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Smooth Muscle Relaxants for Intrauterine Device Placement: A Systematic Review

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Abstract

Objectives: To systematically review evidence on whether medications with smooth muscle relaxant properties improve patient and provider outcomes for intrauterine device (IUD) placement.

Study design: We searched multiple databases through August 2022 for randomized clinical trials assessing smooth muscle relaxants for IUD placement. Primary outcomes were pain experienced with IUD placement, provider ease of placement, need for adjunctive placement measures, placement success, patient satisfaction with procedure, medication side effects occurring before clinic discharge, and adverse events occurring before clinic discharge. We extracted data from included articles, assessed risk of bias for each trial, narratively summarized results, and determined certainty of evidence for all outcomes.

Results: Five trials met inclusion criteria; four trials had low risk of bias and one had moderate risk. Two trials of topical nitroprusside gel or nitroglycerin ointment found no differences in patient pain, provider ease of placement, patient satisfaction, placement success, side effects, or adverse events. One trial suggested that drotaverine plus mefenamic acid reduced patient pain but did not improve placement success. Two trials suggested that isonicotinic acid hydrazide reduced patient pain, improved provider ease of placement and patient satisfaction, reduced need for analgesia and for cervical dilation (in one trial) and did not increase side effects; neither trial reported improved placement success.

Conclusions: Evidence on smooth muscle relaxants for IUD placement remains sparse with inconsistent findings across specific medications. Certainty of evidence for all outcomes was low

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for topical nitroprusside gel and nitroglycerin ointment, very low for drotaverine plus mefenamic acid, and mostly high for isonicotinic acid hydrazide.

Implications: Before IUD placement, healthcare providers can counsel patients on the potential for pain during placement and options for pain management. However, more evidence is needed on specific smooth muscle relaxants to determine their effectiveness as an intervention for IUD placement.

Keywords

Contraception; Intrauterine device; Systematic review

1. Introduction

Intrauterine devices (IUDs) are among the most effective contraceptive methods with failure rates of less than 1% with typical use and few contraindications [1, 2]. In 2017–2019, about 8.4% of US women aged 15–49 years used IUDs [3]. While IUDs are safe and highly effective for pregnancy prevention, barriers to IUD placement can include patient concerns about pain with placement and provider concerns about ease of placement, especially among nulliparous patients [4–6]. A recent study reviewing videos on a popular video-sharing platform found that 96% of reviewed videos around IUD placement or removal highlighted pain [7]. Identifying evidence-based methods for decreasing IUD placement pain and easing placement can inform approaches for IUD placement and pain management. Medications with smooth muscle relaxant properties can have different mechanisms of action on the cervix and uterus. Medications such as nitroprusside, nitroglycerin, and isonicotinic acid hydrazide (INH) may cause cervical ripening without additional uterine cramping due to nitric oxide activity [8, 9]. Drotaverine is an antispasmodic with smooth muscle relaxant properties due to phosphodiesterase inhibitor activity [10]. Smooth muscle relaxants have been studied previously for uterine relaxation during labor and first trimester abortion, with some studies showing decreased force required for cervical dilation when using muscle relaxants, although results have not been consistent across studies [11, 12]. Drotaverine use during labor has been associated with shortened first stage of labor and reduced incidence of cervical tears [10, 13]. A meta-analysis of antispasmodics for labor found that antispasmodics reduced the duration of the first stage of labor and increased the cervical dilation rate, although the evidence was of low quality [14]. Smooth muscle relaxants might work to ease IUD placement by facilitating cervical dilation and ripening [10, 13]. Theoretically, these effects could lead to less force applied to the cervix at time of IUD placement, which may lead to easier placement and decreased pain for the patient.

The US Centers for Disease Control and Prevention (CDC) publishes the *US Selected Practice Recommendations for Contraceptive Use* (US SPR), which provides evidence-based guidance for health care providers on the provision of contraceptive methods and the management of side effects and other issues related to contraceptive use [15]. The US SPR includes recommendations on medications for IUD placement [15]. Previous systematic reviews have described the use of medications to improve patient pain and provider outcomes with IUD placement [16, 17]. Two studies included in these reviews examined the use of topical nitroprusside gel and nitroglycerin ointment, which suggested no effect on

provider ease of insertion or need for adjunctive placement measures [18, 19]. The objective of this systematic review, as part of the process to update the US SPR, was to provide an updated summary of the evidence from randomized clinical trials (RCTs) on whether smooth muscle relaxants improve patient and provider outcomes for IUD placement [15].

2. Materials and methods

We conducted this systemic review according to an *a priori* protocol, which has been registered in the international prospective register of systematic reviews (PROSPERO) under the registration number CRD42023424979 [20]. We reported this systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-analyses [21].

2.1 Eligibility criteria

We included RCTs that examined the use of smooth muscle relaxants for IUD placement; RCTs are the appropriate study design to evaluate drug interventions. The study population of interest was women of reproductive age (e.g., 15–49 years, but the age range varied based on individual study criteria) undergoing interval IUD placement (i.e., placement not in the postabortion period or postpartum period [defined as within six weeks of delivery]). We included studies that examined placement of levonorgestrel (LNG) IUDs and copper T IUDs. The interventions of interest were drugs with smooth muscle relaxant properties identified in our broader search of medications for IUD placement (see Section 2.2). The comparator was placebo or no treatment. The outcomes of interest were: (1) pain experienced with IUD placement (as rated by visual analog scale [VAS] or other tool) at specific time points (i.e., during tenaculum placement, during IUD placement, and highest level of pain after placement and before clinic discharge); (2) provider ease of placement (as rated by VAS or other tool); (3) need for adjunctive placement measures (i.e., cervical dilation, ultrasound guidance, local anesthesia, and analgesia); (4) placement success; (5) patient satisfaction with the procedure before clinic discharge (as rated by a Likert scale or other tool); (6) medication side effects occurring before clinic discharge (i.e., nausea, vomiting, and hypotension); and (7) adverse events occurring before clinic discharge (e.g., uterine perforation, vasovagal reaction, cervical laceration, and syncope). RCTs are the most appropriate design to study the interventions and outcomes of interest included in this review; therefore, we included RCTs and excluded non-randomized trials, cohort studies, case-control studies, cross-sectional studies, case reports, commentaries, and reviews.

2.2 Search strategy

We worked with a CDC research librarian to develop a comprehensive search strategy to broadly identify articles on medications for IUD placement. The search was conducted in MEDLINE, EMBASE, CINAHL, Cochrane, and [ClinicalTrials.gov](https://www.clinicaltrials.gov) databases—from database inception to August 16, 2022 (Online Appendix A). We also reviewed references in systematic reviews to optimize our search. We considered articles in all languages for inclusion.

2.3 Study selection and data extraction

The lead author and three co-authors screened titles and abstracts from the search results and identified full-text articles to be reviewed using Covidence software [22]. The authors then reviewed full-text articles to identify articles that met inclusion criteria. Any conflicts identified in the screening process were resolved through discussion. We scanned reference lists of included articles and relevant review articles to identify any additional studies. We used a standardized evidence table to record study information, including first author, publication year, study location, years of data collection, funding source, study population, intervention description, measurement of outcomes, and results. The lead author extracted data from each study and co-authors performed quality control checks of the extracted data. Discrepancies were resolved through discussion.

2.4 Risk of bias assessment

We used the Cochrane approach to assess risk of bias for RCTs and evaluated each trial for the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of reported results; and overall risk of bias [23]. Two authors independently assessed the risk of bias of each included trial, and any conflicts were resolved through discussion.

2.5 Data synthesis

We narratively described and summarized study findings. We did not conduct meta-analysis because of heterogeneity of interventions, outcomes, measurement of outcomes, and variations in study populations (e.g., younger age or participants with cesarean sections) across the included studies.

2.6 Certainty of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence [24–26]. Using the GRADE approach, each outcome (e.g., pain experienced with IUD placement, provide ease of placement) is given a certainty of evidence rating across the studies that assessed that outcome. For each outcome, we considered risk of bias, indirectness, imprecision, and inconsistency as being not serious, serious, or very serious. Based on these assessments, we rated certainty of evidence as high, moderate, low, or very low. Initially, evidence from RCTs is considered to have high certainty, and ratings are then adjusted according to the previously mentioned criteria. We evaluated certainty of evidence for all seven outcomes of interest.

3. Results

The search identified 7433 articles (Figure 1). After removing 22 duplicates, we screened 7411 articles for inclusion. We reviewed 302 full text articles, 297 of which were excluded (145 duplicates, 69 wrong interventions, 43 no full texts, 29 non-RCTs, three without placebo or other comparison group, two medications not commercially available, two wrong population, three studies retracted, and one wrong IUD type [i.e., Dalkon Shield]). Five RCTs were included (Table 1) [18, 19, 27–29]. Two studies were conducted in the United

States [18, 19], two in Egypt [28, 29], and one in India [27]. Three studies included nulliparous participants [18, 19, 29], one included participants with previous cesarean deliveries only [28], and one included nulliparous and parous participants [27]. Two studies examined topical nitroprusside gel [18] or nitroglycerin ointment [19], one examined drotaverine plus mefenamic acid (a non-steroidal anti-inflammatory drug [NSAID]) [27], and two examined INH [28, 29]. Outcomes included pain during tenaculum placement [18, 19, 27–29], pain during IUD placement [18, 19], highest level of pain after placement and before clinic discharge [28, 30], provider ease of placement [18, 19, 28, 29], need for adjunctive placement measures (specifically, cervical dilation and analgesia) [18, 19, 28, 29], placement success [18, 19, 27–29], patient satisfaction [18, 19, 28, 29], medication side effects (specifically, nausea, vomiting, abdominal pain/cramping, diarrhea, and hypotension) [18, 19, 27–29], and adverse events (specifically, vasovagal reaction) [18, 19]. As of the time of this writing, a statement of concern [30] has been published about one study [28], but because the study has not been retracted, it was included in this review.

3.1 Risk of bias

Overall, we determined that the risk of bias for four of the included studies was low [18, 19, 28, 29] and for one study was moderate [27] (Figure 2). The studies used adequate random sequence generation and allocation concealment (with the exception of one study that did not describe allocation concealment [27]). The studies did not deviate from intended interventions, had high percentages of follow-up, and had no concerns for selection of reported results [18, 19, 27–29]. Overall, there were no concerns for risk of bias with the outcome measurements, with the exception that one study did not provide information on how one outcome—need for additional cervical dilation—was measured [29]; while this study was considered to have low risk of bias overall, risk of bias for that one outcome was considered moderate.

3.2 Summary of results for topical nitroprusside or nitroglycerin

An RCT enrolled 24 nulliparous women, aged 18–45 years, with no prior IUD use or attempted placement [18]. Participants were randomized to receive nitroprusside (10 mg) gel or placebo gel, applied intracervically immediately before IUD placement. There were no statistically significant differences in mean pain scores measured via VAS between groups during tenaculum placement (30 mm for nitroprusside group vs. 40 mm for placebo group, $p = 0.35$), IUD placement (passage through cervix: 61 mm for nitroprusside group vs. 74 mm for placebo group, $p = 0.18$; placement at fundus: 59 mm for nitroprusside group vs. 73 mm for placebo group, $p = 0.15$), or the highest level of pain after placement and before clinic discharge (37 mm for nitroprusside group vs. 50 mm for placebo group, $p = 0.30$). The trial also found no statistically significant difference in mean provider ease of placement VAS scores (32.4 mm for nitroprusside vs. 26.5 mm for placebo group, $p = 0.57$). One participant in each group required cervical dilation ($p = 0.90$), none needed paracervical block, and all had successful IUD placements on the first attempt. There was no statistically significant difference between groups in overall patient satisfaction, measured via VAS (82.8 mm for nitroprusside group vs. 94.3 mm for placebo group, $p = 0.06$). There were also no statistically significant differences in side effects, specifically nausea, vomiting, or diarrhea

(data not reported). Related to adverse events, two participants in the nitroprusside group experienced vasovagal reactions after the placement procedure.

Another RCT enrolled 24 nulliparous women, aged 18–45 years, with no prior IUD use or attempted placement [19]. Participants were randomized to receive nitroglycerin (0.5 mg) ointment or placebo, applied at the posterior fornix 30–45 minutes before IUD placement. There were no statistically significant differences in mean pain scores measured via VAS between groups during tenaculum placement (data not reported), IUD placement (passage through cervix: 55.8 mm for nitroglycerin group vs. 53.9 mm for placebo group, $p = 0.86$), or the highest level of pain after placement and before clinic discharge (data not reported). The trial also found no statistically significant difference in mean provider ease of placement VAS scores (29.4 mm for nitroglycerin vs. 22.8 mm for placebo group, $p = 0.56$). One participant in each group required cervical dilation and one participant (group not specified) had paracervical block. All participants had successful IUD placement, and there was no statistically significant difference in patient satisfaction with the overall procedure, as measured by VAS (84.7 mm for nitroglycerin group vs. 82.0 mm for placebo group, $p = 0.77$). The trial found no statistically significant differences in side effects, specifically nausea, vomiting, or diarrhea (data not reported), and no vasovagal reactions or “other complications” were reported.

3.3 Summary of results for drotaverine (plus mefenamic acid)

An RCT enrolled 56 women, aged 20–61 years, and randomized them to receive drotaverine (80mg) and mefenamic acid (250 mg) or placebo, taken orally 30 minutes before IUD placement [27]. The treatment group reported lower mean pain scores as measured by VAS compared with placebo group during IUD placement (2.32 cm vs. 4.32 cm, $p = 0.001$) and 15 minutes after the procedure (1.28 cm vs. 2.01 cm, $p = 0.001$). All participants had successful IUD placements.

3.4 Summary of results for INH

Two RCTs examined INH for IUD placement [28, 29]. The first enrolled 220 parous women, aged 18 years and above, with previous cesarean deliveries only (no vaginal deliveries), and randomized them to receive either INH (900 mg) or placebo, inserted vaginally six hours before IUD placement [28]. The treatment group reported lower median VAS pain scores at tenaculum placement compared with the placebo group (2 cm vs. 4 cm, $p < 0.01$), lower mean VAS pain scores at IUD placement (3.9 cm vs. 5.3 cm, $p < 0.01$), and lower median VAS pain scores five minutes after the procedure (2 cm vs. 3 cm, $p < 0.01$). The study also reported lower median VAS provider ease of placement scores, indicating easier placement for the treatment group compared with the placebo group (3 cm vs. 5 cm, $p < 0.01$). Fewer participants in the treatment group requested analgesia compared with the placebo (4.5% vs. 24.5%, $p < 0.01$). All participants had successful IUD placements, and mean VAS patient satisfaction scores were higher among the treatment group than the placebo group (8.1 cm vs 5.5 cm, $p < 0.01$). There were no significant differences in reported nausea or abdominal cramps between the treatment and placebo groups (3.6% vs. 1.8%, $p = 0.68$; 12.7% vs. 15.5%, $p = 0.56$, respectively) and no participants reported vomiting or diarrhea.

The second RCT enrolled 200 women, aged 18–22 years, and randomized them to receive INH (900 mg) or placebo, self-inserted vaginally 12 hours before IUD placement [29]. Compared with the placebo group, the treatment group reported lower median VAS pain scores at tenaculum placement (3 cm vs 5 cm, $p = 0.0001$), lower mean VAS pain scores during IUD placement (4.0 cm vs. 6.4 cm, $p = 0.0001$), and lower median VAS pain scores 5 minutes after the procedure (2 cm vs. 4 cm, $p = 0.0001$). The study also reported lower provider ease of placement scores, indicating easier placement for the treatment group compared with the placebo group (median: 3 cm vs. 6 cm, $p = 0.0001$). Fewer participants in the treatment group required cervical dilation and fewer requested analgesia compared with the placebo group (7.3% vs. 16.5%, $p = 0.01$; 7% vs. 25%, respectively, $p = 0.0001$). Two participants in the treatment group and four in the placebo group had failed IUD placements ($p = 0.594$). Patient satisfaction was higher in the treatment group ($p = 0.0001$). The study reported no significant differences in nausea or abdominal cramping experienced between the treatment and placebo groups (2% vs. 3%, $p = 0.893$; 15% vs. 18%, $p = 0.639$, respectively), and no participants experienced vomiting or diarrhea.

3.5 Certainty of evidence

For topical nitroprusside gel or nitroglycerin ointment versus placebo, the certainty of evidence for all outcomes was rated as low, due to very serious concerns for imprecision (Online Appendix B) [18, 19]. For drotaverine/mefenamic acid versus placebo, the certainty of evidence for all outcomes was rated as very low due to very serious concerns for imprecision, serious concerns for risk of bias, and the inability to assess consistency because there was only one study [27]. For INH versus placebo, the certainty of evidence for all outcomes was considered high with no concerns [28, 29], with the exception of need for cervical dilation, which was considered moderate due to serious concerns for risk of bias [29].

4. Discussion

We identified five trials that assessed the use of smooth muscle relaxants for IUD placement. The findings of this updated systematic review provide new evidence on additional interventions, including drotaverine (with mefenamic acid) [27] and INH [28, 29]; no new evidence was identified on topical nitroprusside or nitroglycerin. Evidence from the previously identified two trials on topical nitroprusside or nitroglycerin found no differences between treatment and placebo groups on patient or provider outcomes [18, 19], although two patients in one trial who received nitroprusside gel experienced vasovagal reactions [18]. A study comparing drotaverine and mefenamic acid with placebo reported lower pain scores with the intervention, and all participants had successful placements [27]. However, it is not possible to determine if results could be attributed to drotaverine or mefenamic acid alone or as a combination compared with a placebo. Two studies compared INH with placebo and reported lower pain scores, improved provider ease of placement scores, and higher patient satisfaction among the treatment groups [28, 29]. Fewer patients in the treatment groups in both studies required analgesia, and fewer patients in the treatment group in one study required cervical dilation [29]. All participants in both studies had

successful placements, and there were no significant differences in reported side effects between groups in either study.

When interpreting the findings in this body of evidence, it is important to consider whether any differences observed were not only statistically significant, but also whether they were clinically meaningful. While there are no firm thresholds for the minimal clinically important difference in pain measured by VAS [31], some studies assessing interventions for acute pain have considered a difference of at least 1.3 cm on a 10-cm scale to reflect a clinically meaningful difference [32–34]. The mean differences in VAS pain scores seen in this body of evidence ranged from –2.4 cm to +0.2 cm across the pain outcomes at different time points (when converting results from studies that reported findings in mm to cm). When measuring pain, it is important to recognize that the experience of pain is individualized and might be influenced by previous experiences including trauma and mental health conditions [35–37]. The experience of pain with IUD placement may not be completely reflected in the VAS; other measurement tools, such as those that assess expectations about pain and pain acceptability [38], may provide additional information for assessing the effects of interventions for IUD placement.

Another limitation of this body of evidence is poor generalizability. Although sample sizes were generally sufficient for internal validity based on power calculations [19, 27–29], study populations were relatively small, and not all populations or patient experiences are represented. Two trials excluded those with prior attempted or placed IUDs [18, 19] and one included only those with previous cesarean deliveries [28].

The five RCTs included in this review provide insight into the use of smooth muscle relaxants for IUD placement. Before IUD placement, healthcare providers can counsel patients on the potential for pain during placement and options for pain management. However, evidence from RCTs on the use of smooth muscle relaxants for IUD placement remains sparse and provides inconsistent findings across medications. In addition, certainty of evidence across outcomes and interventions ranges from high to very low. More evidence is needed on specific smooth muscle relaxants to determine their effectiveness as an intervention for IUD placement.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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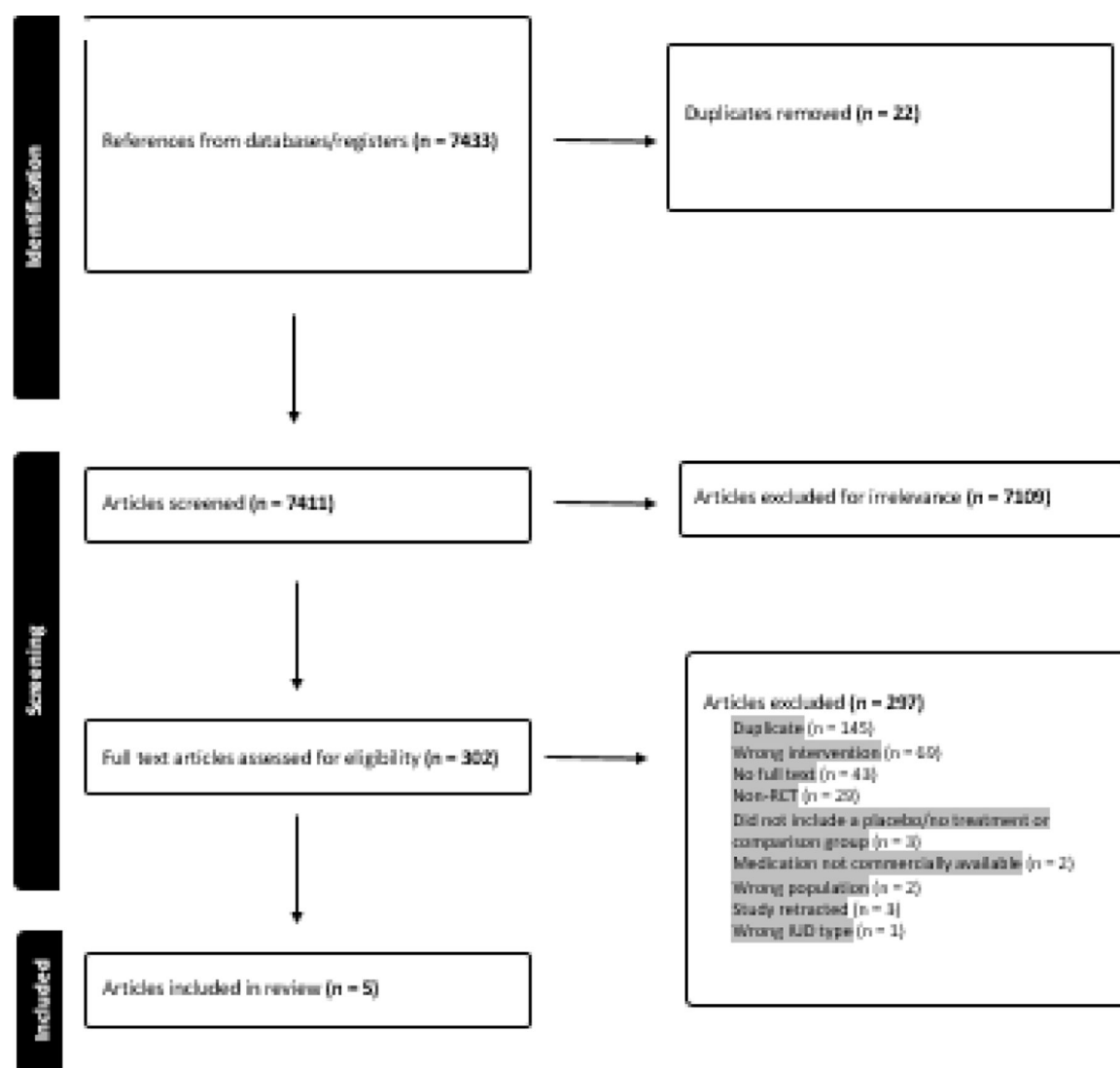


Figure 1.
PRISMA flow chart for the search process for evidence on smooth muscle relaxants for intrauterine device placement

Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of reported results	Overall risk of bias
Bednarek 2013	+	+	+	+	+	+
Micks 2014	+	+	+	+	+	+
Sharma 2015	?	+	+	+	+	?
Shady 2022	+	+	+	+, ?*	+	+, ?*
Shady 2023	+	+	+	+	+	+

Key: Low risk of bias + Moderate risk of bias ? High risk of bias -

*Shady 2022 was considered to have low risk of bias, with the exception of the outcome for need for cervical dilation, which was considered moderate risk of bias due to lack of information on outcome measurement.

Figure 2.
Risk of bias assessment for studies included in systematic review of smooth muscle relaxants for intrauterine device placement

Table 1.

Summary of evidence from randomized clinical trials on smooth muscle relaxants for IUD placement

Author, year, location, years of data collection, funding source	IUD type	Study population	Intervention and control	Outcomes	Results
Bednarek et al. 2013 [18] United States 2010–2011 Society of Family Planning	LNG-IUD	24 nulliparous women, aged 18–45 years Exclusion criteria: previous pregnancy >20 weeks; prior IUD placement or attempted placement; contraindication to nitroprusside or LNG-IUD; history of migraine, or cluster or vascular headache; blood pressure <90/55 or >150/100 at study beginning	Nitroprusside gel (10 mg) ($n = 13$) Placebo gel ($n = 11$) Both applied intracervically, by provider, immediately before IUD placement	100 mm VAS used for pain scores, patient satisfaction, and provider-reported ease of placement <u>Patient pain</u> Pain during tenaculum placement Pain during IUD placement (passage through cervix and placement at fundus) Highest level of pain after placement and before discharge (pain 30 minutes post-procedure) <u>Provider ease of placement</u> Ease of placement <u>Need for adjunctive placement measures</u> Cervical dilation Local anesthesia <u>Placement success</u> Placement success <u>Patient satisfaction with procedure</u> Patient satisfaction <u>Side effects</u> Nausea Vomiting Diarrhea <u>Adverse events</u> Vasovagal reaction	Nitroprusside vs. placebo [mean mm $\pm$ SD or proportion (%); p -value] <u>Patient pain</u> No significant difference in pain during tenaculum placement [30 ± 27 vs. 40 ± 27 ; $p = 0.35$] No significant difference in pain during IUD placement at passage through the cervix [61 ± 25 vs. 74 ± 18 ; $p = 0.18$] or placement at fundus [59 ± 26 vs. 73 ± 17 ; $p = 0.15$] No significant difference in pain at 30 minutes post-procedure [37 ± 33 vs. 50 ± 21 ; $p = 0.30$] <u>Provider ease of placement</u> No significant differences in provider ease of placement [32.4 ± 22.7 vs. 26.5 ± 27.2 ; $p = 0.57$] <u>Need for adjunctive placement measures</u> No significant differences between groups for cervical dilation [1/13 (7.7%) vs. 1/11 (9.1%); $p = 0.90$] No participants needed local anesthesia (paracervical block) <u>Placement success</u> All participants had successful placement <u>Patient satisfaction with procedure</u> No significant difference in patient overall satisfaction with procedure [82.8 ± 17.3 vs. 94.3 ± 6.6 ; $p = 0.06$] <u>Side effects</u> No significant differences in nausea, vomiting, diarrhea [data not reported] <u>Adverse events</u> Two participants in nitroprusside group experienced vasovagal reactions after placement
Micks et al. 2014 [19] United States 2012 American College of Obstetricians and Gynecologists/ Bayer Healthcare Pharmaceuticals	LNG-IUD	24 nulliparous women, aged 18–45 years Exclusion criteria: prior pregnancy >20 weeks; prior IUD placement or attempted placement; prior LEEP/CKC; contraindication to LNG-IUD or nitroglycerin; history of headaches or hypertensive or hypotensive disorder; blood pressure <90/55 or >150/100 before speculum exam in office	Nitroglycerin ointment (0.5 mg) ($n = 12$) Placebo ointment ($n = 12$) Both applied, by provider, at the posterior fornix 30–45 minutes before IUD placement	100 mm VAS used for pain scores, patient satisfaction, and provider-reported ease of placement <u>Patient pain</u> Pain during tenaculum placement Pain during IUD placement (passage through cervix) Highest level of pain after placement and before discharge (pain 30 minutes post-procedure) <u>Provider ease of placement</u> Ease of placement <u>Need for adjunctive placement measures</u> Cervical dilation Local anesthetics <u>Placement success</u> Placement success	Nitroglycerin vs. placebo [mean mm $\pm$ SD or proportion (%); p -value] <u>Patient pain</u> No significant difference in pain during tenaculum placement [data not reported] No significant difference in pain during IUD placement [55.8 ± 25.2 vs. 53.9 ± 28.1 ; $p = 0.86$] No significant difference in pain at 30 minutes post-procedure [data not reported] <u>Provider ease of placement</u> No significant differences in provider ease of placement [29.4 ± 23.8 vs. 22.8 ± 29.9 ; $p = 0.56$] <u>Need for adjunctive placement measures</u> One participant (8.3%) in each group required cervical Dilation One participant had local anesthesia (paracervical block, group not specified) <u>Placement success</u> All participants had successful

Author, year, location, years of data collection, funding source	IUD type	Study population	Intervention and control	Outcomes	Results
				<u>Patient satisfaction with procedure</u> Patient satisfaction <u>Side effects</u> Nausea Vomiting Diarrhea <u>Adverse events</u> Vasovagal reaction	placement <u>Patient satisfaction with procedure</u> No significant difference in patient satisfaction with overall procedure [84.7 ± 22.4 vs. 82.0 ± 23.4; $p = 0.77$] <u>Side effects</u> No significant differences in nausea, vomiting, diarrhea [data not reported] <u>Adverse events</u> No vasovagal reactions or “other complications” reported
Sharma et al. 2015 [27] India 2009 None	Copper IUD	56 women, aged 20–61 years Exclusion criteria: pregnancy; sensitivity to NSAIDs or lignocaine; history of peptic ulcer disease, inflammatory bowel disease, porphyria, genital infection, cervical stenosis, undiagnosed vaginal bleeding; history of cervical surgery	Drotaverine (80 mg) + mefenamic acid (250 mg) ($n = 31$) Placebo ($n = 25$) Taken orally 30 minutes before IUD placement	10 cm VAS used for pain scores <u>Patient pain</u> Pain during IUD placement Highest level of pain after placement and before discharge (pain 15 minutes post-procedure) <u>Placement success</u> Placement success	Drotaverine + mefenamic acid vs. placebo [mean cm ± SD or proportion (%); p -value] <u>Patient pain</u> Drotaverine + mefenamic acid group reported lower pain scores during IUD placement [2.32 ± 1.137 vs. 4.32 ± 1.676; $p = 0.001$] Drotaverine + mefenamic acid group reported lower pain scores 15 minutes after placement [1.28 ± 0.59 vs. 2.01 ± 0.93; $p = 0.001$] <u>Placement success</u> All participants had successful placement
Shady et al. 2023 [28] Egypt 2020–2021 None	Copper IUD	220 women above age 18, had previous deliveries by cesarean only Exclusion criteria: prior attempted or successful IUD placement; prior pregnancy > 13 weeks 6 days; analgesics taken within 48 hours of placement; recent pelvic inflammatory disease, vaginitis, or cervicitis; pregnant within 6 weeks of study; cervical surgery; category 3 or 4 conditions for IUD placement according to WHO medical eligibility criteria; uterine distortion (fibroids); contraindication to INH	INH (900 mg) ($n = 110$) Placebo ($n = 110$) Inserted vaginally, by research nurse, 6 hours before IUD placement	10 cm VAS used for pain scores, patient satisfaction, and provider-reported ease of placement <u>Patient pain</u> Pain during tenaculum placement Pain during IUD placement Highest level of pain after placement and before discharge (pain 30 minutes post-procedure) <u>Provider ease of placement</u> Ease of placement Analgesics <u>Placement success</u> Placement success <u>Patient satisfaction with procedure</u> Patient satisfaction <u>Side effects</u> Nausea Vomiting Abdominal pain/cramping Diarrhea	INH vs placebo [median (min-max), mean cm ± SD, or proportion (%); p -value] <u>Patient pain</u> INH group had lower pain scores at tenaculum placement [2 (1–3) vs. 4 (3–5); $p < 0.01$] INH group had lower pain scores during IUD placement [3.9 ± 0.8 vs. 5.3 ± 0.79; $p < 0.01$] INH group had lower pain scores 5 minutes after placement [2 (1–3) vs. 3 (3–5); $p < 0.01$] <u>Provider ease of placement</u> Provider ease of placement scores were lower (indicating an easier placement) for INH group [3 (1–4) vs. 5 (3–6); $p < 0.01$] Fewer patients in INH group requested analgesia (5/110 or 4.5% vs. 27/110 or 24.5%, $p < 0.01$) <u>Placement success</u> All participants had successful placement <u>Patient satisfaction with procedure</u> Patient satisfaction score was higher in INH group [8.1 ± 0.6 vs. 5.5 ± 0.7; $p < 0.01$] <u>Side effects</u> No significant difference in reported nausea between groups [4/110 (3.6%) vs. 2/110 (1.8%); $p = 0.68$] No reports of vomiting or diarrhea in either group No significant difference in abdominal cramps between groups [14/110 (12.7%) vs. 17/110 (15.5%); $p = 0.56$]

Author, year, location, years of data collection, funding source	IUD type	Study population	Intervention and control	Outcomes	Results
Shady et al. 2022 [29] Egypt 2020 None	Copper IUD	200 women, aged 18–22 years Exclusion criteria: pregnancy within 6 weeks of study; prior pregnancy >14 weeks; analgesics within 48 hours of placement; recent pelvic inflammatory disease, vaginitis, or cervicitis; undiagnosed abnormal uterine bleeding; cervical surgery; category 3 or 4 conditions for IUD placement according to WHO medical eligibility criteria; uterine distortion (fibroids); contraindication to INH	INH (900 mg) ($n = 100$) Placebo ($n = 100$) Self-inserted vaginally 12 hours before IUD placement	10 cm VAS used for pain scores and provider-reported ease of placement <u>Patient pain</u> Pain during tenaculum placement Pain during IUD placement Highest level of pain after placement and before discharge (pain 30 minutes post-procedure) <u>Provider ease of placement</u> Ease of placement <u>Need for adjunctive placement measures</u> Cervical dilation Analgesics <u>Placement success</u> Placement success <u>Patient satisfaction with procedure</u> Patient satisfaction <u>Side effects</u> Nausea Vomiting Abdominal pain/cramping Diarrhea	INH vs. placebo [median (min-max), mean cm $\pm$ SD, or proportion (%); p -value] <u>Patient pain</u> INH group had lower pain scores at tenaculum placement [3 (1–4) vs. 5 (3–6); $p = 0.0001$] INH group had lower pain scores during IUD placement [4.0 $\pm$ 1.0 vs. 6.4 $\pm$ 0.7; $p = 0.0001$] INH group had lower pain scores 5 minutes after placement [2 (1–3) vs. 4 (3–5); $p = 0.0001$] <u>Provider ease of placement</u> Provider ease of placement scores were lower (indicating an easier placement) for INH group [3 (2–5) vs. 6 (3–8); $p = 0.0001$] <u>Need for adjunctive placement measures</u> Fewer participants in the INH group required cervical dilation [7.3% vs. 16.5%; $p = 0.01$] (percentages as reported by authors) Fewer participants in INH group requested analgesia [7/100 (7%) vs. 25/100 (25%); $p = 0.0001$] <u>Placement success</u> Two participants in INH group (2%) and four in placebo group (4%) had failed placements ($p = 0.594$) <u>Patient satisfaction with procedure</u> Patient satisfaction score was higher in INH group ($p = 0.0001$) <u>Side effects</u> No significant difference in reported nausea between groups [2/100 (2%) vs. 3/100 (3%); $p = 0.893$] No reports of vomiting or diarrhea in either group No significant difference in abdominal cramps between groups [15/100 (15%) vs. 18/100 (18%); $p = 0.639$]

CKC, cold knife cone; INH, isonicotinic acid hydrazide; IUD, intrauterine device; LEEP, loop electrosurgical excision procedure; LNG, levonorgestrel; NSAID, nonsteroidal anti-inflammatory drug; RCT, randomized controlled trial; SD, standard deviation; VAS, visual analog scales; WHO, World Health Organization.