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Review article

Pain management in outpatient hysteroscopy

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ABSTRACT

We have performed a review of literature to find evidence on the effectiveness of the different methods used to decrease pain perception during office hysteroscopy and identify risk factors of a painful hysteroscopy. Our methods include a review of literature following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Guidelines for Systematic Reviews of Observational Studies; a literature search of MEDLINE, Embase, PubMed, and the Cochrane Library of Systematic Reviews; and reference search in selected papers, looking for meta-analysis and randomized controlled trials that assess pain management in office hysteroscopy and studies that identify risk factors for painful hysteroscopy. Review for appropriateness and allocation according to type of analgesic method was performed, together with evaluation for risk factors and evidence of pain reduction effects of pharmacological and nonpharmacological analgesic methods. Nonpharmacological methods, such as vaginoscopy or mini-hysteroscopes, are advisable to avoid producing pain. The only pharmacological method that has demonstrated its effectiveness in several meta-analysis and reviews is paracervical block, reducing pain during and 30 minutes after hysteroscopy. Nonsteroidal anti-inflammatory drugs (NSAIDs) seem to be useful in the postoperative period. Evidence is not clear about combination of techniques or misoprostol. Although this review is limited because of heterogeneity of the studies included, it gives a wide overview of the different methods that are available to alleviate pain in office hysteroscopy. Paracervical infiltration is the only anesthetic procedure that has proven effective for pain reduction. Other methods such as using NSAIDs, topical anesthetics, misoprostol, or nitrous oxide have to be better studied to reach conclusions on their effectiveness.

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Introduction

Outpatient hysteroscopy in the office setting is often the preferred procedure for diagnosis of intrauterine pathology and abnormal uterine bleeding, as well as for therapeutic operative treatment and transcervical sterilization. It is desirable to attempt to perform as many procedures as possible with office hysteroscopy, as long as they take place in a safe and effective fashion.

Office hysteroscopy is a diagnostic and operative technique with many advantages compared with operating room-based hysteroscopy: it does not require hospital admission, preoperative tests,

and general or regional anesthesia. Importantly, it has decreased postsurgical recovery period, global cost of the procedure, and rate of complications such as cervical tears, uterine perforation, and those due to distension media. Although it is generally well tolerated, pain, vagal syndrome, hypotension, and uneasiness are common among patients undergoing hysteroscopy.

Although a 'no-touch' approach can be achieved in a large percentage of cases without anesthesia, pain is still the main cause of office hysteroscopy failure.^{1–3} Factors related to pain experience during hysteroscopy are still not well-known. In addition, there is controversy about anesthesia and analgesia for outpatient hysteroscopy, as there is not enough high-quality evidence.

According to Nagele et al,¹ 84% of failed hysteroscopies are due to excessive discomfort. De Iaco et al.² state that 34.8% of patients who undergo anesthesia-free diagnostic hysteroscopy report severe pain. Carvalho et al³ report moderate to severe pain [measured

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by Visual Analog Scale (VAS) score of 5 or more immediately after examination] in 68.4% of patients.

An adequate knowledge of anatomy is essential to understand the physiology of pain in hysteroscopy. Anatomical structures of the female pelvis are innervated by two pathways. The fundus of the uterus is innervated by sympathetic fibers from T10 to L2 via the inferior hypogastric plexus, which enters the uterus by the uterosacral ligaments and by the infundibulopelvic ligament, forming the ovarian plexuses.⁴ The upper vagina, cervix, and lower uterine segment are innervated by parasympathetic fibers from S2 to S4, which form the Frankenhauser or uterovaginal plexus, which enters the uterus following the cardinal ligaments.^{4,5} Myometrium and endometrium are innervated by a plexus at the myometrial–endometrial interface. Only the basal third of the endometrium is innervated.⁶ Myometrial innervation can vary with disease processes such as endometriosis or adenomyosis.⁷

Considering hysteroscopic techniques, pain is mainly produced when 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 walls, such as endometrial biopsy, polypectomy or myomectomy, ablation or tubal sterilization, are also painful.^{3,8,9}

Munro and Brooks⁵ suggest that due to this complex innervation, successful anesthesia requires simultaneous targeting of more than one site, including paracervical and intracervical anesthesia and topical agents in the cervical canal and endometrial cavity.

To avoid pain, the less possible harm has to be done during hysteroscopy. This includes performing a ‘no-touch’ approach (direct entry with vaginoscopy and hydrodistension of the cervix for dilation, while avoiding the use of speculum and tenaculum) and the use of small caliber instruments. Moreover, normal saline has been shown to be more comfortable and safer than carbon dioxide and glycine as distension medium.¹⁰ Although it is thought that warming the distension fluid to physiological temperature (37.5°C) decreases perceived pain, it has not been proven.¹¹ Sagiv et al performed a randomized controlled study of 126 patients comparing vaginoscopy without anesthesia to hysteroscopy with speculum and tenaculum placement and paracervical block. The mean VAS scores were 3.8 and 5.3 in the vaginoscopic and traditional groups, respectively.¹²

In addition, a smaller outer diameter of the hysteroscope decreases pain perceived by the patients. Technological improvements have enabled minimization of the caliber of hysteroscopes (minihysteroscopes ≤ 3.5 mm) and instruments. Reduction in outer diameter by 1 mm or 2 mm as well as reduction in total hysteroscope size reduces the section of area of the instrument by 50–75%. The passage of the minihysteroscope through the cervical canal is consequently smoother, causing less pain. Flexible hysteroscopes have also been developed, making it easier to follow the canal pathway.¹³

However, this ‘no-touch’ technique is not always feasible, and even when it is possible, it is still sometimes painful. For this reason, identification of risk factors for a painful procedure has to be done.

The objective of this review of literature is to identify the factors that influence pain perceived by patients undergoing hysteroscopy and study the different anesthetic and analgesic methods that are used in office hysteroscopy to get the clearer possible view of the ideal method for pain control according to the available evidence.

Materials and methods

A comprehensive literature search has been conducted by a team of medical investigators (including gynecologists, a

pharmacologist, and epidemiologist) to identify studies published in English that evaluate pain during outpatient hysteroscopy and analgesic and anesthetic methods for pain management in outpatient hysteroscopy. The study population includes women undergoing office hysteroscopy. Searched databases include MEDLINE, Embase, PubMed, and the Cochrane Library of Systematic Reviews. We used a combination of the following keywords: “hysteroscopy”, “office hysteroscopy”, “pain”, “VAS”, “anesthetics”, “vagoscopy”, “analgesics”, “NSAIDs”, “local anesthesia”, and “paracervical block”. We searched for meta-analysis and randomized controlled studies mainly from 2000 to 2015, but other types of relevant studies and reviews have also been included, when no or only a few randomized trials were found. Reference sections of the selected papers were also searched for relevant studies to ensure a wide high-quality review.

Of the 49 initially selected papers, 16 were excluded after reading the abstract and methods because pain outcomes were not reported or operating-room procedures were included. No unpublished studies were included. No authors were contacted during the selection.

Database search and careful selection threw three meta-analyses, six reviews, 17 randomized clinical trials, one controlled trial without randomization, two cohort studies, and four observational studies from 2000 to 2015 that were suitable for this review. Some of the papers that were included are not specific to office hysteroscopic procedures,^{9,14} but have been selected because they provide useful information. All the papers assess pain management during office hysteroscopy; however, there is heterogeneity regarding their approach on this subject. Possible confounding factors are the fact that the included studies have different designs, making it difficult to compare and contrast them, and that they include different analgesic methods, and comparisons with placebo, control group, or other methods, thus making analysis even more difficult. Stratification or regression on possible predictors of study results, as well as sensitivity testing could therefore not be performed (Tables 1 and 2). Quality assessment of the trials that have been reviewed is presented in Table 3.

Results and Discussion

Several studies have been performed to establish risk and protective factors for suffering pain during hysteroscopy. de Freitas Fonseca et al.¹⁵ observed 558 patients who underwent outpatient hysteroscopy without anesthesia with vaginoscopic approach, looking for predictors of unacceptable pain. Carta et al.¹⁶ did the same with 284 women attending their clinic. Factors most associated with pain are severe dysmenorrhea and dyspareunia,¹⁵ menopause, nulliparity, and chronic pelvic pain.^{3,16}

Anxiety, although it is difficult to assess, also has a role in pain perception.^{16,17} Methods for controlling anxiety have been proposed to reduce pain perception. Reducing waiting time has a statistically significant positive correlation, even if weak, with pain perception during hysteroscopy ($r = 0.45$; $p < 0.01$). However, anxiety *per se*, measured by values of anxiety state (State-Trait Anxiety Inventory scales), was not significantly correlated with pain.¹⁶ A randomized trial using music to reduce anxiety during hysteroscopy has proven that it decreases anxiety and pain perceived during the procedure [VAS score 4.83 (no music group) vs. 2.95 (music group); $p < 0.001$]. It also reduces systolic blood pressure and heart rate and, according to Angioli et al.,¹⁷ distracts the patient from anxiety—provoking thoughts and makes them focus in more pleasant stimuli.

Procedure-related risk factors for pain during hysteroscopy are the use of 5 mm or wider hysteroscopes, speculum, tenaculum, cervical dilators, carbon dioxide for uterine distension, resection of

Table 1
Characteristics of studies identifying risk factors for a painful hysteroscopy.

Study	Type of study	Participants	Intervention	Comparison	Outcome measure	Data reported
De Freitas et al. ¹⁵	Prospective observational study	Women undergoing office hysteroscopy with no analgesia or sedation	Hysteroscopy with 3.5-mm outer diameter sheath and vaginoscopy approach	No analgesia for all patients	Verbal Rating Scale (VRS): 0–10, 0 min and 15 min after the procedure, dichotomized to acceptable (VRS < 7) or unacceptable pain (VRS > 7)	Percentage
Cicinelli ¹³	Review	Women undergoing diagnostic and operative hysteroscopy	Review of observational and randomized controlled studies	Pain with traditional hysteroscopy, vaginoscopy, and paracervical block	Visual Analog Scale (VAS)	Mean (SD) or median (range)
Carta et al. ¹⁶	Prospective observational study	Women undergoing hysteroscopy	Diagnostic hysteroscopy with endometrial biopsy	Pain and anxiety rates before and after the procedure	State-Trait Anxiety Inventory and VAS	Odds ratio
Carvalho et al. ³	Cohort	Patients undergoing diagnostic hysteroscopy	Anesthesia-free diagnostic hysteroscopy	Pain at the end of the procedure and at 15 min, 30 min, and 60 min after.	VAS	Median

SD = standard deviation.

polyps larger than 2.2 cm, and long procedures (>15 minutes).^{13,15} Carvalho et al.³ report 30% more risk of pain when procedures exceed 3 minutes.

Protective factors against unacceptable pain are a higher degree of hysteroscopist experience (reducing the risk by half), and a 'no-touch' approach.^{13,16}

Patients with high risk factors of suffering a painful procedure may be candidates for anesthesia. Although many studies have been performed about anesthesia in hysteroscopy, there is no ideal anesthetic and, conversely, sometimes anesthesia delivery can be more painful than not receiving any anesthesia, as occasionally occurs with intracervical, paracervical, and topical cervical anesthesia.^{18,19}

Anesthetic and analgesic methods reported in literature for outpatient hysteroscopy include oral and intravenous analgesia; nonopioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol; opioid analgesics; intrauterine, paracervical, transcervical, or uterosacral local anesthetics; and spray, gel, and cream topical anesthetics.²⁰

NSAIDs are systemic analgesics that decrease uterine activity and pain by inhibiting cyclooxygenase and reducing circulating prostaglandins. They are effective in decreasing pain in some gynecologic procedures, especially in the postsurgical period. They include naproxen, diclofenac, ibuprofen, and ketorolac.⁹ However, studies throw controversial results regarding the use of NSAIDs in hysteroscopic procedures. Tam and Yuen²¹ found no beneficial effects from oral diclofenac given 1–2 hours before the procedure during and after conventional hysteroscopy. Hassa et al.²² were also unable to demonstrate a benefit in pain reduction with the use of 100-mg rectal diclofenac 60 minutes before outpatient hysteroscopy in a randomized controlled trial in nulliparous infertile women. Ketoprofen has also failed to decrease intraoperative pain, but seemed effective for postoperative pain after hysteroscopy.²³ Ketoprofen VAS scores during and immediately after hysteroscopy were higher than misoprostol VAS scores in a randomized controlled trial.²⁴

Acetaminophen also inhibits cyclooxygenase, acting in the central nervous system instead of the periphery. It is a good option in cases of allergy or intolerance to NSAIDs.⁹ Mefenamic acid, a prostaglandin synthesis inhibitor, also reduces circulating prostaglandins.¹ Controversially, a randomized placebo controlled trial concluded that mefenamic acid (500 mg) given 1 hour before

outpatient hysteroscopy is not superior to placebo in reducing discomfort during the procedure but significantly reduced postoperative pain (30 minutes and 60 minutes after the procedure).¹

A Cochrane Review meta-analysis, *Pain relief for outpatient hysteroscopy*, did not demonstrate any significant reduction with NSAIDs or opioid analgesics during or after the procedure.²⁰ Nevertheless, the Royal College of Obstetricians and Gynecologists Green-top Guideline Number 59 advises women without contraindications to take a standard dosage of NSAIDs 1 hour before hysteroscopy to reduce pain in the immediate postoperative period.²⁵

Opioids have also been used for pain treatment in hysteroscopy. They produce analgesic effects through interaction with endogenous opioid mu receptors. They provide analgesic effects and cause euphoria. The most frequently used opioid for gynecologic procedures is fentanyl, which causes moderate sedation with a rapid onset and brief duration. It can be reversed by naloxone.⁹ The only randomized study on opioid analgesics that we found in our literature search was performed by Lin et al.²⁶ They stated that sublingual buprenorphine is not only unhelpful in relieving pain associated with hysteroscopy, but is also associated with significant adverse reactions. It reported 38.8% of adverse reactions, including 5% drowsiness, 2.5% nausea or vomiting, and 31.3% of both. The high incidence of these adverse effects limits the use of opioids in the outpatient setting.²⁰

To reduce intraoperative pain, other analgesic or anesthetic methods may be considered, such as local anesthesia. According to the aforementioned Cochrane Review, only local anesthetics provide a significant reduction in the mean pain scores during and 30 minutes after the procedure.²⁰ They include paracervical, intracervical, transcervical, or uterosacral block and topical application in spray, cream, or gel form. The British Medical Journal meta-analysis by Cooper et al.¹⁸ found that intracervical and paracervical injections of local anesthetic significantly reduced pain in women undergoing outpatient hysteroscopy, whereas transcervical and topical application did not. Paracervical injection was significantly superior to the other anesthetic methods. They also concluded that local anesthetics did not have a significant effect on the incidence of vasovagal episodes. Munro and Brooks' review of local anesthesia for office hysteroscopy also supports that a consistent positive anesthetic effect is only demonstrated with paracervical anesthesia. Five of the six randomized clinical trials

Table 2
Characteristics of studies that assess pain reduction using pharmacological/nonpharmacological methods.

Study	Type of study	Participants	Intervention	Comparison	Outcome measure	Data reported
Ahmad et al. ²⁰	Cochrane systematic review and meta-analysis	Randomized controlled trials (RCTs) investigating pharmacological interventions for pain relief during hysteroscopy	Systematic review and meta-analysis	1. Analgesics versus placebo/no treatment 2. Analgesics versus other analgesics	Reduction in the mean pain score	Standardized mean difference (SMD)
Tangsirawatthana et al. ¹⁴	Systematic review	RCTs involving women who underwent cervical dilation and uterine intervention	Systematic review	Paracervical versus placebo for cervical dilation and uterine intervention	Reduction in the mean pain score	SMD
Kaneshiro et al. ²⁷	Systematic review	RCTs evaluating pain management at the time of sterilization by hysteroscopy	Systematic review	1. Paracervical block with lidocaine versus normal saline 2. Intravenous conscious sedation versus oral analgesia	Visual Analog Scale (VAS)	Mean (SD)
Cooper et al. ¹⁸	Systematic review and meta-analysis	Women undergoing diagnostic or operative hysteroscopy as outpatients	Systematic review and meta-analysis	Different types of local anesthetics	VAS Incidence of vasovagal episodes	SMD Percentage
Munro and Brooks ⁵	Review	Published RCT comparing local anesthesia with placebo or no treatment for the performance of office hysteroscopy	Review	Intracervical/paracervical/topical intracavitary/topical cervical/combined local anesthesia versus placebo/no treatment	Reduction in pain	SMD
Kabli and Tulandi ³²	Randomized trial	Women undergoing outpatient hysteroscopy	Hysteroscopy under local anesthesia with 2 mL of 1% lidocaine or local and intrauterine anesthesia with 18 mL of lidocaine in 250 mL of saline as distension medium	Local cervical versus combined cervical and intrauterine anesthesia	VAS during the procedure and at 10 min, 30 min, and 60 min after the procedure	Median (SD)
Al-Sunaidi and Tulandi ³⁰	Randomized trial	Women undergoing outpatient hysteroscopy for evaluation of the uterine cavity	Local anesthesia with 0.2 mL of 0.5% bupivacaine hydrochloride. Paracervical anesthesia with 4 mL of 0.5% bupivacaine hydrochloride at 3 o'clock and 9 o'clock positions of the fornix	Local intracervical versus combined local and paracervical anesthesia	VAS during the procedure and at 10 min, 30 min, and 60 min after	Mean (SD)
Chudnoff et al. ²⁸	Randomized controlled trial	Women undergoing hysteroscopic sterilization	Paracervical anesthesia with 11 mL of 1% lidocaine. Paracervical injection of 11 mL normal saline	Paracervical block versus placebo	VAS at injection, tenaculum placement, introduction of hysteroscope through external and internal os, and placement of tubal devices	Mean (SD)
Lukes et al. ²⁹	Randomized trial	Women undergoing hysteroscopic removal of uterine polyps and myomas using MyoSure device	Paracervical–intracervical injection or only intracervical block of 1:1 mixture of 1% lidocaine and 0.25% bupivacaine	Paracervical–intracervical block versus intracervical block.	Wong–Baker Faces Rating Scale 0–10	Mean (SD)
Issat et al. ²⁴	Randomized controlled trial	Women undergoing outpatient hysteroscopy	400 µg vaginal misoprostol/ 50 mg/mL (intravenously) intravenous (i.v.) ketoprofen in 100 mL of 5% i.v. glucose/ 100 mL of 5% i.v. glucose/ vaginal placebo tablets	Group 1: vaginal misoprostol and 100 mL of 5% i.v. glucose. Group 2: i.v. ketoprofen and placebo vaginal tablets. Group 3: 100 mL of 5% i.v. glucose and placebo tablets	VAS before, during, and at 5 min and 15 min after the procedure	Median (range)
Esin et al. ³⁶	Randomized controlled trial	Premenopausal women undergoing office hysteroscopy	200 µg sublingual misoprostol 2 h before hysteroscopy or xylocaine pump spray 10% during the procedure	Group 1: sublingual misoprostol and placebo spray Group 2: lidocaine pump spray and placebo tablets	VAS during and 10 min after the procedure	Mean (SD)
Hassa et al. ²²	Randomized controlled trial	Primarily infertile women who underwent outpatient	200-µg vaginal misoprostol 6 h before hysteroscopy or 100 mg	Group 1: 200-µg vaginal misoprostol and placebo tablets rectally.	VAS during hysteroscopy	Median (range)

Nagele et al. ¹	hysteroscopy for evaluation of infertility	sodium diclofenac rectally 60 min before	Group 2: placebo tablets vaginally and rectal diclofenac. Group 3: placebo tablets rectally and vaginally	VAS immediately before, at the moment of worst pain, immediately after, and 30 min and 60 min after the procedure	Median and quartiles
Lin et al. ²⁶	Randomized controlled trial	500-mg oral mefenamic acid or placebo tablets 1 h before hysteroscopy	Mefenamic acid versus placebo tablets.	VAS at the moment of worst pain during the procedure evaluated by a trained nurse	Mean (SD)
Lin et al. ²⁶	Randomized trial	0.2-mg buprenorphine or placebo tablets	Buprenorphine versus placebo	VAS before and after the procedure	Mean (SD)
Angioli et al. ¹⁷	Randomized trial	Music administered through a stereo at a volume of 50–60 dB during hysteroscopy	Group 1: music group Group 2: No music	VAS and State-Trait Anxiety Inventory before and after the procedure	Mean (SD)
Del Valle et al. ²⁹	Controlled trial without randomization	Inhalatory analgesia with 50% protioxide and oxygen, paracervical block with 1% lidocaine	Group 1: control group Group 2: paracervical block. Group 3: inhaled nitrous oxide	VAS at the end of the procedure	Mean (SD) and median
Keyhan and Munro ¹⁹	Retrospective cohort trial	Multimodality local anesthetic protocol addressing vagina, cervix, paracervix, paracervical region, and endometrial cavity	None		Mean (SD) Total number

SD = standard deviation.

that their review included demonstrated reduced pain in patients who received paracervical anesthesia compared with placebo.⁵ Paracervical anesthesia is also effective in hysteroscopic tubal sterilization, but only for passage of the hysteroscope through the cervical canal and for cervical manipulation, not for tubal insertion of the devices.^{27,28}

Although the Cochrane Review of paracervical local anesthesia for uterine intervention does not recommend the use of paracervical injection because it does not reduce intraoperative pain, this does not apply to office hysteroscopy, as the review includes procedures that require cervical dilation. Exclusively local anesthesia is not recommended by the Cochrane Review if cervical dilation is needed.¹³

Combined cervical block protocols have been studied for resection of polyps and myomas by hysteroscopy.^{29,30} Lukes et al's²⁹ randomized trial found a statistically significant difference in pain score between a group receiving paracervical and intracervical block and a group only receiving intracervical block (1.3 vs. 2.1, respectively). This is supported by another clinical trial, which demonstrated a significant decrease of pain with combined paracervical/intracervical anesthesia during and after 30 minutes of the procedure.³⁰

There are very few studies assessing intrauterine transcervical local anesthesia. Whereas one randomized study proved that instillation of 5 mL of 2% lidocaine in the uterine cavity is effective for hysteroscopy-related pain,³¹ lidocaine diluted in saline as distension medium was ineffective in another.³²

Topical application of local anesthetic does not reduce the pain of the hysteroscopy but should be used when a tenaculum is applied to the cervix.^{9,18} There are no differences in pain scores for tenaculum placement between lidocaine spray and gel according to Costello et al³³ (median in VAS scale of 18.5 and 15.3, respectively; $p = 0.61$).

One limitation of studies that assess local anesthesia is that they might not take into account the pain experienced by the patients during the injection of local anesthetic, which is a painful procedure itself.¹⁸ A certain time is usually left for the local anesthetic to be effective, and that might not be considered by the patient when asked about the pain felt during hysteroscopy. Moreover, speculum placement is considered by some authors as one of the most painful parts of hysteroscopy, as well as the injection of anesthetics, and could limit the beneficial effect of local anesthesia.^{18,19} Keyhan and Munro¹⁹ in a retrospective cohort study assessing multimodality local anesthesia found that pain associated with anesthesia application was rated higher than pain associated with the procedure itself for diagnostic hysteroscopy [2.7 (anesthesia score) vs. 2.1 (procedure score)].

The main issue of studies that assess local anesthesia for hysteroscopy is that there is no unification of concept of local anesthetics block, with different sites and depths of injection in each study, and the use of different anesthetics, concentrations, volumes, and time from injection to procedure.⁵

Another issue is the low knowledge about local anesthetics toxicity and management of their complications. According to Allen,⁹ the most common local anesthetics used in the office are lidocaine or bupivacaine, associated with fewer allergic reactions and lower cost. Lidocaine has a rapid onset of action with intermediate duration. Toxicity is intermediate with an estimated adult toxic dose of 4 mg/kg (higher when used with epinephrine). It provides good topical anesthesia at 1–4% concentration, but results in a high level of vascular absorbance. Mepivacaine has a rapid onset, intermediate duration, and intermediate toxicity. Infiltration at 1% concentration provides 1.5–3 hours of anesthesia. Bupivacaine has a slow onset, long duration, and high toxicity potential (toxic dose: 2.5–3 mg/kg), providing 2–4 hours

Table 3
Methodological quality assessment (Jadad scoring system) of trials included in the review that assess pain reduction with pharmacological/nonpharmacological methods.

Study	Randomized	±1 ^a	Double blind	±1 ^a	Withdrawals and dropouts	Total	Quality (>3 high)
Al-Sunaidi and Tulandi ³⁰	1	1	0	0	1	3	Low
Costello et al. ³³	1	1	1	1	1	5	High
Kabli and Tulandi ³²	1	1	0	0	1	3	Low
Lau et al. ³¹	1	1	1	1	1	5	High
Sagiv et al. ¹²	1	1	0	0	1	3	Low
Shankar et al. ¹⁰	1	1	0	0	1	3	Low
Chudnoff et al. ²⁸	1	1	1	1	0	4	High
Lukes et al. ²⁹	1	1	0	0	1	3	Low
Issat et al. ²⁴	1	1	1	1	0	4	High
Esin et al. ³⁶	1	1	1	1	1	5	High
Hassa et al. ²²	1	1	1	1	1	5	High
Nagele et al. ¹	1	1	1	1	0	4	High
Lin et al. ²⁶	1	-1	0	0	0	0	Low
Angioli et al. ¹⁷	1	1	0	0	0	2	Low

^a Description of randomization and blinding: If methods are described and are adequate, an extra point is added; if not, it is deducted.

of anesthesia at 0.25%. Toxicity includes numbness, vasodilation, methemoglobinemia and cyanosis, visual disturbances, confusion, seizures, and ventricular tachycardia or fibrillation.³⁴ Techniques to lower the risk of toxicity include adding vasopressin or epinephrine to reduce systematic absorption and aspirating before injecting to avoid intravascular instillation.⁹

Besides anesthetics or NSAIDs, some studies have assessed the use of misoprostol, a prostaglandin E1 analog used for cervical ripening, in office hysteroscopy. It may facilitate the hysteroscopic procedure and lower the risk of cervical laceration because it dilates and softens the cervix. It may be self-administered by the patient (rectal or sublingually) and has no effect on the no-touch technique of outpatient hysteroscopy.²² Nevertheless, there is no consensus in literature on the effect of misoprostol in hysteroscopy. Vaginal misoprostol (400 µg) administered rectally the day before hysteroscopy in Sordia-Hernández et al's study³⁵ provided a considerable decrease of pain and time of the procedure. However, this was an unblinded study with a high risk of observational bias. A randomized trial comparing sublingual misoprostol with lidocaine spray reported significantly lower VAS scores with misoprostol.³⁶ Conversely, this was not confirmed in three randomized clinical trials, in which there was an increase in preoperative pain and vaginal bleeding.^{22,37,38} Misoprostol was not assessed in the Cochrane Reviews and meta-analysis of pain management in outpatient hysteroscopy, pain management for tubal sterilization by hysteroscopy, anesthesia for cervical dilation and uterine intervention, and the British Medical Journal meta-analysis of pain control in outpatient hysteroscopy.^{2,18,20,27} No reviews on misoprostol for office hysteroscopy were found. There is a lack of consensus evidence and that more studies are needed to encourage the use of misoprostol in hysteroscopy.

Only one published study was found about the use of inhalatory analgesia with nitrous oxide in hysteroscopic polypectomy, which was performed by our group. To date, no other studies about analgesia with nitrous oxide in hysteroscopy have been published in scientific literature, although it has been widely used for other painful procedures, such as prostate, liver, or bone marrow biopsy.³⁹ Nitrous oxide is an inhalatory gas that provides short-action analgesia without respiratory depression. VAS scores for outpatient hysteroscopic polypectomy in our pilot study were 5.49, 4.22, and 3.55 for the control group, paracervical infiltration, and nitrous oxide, respectively ($p < 0.05$).³⁹ Although this pilot study has many limitations, we are actually performing a wide randomized controlled clinical trial comparing nitrous oxide with paracervical block and a control group. Conclusions cannot be drawn until the global trial is finished and results are analyzed.

Conclusion

Individual studies examining the effect of anesthetics and analgesics for pain control in outpatient hysteroscopy provide controversial results. The lack of uniformity in the published papers makes it difficult to draw conclusions. Although ambitious, this review's aim is probably too wide, attempting to assess the subject of analgesia for hysteroscopy, which presents many alternatives and no clear conclusions. A more focused objective would make research and drawing conclusions easier. Potential biases of this review include language restriction to only English papers and publication bias, as only published papers were included, as well as operator bias and departmental policy bias. Heterogeneity is also present, due to the variety of studies included, which was necessary to not incur in a too strict selection that could limit our search. Observational studies were not included in this analysis, due to their low quality. However, the aim of this paper is to give a wide view of the available methods of analgesia for office hysteroscopy according to literature and the factors that influence it, so that we can take them into account to reduce pain when performing hysteroscopy.

Future research should be directed to identifying the best analgesic method for office hysteroscopy, to avoid heterogeneity and the use of ineffective methods that can even cause morbidity, and to unification of doses and techniques that could generate international guidelines for this procedure that has no standards for pain control.

The main conclusion of this revision is that, at present, injectable local anesthetics, particularly paracervical infiltration, are the methods that seem more effective, according to the revised literature.^{8,18,25,27,28} Other local anesthetics via topical or intrauterine route seem to be ineffective.^{9,25,31} An adequate selection of local anesthetic is important to control pain during the procedure and avoid toxicity.⁹

NSAIDs seem useful to alleviate pain in the postoperative period.²¹ No clear evidence has been found to encourage the use of misoprostol in office hysteroscopy.^{37,38} Inhalatory analgesia with nitrous oxide offers promising results, but more studies have to be performed to prove its effectiveness.³⁹

Nonpharmacological methods could also be useful in reducing hysteroscopy-related pain, such as a 'no-touch' approach with vaginoscopy and minihysteroscopes, reducing waiting time before hysteroscopy, and the use of music during the procedure to reduce anxiety.^{16,17} Risk and protective factors of suffering pain during outpatient hysteroscopy are important for identifying patients who are susceptible to receiving anesthesia. Risk factors include

menopause, nulliparity, dysmenorrhea, and a longer time of procedure.^{3,13,15,16} Experience of the hysteroscopist is a significant protective factor against pain perception during hysteroscopy.^{13,16}

A correct selection of the patient and the analgesic method is the key to painless outpatient hysteroscopy.

References

- Nagele F, Lockwood G, Magos AL. Randomised placebo controlled trial of mefenamic acid for premedication at outpatient hysteroscopy: a pilot study. *Br J Obstet Gynaecol.* 1997;104:842–844.
- De Iaco P, Marabini A, Stefanetti M, Del Vecchio C, Bovicelli L. Acceptability and pain of outpatient hysteroscopy. *J Am Assoc Gynecol Laparosc.* 2000;7:71–75.
- de Carvalho Schettini JA, Ramos de Amorim MM, Ribeiro Costa AA, Albuquerque Neto LC. Pain evaluation in outpatients undergoing diagnostic anesthesia-free hysteroscopy in a teaching hospital: a cohort study. *J Minim Invasive Gynecol.* 2007;14:729–735.
- Nichols MD, Halvorson-Boyd G, Goldstein R, et al. Pain management. In: Paul M, Lichtenberg ES, Borgatta L, et al., eds. *Management of Unintended and Abnormal Pregnancy.* Hoboken, NJ: Wiley-Blackwell; 2009:90–110.
- Munro MG, Brooks PG. Use of local anesthesia for office diagnostic and operative hysteroscopy. *J Minim Invasive Gynecol.* 2010;17:709–718.
- Krantz KE. Innervation of the human uterus. *Ann N Y Acad Sci.* 1959;75:770–784.
- Tokushige N, Markham R, Russell P, Fraser IS. High density of small nerve fibres in the functional layer of the endometrium in women with endometriosis. *Hum Reprod.* 2006;21:782–787.
- Quinn MJ, Kirk N. Differences in uterine innervation at hysterectomy. *Am J Obstet Gynecol.* 2002;187:1515–1519.
- Allen RH, Micks E, Edelman A. Pain relief for obstetric and gynecologic ambulatory procedures. *Obstet Gynecol Clin North Am.* 2013;40:625–645.
- Shankar M, Davidson A, Taub N, Habiba M. Randomised comparison of distension media for outpatient hysteroscopy. *BJOG.* 2004;111:57–62.
- Evangelista A, Oliveira MA, Crispi CP, Lamblat MF, Raymundo TS, Santos LC. Diagnostic hysteroscopy using liquid distention medium: comparison of pain with warmed saline solution vs room-temperature saline solution. *J Minim Invasive Gynecol.* 2011;18:104–107.
- Sagiv R, Sadan O, Boaz M, Dishi M, Schechter E, Golan A. A new approach to office hysteroscopy compared with traditional hysteroscopy: a randomized controlled trial. *Obstet Gynecol.* 2006;108:387–392.
- Cicinelli E. Hysteroscopy without anesthesia: review of recent literature. *J Minim Invasive Gynecol.* 2010;17:703–708.
- Tangsiwatthana T, Sangkomkamhang US, Lumbiganon P, Laopaiboon M. Paracervical local anesthesia for cervical dilation and uterine intervention. *Cochrane Database Syst Rev.* 2013;9:CD005056.
- de Freitas Fonseca M, Sessa FV, Resende Jr JA, Guerra CG, Andrade Jr CM, Crispi CP. Identifying predictors of unacceptable pain at office hysteroscopy. *J Minim Invasive Gynecol.* 2014;21:586–591.
- Carta G, Palermo P, Marinangeli F, et al. Waiting time and pain during office hysteroscopy. *J Minim Invasive Gynecol.* 2012;19:360–364.
- Angioli R, De Cicco Nardonne C, Plotti F, et al. Use of music to reduce anxiety during office hysteroscopy: prospective randomized trial. *J Minim Invasive Gynecol.* 2014;21:454–459.
- Cooper NA, Khan KS, Clark TJ. Local anaesthesia for pain control during outpatient hysteroscopy: systematic review and meta-analysis. *BMJ.* 2010;340:c1130.
- Keyhan S, Munro MG. Office diagnostic and operative hysteroscopy using local anesthesia only: an analysis of patient reported pain and other procedural outcomes. *J Minim Invasive Gynecol.* 2014;21:791–798.
- Ahmad G, O'Flynn H, Attarbashi S, Duffy JM, Watson A. Pain relief for outpatient hysteroscopy. *Cochrane Database Syst Rev.* 2010;11:CD007710.
- Tam WH, Yuen PM. Use of diclofenac as an analgesic in outpatient hysteroscopy: a randomized, double-blind, placebo-controlled study. *Fertil Steril.* 2001;75:1070–1072.
- Hassa H, Aydin Y, Oge T, Cicek K. Effectiveness of vaginal misoprostol and rectal nonsteroidal anti-inflammatory drug in vaginoscopy diagnostic outpatient hysteroscopy in primarily infertile women: double-blind, randomized, controlled trial. *J Minim Invasive Gynecol.* 2013;20:880–885.
- Mercorio F, De Simone R, Landi P, Sarchianaki A, Tessitore G, Nappi C. Oral dexamethasone for pain treatment during diagnostic hysteroscopy in postmenopausal women. *Maturitas.* 2002;43:277–281.
- Issat T, Beta J, Nowicka MA, Maciejewski T, Jakimiuk AJ. A randomized, single blind, placebo-controlled trial for the pain reduction during the outpatient hysteroscopy after ketoprofen or intravaginal misoprostol. *J Minim Invasive Gynecol.* 2014;21:921–927.
- Royal College of Obstetricians and Gynecologists. *RCOG Green-top Guideline No. 59. Best Practice in Outpatient Hysteroscopy.* London, UK: Royal College of Obstetricians and Gynecologists; 2011.
- Lin YH, Hwang JL, Huang LW, Chen HJ. Use of sublingual buprenorphine for pain relief in office hysteroscopy. *J Minim Invasive Gynecol.* 2005;12:347–350.
- Kaneshiro B, Grimes DA, Lopez LM. Pain management for tubal sterilization by hysteroscopy. *Cochrane Database Syst Rev.* 2012;CD009251.
- Chudnoff S, Einstein M, Levie M. Paracervical block efficacy in office hysteroscopic sterilization: a randomized controlled trial. *Obstet Gynecol.* 2010;115:26–34.
- Lukes AS, Roy KH, Presthus JB, Diamond MP, Berman JM, Konsker KA. Randomized comparative trial of cervical block protocols for pain management during hysteroscopic removal of polyps and myomas. *Int J Womens Health.* 2015;7:833–839.
- Al-Sunaidi M, Tulandi T. A randomized trial comparing local intracervical and combined local and paracervical anesthesia in outpatient hysteroscopy. *J Minim Invasive Gynecol.* 2007;14:153–155.
- Lau WC, Tam WH, Lo WK, Yuen PM. A randomized double-blind placebo-controlled trial of transcervical intrauterine local anaesthesia in outpatient hysteroscopy. *BJOG.* 2000;107:610–613.
- Kabli N, Tulandi T. A randomized trial of outpatient hysteroscopy with and without intrauterine anesthesia. *J Minim Invasive Gynecol.* 2008;15:308–310.
- Costello MF, Steigrad S, Collet A. A prospective, randomised, single-blinded, controlled trial comparing two topical anaesthetic modalities for the application of a tenaculum to the cervix. *J Obstet Gynaecol.* 2005;25:781–785.
- Tetzlaff JE. The pharmacology of local anesthetics. *Anesthesiol Clin North America.* 2000;18:217–233.
- Sordia-Hernández LH, Rosales-Tristan E, Vazquez-Mendez J, et al. Effectiveness of misoprostol for office hysteroscopy without anesthesia in infertile patients. *Fertil Steril.* 2011;95:759–761.
- Esin S, Baser E, Okuyan E, Kucukozkan T. Comparison of sublingual misoprostol with lidocaine spray for pain relief in office hysteroscopy: a randomized, double-blind, placebo-controlled trial. *J Minim Invasive Gynecol.* 2013;20:499–504.
- Fernandez H, Alby JD, Tournoux C, et al. Vaginal misoprostol for cervical ripening before operative hysteroscopy in premenopausal women: a double-blind, placebo controlled trial with three dose regimens. *Hum Reprod.* 2004;19:1618–1621.
- Valente EP, de Amorim MM, Costa AA, de Miranda DV. Vaginal misoprostol prior to diagnostic hysteroscopy in patients of reproductive age: a randomized clinical trial. *J Minim Invasive Gynecol.* 2008;15:452–458.
- Del Valle Rubido C, Solano Calvo JA, Rodríguez Miguel A, Delgado Espeja JJ, González Hinojosa J, Zapico Goñi Á. Inhalation analgesia with nitrous oxide versus other analgesic techniques in hysteroscopic polypectomy: a pilot study. *J Minim Invasive Gynecol.* 2015;22:595–600.