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Martin-Hirsch PPL, Bryant A

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[Intervention Review]

Interventions for preventing blood loss during the treatment of cervical intraepithelial neoplasia

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ABSTRACT

Background

Cervical intraepithelial neoplasia (CIN) is the most common pre-malignant lesion. Surgical treatments for CIN are commonly associated with blood loss.

Objectives

To assess the effectiveness and safety of interventions for preventing blood loss during the treatment of CIN.

Search methods

We searched the Cochrane Gynaecological Cancer Group Trials Register, MEDLINE, EMBASE and CENTRAL up to November 2012. We also searched registers of clinical trials, abstracts of scientific meetings and reference lists of included studies.

Selection criteria

Randomised controlled trials (RCTs) of vasopressin, tranexamic acid, haemostatic sutures, Amino-Cerv or Monsel's solution in women undergoing surgery for CIN.

Data collection and analysis

Two reviewers independently abstracted data and assessed risk of bias. Risk ratios comparing adverse events in women who received one of the interventions were pooled in a random-effects meta-analyses or included in single trial analyses.

Main results

Twelve RCTs (N = 1602, of whom 1512 were assessed) were included.

Vasopressin significantly reduced perioperative bleeding (mean difference (MD) = -100.80, 95% confidence interval (CI) -129.48 to -72.12) and was associated with a decreased risk of bleeding that required haemostatic sutures or further vasopressin, compared to placebo (risk ratio (RR) = 0.39, 95% CI 0.27 to 0.56).

Tranexamic acid significantly reduced risk of secondary haemorrhage (RR = 0.23, 95% CI 0.11 to 0.50), but not primary haemorrhage (RR = 1.24, 95% CI 0.04 to 38.23) after knife and laser cone biopsy, compared with placebo. There was also a statistically significant reduction in postoperative blood loss compared with placebo (MD = -55.60, 95% CI -94.91 to -16.29).

Packing with Monsel's solution resulted in less perioperative blood loss (MD = -22.00, 95% CI -23.09 to -20.91) and decreased the risk of dysmenorrhoea (RR = 0.37, 95% CI 0.16 to 0.84), unsatisfactory colposcopy (RR = 0.43, 95% CI 0.30 to 0.63) and cervical stenosis (RR =

0.35, 95% CI 0.25 to 0.49) compared to routine suturing, but was not statistically different to sutures for risk of primary and secondary haemorrhages.

Amino-Cerv antibiotic gel failed to make a difference on secondary haemorrhage but was associated with significantly less vaginal discharge at 2 weeks compared with routine care (RR = 0.27, 95% CI 0.09 to 0.86).

There was no significant difference in blood loss between women who received ball electrode diathermy and those who received Monsel's paste (MD = 4.82, 95% CI -3.45 to 13.09).

Authors' conclusions

Bleeding associated with surgery of the cervix appears to be reduced by vasopressin, used in combination with local anaesthetic. Tranexamic acid appears to be beneficial after knife and laser cone biopsy. There are insufficient data to assess the effects on primary haemorrhage. There is some evidence that haemostatic suturing has an adverse effect on blood loss, cervical stenosis and satisfactory colposcopy.

PLAIN LANGUAGE SUMMARY

Interventions to prevent blood loss during the treatment of pre-cancerous abnormalities in the cervix (cervical intraepithelial neoplasia).

Surgery for pre-cancerous cervix lesions (cervical intraepithelial neoplasia) often causes significant bleeding during surgery or within 14 days. This review found that good surgical technique can reduce immediate blood loss and bleeding can also be reduced by some drugs. Vasopressin reduces blood flow by constricting blood vessels. Tranexamic acid reduces blood loss after knife and laser cone biopsy. Stitches also reduce blood loss but can interfere with later visual examination of the cervix.

BACKGROUND

Description of the condition

Cervical cancer is the second most common cancer among women (GLOBOCAN 2002). A woman's risk of developing cervical cancer by age 65 years ranges from 0.8% in developed countries to 1.5% in developing countries (IARC 2002). In Europe, about 60% of women with cervical cancer are alive five years after diagnosis (EUROCARE 2003). Cervical screening aims to identify women with asymptomatic disease, treat the disease with a low morbidity procedure, and thus lower the risk of developing invasive disease. In countries with effective screening programmes, there have been dramatic reductions in the incidence of disease and the stage of disease of cancer, if disease is diagnosed (Peto 2004). Cervical intra-epithelial neoplasia (CIN) is the most common pre-malignant lesion characterised by atypical squamous changes in the transformation zone of the cervix; with mild, moderate or severe changes described by their depth (CIN 1, 2 or 3). If CIN progresses it becomes squamous cancer; in contrast, the much rarer glandular pre-cancerous abnormalities (cervical glandular intra-epithelial neoplasia; CGIN) develop into cervical adenocarcinoma.

Human Papillomavirus (HPV) is the cause of pre-cancerous abnormalities of the cervix. HPV has over 100 subtypes and is present in over 95% of preinvasive and invasive squamous carcinomas of the cervix. Serotypes associated with cervical squamous lesions may be designated as having a high or low risk for progression to malignancy. HPV infection in young women is commonly a transient infection and the body's own immune response clears the disease from the cervical tissues. If pre-invasive disease has been present and the immunological response clears HPV infection then the pre-invasive disease will resolve. Sexually active young women under 30 years of age have a very high rate of HPV infection whilst women over 30 years of age have a much lower HPV infection rate (Sargent 2008). This is a reflection of the natural history of disease with a 50% regression rate and only a 10% progression rate of low grade CIN in young women (Ostor 1993).

The frequency of abnormal Papanicolaou smear test results and subsequent CIN varies with the population tested, the test used and accuracy reported. It is estimated to range between 1.5 to 6% (Cirisano 1999).

When CIN is identified, colposcopists generally treat CIN 2 or high grade disease and either observe or immediately treat CIN 1 depending on personal preference. The majority of treatments can be associated with perioperative bleeding. This can obviously make the procedures technically difficult, and can cause anxiety to the patient. This review evaluated interventions designed to reduce blood loss associated with treatment of CIN.

Description of the intervention

Surgical treatments for CIN are commonly associated with immediate and long term complications. The majority of surgical therapies (knife or laser cone biopsy, large loop excision, laser ablation) can cause significant bleeding during the procedure, within the first 24 hours (primary haemorrhage) or within the first 14 days (secondary haemorrhage). They can also result in persistent bleeding or discharge following treatment. Surgical trauma to the cervix can result in disruption of the anatomy of the cervix, prohibiting adequate colposcopy if the transformation zone is within the canal or narrowing of the cervical canal, which can result in dysmenorrhoea.

Reduction of immediate blood loss during surgical treatment can be achieved by good operator technique and may be enhanced by various interventions.

Knife cone biopsy is still commonly performed for the treatment of CIN despite the advent of out-patient excisional treatment. Many authorities still recommend knife cone biopsy, if the squamo-columnar junction is deep in the cervical canal or if there is suspicion of invasive disease or glandular intra-epithelial neoplasia, as excision is likely to be in a single specimen and to reduce the risk of diathermy damage. Knife cone biopsy is associated with a higher morbidity compared to other modalities of treatment, particularly for obstetric outcomes (Kyrgiou 2004). The majority of randomised controlled trials (RCTs) available have examined different interventions designed to reduce morbidity during knife cone biopsy.

Vasopressin is commonly used in combination with local analgesics for out-patient ablative or excisional treatments.

Tranexamic acid (an antifibrinolytic agent) has been advocated as a prophylactic measure against significant secondary bleeding after knife cone biopsy. It is not commonly used in current practice.

The surgical technique of knife cone biopsy has been poorly evaluated by RCTs. Modifications in cutting technique, cautery to wound and haemostatic suturing have all been advocated.

Why it is important to do this review

This review is an update of the review completed in 1999. Since then, further trials have come to light which are suitable for inclusion and may increase the evidence base. The initial review mapped out the evidence but most interventions were not investigated by well conducted studies and a minority investigated interventions that are not commonly used in clinical practice. This updated review has been conducted to assess the current evidence base ten years after the original review.

OBJECTIVES

To assess the effectiveness and safety of interventions for preventing blood loss during the treatment of CIN, in particular to assess their effects on immediate, short and long term morbidity.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Women with CIN, proven by biopsy, undergoing surgical treatment.

Types of interventions

The following interventions are designed to reduce perioperative and postoperative morbidity associated with surgical treatment of CIN:

- vasopressin;
- tranexamic acid;
- haemostatic sutures;
- Monsel's solution;
- other relevant interventions found during the literature search were also considered.

We considered direct comparisons between any of the above interventions.

Types of outcome measures

Primary outcomes

Short term complications

- Objective and subjective perioperative bleeding.
- Primary and secondary haemorrhage.

Long term complications

- Amenorrhoea, dysmenorrhoea.
- Unsatisfactory colposcopy and cervical stenosis.

Search methods for identification of studies

There were no language restrictions in this review.

Electronic searches

See: Cochrane Gynaecological Cancer Group methods used in reviews.
We searched the following electronic databases.

- The Cochrane Gynaecological Cancer Collaborative Review Group's Trial Register.
- Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library.*
- MEDLINE.
- EMBASE.

The MEDLINE, EMBASE and CENTRAL search strategies aiming to identify RCTs comparing interventions designed to reduce morbidity of surgical treatment of CIN before 2009 are presented in Appendix 1, Appendix 2 and Appendix 3, respectively.

Databases were searched from January 1966 until December 2000 in the original review and updated in April 2009 and November 2012. All relevant articles found were identified on PubMed and using the 'related articles' feature, a further search was carried out for newly published articles.

Searching other resources

We also searched Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials for ongoing trials.

Handsearching

We searched the citation lists of included studies through handsearching and contacted experts in the field to identify further reports of trials. Sixteen journals thought to be most likely to contain relevant publications were handsearched to perform the original review: (Acta Cytologica, Acta Obstetrica Gynecologica Scandinavia, Acta Oncologica, American Journal of Obstetrics and Gynaecology, British Journal of Cancer, British Journal of Obstetrics and Gynaecology, Cancer, Cytopathology, Diagnostic Cytopathology, Gynaecologic Oncology, International Journal of Cancer, International Journal of Gynaecological Cancer, Journal of Family Practice, Obstetrics and Gynaecology).

Hand-searching of the above journals was not repeated in the update as electronic databases are now very accurate at identifying RCTs and there would have been no added advantage in hand-searching.

Data collection and analysis

Selection of studies

All titles and abstracts retrieved by electronic searching were downloaded to the reference management database Endnote. Duplicates were then removed and the remaining references examined independently by four reviewers (AB, HD, PM-H, SK). Those studies which clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. The eligibility of retrieved papers was assessed independently by two reviewers (AB, SK). Disagreements were resolved by discussion between the two reviewers. Reasons for exclusion are documented.

Data extraction and management

For included studies, the following data were abstracted.

- Author, year of publication and journal citation (including language).
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study design, methodology.
- Study population:
  - total number enrolled;
  - patient characteristics;
  - age.
- CIN details.
- Intervention details:
  - type of surgical treatment;
  - type of treatment designed to reduce morbidity;
  - variations in technique;
- Risk of bias in study (see below).
- Duration of follow-up.
- Outcomes – see below.

Data on outcomes were extracted as below:

- For dichotomous outcomes (e.g. cervical stenosis), we extracted the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a risk ratio.
- For continuous outcomes (e.g. peri/postoperative bleeding), we extracted the final value and standard deviation of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and its standard error.

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

The time points at which outcomes were collected and reported were noted.

Data were abstracted independently by two reviewers (AB, SK) onto a data abstraction form specially designed for the review. Differences between reviewers were resolved by discussion.

Assessment of risk of bias in included studies

The risk of bias in included RCTs was assessed using the following questions and criteria:

Sequence generation

Was the allocation sequence adequately generated?

- Yes: e.g. a computer-generated random sequence or a table of random numbers.
- No: e.g. date of birth, clinic identification number or surname.
- Unclear: e.g. not reported.

Allocation concealment

Was allocation adequately concealed?

- Yes: e.g. where the allocation sequence could not be foretold.
- No: e.g. allocation sequence could be foretold by patients, investigators or treatment providers.
- Unclear: e.g. not reported.

Blinding

Assessment of blinding was restricted to blinding of outcome assessors, since it is generally not possible to blind participants and treatment providers to surgical interventions.

Was knowledge of the allocated interventions adequately prevented during the study?

- Yes.
- No.
- Unclear.

Incomplete reporting of outcome data

We recorded the proportion of participants whose outcomes were not reported at the end of the study; we noted if loss to follow-up was not reported.

Were incomplete outcome data adequately addressed?

- Yes, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms.
- No, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms.
- Unclear, if loss to follow-up was not reported.

Selective reporting of outcomes

Are reports of the study free of suggestion of selective outcome reporting?

- Yes, e.g. if review reported all outcomes specified in the protocol.
- No, otherwise.
- Unclear, if insufficient information available.

Other potential threats to validity

Was the study apparently free of other problems that could put it at a high risk of bias?

- Yes.
- No.
- Unclear.

The risk of bias tool was applied independently by two reviewers (AB, SK) and differences were resolved by discussion. Results were presented in both a risk of bias graph and a risk of bias summary. Results of meta-analyses were interpreted in light 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 risk ratio;
- for continuous outcomes, we used the mean difference between treatment arms.

Dealing with missing data

We did not impute missing outcome data for any outcomes.

Assessment of heterogeneity

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

Data synthesis

The results of clinically similar studies were pooled in meta-analyses.

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

Random-effects models with inverse variance weighting were used for all meta-analyses (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

No subgroup analyses were planned.

RESULTS

Description of studies

Results of the search

The original search strategy identified 900 unique references of which screening their titles and abstracts identified 11 references as potentially eligible for this review. The updated search strategy identified 1225 unique references in 2009. The title and abstract screening of these references identified seven references as potentially eligible for the review. Overall, the full text screening of these 18 references resulted in seven of them being excluded, for the reasons described in the table Characteristics of excluded studies. The remaining 11 references identified 12 RCTs that met our inclusion criteria and these are described in the table Characteristics of included studies. No new studies were identified for inclusion in November 2012. Searches of the grey literature did not identify any additional relevant studies.

Included studies

The 12 included trials randomised a total of 1602 women of whom 1512 were assessed at the end of the trials. Of these trials, four were from the UK (Doyle 1992; Gilbert 1989; Howells 2000; Lee 1986), two from the USA (Gimpleson 1999; Lipscomb 2006), one from Denmark (Lundvall 1984), three from Sweden (Grundsell 1984(a); Grundsell 1984(b); Rybo 1972) and one from Turkey (Dane 2008).The largest trial recruited 230 women (Lundvall 1984), with the smallest recruiting 48 (Gimpleson 1999) participants.

Of these trials, the majority are single centre (Dane 2008; Doyle 1992; Gilbert 1989; Gimpleson 1999; Grundsell 1984(a); Howells 2000; Lee 1986; Lipscomb 2006; Rybo 1972; Sabol 1971), with only one trial conducted at two or more centres (Lundvall 1984). Of three trials (Dane 2008; Gimpleson 1999; Howells 2000) that reported data on stage, 80 women had CIN 1, 53 had CIN 2, 114 women had CIN 2-3, 60 had CIN 3 with a further 12 having normal histology and seven having missing data or having a different histology. Classification was not reported in nine trials (Doyle 1992; Gilbert 1989; Grundsell 1984(a); Grundsell 1984(b); Lee 1986; Lipscomb 2006; Lundvall 1984; Rybo 1972; Sabol 1971).

The interventions investigated in these trials included tranexamic acid (Grundsell 1984(a); Grundsell 1984(b); Lundvall 1984; Rybo 1972), Amino-Cerv preparation versus control (Gimpleson 1999), cerclage suture compared to electrocautery (Dane 2008)' Monsel's paste compared to electrocautery (Lipscomb 2006), control (Doyle 1992) or absorbable sutures (Gilbert 1989) and administration of different intracervical local anaesthetic preparations (prilocaine with felypressin compared to lignocaine with adrenaline) (Howells 2000) or intracervical vasopressin compared to control (Sabol 1971).

The randomised trials reported many different outcomes with bleeding the most common. Perioperative blood loss was reported in six trials. Six trials reported primary haemorrhage and seven reported secondary haemorrhage as an outcome measure. Other outcome measures reported include dysmenorrhoea, amenorrhoea, operative duration, vaginal discharge, cervical healing and inflammation, malodour, pain, recurrent abnormal smears and post-procedural symptoms such as nausea or shivering.

Excluded studies

Two trials were excluded as women enrolled did not have CIN confirmed by biopsy (Chan 2007; Foden-Shroff 1998). Further studies were excluded as they were not RCTs (Harper 1997), used quasi-randomisation (Paraskevaidis 2001; Stefanidis 1998), did not compare relevant interventions (Paraskevaidis 2002) or reported outcomes which were not appropriate to this review (Cruickshank 2005).

Risk of bias in included studies

All trials were at high risk of bias, except for Sabol 1971 which was at moderate risk of bias as it adequately satisfied three of the criteria used to assess risk of bias (see Figure 1; Figure 2).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

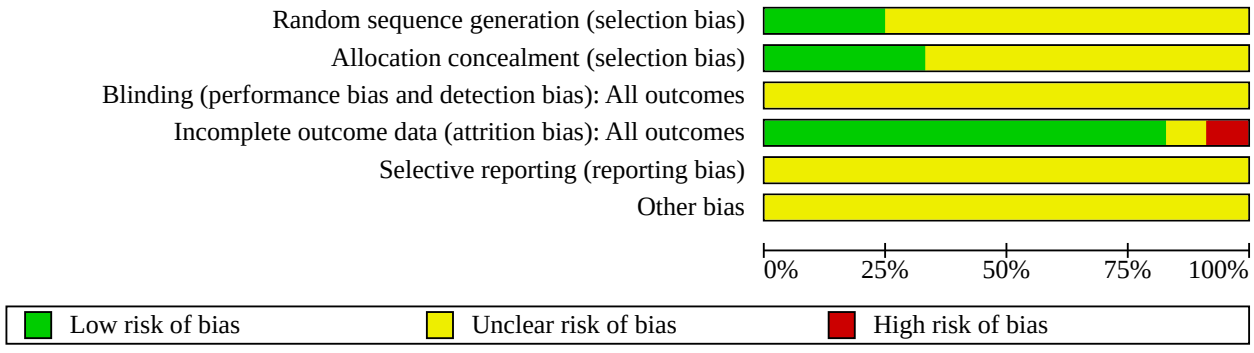
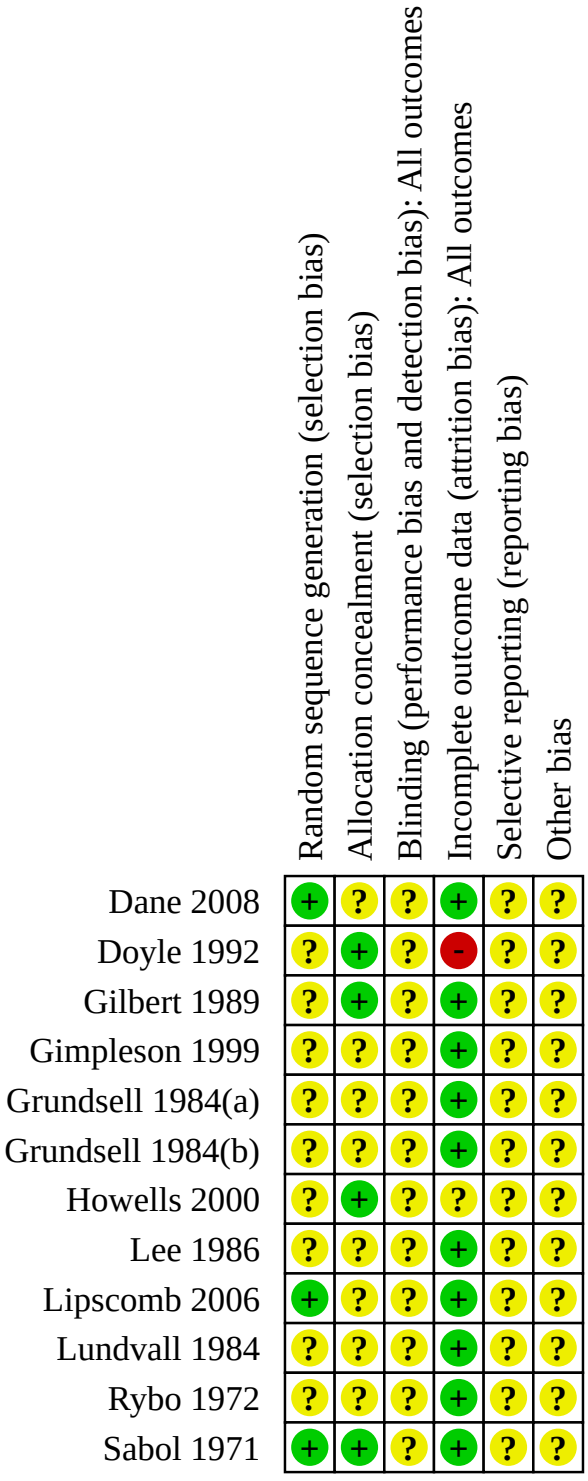


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Adequacy of randomisation was confirmed in only three trials (Dane 2008; Lipscomb 2006; Sabol 1971), where an appropriate method of sequence generation was used to assign women to treatment groups. The method of randomisation was not reported in the other nine trials. Concealment of allocation was satisfactory in only four trials (Doyle 1992; Gilbert 1989; Howells 2000; Sabol 1971), but was not reported in any of the other eight trials.

Blinding

None of the trials reported whether or not the outcome assessor was blinded.

Incomplete outcome data

Loss to follow-up was low in 10 of the trials, with at least 80% of women being assessed at the end of the study. It was unsatisfactory in the trial of Doyle 1992 as only 69% of women were assessed at endpoint and was unclear in the trial of Howells 2000.

Selective reporting

In all 12 trials it was unclear as to whether outcomes had been selectively reported as there was insufficient information to permit judgement.

Other potential sources of bias

In all 12 trials there was insufficient information to assess whether any important additional risk of bias existed.

Effects of interventions

Vasopressin versus placebo

Measured blood loss

In the trial of Sabol 1971, the use of vasopressin was associated with a large and statistically significant reduction in blood loss compared with placebo (MD = -100.80, 95% CI -129.48 to -72.12). (see Analysis 1.1)

Subjective troublesome bleeding

In the trial of Lee 1986, there was no significant difference in the risk of troublesome bleeding in women who received vasopressin and placebo (RR = 0.40, 95% CI 0.09 to 1.87). (see Analysis 1.2)

Bleeding requiring haemostatic sutures

In the trial of Sabol 1971, the use of vasopressin was associated with a statistically significant decreased risk of bleeding that required haemostatic sutures or further vasopressin compared with placebo (RR = 0.39, 95% CI 0.27 to 0.56). (see Analysis 1.3)

Cervical stenosis

In the trial of Sabol 1971, there was no significant difference in the risk of cervical stenosis in women who received vasopressin and placebo (RR = 0.32, 95% CI 0.06 to 1.67). (see Analysis 1.4)

Tranexamic acid versus control

Postoperative blood loss

In the trial of Rybo 1972, tranexamic acid was associated with a statistically significant reduction in postoperative blood loss compared with placebo (MD = -55.60, 95% CI -94.91 to -16.29). (see Analysis 2.1)

Primary haemorrhage

Meta-analysis of two trials (Grundsell 1984(a); Grundsell 1984(b)), assessing 360 participants, showed little difference in the risk of primary haemorrhage in women who received tranexamic acid and control (RR = 1.24, 95% CI 0.04 to 38.10). The percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) may represent substantial heterogeneity (I^2 = 62%). (see Analysis 2.2)

Secondary haemorrhage

Meta-analysis of four trials (Grundsell 1984(a); Grundsell 1984(b); Lundvall 1984; Rybo 1972), assessing 633 participants, found that the use of tranexamic acid was associated with a statistically significant decrease in the risk of secondary haemorrhage compared with control (RR = 0.23, 95% CI 0.11 to 0.50). The percentage of the variability in effect estimates that is due to heterogeneity rather than by chance is not important (I^2 = 0%). (see Analysis 2.3)

Vaginal pack with Monsel's solution versus haemostatic suture

Only the trial of Gilbert 1989 compared vaginal packs with sutures.

Perioperative blood loss

Vaginal packs were associated with a large and statistically significant reduction in perioperative blood loss compared with sutures (MD = -22.00, 95% CI -23.09 to -20.91). (see Analysis 3.1)

Primary haemorrhage

There was no evidence that vaginal packs had an advantage over sutures in reducing the risk of primary haemorrhage (RR = 1.00, 95% CI 0.36 to 2.75). (see Analysis 3.2)

Secondary haemorrhage

There was no significant difference in the risk of secondary haemorrhage in women who used vaginal packs and haemostatic sutures (RR = 0.44, 95% CI 0.19 to 1.02). (see Analysis 3.3)

Amenorrhoea

There was no significant difference in the risk of amenorrhoea in women who used vaginal packs and haemostatic sutures (RR = 0.20, 95% CI 0.01 to 4.11). (see Analysis 3.4)

Dysmenorrhoea

Vaginal packs were associated with a statistically significant decreased risk of dysmenorrhoea compared with sutures (RR = 0.37, 95% CI 0.16 to 0.84). (see Analysis 3.5)

Transformation zone not visible at colposcopy

Vaginal packs were associated with a statistically significant decreased risk of unsatisfactory colposcopy compared with sutures (RR = 0.43, 95% CI 0.30 to 0.63). (see Analysis 3.6)

Cervical stenosis

Vaginal packs were associated with a statistically significant decreased risk of cervical stenosis compared with sutures (RR = 0.35, 95% CI 0.25 to 0.49). (see Analysis 3.7)

Postoperative vaginal bleeding

In the trial of Doyle 1992, prophylactic application of Monsel's solution to the cervical wound after loop excision did not significantly reduce postoperative bleeding compared with not using Monsel's solution. (see Analysis 4.1)

Cerclage suture versus electrical coagulation

Only the trial of Dane 2008 reported data on cerclage suture versus electrical coagulation.

Duration of procedure

Cerclage sutures were associated with statistically significantly less treatment time than electrical coagulation (MD = -9.50, 95% CI -11.57 to -7.43).

Primary haemorrhage

There was no significant difference in the risk of primary haemorrhage between women who received cerclage sutures and those who received electrical coagulation (RR = 0.86, 95% CI 0.06 to 13.22). (see Analysis 4.2)

Secondary haemorrhage

There was no significant difference in the risk of secondary haemorrhage between women who received cerclage sutures and those who received electrical coagulation (RR = 0.14, 95% CI 0.02 to 1.13). (see Analysis 4.3)

Dysmenorrhoea

There was no significant difference in the risk of dysmenorrhoea in women who received cerclage sutures and those who received electrical coagulation (RR = 0.48, 95% CI 0.18 to 1.29). (see Analysis 4.4)

Unsatisfactory colposcopy

Cerclage sutures were associated with a statistically significant decreased risk of unsatisfactory colposcopy than electrical coagulation (RR = 0.61, 95% CI 0.39 to 0.94). *(see* Analysis 4.5 *)*

Vaginal Amino-Cerv versus routine treatment

Only the trial of Gimpleson 1999 reported data on Amino-Cerv versus routine treatment.

Secondary haemorrhage

No women experienced secondary haemorrhage in either the Amino-Cerv or the routine care group. (see Analysis 5.1)

Vaginal discharge at 2 weeks

Amino-Cerv was associated with statistically significantly less vaginal discharge at 2 weeks than routine care (RR = 0.27, 95% CI 0.09 to 0.86). (see Analysis 5.2)

Vaginal discharge at 4 weeks

There was no significant difference in the risk of vaginal discharge at 4 weeks in women who received Amino-Cerv and those who received routine care (RR = 0.33, 95% CI 0.04 to 2.98). (see Analysis 5.3)

Prilocaine with felypressin versus lignocaine with adrenaline in Large Loop Excision of the Transformation Zone (LLETZ)

Duration of procedure

In the trial of Howells 2000, there was no significant difference in the duration of treatment between women who received prilocaine with felypressin and those who received lignocaine with adrenaline in LLETZ (MD = 0.40, 95% CI -0.19 to 0.99). (see Analysis 6.1)

Ball electrode versus Monsel's paste for haemostasis after Loop Electrosurgical Excision Procedure (LEEP)

Blood loss

In the trial of Lipscomb 2006, there was no significant difference in blood loss between women who received ball electrode and those who received Monsel's paste (MD = 4.82, 95% CI -3.45 to 13.09). (see Analysis 7.1)

DISCUSSION

Summary of main results

We found 12 trials, enrolling 1602 women, that met our inclusion criteria. These trials compared a variety of interventions aimed at reducing morbidity in women with CIN who underwent surgery, including intracervical vasopressin (a potent vasoconstrictor), tranexamic acid (an antifibrinolytic agent), vaginal pack, haemostatic and cerclage sutures, electrical coagulation, Amino-Cerv, ball electrode and Monsel's paste. The evidence from Sabol 1971, which assessed 92 women suggested that vasopressin reduces perioperative bleeding during surgical treatment of the cervix. However, the trial of Lee 1986 showed no evidence of subjective troublesome bleeding, although there were only 50 women in this trial and seven cases of troublesome bleeding.

The comparison of tranexamic acid versus control includes the only meta-analyses in the review. However, the evidence is inconsistent as tranexamic acid appears to significantly reduce postoperative blood loss and the incidence of secondary haemorrhage, but there were conflicting results regarding primary haemorrhage. This is probably a reflection of the low incidence of primary haemorrhage and the small number of women recruited in the trials.

Vaginal packs during knife cone surgery (conisation) appear to reduce morbidity compared to elective haemostatic sutures. In the trial of Gilbert 1989, packs significantly reduced the amount of perioperative blood loss, reduced the risk of dysmenorrhoea and, unlike haemostatic sutures, did not promote migration of the transformation zone into the cervical canal preventing satisfactory colposcopy and cervical stenosis. There was no evidence of a difference between the two interventions for primary and secondary haemorrhage and amenorrhoea, but there did seem to be a statistically non-significant benefit in favour of vaginal packs.

In the trial of Dane 2008, it appeared that cerclage sutures were more beneficial than electrical coagulation as the duration of treatment was shorter and more women received a satisfactory

colposcopy. There was no evidence of a difference between cerclage sutures and coagulation in the number of women who had primary and secondary haemorrhages and dysmenorrhoea, but there did seem to be a statistically non-significant benefit in favour of the sutures.

There was no clear evidence as to whether Amino-Cerv or routine care, prilocaine with felypressin or lignocaine with adrenaline and ball electrode or Monsel's solution were best for reducing morbidity after surgery for CIN. The evidence for all these comparisons came from small single trials so the results are unconvincing.

The main limitation of this review is that there are many single trial analyses so the conclusions are very tentative as none of these trials were sufficiently large. Many of the analyses showed the magnitude of the point estimate to be large, but due to the uncertainty, no statistically significant difference was observed. This was largely because the trials reported relatively few morbidities and so lacked the statistical power to detect any difference in risk that might be present.

Overall completeness and applicability of evidence

This review consists of many single trial analyses of small numbers of participants which limits the conclusions that can be drawn. In modern day colposcopy practice, commonly used interventions are local anaesthetic application with vasopressin following by large loop excision of the cervix, cryotherapy, laser ablation or conisation with a knife. To best quantify the benefits of these interventions in the reduction of blood loss and other symptoms, without significant side effects, larger randomised controlled trials are required.

Quality of the evidence

This review incorporates evidence from 12 randomised clinical trials which assessed 1512 participants in total. Due to the heterogeneity of the outcomes and treatments considered, there are many single trial analyses and limited consistent data available to compare between trials. The majority of the included trials were underpowered to demonstrate a significant effect and most 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 a thorough search of the grey literature and all studies were sifted and data extracted by at least two reviewers 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 treatment to have been effective may not have been published. We were unable to assess this possibility as the analyses were restricted to meta-analyses of a small number of trials or single trials.

Agreements and disagreements with other studies or reviews

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

We elected to exclude the two studies that used prophylactic antibiotics (Chan 2007; Foden-Shroff 1998) as they included patients that did not have disease. Both these studies did not demonstrate a significant benefit from vaginally administered or oral antibiotics. The other excluded studies evaluated interventions that were not included in the final review.

AUTHORS' CONCLUSIONS

Implications for practice

Vasopressin administration reduces perioperative bleeding during surgical treatment of CIN (Sabol 1971) but a further trial (Lee 1986) showed no evidence of the reduction of subjective troublesome bleeding. However, this was a small trial with only 50 participants and seven cases of troublesome bleeding.

Tranexamic acid significantly reduces postoperative blood loss and the incidence of secondary haemorrhage. There are conflicting results regarding the impact of tranexamic acid on primary haemorrhage which is probably a reflection of the low incidence and the small number of women recruited in the trials to date.

Vaginal packing during knife conisation reduces morbidity compared to elective haemostatic sutures. Packs significantly reduced the amount of perioperative blood loss, the risk of dysmenorrhoea, unsatisfactory colposcopy at follow-up and cervical stenosis (Gilbert 1989). There was also a non-statistically significant benefit of vaginal packs in reducing the rates of primary and secondary haemorrhage and amenorrhoea.

The application of cerclage sutures is faster and provides better colposcopic outcomes compared to electrical coagulation (Dane 2008). Sutures also provide a statistically non-significant benefit in reducing the number of women who have primary and secondary haemorrhages and dysmenorrhoea.

Implications for research

This review has demonstrated that there should be further RCTs to objectively assess the best interventions to reduce blood loss associated with treatment.

Pragmatically, the majority of treatments are conducted in an out-patient setting and the most common treatment is Large Loop Excision of the Transformation Zone. This is conducted under local anaesthesia in combination with vasopressin or adrenaline. Ideally, a RCT should be conducted comparing these two vasoconstrictors to evaluate which one is superior.

The RCTs identified provide evidence that the use of tranexamic acid after knife cone biopsy may be beneficial. We would advocate a further trial of sufficient power to establish the precise reduction in postoperative bleeding and secondary haemorrhage, including an assessment by patients if there is a subjective reduction in the volume and duration of symptoms to warrant routine use of tranexamic acid.

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CHARACTERISTICS OF STUDIES

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

Dane 2008

Study characteristics	
Methods	RCT
Participants	78 women with histologically documented cervical intraepithelial neoplasia (CIN) 2/3. Mean age in the trial was 34 years (Range: 22 and 60 years). There were 32 (41%) women with CIN II and 46 (59%) with CIN 3.
Interventions	**Intervention:**

Dane 2008 *(Continued)*

	Following routine colposcopy a knife cone biopsy was taken with subsequent haemostasis achieved with a cerclage suture using No. 1 Vicryl suturing at 11 to 9 o'clock and 8 to 6 o'clock and 5 to 3 o'clock and 2 to 12 o'clock on the external surface, and knots tied at 11 and 12 o'clock with the aim of limiting blood loss from the uterine vessels. **Comparison:** **Following routine colposcopy a knife cone biopsy was taken with subsequent haemostasis achieved with electrical coagulation using a ball electrode.**
Outcomes	• Operative time • Intraoperative blood loss • Early/late bleeding • Dysmenorrhea • Transformation zone visible
Notes	Women were followed up at 4 weeks and 6 months following procedure.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Women were assigned to the suture or cautery group using a random-number table."
Allocation concealment (selection bias)	Unclear risk	"Group allocation (was) predetermined and placed in consecutively numbered sealed envelopes."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"At six-month follow-up, symptoms were assessed, a menstrual history was taken, and cytological and colposcopic examinations were performed by an independent observer unaware of which treatment method had been used." Unclear as to whether the outcome assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	% analysed: 70/78 (90%) By treatment arm: Cerclage: 37/42 (88%) Electrocautery: 33/36 (92%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

Doyle 1992

Study characteristics

Methods	RCT
Participants	182 women undergoing Large Loop Excision of the Transformation Zone (LLETZ) of the cervix.
Interventions	Monsel's Solution applied to cervical wound.

Doyle 1992 *(Continued)*

	No extra treatment.
Outcomes	Discharge as measured subjectively by women on daily sanitary pad chart.
Notes	50 women failed to complete their follow-up questionnaires excluded from analysis. 2 women had primary haemorrhages, 5 women were deemed to be unsuitable after randomisation. Assumed that randomisation is 1:1 so 63 randomised to Monsel's solution and 62 randomised to control, "it was calculated that by entering 60 patients into each arm of the study, there would be a greater than 85% chance of detecting a fall of 25% in the discharge score ...".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	"The women were randomised ... by sealed opaque envelope to either the control or the Monsel's group".
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	For all outcomes: % analysed: 125/182 (69%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Gilbert 1989

Study characteristics

Methods	RCT
Participants	200 consecutive women, 5 women did not wish to participate All women underwent a knife conisation under general anaesthesia, vasoconstrictors were not used.
Interventions	Haemostatic absorbable lateral sutures and additional sutures as deemed necessary Vaginal pack with Monsel's solution localised against cervix
Outcomes	Perioperative blood loss, primary and secondary haemorrhage, amenorrhoea and dysmenorrhoea, satisfactory colposcopy at follow-up
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Gilbert 1989 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Details about the sequence generation was not given, "Patients were randomly allocated to one or the other haemostatic method".
Allocation concealment (selection bias)	Low risk	"We performed the method allocation after the cone excision to ensure that previous knowledge of the haemostatic method could not influence the operator as to the size or shape of the cone". The method of concealment of allocation was carried out, "by opening one of a batch of sealed envelopes containing the appropriate instruction".
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	For all outcomes: % analysed: 200/205 (98%) 5 women did not wish to participate
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Gimpleson 1999

Study characteristics	
Methods	RCT
Participants	48 women undergoing Loop Electrosurgical Excision Procedure (LEEP) with various grades of CIN. There were 13 (27%) women with CIN 1, 21 (44%) with CIN 2 and 14 (29%) women with CIN 3.
Interventions	**Intervention:** Daily administration of intravaginal Amino-Cerv for two weeks following LEEP completed in a private office setting **Comparison:** Routine care: No intravaginal medication, refrain from intercourse, tampon use or douching for four weeks.
Outcomes	• Vaginal discharge • Cervical healing • Malodour • Inflammation
Notes	All patients were followed up at 2 and 4 weeks Secondary haemorrhage was deduced by fact that, "No patients needed to be seen for post-LEEP bleeding". **Healing of cervix:** At 2 weeks - Amino-Cerv: 19/24 not healed, routine care 24/24 not healed. At 4 weeks - Amino-Cerv: 4/24 not healed, routine care 15/24 not healed.

Gimpleson 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	% analysed: 48/48 (100%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Grundsell 1984(a)

Study characteristics

Methods	RCT
Participants	140 women undergoing laser cone biopsy as an out-patient procedure for severe dyskaryosis. All women had vasopressin injected into the cervix prior to treatment.
Interventions	Intravenous tranexamic acid during procedure and 1 g orally three times daily (tds) for 14 days
Outcomes	Primary and secondary haemorrhage
Notes	Citation duplicated to demonstrate two different study groups in analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported, "women ... prospectively randomised into one of two groups".
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	For primary and secondary haemorrhage: % analysed: 140/140 (100%)

Grundsell 1984(a) *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Patient baseline characteristics in the two groups were not reported so possibility of inexplicable differences between two groups.

Grundsell 1984(b)

Study characteristics	
Methods	RCT
Participants	220 women undergoing laser miniconization as an out-patient procedure for mild/moderate dyskaryosis. All women had vasopressin injected into the cervix prior to treatment.
Interventions	Intravenous tranexamic acid during procedure and 1 g orally tds for 14 days
Outcomes	Primary and secondary haemorrhage
Notes	Citation duplicated to demonstrate two different study groups in analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported, "patients were prospectively randomised into one group given tranexamic acid ... and another group not given antifibrinolytic therapy".
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	For primary and secondary haemorrhage: % analysed: 220/220 (100%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Patient baseline characteristics in the two groups were not reported so possibility of inexplicable differences between two groups.

Howells 2000

Study characteristics	
Methods	RCT
Participants	200 consecutive women undergoing LLETZ of the cervix.

Howells 2000 *(Continued)*

	Mean age in the trial was 35.5 years (SD = 10). Histology was given as follows: Normal: 12 (6%), CIN 1: 67 (33.5%), CIN 2/3: 114 (57%), Others: 5 (2.5%), Missing: 2 (1%).
Interventions	**Interventions:** Two different local anaesthetic combinations prior to LLETZ: • Prilocaine with felypressin • Lignocaine with adrenaline
Outcomes	• Bleeding • Discomfort • Pain from injection/LLETZ • Nausea
Notes	12/200 women had normal histology and 2 had missing histology data. Inclusion criteria included no prior treatment to the cervix and women within age range 20-60 years. The colposcopist was required to score 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'). Other side effects, such as feeling faint, nausea and shaking, were also scored in a similar fashion (0 = 'none; 5 = 'a great deal'). Prilocaine with felypressin | Lignocaine with adrenaline: Bleeding: 1.74 (0.98) | 1.33 (1.05) Pain from injection: 0.99 (0.97) | 1.15 (1.03) Pain from LLETZ: 0.45 (0.73) | 0.50 (0.79) Nausea: 0.18 (0.55) | 0.18 (0.64)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	"The women were randomised by an independent observer using simple randomisation with opaque sealed envelopes".
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Lee 1986

Study characteristics	
Methods	RCT
Participants	50 women undergoing laser vaporization
Interventions	Citanest (prilocaine with octapressin) No analgesia/ vasoconstrictor
Outcomes	Subjective grading of perioperative bleeding by operator
Notes	25 women randomised to Citanest 25 women randomised to no analgesia/ vasoconstrictor All patients were menopausal and aged between 19 and 39 years

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported, merely states, "study was a randomised comparison of two groups of 25 patients each ...".
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	For troublesome bleeding: % analysed: 50/50 (100%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Lipscomb 2006

Study characteristics	
Methods	RCT
Participants	100 women undergoing LEEP. Mean age in the trial was 29.4 years (SD = 9.9).
Interventions	**Interventions:** • Monsel's paste with fulguration • Ball electrode for haemostasis
Outcomes	• Pain

Lipscomb 2006 *(Continued)*

- Blood loss
- Discharge
- Recurrent abnormal pap

Notes	From CONSORT diagram it can be deduced that at least 71/77 women had CIN (71 were analysed for recurrent abnormal pap and 23 of initial 100 women enrolled in trial were lost to follow up). Haemostasis had a mean of 207.5 (SD = 393.6) in the ball electrode group and 118.7 (SD = 179.5) in the Monsel's paste group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were assigned randomly by computer-generated numbers".
Allocation concealment (selection bias)	Unclear risk	"Patients were assigned randomly by computer-generated numbers were placed in sealed envelopes".
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Follow-up information was collected by researchers who were unaware of the assigned treatment method".
Incomplete outcome data (attrition bias) All outcomes	Low risk	For vaginal discharge: % analysed: 94/100 (94%) For all other outcomes specified in our review the number of women analysed is at least 94%
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Lundvall 1984

Study characteristics

Methods	RCT: Placebo-controlled study
Participants	230 women undergoing knife cone biopsy under general anaesthesia 80 cones were performed with lateral and continuous wound sutures 150 cones were performed with lateral and Sturmdorf sutures
Interventions	Oral tranexamic acid 4.5 g daily for 12 days Placebo
Outcomes	Secondary haemorrhage, diarrhoea, nausea, perspiration, coldness, exanthema
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Lundvall 1984 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported, "we have carried out a randomized, double-blind study".
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double-blind study", but not reported whether or not outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For secondary haemorrhage: % analysed: 228/230 (99%) Tranexamic acid: 113/115 (98%) Placebo: 115/115 (100%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists. "The groups were homogeneous with regard to age and size of conus". However there may have been imbalances in other prognostic factors that were not reported.

Rybo 1972

Study characteristics	
Methods	RCT: Double-blind placebo-controlled study
Participants	50 women undergoing knife cone biopsy under general anaesthesia Haemostatic sutures were only inserted if troublesome perioperative bleeding Patients remained in hospital for at least 7 days post surgery
Interventions	Oral tranexamic acid 0.5 g tds for 12 days started on evening of surgery Placebo
Outcomes	Blood loss during first 7 postoperative days measured by examination of sanitary towels Significant secondary haemorrhage
Notes	2 patients from treatment group, 1 from placebo group excluded, patients had perioperative intracervical vasopressin 1 patient excluded from placebo group, had perioperative intravenous amino-caproic acid

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Rybo 1972 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double-blind placebo-controlled study", but not reported whether or not outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For secondary haemorrhage: % analysed: 45/50 (90%) Oral tranexamic acid; 22/25 (88%) Placebo; 23/25 (92%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Patient baseline characteristics in the two groups were not reported so possibility of inexplicable differences between two groups.

Sabol 1971

Study characteristics	
Methods	RCT: Double-blind placebo study
Participants	98 women undergoing knife cone biopsy under general anaesthesia women who were pregnant or had cardiovascular disease were excluded (6 in total) Cervical sutures were avoided but allowed if significant perioperative bleeding
Interventions	Intracervical vasopressin Intracervical saline
Outcomes	Perioperative blood loss, insertion of perioperative haemostatic sutures, primary and secondary haemorrhage
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Numbered vials containing either 30 ml of saline or 30 ml of saline containing vasopressin were prepared, where the numbers corresponded to a randomised code contrived and kept by member of pharmacy service who didn't participate in the study".
Allocation concealment (selection bias)	Low risk	"The randomisation code was not broken until the entire study was terminated".
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double-blind placebo study", but not reported whether or not outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For all outcomes: % analysed: 92/92 (100%)

Sabol 1971 *(Continued)*

		Some women were excluded but this was due to exclusion criteria rather than loss to follow up.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Patient baseline characteristics in the two groups were not reported so possibility of inexplicable differences between two groups.

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

Study	Reason for exclusion
Chan 2007	Women in trial did not have CIN confirmed by biopsy.
Cruickshank 2005	Trial does not report outcome measures as specified in protocol.
Foden-Shroff 1998	133 women had negative CIN histology, 5 had stage Ia carcinoma and 1 had adenocarcinoma in situ out of 500 women in the trial.
Harper 1997	This study was not an RCT.
Paraskevaidis 2001	Quasi-randomised trial, "One hundred one consecutive women ... were assigned alternately to two groups... as groups were assigned alternatively".
Paraskevaidis 2002	No comparison of relevant interventions.
Stefanidis 1998	Quasi-randomised trial, "Patients were randomly allocated to one of two groups according to the date of the procedure (odd date group A, even date group B)".

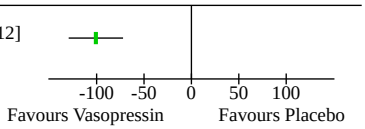
DATA AND ANALYSES

Comparison 1. Vasopressin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Measured blood loss (ml)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2 Subjective troublesome bleeding	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.3 Bleeding requiring haemostatic sutures, Vasopressin	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.4 Cervical stenosis	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

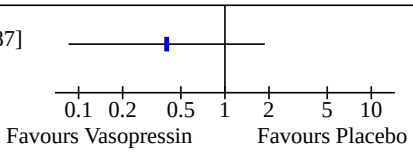
Analysis 1.1. Comparison 1: Vasopressin versus placebo, Outcome 1: Measured blood loss (ml)

Study or Subgroup	Vasopressin Mean	Vasopressin SD	Vasopressin Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Random, 95% CI
Sabol 1971	35.4	30.16	56	136.2	84.4	36	-100.80 [-129.48 , -72.12]



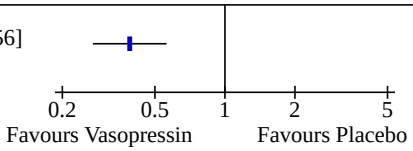
Analysis 1.2. Comparison 1: Vasopressin versus placebo, Outcome 2: Subjective troublesome bleeding

Study or Subgroup	Vasopressin Events	Vasopressin Total	Placebo Events	Placebo Total	Risk Ratio IV, Random, 95% CI
Lee 1986	2	25	5	25	0.40 [0.09 , 1.87]



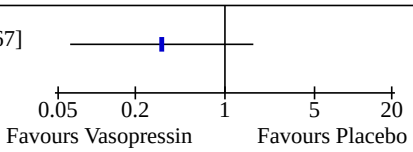
Analysis 1.3. Comparison 1: Vasopressin versus placebo, Outcome 3: Bleeding requiring haemostatic sutures, Vasopressin

Study or Subgroup	Vasopressin Events	Vasopressin Total	Placebo Events	Placebo Total	Risk Ratio IV, Random, 95% CI
Sabol 1971	20	56	33	36	0.39 [0.27 , 0.56]



Analysis 1.4. Comparison 1: Vasopressin versus placebo, Outcome 4: Cervical stenosis

Study or Subgroup	Vasopressin Events	Vasopressin Total	Placebo Events	Placebo Total	Risk Ratio IV, Random, 95% CI
Sabol 1971	2	56	4	36	0.32 [0.06 , 1.67]



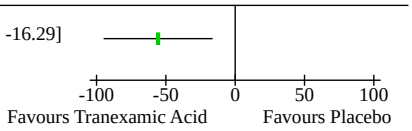
Comparison 2. Tranexamic acid versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Postoperative blood loss	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Primary haemorrhage	2	360	Risk Ratio (IV, Random, 95% CI)	1.24 [0.04, 38.10]
2.3 Secondary haemorrhage	4	633	Risk Ratio (IV, Random, 95% CI)	0.23 [0.11, 0.50]

Analysis 2.1. Comparison 2: Tranexamic acid versus control, Outcome 1: Postoperative blood loss

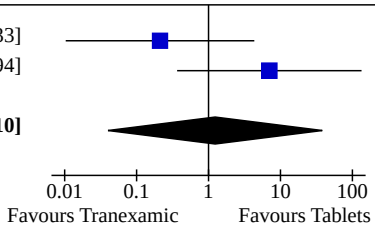
Study or Subgroup	Tranexamic acid Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
Rybo 1972	23.1	14.8	22	78.7	95	23	-55.60 [-94.91 , -16.29]



Analysis 2.2. Comparison 2: Tranexamic acid versus control, Outcome 2: Primary haemorrhage

Study or Subgroup	Tranexamic acid Events	Total	Oral tablets Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Grundsell 1984(a)	0	68	2	72	49.6%	0.21 [0.01 , 4.33]
Grundsell 1984(b)	3	110	0	110	50.4%	7.00 [0.37 , 133.94]
Total (95% CI)		**178**		**182**	**100.0%**	**1.24 [0.04 , 38.10]**
Total events:	3		2			

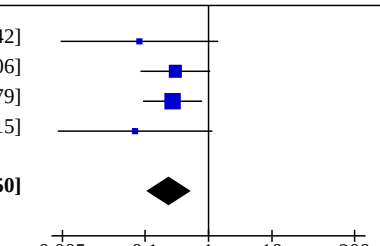
Heterogeneity: Tau² = 3.80; Chi² = 2.64, df = 1 (P = 0.10); I² = 62%
Test for overall effect: Z = 0.12 (P = 0.90)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Tranexamic acid versus control, Outcome 3: Secondary haemorrhage

Study or Subgroup	Tranexamic acid Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Grundsell 1984(a)	0	68	6	72	7.0%	0.08 [0.00 , 1.42]
Grundsell 1984(b)	3	110	10	110	35.9%	0.30 [0.08 , 1.06]
Lundvall 1984	4	113	15	115	49.8%	0.27 [0.09 , 0.79]
Rybo 1972	0	22	7	23	7.3%	0.07 [0.00 , 1.15]
Total (95% CI)		**313**		**320**	**100.0%**	**0.23 [0.11 , 0.50]**
Total events:	7		38			

Heterogeneity: Tau² = 0.00; Chi² = 1.47, df = 3 (P = 0.69); I² = 0%
Test for overall effect: Z = 3.76 (P = 0.0002)
Test for subgroup differences: Not applicable

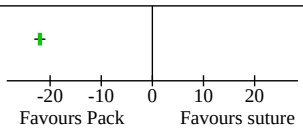


Comparison 3. Pack versus haemostatic suture

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Perioperative blood loss (ml)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.2 Primary haemorrhage	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.3 Secondary haemorrhage	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.4 Amenorrhoea	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.5 Dysmenorrhoea	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.6 Transformation zone not visible at colposcopy	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.7 Cervical stenosis	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

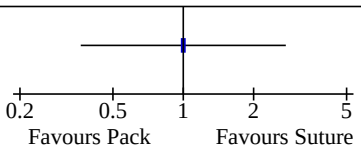
Analysis 3.1. Comparison 3: Pack versus haemostatic suture, Outcome 1: Perioperative blood loss (ml)

Study or Subgroup	Vaginal pack Mean	SD	Total	Suture Mean	SD	Total	Mean Difference IV, Random, 95% CI
Gilbert 1989	26	2.4	100	48	5	100	-22.00 [-23.09 , -20.91]



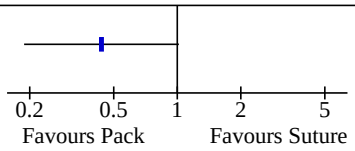
Analysis 3.2. Comparison 3: Pack versus haemostatic suture, Outcome 2: Primary haemorrhage

Study or Subgroup	Vaginal pack Events	Total	Suture Events	Total	Risk Ratio IV, Random, 95% CI
Gilbert 1989	7	100	7	100	1.00 [0.36 , 2.75]



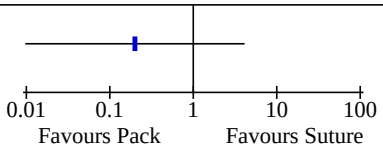
Analysis 3.3. Comparison 3: Pack versus haemostatic suture, Outcome 3: Secondary haemorrhage

Study or Subgroup	Vaginal pack Events	Total	Suture Events	Total	Risk Ratio IV, Random, 95% CI
Gilbert 1989	7	100	16	100	0.44 [0.19 , 1.02]



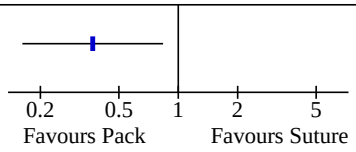
Analysis 3.4. Comparison 3: Pack versus haemostatic suture, Outcome 4: Amenorrhoea

Study or Subgroup	Vaginal Pack Events	Vaginal Pack Total	Suture Events	Suture Total	Risk Ratio IV, Random, 95% CI
Gilbert 1989	0	100	2	100	0.20 [0.01 , 4.11]



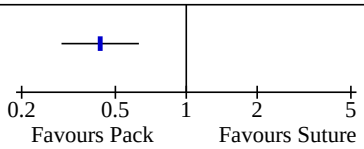
Analysis 3.5. Comparison 3: Pack versus haemostatic suture, Outcome 5: Dysmenorrhoea

Study or Subgroup	Vaginal pack Events	Vaginal pack Total	Suture Events	Suture Total	Risk Ratio IV, Random, 95% CI
Gilbert 1989	7	100	19	100	0.37 [0.16 , 0.84]



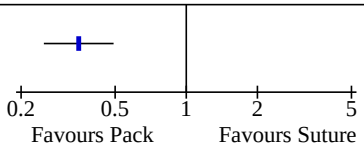
Analysis 3.6. Comparison 3: Pack versus haemostatic suture, Outcome 6: Transformation zone not visible at colposcopy

Study or Subgroup	Vaginal pack Events	Vaginal pack Total	Suture Events	Suture Total	Risk Ratio IV, Random, 95% CI
Gilbert 1989	25	100	58	100	0.43 [0.30 , 0.63]



Analysis 3.7. Comparison 3: Pack versus haemostatic suture, Outcome 7: Cervical stenosis

Study or Subgroup	Vaginal pack Events	Vaginal pack Total	Suture Events	Suture Total	Risk Ratio IV, Random, 95% CI
Gilbert 1989	27	100	77	100	0.35 [0.25 , 0.49]



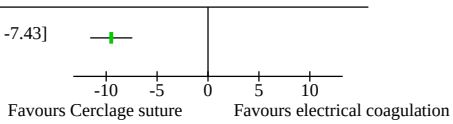
Comparison 4. Cerclage suture versus electrical coagulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Duration of procedure	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Primary haemorrhage	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.3 Secondary haemorrhage	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.4 Dysmenorrhoea	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.5 Unsatisfactory colposcopy	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

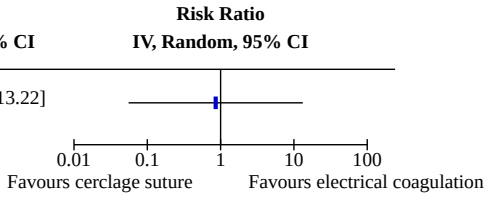
Analysis 4.1. Comparison 4: Cerclage suture versus electrical coagulation, Outcome 1: Duration of procedure

Study or Subgroup	Cerclage suture Mean	SD	Total	Electrical coagulation Mean	SD	Total	Mean Difference IV, Random, 95% CI
Dane 2008	5.7	1.8	42	15.2	6.1	36	-9.50 [-11.57 , -7.43]



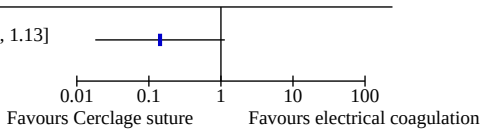
Analysis 4.2. Comparison 4: Cerclage suture versus electrical coagulation, Outcome 2: Primary haemorrhage

Study or Subgroup	Cerclage suture Events	Total	Electrical coagulation Events	Total	Risk Ratio IV, Random, 95% CI
Dane 2008	1	42	1	36	0.86 [0.06 , 13.22]



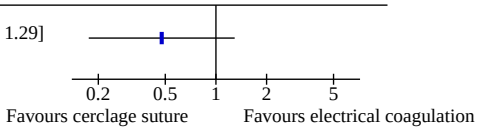
Analysis 4.3. Comparison 4: Cerclage suture versus electrical coagulation, Outcome 3: Secondary haemorrhage

Study or Subgroup	Cerclage suture Events	Total	Electrical coagulation Events	Total	Risk Ratio M-H, Random, 95% CI
Dane 2008	1	42	6	36	0.14 [0.02 , 1.13]

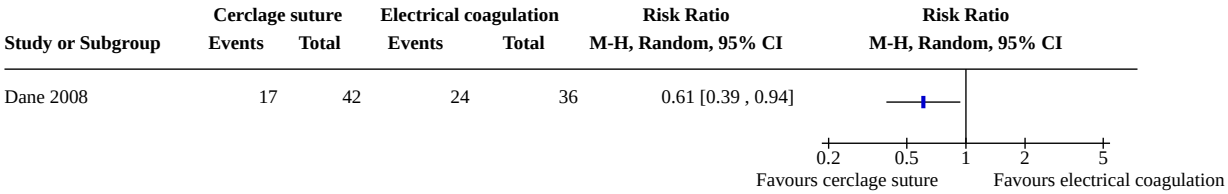


Analysis 4.4. Comparison 4: Cerclage suture versus electrical coagulation, Outcome 4: Dysmenorrhoea

Study or Subgroup	Cerclage suture Events	Total	Electrical coagulation Events	Total	Risk Ratio M-H, Random, 95% CI
Dane 2008	5	42	9	36	0.48 [0.18 , 1.29]



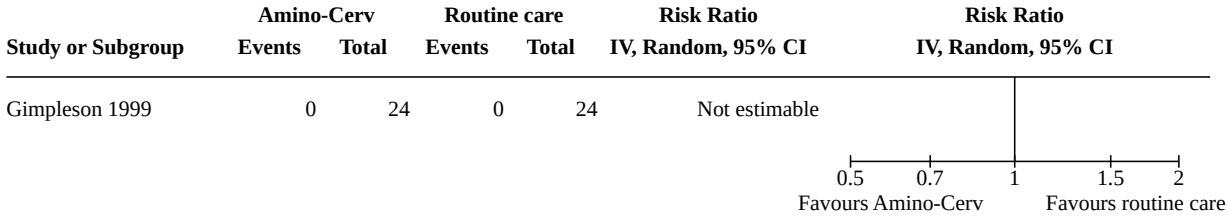
Analysis 4.5. Comparison 4: Cerclage suture versus electrical coagulation, Outcome 5: Unsatisfactory colposcopy



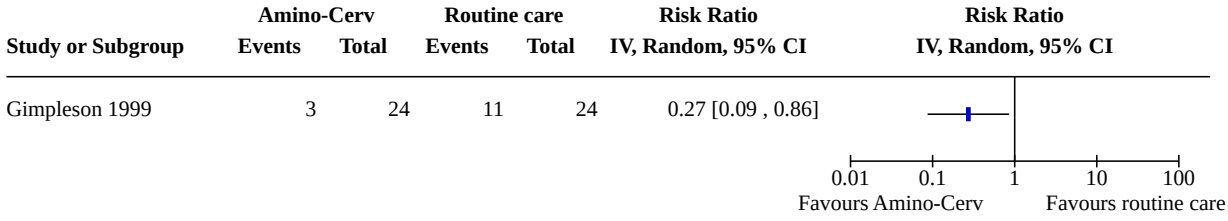
Comparison 5. Vaginal Amino-Cerv versus routine treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Secondary haemorrhage	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.2 Vaginal discharge at 2 weeks	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.3 Vaginal discharge at 4 weeks	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 5.1. Comparison 5: Vaginal Amino-Cerv versus routine treatment, Outcome 1: Secondary haemorrhage

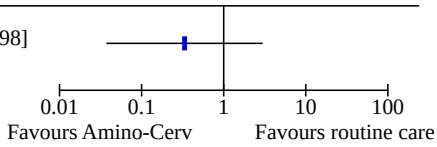


Analysis 5.2. Comparison 5: Vaginal Amino-Cerv versus routine treatment, Outcome 2: Vaginal discharge at 2 weeks



Analysis 5.3. Comparison 5: Vaginal Amino-Cerv versus routine treatment, Outcome 3: Vaginal discharge at 4 weeks

Study or Subgroup	Amino-Cerv Events	Amino-Cerv Total	Routine care Events	Routine care Total	Risk Ratio IV, Random, 95% CI
Gimpleson 1999	1	24	3	24	0.33 [0.04 , 2.98]

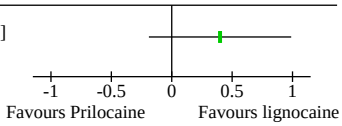


Comparison 6. Prilocaine with felypressin versus lignocaine with adrenaline in LLETZ

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Duration of procedure	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Analysis 6.1. Comparison 6: Prilocaine with felypressin versus lignocaine with adrenaline in LLETZ, Outcome 1: Duration of procedure

Study or Subgroup	Prilocaine with felypressin Mean	SD	Total	lignocaine with adrenaline Mean	SD	Total	Mean Difference IV, Random, 95% CI
Howells 2000	2.9	2.3	94	2.5	1.9	106	0.40 [-0.19 , 0.99]

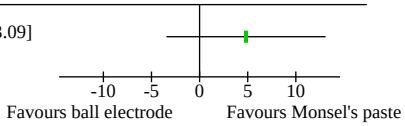


Comparison 7. Ball electrode versus Monsel's paste for haemostasis after LEEP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Blood loss	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Analysis 7.1. Comparison 7: Ball electrode versus Monsel's paste for haemostasis after LEEP, Outcome 1: Blood loss

Study or Subgroup	Ball electrode Mean	SD	Total	Monsel's solution Mean	SD	Total	Mean Difference IV, Random, 95% CI
Lipscomb 2006	20.2	26.2	53	15.38	15.1	47	4.82 [-3.45 , 13.09]



APPENDICES

Appendix 1. MEDLINE Search strategy

Medline Ovid

1 exp Cervical Intraepithelial Neoplasia/
2 CIN.mp.
3 (cervi* and (intraepithel* or epithel*)).mp.
4 (cervi* and dysplasia).mp.
5 (cervi* and carcinoma in situ).mp.
6 (cervi* and cancer in situ).mp.
7 (cervi* and (precancer* or pre-cancer*)).mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 randomized controlled trial.pt.
10 controlled clinical trial.pt.
11 randomized.ab.
12 placebo.ab.
13 clinical trials as topic.sh.
14 randomly.ab.
15 trial.ti.
16 9 or 10 or 11 or 12 or 13 or 14 or 15
17 (animals not (humans and animals)).sh.
18 16 not 17
19 8 and 18
20 limit 19 to yr="1997 - 2009"

key: mp=title, original title, abstract, name of substance word, subject heading word
pt=publication type
sh=Medical Subject Heading (Mesh)

Appendix 2. EMBASE search strategy

EMBASE Ovid

1. exp Uterine Cervix Carcinoma in Situ/
2. CIN.mp.
3. (cervi* and (intraepithel* or epithel*)).mp.
4. (cervi* and dysplasia).mp.
5. (cervi* and carcinoma in situ).mp.
6. (cervi* and cancer in situ).mp.
7. (cervi* and (precancer* or pre-cancer*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Randomized Controlled Trial/
10. Crossover Procedure/
11. Double Blind Procedure/
12. Single Blind Procedure/
13. random*.mp.
14. factorial*.mp.
15. (crossover* or cross over* or cross-over*).mp.
16. placebo*.mp.
17. (doubl* adj blind*).mp.
18. (singl* adj blind*).mp.
19. assign*.mp.
20. allocat*.mp.
21. volunteer*.mp.
22. or/9-21
23. 8 and 22
24. limit 23 to yr="1997 - 2009"

key: mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name

Appendix 3. CENTRAL search strategy

CENTRAL

1. MeSH descriptor Cervical Intraepithelial Neoplasia explode all trees
2. CIN
3. cervi* and (intraepithel* or epithel*)
4. cervi* and dysplasia
5. cervi* and carcinoma in situ
6. cervi* and cancer in situ
7. cervi* and (precancer* or pre-cancer*)
8. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
9. (#8), from 1997 to 2009

WHAT'S NEW

Date	Event	Description
23 November 2020	Review declared as stable	Four studies identified through horizon scanning of literature and added to Studies awaiting classification and Ongoing studies. These studies have not yet been incorporated into this Cochrane Review but the new information is unlikely to change the review findings. The conclusions of this Cochrane Review are therefore still considered up to date.

HISTORY

Review first published: Issue 1, 1999

Date	Event	Description
18 November 2013	New citation required but conclusions have not changed	No new studies identified for inclusion.
26 November 2012	New search has been performed	Literature searches re-run
11 May 2010	New citation required but conclusions have not changed	Review updated to reflect new Cochrane methodology and authorship.
20 November 1998	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Pierre Martin-Hirsch contributed to the original review and sifting, preparation and discussions of the updates. Andrew Bryant and Heather Dickinson updated the review in 2010.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Manchester, UK

External sources

- Department of Health, UK

  NHS Cochrane Collaboration programme Grant Scheme CPG-506

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There was an insufficient number of trials in each of the meta-analyses to assess reporting biases and carry out sensitivity analysis so the following sections were 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 such as publication bias. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random effects model, further meta-analyses will be performed using fixed-effect models.

Sensitivity analysis

Sensitivity analyses will be performed excluding trials which did not report adequate (i) concealment of allocation, (ii) blinding of the outcome assessor.

None of the trials imputed missing data. Although some of the outcomes that we specified were not reported in included trials, we did not contact trial authors as all trials except two reported over 10 years ago. The most recent trials of Dane 2008 and Lipscomb 2006 reported the primary outcomes that we specified. We removed the following text from the 'dealing with missing data' section:

Dealing with missing data

If data were missing or only imputed data were reported we contacted trial authors to request data on the outcomes only among participants who were assessed.

INDEX TERMS

Medical Subject Headings (MeSH)

Blood Loss, Surgical [prevention & control]; Cervical Intraepithelial Neoplasia [*surgery]; Ferric Compounds [therapeutic use]; Hemostasis, Surgical [*methods]; Hemostatics [therapeutic use]; Inositol [therapeutic use]; Methionine [therapeutic use]; Randomized Controlled Trials as Topic; Sulfates [therapeutic use]; Sutures; Tranexamic Acid [therapeutic use]; Urea [therapeutic use]; Uterine Cervical Neoplasms [*surgery]; Vaginal Creams, Foams, and Jellies [therapeutic use]; Vasopressins [therapeutic use]

MeSH check words

Female; Humans