%)): Intervention: HPV/CIN1 = 17/46 (37%), CIN2,3 = 29/46 (63%), microinvasion = 0/46 Comparison: HPV/CIN1 = 17/47 (36.2%), CIN2,3 = 29/47 (61.7%), microinvasion = 1/47 (2.1%)			
Frega 1994	63 women undergoing CO_2 laser vaporisation for CIN 3- arm trial	(1) Naproxen sodium 550 mg 30 minutes before treatment, N = 21 (2) Placebo 30 minutes before treatment, N = 21 and (3) No drug, N = 21	Pain relief on VAS 100-mm scale	
Howells 2000	200 women, aged 20-60 years, undergoing LLETZ for CIN (final histology was negative for 4/94 in intervention arm and 8/106 in comparison arm) Characteristic for prilocaine with felypressin (N = 94) vs. lignocaine with adrenaline (N = 106) Age (years) - mean (SD): 36.6 (10.3) vs. 34.6 (9.7)	Intervention group: (N = 94) prilocaine 3% (30 mg/mL) with felypressin 0.03 IU/mL (Citanest) Comparison group: (N = 106) lignocaine 2% with adrenaline 1:80,000 (xylocaine)	Duration of procedure Degree of bleeding (0 = none; 5 = heavy) Pain relief: patient reported (0 = none; 5 = unbearable)	Other side effects, such as feeling faint, nausea and shaking, were also scored in a similar fashion (0 = none; 5 = a great deal)
Johnson 1989	70 women undergoing CO_2 laser ablation for cervical dysplastic lesion Size of transformation zone was recorded as a score out of 2 Intervention group: 1.4 vs. comparison group: 1.2	Bilateral paracervical block by injecting 10 mL into the paracervical tissues Intervention group: (N = 35) lignocaine 2% Comparison group: (N = 35)	Pain relief: VAS on 120-mm scale and objective scoring by nurse and attending operator Blood loss (recorded as a score)	Anxiety and depression HAD scores (Zigmond 1983) and premenstrual syndrome scores were also recorded

Table 1. Overview of included studies (*Continued*)

		normal saline		
Johnson 1996	44 women undergoing CO_2 laser treatment for CIN	Intervention group: (N = 23) 10 mL of paracervical 2% lignocaine Comparison group: (N = 21) 2 mL of lignocaine 2% directly into the TZ	Pain relief: VAS (expressed as percentage) and objective scoring by nurse and laser operator	
Lee 1986	50 women undergoing laser vaporisation of cervix for CIN	Intervention group: (N = 25) ectocervix was infiltrated with 2 mL of citanest (prilocaine 3% with 0.03 IU/mL of felypressin) Control group: (N = 25) no analgesia or anaesthesia	Pain relief: VAS on 100-mm scale (VRS none, mild, moderate or severe) Blood loss: none, slight, moderate, troublesome	Side effects such as sweating, nausea, dizziness and cramps were also reported but not included in analysis as they were minor side effects
Lipscomb 1995	50 women scheduled for the loop electrosurgical excision for treatment of CIN Age - mean (SD): intervention group: 29.5 (10.5) and comparison group: 28.4 (8.9) Parity - mean (SD): intervention group: 2.1 (2.1) and comparison group: 2.3 (1.6) Loop passes: mean (SD) : intervention group: 1.2 (0.4) and comparison group: 1.3 (0.6) positive margins: Mean (SD): intervention group: 2/25 and comparison group: 3/25	Intervention group: (N = 25) cervical application of benzocaine gel 20% Comparison group: (N = 25) placebo gel After 1 minute of gel application, 4 mL of lignocaine 1% with adrenaline 1:100,000 was injected in cervix	Pain relief: VAS on 10-cm scale	
Mikhail 1988	50 women undergoing laser vaporisation of the cervix for CIN Intervention group: mean (SD): age: 27.4 (3.9); parity: 0.9 (1.24)	Intervention group: (N = 25) cervix was sprayed with 3-4 mL of a cocaine 10% solution Comparison group: (N = 25)	Duration of procedure Blood loss: minimal, moderate, severe Pain relief: VAS on 100-mm scale and VRS: none, mild, moder-	

Table 1. Overview of included studies (*Continued*)

	Comparison group: age: 26.7 (4.57); parity: 1 (1)	cervix sprayed with a similar quantity of the preservative alone	ate or severe	
Rogstad 1992	60 women undergoing cold coagulation for cervical abnormalities	Intervention group: (N = 29) 2 mL of lignocaine 2% Comparison group: (N = 31) normal saline	Pain relief: VAS on 0 to 10 scale and VRS	Other outcomes like pain of injection and 3-6 weeks' follow-up questionnaire of pain and bleeding were excluded from the analysis
Sammarco 1993	45 women undergoing cryocoagulation with liquid nitrogen using cryo-2000 by double-freeze technique for CIN	Intervention group: (N = 19) 2-3 mL of lignocaine 1% + adrenaline 1:100,000 dilution Comparison group: (N = 26) no treatment Both groups also received single dose of ketoprofen 75 mg, within 1 hour of the procedure; 2 women received naproxen sodium 550 mg	Pain relief: VAS on 100-mm scale Mean VAS score recorded by nurses was not included in analysis owing to high risk of bias	
Sarkar 1993	70 women undergoing laser treatment for CIN Age mean (SD): EMLA cream: 27.8 years (6.3) and placebo: 28 years (5.4)	Intervention group: (N = 35) EMLA cream (lignocaine 2.5% and prilocaine 2.5%) Comparison group: (N = 35) placebo cream	Pain relief: assessed by McGill's pain questionnaire (Melzack 1975) and the VAS Blood loss: none, mild, moderate, troublesome	Minor adverse experiences during treatment such as feeling hot, sweating, dizziness, fainting and sickness were not included in analysis
Winters 2009	60 women undergoing LLETZ for CIN	Intervention group: (N = 30) prilocaine 3% with felypressin injected deep into the cervical stroma around TZ Comparison group: (N = 30) prilocaine 3% with felypressin injected superficial followed by deep into the cervical stroma around TZ	Pain relief: VAS on 100-mm scale	Pain experienced during local anaesthetic injection was also evaluated

Table 1. Overview of included studies (*Continued*)

		Same amount used for both groups		

CIN: cervical intraepithelial neoplasia; HAD: Hospital Anxiety and Depression; HPV: human papillomavirus; LLETZ: loop excision of the transformation zone; SD: standard deviation; TENS: transcutaneous electrical nerve stimulation; VAS: visual analogue scale; VRS: verbal rating score; TZ: transformation zone.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Analgesia explode all trees
#2 MeSH descriptor Anesthetics explode all trees
#3 MeSH descriptor Analgesics explode all trees
#4 MeSH descriptor Pain explode all trees with qualifiers: DT,TH
#5 MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal explode all trees
#6 analgesia or analgesic*
#7 anesthetic* or anaesthetic*
#8 anti-inflammator*
#9 transcutaneous electrical nerve stimulation or TENS
#10 pain next/3 (relief or drug* or therap* or treat*)
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 MeSH descriptor Uterine Cervical Neoplasms explode all trees
#13 MeSH descriptor Cervical Intraepithelial Neoplasia explode all trees
#14 MeSH descriptor Uterine Cervical Dysplasia explode all trees
#15 cervi* near/5 (intraepithel* or dysplasia or cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan*)
#16 CIN or CIN1 or CIN2 or CIN3
#17 (#12 OR #13 OR #14 OR #15 OR #16)
#18 MeSH descriptor Colposcopy explode all trees
#19 colposcop*
#20 LLETZ
#21 LEEP
#22 excis* or ablat* or laser* or cryosurg*
#23 (#18 OR #19 OR #20 OR #21 OR #22)
#24 (#11 AND #17 AND #23)

Appendix 2. MEDLINE search strategy

MEDLINE Ovid 1950 to present
1 exp Analgesia/
2 exp Anesthetics/
3 exp Analgesics/
4 exp Pain/dt, th [Drug Therapy, Therapy]
5 exp Anti-Inflammatory Agents, Non-Steroidal/
6 (pain adj3 (relief or drug* or therap* or treat*)).mp.
7 (analgesia or analgesic*).mp.
8 (anesthetic* or anaesthetic*).mp.
9 anti-inflammator*.mp.
10 (Transcutaneous Electrical Nerve Stimulation or TENS).mp.
11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12 exp Uterine Cervical Neoplasms/
13 Cervical Intraepithelial Neoplasia/
14 Uterine Cervical Dysplasia/
15 (cervi* adj5 (intraepithel* or dysplasia or cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan*)).mp.
16 (CIN or CIN1 or CIN2 or CIN3).mp.
17 12 or 13 or 14 or 15 or 16
18 Colposcopy/
19 colposcop*.mp.
20 LLETZ.mp.
21 LEEP.mp.
22 (excis* or ablat* or laser* or cryosurg*).mp.
23 18 or 19 or 20 or 21 or 22
24 11 and 17 and 23
key:
mp=title, original title, abstract, name of substance word, subject heading word, unique identifier

Appendix 3. EMBASE search strategy

EMBASE Ovid 1980 to present
1 exp analgesia/
2 exp anesthetic agent/
3 exp analgesic agent/
4 exp pain/dt, th [Drug Therapy, Therapy]
5 exp nonsteroid antiinflammatory agent/
6 (pain adj3 (relief or drug* or therap* or treat*)).mp.
7 (analgesia or analgesic*).mp.
8 (anesthetic* or anaesthetic*).mp.
9 anti-inflammator*.mp.
10 transcutaneous nerve stimulation/
11 (transcutaneous electrical nerve stimulation or TENS).mp.
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13 exp uterine cervix tumor/
14 uterine cervix dysplasia/
15 uterine cervix carcinoma in situ/
16 (cervi* adj5 (intraepithel* or dysplasia or cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan*)).mp.
17 (CIN or CIN1 or CIN2 or CIN3).mp.
18 13 or 14 or 15 or 16 or 17
19 colposcopy/
20 colposcop*.mp.

21 LLETZ.mp.
22 LEEP.mp.
23 (excis* or ablat* or laser* or cryosurg*).mp.
24 19 or 20 or 21 or 22 or 23
25 12 and 18 and 24
key:
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 10, 2012

Date	Event	Description
24 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Ketan Gajjar - primary author.

Andrew Bryant - statistical and methodological support.

Pierre Martin-Hirsch - editing and clinical expertise.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of Health, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not identify any ongoing trials so the following sentence was removed from the 'searching other resources section':

- "If ongoing trials which have not been published are identified through these searches, the principal investigators will be approached for relevant data."

The review included 17 trials but comparisons were restricted to single trial analyses or meta-analysis of few trials so the following section on reporting biases was removed:

- "**Assessment of reporting biases** Funnel plots corresponding to meta-analysis of the primary outcome will be examined to assess the potential for small study effects. When there is evidence of small-study effects, publication bias will be considered as only one of a number of possible explanations. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random effects model, sensitivity analyses will be performed using fixed effects models."

Subgroup analyses were not carried out so we removed the following section:

- "**Subgroup analysis and investigation of heterogeneity** If possible, subgroup analysis will be performed, grouping the trials by different routes of administering analgesia i.e. oral, injectable or inhalation and pain relief for different treatment types. Factors such as age, CIN grade, length of follow-up, adjusted/unadjusted analysis will be considered in interpretation of any heterogeneity."

We did not carry out sensitivity analysis. We had specified the following in the protocol:

- "**Sensitivity analysis** We will perform sensitivity analyses excluding studies at moderate or high risk of bias."

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Analgesics [*administration & dosage]; Cervical Intraepithelial Neoplasia [*surgery]; Colposcopy [*adverse effects]; Drug Therapy, Combination [methods]; Intraoperative Complications [*therapy]; Pain Management [*methods]; Pain Measurement; Pain, Postoperative [*therapy]; Randomized Controlled Trials as Topic; Transcutaneous Electric Nerve Stimulation [methods]; Uterine Cervical Neoplasms [*surgery]

MeSH check words

Adult; Female; Humans