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Pain relief for outpatient hysteroscopy (Review)

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[Intervention Review]

Pain relief for outpatient hysteroscopy

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ABSTRACT

Background

Hysteroscopy is increasingly performed in an outpatient setting. Pain is the primary reason for abandonment of procedure or incomplete assessment. There is no consensus upon routine use of analgesia during hysteroscopy.

Objectives

To assess the effectiveness and safety of pharmacological interventions for pain relief in women undergoing outpatient hysteroscopy, compared with placebo, no treatment or other pharmacological therapies.

Search methods

In September 2016 we searched the Cochrane Gynaecology and Fertility (CGF) Trials Register, CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL and two trials registers (ClinicalTrials.gov and WHO ICTRP), together with reference checking and contact with study authors and experts.

Selection criteria

We included randomised controlled trials (RCTs) comparing use of pharmacological interventions with other pharmacological interventions and pharmacological interventions versus placebo or no treatment.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Our primary outcome was mean pain score.

Main results

We included 32 RCTS (3304 participants), of which only 19 reported data suitable for analysis. Most studies were at unclear or high risk of bias in most of the domains assessed. The evidence was low or very low quality, mainly due to risk of bias and imprecision. Baseline pain scores were relatively low in all groups.

Analgesic versus placebo or no treatment

Local anaesthetics

Local anaesthetics reduced mean pain scores during the procedure [(SMD) -0.29, 95% CI -0.39 to -0.19, 10 RCTs, 1496 women, I^2 = 80%, low-quality evidence)] and within 30 minutes (SMD 0.50, 95% CI -0.67 to -0.33, 5 RCTs, 545 women, I^2 = 43%, low-quality

evidence). This translates to a difference of up to 7 mm on a 0-10 cm visual analogue scale (VAS) during the procedure and up to 13 mm within 30 minutes, which is unlikely to be clinically meaningful. There was no clear evidence of a difference between the groups in mean pain scores after > 30 minutes (SMD -0.11, 95% CI -0.30 to 0.07, 4 RCTs, 450 women, I^2 = 0%, low-quality evidence), or in rates of vasovagal reactions (OR 0.70, 95% CI 0.43 to 1.13, 8 RCTs, 1309 women, I^2 = 66%, very low-quality evidence). There was insufficient evidence to determine whether there was a difference in rates of non-pelvic pain (OR 1.76, 95% CI 0.53 to 5.80, 1 RCT, 99 women, very low-quality evidence).

Nonsteroidal anti-inflammatory drugs (NSAIDs)

There was insufficient evidence to determine whether there was a difference between the groups in mean pain scores during the procedure (SMD -0.18, 95% CI -0.35 to 0.00, 3 RCTs, 521 women, I^2 = 81%, low-quality evidence). Pain scores were lower in the NSAIDs group within 30 minutes (SMD -0.25, 95% CI -0.46 to -0.04, 2 RCTs, 340 women, I^2=29%, low-quality evidence) and at over 30 minutes (SMD -0.27, 95% CI -0.49 to -0.05, 2 RCTs, 321 women, I^2 = 78%, low-quality evidence). This equates to maximum differences of under 7.5 mm on a 0-10 cm scale, which are unlikely to be clinically significant. One RCT (181 women) reported adverse events: there was insufficient evidence to determine whether there was a difference between the groups in vasovagal reactions (OR 0.76, 95% CI 0.20 to 2.94, very low-quality evidence). For other reported adverse events (non pelvic pain and allergic reactions) evidence was lacking.

Opioids

One RCT utilised sublingual buprenorphine and one utilised oral tramadol. Data on pain scores during the procedure were unsuitable for pooling due to inconsistency. Tramadol was associated with a benefit of up to 22 mm on a 0-10 cm scale (SMD -0.76, 95% CI -1.10 to -0.42, 1 RCT, 140 women). However, the effect estimate for this outcome for sublingual opioids did not support a benefit from the intervention (SMD 0.08, 95% CI -0.22 to 0.39, 164 women). Compared with placebo, the pain score within 30 minutes of the procedure was reduced in the tramadol group, with a difference of up to 17mm on a 0-10cm scale (SMD -0.57, 95% CI -0.91 to -0.23 , 1 RCT, 140 women, low-quality evidence. There was no clear evidence of a difference between the tramadol and placebo groups at over 30 minutes (SMD -0.17, 95% CI -0.51 to 0.16, 1 RCT, 140 women, low-quality evidence). Nausea and vomiting occurred in 39% of the buprenorphine group, and in none of the placebo group (OR 107.55, 95% CI 6.44 to 1796.46)

Analgesic versus any other analgesic

Some comparisons did not report pain scores at all time frames of interest, and none reported data on adverse events.

One RCT (84 women) compared local intracervical anaesthesia versus combined intracervical and paracervical anaesthesia. Pain scores were higher in the group with local intracervical anaesthesia during the procedure (SMD 4.27, 95% CI 3.49 to 5.06, very low-quality evidence), within 30 minutes (SMD 1.55, 95% CI 1.06 to 2.05, very low-quality evidence) and at more than 30 minutes (SMD 3.47, 95% CI 2.78 to 4.15, very low-quality evidence). This translates to a possible benefit in the combined group of up to 12 mm on a 0-10 cm scale during the procedure. Benefits at longer follow-up were smaller.

One RCT compared antispasmodic + NSAID versus local paracervical anaesthesia. Pain scores were lower in the NSAID group than in the local anaesthesia group (during procedure: SMD -1.40, 95% CI -1.90 to -0.91; >30 minutes after procedure: SMD -0.87, 95% CI -1.33 to -0.41; 80 women, very low-quality evidence). This suggests a possible benefit of during the procedure of up to 23 mm on a 0-10 VAS scale and up to 11 mm >30 minutes after the procedure.

Other comparisons included local intracervical anaesthesia versus combined intracervical, paracervical and topical anaesthesia, and opioid versus NSAIDs. Findings were inconclusive.

Authors' conclusions

There was no consistent good-quality evidence of a clinically meaningful difference in safety or effectiveness between different types of pain relief compared with each other or with placebo or no treatment in women undergoing outpatient hysteroscopy.

PLAIN LANGUAGE SUMMARY

Pain relief for hysteroscopy as an outpatient

Review question

The purpose of this review was to determine which, if any, pain relief drug is effective at reducing the discomfort experienced with outpatient hysteroscopy.

Background

Hysteroscopy is a diagnostic test undertaken to identify the cause of abnormal uterine bleeding. Hysteroscopy involves fluid or gas being injected via the cervix into the uterus, enabling the visualisation of the cervical canal and uterine cavity with a hysteroscope, which can be painful. There is disagreement regarding the best form of pain relief during the procedure.

Study characteristics

We included 32 randomised controlled trials (RCTs), with 3304 participants, of which only 19 reported data suitable for analysis.

All studies took place in a clinical setting. The age of the participants ranged from 33 to 61 years. Studies took place in Australia, Belgium, Brazil, Canada, China, France, Greece, India, Italy, Spain, Taiwan, UK, USA. Baseline pain scores in all groups were relatively low. The evidence is current to September 2016.

Key results

There was no consistent good-quality evidence of a clinically meaningful difference in safety or effectiveness between different types of pain relief compared with each other or with placebo or no treatment in women undergoing outpatient hysteroscopy.

Quality of the evidence

Most studies were at unclear or high risk of bias in most of the domains assessed. The evidence was low or very low quality, mainly due to risk of bias and imprecision.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Local anaesthetic compared to placebo or no treatment for outpatient hysteroscopy

Population: women undergoing outpatient hysteroscopy
Setting: outpatient hysteroscopy clinic
Intervention: local anaesthetic
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with local anaesthetic				
Pain score during procedure	The mean pain score ranged from 0.86 to 4.3 on a 0-10 cm VAS	SMD 0.29 SD lower (0.39 lower to 0.19 lower)	-	1496 (10 studies)	⊕⊕◯◯ **low**[1,2]	This suggests a marginally lower pain score in the intervention group, equating to up to 7 mm on a 0-10 cm point VAS. This is unlikely to be clinically significant
Pain score within 30 min of procedure	The mean pain score ranged from 1.8 to 6.3 on a 0-10 cm VAS	SMD 0.5 SD lower (0.67 lower to 0.33 lower)	-	545 (5 studies)	⊕⊕◯◯ **low**[1]	This suggests a marginally lower pain score in the intervention group, equating to up to 13 mm on a 0-10 cm point VAS. This is unlikely to be clinically significant
Pain score more than 30 min after procedure	The mean pain score ranged from 0.62 to 1.8 on a 0-10 cm VAS	SMD 0.11 SD lower (0.3 lower to 0.07 higher)	-	450 (4 studies)	⊕⊕◯◯ **low**[3,4]	There was no clear evidence of a difference between the groups

Vasovagal reaction	63 per 1000	45 per 1000 (28 to 71)	OR 0.70 (0.43 to 1.13)	1309 (8 studies)	⊕◯◯◯ **very low**[1,4]	There was no clear evidence of a difference between the groups
Non-pelvic pain	100 per 1000	164 per 1000 (56 to 392)	OR 1.76 (0.53 to 5.80)	99 (1 study)	⊕◯◯◯ **very low**[1,3]	There was insufficient evidence to determine whether there is a difference between the groups

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the mean risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **SMD**: standardised mean difference; **SD**: standard deviation; **OR:** odds ratio; **VAS**: visual analogue scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded two levels for serious risk of bias: none of the studies adequately described methods of allocation concealment and methods of blinding were unclear or inadequate in many studies.
[2]High statistical heterogeneity (I^2 = 80%), but not downgraded as direction of effect was consistent.
[3]Downgraded one level for serious risk of bias: none of the studies adequately described methods of allocation concealment.
[4]Downgraded one level due to serious imprecision - wide confidence interval or low event rate, or both.

BACKGROUND

Description of the condition

Outpatient hysteroscopy is an established diagnostic gynaecological procedure that enables a clinician to visualise the uterine cavity and take endometrial biopsies or perform small intracavitary procedures as required. Hysteroscopy involves the use of miniaturised endoscopic equipment to examine the uterine cavity. As one of the principal investigations of abnormal uterine bleeding, hysteroscopy has an integral role in the identification of structural abnormalities of the endometrium (NICE guidelines 2007). Outpatient hysteroscopy can also be employed for procedures such as removal of lost intrauterine devices, endometrial polypectomy and work-up of reproductive problems (Robinson 2013; Sinha 2007). The procedure is performed without the need for theatre facilities and regional or general anaesthesia. Advantages to both the healthcare providers and women, include decreased complication rates, shorter recovery time, decreased costs and the scope for a 'see and treat' service (Ma 2016; Saridogan 2010). Although safe, studies of the acceptability of outpatient hysteroscopy have displayed various completion rates, ranging between 77% to 97.2% (Agostini 2003; Critchley 2004; De Iaco 2000; De Jong 1990), with pain cited as the most common cause for failure to complete the investigation (Critchley 2004; Jivraj 2004; Nagele 1997; Paschopoulos 1997). During hysterosalpingography (HSG), pain peaks from the time of instillation of the contrast media until five minutes after the procedure; the pain starts to decrease rapidly between five and 10 minutes after the procedure so that at 30 minutes most women classify it as a 'discomfort' (Owens 1985).

The pain experienced is due to several factors including cervical instrumentation, uterine distension and peritoneal irritation from spill of dilatation media. Pain stimuli from the cervix and vagina are conducted by the pelvic splanchnic nerves whereas pain sensation from intraperitoneal structures, such as the uterine body, is conducted by the hypogastric nerves (Moore 2006). Destruction of the endometrium and endometrial biopsy can cause further pain as they may induce uterine contraction (Zupi 1995). Additional delayed pain is also caused by the release of prostaglandins from the cervical manipulation as well as distension of the uterus. Furthermore, blind cervical dilatation, cervical stenosis or tortuosity may increase chances of uterine lacerations (Jansen 2000; Pasini 2001).

Other factors that may impact on pain experienced include the type and size of hysteroscope used, choice of distension media and technique employed. It is recommended that miniature hysteroscopes (2.7 mm, with a 3 mm to 3.5 mm sheath) should be used for diagnostic outpatient hysteroscopy to reduce discomfort (Green-top Guidelines No. 59; Paulo 2015). Use of a vaginoscopic approach has also been advocated to reduce pain experienced (Cooper 2010b). Systematic reviews have demonstrated varied results for difference in pain experienced based upon distension media used although fewer vasovagal episodes are reported with the use of saline when compared to carbon dioxide (Cooper 2011; Craciunas 2013).

Description of the intervention

There are numerous studies that have reported varied outcomes in terms of the effectiveness of different pharmacological interventions for pain relief during hysteroscopy. We have investigated the effect of any one type of pharmacological intervention (opioids, local anaesthetic, non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol) for pain relief during hysteroscopy compared with another type, or with placebo.

How the intervention might work

De Iaco 2000 observed that 34.8% of women who undergo anaesthesia-free diagnostic hysteroscopy reported severe pain. Pain is mainly produced when the speculum or tenaculum are placed, with cervical dilation, passage of the hysteroscope through the cervical canal, and distension of the uterus with fluid. Operative procedures that damage the endometrial wall are also painful. The pain experienced can have a negative impact on the woman's ability to fully co-operate with the procedure. Through successful anaesthesia (including paracervical and intracervical anaesthesia) and application of topical agents in the cervical canal and endometrial cavity, we hope to target more than one site. This will result in pain relief and better tolerance of the procedure.

Why it is important to do this review

A study reported a wide variation in clinical practice in the UK in terms of the use of analgesia for outpatient hysteroscopy (O'Flynn 2011). Generally, while pain relief is common in clinical practice the evidence is uncertain on its effect. The review aims to assess the effectiveness of the various pain relief methods available.

The Royal College of Obstetricians and Gynaecologists recommend that women with no contraindications should consider taking a standard dose of a NSAID at least an hour before their appointment (Green-top Guidelines No. 59). These guidelines also recommended consideration of the use of topical local cervical anaesthesia during cervical tenaculum use.

With the vast potential for its use in the primary care setting, a consensus upon the safest and most efficacious method of pain relief for outpatient hysteroscopy would be advantageous.

The purpose of the meta-analysis was therefore to compare the effectiveness and safety of different types of pharmacological interventions for pain relief in women undergoing outpatient hysteroscopy.

OBJECTIVES

To assess the effectiveness and safety of pharmacological interventions for pain relief in women undergoing outpatient hysteroscopy, compared with placebo, no treatment or other pharmacological therapies.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing any one type of pharmacological intervention for pain relief during outpatient hysteroscopy with another type, placebo, or no treatment. We excluded non-randomised studies (e.g. studies with inadequate sequence generation, patient numbers) as they are associated with a high risk of bias. We also excluded cross-over trials, as the design is not valid in this context.

Types of participants

Adult (aged over 18 years) women attending for an outpatient hysteroscopy.

Types of interventions

We analysed the following interventions.

- Analgesics (topical or oral) versus placebo or no treatment
  - Opioids versus placebo or no treatment
  - Local anaesthetics versus placebo or no treatment
  - NSAIDs versus placebo or no treatment
  - Paracetamol or similar versus placebo or no treatment.
- Analgesics (topical or oral or inhaled) versus other analgesics
  - Opioids versus paracetamol
  - Opioids versus local anaesthetics
  - Opioids versus NSAIDS
  - Local anaesthetics versus NSAIDs
  - NSAIDs versus paracetamol
  - Paracetamol versus local anaesthetics (LA)
  - Any analgesic versus any other analgesic

We performed subgroup analysis by route of administration. Dosages and routes used in the studies are displayed in Table 1.

Types of outcome measures

Primary outcomes

- Pain score
  - Pain score during the procedure (validated pain scale)
  - Pain score after the procedure (validated pain scale): a) within the first 30 minutes of the procedure b) more than 30 minutes after the procedure

We used the earliest mean pain score if a study reported a mean pain score on two different occasions, within the same group.
In the meta-analysis, where it was reported we used a VAS score, as this was the one validated score consistently reported across the studies.
Jensen 2002 performed an analysis of two RCTs to assess the amount of change on a VAS, corresponding to differing levels of pain relief. The findings suggested that a 33% decrease in pain represents a reasonable standard for determining that a change in pain is meaningful from the patient's perspective.

Secondary outcomes

- Failure to complete the procedure
- Adverse effects and complications: nausea, vomiting, constipation, drowsiness, respiratory depression, hypotension, allergic reaction, and infection

Search methods for identification of studies

Electronic searches

We searched the Cochrane Gynaecology and Fertility (formerly MDSG) Specialised Register of controlled trials for any trials, with key words and title, from inception until 15 September 2016 (Appendix 1). We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, issue 9) via the Cochrane Register of Studies Online (CRSO) (Appendix 2), Ovid MEDLINE from inception to 15 September 2016 (Appendix 3), Ovid Embase from inception to 15 September 2016 (Appendix 4), Ovid PsycINFO from inception to 15 September 2016 (Appendix 5), and EBSCO CINAHL from inception to 15 September 2016 (Appendix 6). Additional keywords and Mesh terms were added to the search strategies for this update.

Searching other resources

We searched references from reviewed articles to identify any eligible trials not found in the primary search, however we did not identify any additional eligible trials. We also searched registers of ongoing trials including US National Institutes of Health (ClinicalTrials.gov), The World Health Organization International Trials Registry Platform search portal (WHO ICTRP) and LILACS.

Data collection and analysis

Selection of studies

Two review authors (GA and HO'F, initial review; HO'F, DL and SS, 2017 update) independently assessed the trials for eligibility to be included in accordance with the eligibility criteria. AW resolved disagreements.

Data extraction and management

We examined titles and abstracts in order to include trials that matched the inclusion criteria. We sought full-text reports to confirm eligibility and contacted study authors where necessary. Review authors (GA, SA, HO'F, initial review; GA, DL, SS and HO'F for 2017 update) independently extracted data. GA resolved disagreements (AW, initial review). We examined trials for the following: source, eligibility, methodological details, interventions (routes of delivery, doses, timing), descriptive data of participants (age, co-morbidities), outcomes, and funding sources. Data were entered into a data collection form and managed within a Microsoft Access database before input into Review Manager 5 (RevMan 5) (RevMan 2014).

Assessment of risk of bias in included studies

We used the Cochrane 'Risk of bias' tool for assessing risk of bias in each study (Higgins 2011). The domains that we considered were: sequence generation and allocation concealment (selection bias); blinding of personnel, participants and outcome assessors (performance and detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other bias. We managed information within 'Risk of bias' tables (see Characteristics of included studies; Figure 1; Figure 2). Three review authors (SS, HO'F and GA,) independently performed all assessments of the risk of bias of trials and extracted data (2017 update). All discrepancies were resolved by GA (2017 update; AW, initial review). We sought additional information on trial methodology and trial data from the authors of trials that appeared to meet the eligibility criteria but had aspects of methodology that were unclear, or where the data were in a form that was unsuitable for meta-analysis.

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

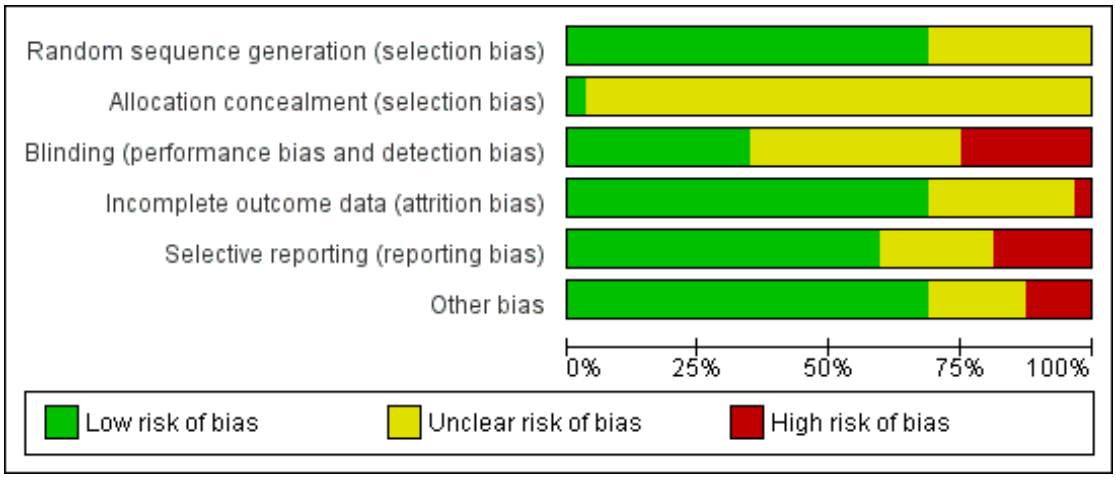
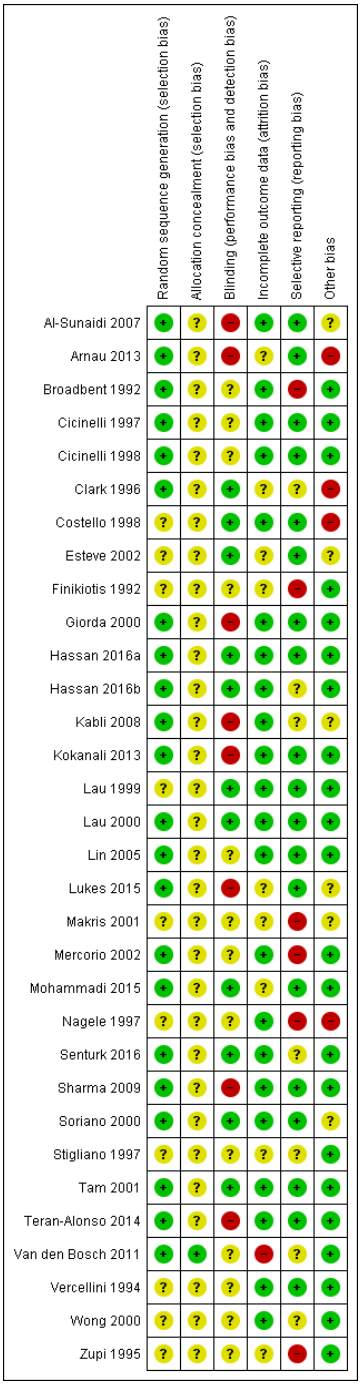


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study



Measures of treatment effect

Any validated pain scale was acceptable for inclusion of a trial into the review. We have translated our main results into a difference on a commonly used scale (visual analogue scale (VAS)) to demonstrate clinical importance. We used this instead of the peak mean pain score, as pain peaks from the time of distension until five minutes after the procedure, so that at 30 minutes most women classify the pain as a discomfort (Owens 1985). For significant results we used the smallest standard deviations and for results of no significance we used the largest standard deviations. We analysed the data and compared them according to the timing of the pain. We divided the groups as follows: pain during the procedure; pain within the first 30 minutes of the procedure; and pain more than 30 minutes following the procedure. For dichotomous data (e.g. adverse events), we used the numbers of events in the control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (ORs). For continuous data, we calculated the standardised mean difference (SMD).

Unit of analysis issues

Primary analysis for this review was per woman randomised. We addressed the following:

- groups of individuals randomised together to the same intervention;
- individuals undergoing more than one intervention.

Dealing with missing data

We analysed data on an intention-to-treat basis as far as possible and attempted to obtain missing data from the original trialists. We did not undertake imputation and only analysed available data.

Assessment of heterogeneity

We used four methods to assess heterogeneity.

- We performed a Chi² test. If significant, we judged that there would be a strong possibility of high heterogeneity.
- We calculated the I² statistic to help determine heterogeneity (Higgins 2003). As a guide, we used the following thresholds (Deeks 2011):
    - 0% to 40%: might not be important;
    - 30% to 60%: may represent moderate heterogeneity;
    - 50% to 90%: may represent substantial heterogeneity;
    - 75% to 100%: considerable heterogeneity.
- Overlap of the confidence interval of individual trials
- Variations in the point estimate of individual trials

After considering these four methods we made a judgement on whether there was significant heterogeneity in the meta-analysis, and detailed our reasons in the text.

Assessment of reporting biases

We aimed to minimise the potential impact of reporting bias by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. We planned to use a funnel plot to assess publication bias, if there were more than 10 studies in the same analysis (Sterne 2011).

Data synthesis

We performed statistical analysis in accordance with the guidelines for statistical analysis developed by Cochrane (Deeks 2011). When interpreting the results of the comparison of an intervention to a placebo, a negative SMD indicates that an intervention is superior to a placebo in terms of ability to reduce levels of pain and a positive SMD indicates that a placebo is superior to an intervention. We reported adverse effects as odds ratios (OR), with a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

Where data were available, we planned to conduct subgroup analyses for the primary outcome, to determine the separate evidence within the following subgroups:

- Postmenopausal women
- Different routes of delivery

If there was substantial heterogeneity (I^2 greater than 50%), we planned to explore differences between the studies that might account for the heterogeneity.

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding eligibility of studies and analysis. These analyses included consideration of whether review conclusions differed if:

- eligibility was restricted to studies without high risk of bias;
- a random-effects model had been adopted; or
- risk ratio had been used as the summary effects measure.

Overall quality of the body of evidence: 'Summary of findings' table

We assessed the quality of the evidence using GRADE criteria: risk of bias (with regard to internal validity), consistency of effect, imprecision, indirectness and publication bias). Two review authors

working independently made judgements about evidence quality (high, moderate, low or very low), resolving any disagreements by discussion. We prepared 'Summary of findings' tables for the review outcomes pain score during and post procedure and adverse events for the main review comparison (local anaesthetic versus placebo). We also prepared additional 'Summary of findings' tables for the main review outcomes for other important comparisons (NSAIDS versus placebo or no treatment, opioids versus placebo or no treatment, selected head-to-head comparisons as space allowed). We justified and documented our judgements, and incorporated them into reporting of results for each outcome.

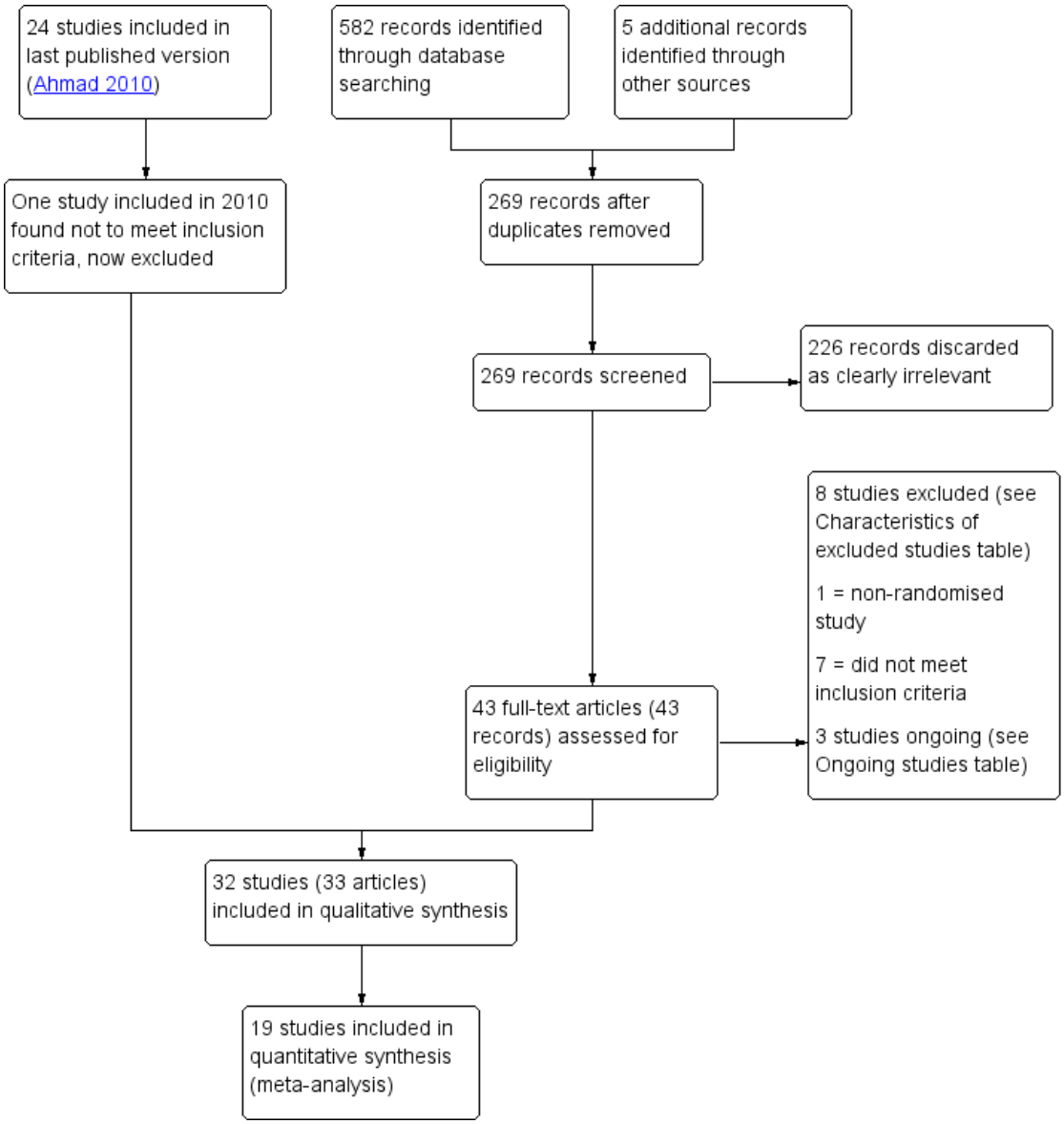
RESULTS

Description of studies

Results of the search

We identified a total of 47 potentially eligible studies using the search strategy and included 32 (3304 participants) studies within our review; however, we included only 19 studies (2801 participants) in the analyses as we could not accurately interpret the data from the other 13 studies and our attempts to obtain the missing data were unsuccessful. Three studies are ongoing. See Figure 3 for details of the screening and selection process. See also Characteristics of included studies and Characteristics of excluded studies.

Figure 3. Study flow diagram



Included studies

We included 32 RCTs (3304 participants), of which only 19 (Figure 3) reported data relevant to our review outcomes that were suitable for analysis (Al-Sunaidi 2007; Arnau 2013; Cicinelli 1997; Cicinelli 1998; Costello 1998; Esteve 2002; Giorda 2000; Hassan 2016a, Kokanali 2013; Lau 1999; Lau 2000; Lin 2005; Lukes 2015; Sharma 2009; Soriano 2000; Tam 2001; Teran-Alonso 2014; Vercellini 1994; Wong 2000).

Studies took place in Australia, Belgium, Brazil, Canada, China, France, Greece, India, Italy, Spain, Taiwan, UK and USA.

Interventions

Three studies compared analgesic methods versus no treatment: Kokanali 2013; Teran-Alonso 2014; and Vercellini 1994.

Twenty-one studies compared analgesic methods versus placebo: Al-Sunaidi 2007; Arnau 2013; Broadbent 1992; Cicinelli 1997; Cicinelli 1998; Clark 1996; Costello 1998; Esteve 2002; Giorda 2000; Hassan 2016a; Hassan 2016b; Lau 1999; Lau 2000; Lin 2005; Makris 2001; Nagele 1997; Senturk 2016; Soriano 2000; Tam 2001; Van den Bosch 2011; Wong 2000; and Zupi 1995.

Eight studies compared different types of analgesia: Finikiotis 1992; Hassan 2016a; Kabli 2008; Lukes 2015; Mercorio 2002; Mohammadi 2015; Sharma 2009; and Stigliano 1997.

Some studies included more than one type of comparison.

The studies with data suitable for analysis made the following comparisons:

- local anaesthetic versus placebo (Arnau 2013; Cicinelli 1997; Cicinelli 1998; Costello 1998; Esteve 2002; Kokanali 2013; Lau 1999; Lau 2000; Soriano 2000; Wong 2000);
- local anaesthetic versus no intervention (Giorda 2000; Vercellini 1994);
- NSAID (with or without paracetamol) versus no medication (Hassan 2016a; Tam 2001; Teran-Alonso 2014);
- oral or sublingual opioid versus placebo (Hassan 2016a; Lin 2005);
- intracervical anaesthesia versus combined intracervical and paracervical anaesthesia (Al-Sunaidi 2007);
- intracervical anaesthesia versus combined intracervical, paracervical and topical anaesthesia (Lukes 2015);
- antispasmodic plus NSAID (mefenamic acid and oral drotaverine) versus local paracervical anaesthesia (Sharma 2009);
- oral opioid (tramadol) versus oral NSAID (celecoxib) (Hassan 2016a).

Local anaesthetics used in these studies included mepivacaine paracervical block (Giorda 2000; Vercellini 1994), lignocaine paracervical block (Lau 1999), 1% lidocaine applied for a set time to the cervix before injection of local anaesthetic (Lukes 2015), lidocaine intracervical block (Esteve 2002; Kokanali 2013), lignocaine transcervical intrauterine local anaesthetic (Costello 1998; Lau 2000), mepivacaine transcervical intrauterine local anaesthetic (Cicinelli 1997; Cicinelli 1998), lignocaine spray (Soriano 2000), lignocaine gel (Wong 2000) and endocervical and exocervical lidocaine/prilocaine cream (Arnau 2013). See Table 1 for details.

We did not identify any studies that investigated the use of paracetamol alone.

The studies that did not report data suitable for analysis for our review outcomes made the following comparisons:

- local anaesthesia versus placebo or no treatment (Broadbent 1992; Clark 1996; Makris 2001; Van den Bosch 2011; Zupi 1995). Interventions used in these studies included intracervical block (Broadbent 1992; Makris 2001), lidocaine gel (Clark 1996; Van den Bosch 2011) and mepivacaine (Zupi 1995);
- oral mefenamic acid versus placebo (Nagele 1997);
- oral opioid (tramadol) versus placebo (Hassan 2016b);
- paracervical block versus uterosacral block (Finikiotis 1992);
- oral dexketoprofen versus intracervical block (Mercorio 2002);
- lidocaine and prilocaine cream versus lidocaine spray (Stigliano 1997);
- rectal diclofenac versus intrauterine lidocaine (Mohammadi 2015);
- local cervical versus combined cervical and intrauterine anaesthesia (Kabli 2008);
- intrauterine lidocaine versus rectal indomethacin and placebo (Senturk 2016).

Participants

The mean age of participants in the review ranged from 29 to 61 years. Both pre- and postmenopausal women were included in the majority of selected trials. Three studies investigated the use of analgesia in outpatient hysteroscopy amongst women who were postmenopausal (Cicinelli 1997; Cicinelli 1998; Giorda 2000).

Outcomes

Among studies with data suitable for analysis, 18 studies investigated the use of analgesia upon pain relief during hysteroscopy; eight studies investigated the use of analgesia upon pain relief within 30 minutes after hysteroscopy; and nine studies investigated the use of analgesia upon pain relief more than 30 minutes after hysteroscopy. Most of these studies used a standardised 0-10 cm-point VAS (Al-Sunaidi 2007; Arnau 2013; Costello 1998; Esteve 2002; Hassan 2016a; Kokanali 2013; Lau 1999; Lau 2000; Sharma 2009; Soriano 2000; Tam 2001; Teran-Alonso

2014; Vercellini 1994). Two studies used a 5-point 20 cm VAS (Cicinelli 1997; Cicinelli 1998). One study (Lukes 2015) used the 0-10 cm Wong-Baker face-rating scale, which provides a scale ranging from 0 to 10, with 0 indicating no pain and 10 indicating maximum pain (Lukes 2015). Two studies also presented data as percentages (Giorda 2000; Lin 2005) and another presented data with area under the curve statistics (Wong 2000).

Among studies not included in analysis, 10 assessed the effect of analgesia on pain relief during hysteroscopy; four studies investigated the use of analgesia upon pain relief within 30 minutes after hysteroscopy; and three studies investigated the use of analgesia upon pain relief more than 30 minutes after hysteroscopy.

Eleven RCTs reported adverse effects.

Excluded studies

We excluded eight studies from the review (Canovas 2006; De Angelis 2003; Goldenberg 2001; Guida 2003; Kaya 2005; Mizrak 2010; Pace 2008; Wallage 2003). We excluded six studies as they used either general anaesthetic or an intravenous analgesic as an intervention (Goldenberg 2001; Guida 2003; Kaya 2005; Mizrak 2010; Pace 2008; Wallage 2003). One study was excluded as it was not randomised (Canovas 2006) and one study was excluded as the intervention investigated was non-pharmacological (De Angelis 2003).

Risk of bias in included studies

See (Characteristics of included studies, Figure 1, Figure 2).

Allocation

Sequence generation

The method of sequence generation was unclear for 10 studies (Costello 1998; Esteve 2002; Finikiotis 1992; Lau 1999; Makris 2001; Nagele 1997; Stigliano 1997; Vercellini 1994; Wong 2000; Zupi 1995). The remaining studies described the use of random computer-generated block randomisation, random table, random number or random codes and we therefore classified them as being at low risk of bias in this domain.

Allocation concealment

Only one of the included studies (Van den Bosch 2011) clearly described the method of allocation concealment and we classified it as being at low risk of bias in this domain. We rated the other studies as unclear risk of bias.

Blinding

Eleven studies were double-blinded, defined as blinding of both the participant and healthcare provider (Clark 1996; Costello 1998; Esteve 2002; Hassan 2016a; Hassan 2016b; Lau 1999; Lau 2000; Mohammadi 2015; Senturk 2016; Soriano 2000; Tam 2001). Eight studies were not double-blinded, and we rated them at high risk of bias (Al-Sunaidi 2007; Arnau 2013; Giorda 2000; Kabli 2008; Kokanali 2013; Lukes 2015; Sharma 2009; Teran-Alonso 2014). We rated the rest of the studies as unclear in this domain, as there was insufficient information to determine whether they were effectively double-blinded.

Incomplete outcome data

Twenty two studies reported no attrition or relatively low levels of attrition and we rated them as being at low risk of bias in this domain (Al-Sunaidi 2007; Broadbent 1992; Cicinelli 1997; Cicinelli 1998; Costello 1998; Giorda 2000; Hassan 2016a; Hassan 2016b; Kabli 2008; Kokanali 2013; Lau 1999; Lau 2000; Lin 2005; Mercorio 2002; Nagele 1997; Senturk 2016; Sharma 2009; Soriano 2000; Tam 2001; Teran-Alonso 2014; Vercellini 1994; Wong 2000). One study had a high level of dropouts before hysteroscopy and we rated it as at high risk (Van den Bosch 2011). The rest of the studies did not clearly state whether any participants were excluded from analysis or did not state the reason for exclusions from analysis, or both; we rated these studies as being at unclear risk of bias in this domain.

Selective reporting

We rated 19 studies as being at low risk of bias due to selective reporting (Al-Sunaidi 2007; Arnau 2013; Cicinelli 1997; Cicinelli 1998; Costello 1998; Esteve 2002; Giorda 2000; Hassan 2016a; Kokanali 2013; Lau 1999; Lau 2000; Lin 2005; Lukes 2015; Mohammadi 2015; Sharma 2009; Soriano 2000; Tam 2001; Teran-Alonso 2014; Vercellini 1994). They reported data in a standard manner, provided data for all time points stated to have data collected and did not utilise change from baseline scores or convert to dichotomous outcomes.

We rated six studies as being at high risk of selective reporting bias. In two of these studies continuous data recording meant that pain scores were converted into dichotomous data without providing an opportunity to interpret data as mean pain scores (Broadbent 1992; Finikiotis 1992). Four studies presented data in graphical form, which we could not accurately interpret as mean pain scores (Makris 2001; Mercorio 2002; Nagele 1997; Zupi 1995).

We rated seven studies as being at unclear risk of selective reporting bias: Clark 1996 used a 4-point descriptive scale and converted data into two outcomes; Stigliano 1997 used a 4-point descriptive scale; Van den Bosch 2011 did not report standard deviations; Wong 2000 presented data as area under the curve statistics; and three studies (Hassan 2016b; Kabli 2008; Senturk 2016) presented

results as median pain scores, which could not be converted into mean pain scores.

We considered that failure to report standard deviations and graphical representation of data without numerical values may be considered as a form of under reporting.

Other potential sources of bias

We rated four studies as being at high risk of other bias, due to co-interventions that did not apply to all participants (Arnau 2013; Clark 1996; Nagele 1997), or assessment of procedural pain when the scope had already been introduced (Costello 1998). Six studies were rated as at unclear risk of other bias, due to variation in the doses used (Makris 2001), unequal numbers of participants in the two groups (Esteve 2002; Soriano 2000), use of additional sedation or analgesia in both groups (Al-Sunaidi 2007; Kabli 2008; Lukes 2015). We did not identify any risk of other potential bias in the remaining 23 studies, which we rated as being at low risk of bias in this domain.

Effects of interventions

See: **Summary of findings for the main comparison** Local anaesthetic compared to placebo or no treatment for outpatient hysteroscopy; **Summary of findings 2** Oral NSAID compared to placebo or no treatment for outpatient hysteroscopy; **Summary of findings 3** Opioid compared to placebo or no treatment for outpatient hysteroscopy; **Summary of findings 4** Intracervical versus combined intracervical and paracervical anaesthesia; **Summary of findings 5** Antispasmodic plus NSAID versus paracervical anaesthesia

We have translated our main results into a difference on a commonly used scale (visual analogue scale (VAS)) to demonstrate clinical importance.

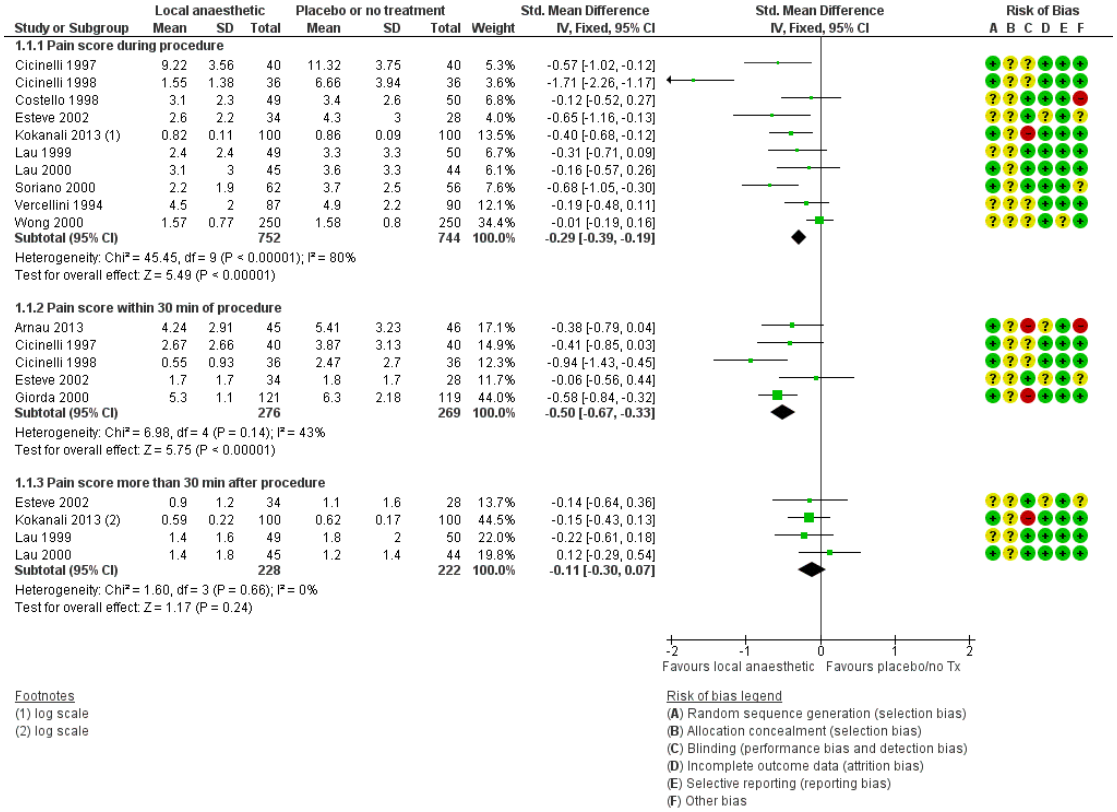
1. Analgesic versus placebo or no treatment

1.1 Local anaesthetic versus placebo or no treatment

1.1.1. Primary outcome: pain score

Analysis 1.1; Figure 4

Figure 4. Forest plot of comparison: 1 Local anaesthetic versus placebo or no treatment, outcome: 1.1 Pain score.



Pain score during the procedure

Meta-analysis of ten RCTs including 1496 women (Cicinelli 1997; Cicinelli 1998; Costello 1998; Esteve 2002; Kokanali 2013; Lau 1999; Lau 2000; Soriano 2000; Vercellini 1994; Wong 2000) demonstrated a significant reduction in the mean pain score during hysteroscopy with the use of local anaesthetic (SMD -0.29, 95% CI -0.39 to -0.19, I^2 = 80%, low-quality evidence). This translates to a difference of between 0.2 mm (lower) and 0.7 mm (lower) on a 10 cm VAS. This is unlikely to be clinically significant.

Pain score within 30 minutes of the procedure

Meta-analysis of five RCTs (Arnau 2013; Cicinelli 1997; Cicinelli 1998; Esteve 2002; Giorda 2000) including 545 women revealed a significant reduction in the mean pain score within 30 minutes after the procedure with the use of local anaesthetics (SMD -0.50, 95% CI -0.67 to -0.33, I^2 = 43%, low-quality evidence). This translates to a difference of between 7 mm (lower) and 13 mm (lower) on a 10 cm VAS. This is unlikely to be clinically significant.

Pain score more than 30 minutes after the procedure

Meta-analysis of four RCTs (Esteve 2002; Kokanali 2013; Lau 1999; Lau 2000) including 450 women did not demonstrate clear evidence of a difference between the groups (SMD -0.11, 95% CI -0.30 to 0.07, I^2 = 0%, low-quality evidence).

1.1.2. Secondary outcome: failure to complete the procedure

Analysis 1.2

These studies considered two different outcome measures as reasons for failure to complete the procedure. These were cervical stenosis and pain, respectively.

Failure to complete the procedure due to cervical stenosis

Six RCTs including 805 women reported failure to complete the procedure due to cervical stenosis (Costello 1998; Esteve 2002; Giorda 2000; Lau 1999; Soriano 2000; Vercellini 1994). There was insufficient evidence to determine whether there was a difference between the groups (OR 1.23, 95% CI 0.62 to 2.43, I^2 = 0%).

Failure to complete the procedure due to pain

Two RCTs including 330 women reported failure to complete the procedure due to pain (Giorda 2000; Lau 2000). Thre were fewer incidents of failure to complete the procedure in the intervention group than in the control group (OR 0.29, 95% CI 0.12 to 0.69, I^2 = 0%).

1.1.3. Secondary outcome: adverse effects

Analysis 1.3

Eight RCTs reported adverse effects for this comparison (Arnau 2013; Cicinelli 1997; Cicinelli 1998; Giorda 2000; Lau 1999; Lau 2000; Soriano 2000; Wong 2000). There was no clear evidence of difference between the groups in the rate of vasovagal reactions (OR 0.70, 95% CI 0.43 to 1.13, 8 RCTs, 1309 women, I^2 = 66%, very low-quality evidence) and insufficient evidence to determine whether there was a difference between the groups in rates of non-pelvic pain (OR 1.76, 95% CI 0.53 to 5.80, 1 RCT, 99 women, very low-quality evidence).

Subgroup analyses

Subgroup analysis of postmenopausal women

In subgroup analysis of studies investigating the use of local anaesthetic exclusively in postmenopausal women, two studies (Cicinelli 1997; Cicinelli 1998) demonstrated a significant benefit for pain relief during hysteroscopy. There was very high heterogeneity, though the direction of effect was consistent (SMD -1.13, 95% CI -2.25 to -0.01, I^2 = 90%). Three studies (Cicinelli 1997; Cicinelli 1998; Giorda 2000) demonstrated a significant reduction in the mean pain score within 30 minutes after hysteroscopy (SMD -0.61, 95% CI -0.86 to -0.37, I^2 = 23%). The clinical significance of these findings is unclear, given the very low quality of the evidence.

Subgroup analysis by route of intervention

Paracervical block

Pooling of three studies (Cicinelli 1998; Lau 1999; Vercellini 1994) investigating the use of paracervical block compared to placebo or a control group did not demonstrate clear evidence of reduction of the mean pain score during hysteroscopy (SMD -0.71, 95% CI -1.51 to 0.10, I^2 = 92%).

One study (Lau 1999) reported pain scores at more than 30 minutes after hysteroscopy but there was insufficient evidence to determine whether there was a difference between the groups (SMD -0.22, 95% CI -0.61 to 0.18).

Intracervical block

Two studies (Esteve 2002; Kokanali 2013) investigating the use of intracervical block compared to placebo or a control group demonstrated a significant reduction in the mean pain score during hysteroscopy (SMD -0.45, 95% CI -0.70 to -0.21). There was no clear evidence of a difference between the groups at up to 30 minutes' follow-up (SMD -0.06, 95% CI -0.56 to 0.44) nor at follow-up of more than 30 minutes after hysteroscopy (SMD -0.15, 95% CI -0.39 to 0.09).

Transcervical or intrauterine block

Three studies (Cicinelli 1997; Costello 1998; Lau 2000) investigating the use of intrauterine or transcervical block compared to placebo or a control group did not demonstrate clear evidence of a difference between the groups during hysteroscopy (SMD -0.27, 95% CI -0.54 to 0.00, I^2 = 21%) nor at follow-up of up to 30 minutes after hysteroscopy (SMD -0.41, 95% CI -0.85 to 0.03 (Cicinelli 1997)), or at more than 30 minutes (SMD 0.12, 95% CI -0.29 to 0.54 (Lau 2000)).

Topical sprays, gels, and creams

Two studies (Soriano 2000; Wong 2000) investigating the use of topical sprays, gels, and creams compared to placebo or a control group did not demonstrate clear evidence a difference between the groups in the mean pain score during hysteroscopy (SMD -0.32, 95% CI -0.97 to 0.33, I^2 = 90%).

Local anaesthetic versus placebo or no treatment: findings in studies without data suitable for analysis

- Broadbent 1992 compared the use of 10 mL of 1% lignocaine intracervically to saline, in 100 women. The study authors reported no evidence of a difference between the groups, either during or after hysteroscopy.
- Clark 1996 compared the use of 10 mL of 2% lignocaine gel to placebo gel or no treatment in 123 women. The study authors reported no evidence of a difference between the groups during hysteroscopy. Postoperative pain levels were not reported.
- Makris 2001 compared the use of 1 mL to 3 mL (30 to 90 mg) of 3% mepivacaine to saline when administered 3 minutes

prior to hysteroscopy in 200 women. The study authors reported no evidence of difference between the groups, either during or after hysteroscopy.

- Senturk 2016 compared intrauterine lidocaine versus placebo in 138 women. The authors reported that the NSAID was more effective than placebo, with lower median pain scores both during the procedure and during follow-up.
- Stigliano 1997 compared the use of 1 cm^3 of 5% prilocaine cream and 10 mg of lidocaine spray versus no treatment in 345 women. Data were presented as percentages. The study authors reported significant evidence of benefit in pain levels in the cream group (compared to the no-treatment group) during placement of the tenaculum and a benefit in both active intervention groups (compared to the no-treatment group) during progression through the cervical canal and evaluation of the uterine cavity.
- Van den Bosch 2011 compared lignocaine gel versus placebo gel in 142 women, and reported no evidence of a difference in procedure-related pain
- Zupi 1995 compared 5 mL of 2% mepivacaine to saline transcervically and the authors reported no significant evidence of a difference between the groups during the procedure, however a significant benefit was found in the mepivacaine groups 30 minutes after the procedure.

1.2 NSAID versus placebo or no treatment

We identified three RCTs for this comparison (Hassan 2016a; Tam 2001; Teran-Alonso 2014). Tam 2001 included 181 women, Teran-Alonso 2014 included 200 women and Hassan 2016a included 140 women. Teran-Alonso 2014 used 1 g of paracetamol in conjunction with the NSAID.

1.2.1. Primary outcome: pain score

Analysis 2.1

Pain score during the procedure

There was no clear evidence of a difference between the groups (SMD -0.18, 95% CI -0.35 to -0.00, 3 RCTs, 521 women, I^2 = 81%, low-quality evidence).

Pain score within 30 minutes of the procedure

Teran-Alonso 2014 and Hassan 2016a reported this outcome. Pain scores were lower in the intervention group (SMD -0.25, 95% CI -0.46 to -0.04, 2 RCTs, 340 women, I^2 = 29%, low-quality evidence). This equates to a difference of up to 2 mm on a 0-10 cm VAS, which is unlikely to be clinically significant.

Pain score more than 30 minutes after the procedure

Pain scores were significantly lower in the intervention group (SMD -0.27, 95% CI -0.49 to -0.05, 2 RCTs, 321 women, I^2 = 78%, low-quality evidence). This equates to a difference of up to 7 mm on a 0-10 cm VAS, which is unlikely to be clinically significant.

1.2.2. Secondary outcome: failure to complete the procedure

This outcome was not reported.

1.2.3 Secondary outcome: adverse effects

Analysis 2.2

There was insufficient evidence to determine whether there was a difference between the groups in the rate of vasovagal reactions (OR 0.76, 95% CI 0.20 to 2.94, 1 RCT, 181 women, very low-quality evidence), non-pelvic pain (OR 2.93, 95% CI 0.12 to 72.99, 1 RCT, 181 women, very low-quality evidence) or allergic reactions (OR 2.93, 95% CI 0.12 to 72.99, 1 RCT, 181 women, very low-quality evidence).

NSAID versus placebo: findings in studies without data suitable for analysis

- Nagele 1997 compared the use of 500 mg mefenamic acid versus placebo in 95 women. The study authors reported that there was no clear evidence of a difference between the groups during hysteroscopy, but pain was significantly less in the intervention group at 60 minutes after the procedure.
- Senturk 2016 compared rectal indomethacin versus placebo in 130 women. The authors reported that the NSAID was more effective than placebo, with lower median pain scores both during the procedure and during follow-up.

1.3 Opioid versus placebo or no treatment

1.3.1. Primary outcome: pain score

Pain score during the procedure

We identified two RCTs (Hassan 2016a; Lin 2005) for this comparison. One RCT utilised oral tramadol and one utilised sublingual buprenorphine. Data on pain scores during the procedure were unsuitable for pooling due to inconsistency. Tramadol was associated with a benefit of up to 22 mm on a 0-10 cm scale, which may possibly be clinically significant (SMD -0.76, 95% CI -1.10 to -0.42, 1 RCT, 140 women). However the effect estimate for this outcome for sublingual opioids did not support a benefit

from the intervention (SMD 0.08, 95% CI -0.22 to 0.39, 164 women).

Pain score within 30 minutes of the procedure

Compared with placebo, the pain score during within 30 minutes of the procedure was lower in the tramadol group (SMD -0.57, 95% CI -0.91 to -0.23, 1 RCT, 140 women, low-quality evidence), suggesting a difference of up to 17 mm on a 0-10 cm scale, which may possibly be clinically significant.

Pain score more than 30 minutes after the procedure

There was no clear evidence of a difference between the tramadol and placebo groups at over 30 minutes (-0.17, 95% CI -0.51 to 0.16, 1 RCT, 140 women, low-quality evidence). Nausea and vomiting occurred in 39% of the buprenorphine group, and in none of the placebo group

1.3.2. Secondary outcome: failure to complete the procedure

Hassan 2016a reported this outcome. There were no events in the intervention group, but one woman in the placebo group failed to complete treatment due to pain (OR 0.33, 95% CI0.01 to 8.21, 1 RCT, 140 women)

1.3.3. Secondary outcome: adverse effects

Lin 2005 reported that 31/80 women in the intervention group experienced nausea and vomiting, while none of the placebo group did so (OR 107.55, 95% CI 6.44 to 1796.46, 1 RCT, 164 women).

Opioid versus placebo: findings in studies without data suitable for analysis

Hassan 2016b compared the use of oral tramadol versus placebo in 140 women. The authors reported lower levels of pain in the intervention group during the procedure, immediately afterwards and at follow-up at 30 minutes. Data were reported as medians.

2. Analgesic versus any other analgesic

2.1 Local intracervical anaesthesia compared to combined intracervical and paracervical anaesthesia

2.1.1. Primary outcome: pain score

Analysis 4.1

Pain score during the procedure

One RCT (Al-Sunaidi 2007), including 84 women, demonstrated a significant benefit in the combined anaesthesia group, with higher pain scores in the group receiving intracervical anaesthesia only (SMD 4.27, 95% CI 3.49 to 5.06, very low-quality evidence). This translates to a difference of up to 12 mm on a 10 cm VAS. This is unlikely to be clinically significant.

Pain score within 30 minutes of the procedure

There was evidence of beneficial effect of combined anaesthesia within the 30 minutes after the procedure, with higher pain scores in the group receiving intracervical anaesthesia only (SMD 1.55, 95% CI 1.06 to 2.05, 1 RCT, 84 women, very low-quality evidence). This translates to a difference of up to 5 mm on a 10 cm VAS. This is unlikely to be clinically significant.

Pain score more than 30 minutes after the procedure

There was evidence of beneficial effect of combined anaesthesia over 30 minutes after the procedure with higher pain scores in the group receiving intracervical anaesthesia only (SMD 3.47, 95% CI 2.78 to 4.15, 1 RCT, 84 women, very low-quality evidence). This translates to a difference of up to 8 mm on a 10 cm VAS. This is unlikely to be clinically significant.

2.1.2. Secondary outcome: failure to complete the procedure

Analysis 4.2

Al-Sunaidi 2007 reported failure to complete the procedure due to pain. There was insufficient evidence to determine whether there was a difference between the groups (OR 3.00, 95% CI 0.12 to 75.74, 85 women).

2.1.3. Secondary outcome: adverse effects

This outcome was not reported.

2.2 Local intracervical anaesthesia compared to combined intracervical, paracervical anaesthesia and local topical anaesthesia

2.2.1. Primary outcome: pain score

Analysis 5.1

Pain score during the procedure

One RCT (Lukes 2015) including 37 women demonstrated no clear evidence of a difference between the groups in mean pain score during the procedure (SMD -0.54, 95% CI -1.20 to 0.12, very low-quality evidence).

Pain score within 30 minutes of the procedure

This outcome was not reported.

Pain score more than 30 minutes after the procedure

This outcome was not reported.

2.2.2. Secondary outcome: failure to complete the procedure

This outcome was not reported.

2.2.3. Secondary outcome: adverse effects

This outcome was not reported.

2.3 Antispasmodic plus NSAID versus local paracervical anaesthesia

2.3.1. Primary outcome: pain score

Analysis 6.1

Pain score during the procedure

One RCT (Sharma 2009) demonstrated a significantly higher mean pain score during the procedure with the use of drotaverine hydrochloride and mefenamic acid in comparison to paracervical block (SMD -1.40, 95% CI -1.90 to -0.91, 80 women, very low-quality evidence). This translates to a difference of up to 23 mm on a 10 cm VAS, which may be be clinically significant.

Pain score within 30 minutes of the procedure

This outcome was not reported.

Pain score more than 30 minutes after the procedure

There was a significant reduction in the mean pain score more than 30 minutes after the procedure with the use of drotaverine hydrochloride and mefenamic acid in comparison to paracervical block (SMD -0.87, 95% CI -1.33 to -0.41). This translates to a difference of up to 11 mm on a 10 cm VAS. This may not be clinically significant.

Secondary outcomes

2.3.2. Secondary outcome: failure to complete the procedure

This outcome was not reported.

2.3.3. Secondary outcome: adverse effects

This outcome was not reported.

2.4 Opioid versus NSAID

Hassan 2016a compared 100 mg of oral tramadol versus 200 mg of oral celecoxib Analysis 7.1.

2.4.1. Primary outcome: pain score

Pain score during the procedure

There was no clear evidence of a difference between the groups (SMD -0.15, 95% CI -0.48 to 0.18, 1 RCT, 140 women).

Pain score within 30 minutes of the procedure

There was no clear evidence of a difference between the groups (SMD -0.25, 95% CI -0.58 to 0.08, 1 RCT, 140 women).

Pain score more than 30 minutes after the procedure

There was no clear evidence of a difference between the groups (SMD -0.17, 95% CI -0.51 to 0.16, 1 RCT, 140 women).

2.4.2. Secondary outcomes: failure to complete the procedure

This outcome was not reported.

2.4.3. Secondary outcomes: adverse effects

There was insufficient evidence to determine whether there was a difference between the groups in rates of nausea and vomiting. There were only four events, all in the opioid group (OR 9.54, 95% CI 0.50, to180.64, 1 RCT, 140 women) Analysis 7.2.

Analgesic versus any other analgesic: findings in studies without data suitable for analysis

Six studies made comparisons between different types of analgesics and reported data unsuitable for analysis, as follows.

- Finikiotis 1992 compared paracervical block versus uterosacral block. The study authors reported no clear evidence of a difference in pain during the procedure between the use of 20 mL of 1% lignocaine for paracervical block and 2 mL of 2% lignocaine for a uterosacral block, in 120 women. The study grouped results into three categories depending on severity of pain so we could not obtain the mean pain scores; therefore we could not include this study in the meta-analysis.
- Kabli 2008 compared local cervical anaesthesia (2 mL of 1% lignocaine) versus combined cervical and intrauterine anaesthesia (8 mL of lidocaine in 250 mL of saline) in 78 women. The study authors reported that there was no clear evidence of a difference between the groups in median pain scores either during the procedure or within 30 or 60 minutes after. We could not calculate the results as mean pain score.
- Mercorio 2002 compared NSAID versus intracervical anaesthetic (oral dexketoprofen versus intracervical block) in 298 women. The study authors reported no clear evidence of a difference between the groups in mean pain scores during hysteroscopy.
- Mohammadi 2015 compared rectal diclofenac versus intrauterine lidocaine (100 mg of rectal diclofenac versus 5 mL of 2% intrauterine lidocaine). The study authors reported no clear evidence of a difference between the groups in pain score measured during visualisation of uterine cavity (P = 0.500). The mean pain score was significantly lower during insertion and extrusion of the hysteroscope in the diclofenac group (P = 0.001 and P = 0.030, respectively).
- Senturk 2016 compared a rectal NSAID (indomethacin) versus intrauterine lidocaine in 138 women. The study authors reported that median pain scores were lower in the lidocaine group, both during the procedure and 10 minutes afterwards.
- Stigliano 1997 compared the use of 1 cm^3 of 5% prilocaine cream and 10 mg of lidocaine spray in 180 women. They presented data as percentages. The study authors reported significant evidence of benefit in pain levels in the cream group (compared to the spray group) during placement of the tenaculum. There was no clear evidence of a difference between the intervention groups in pain levels during progression through the cervical canal and evaluation of the uterine cavity.

Other analyses

Sensitivity analyses

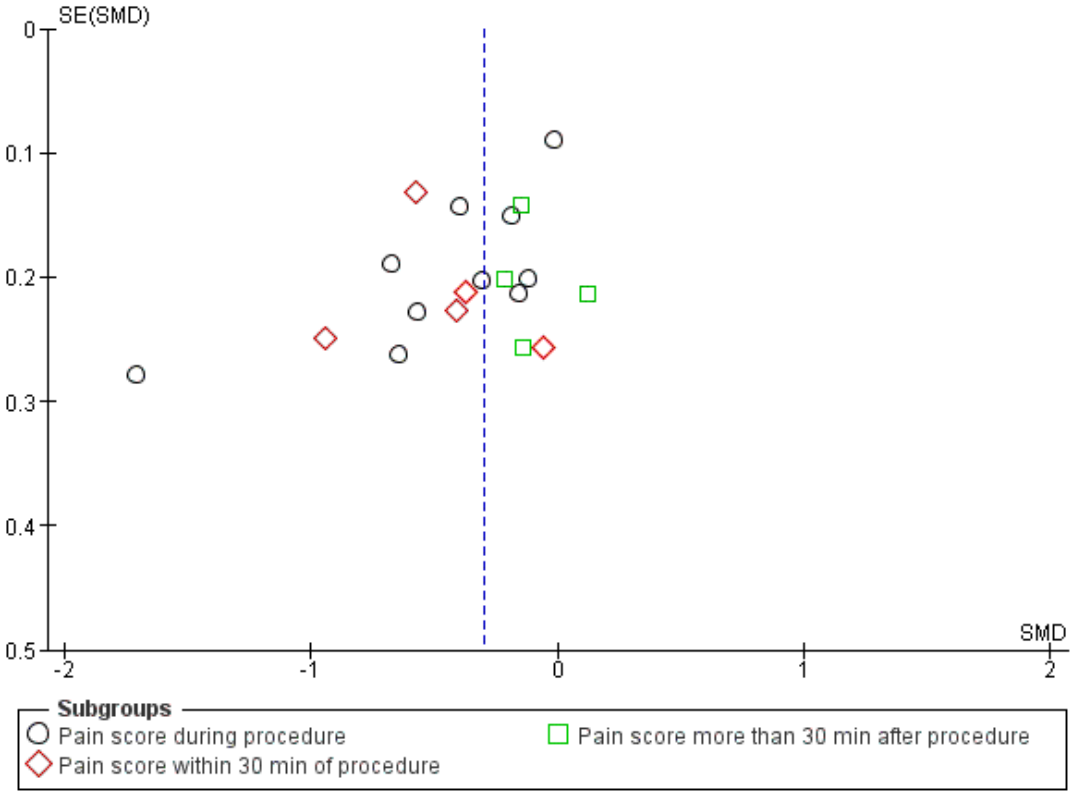
Our main findings were not substantially changed when we used a random-effects model, or when we calculated risk ratios for dichotomous outcomes.

We were unable to conduct our planned sensitivity analysis by risk of bias, as none of the included studies were deemed to be at low risk of bias overall.

Funnel plot

We constructed a funnel plot for analysis 1.1. It did not show any strong suggestion of publication bias (Figure 5).

Figure 5. Funnel plot of comparison local anaesthetic versus placebo or no treatment, outcome: pain score



ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Oral NSAID compared to placebo or no treatment for outpatient hysteroscopy

Population: women undergoing outpatient hysteroscopy
Setting: outpatient hysteroscopy clinic
Intervention: oral nonsteroidal anti-inflammatory drug (NSAID)
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with oral NSAID				
Pain score during procedure	The mean pain score ranged from 2.1 to 5.92 on a 0-10 cm VAS	SMD 0.18 lower (0.35 lower to 0.00)	-	521 (3 studies)	⊕⊕◯◯ **low**[1,2,3]	There was no clear evidence of a difference between the groups
Pain score within 30 min of procedure	The mean pain score ranged from 0.65 to 2.02 on a 0-10 cm VAS	SMD 0.25 SD lower (0.46 lower to 0.04 lower)	-	340 participants (2 studies)	⊕⊕◯◯ **low**[1,2]	The evidence suggests a benefit in the NSAID group, equivalent to up to 2 mm on a 0-10 cm VAS. This is unlikely to be clinically significant
Pain score more than 30 min after procedure	The mean pain score ranged from 1.2 to 1.55 on a 0-10 cm VAS	SMD 0.27 lower (0.49 lower to 0.05 lower)	-	321 (2 studies)	⊕⊕◯◯ **low**[1,2,3]	The evidence suggests a benefit in the NSAID group, equivalent to up to 7mm on a 0-10 cm VAS. This is unlikely to be clinically significant
Vasovagal reaction	56 per 1,000	43 per 1,000 (12 to 149)	OR 0.76 (0.20 to 2.94)	181 participants (1 study)	⊕⊕◯◯ **very low**[1,4]	Only 9 events There was insufficient evidence to determine whether there is a dif-

					ference between the groups
Non pelvic pain	Not calculable: no events in one group	OR 2.93 (0.12 to 72.99)	181 participants (1 study)	⊕⊕◯◯ **very low**[1,4]	Only 1 event There was insufficient evidence to determine whether there is a difference between the groups
Allergic reaction	Not calculable: no events in one group	OR 2.93 (0.12 to 72.99)	181 participants (1 study)	⊕⊕◯◯ **very low**[1,4]	Only 1 event There was insufficient evidence to determine whether there is a difference between the groups

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the mean risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **SMD**: standardised mean difference; **SD**: standard deviation; **NSAID**: nonsteroidal anti-inflammatory drugs; **OR:** odds ratio; **VAS**: visual analogue scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level due to serious risk of bias: none of the studies adequately described methods of allocation concealment.
[2]Downgraded one level due to serious imprecision: effect estimate touches or crosses 0.
[3]High heterogeneity (I^2 = 78% to 81%): not downgraded for inconsistency as direction of effect is consistent.
[4]Downgraded two levels due to very serious imprecision: very few events.

Opioid compared to placebo or no treatment for outpatient hysteroscopy

Population: women undergoing outpatient hysteroscopy
Setting: outpatient hysteroscopy clinic
Intervention: oral or sublingual opioid
Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with opioid				
Pain score during procedure: oral opioid	The mean pain score was 5.92 mm on a 0-10 cm VAS	Oral opioid: SMD was 0.76 lower (95% CI 1.10 lower to 0.42 lower)	-	140 (1 study)	**low**[1,2]	Data from the two studies were unsuitable for pooling due to extreme heterogeneity (I^2 = 92%) with conflicting directions of effect. There is a suggestion of benefit from oral opioid, equating to a difference of up to 22 mm on a 0-10 cm VAS. This may possibly be clinically significant
Pain score during procedure: sublingual opioid	The mean pain score was from 3.2 mm on a 0-10 cm VAS	Sublingual opioid: SMD was 0.08 higher (95% CI 0.22 lower to 0.39 higher)		164 (1 study)	**low**[1,2]	
Pain score within 30 min of procedure oral opioid	The mean pain score was 3.27 mm on a 0-10 cm VAS	SMD -0.57 lower (-0.91 to -0.23 lower)	-	140 (1 study)	**low**[1,2]	There is a suggestion of benefit from oral opioid, equating to a difference of up to 17 mm on a 0-10 cm VAS. This may possibly be clinically significant

Pain score more than 30 min after procedure oral opioid	The mean pain score was 0.77 on a 0-10 cm VAS	SMD 0.17 lower (0.51 lower to 0.16 higher)	-	140 (1 study)	**very low**[1,2,3]	
Nausea and vomiting sublingual opioid	Not calculable as all 31 events were in the opioid group and none in the placebo group		OR 107.55 (6.44 to 1796.46)	164 (1 study)	**low**[1]	There were 4 events in the intervention group of the oral opioid study, but events in the placebo group were not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the mean risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **SMD**: standardised mean difference; **SD**: standard deviation; **OR:** odds ratio; **VAS**: visual analogue scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level for serious risk of bias: method of allocation concealment or blinding, or both, not described.
[2]Downgraded one level for inconsistency: findings for different types of morphine differ in direction of effect.
[3]Downgraded one level due to serious imprecision - wide confidence interval.

Intracervical versus combined intracervical and paracervical anaesthesia

Population: women undergoing outpatient hysteroscopy
Setting: outpatient hysteroscopy clinic
Intervention: localintracervical anaesthesia
Comparison: combined intracervical and paracervical anaesthesia

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with combined intracervical and paracervical anaesthesia	Risk with local intracervical anaesthesia				
Pain score during procedure	The mean pain score was 2.1 (SD 0.2) on a 0-10 cm VAS	SMD 4.27 SD higher (3.49 higher to 5.06 higher)	-	84 participants (1 study)	⊕◯◯◯ **very low**[1,2]	This suggests a significant benefit from combined anaesthesia, equating to up to 12 mm on a 0-10 cm point VAS. This is unlikely to be be clinically significant
Pain score within 30 minutes of the procedure	The mean pain score was 1.5 (SD 0.3) on a 0-10 cm VAS	(SMD 1.55, 95% CI 1.06 higher to 2.05 higher)	-	84 participants (1 study)	⊕◯◯◯ **very low**[1,2]	This suggests a significant benefit from combined anaesthesia, equating to up to 5 mm on a 0-10 cm point VAS. This is unlikely to be clinically significant
Pain score more than 30 minutes of the procedure	The mean pain score was 1 (SD 0.2) on a 0-10 cm VAS	(SMD 3.47, 95% CI 2.78 higher to 4.15 higher)	-	84 participants (1 study)	⊕◯◯◯ **very low**[1,2]	This suggests a significant benefit from combined anaesthesia, equating to up to 8 mm on a 0-10 cm point VAS. This is unlikely to be clinically significant

Adverse effects	No data available	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the mean risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **SMD**: standardised mean difference; **SD**: standard deviation; **VAS**: visual analogue scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded two levels for very serious risk of bias: allocation concealment not described, participants not blinded.
[2]Downgraded two levels for very serious imprecision: very small sample size. In practice, full downgrading not possible as already low quality.

Antispasmodic plus NSAID versus paracervical anaesthesia

Population: women undergoing outpatient hysteroscopy
Setting: outpatient hysteroscopy clinic
Intervention: antispasmodic plus nonsteroidal anti-inflammatory drugs (NSAID)
Comparison: local paracervical anaesthesia

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Paracervical anaesthesia	Antispasmodic plus NSAID				
Pain score during procedure	The mean pain score was 5.93 (SD -1.26) on a 0-10 cm VAS	SMD 1.40 SD lower (1.90 lower to 0.91 lower)	-	80 (1 study)	⊕◯◯◯ **very low**[1,2]	This suggests a beneficial effect in the drotaverine hydrochloride and mefenamic acid group, equating to up to 23 mm on a 0-10 cm point VAS. This may possibly be clinically significant
Pain score within 30 minutes of the procedure	This outcome was not reported					
Pain score more than 30 minutes after the procedure	The mean pain score was 2.53 (SD -0.81) on a 0-10 cm VAS	SMD 0.87 SD lower (1.33 lower to 0.41 lower)	-	80 (1 study)	⊕◯◯◯ **very low**[1,2]	This suggests a beneficial effect in the drotaverine hydrochloride and mefenamic acid group, equating toup to11mm on a 0-10 cm point VAS. This is unlikely to be clinically significant

Adverse effects	This outcome was not reported	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the mean risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **SMD**: standardised mean difference; **SD**: standard deviation; **VAS**: visual analogue scale

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Downgraded two levels for very serious risk of bias: methods of allocation concealment not described, not blinded.
[2]Downgraded one level for serious imprecision: small sample size.

DISCUSSION

Summary of main results

Our review has shown a beneficial effect of using local anaesthetic compared to placebo during hysteroscopy, within 30 minutes of the procedure and more than 30 minutes after the procedure. However, while this effect is statistically significant, it is too minimal to be clinically significant. There was some evidence of benefit for the use of oral analgesics, both opioids and NSAIDs, but findings were inconsistent and evidence was poor quality. The study of sublingual opioid reported a high rate of nausea and vomiting in the intervention group. Data on other adverse events were scanty and inconclusive.

Local anaesthetics were associated with a lower rate of failure to complete the procedure due to pain, but data on failure to proceed due to cervical stenosis did not clearly show a difference.

Overall completeness and applicability of evidence

Measurement of pain

Measurement of pain is predominantly subjective and dependent on independent variables such as prior experience of the procedure and level of anxiety, the majority of which are not reported in studies (De Iaco 2000).

The studies included in the review used several validated scales for the measurement of pain, which may influence the accuracy of the outcome, as complexity of the rating task for the measure influences the sensitivity and specificity (Jensen 2002).

Baseline pain scores were relatively low in all groups and pain experienced during hysteroscopy was mild to moderate across all the studies included within the review. Thus the clinical importance of an intervention is difficult to interpret. However, we have translated results to a commonly used visual analogue scale.

Essentially there are many factors that contribute towards pain during outpatient hysteroscopy. Factors such as indication for hysteroscopy, menopausal status of the woman, diameter of the scope, use of distension media and use of a speculum will all have an impact on perception of pain in women undergoing this procedure. This may explain the heterogeneity between the studies too. Furthermore, seven out of 19 studies gave additional pain medications (as mentioned under 'other potential sources of bias'). This may have introduced further heterogeneity.

There were too few studies to combine participants according to menopausal status, indication for hysteroscopy or whether women were nulliparous or multiparous. However, we ensured that any confounding caused by procedural factors would have been eradicated because all studies were RCTs.

Effective pain relief from local anaesthesia is dependent on various factors, including route of administration, concentration and classification of drug, and sufficient time interval between the administration of the analgesic and start of the procedure. The studies investigated various methods of administration of local anaesthesia, including paracervical block, intracervical anaesthesia, intrauterine anaesthesia, and topical anaesthesia in gel and spray forms. This review was unable to establish the most effective method of administration of local anaesthetic, as demonstrated by the subgroup analysis. These factors differed between the studies. With regards to current practice there is no unanimous decision as to what pain relief should be used for an outpatient hysteroscopy procedure. Therefore, we cannot comment on whether our review supports current practice.

Time interval between administration and start of the procedure

The five RCTs using paracervical block as an intervention for pain relief during hysteroscopy reported different time intervals between the administration of anaesthesia and the start of the procedure. In the only RCT showing significant beneficial effect the authors allowed 10 minutes between the administration of the drug and start of the procedure. While using a higher concentration of the drug (mepivacaine), this was in contrast to the other four studies, which failed to show any benefit using lower concentrations and shorter time intervals. The studies that supported the use of paracervical anaesthesia were restricted to postmenopausal women. This group tends to have a higher incidence of cervical atrophy and stenosis, and may experience more pain during the procedure thereby demonstrating a greater contrast between the placebo and anaesthetised subgroups.

Deep nerve endings in the myometrium, cervical stroma, and visceral peritoneum may be insufficiently blocked at five minutes after administration; this may explain the beneficial effect found in studies allowing a longer time interval between administration of anaesthetic and start of the procedure (Owens 1985). Two studies included in the meta-analysis suggested that paracervical block may well decrease the pain caused by cervical manipulation but is unable to affect the pain due to uterine distension.

Route of administration

Subgroup analysis failed to demonstrate an optimal route of administration of local anaesthetics for pain relief during and after hysteroscopy.

Different dosages used between studies investigating the use of local anaesthetics are outlined in Table 1.

Dilatation of the cervix and uterine distension account for the pain during hysteroscopy. The sensory nerve supply to the uterus is derived from two pathways; the Frankenhauser's plexus (parasympathetic S2 to S4) supplies the cervix and the lower portion of the uterus, while the uterine fundus receives sympathetic nerve supply via the infundibulo-pelvic ligament from the ovarian plexus. Lau 2000 argued that paracervical anaesthesia blocks the pain arising from the cervix and fails to block the pain arising from uterine

distension. Anatomically, sensory innervation of the pelvic organs is from the superior hypogastric plexus or pre-sacral nerve, pelvic nerves, and ovarian plexus. Sensory fibres from the upper part of the vagina, uterus, proximal portion of the tubes, bladder, urethra, and rectum run through the paracervical tissue and within the uterosacral folds and meet in the hypogastric and pelvic nerves. Thus, on the basis of the above anatomical observations, paracervical block should block not only cervical but uterine pain (Bonica 1990; Rapkin 1990). This confirms the positive results observed by Cicinelli 1998.

The failure of four RCTs to demonstrate a beneficial effect of the use of intrauterine local anaesthetic may be attributed to bypassing the sensory fibres located in the paracervical tissues and uterosacral ligaments and thus being unable to inhibit cervical pain. However, this hypothesis fails to explain the results of one RCT that found a beneficial effect with the use of intrauterine anaesthetic (Costello 1998).

Mohammadi 2015 demonstrated that while there was insufficient evidence of differences between the study group of women with regard to the mean pain score during visualisation of uterine cavity (P = 0.500), the mean pain score was significantly lower during insertion and extrusion of the hysteroscope in the diclofenac group (P = 0.001 and P = 0.030, respectively) compared to intrauterine lidocaine. This correlates with another study (Sharma 2009), which showed that in women undergoing hysteroscopy with or without biopsy there was significant reduction in mean pain score with the use of oral NSAID (mefenamic acid) compared to paracervical block and intravenous sedation.

Lignocaine sprays, gels, and creams provide anaesthesia to superficial pain receptors, advantages being painless application and a decreased rate of infection in comparison to anaesthetic blocks (Soriano 2000). Lignocaine spray was found to beneficial in comparison with lignocaine gel. However, hysteroscopy was performed immediately after application of the gel (Wong 2000). This may not have allowed sufficient time for the effect of the anaesthesia. The use of spray may allow more consistent application under a pressurised environment in comparison to a gel applied with gauze. Stigliano 1997 demonstrated significant pain relief compared to lignocaine spray and placebo, however, the cream was applied 10 minutes prior to the start of the procedure and the spray was administered immediately prior to the start of the procedure.

Use of oral analgesics

Delayed pain may be attributed to the release of prostaglandins from cervical manipulation and uterine distension; therefore, the use of a prostaglandin-synthetase inhibitor would seem a logical intervention for pain relief after rather than during the procedure. Mean peak plasma concentrations of 3.8 µmol/L are attained after 20 minutes to 60 minutes from ingestion of one tablet of 50 mg of diclofenac (New Zealand Medicines Safety Authority 2007). An NSAID administered two hours prior to hysteroscopy will have its peak analgesic effect before the completion of the procedure, thus having a suboptimal effect on delayed pain. Differences in the time interval between administration (one to two hours) and start of the procedures in the studies of NSAIDs may account for the inconsistency in their results.

Although buprenorphine is an opioid 35 times more potent than morphine, no benefit was noted when compared with placebo. This was in contrast to the relative effectiveness of the other opioid used, oral tramadol. It is possible that the lack of effectiveness of buprenorphine relates to the opioid being given 40 minutes before the procedure, as the peak pain relief due to this drug appears to occur between one and two hours after sublingual administration of buprenorphine (Dobkin 1977). A high incidence of nausea and drowsiness limits its use in the outpatient setting.

There was a significant reduction in pain during and after the procedure with the use of drotaverine hydrochloride and mefenamic acid in comparison with paracervical block. Mefenamic acid is a NSAID that acts as a potent inhibitor of prostaglandin synthesis, and has a peak plasma concentration between two and four hours following administration (Foye 2007). Drotaverine hydrochloride is an anti-spasmodic agent and selective phosphodiesterase inhibitor, with a peak plasma concentration at one hour (Blasko 1998); which may account for the combined analgesic effect both during and after hysteroscopy. However, a wide variation in the bioavailability of drotaverine hydrochloride has been demonstrated following oral administration and individual response may therefore be variable (Bolaji 1996).

Quality of the evidence

Most studies were at unclear or high risk of bias in most of the domains assessed. The evidence was low or very low quality, mainly due to risk of bias and imprecision. (See Figure 1 , Figure 2 and Summary of findings for the main comparison, Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5).

A major limitation in our review is the failure of many of the included studies to report data suitable for analysis. Thirteen studies included in the review could not be included within the meta-analysis due to limitations in presentation and conversion of data. Most of those studies reported no improvement in the mean pain scores with the use of analgesics, and we acknowledge that their inclusion in our meta-analysis could influence the results. We converted continuous data that recorded mean pain scores into dichotomous data in two studies without opportunity to interpret data as mean pain scores (Broadbent 1992; Finikiotis 1992). Clark 1996 used a 4-point descriptive scale and converted data into two outcomes. Stigliano 1997 used a 4-point descriptive scale, and also measured the pain experienced during hysteroscopy, as well as shoulder pain, 10 minutes after the procedure using a 4-point scale. The data were presented in graphical form in four studies

and could not be converted into mean pain scores. All studies included within the review reported data collected at all stated time points. Correspondence with the study authors did not produce any additional data.

An element of under reporting has been demonstrated, especially where specific P values and standard deviations were not stated, and this must be considered when interpreting the results.

There was no significant difference in any of the studies for the use of co-interventions between the placebo and control groups. However, we made no adjustment for potential differences between groups.

Potential biases in the review process

We did not identify any potential biases in the review process, apart from the limitation that we were unable to obtain additional data from study authors.

Agreements and disagreements with other studies or reviews

A recent systematic review (Del Valle 2016) analyzed 33 studies, 17 of which were RCTs. This review claimed the effectiveness of the different methods used to decrease pain perception during office hysteroscopy shows that injectable local anaesthetics, particularly paracervical infiltration, is the most effective form of analgesia. Other local anaesthetics via topical or intrauterine route seem to be ineffective. This review indicates that further studies are required to investigate the effect of NSAIDs, misoprostol, topical anaesthesia and nitrous oxide. However, this review is greatly limited due to the heterogeneity of studies included.

A systematic review in 2010 analysing the use of local anaesthesia in outpatient hysteroscopy concluded that paracervical local anaesthetic injection is superior to other methods of local anaesthesia. However, this review did not include studies analysing oral analgesia as a method of pain relief and did not include studies providing data in forms other than mean pain scores. Data were not translated into a commonly used scale (Cooper 2010).

Meta-analysis revealed a beneficial effect of the use of local anaesthetics for hysteroscopy but not for hysterosalpingography (HSG) in another review (Ahmad 2011). This effect may be due to the fact that more RCTs were identified investigating the role of local anaesthetics in hysteroscopy. Moreover, there is evidence to suggest that higher intrauterine pressure is required in HSG, resulting in the procedure being more painful than hysteroscopy. The median intrauterine perfusion pressure that will produce spill from the fallopian tubes into the peritoneal cavity is 100 mm Hg, with no spill occurring at pressures less than 70 mm Hg. This is in comparison to hysteroscopy where pressures of up to 40 mm Hg are considered adequate to distend the uterus (Baker 1995; Baker 1998).

AUTHORS' CONCLUSIONS

Implications for practice

There was no consistent good-quality evidence of a clinically meaningful difference in safety or effectiveness between different types of pain relief compared with each other or with placebo or no treatment in women undergoing outpatient hysteroscopy.

Implications for research

Further high-quality, adequately powered trials should be undertaken in order to provide the data necessary to estimate the efficacy of oral analgesics and the optimal route of administration and dose of local anaesthetics. There is a need for standardisation within trials with regards to the type of hysteroscope used, distension media, technique of hysteroscopy, type of hysteroscopy (diagnostic versus intervention), as well as populations studied.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Al-Sunaidi 2007

Methods	Randomised, single-blind study. No loss to follow-up. Single-centre trial at McGill University Health Centre, Montreal, Canada. 42 women in intervention group and 42 women in placebo group
Participants	Women undergoing hysteroscopy. Study included 84 women. Mean age of women was 36 years in intervention group and 35 in the placebo group. 1 woman dropped out of the study
Interventions	Local intracervical anaesthesia compared to combined intracervical and paracervical anaesthesia. 0.5% bupivacaine hydrochloride into anterior wall of cervix compared to 0.5% bupivacaine hydrochloride into anterior wall of cervix plus bupivacaine into lateral vaginal fornix at 3 and 9 o'clock at 10 mm depth. Both interventions were performed 5 min before the procedure
Outcomes	Mean pain score during the procedure, 10, 30 and 60 min after the procedure. 10-point VAS used
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was done using a computer generated random table."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Single-blinded - outcome assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 woman dropped out of the study but included in the final analysis (ITT). "A patient could not tolerate speculum examination and the procedure was aborted."
Selective reporting (reporting bias)	Low risk	1 measuring instrument used (10 cm VAS) and data reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes

Al-Sunaidi 2007 (*Continued*)

Other bias	Unclear risk	Co-administration of 10 mg lorazepam 30 min prior to procedure

Arnau 2013

Methods	Randomised, non-blinded, controlled study. Single-centre trial at the Obstetrics and Gynaecology Service, Health Consortium of Terrassa, Barcelona, Spain
Participants	102 consecutive women scheduled for diagnostic or operative hysteroscopy were invited; 10 declined. Following randomisation there was 1 loss from the EMLA (intervention) group due to "deviation from protocol". No mean ages stated, no exclusions
Interventions	"Either 3 mL EMLA cream 5% or 3 mL ultrasound gel was applied in the endocervical canal 10 min before surgery, with a 5-mL needleless syringe. A subsequent application of either gel was made with a swab at ectocervix level."
Outcomes	10 cm VAS. Pain score within 30 min of procedure. Women who completed the hysteroscopy were asked if they would recommend the procedure to other women, if they had wished to abandon the hysteroscopy and whether they would repeat the procedure if needed
Notes	This study was added to this review in 2014.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Women were randomized to the EMLA or control group using computer-generated random numbers."
Allocation concealment (selection bias)	Unclear risk	"Randomization was conducted with sealed envelopes containing computer-generated randomization numbers."
Blinding (performance bias and detection bias) All outcomes	High risk	Study is described as non-blinded in the title, however in the discussion comments that "the main limitation of our study was that it was not double-blinded, as we were unable to prepare a placebo with identical appearance and texture to the EMLA gel in our laboratory." This suggests that the operator would not be blinded, the participant may have been
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"One of the women in the EMLA group was excluded for protocol violation". Nature of violation not specified

Arnau 2013 (*Continued*)

Selective reporting (reporting bias)	Low risk	No pre-published protocol seen, however all planned outcomes from methods are reported, together with adverse outcomes
Other bias	High risk	All women were given 600 mg ibuprofen (if allergic 1 g paracetamol) and 5 mg diazepam 2 h before procedure and misoprostol was administered only to postmenopausal women

Broadbent 1992

Methods	Randomised, placebo-controlled trial. No loss to follow-up. Single-centre trial at The Minimally Invasive Therapy Unit, University Department of Obstetrics & Gynaecology, The Royal Free Hospital, London, UK. 50 women in the placebo group and 50 women in the intervention group
Participants	100 consecutive women undergoing outpatient hysteroscopy for abnormal uterine bleeding consented to be included in the study. The median age of the women was 43 years. 3 exclusions
Interventions	Intracervical injection of either 10 mL of lignocaine 1% with 1:200 000 adrenaline or normal saline was injected into the cervix at 1, 5, 7, and 11 o'clock
Outcomes	10 cm VAS. Pain score before, during, after and 60 min after the procedure. Data grouped into dichotomous outcomes
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Each patient was randomly allocated to receive either lignocaine 1 % or normal saline intra cervically. Randomization was performed using a predetermined randomization code in a double blind fashion."
Allocation concealment (selection bias)	Unclear risk	"Each patient was randomly allocated to receive either lignocaine 1 % or normal saline intracervically. Randomization was performed using a predetermined randomization code in a double blind fashion."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Randomization was performed using a predetermined randomization code in a double blind fashion."

Broadbent 1992 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	"Hysteroscopy was unsuccessful in three women: two (one from each group) found the procedure too painful, and one patient fainted after the intracervical injection of saline. These women were excluded from further analysis."
Selective reporting (reporting bias)	High risk	Data converted into a dichotomous manner. 1 measuring instrument used (10 cm VAS). All time points stated to have data collected were reported. Did not record change from baseline. No P values stated, which may indicate an element of under reporting
Other bias	Low risk	Nothing detected

Cicinelli 1997

Methods	Randomised, double-blinded, placebo-controlled trial. No loss to follow-up. Single-centre trial at University of Bari, Italy. 40 women in intervention group and 40 women in placebo group
Participants	Postmenopausal women undergoing diagnostic hysteroscopy and endometrial biopsy. Mean age of women was 59 years in both the intervention and placebo group. No dropouts or exclusions
Interventions	2 mL of 2% mepivacaine or 2 mL of 0.9% saline injected transcervically (inserted up the cervical canal to the internal os) 5 min before the procedure
Outcomes	Mean pain score before the procedure, during the procedure, at endometrial biopsy and 15 min after the procedure. 20 cm VAS
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was done by opening sealed envelopes containing computer generated block-randomisation numbers."
Allocation concealment (selection bias)	Unclear risk	"Randomisation was done by opening sealed envelopes containing computer generated block-randomisation numbers."

Cicinelli 1997 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Women were randomly and double blindly assigned."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts or exclusions. "Hysteroscopy performed in all patients."
Selective reporting (reporting bias)	Low risk	1 measuring instrument used (20 cm VAS) and data reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes. Insufficient evidence of under reporting
Other bias	Low risk	Nothing detected

Cicinelli 1998

Methods	Randomised, double-blinded, placebo controlled trial. No loss to follow-up. Single-centre trial at University of Bari, Italy. 36 women in intervention group and 36 women in placebo group
Participants	Postmenopausal women undergoing diagnostic hysteroscopy and endometrial biopsy. Mean age of women was 55 years in the intervention group and 56 in the placebo group. No dropouts or exclusions
Interventions	10 mL of 1.5% mepivacaine or saline injected into junction of cervix and vagina (4 and 8 o'clock positions) 10 min before procedure
Outcomes	Mean pain score before the procedure, during the procedure, at endometrial biopsy and 15 min after the procedure. 20 cm VAS
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was done by opening sealed envelopes containing computer generated block-randomisation numbers."
Allocation concealment (selection bias)	Unclear risk	"Randomisation was done by opening sealed envelopes containing computer generated block-randomisation numbers."

Cicinelli 1998 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Women were randomly and double blindly assigned."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts or exclusions. "Hysteroscopy performed in all patients."
Selective reporting (reporting bias)	Low risk	1 measuring instrument used (20 cm VAS) and data reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes. Insufficient evidence of under reporting
Other bias	Low risk	Nothing detected

Clark 1996

Methods	A randomised, double-blind, placebo-controlled trial. No loss to follow-up. Single-centre trial at Day Unit, Queen Charlotte's and Chelsea Hospital, London. 44 women in the intervention arm, 44 women in the placebo arm and 35 women in the control arm
Participants	Women undergoing outpatient hysteroscopy. Mean age of women 44.5 years in intervention group ad 44.6 and 43.4 in the placebo and control group respectively. 14 exclusions
Interventions	Lignocaine gel, placebo gel or no gel administered. Some women received intracervical lignocaine block if determined to need cervical dilatation
Outcomes	Mean pain score across the whole procedure, at gel administration, at lignocaine injection, cervical dilatation, hysteroscopy and endometrial biopsy. 4-point descriptive scale used
Notes	Co-administration in some women of intracervical block.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A total of 88 consecutive women undergoing outpatient hysteroscopy were allocated in a double-blind manner to one of two groups using a pre determined randomization code."
Allocation concealment (selection bias)	Unclear risk	"A total of 88 consecutive women undergoing outpatient hysteroscopy were allocated in a double-blind manner to one of two groups using a pre determined randomiza-

Clark 1996 (*Continued*)

		tion code.“
Blinding (performance bias and detection bias) All outcomes	Low risk	”Gel was given prior to the investigation by a different operator from those who carried out hysteroscopy, and the patient, hysteroscopist and other staff were unaware of which gel had been used.“
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Failed procedure in 14 women. No reasons given
Selective reporting (reporting bias)	Unclear risk	Data grouped into two outcomes. 1 measuring instrument used (4-point descriptive scale). All time points stated to have data collected were reported. Did not record change from baseline
Other bias	High risk	Co-administration of intracervical block in some women

Costello 1998

Methods	Randomised, double-blind, placebo-controlled study. No loss to follow-up. Single-centre trial at Royal Hospital for Women, Sydney, Australia. 50 women in intervention group and 50 women in placebo group
Participants	Women undergoing outpatient hysteroscopy with or without endometrial biopsy. Mean age of women was 46 years in the intervention group and 47 in the placebo group. 1 exclusion as no cervical os could be identified
Interventions	5 mL of 2% lignocaine or 5 mL of 0.9% saline injected into cervical canal and uterine cavity via hysteroscope 2 min before hysteroscope was manoeuvred
Outcomes	Mean pain score during the procedure. 10 cm VAS
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	”Pre determined randomization code administered by the hospital pharmacy.“
Allocation concealment (selection bias)	Unclear risk	”Pre determined randomization code administered by the hospital pharmacy.“

Costello 1998 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"The physicians performing the procedure and the patients were blinded to treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One patient was unable to undergo hysteroscopy as there was no identifiable cervical os."
Selective reporting (reporting bias)	Low risk	1 measuring instrument used (10 cm VAS) and data reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes
Other bias	High risk	All women were instructed to take 2 naproxen tablets 275 mg prior to procedure. As women had received naproxen already, the study was more or less on the pain level of manoeuvring the scope, not introduction of the scope, as the pain medication was infused though the scope which was already in the uterine cavity. This may have introduced bias too In 2 women, hysteroscopy was abandoned due to pain. In both cases, the randomisation code was broken. In both cases normal saline had been used: following the administration of 5 mL 2% lignocaine the procedure was completed

Esteve 2002

Methods	Randomised, double-blind, placebo-controlled trial. No loss to follow-up. 34 women in intervention group and 28 women in placebo group. Single-centre trial in day hospital, Bahia, Brazil
Participants	Women undergoing diagnostic hysteroscopy. Age of women ranged between 20 and 71 years, with the mean age of 45 years in both groups. 3 dropouts due to stenosis of the internal uterine cavity
Interventions	Intracervical application at 1, 5, 7 and 11 o'clock positions of 4 x 2 mL ampoules of 2% lidocaine hydrochloride ampoules or saline
Outcomes	Pain score during hysteroscopy, during the biopsy, at the end of the procedure and 30 min after the procedure. 10-point Huskinssion VAS used
Notes	

Esteve 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly allocated into two groups."
Allocation concealment (selection bias)	Unclear risk	Not stated in study
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded, "neither the patient nor the attendant physician were aware of the content of the ampoules."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	65 women initially enrolled into study with two exclusions. 1 woman not accounted for in results
Selective reporting (reporting bias)	Low risk	1 measuring instrument used (10 cm VAS) and data reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes
Other bias	Unclear risk	Unequal numbers in 2 groups - could happen by chance

Finikiotis 1992

Methods	Prospective randomised study. No loss to follow-up. 60 women in both intervention groups Single-centre trial at Flinders Medical Centre, Adelaide, Australia
Participants	Women undergoing hysteroscopy referred from GPs and other gynaecologists. Mean ages not stated. No exclusions
Interventions	20 mL of 1% lignocaine paracervical block or 2% uterosacral block
Outcomes	Pain during hysteroscopy. 10 cm VAS
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The patients were randomised according to an odd or even unit record number."

Finikiotis 1992 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	"The patients were randomised according to an odd or even unit record number."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No exclusions
Selective reporting (reporting bias)	High risk	Data grouped into 3 dichotomous outcomes. 1 measurement scale used. All time points stated to have data collected were reported. Did not record change from baseline
Other bias	Low risk	Nothing detected

Giorda 2000

Methods	Randomised, unblinded study. No loss to follow-up. 3-arm study; 5 mm diagnostic sheath, 5 mm diagnostic sheath with paracervical block and 3.5 mm sheath. 119 women in group 1 and 121 women in groups 2 and 3. Results for groups 1 and 2 only were included within the meta-analysis. Single-centre trial in Centro di Fiferimento Oncologico in Aviano, Italy
Participants	Postmenopausal women referred for outpatient diagnostic hysteroscopy. The mean ages of women were 60 years in group 1 and 61 years in group 2. 22 women were excluded
Interventions	20 mL of 1% mepivacaine injected para cervically at 3, 5, 7 and 9 o'clock position of the junction of cervix and vagina at least 5 min before the procedure
Outcomes	Pain score after the procedure. 10 cm VAS
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Procedures were randomly assigned through a computer randomization list."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded

Giorda 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Excluded 22 women and 38 women not randomised (previous hysteroscopy, severe previous vagal reaction, allergy to local anaesthesia, vaginal stenosis, cervical stenosis, gas leakage, bubble formation, large polyps)
Selective reporting (reporting bias)	Low risk	1 measuring instrument used (10 cm VAS) and data reported; data were further subgrouped into those receiving hormonal treatment. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes but data presented as percentages in the abstract. SE stated rather than SDs
Other bias	Low risk	No other source of potential bias identified

Hassan 2016a

Methods	Prospective, double-blind RCT on 210 women between 20-45 years old undergoing diagnostic hysteroscopy. No losses to follow-up. 70 women allocated to the tramadol group; 70 to the celecoxib group and the remaining 70 to the placebo group Cairo University Hopsitals, Egypt. May 2014-November 2014
Participants	Women undergoing diagnostic hysteroscopy. Study included 210 after 23 women declined to participate and 12 women were excluded. Mean age of women in tramadol group 29.25 ± 6.39; mean age of women in Clecoxib group 29.52 ± 6.44; mean age of women in placebo group 30.8 (6%). None of the procedures had to be stopped in the tramadol and celecoxib groups however, 1 procedure had to be stopped in the placebo group due to severe, intolerable pain (VAS 0-10 cm)
Interventions	Women were assigned into 1 of three groups to receive either 100 mg of oral tramadol (Tramaw, Global Napi, Giza, Egypt) or 200 mg of Celecoxib (Celebrexw 200, Pfizer, USA) or placebo in the control group. All women received the medication 1 h before the intervention. The procedure was performed in the lithotomy position. A 30º angle was used to introduce a 2.9 mm rigid hysteroscope with 3.8 mm diagnostic sheath (Karl Storzw, Germany). The vaginoscopic approach was used for insertion of the hysteroscope in all cases (no use of speculum or tenaculum). The hysteroscope was gently introduced into the uterine cavity after visualisation of the cervix and identification of the external os. Saline was used as the distension medium and the maximum pressure was set at 100 mmHg
Outcomes	Before surgery, women were educated about the VAS, in which 0 indicated no pain and 10 the worst pain imaginable. Women's perception of pain was assessed for each group during, immediately after and 30 min after the procedure with the use of the score on VAS. Time until no pain was estimated by asking women to report the time when they

Hassan 2016a (*Continued*)

	thought pain had completely gone. All women stayed in the clinic for at least 30 min and for up to 2 h until the time no pain was reported, and all women were pain free before leaving the clinic. Women were also asked to report side effects
Notes	With regard to Hassan 2016a and Hassan 2016b, the corresponding author confirmed by email (20 September 2017) "that the 2 papers represent 2 different studies with independent data"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"An independent person generated the allocation sequence using computer generated random numbers in a 3 block table"
Allocation concealment (selection bias)	Unclear risk	"Drugs were enclosed in sequentially numbered, sealed envelopes and were kept with the attending nurse."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinding. "Neither the patient nor the physician were aware of the drug used. "
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	1 measuring instrument was used (10 cm VAS). All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes
Other bias	Low risk	None detected

Hassan 2016b

Methods	Prospective, double-blind RCT on 140 women undergoing diagnostic hysteroscopy of reproductive age (12-49 years). 70 women allocated to the tramadol group; 70 allocated to the placebo group Cairo University Hopsitals, Egypt, from May 2014-March 2015
Participants	Women undergoing diagnostic hysteroscopy. Study included 140 after 46 women declined to participate and 26 women were excluded. Mean age of women in tramadol group 31.5 (+/- 7.4); mean age of women in placebo group 32.3 (+/- 8.1). None of the procedures had to be stopped in the tramadol group; 1 procedure had to be stopped in the placebo group due to severe, intolerable pain (VAS 0-10 cm)

Hassan 2016b (*Continued*)

Interventions	Women were assigned to 1 of two groups to receive either 50 mg of oral tramadol (Tramaw, Global Napi, Gisa, Egypt) or placebo in the control group. All women received the medication 1 h before the intervention. The procedure was performed in the lithotomy position. A 30º angle was used to introduce a 2.9 mm rigid hysteroscope with 3.8 mm diagnostic sheath (Karl Storzw, Germany). The vaginoscopic approach was used for insertion of the hysteroscope in all cases (no use of speculum or tenaculum). The hysteroscope was gently introduced into the uterine cavity after visualisation of the cervix and identification of the external os. Saline was used as the distension medium and the maximum pressure was set at 100 mmHg. All procedures done by the same operator with same technique
Outcomes	Women's perception of pain was assessed for each group during, immediately after and 30 min after the procedure with the use of the score on a VAS. Women were also asked to report side effects
Notes	With regard to Hassan 2016a and Hassan 2016b, the corresponding author confirmed by email (20 September 2017) "that the 2 papers represent 2 different studies with independent data"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"An independent person generated the allocation sequence using computer generated random numbers"
Allocation concealment (selection bias)	Unclear risk	"Drugs were enclosed in sequentially numbered, sealed envelopes and were kept with the attending nurse."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinding. "The nurse, the patient and the physician were not aware of the drug used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Unclear risk	1 measuring instrument was used (10 cm VAS). All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes. Pain outcomes reported as median scores and not means
Other bias	Low risk	None detected

Kabli 2008

Methods	A prospective, randomised trial. No loss to follow-up. 36 women in local cervical group and 42 women in combined local cervical and intrauterine anaesthesia group Single-centre trial at Academic Teaching Centre, McGill University, Montreal, Canada
Participants	Infertile women undergoing hysteroscopy. Mean age of 37 years in local cervical group and 38 in combined local cervical and intrauterine anaesthesia group. 4 exclusions
Interventions	2 mL of 1% lidocaine into anterior wall. Distension medium of either saline only or 18 mL of lidocaine in 250 mL of saline
Outcomes	Pain score during hysteroscopy and 10, 30 and 60 min after hysteroscopy. 10-point VAS
Notes	Co-administration of lorazepam 10 mg orally 30 min before the procedure

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was done using a computer generated random number table."
Allocation concealment (selection bias)	Unclear risk	"Randomisation was done using a computer generated random number table."
Blinding (performance bias and detection bias) All outcomes	High risk	Single blinded. "The patients were blinded but the operators were aware of the content of the solution."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Three withdrew consent and one could not tolerate speculum examination."
Selective reporting (reporting bias)	Unclear risk	Data presented as medians. 1 measuring instrument used (10 cm VAS). All time points stated to have data collected were reported. Did not record change from baseline
Other bias	Unclear risk	Co-administration of lorazepam 10 mg orally

Kokanali 2013

Methods	Prospective RCT on 200 women undergoing hysteroscopy for abnormal uterine bleeding. No losses to follow-up. 100 women received local anaesthesia while 100 women did not receive any local anaesthesia Department of Gynaecology of Zekai Tahir Burak Woman's Health Research and Education Hospitals, Ankara, Turkey, May 2013-September 2013
Participants	Study included 200 women undergoing diagnostic hysteroscopy. Mean age of women in Group 1 (received local anaesthesia) 41.94 ± 9.01; mean age of women in Group 2 (no local anaesthesia) 42.03 ± 8.30 None of the procedures had to be stopped in Group 1 or 2
Interventions	All women were examined between the 5 LH and 10 LH cycle days. A disposable speculum was used to visualise the cervix and the cervix was cleaned with a water solution of octenidine hydrochloride 0.1% and 2-phenoxyethanol 2%. Intracervical local anaesthesia (10 mL of 1% prilocaine) was applied at the 4 and 8 o'clock positions on the posterior lip of the cervix in divided doses and then the speculum was removed. A rigid, 3-mm outer diameter Storz® hysteroscope was used for the procedure. Hysteroscopy was performed without the use of a tenaculum and without cervical dilatation by the same physician who knew the group to which the women belonged. Uterine distension was maintained by a steady stream of 1.5% Glycine solution
Outcomes	Before surgery, women were educated about the VAS in which 0 indicated no pain and 10 the worst pain imaginable. Women were observed for 60 min and they were asked to complete a standardised pain evaluation form to evaluate the worst pain experienced during the procedure after 30 min and 60 min of the procedure by a clinician who did not know who did not know the group to which the women belonged
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	All the 200 women were randomised using a computer generated randomisation programme into 2 groups.
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Physician performing the procedure were not blinded to the allocation. However, physicians evaluating the pain score using VAS were blinded to the procedure. Unclear as to whether the women were blinded to the procedure
Incomplete outcome data (attrition bias) All outcomes	Low risk	No exclusions reported

Kokanali 2013 (*Continued*)

Selective reporting (reporting bias)	Low risk	1 measuring instrument used (10cm VAS) and data reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes
Other bias	Low risk	No other potential bias detected

Lau 1999

Methods	Double-blinded, randomised, placebo-controlled trial. No loss to follow-up. 49 women in intervention group, 50 in placebo group Single-centre trial at The Chinese University of Hong Kong
Participants	Women undergoing outpatient hysteroscopy for abnormal uterine bleeding. Mean age of 49 years in intervention and placebo group
Interventions	Paracervical block at 3, 5, 7 and 9 o'clock positions of 10 mL of 2% lignocaine or saline, 5 min prior to procedure
Outcomes	Pain score before the procedure, at grasping the cervix, after injection, at insertion of hysteroscope, distension of uterus, after endometrial biopsy and 30 min after the procedure. 10 cm VAS
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"They were randomized into two groups using a computer generated block number and put inside a sealed envelope."
Allocation concealment (selection bias)	Unclear risk	"They were randomized into two groups using a computer generated block number and put inside a sealed envelope."
Blinding (performance bias and detection bias) All outcomes	Low risk	"The attending doctor, nursing staff and the women were all blinded to the identity of the medication used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 exclusion reported. "Hysteroscopy failed in one woman because of cervical stenosis"

Lau 1999 (*Continued*)

Selective reporting (reporting bias)	Low risk	1 measuring instrument used (10 cm VAS) and data reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes
Other bias	Low risk	Nothing detected

Lau 2000

Methods	Double-blinded, randomised, placebo-controlled trial. No loss to follow-up. 45 women in intervention group, 44 in placebo group. Single-centre study at Prince Wales Hospital, Hong Kong
Participants	Women undergoing diagnostic hysteroscopy. Mean age 48 years in intervention group and 44 in placebo group. 1 exclusion
Interventions	Transcervical intrauterine instillation of 5 mL of 2% lignocaine or normal saline into the uterine cavity 5 min before procedure
Outcomes	Pain score before the procedure, at grasping of the cervix, after instillation, at insertion of hysteroscope, during hysteroscopy, at endometrial sampling and 30 min after the procedure. 10 cm VAS
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The woman was randomized into one of the two groups using random numbers generated by a computer."
Allocation concealment (selection bias)	Unclear risk	"The allocations placed into opaque sealed envelopes."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinded. "Both the woman and the attending medical staff were unaware of the medication used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 exclusion. "One woman in the placebo group who experienced intolerable pain."
Selective reporting (reporting bias)	Low risk	1 measuring instrument used (10 cm VAS) and data reported in 1 standard manner. All time points stated to have data collected

Lau 2000 (*Continued*)

		were reported. Did not record change from baseline. Did not convert to dichotomous outcomes
Other bias	Low risk	Nothing detected

Lin 2005

Methods	Randomised, placebo-controlled study. No loss to follow-up. 80 women in intervention group. 84 in placebo group. Single-centre trial at Wu Ho-Su Memorial Hospital, Taiwan
Participants	Women undergoing office hysteroscopy. 15 exclusions. Mean age of 41 years in intervention group and 40 in placebo group
Interventions	0.2 mg of buprenorphine or placebo given under tongue 40 min prior to procedure
Outcomes	Pain score during the procedure. 10 cm VAS used
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The patients were randomized by computer generated numbers."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The procedure failed in 15 patients because of cervical stenosis."
Selective reporting (reporting bias)	Low risk	1 measuring instrument used (10 cm VAS) and data reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes. The P values were described as not significant but were not actually reported, which may suggest an element of under reporting
Other bias	Low risk	Nothing detected

Lukes 2015

Methods	Randomised, comparative treatment trial conducted by 5 private obstetrics and gynaecology practices in the USA with 1 investigator per site. 3 women lost to follow-up. 40 premenopausal women randomised to combined para/intracervical anaesthetic block protocol of 37 cc local anaesthetic administered at 6 different injection sites in association with application of topical 1% lidocaine gel or intracervical only anaesthetic block protocol of 22 cc administered at 3 different injection sites without topical anaesthesia
Participants	Women undergoing hysteroscopy for removal of intrauterine polyps and myomas using the MyoSure device. Study included 40 women. 19 randomised to the para/intracervical group and 21 to the intracervical group. Mean age of women was 44.2 ± 7.7 in the combined para/intracervical block group and 41.8 ± 7.5 n the intracervical group. All randomised subjects underwent the procedure
Interventions	The para/intracervical block group received a total of 37 cc of anaesthetic at 6 different sites. Topical 1 % lidocaine was applied to the cervix, with a set time of 2-3 min before the injection of anaesthetic, for para/intracervical group only. The intracervical group received a total of 22 cc of anaesthetic administered at 3 different sites
Outcomes	The main outcome measure was composite score for procedure-related pain, which incorporated individual pain scores during: 1) the cervical block injection; 2) cervical dilatation; 3) uterine distension; 4) the tissue resection
Notes	This study used the Wong Baker scale, a 0-10 cm measure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Women were randomised on the day to combined para/intracervical block or an intracervical block group in a 1:1 ratio, using a computer-generated randomisation scheme
Allocation concealment (selection bias)	Unclear risk	The randomisation sequence was provided to sites, using sealed, sequentially labelled opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Single-blinded - women were blinded to the assignment because they were not told how many injections each group would be receiving
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All randomised women underwent the procedure however, 2 women failed to meet the inclusion and exclusion criteria and 1 woman had a major protocol deviation. As a result the final analysis included 17 women in the para/intracervical block and

Lukes 2015 (*Continued*)

		20 in the intracervical block
Selective reporting (reporting bias)	Low risk	1 measuring instrument, the Wong-baker face rating scale was used. This scale provides a scale ranging from 0-10 cm, with 0 indicating no pain with 10 indicating maximum pain. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes
Other bias	Unclear risk	Women were told to take 800 mg of ibuprofen the night before the procedure. 1 h before the procedure the women received 10 mg of diazepam and 10 mg of hydrocodone/acetaminophen, followed by an intramuscular injection of 30 mg ketorolac and 0.4% of atropine

Makris 2001

Methods	A randomised, placebo-controlled study. No loss to follow-up. 200 women were prospectively randomised into two groups, the study group (n = 100) and the control group (n = 100). Single-centre trial at the hysteroscopy unit of the First Department of Obstetrics and Gynecology of the University of Athens
Participants	Women undergoing diagnostic hysteroscopy, with or without endometrial biopsy. Mean age of 35.4 years in the intervention group and 36.1 in the placebo group
Interventions	1 mL to 3 mL (30 to 90 mg) of mepivacaine 3% or saline administered intracervically 3 min prior to procedure
Outcomes	Pain score during the procedure, 30 min after the procedure and 60 min after the procedure. 11-point scale used
Notes	Varying dose of mepivacaine given

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"200 patients were prospectively randomised into two groups."
Allocation concealment (selection bias)	Unclear risk	"200 patients were prospectively randomised into two groups."

Makris 2001 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"No patient from either group needed to be hospitalised. All patients left the hospital within 90 min after the end of the procedure."
Selective reporting (reporting bias)	High risk	1 measuring instrument used (11-point scale). Data were reported in a graphical form as well as numerical form. However, these data could not be accurately included within the review as the P values and SDs were described as not significant but were not actually reported, which may indicate an element of under reporting. All time points stated to have data collected were reported in the graph, but could not be interpreted accurately. Did not record change from baseline. Did not convert to dichotomous outcomes
Other bias	Unclear risk	Varying dose of mepivacaine administered

Mercorio 2002

Methods	A randomised prospective study. No loss to follow-up. A total of 148 women received dexketoprofen tablets and 150 women received local anaesthetic drug. Single-centre trial at Menopause Clinic, University 'Federico II' of Naples, Via Pansini 5, Naples, Italy	
Participants	305 consecutive postmenopausal women were referred to outpatient Menopause Clinic for hysteroscopy because of uterine bleeding. Mean ages not stated. Postmenopausal women	
Interventions	The women were randomly allocated to receive either local infiltration of the cervix by injecting of 5 mL mepivacaine 2% intracervically up to the level of the internal os or 1 tablet of dexketoprofen given 1 h before the procedure	
Outcomes	Pain experienced during hysteroscopy and at 30, 60 and 120 min after the procedure using an 11-point VAS	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Mercorio 2002 (*Continued*)

Random sequence generation (selection bias)	Low risk	"Randomisation was achieved with sealed envelopes containing computer generated block randomisation numbers."
Allocation concealment (selection bias)	Unclear risk	"Randomisation was achieved with sealed envelopes containing computer generated block randomisation numbers."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Seven women were excluded from the study. Five of these thought to be too anxious to tolerate hysteroscopy under local anaesthesia or pharmacological sedation, two because previous conisation."
Selective reporting (reporting bias)	High risk	Data presented in a graphical form only with no numerical values. 1 measuring instrument used (10 cm VAS). All time points stated to have data collected were reported. Did not record change from baseline
Other bias	Low risk	Nothing detected

Mohammadi 2015

Methods	Double-blind RCT. 70 nulliparous women with primary infertility undergoing diagnostic hysteroscopy. 18 lost to follow-up. 44 women in lidocaine group (9 lost to follow-up in this group so final analysis of 35 women) and 44 (9 lost to follow-up so final analysis of 35 women) women in diclofenac group Center of Reproductive Medicine, Dr. Shariati Hospital, July 2012-April 2013
Participants	Women undergoing hysteroscopy. Study included 70 women after excluding 24 due to not meeting inclusion criteria or being lost to follow-up. Mean age of women in lidocaine group 29.3 ± 4.4; mean age of women in diclofenac group 30.8 ± 4.4. 9 women in the lidocaine group needed sedation with propofol. 5 women in the diclofenac group needed sedation and 4 women needed an invasive procedure in the diclofenac group
Interventions	Women were assigned into 1 of two groups to receive either 100 mg of rectal diclofenac or 5 mL of 2% intrauterine lidocaine. In the gynaecologic ward, 30 min before transferring to the operating room, the staff gave 100 mg rectal diclofenac to women in the diclofenac group. The study drugs (lidocaine or saline) were prepared by the anaesthesia staff who gave it to the surgeon who was blinded to allocation. Then 5 mL of 2% lidocaine or the same volume of saline was instilled through the endocervix into the uterine cavity with an 18-gauge angiocatheter. The angiocatheter was left in place for 3 min before it was withdrawn while women were in the Trendelenburg position to limit backflow and to

	allow the anaesthetic to take effect	
Outcomes	Before surgery, women were educated about the NRS, 0 indicated no pain and 10 the worst pain imaginable. Pain scoring was performed during insertion of the hysteroscope, during visualisation of the intrauterine cavity, and during extrusion of the hysteroscope	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed using computer-generated codes. Sealed envelopes containing the information of the randomisation code were kept by the staff not involved in the study. The envelope was transferred to a specific member of the gynaecologic staff
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes containing the information of the randomisation code, generated by a computer were given to a member of the gynaecology staff
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blinded - outcome assessor and the women were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of the 88 women randomised, 18 were lost to follow-up (9 needed propofol in the lidocaine group); 5 needed sedation with propofol and 4 needed an invasive procedure in the diclofenac group
Selective reporting (reporting bias)	Low risk	1 measuring instrument was used (NRS 0-10) and the data were reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes
Other bias	Low risk	Nothing detected

Nagele 1997

Methods	Randomised, placebo-controlled trial. 49 women were randomised to the active drug, and 46 to placebo. No loss to follow-up. Single-centre trial at Minimally Invasive Therapy Unit and Endoscopy Training Centre, University Department of Obstetrics and Gynaecology, The Royal Free Hospital, London, UK
Participants	The mean age of the women was 43 to 49 years. Women attending for diagnostic hysteroscopy
Interventions	Active mefenamic acid 500 mg or placebo tablets 1 h before the procedure
Outcomes	Pain scores during, immediately after (0 min), 30 min and 60 min after outpatient hysteroscopy. 10 cm VAS
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Active (mefenamic acid 500 mg) and placebo tablets, which were identical in appearance, were packaged in coded bottles, randomisation being provided by the manufacturer."
Allocation concealment (selection bias)	Unclear risk	"Active (mefenamic acid 500 mg) and placebo tablets, which were identical in appearance, were packaged in coded bottles, randomisation being provided by the manufacturer."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Active (mefenamic acid 500 mg) and placebo tablets, which were identical in appearance, were packaged in coded bottles, randomisation being provided by the manufacturer."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Hysteroscopy was unsuccessful in 4 women (2 in each group): 2 refused because they were too anxious and 2 procedures had to be abandoned because of pain
Selective reporting (reporting bias)	High risk	Data presented graphically with no numerical values. 1 measuring instrument used (10 cm VAS). All time points stated to have data collected were reported. Did not record change from baseline. Odds ratio of experiencing pain calculated

Nagele 1997 (*Continued*)

Other bias	High risk	Some women given local anaesthesia as well as intervention

Senturk 2016

Methods	Double-blind RCT. 206 women suspected of having endometrial polyp, abnormal uterine bleeding or diagnosis of myoma and infertility. No losses to follow-up. The total 206 women comprised 68 (33%) in the placebo group, 76 (36.89%) in the lidocaine group and 62 (30.09%) in the indomethacin group Bakirköy Dr. Sadi Konuk Training and Research Hospital. July 2014-March 2015
Participants	Women undergoing diagnostic hysteroscopy. Study included 206 women. Mean age of women in placebo group 45.62 ± 9.04; mean age of women in lidocaine group 45.54 ± 11.73; mean age of women in indomethacin group 44.71 ± 9.97
Interventions	The control group was administered with a 1000 mL distention medium containing 18 mL serum physiologic per 250 mL and a rectal placebo. The second group was administered with a 1000 mL distention medium containing 18 mL lidocaine per 250 mL (Jetokain ampoule 20 mg 2% Adeka, Samsun, Turkey) and rectal placebo. The third group was administered with rectal indomethacin suppository (Endol 100 mg supp. Deva, Istanbul, Turkey) 45 min before the procedure and with a 1000 mL distention medium containing 18 mL serum physiologic per 250 mL
Outcomes	Before the procedure, women were educated about the NRS in which 0 indicated no pain and 10 the worst pain imaginable. Pain scoring was performed during insertion of the hysteroscope, during visualisation of the intrauterine cavity and 10 min after the procedure
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Women were selected using random-number tables
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	The hysteroscopist and woman were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no loss to follow-up

Senturk 2016 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	1 measuring instrument was used (NRS 0-10) and the data were reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes. Pain score outcomes were reported as medians
Other bias	Low risk	No other potential risk identified

Sharma 2009

Methods	Randomised trial. No loss to follow-up. Single-centre trial at outpatient gynaecology department of All India Institute of Medical Sciences, New Delhi, India. 40 women in each intervention group with a total of 120 women
Participants	A total of 120 women with a medical indication for hysteroscopy and endometrial biopsy (infertility, abnormal uterine bleeding) were recruited. The mean ages were 36.28 years in group 1, 37.75 in group 2 and 36.82 years in group 3
Interventions	Group 1 women received fixed-dose oral tablet containing drotaverine (80 mg) with mefenamic acid (250 mg) 1 h prior to the procedure. Group 2 women received paracervical block with 10 mL of 1% lignocaine solution injected at 3 and 9-o'clock position at the junction of the cervix and vagina in divided doses 5 min prior to the procedure. Group 3 women received intravenous sedation with diazepam (0.2 mg/kg body weight) and pentazocine (0.6 mg/kg body weight) 10 min prior to the procedure. This group was not included in the review
Outcomes	The worst pain experienced during the procedure and the degree of their discomfort after 30 min and 60 min of the procedure using a 10 cm VAS
Notes	Only 2 of the 3 comparison groups were eligible for this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"This study was an open-label randomised trial where all the 120 patients were randomised using a predetermined computer-generated randomisation code into 3 groups."
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias)	High risk	"This study was an open-label randomised trial."

Sharma 2009 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Of the 120 patients recruited, procedure was performed successfully in all, and at no point anyone was excluded from the study. "
Selective reporting (reporting bias)	Low risk	1 measuring instrument used (10 cm VAS) and data reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes
Other bias	Low risk	Nothing detected

Soriano 2000

Methods	Double-blinded RCT. 62 in intervention group, 56 in placebo group. None lost to follow-up. Single-centre trial at Hopital Hotel-Dieu de Paris, Paris, France
Participants	Women undergoing diagnostic hysteroscopy for abnormal uterine bleeding or infertility. Mean age of 41 years in intervention group and 40 in placebo group
Interventions	30 mg (3 metered doses) of lignocaine or placebo sprayed onto surface of cervix and cervical canal through 360° 5 min prior to procedure. 3 exclusions
Outcomes	Pain score during the procedure. 10 cm VAS (pain)
Notes	Unequal number in groups. No re-inclusion of exclusions into analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Women were assigned to receive either lidocaine spray or placebo according to a computer generated randomisation code."
Allocation concealment (selection bias)	Unclear risk	"Lidocaine and placebo were packaged in identical bottles and could not be differentiated."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded. "Lidocaine and placebo were packaged in identical bottles and could not be differentiated."

Soriano 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	3 women excluded. "Two women did not fill out the questionnaire properly"; "one woman the diagnostic hysteroscopy was not done due to cervical stenosis."
Selective reporting (reporting bias)	Low risk	1 measuring instrument used (10 cm VAS) and data reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes
Other bias	Unclear risk	Unequal numbers in intervention and placebo groups - could happen by chance

Stigliano 1997

Methods	Randomised, prospective study. No loss to follow-up. 88 women in prilocaine cream group and 92 women in lignocaine spray group. Study refers to 165 in control group, but these women not part of RCT. Single-centre trial at Castrovillari Hospital, Naples, Italy
Participants	Women attending for diagnostic hysteroscopy. No mean ages given
Interventions	1 cm^3 of 5% prilocaine cream onto esocervix and 2 cm^3 inserted 3 cm into cervical canal 10 min before procedure or 20 mg of lidocaine spray directed onto esocervix and 20 mg 3 cm into cervical canal immediately before procedure or no intervention
Outcomes	4-point pain scale. Placement of tenaculum, progression through cervical canal and evaluation of uterine cavity
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"180 patients were included in the study and randomly allocated to group A or B"
Allocation concealment (selection bias)	Unclear risk	"180 patients were included in the study and randomly allocated to group A or B."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"180 patients were included in the study and randomly allocated to group A or B."

Stigliano 1997 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if any women excluded
Selective reporting (reporting bias)	Unclear risk	1 measuring instrument used (4-point descriptive scale) and data reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Data converted into two dichotomous groups
Other bias	Low risk	Nothing detected

Tam 2001

Methods	Randomised, double-blind, placebo-controlled study. 92 in intervention group and 89 in placebo group. Single-centre study at Prince of Wales Hospital, Hong Kong
Participants	Women undergoing outpatient hysteroscopy. 2 women excluded and 19 women had procedure cancelled. Mean age of women was 50 years in intervention group and 48 in placebo group
Interventions	50 mg of oral diclofenac sodium or placebo tablet given 1-2 h prior to procedure
Outcomes	Pain score before the procedure, at grasping of the cervix, at insertion of the hysteroscope, during hysteroscopy, at endometrial sampling and 30 min after the procedure. VAS used
Notes	Re-inclusion of two exclusions into analysis but not of cancelled procedures

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was performed by using a computer generated random numbers in blocks of 2."
Allocation concealment (selection bias)	Unclear risk	Tablets individually placed into plastic bags according to group number and delivered to the woman by the research nurse
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded. "Participants, attending medical staff and research nurses were blinded to the treatment used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	22 cases not included. "Cancelled in 19"; "failure in inserting the hysteroscope in one case"; "intolerable pain in another"

Tam 2001 (*Continued*)

Selective reporting (reporting bias)	Low risk	1 measuring instrument used (10 cm VAS) and data reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes. Insufficient evidence of under reporting
Other bias	Low risk	Nothing detected

Teran-Alonso 2014

Methods	Prospective, randomised trial comprising women referred to the Hysteroscopy Unit of the "Sanitas La Moraleja" Hospital in Madrid between November 2011 and May 2012. No losses to follow-up. 200 women randomised to 2 groups: 100 women received 1000mg paracetamol and 600mg ibuprofen 1 h before the procedure and 100 did not receive any medication
Participants	200 women undergoing office hysteroscopy from November 2011-May 2012. 100 women were randomised to a pre-medication group (receiving 1 g of paracetamol and 600 mg of ibuprofen 1 h prior to hysteroscopy) and 100 women received no medication. Mean age of women was 45.9 ± 10.7 in the premedication group and 42.9 ± 11.9 in the no pre medication group
Interventions	1 g paracetamol and 600 mg ibuprofen were administered orally to the group receiving medication 1 h prior to hysteroscopy
Outcomes	Pain was evaluated during the test at the time of cervical dilatation, as well as 5 and 30 min after completion of the test, by means of a VAS (5 faces on a scale of 0-10)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	200 women were randomised 1:1 (by means of a computer-generated randomisation list, with same number of women in each group
Allocation concealment (selection bias)	Unclear risk	Not available
Blinding (performance bias and detection bias) All outcomes	High risk	The investigators assessing outcomes and statistician were blinded to the treatment assignment. Placebo was not used, so women and clinician who performed the intervention knew pre-medicated women

Teran-Alonso 2014 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No one was lost to follow-up or not analyzed after randomisation
Selective reporting (reporting bias)	Low risk	1 measuring instrument, VAS was used. This scale provides a scale ranging from 0-10 cm, with 0 indicating no pain with 10 indicating maximum pain. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes
Other bias	Low risk	No other source of bias detected

Van den Bosch 2011

Methods	Randomised, double-blinded, controlled study. Single-centre study at the Department of Gynaecology of the University Hospitals Leuven, Belgium
Participants	142 consecutive women presenting at the department's "One-Stop Bleeding Clinic". Study does not mention if any women declined to participate prior to randomisation. From the population of 142 women who underwent gel installation sonohysterography (GIS), 132 went on to undergo hysteroscopy. Of these 132; mean age 50.6 years, premenopausal 78 (59.1%), perimenopausal 3 (2.3%), postmenopausal 51 (38.6%), nulliparity 21 (15.9%), median endometrial thickness on ultrasound 7.5 mm
Interventions	Intervention group (n = 79 of 142) gel used for installation contained lidocaine (Instillagel) versus control group (n = 63 of 142) gel used for installation did not contain lidocaine (Endosgel)
Outcomes	100 mm VAS asking for perception of pain during the hysteroscopy, the questionnaire was completed shortly following the procedure
Notes	This study was added to this review in 2014.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"...randomised into on of two groups using numbers generated randomly by a computer" further detail of the nature of the generation given
Allocation concealment (selection bias)	Low risk	"...placed in opaque-sealed, numbered envelopes"

Van den Bosch 2011 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	"The patients as well as the medical staff performing the hysteroscopy were unaware which gel had been used." However the examiner performing the gel-instillation sonography (GIS) was aware of which gel had been used. Although the relevant intervention was blinded there is a high risk that the blinding could be broken, although the likely impact of this on the results is unclear
Incomplete outcome data (attrition bias) All outcomes	High risk	Not all women who were randomised went on to have hysteroscopy, as some had GIS only. It is not specified if this was planned in advance or due to drop outs. In addition the number of responders was poor
Selective reporting (reporting bias)	Unclear risk	Although the outcome described in the method is reported, adverse events and reasons for non-completion are not documented. Data was reported with interquartile ranges instead of SD. Study author failed to respond to attempts to make contact
Other bias	Low risk	Nothing detected

Vercellini 1994

Methods	Open-label, randomised trial. No loss to follow-up. 87 in intervention group and 90 in no intervention group. Single-centre study at University of Milan, Milan, Italy
Participants	Women attending for diagnostic hysteroscopy. 4 women excluded. Mean age of 40 years in intervention group and 42 in no intervention group
Interventions	Paracervical block at 3, 5, 7 and 9 o'clock positions of 10 mL 1% mepivacaine 5 min before procedure or no intervention given
Outcomes	Pain score at hysteroscopy and endometrial biopsy. 10 cm VAS used
Notes	Exclusions were not re-included into final analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"A randomisation list was used."

Vercellini 1994 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	"Patients were aware of which group they had been assigned to."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Women were aware of group
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 women excluded
Selective reporting (reporting bias)	Low risk	1 measuring instrument used (10 cm VAS) and data reported in 1 standard manner. All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes
Other bias	Low risk	Nothing detected

Wong 2000

Methods	Randomised, double-blind, placebo-controlled trial. No loss to follow-up. 250 women in intervention and placebo group. Single-centre trial at Kwong Wah Hospital, Hong Kong
Participants	Women undergoing outpatient hysteroscopy. Mean age of 49 years in intervention and placebo group. No exclusions or dropouts
Interventions	4 mL of 2% lignocaine or placebo gel applied onto cervix before procedure
Outcomes	Pain score at insertion of speculum, sounding of uterus, cervical dilatation, insertion of hysteroscope, inspection of uterine cavity and aspiration of tissue. 6-point present pain intensity scale used
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomized into two groups with the use of a pre determined randomisation chart."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind, "Neither the patient nor the gynaecologist were aware of the gel being

Wong 2000 (*Continued*)

		applied"
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 cases excluded, "Severe pain or technical difficulty"
Selective reporting (reporting bias)	Unclear risk	1 measuring instrument used (6-point present pain intensity scale). All time points stated to have data collected were reported. Did not record change from baseline. Did not convert to dichotomous outcomes. Total area under curve also presented
Other bias	Low risk	Nothing detected

Zupi 1995

Methods	A randomised, double-blind trial. No loss to follow-up. Included 18 women
Participants	Women undergoing hysteroscopy for infertility or abnormal uterine bleeding. Mean age not stated
Interventions	5 mL of 2% mepivacaine or 5 mL of saline intrauterine via 3 mm catheter
Outcomes	20 cm VAS. Pain score during the procedure, 15, 30, 60 and 120 min after the procedure
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The women were randomised prospectively double blind into two groups."
Allocation concealment (selection bias)	Unclear risk	"The women were randomised prospectively double blind into two groups."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"The women were randomised prospectively double blind into two groups."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear if any exclusions
Selective reporting (reporting bias)	High risk	Data presented graphically and without opportunity to calculate mean pain scores and SD. 1 measuring instrument used (20 cm VAS). All time points stated to have data

Zupi 1995 (*Continued*)

		collected were reported. Did not record change from baseline
Other bias	Low risk	Nothing detected

GP: general practitioner; ITT: intention-to-treat; LH: luteinizing hormone; NRS: numeric rating scale; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale

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

Study	Reason for exclusion
Canovas 2006	Hysteroscopy - the study was not randomised
De Angelis 2003	Hysteroscopy - intervention was TENs. Not pharmacological
Goldenberg 2001	Hysteroscopy - used general anaesthetic as an intervention
Guida 2003	Use of IV sedation
Kaya 2005	Hysteroscopy - use of IV remifentanil
Mizrak 2010	Hysteroscopy - used IV propofol
Pace 2008	Hysteroscopy - conscious sedation used as an intervention
Wallage 2003	Microwave endometrial ablation - use of general anaesthetic as an intervention

IV: intravenous; TENs: transcutaneous electrical nerve stimulation

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

NCT02640183

Trial name or title	A comparison between lidocaine-prilocaine cream (EMLA) application and wound infiltration with lidocaine for post caesarean section pain relief : a randomized controlled trial
Methods	Allocation: randomised Intervention model: parallel assignment Masking: single blind (investigator) Primary purpose: treatment

NCT02640183 (*Continued*)

Participants	Women aged 18-40 years
Interventions	Drug: EMLA cream 5 mg Drug: lidocaine 1 %
Outcomes	Primary outcome measures: time to the first dose of rescue analgesic in the first 6 h (time frame: 6 h) Secondary outcome measures: postoperative pain according to VAS (time frame: 24 h)
Starting date	October 2014
Contact information	Contact: Hany A Ibrahim MBBCH dr.hany_ayad@yahoo.com Contact: Ahmed M Mamdouh, MD
Notes	

NCT02714699

Trial name or title	Oral hyoscine butyl bromide versus diclofenac potassium before office hysteroscopy
Methods	Allocation: randomised Intervention model: parallel assignment Masking: single blind (participant) Primary purpose: prevention
Participants	Women ≥ 20 years
Interventions	• Drug: diclofenac potassium: women will take oral diclofenac potassium; 1 tablet (Cataflam 50 mg) and 1 tablet placebo 30 min before the procedure. Other name: Cataflam • Drug: hyoscine butyl bromide: women will take oral hyoscine butyl bromide; 2 tablets (Biscolan 10 mg) 30 min before the procedure. Other name: Buscopan • Drug: women in placebo group will take oral placebo; 2 tablets 30 min before the procedure
Outcomes	Mean pain score during hysteroscopy (time frame: intraoperative)
Starting date	April 2016
Contact information	Sponsored by: Assiut University
Notes	

NCT02760888

Trial name or title	Oral tramadol versus diclofenac for pain relief before outpatient hysteroscopy: (OPH)
Methods	Prospective, double-blind, randomised, clinical trial. This will be conducted at Ain Shams University Maternity Hospital - Early Cancer Detection Unite (ECDU)
Participants	Women aged 18-35 years
Interventions	Women fulfilling inclusion and exclusion criteria will be divided into three groups Group I (study group): 34 women who will receive tramadol 100 mg orally 1 h before the procedure Group II (study group): 34 women who will receive diclofenac 100 mg orally 1 h before the procedure Group III (control group) 34 women who will receive a placebo Pain will be evaluated on 2 separate occasions: immediately after the procedure and 15 min after procedure using a 100 mm line VAS
Outcomes	• Pain during the procedure (time frame: intraoperative; designated as safety issue: no). Pain will be assessed using a VAS immediately after inserting the hysteroscopy • Pain after the procedure (time frame: 15 min after completing the procedure; designated as safety issue: no) 15 min after procedure using a 100 mm line VAS
Starting date	May 2016
Contact information	elbohoty79@yahoo.com
Notes	

VAS: visual analogue scale

DATA AND ANALYSES

Comparison 1. Local anaesthetic versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	12		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Pain score during procedure	10	1496	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-0.39, -0.19]
1.2 Pain score within 30 min of procedure	5	545	Std. Mean Difference (IV, Fixed, 95% CI)	-0.50 [-0.67, -0.33]
1.3 Pain score more than 30 min after procedure	4	450	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.30, 0.07]
2 Failure to complete procedure	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Cervical stenosis	6	805	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.62, 2.43]
2.2 Pain	2	330	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.12, 0.69]
3 Adverse events	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Vasovagal reaction	8	1309	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.43, 1.13]
3.2 Non-pelvic pain	1	99	Odds Ratio (M-H, Fixed, 95% CI)	1.76 [0.53, 5.80]

Comparison 2. Oral NSAID versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Pain score during procedure	3	521	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.35, -0.00]
1.2 Pain score within 30 min of procedure	2	340	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.46, -0.04]
1.3 Pain score more than 30 min after procedure	2	321	Std. Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.49, -0.05]
2 Adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Vasovagal reaction	1	181	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.20, 2.94]
2.2 Non pelvic pain	1	181	Odds Ratio (M-H, Fixed, 95% CI)	2.93 [0.12, 72.99]
2.3 Allergic reactions	1	181	Odds Ratio (M-H, Fixed, 95% CI)	2.93 [0.12, 72.99]

Comparison 3. Opioid versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Pain score during procedure	2		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Pain score within 30 min of procedure	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Pain score more than 30 min after procedure	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Failure to complete procedure (due to pain)	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.21]
3 Adverse effects	1	164	Odds Ratio (M-H, Fixed, 95% CI)	107.55 [6.44, 1796.46]
3.1 Nausea and vomiting	1	164	Odds Ratio (M-H, Fixed, 95% CI)	107.55 [6.44, 1796.46]

Comparison 4. Local intracervical anaesthesia versus combined intracervical and paracervical anaesthesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Pain score during procedure	1	84	Std. Mean Difference (IV, Fixed, 95% CI)	4.27 [3.49, 5.06]
1.2 Pain score within 30 min of procedure	1	84	Std. Mean Difference (IV, Fixed, 95% CI)	1.55 [1.06, 2.05]
1.3 Pain score more than 30 min after procedure	1	84	Std. Mean Difference (IV, Fixed, 95% CI)	3.47 [2.78, 4.15]
2 Failure to complete procedure	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 5. Local intracervical anaesthesia versus combined intracervical, paracervical and topical anaesthesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Pain score during procedure	1	37	Std. Mean Difference (IV, Fixed, 95% CI)	-0.54 [-1.20, 0.12]

Comparison 6. Antispasmodic + NSAID versus local paracervical anaesthesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Pain score during procedure	1	80	Std. Mean Difference (IV, Fixed, 95% CI)	-1.40 [-1.90, -0.91]
1.2 Pain score more than 30 min after procedure	1	80	Std. Mean Difference (IV, Fixed, 95% CI)	-0.87 [-1.33, -0.41]

Comparison 7. Opioid versus NSAID

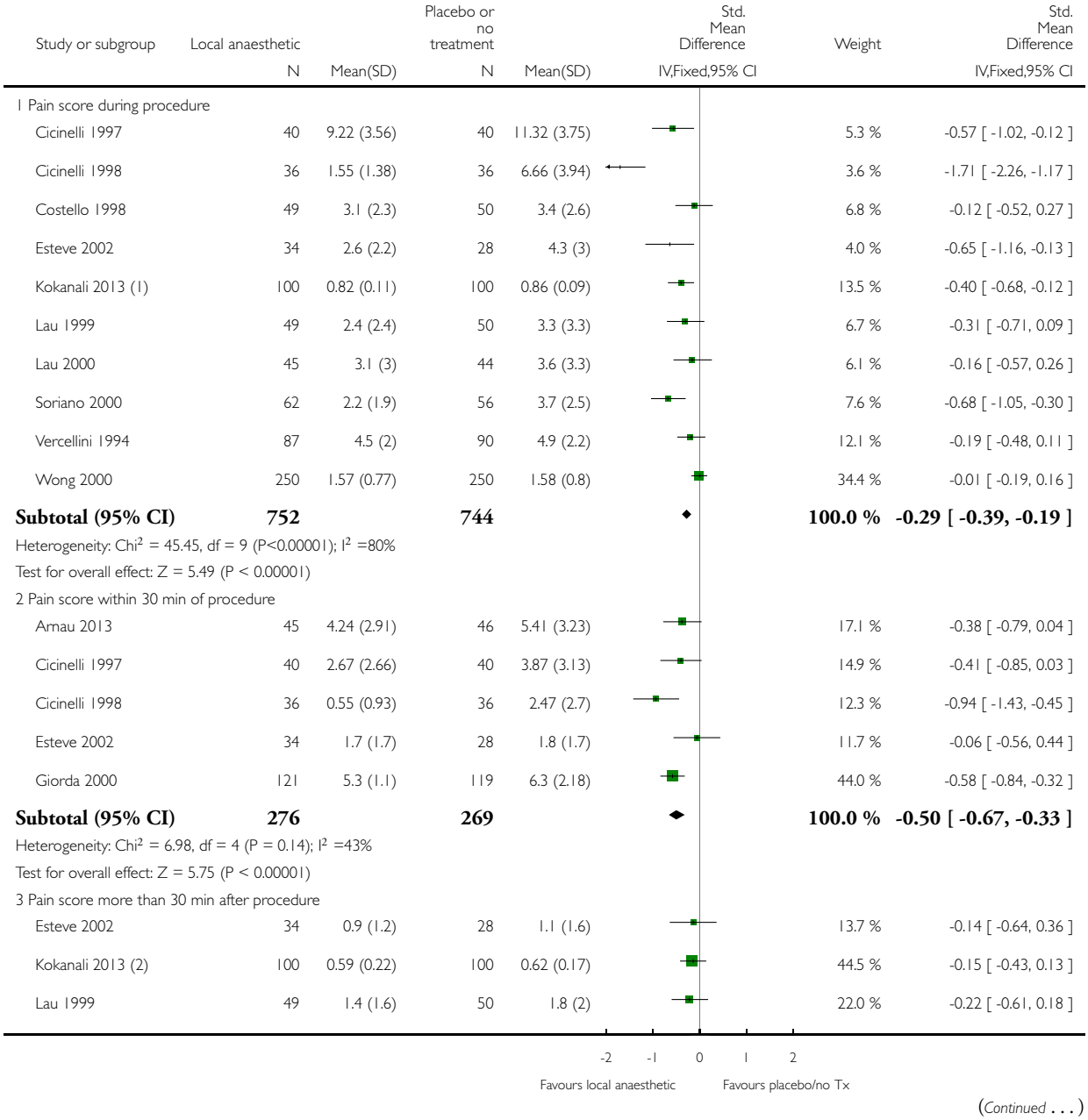
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Pain score during procedure	1	140	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.48, 0.18]
1.2 Pain score within 30 min of procedure	1	140	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.58, 0.08]
1.3 Pain score more than 30 min after procedure	1	140	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.51, 0.16]
2 Adverse effects	1	140	Odds Ratio (M-H, Fixed, 95% CI)	9.54 [0.50, 180.64]
2.1 Nausea and vomiting	1	140	Odds Ratio (M-H, Fixed, 95% CI)	9.54 [0.50, 180.64]

Analysis 1.1. Comparison 1 Local anaesthetic versus placebo or no treatment, Outcome 1 Pain score.

Review: Pain relief for outpatient hysteroscopy

Comparison: 1 Local anaesthetic versus placebo or no treatment

Outcome: 1 Pain score



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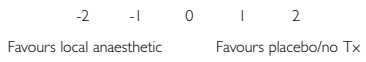
Study or subgroup	Local anaesthetic N	Mean(SD)	Placebo or no treatment N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Lau 2000	45	1.4 (1.8)	44	1.2 (1.4)		19.8 %	0.12 [-0.29, 0.54]
Subtotal (95% CI)	**228**		**222**			**100.0 %**	**-0.11 [-0.30, 0.07]**
Heterogeneity: Chi^2 = 1.60, df = 3 (P = 0.66); I^2 =0.0%							
Test for overall effect: Z = 1.17 (P = 0.24)							



(1) log scale

(2) log scale

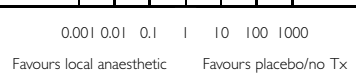
Analysis 1.2. Comparison 1 Local anaesthetic versus placebo or no treatment, Outcome 2 Failure to complete procedure.

Review: Pain relief for outpatient hysteroscopy

Comparison: 1 Local anaesthetic versus placebo or no treatment

Outcome: 2 Failure to complete procedure

Study or subgroup	Local anaesthetic n/N	Placebo or no treatment n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Cervical stenosis					
Costello 1998	1/50	0/50		3.2 %	3.06 [0.12, 76.95]
Esteve 2002	2/36	1/29		7.0 %	1.65 [0.14, 19.13]
Giorda 2000	12/121	11/119		66.7 %	1.08 [0.46, 2.56]
Lau 1999	1/50	0/50		3.2 %	3.06 [0.12, 76.95]
Soriano 2000	1/63	1/56		7.0 %	0.89 [0.05, 14.52]
Vercellini 1994	2/89	2/92		12.8 %	1.03 [0.14, 7.51]
Subtotal (95% CI)	**409**	**396**		**100.0 %**	**1.23 [0.62, 2.43]**
Total events: 19 (Local anaesthetic), 15 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 0.84, df = 5 (P = 0.97); I^2 =0.0%					



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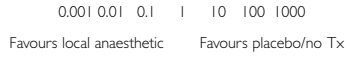
Study or subgroup	Local anaesthetic n/N	Placebo or no treatment n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.59 (P = 0.55)					
2 Pain					
Giorda 2000	7/121	21/119		93.1 %	0.29 [0.12, 0.70]
Lau 2000	0/45	1/45		6.9 %	0.33 [0.01, 8.22]
Subtotal (95% CI)	**166**	**164**		**100.0 %**	**0.29 [0.12, 0.69]**
Total events: 7 (Local anaesthetic), 22 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 2.81 (P = 0.0049)					



Analysis 1.3. Comparison 1 Local anaesthetic versus placebo or no treatment, Outcome 3 Adverse events.

Review: Pain relief for outpatient hysteroscopy

Comparison: 1 Local anaesthetic versus placebo or no treatment

Outcome: 3 Adverse events

Study or subgroup	Local anaesthetic n/N	Placebo or no treatment n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Vasovagal reaction					
Arnau 2013	0/45	2/46		6.2 %	0.20 [0.01, 4.19]
Cicinelli 1997	2/50	13/50		31.4 %	0.12 [0.03, 0.56]
Cicinelli 1998	0/36	9/36		23.6 %	0.04 [0.00, 0.71]
Giorda 2000	8/121	6/119		14.2 %	1.33 [0.45, 3.97]
Lau 1999	15/49	5/50		8.6 %	3.97 [1.31, 12.00]
Lau 2000	3/45	3/44		7.1 %	0.98 [0.19, 5.12]
Soriano 2000	0/62	1/56		3.9 %	0.30 [0.01, 7.42]
Wong 2000	1/250	2/250		5.0 %	0.50 [0.04, 5.53]

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Study or subgroup	Local anaesthetic n/N	Placebo or no treatment n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**658**	**651**		**100.0 %**	**0.70 [0.43, 1.13]**
Total events: 29 (Local anaesthetic), 41 (Placebo or no treatment)					
Heterogeneity: Chi^2 = 20.85, df = 7 (P = 0.004); I^2 =66%					
Test for overall effect: Z = 1.46 (P = 0.14)					
2 Non-pelvic pain					
Lau 1999	8/49	5/50		100.0 %	1.76 [0.53, 5.80]
Subtotal (95% CI)	**49**	**50**		**100.0 %**	**1.76 [0.53, 5.80]**
Total events: 8 (Local anaesthetic), 5 (Placebo or no treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.36)					

Analysis 2.1. Comparison 2 Oral NSAID versus placebo or no treatment, Outcome 1 Pain score.

Review: Pain relief for outpatient hysteroscopy

Comparison: 2 Oral NSAID versus placebo or no treatment

Outcome: 1 Pain score

Study or subgroup	NSAID N	Mean(SD)	Placebo or no treatment N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Pain score during procedure							
Hassan 2016a	70	4.63 (1.63)	70	5.92 (2.26)		25.9 %	-0.65 [-0.99, -0.31]
Teran-Alonso 2014 (1)	100	4.52 (2.82)	100	4.71 (2.9)		38.9 %	-0.07 [-0.34, 0.21]
Tam 2001	92	2.2 (2.1)	89	2.1 (2)		35.2 %	0.05 [-0.24, 0.34]
Subtotal (95% CI)	**262**		**259**			**100.0 %**	**-0.18 [-0.35, 0.00]**
Heterogeneity: Chi² = 10.38, df = 2 (P = 0.01); I² =81%							
Test for overall effect: Z = 2.01 (P = 0.045)							
2 Pain score within 30 min of procedure							
Hassan 2016a	70	2.55 (1.46)	70	3.27 (2.02)		40.7 %	-0.41 [-0.74, -0.07]
Teran-Alonso 2014 (2)	100	0.04 (0.24)	100	0.11 (0.65)		59.3 %	-0.14 [-0.42, 0.14]
Subtotal (95% CI)	**170**		**170**			**100.0 %**	**-0.25 [-0.46, -0.04]**
Heterogeneity: Chi² = 1.42, df = 1 (P = 0.23); I² =29%							
Test for overall effect: Z = 2.29 (P = 0.022)							
3 Pain score more than 30 min after procedure							
Hassan 2016a	70	0.77 (1)	70	1.55 (1.71)		42.7 %	-0.55 [-0.89, -0.22]
Tam 2001 (3)	92	1.1 (1.3)	89	1.2 (1.7)		57.3 %	-0.07 [-0.36, 0.23]
Subtotal (95% CI)	**162**		**159**			**100.0 %**	**-0.27 [-0.49, -0.05]**
Heterogeneity: Chi² = 4.59, df = 1 (P = 0.03); I² =78%							
Test for overall effect: Z = 2.44 (P = 0.015)							

(1) This study used 1 g of paracetamol in conjunction with the NSAID.

(2) This study used 1 g of paracetamol in conjunction with the NSAID.

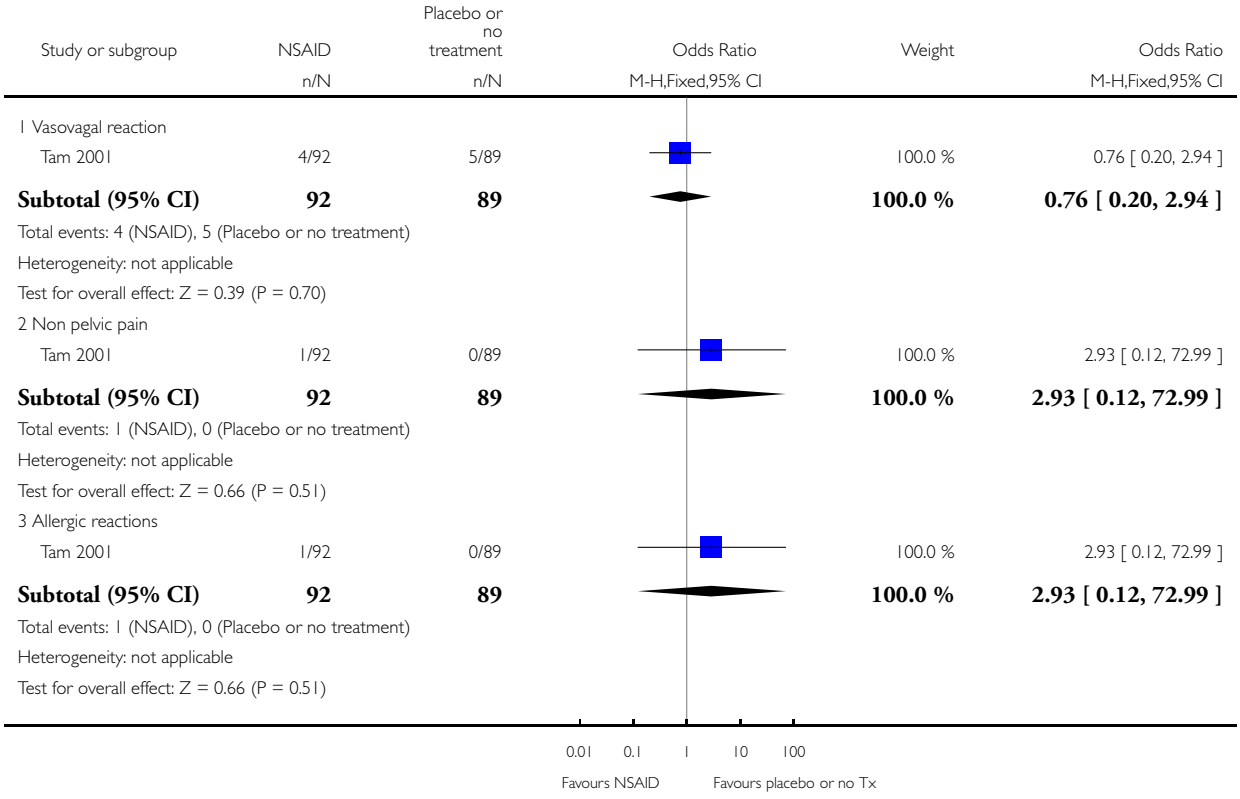
(3) This study used 1 g of paracetamol in conjunction with the NSAID.

Analysis 2.2. Comparison 2 Oral NSAID versus placebo or no treatment, Outcome 2 Adverse events.

Review: Pain relief for outpatient hysteroscopy

Comparison: 2 Oral NSAID versus placebo or no treatment

Outcome: 2 Adverse events



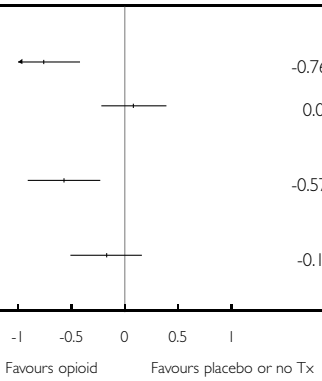
Analysis 3.1. Comparison 3 Opioid versus placebo or no treatment, Outcome 1 Pain score.

Review: Pain relief for outpatient hysteroscopy

Comparison: 3 Opioid versus placebo or no treatment

Outcome: 1 Pain score

Study or subgroup	Opioid		Placebo or no treatment		Std. Mean Difference	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
1 Pain score during procedure						
Hassan 2016a (1)	70	4.37 (1.77)	70	5.92 (2.26)		-0.76 [-1.10, -0.42]
Lin 2005 (2)	80	3.3 (1.1)	84	3.2 (1.3)		0.08 [-0.22, 0.39]
2 Pain score within 30 min of procedure						
Hassan 2016a	70	2.18 (1.77)	70	3.27 (2.02)		-0.57 [-0.91, -0.23]
3 Pain score more than 30 min after procedure						
Hassan 2016a	70	0.6 (0.95)	70	0.77 (1)		-0.17 [-0.51, 0.16]



(1) Oral tramadol 100 mgs

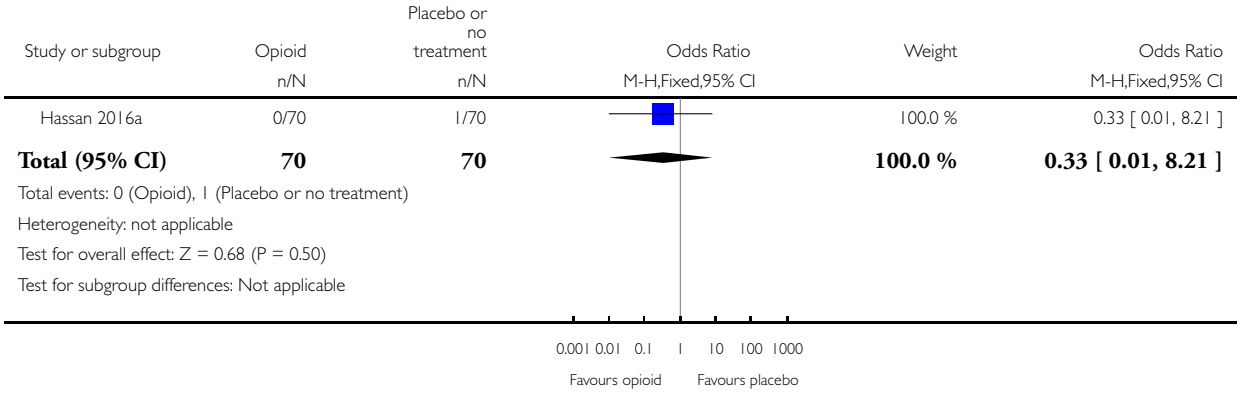
(2) Sublingual buprenorphine 0.2 mgs

Analysis 3.2. Comparison 3 Opioid versus placebo or no treatment, Outcome 2 Failure to complete procedure (due to pain).

Review: Pain relief for outpatient hysteroscopy

Comparison: 3 Opioid versus placebo or no treatment

Outcome: 2 Failure to complete procedure (due to pain)

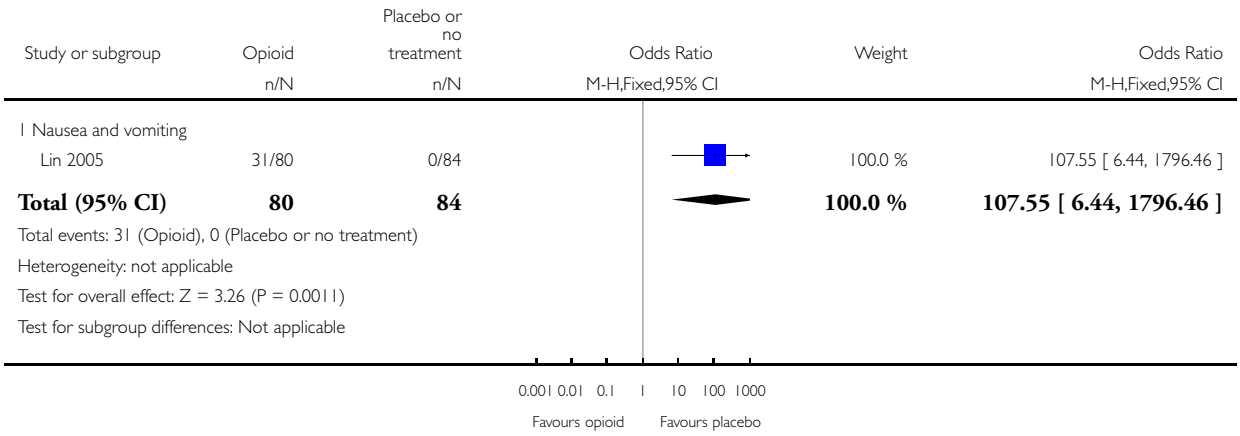


Analysis 3.3. Comparison 3 Opioid versus placebo or no treatment, Outcome 3 Adverse effects.

Review: Pain relief for outpatient hysteroscopy

Comparison: 3 Opioid versus placebo or no treatment

Outcome: 3 Adverse effects



Analysis 4.1. Comparison 4 Local intracervical anaesthesia versus combined intracervical and paracervical anaesthesia, Outcome 1 Pain score.

Review: Pain relief for outpatient hysteroscopy

Comparison: 4 Local intracervical anaesthesia versus combined intracervical and paracervical anaesthesia

Outcome: 1 Pain score

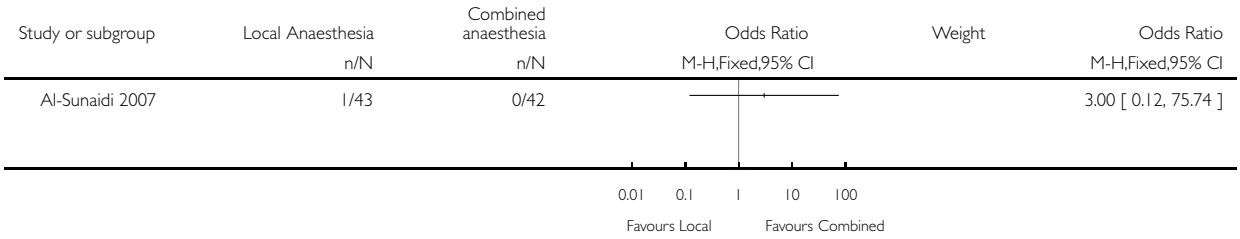
Study or subgroup	Local Anaesthesia N	Mean(SD)	Combined anaesthesia N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Pain score during procedure							
Al-Sunaidi 2007	42	3.2 (0.3)	42	2.1 (0.2)		100.0 %	4.27 [3.49, 5.06]
Subtotal (95% CI)	**42**		**42**			**100.0 %**	**4.27 [3.49, 5.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 10.63 (P < 0.00001)							
2 Pain score within 30 min of procedure							
Al-Sunaidi 2007	42	1.9 (0.2)	42	1.5 (0.3)		100.0 %	1.55 [1.06, 2.05]
Subtotal (95% CI)	**42**		**42**			**100.0 %**	**1.55 [1.06, 2.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.21 (P < 0.00001)							
3 Pain score more than 30 min after procedure							
Al-Sunaidi 2007	42	1.7 (0.2)	42	1 (0.2)		100.0 %	3.47 [2.78, 4.15]
Subtotal (95% CI)	**42**		**42**			**100.0 %**	**3.47 [2.78, 4.15]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.90 (P < 0.00001)							

Analysis 4.2. Comparison 4 Local intracervical anaesthesia versus combined intracervical and paracervical anaesthesia, Outcome 2 Failure to complete procedure.

Review: Pain relief for outpatient hysteroscopy

Comparison: 4 Local intracervical anaesthesia versus combined intracervical and paracervical anaesthesia

Outcome: 2 Failure to complete procedure

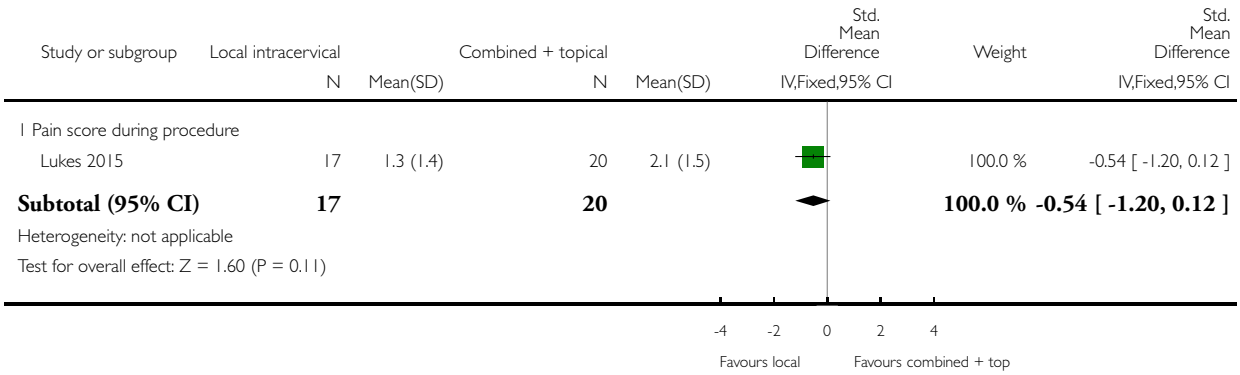


Analysis 5.1. Comparison 5 Local intracervical anaesthesia versus combined intracervical, paracervical and topical anaesthesia, Outcome 1 Pain score.

Review: Pain relief for outpatient hysteroscopy

Comparison: 5 Local intracervical anaesthesia versus combined intracervical, paracervical and topical anaesthesia

Outcome: 1 Pain score

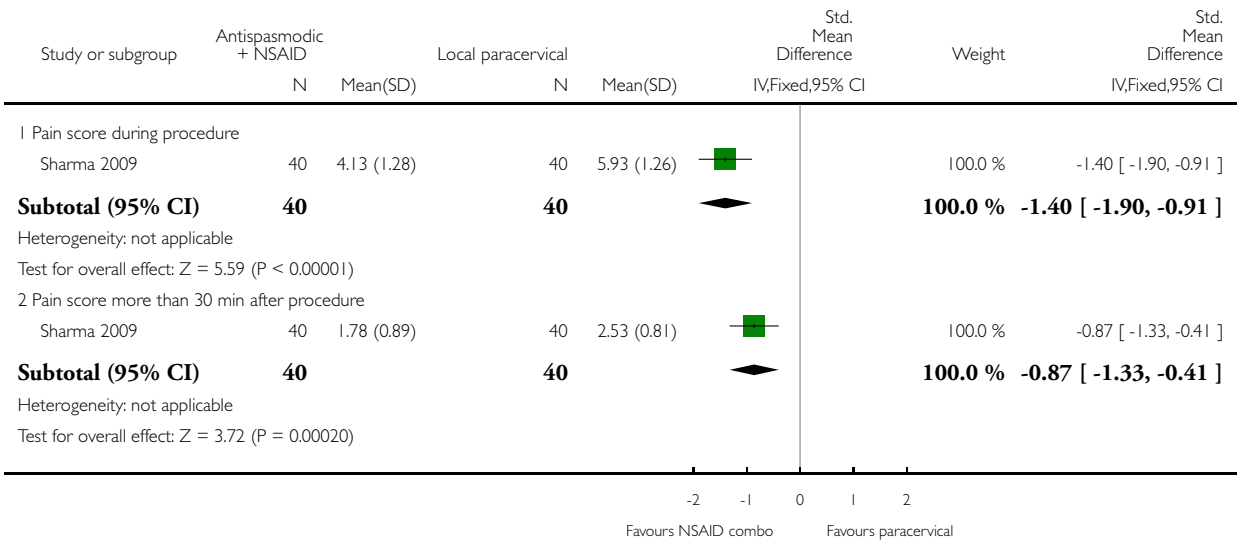


Analysis 6.1. Comparison 6 Antispasmodic + NSAID versus local paracervical anaesthesia, Outcome 1 Pain score.

Review: Pain relief for outpatient hysteroscopy

Comparison: 6 Antispasmodic + NSAID versus local paracervical anaesthesia

Outcome: 1 Pain score

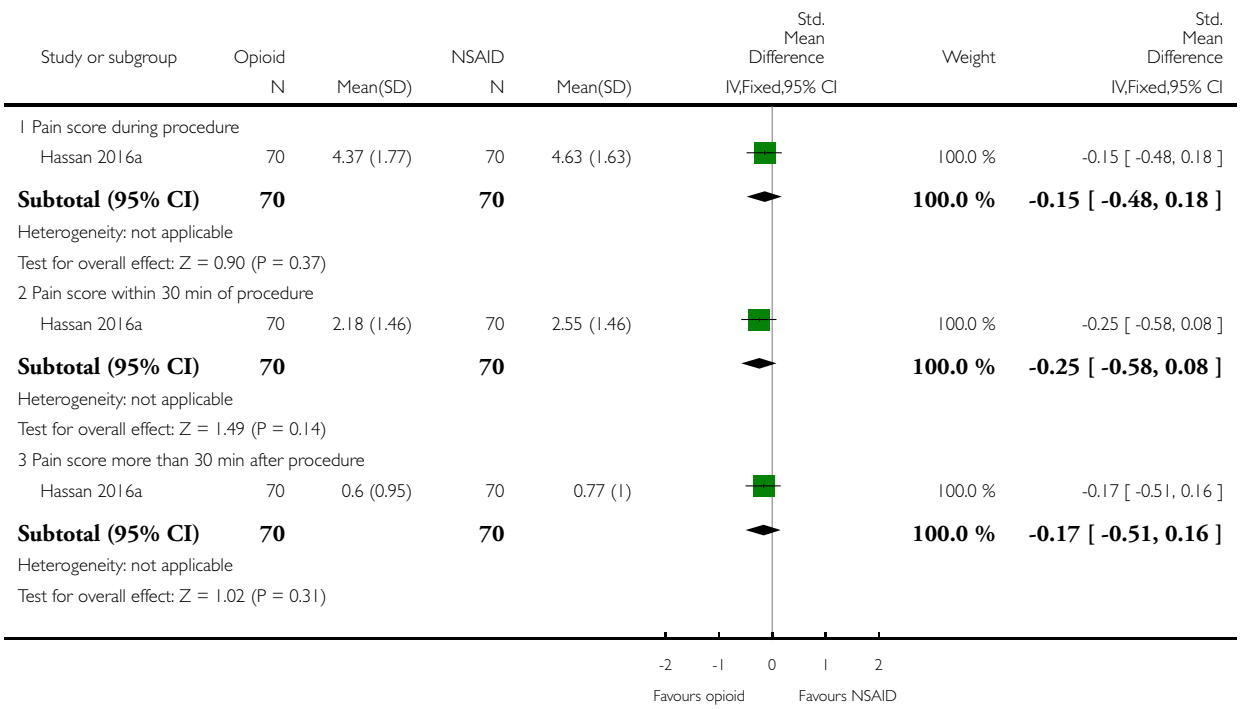


Analysis 7.1. Comparison 7 Opioid versus NSAID, Outcome 1 Pain score.

Review: Pain relief for outpatient hysteroscopy

Comparison: 7 Opioid versus NSAID

Outcome: 1 Pain score

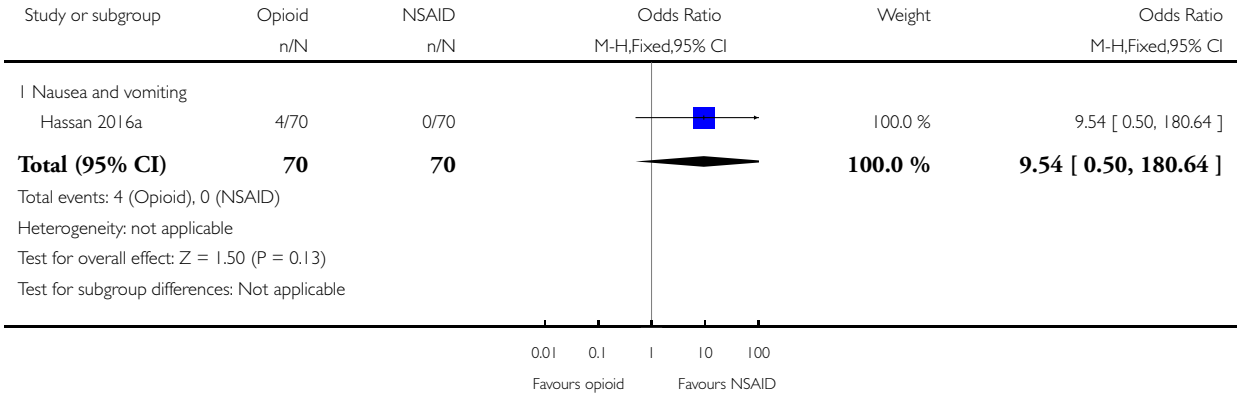


Analysis 7.2. Comparison 7 Opioid versus NSAID, Outcome 2 Adverse effects.

Review: Pain relief for outpatient hysteroscopy

Comparison: 7 Opioid versus NSAID

Outcome: 2 Adverse effects



ADDITIONAL TABLES

Table 1. Dosing of local anaesthetics

Study	Route	Dose
Al-Sunaidi 2007	Intracervical versus intra and paracervical	Local intracervical anaesthesia compared to combined intracervical and paracervical anaesthesia. 0.5% bupivacaine hydrochloride into anterior wall of cervix compared to 0.5% bupivacaine hydrochloride into anterior wall of cervix plus bupivacaine into lateral vaginal fornix at 3 and 9 o'clock at 10 mm depth
Arnau 2013	Endocervical topical cream	3 mL of EMLA cream 5% or 3 mL ultrasound gel applied in the endocervical canal 10 min before surgery with 5 mL needleless syringe via speculum. A subsequent application of either gel was made with a swab at ectocervix level during vaginoscopic approach
Broadbent 1992	Intracervical	Intracervical injection of 10 mL of lignocaine 1% with 1:200 000 adrenaline or normal saline was injected into the cervix at 1, 5, 7, and 11 o'clock
Cicinelli 1997	Transcervical	2 mL of 2% mepivacaine or 2 mL of 0.9% saline injected trans cervically (inserted up the cervical canal

Table 1. Dosing of local anaesthetics (*Continued*)

		to the internal os)
Cicinelli 1998	Paracervical	10 mL of 1.5% mepivacaine or saline injected into junction of cervix and vagina (4 and 8 o'clock positions)
Clark 1996	Topical spray	10 mL of 2% lignocaine gel, placebo gel or no gel administered into cervical canal. Some women received intracervical lignocaine block if determined to need cervical dilatation
Costello 1998	Intrauterine	5 mL of 2% lignocaine or 5 mL or 0.9% saline injected into cervical canal and uterine cavity via hysteroscope
Esteve 2002	Intracervical	Intracervical application at 1, 5, 7 and 11 o'clock positions of 4 x 2 mL ampoules of 2% lidocaine hydrochloride ampoules or saline
Finikiotis 1992	Paracervical versus uterosacral	20 mL of 1% lignocaine paracervical block or 2 mL of 2% lignocaine uterosacral block
Giorda 2000	Paracervical	20 mL of 1% mepivacaine injected paracervically at 3, 5, 7 and 9 o'clock position of the junction of cervix and vagina at least 5 min before the procedure
Kabli 2008	Intracervical versus intracervical and intrauterine	2 mL of 1% lidocaine into anterior wall. Distension medium of either saline only or 18 mL of lidocaine in 250 mL of saline
Kokanali 2013	Intracervical	Intracervical local anaesthesia (10 mL of 1% prilocaine) was applied at the 4 and 8 o'clock position on the posterior lip of the cervix in divided doses
Lau 1999	Paracervical	Paracervical block at 3, 5, 7 and 9 o'clock positions of 10 mL of 2% lignocaine or saline, 5 min prior to procedure
Lau 2000	Transcervical	Transcervical intrauterine instillation of 5 mL of 2% lignocaine or normal saline into the uterine cavity 5 min before procedure
Lukes 2015	Para/intracervical versus intracervical only anaesthetic block	The para/intracervical group received a total of 37 cc of anaesthesia injected at 6 different sites. 2-3 min prior to the injection, topical 1% lidocaine was applied to the cervix in this group. The intracervical group received a total of 22 cc of anaesthetic given at 3 different injection sites

Table 1. Dosing of local anaesthetics (*Continued*)

Makris 2001	Intracervical	1 mL to 3 mL (30 to 90 mg) of mepivacaine 3% or saline administered intracervically 3 min prior to procedure
Mercorio 2002	Intracervical versus NSAID	5 mL mepivacaine 2% intracervically up to the level of the internal os or one tablet of dexketoprofen given 1 h before the procedure
Mohammadi 2015	Transcervical intrauterine lidocaine instillation versus rectal diclofenac	5 mL of 2% lidocaine or the same volume of saline was instilled through the endocervix into the uterine cavity with an 18-gauge angiocatheter 3 min prior to the procedure
Senturk 2016	Intracervical	The second group was administered with a 1000 mL distention medium containing 18 mL lidocaine per 250 mL (Jetokain ampoule 20 mg 2% Adeka, Samsun, Turkey)
Soriano 2000	Topical spray	30 mg (3 metered doses) of lignocaine or placebo sprayed onto surface of cervix and cervical canal through 360° 5 min prior to procedure
Stigliano 1997	Topical cream versus topical spray	1 cm^3 of 5% prilocaine cream onto esocervix and 2 cm^3 inserted 3 cm into cervical canal 10 min before procedure or 20 mg of lidocaine spray directed onto esocervix and 20 mg 3 cm into cervical canal immediately before procedure or no intervention
Van den Bosch 2011	Intrauterine	Unspecified volume of Instillagel (contains 2% lidocaine) or Endosgel (does not contain local anaesthetic) warmed to 37°C and instilled via a 2 mm neonatal suction catheter as part of sonography procedure 30 min prior to hysteroscopy
Vercellini 1994	Paracervical	Paracervical block at 3, 5, 7 and 9 o'clock positions of 10 mL 1% mepivacaine 5 min before procedure or no intervention given
Wong 2000	Topical gel	4 mL of 2% lignocaine or placebo gel applied onto cervix before procedure
Zupi 1995	Intrauterine	5 mL of 2% mepivacaine or 5 mL of saline intrauterine via 3 mm catheter

NSAID: nonsteroidal anti-inflammatory drug

APPENDICES

Appendix 1. Search strategy - Cochrane Gynaecology and Fertility specialised register search strategy

PROCITE platform
Inception to 21 September 2016
Keywords CONTAINS "office hysteroscopy" or "office polypectomy" or "hysterosonography" or "hysteroscopy" or "out patient" or "endometrial biopsy" or "hysteroscopic " or "hysteroscopic endometrial resection" or "hysteroscopic metroplasty" or "hysteroscopy pain" or "hysteroscopy pain -surgical"or "hysteroscopy-second look" or "hysteroscopy, techniques" or "hysterscope" or "outpatient" or "outpatient care" or "Outpatient hysteroscopy" or "office" or Title CONTAINS "office hysteroscopy" or "office polypectomy" or "hysterosonography" or "hysteroscopy" or "out patient" or "endometrial biopsy" or "hysteroscopic " or "hysteroscopic endometrial resection" or "hysteroscopic metroplasty" or "hysteroscopy pain" or "hysteroscopy pain -surgical" or "hysteroscopy-second look" or "hysteroscopy, techniques" or "hysterscope" or "outpatient" or "outpatient care" or "Outpatient hysteroscopy" or "office"
AND
Keywords CONTAINS "pain-control" or "pain management" or "pain - operative" or "pain relief" or "paracervical" or "paracervical block" or "Nerve Block" or "anaesthesia" or "anaesthetics" or "analgesia" or "*Analgesics, Opioid" or "topical" or "intrauterine anaesthetic" or "intrauterine anaesthesia" or "lidocaine" or "lignocaine" or "opiod analgesic" or "opioid analgesia" or "opioids" or "fentanyl" or "fentenyl" or "remifentanil" or "midazolam" or "midolazam" or "Morphine" or "Benzodiazepine" or "Benzydamine hydrochloride" or "Paracetamol" or "acetaminophen" or "acetly salicylic acid" or "NSAID" or "NSAIDs" or "non steroidal"or"diclofenac"or"EMLA"or"mefenamic acid" or "COX-2 inhibitors" or "pain"or"pain reduction" or "hysteroscopy pain" or "hysteroscopy pain -surgical" or Title CONTAINS "pain-control" or "pain management" or "pain - operative" or "pain relief" or "paracervical" or "paracervical block" or "Nerve Block" or "anaesthesia" or "anaesthetics" or "analgesia" or "*Analgesics, Opioid" or "topical" or "lidocaine" or "lignocaine"
(59 hits)

Appendix 2. Search strategy - Central CRSO

Web platform
Inception to 21 September 2016
#1 MESH DESCRIPTOR Hysteroscopy EXPLODE ALL TREES 313
#2 hysteroscop*:TI,AB,KY 726
#3 (endometri* adj2 biops*):TI,AB,KY 527
#4 #1 OR #2 OR #3 1165
#5 MESH DESCRIPTOR Gynecologic Surgical Procedures EXPLODE ALL TREES 3623
#6 #2 AND #5 337
#7 #4 OR #6 1165
#8 MESH DESCRIPTOR Nerve Block EXPLODE ALL TREES 2916
#9 MESH DESCRIPTOR Autonomic Nerve Block EXPLODE ALL TREES 205
#10 (nerve* adj3 block*):TI,AB,KY 4741
#11 (para cervi* or paracervi*):TI,AB,KY 203
#12 MESH DESCRIPTOR Anesthetics EXPLODE ALL TREES 22458
#13 MESH DESCRIPTOR Hypnotics and Sedatives EXPLODE ALL TREES 11372
#14 MESH DESCRIPTOR Narcotics EXPLODE ALL TREES 12586
#15 MESH DESCRIPTOR Analgesics, Opioid EXPLODE ALL TREES 12428
#16 (An?esthetic* adj2 Local*):TI,AB,KY 6638
#17 (intra cervical or intracervical or intra-cervcal):TI,AB,KY 450
#18 topical:TI,AB,KY 18401
#19 (intrauter* adj5 an?esth*):TI,AB,KY 25
#20 (intrauter* adj3 instillation*):TI,AB,KY 27
#21 (intrauterine adj3 block*):TI,AB,KY 8
#22 MESH DESCRIPTOR Anesthesia and Analgesia EXPLODE ALL TREES 22873
#23 analges*:TI,AB,KY 34399
#24 (lidocaine or lignocaine):TI,AB,KY 7929

#25 (opioid* or opiate*):TI,AB,KY 13677
#26 (fentanyl or remifentanil):TI,AB,KY 11490
#27 (hypnovel or midazolam):TI,AB,KY 5860
#28 morphine:TI,AB,KY 8370
#29 MESH DESCRIPTOR Benzodiazepinones EXPLODE ALL TREES 4115
#30 Benzodiazep*:TI,AB,KY 4773
#31 (pain adj2 relief):TI,AB,KY 8310
#32 MESH DESCRIPTOR Acetaminophen EXPLODE ALL TREES 1893
#33 paracetamol:TI,AB,KY 4163
#34 MESH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL TREES 14842
#35 MESH DESCRIPTOR Cyclooxygenase Inhibitors EXPLODE ALL TREES 11622
#36 MESH DESCRIPTOR Analgesics, Short-Acting EXPLODE ALL TREES 0
#37 (Non steroidal anti-inflammatory*):TI,AB,KY 1509
#38 NSAID*:TI,AB,KY 2857
#39 diclofenac:TI,AB,KY 3552
#40 MESH DESCRIPTOR Diclofenac EXPLODE ALL TREES 1422
#41 (conscious sedation):TI,AB,KY 1594
#42 (pain control):TI,AB,KY 2824
#43 (pain management):TI,AB,KY 4015
#44 (uterosacral block):TI,AB,KY 2
#45 (transcervical adj2 an?esthe*):TI,AB,KY 2
#46 MESH DESCRIPTOR Mefenamic Acid EXPLODE ALL TREES 111
#47 (Mefenamic Acid):TI,AB,KY 256
#48 (intravenous sedate*):TI,AB,KY 1
#49 levobupivacaine:TI,AB,KY 856
#50 dexketoprofen:TI,AB,KY 131
#51 drotaverine:TI,AB,KY 35
#52 etodolac:TI,AB,KY 189
#53 mepivacaine:TI,AB,KY 739
#54 buprenorphine:TI,AB,KY 1425
#55 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 106831
#56 #7 AND #55 203

Appendix 3. Search strategy - MEDLINE

Ovid platform
From 1946 to 21 September 2016

1 exp hysteroscopy/ (4085)
2 hysteroscop$.tw. (5643)
3 gynecologic surgical procedures/ and hysteroscop$.tw. (150)
4 (endometri$ adj2 biops$).tw. (3739)
5 or/1-4 (9772)
6 exp nerve block/ or exp autonomic nerve block/ (18544)
7 (nerve$ adj3 block$).tw. (11201)
8 (para cervi$ or paracervi$).tw. (878)
9 exp anesthetics, local/ or exp "hypnotics and sedatives"/ or exp narcotics/ or exp analgesics, opioid/ (292579)
10 (An?esthetic$ adj2 Local$).tw. (22063)
11 (intra cervical or intracervical or intra-cervcal).tw. (859)
12 topical.tw. (79808)

13 (intrauter$ adj5 an?esthe$).tw. (67)
14 (intrauter$ adj3 instillation).tw. (103)
15 (intrauterine adj3 block$).tw. (42)
16 exp "Anesthesia and Analgesia"/ (213256)
17 analges$.tw. (102239)
18 (lidocaine or lignocaine).tw. (21423)
19 (opioid$ or opiate$).tw. (84676)
20 (fentanyl or remifentanil).tw. (18967)
21 (hypnovel or midazolam).tw. (11250)
22 morphine.tw. (44746)
23 exp Benzodiazepinones/ (35092)
24 Benzodiazep$.tw. (31192)
25 (pain adj2 relief).tw. (29640)
26 exp Acetaminophen/ (15642)
27 paracetamol.tw. (9487)
28 exp anti-inflammatory agents, non-steroidal/ or exp cyclooxygenase inhibitors/ or exp analgesics, short-acting/ (177367)
29 Non steroidal anti-inflammator$.tw. (13414)
30 NSAIDS.tw. (16128)
31 diclofenac.tw. (9398)
32 conscious sedation.tw. (2320)
33 pain control.tw. (9979)
34 pain management.tw. (16620)
35 uterosacral block.tw. (10)
36 (transcervical adj2 an?esthe$).tw. (11)
37 Mefenamic Acid/ (982)
38 intravenous sedati$.tw. (1503)
39 levobupivacaine.tw. (1029)
40 dexketoprofen.tw. (197)
41 drotaverine.tw. (88)
42 etodolac.tw. (586)
43 mepivacaine.tw. (1514)
44 buprenorphine.tw. (5136)
45 or/6-44 (850121)
46 randomized controlled trial.pt. (431538)
47 controlled clinical trial.pt. (91740)
48 randomized.ab. (371253)
49 randomised.ab. (76239)
50 placebo.tw. (184070)
51 clinical trials as topic.sh. (179588)
52 randomly.ab. (264335)
53 trial.ti. (162433)
54 (crossover or cross-over or cross over).tw. (71283)
55 or/46-54 (1122034)
56 exp animals/ not humans.sh. (4318986)
57 55 not 56 (1034573)
58 5 and 45 and 57 (162)

Appendix 4. Search strategy - Embase

Ovid platform
From 1980 to 21 September 2016

1 exp hysteroscopy/ (9657)
2 hysteroscop$.tw. (9239)
3 exp gynecologic surgery/ and hysteroscop$.tw. (3096)
4 (endometri$ adj2 biops$).tw. (5099)
5 or/1-4 (15684)
6 exp nerve block/ (32344)
7 (nerve$ adj3 block$).tw. (15129)
8 (para cervi$ or paracervi$).tw. (1007)
9 exp local anesthetic agent/ (211361)
10 exp hypnotic agent/ (11819)
11 exp sedative agent/ (18753)
12 exp narcotic analgesic agent/ (281375)
13 (An?esthetic$ adj2 Local$).tw. (28033)
14 (intra cervical or intracervical or intra-cervcal).tw. (1055)
15 topical.tw. (102847)
16 (intrauter$ adj5 an?esthe$).tw. (80)
17 (intrauter$ adj3 instillation).tw. (98)
18 (intrauterine adj3 block$).tw. (54)
19 exp local anesthesia/ or exp regional anesthesia/ or exp intravenous regional anesthesia/ or exp spinal anesthesia/ or exp topical anesthesia/ or exp intravenous anesthesia/ (99821)
20 exp analgesia/ (142313)
21 analges$.tw. (137631)
22 (lidocaine or lignocaine).tw. (26984)
23 (opioid$ or opiate$).tw. (108900)
24 (fentanyl or remifentanil).tw. (26964)
25 (hypnovel or midazolam).tw. (16259)
26 morphine.tw. (54843)
27 exp benzodiazepine derivative/ (161941)
28 Benzodiazep$.tw. (41365)
29 (pain adj2 relief).tw. (41540)
30 exp paracetamol/ (74089)
31 Acetaminophen.tw. (16800)
32 paracetamol.tw. (14957)
33 exp nonsteroid antiinflammatory agent/ (503962)
34 exp prostaglandin synthase inhibitor/ (471722)
35 cyclooxygenase inhibitor$.tw. (4926)
36 Non steroidal anti-inflammator$.tw. (17617)
37 NSAIDS.tw. (25584)
38 diclofenac.tw. (13826)
39 conscious sedation.tw. (3786)
40 pain control.tw. (14421)
41 pain management.tw. (23928)
42 uterosacral block.tw. (5)
43 (transcervical adj2 an?esthe$).tw. (9)
44 exp mefenamic acid/ (5121)
45 intravenous sedati$.tw. (1983)
46 levobupivacaine.tw. (1818)
47 dexketoprofen.tw. (330)

48 drotaverine.tw. (160)
49 etodolac.tw. (839)
50 mepivacaine.tw. (1873)
51 buprenorphine.tw. (6739)
52 or/6-51 (1367568)
53 5 and 52 (1236)
54 Clinical Trial/ (968023)
55 Randomized Controlled Trial/ (449241)
56 exp randomization/ (82532)
57 Single Blind Procedure/ (25477)
58 Double Blind Procedure/ (134592)
59 Crossover Procedure/ (52794)
60 Placebo/ (317003)
61 Randomi?ed controlled trial$.tw. (144962)
62 Rct.tw. (21660)
63 random allocation.tw. (1597)
64 randomly.tw. (332435)
65 randomly allocated.tw. (26085)
66 allocated randomly.tw. (2186)
67 (allocated adj2 random).tw. (836)
68 Single blind$.tw. (18279)
69 Double blind$.tw. (170392)
70 ((treble or triple) adj blind$).tw. (616)
71 placebo$.tw. (243412)
72 prospective study/ (375509)
73 or/54-72 (1918946)
74 case study/ (90531)
75 case report.tw. (317364)
76 abstract report/ or letter/ (977135)
77 or/74-76 (1376089)
78 73 not 77 (1869238)
79 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5679505)
80 78 not 79 (1748106)
81 53 and 80 (376)

Appendix 5. Search strategy - PsycINFO

Ovid platform
From 1806 to 21 September 2016
1 exp Gynecology/ (670)
2 hysteroscop$.tw. (14)
3 (office$ adj2 gyn?ecolog$).tw. (12)
4 (endometri$ adj4 ablation$).tw. (5)
5 (outpatient$ adj4 gyn?ecolog$).tw. (109)
6 or/1-5 (786)
7 (nerve$ adj3 block$).tw. (562)
8 (para cervi$ or paracervi$).tw. (6)
9 exp Local Anesthetics/ (12915)
10 (Anesthetic$ adj5 Local$).tw. (571)
11 (intra cervical or intracervical or intra-cervcal).tw. (3)
12 topical.tw. (3567)
13 (intrauterine adj5 anaesthetic$).tw. (0)
14 (intrauterine adj5 block$).tw. (1)

15 exp Analgesia/ (3881)
16 analges$.tw. (12383)
17 (lidocaine or lignocaine).tw. (954)
18 opioid$.tw. (17049)
19 (fentanyl or remifentanil).tw. (988)
20 (hypnovel or midazolam).tw. (931)
21 morphine.tw. (9473)
22 Benzodiazep$.tw. (10381)
23 (pain adj2 relief).tw. (3080)
24 or/7-23 (58307)
25 random.tw. (45074)
26 control.tw. (349252)
27 double-blind.tw. (19316)
28 clinical trials/ (9124)
29 placebo/ (4281)
30 exp Treatment/ (633157)
31 or/25-30 (971820)
32 6 and 24 and 31 (21)

Appendix 6. Search strategy - CINAHL

Ovid platform
From 1982 to 21 September 2016

#	Query	Results
S33	S18 AND S32	145
S32	S19 OR S20 or S21 or S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31	1,075,314
S31	TX allocat* random*	5,255
S30	(MH "Quantitative Studies")	14,862
S29	(MH "Placebos")	9,815
S28	TX placebo*	39,502
S27	TX random* allocat*	5,255
S26	(MH "Random Assignment")	41,596
S25	TX randomi* control* trial*	109,973
S24	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	852,017

(*Continued*)

S23	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	147
S22	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	0
S21	TX clinic* n1 trial*	189,469
S20	PT Clinical trial	79,715
S19	(MH "Clinical Trials+")	202,772
S18	S4 AND S17	553
S17	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	2,175,158
S16	TX (pain N2 relief)	10,274
S15	TX Benzodiazep*	5,542
S14	TX morphine	7,596
S13	TX (hypnovel or midazolam)	2,717
S12	TX (fentanyl or remifentanil)	5,005
S11	TX opioid*	20,033
S10	TX (lidocaine or lignocaine)	4,758
S9	TX(intrauterine N5 block*)	5
S8	TX an?esthetic*	2,167,399
S7	(MM "Anesthetics, Local") OR (MH "Anesthesia, Local") OR "local anesthetics"	6,181
S6	(MM "Nerve Block") OR "nerve block"	6,264
S5	(MH "Analgesia+") OR "analgesia"	17,262
S4	S1 OR S2 OR S3	1,078
S3	TX(outpatient* N5 gyn?ecolog*)	78
S2	TX (office* N5 gyn?ecolog*)	33
S1	(MM "Hysteroscopy") OR "hysteroscopy"	972

#	Query	Results
S33	S18 AND S32	145
S32	S19 OR S20 or S21 or S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31	1,075,314
S31	TX allocat* random*	5,255
S30	(MH "Quantitative Studies")	14,862
S29	(MH "Placebos")	9,815
S28	TX placebo*	39,502
S27	TX random* allocat*	4,464
S26	(MH "Random Assignment")	39,802
S25	TX randomi* control* trial*	93,467
S24	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	789,912
S23	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	120
S22	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	0
S21	TX clinic* n1 trial*	175,948
S20	PT Clinical trial	78,685
S19	(MH "Clinical Trials+")	192,364
S18	S4 AND S17	532
S17	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	2,187,703
S16	TX (pain N2 relief)	9,484
S15	TX Benzodiazep*	4,962
S14	TX morphine	6,858
S13	TX (hypnovel or midazolam)	2,528

(*Continued*)

S12	TX (fentanyl or remifentanil)	4,546
S11	TX opioid*	17,279
S10	TX (lidocaine or lignocaine)	4,495
S9	TX(intrauterine N5 block*)	3
S8	TX an?esthetic*	2,182,073
S7	(MM "Anesthetics, Local") OR (MH "Anesthesia, Local") OR "local anesthetics"	5,943
S6	(MM "Nerve Block") OR "nerve block"	5,858
S5	(MH "Analgesia+") OR "analgesia"	16,078
S4	S1 OR S2 OR S3	940
S3	TX(outpatient* N5 gyn?ecolog*)	68
S2	TX (office* N5 gyn?ecolog*)	25
S1	(MM "Hysteroscopy") OR "hysteroscopy"	850

Appendix 7. Search strategies for The WHO portal (ICTRP) and clinicaltrials.gov

Web platforms
Keywords used: hysteroscopy, pain relief, intervention and outpatient.

WHAT'S NEW

Last assessed as up-to-date: 21 September 2016.

Date	Event	Description
19 September 2017	New citation required and conclusions have changed	The conclusion of the review is as follows with the inclusion of 8 new studies: there was insufficient evidence of a clinically meaningful effect when different types of pain relief were compared with placebo or other types of pain relief in women undergoing outpatient hysteroscopy

(*Continued*)

19 September 2017	New search has been performed	We have added 8 new studies to this review Hassan 2016a; Hassan 2016b; Kokanali 2013; Lukes 2015; Mohammadi 2015; Senturk 2016; Teran-Alonso 2014; Van den Bosch 2011) and excluded one previously included study (Guida 2003).

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 11, 2010

Date	Event	Description
1 August 2010	Amended	Change in title as per discussion with editorial office
18 July 2010	Amended	The title of the comparison 1b) has been changed to 1b) Local anaesthetics and 1c) NSAIDs separately as requested by the peer review

CONTRIBUTIONS OF AUTHORS

Gaity Ahmad (GA): main review author, designed the protocol; performed the search, screened the search results, organised the retrieval of the RCTs, screened them against the inclusion criteria, extracted the data from the RCTs, managed the data, interpreted the results, wrote the review and supervised HO'F and SA throughout the process.

Sushant Saluja (SS): update contributor, organised the retrieval of the RCTs for the update, screened them against the inclusion criteria, extracted the data from newly identified RCTs, wrote to authors when required, managed the new data and amended the review text.

Helena O'Flynn (HO'F): co-review author, organised the retrieval of the RCTs, screened them against the inclusion criteria, extracted the data from RCTs, wrote to study authors when required, managed the data.

Daniel Leach (DL); update contributor, organised the retrieval of the RCTs for the update, screened them against the inclusion criteria, extracted the data from newly identified RCTs, wrote to authors when required, managed the new data and amended the review text.

Andrew Watson (AW): helped design the review, supervised all the steps undertaken for the review, and settled differences of opinion between GA and HO'F regarding inclusion of studies, supervised and helped draft the discussion and conclusions.

Alessandra Sorrentino (AS): update contributor, managed the new data and amended the review text.

DECLARATIONS OF INTEREST

Gaity Ahmad (GA): none

Sushant Saluja (SS): none

Helena O'Flynn (HO'F): none

Daniel Leach (DL): none

Andrew Watson (AW): none

Alessandra Sorrentino (AS): none

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Within types of interventions, analgesics (topical or oral) versus placebo or no treatment, to separate local anaesthesia from NSAIDs. Some of the wording also has slight changes.

We performed subgroup analyses of postmenopausal women and by route of intervention to see if this had an effect on pain relief during and after the procedure. We performed analyses for the following groups:

- analgesia versus placebo or no treatment (during the procedure and within 30 minutes of the procedure) for both postmenopausal women and by route of intervention;
- analgesia versus placebo or no treatment (more then 30 minutes after the procedure) - performed only for routes of intervention.

In the protocol we planned to express results for each study as mean difference (MD) using a random-effects model with 95% confidence intervals (CI) unless the included studies reported differing validated scales, in which case we would use a standard mean difference (SMD). In the review we have used the SMD for all continuous outcomes. We chose this measure as it allowed comparison of outcome data from studies that used different scales to quantify pain.

INDEX TERMS

Medical Subject Headings (MeSH)

Ambulatory Surgical Procedures [*adverse effects]; Analgesia [*methods]; Anesthetics, Local [*therapeutic use]; Hysteroscopy [*adverse effects]; Pain, Postoperative [*drug therapy]

MeSH check words

Female; Humans