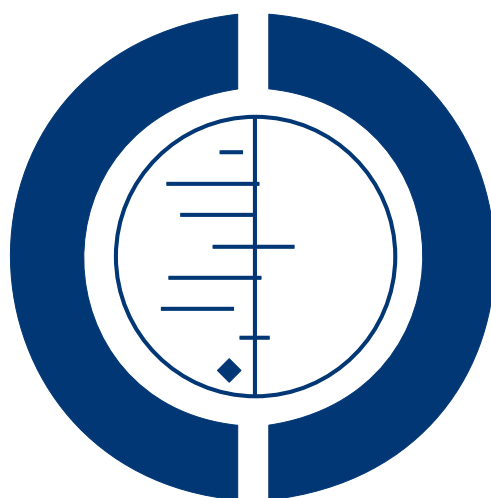


Interventions for pain with intrauterine device insertion (Review)

Allen RH, Bartz D, Grimes DA, Hubacher D, O'Brien P



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[Intervention Review]

Interventions for pain with intrauterine device insertion

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Editorial group: Cochrane Fertility Regulation Group.

Publication status and date: New, published in Issue 3, 2009.

Review content assessed as up-to-date: 22 February 2009.

Citation: Allen RH, Bartz D, Grimes DA, Hubacher D, O'Brien P. Interventions for pain with intrauterine device insertion. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD007373. DOI: 10.1002/14651858.CD007373.pub2.

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ABSTRACT

Background

Fear of pain during intrauterine device (IUD) insertion is a barrier to use of this contraceptive method. Interventions for pain during IUD insertion include non-steroidal anti-inflammatory drugs (NSAIDs), local cervical anesthetics, and cervical ripening agents such as misoprostol.

Objectives

To review all randomized controlled trials that have evaluated a treatment for IUD insertion-related pain.

Search strategy

We searched the computerized databases MEDLINE, POPLINE, CENTRAL, and EMBASE for relevant trials. We also examined reference lists of pertinent articles and wrote to known investigators for information about other published or unpublished trials.

Selection criteria

We included all randomized controlled trials in any language that evaluated a treatment for IUD insertion-related pain. The intervention could be compared to a placebo or another active intervention.

Data collection and analysis

Two authors independently abstracted data from relevant trials and data were entered into RevMan 5.0 for analysis. For dichotomous variables, the Peto odds ratios with 95% confidence intervals was calculated. For continuous variables, the mean differences with 95% confidence interval was computed.

Main results

Four trials met the inclusion criteria; the total number of participants was 2204. Nonsteroidal anti-inflammatory drugs of varying types and doses were not effective for reducing pain during IUD insertion. Misoprostol for cervical ripening did not reduce pain with IUD insertion in nulliparous women. Two trials evaluated pain that occurs after IUD insertion using nonsteroidal anti-inflammatory drugs. In one trial, naproxen taken prior to IUD insertion was effective in reducing pain compared with placebo in the first two hours after IUD insertion in mostly nulliparous women. However, this trial utilized the Dalkon Shield, an IUD with a wider diameter than

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modern IUDs. In another trial, ibuprofen 600 mg taken before IUD insertion did not show evidence of an effect on pain four to six hours after IUD insertion.

Authors' conclusions

No interventions that have been properly evaluated reduce pain during or after IUD insertion. One poorly controlled trial suggested that topical lidocaine gel may reduce insertion-related pain and warrants further investigation.

PLAIN LANGUAGE SUMMARY

Interventions to reduce pain during intrauterine device insertion

Fear of pain during intrauterine device (IUD) insertion is one reason women may not want to use this highly effective birth control method. Different ways of reducing pain during IUD insertion have been explored. These include drugs that reduce cramping of the uterus (nonsteroidal anti-inflammatory drugs, or NSAIDs), drugs that soften and open the cervix (the opening to the uterus), and drugs that numb the cervix. We searched for and summarized all the randomized controlled trials that looked at these ways of reducing pain during IUD insertion. We found four trials from four countries, with 2204 women studied. The NSAID ibuprofen at doses of 400 mg and 600 mg did not help to reduce pain during IUD insertion. Whether higher doses would have worked is unknown. Naproxen, another NSAID, may help with pain in the first two hours after IUD insertion, but the trial studying this used a larger IUD type that is not currently available. Misoprostol, a drug to soften and open the cervix, did not help to reduce pain during IUD insertion in women who had never given birth before. However, the study was not focused on women's pain, but rather the ease of placing the IUD from the provider's perspective. Currently, we have no good evidence to recommend any method of reducing pain.

BACKGROUND

Description of the condition

The intrauterine device (IUD) provides long-term, reversible contraception equal in efficacy to tubal sterilization (Grimes 2008). Depending on the country, the use of IUDs worldwide ranges from 2% to 75%. On average, 15% of reproductive-aged women in developing countries and 8% in developed countries use IUDs (d'Arcangues 2007). Increasing the number of women using IUDs is an important public health goal. One barrier to IUD use is the fear of pain during insertion. Components of the insertion procedure that may cause pain include the application of the tenaculum to the cervix to stabilize the uterus and provide traction for straightening the cervical canal, passing the uterine sound, inserting the IUD in the inserter tube through the cervix, and irritation of the endometrial cavity with the device. Cervical pain is mediated by S2 to S4 parasympathetic nerves and the T10 to L1 sympathetic fibers innervate the uterine fundus. While some IUDs are inserted postpartum or postabortal, most are inserted remote (> four weeks) from pregnancy as a clinic-based procedure. The

levels of pain that women experience during IUD insertion vary in published reports. Most women experience mild to moderate discomfort during IUD insertion. Rarely, the pain is severe and associated with nausea and weakness. Pain may persist for a few days after insertion. Predictors of pain during IUD insertion include nulliparity, age greater than 30 years, lengthier time since last pregnancy or last menses, and not currently breastfeeding (Hubacher 2006). Psychosocial factors including expected pain also influence the pain perceived by women undergoing the procedure (Goldstuck 1985; Murty 2003).

Description of the intervention

Pharmacological methods of pain control used for IUD insertion commonly include non-steroidal anti-inflammatory drugs (NSAIDs), anxiolytics, and local anesthetics in the form of intracervical gel, cervical and paracervical block. One survey of United Kingdom (UK) physicians found a wide variation in the use of analgesia or anesthesia for IUD insertions from no routine use to always using prophylactic NSAIDs or 2% lidocaine gel intracer-

vically during the procedure (Tolcher 2003). Other interventions to ease IUD insertion include the use of prostaglandins to soften the cervix.

How the intervention might work

Local anesthetics that are administered topically or through injection may decrease cervical pain by blocking nerve fibers. Anxiolytics reduce pre-insertion anxiety and may lead to decreased pain perception by the woman (Murty 2003). NSAIDs have been shown to reduce pain associated with IUD use (Grimes 2006). In the context of IUD insertion, NSAIDs may reduce cervical or uterine pain. Other interventions, such as misoprostol, a prostaglandin E1 analogue, may decrease pain by dilating and softening the cervix prior to insertion (Goldberg 2003).

Why it is important to do this review

Pain at insertion of an IUD can be distressing and may deter women from using the method. Pain relief at insertion has not been systematically reviewed before. This review evaluates both prophylactic and procedural interventions to reduce pain. Determining the optimal method for reducing pain during IUD insertion will benefit women and may increase the uptake of IUDs as a contraceptive method.

OBJECTIVES

To review all randomized controlled trials that have evaluated a treatment for IUD insertion-related pain.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials in any language that evaluated a treatment for IUD insertion-related pain. The intervention could be compared to a placebo or another active intervention.

Types of participants

All women having any type of IUD inserted.

Types of interventions

We included any type of pharmacological or other intervention administered prior to or during IUD insertion in order to reduce pain with insertion and up to six hours afterwards.

Types of outcome measures

Primary Outcome

Perceived pain during and after IUD insertion up to six hours, both as reported by the women.

Secondary outcomes

Side effects, adverse events, and patient satisfaction.

Search methods for identification of studies

See: Cochrane Fertility Regulation Group methods used in reviews.

Trials were identified using PubMed for MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), POPLINE, EMBASE, and ClinicalTrials.gov.

We searched MEDLINE via PubMed using the following strategy: (iud* OR iucd* OR ius* OR intrauterine devices OR intrauterine device*) AND insert* AND (pain OR cramping OR discomfort) AND (control* OR therapy OR treat* OR alleviate* OR ameliorate* OR reduc* OR minimiz* OR analgesics OR analgesic* OR anodynes OR anesthesia and analgesia)

We searched CENTRAL using the following strategy: pain and (intrauterine device* or intrauterine contraception* or intrauterine system*) and (analgesia* or therapy) and insert*

We searched POPLINE using the following strategy: (intrauterine device*/iud*/iucd*/ius*/intrauterine contracept*) & (analgesi*/nsaids/local anesthesia/cervical block/therapy/treat*/alleviat*/ameliorat*/reduc*/minimiz*/control*) & (pain/discomfort/cramping/analgesi*/nsaids/local anesthesia/cervical block) & insert* & clinical trial*

We searched EMBASE using the following strategy: (intrauterine(w)contraceptive(w)device? or intrauterine(w)device? or iud? or iucd? or ius? or intrauterine(w)contracept?) AND insert? AND ((analgesic? or analgesic agent! or local anesthesia agent or local anesthesia! or cervical(w)block) OR (pain or pain/ or pain/ or pain! or cramping or discomfort)) AND ((analgesic? or analgesic agent! or local anesthesia agent or local anesthesia! or cervical(w)block) OR (control? or treat? or alleviat? or ameliorat? or reduc? or limit? or minimiz?))

We searched ClinicalTrials.gov for "intrauterine device".

We used no date or language restriction in our search. We searched the reference lists of retrieved titles for previously unidentified studies. We wrote to authors of published trials to solicit information regarding other published or unpublished trials that may have been missed in our initial search.

Data collection and analysis

We assessed all retrieved abstracts for possible inclusion. We reviewed the methodology of the trials for potential bias through qualitative assessment of study design, randomization process, allocation concealment, blinding, and early discontinuation and loss to follow-up rates using the guidelines in the Cochrane Reviewers' Handbook (Higgins 2008). Two independent reviewers (Allen and Bartz) assessed and extracted data from the studies. Discrepancies or disagreements were resolved through the use of a third reviewer. One author entered data into RevMan 5.0 for data entry and a second confirmed correct data entry. Peto odds ratios with 95% confidence intervals were used for dichotomous variables. Mean differences with 95% confidence interval were calculated for continuous variables. We contacted trial report authors as needed to supplement published information.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

Results of the search

The initial search strategy yielded 349 articles of which four randomized controlled trials met criteria for this review. The four trials had a total of 2204 women. The number of participants in each trial ranged from 50 (Massey 1974) to 2019 (Hubacher 2006). The trials were published from 1974 to 2007 and conducted in the United States, Chile, Denmark, and Sweden. Three trials evaluated NSAIDs and one trial studied misoprostol. Two trials used a 10 cm visual analog scale to measure pain during IUD insertion and two trials used numerical rating scales.

Included studies

The earliest study randomized 50 women, 48 (96%) of them nulliparous, to 300 mg of naproxen or placebo taken the night before and 90 minutes prior to Dalkon Shield IUD insertion as well as at two and six hours after IUD insertion (Massey 1974). All women received a paracervical block consisting of a total of 8 mL of 1% lidocaine before IUD insertion given the wide diameter of the device (24 mm) and the nulliparous status of most participants. Both participants and investigators were blinded to treatment assignment. The women were aged 18 to 29 years, and the IUD was inserted during menses in all but one participant. Pain was measured on a numerical rating scale from one to five; one was no pain and five was very severe pain. Pain was measured during

IUD insertion, immediately after IUD insertion, at hourly intervals thereafter for a total of 10 hours, and at 24 hours.

The Danish trial randomized 55 women, three (6%) of them nulliparous, to 600 mg of ibuprofen or placebo one to four hours prior to insertion of the IUD, four to six hours after insertion, and the morning after insertion (Jensen 1998). Randomization was stratified by IUD type, TCu380S or Nova-T, creating four groups of equal sizes. Both participants and investigators were unaware of the analgesia assigned. Pain was measured on a numerical rating scale from 1 to 10: 1 was the least pain and 10 the most intense. Pain was measured during insertion, in the first four to six hours after insertion, and over the following three days.

A recent trial conducted in Chile randomized 2019 first-time IUD users to 400 mg of ibuprofen or placebo at least 45 minutes prior to insertion of a copper T380A IUD (Hubacher 2006). A total of 102 (5%) women were nulliparous and more than half of participants were under 25 years of age. Both participants and investigators were unaware of the treatment assignment and pain during IUD insertion was measured on a 10 cm visual analog scale. This study was a substudy of a randomized trial testing the possible benefit of repeated doses of prophylactic ibuprofen taken during menses for six months to improve IUD continuation rates.

The Swedish trial assessed the use of misoprostol for IUD insertion in nulliparous women (Sääv 2007). Eighty women were randomized to 400 µg of sublingual misoprostol plus 100 mg of diclofenac or 100 mg of diclofenac alone one hour before Nova-T IUD insertion. The participants were aware of the treatment assignment, but the investigators were not. Pain during IUD insertion was measured on a 10 cm visual analog scale, and the insertion experience was also rated by the participants as very unpleasant, unpleasant, or 'very little unpleasant.' The women were aged 18 to 36 years. Of note, the primary outcome of the study was not pain during insertion but rather ease of IUD insertion as judged by the provider.

Excluded studies

Five studies were excluded because they lacked randomization (Newton 1977; Hepburn 1980; Thiery 1985). One study (Oloto 1996) assigned participants to treatment by date of birth and was excluded because the risk of selection bias was high. Two studies were excluded because they were review articles, not intervention studies (Goldstuck 1987; Hollingworth 1995). One randomized controlled trial was excluded because it did not examine the outcome of interest, pain during or after IUD insertion up to six hours (Goldstuck 1983).

Risk of bias in included studies

The U.S. trial of naproxen (Massey 1974) featured permuted block randomization with a block size of 10. Allocation concealment

was not described. Blinding of treatment appears to have been adequate, with identical appearing capsules provided in sealed strips. The sample size calculation was not provided. All participants who requested additional analgesia were dropped from the trial at that point, leading to considerable missing data. Despite recording symptoms such as backache, headache, cold sweats, nausea, and vomiting before and after taking study medications and before and after the IUD insertion, these were not reported by the investigators.

Correspondence with the author indicated that the Danish trial (Jensen 1998) of prophylactic ibuprofen used a computer-generated randomization scheme. Allocation concealment was provided by having pharmacy-generated opaque sealed envelopes containing pills. A formal sample size calculation was done in advance. Participants had a stratified randomization by IUD type. A placebo was used to keep participants and investigators unaware of treatment. Three women in the ibuprofen group and four women in the placebo group took additional pain medication after insertion and were excluded from the analysis at four to six hours, one day, two days, and three days after insertion.

The trial from Chile (Hubacher 2006) featured randomization by random permuted blocks and central pharmacy distribution ensured allocation concealment. Blinding of participants and investigators was provided by using an identical-appearing placebo. No formal sample size was calculated because the trial was a sub-study with a known, fixed sample size from the primary study. One ibuprofen participant did not have pain score data and was not analyzed.

The Swedish study (Sääv 2007) reported a computer-generated randomization scheme with adequate allocation concealment using sequentially-numbered, sealed, opaque envelopes. No placebos were utilized as the study was blinded only to investigators, not participants. The sample size calculation was estimated from previous studies on misoprostol for cervical priming but no formal

calculation was performed. Two participants in the diclofenac-only arm had failed insertions but were included in the analysis. One participant in the misoprostol arm withdrew consent prior to insertion and was not analyzed.

Effects of interventions

No trials were combined in a meta-analysis due to differences in the interventions.

Pain during IUD insertion

The U.S. trial failed to show evidence of an effect with the administration of 300 mg of naproxen the night before and 90 minutes prior to Dalkon Shield insertion (Massey 1974). The mean pain score during IUD insertion on a scale from one to five was 2.54 in the control group and 2.46 in the treatment group (mean difference -0.08; 95% confidence interval (CI) -0.72 to 0.56) (Figure 1). The Danish trial also failed to find evidence of an effect on pain with the administration of 600 mg of ibuprofen one to four hours prior to insertion (Jensen 1998). The median pain scores for the ibuprofen and placebo groups at the time of insertion were 3.3 and 2.5 on a scale from 1 to 10, respectively. Of 27 women in the ibuprofen arm, 18 reported moderate to severe pain (3 or greater on the 1 to 10 scale) compared with 14 women of 28 in the placebo arm (odds ratio (OR) 2.00; 95% CI 0.67 to 5.95) (Figure 2). No important differences were seen in pain by type of IUD. Prophylactic administration of 400 mg of ibuprofen at least 45 minutes prior to IUD insertion had no effect of pain in the Chilean trial (Hubacher 2006). Mean pain scores were 1.8 in the ibuprofen arm and 2.0 in the control arm on a 10 cm visual analog scale (mean difference -0.20; 95% CI -0.41 to 0.01) (Figure 3). Increasing age, lower parity, lengthier time since last pregnancy, and no lactation were associated with increased pain, but ibuprofen was no more effective in any of these groups.

Figure 1. Forest plot of comparison: I Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, outcome: I.1 Mean pain score during IUD insertion.

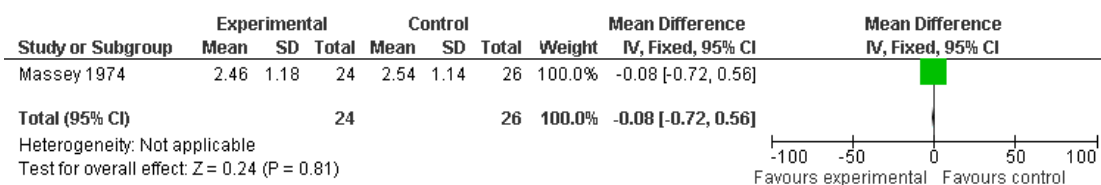


Figure 2. Forest plot of comparison: 2 Ibuprofen 600 mg versus placebo, outcome: 2.1 Number of patients reporting moderate to severe pain during IUD insertion (3 or greater on the 1 to 10 scale)

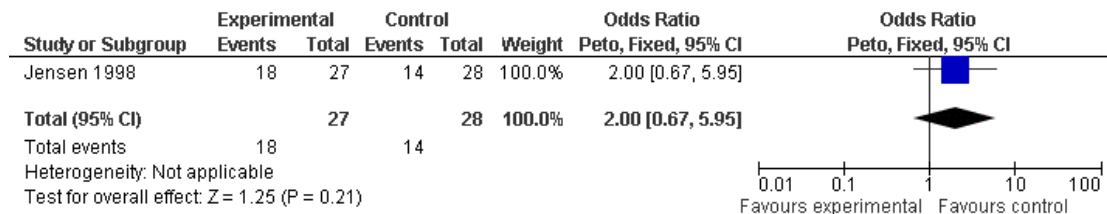
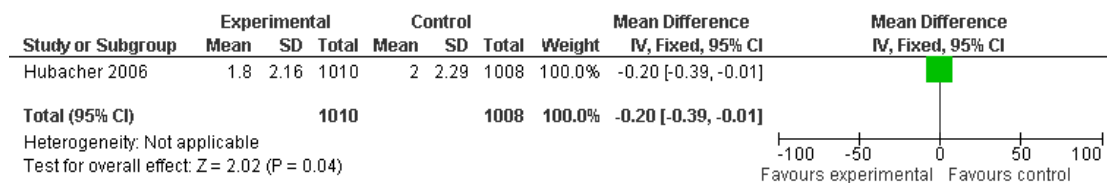


Figure 3. Forest plot of comparison: 3 Ibuprofen 400 mg versus placebo, outcome: 3.1 Mean pain score during IUD insertion.



The Swedish trial failed to find evidence of an effect with the administration of misoprostol, 400 µg sublingually, combined with diclofenac, one hour prior to IUD insertion compared with diclofenac alone (Saäv 2007). The median pain scores for the misoprostol and control groups at the time of insertion were 7 compared with 6.5, respectively. In the misoprostol group, 35 out of 39 women rated the insertion as very unpleasant or unpleasant compared with 32 out of 40 women in the control group (OR 2.19; 95% CI 0.60 to 7.97) (Figure 4). There was no evidence of a difference between the groups in reported side effects with 23 out of 29 women in the misoprostol group reporting any side effect (shivering, diarrhea, nausea, or vomiting) compared with 18 out of 40 participants in the control group (OR 1.76; 95% CI 0.72 to 4.29) (Figure 5). Examined individually, the only side effect that was significantly different between the two groups was shivering, suffered by 12 women in the misoprostol arm compared with 3 in the control group (P=0.008). Side effects were measured after IUD insertion.

Figure 4. Forest plot of comparison: 4 Misoprostol 400 µg and diclofenac 100 mg versus diclofenac 100 mg alone, outcome: 4.1 Number of patients rating insertion experience as very unpleasant or unpleasant.

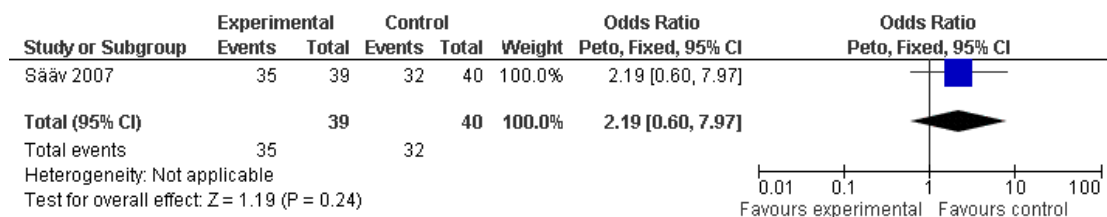
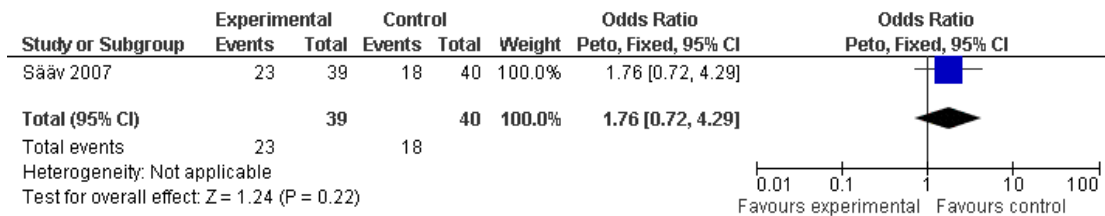


Figure 5. Forest plot of comparison: 4 Misoprostol 400 µg and diclofenac 100 mg versus diclofenac 100 mg alone, outcome: 4.2 Number of patients with any side effect.



Pain after IUD insertion (up to 6 hours)

Two trials evaluated pain experienced in the first six hours after IUD insertion. The U.S. trial administered 300 mg of naproxen or placebo the night before and 90 minutes prior to Dalkon Shield IUD insertion as well as at two and six hours after IUD insertion (Massey 1974). Pain was measured at hourly intervals after IUD insertion but women who requested additional medication were dropped from the study. Mean pain scores were significantly lower at one and two hours after IUD insertion with naproxen compared to placebo. At one hour, mean pain scores on a scale from one to five were 2.58 and 3.62 in the naproxen and placebo arms, respectively (mean difference -1.04; 95% CI -1.67 to -0.41) (Figure 6). At two hours, mean pain scores were 2.36 and 3.34 in the naproxen and placebo arms, respectively, (mean difference -0.98; 95% CI -1.64 to -0.32) (Figure 7). There was no difference between the two groups at three, four, five, and six hours after IUD insertion (Figure 8; Figure 9; Figure 10; Figure 11). However, many women were dropped from the study at that point. The authors reported that, during the 24-hour period of the study, of 24 patients assigned to naproxen, seven asked for additional medication compared with 17 of 26 in the placebo group (P = 0.01).

Figure 6. Forest plot of comparison: 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, outcome: 1.2 Mean pain score 1 hour after IUD insertion.

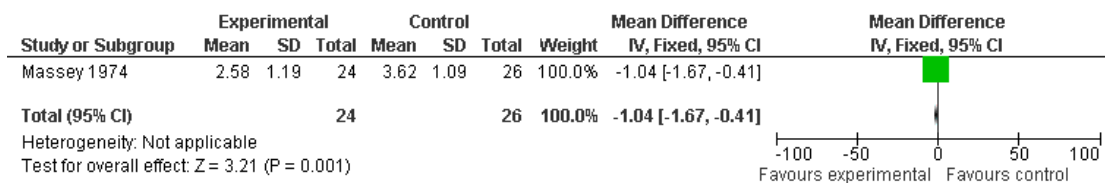


Figure 7. Forest plot of comparison: I Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, outcome: I.3 Mean pain score 2 hours after IUD insertion.

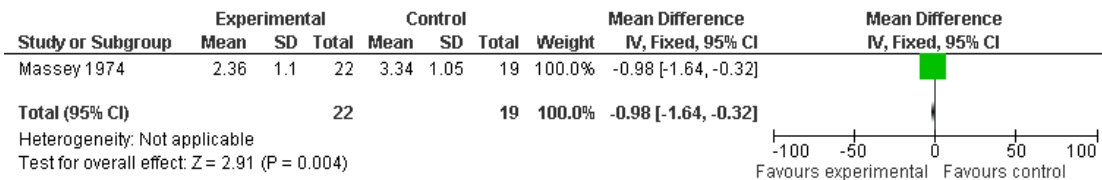


Figure 8. Forest plot of comparison: I Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, outcome: I.4 Mean pain score 3 hours after IUD insertion.

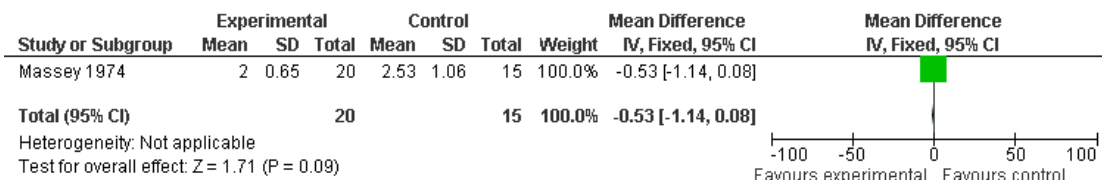


Figure 9. Forest plot of comparison: I Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, outcome: I.5 Mean pain score 4 hours after IUD insertion.

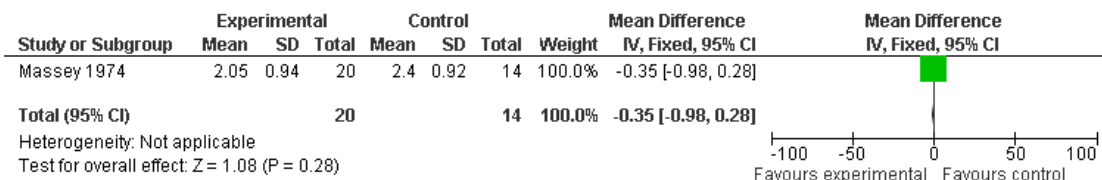


Figure 10. Forest plot of comparison: I Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, outcome: I.6 Mean pain score 5 hours after IUD insertion.

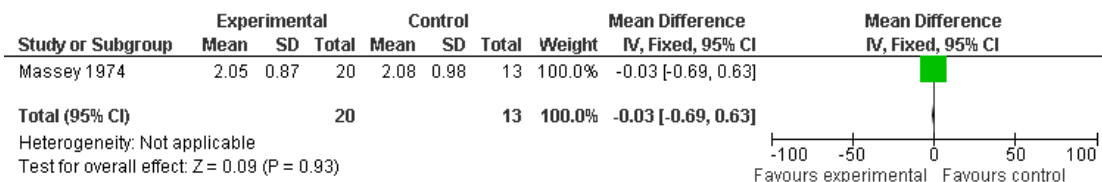
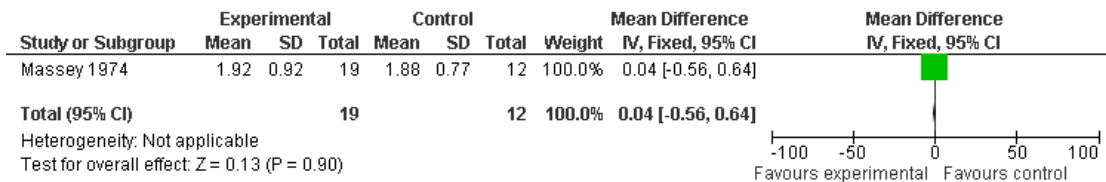


Figure 11. Forest plot of comparison: 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, outcome: 1.7 Mean pain score 6 hours after IUD insertion.



The Danish trial failed to find evidence of an effect of pain after insertion with ibuprofen 600 mg administered one to four hours prior to insertion (Jensen 1998). The median pain scores for the ibuprofen and placebo groups four to six hours after insertion were 1.7 and 1.8 on a scale from 1 to 10, respectively. Correspondence with the author indicated that subjects measured their pain at 4 to 6 hours after insertion before ingesting the study medication scheduled at four to six hours after insertion. Women who requested additional pain medication were excluded from the analysis.

DISCUSSION

Summary of main results

Prophylactic NSAIDs, as studied, do not appear to reduce pain during IUD insertion, or four to six hours after IUD insertion. (Massey 1974; Jensen 1998; Hubacher 2006). Benefit may occur in the first couple hours after IUD insertion in nulliparous women given naproxen, however (Massey 1974). The use of misoprostol to prime the cervix in addition to diclofenac before IUD insertion in nulliparous women did not appear to reduce pain and may increase side effects (Sääv 2007). No serious harms were reported in these trials, although such reporting was incomplete.

Overall completeness and applicability of evidence

The studies identified are insufficient to determine whether NSAIDs impact pain during and after IUD insertion. The US trial showing a benefit of naproxen may not be relevant, since the IUD used in the trial (the Dalkon Shield) had unique insertion mechanics and the device is no longer available (Massey 1974). The largest trial used a dose of ibuprofen (400 mg) that may be lower than that (800 mg) sometimes used in clinical practice for acute gynecological pain (Hubacher 2006). The trial of misoprostol studied an intervention commonly used for gynecological procedures and also employed a modern IUD (Sääv 2007), therefore, these findings are more relevant to contemporary practice.

Quality of the evidence

Trial reports varied widely in quality. Three trials evaluated different types and doses of NSAIDs. The trial of 2019 participants had sufficient power and rigor to conclude that 400 mg of ibuprofen has no effect on IUD insertion pain overall or in groups such as nulliparous women who had experienced more pain at insertion (Hubacher 2006). As discussed in the original report, this finding may have been due to the overall low pain scores in the study population, thus making it difficult to measure any possible improvement from ibuprofen. However, there is no evidence to suggest that ibuprofen would decrease pain in a population with higher pain scores from the procedure. In the Danish trial with 55 participants, the 95% confidence interval could be consistent with more pain in the ibuprofen group rather than less (Jensen 1998). While, the study was well designed, its small sample size limits interpretation. The U.S. trial of 300 mg of naproxen was of lesser quality and firm conclusions cannot be drawn from the data (Massey 1974). The Swedish trial of misoprostol was not specifically designed to evaluate IUD insertion pain, rather, the primary outcome was ease of insertion as rated by the provider (Sääv 2007). This study blinded only the investigators, so participant ratings of discomfort during insertion may have been biased by knowledge of their treatment.

One excluded trial of 2% lidocaine gel had a faulty randomization scheme, lack of blinding, lack of a priori sample size calculation, and lack of allocation concealment (Olotto 1996). However, the trial showed that the application of 2% lidocaine gel to the cervix one minute prior to insertion was more effective than no treatment in reducing pain with IUD insertion. Of 44 women in the 2% lidocaine gel arm, 29 reported moderate to severe pain compared with 36 women of 38 in the no-treatment arm (OR 0.11; 95% CI 0.02 to 0.51). Given that this is the only treatment found to be effective in the literature, further studies are indicated.

AUTHORS' CONCLUSIONS

Implications for practice

Although NSAIDs have been used to reduce pain during IUD insertion, published trials show no evidence of benefit. Naproxen might be beneficial in the first hours *after* IUD insertion, but only one trial showed this benefit and used an IUD with a wider diameter than modern IUDs. While misoprostol may facilitate IUD insertion in nulliparous women, no evidence indicates that it reduces pain and it may increase rates of side effects. Different misoprostol regimens may have different effects, however. There is insufficient evidence to recommend topical lidocaine gel.

Implications for research

This review highlights the need for more randomized controlled trials to evaluate interventions for pain with IUD insertion. Future trials should measure pain both during and after IUD insertion as well as the number of women requesting additional pain medication. Interventions for pain with the levonorgestrel IUD have yet to be studied. Misoprostol trials should be compared with placebo among nulliparous women and should be conducted with pain during IUD insertion as one of the primary outcomes. In addition, the side effects of misoprostol should be assessed before and after IUD insertion. Topical lidocaine gel merits further study with proper methods.

ACKNOWLEDGEMENTS

Carol Manion of Family Health International and Carol Mita of Harvard University assisted with the literature searches.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Hubacher 2006

Methods	Location: Santiago, Chile Recruitment: June 2002 to August 2003 Randomized sequence generation: computer-generated random permuted blocks with block sizes of 20, 10, 4, and 2 Allocation concealment: central pharmacy dispensed sealed pill bottles labeled group A and group B Blinding: participants and investigators were unaware of the assignment; identical-appearing placebo and ibuprofen tablets Sample size calculation: None (subanalysis), trial size determined by main outcome
Participants	N: 2019 women, 204 nulliparous Source: 42 Ministry of Health facilities and one private clinic Inclusion criteria: aged 18 to 49 years, literate, had menstruated in the last 6 weeks, had never used an IUD, were more than 6 weeks postpartum if recently pregnant Exclusion criteria: medical contraindications to IUDs or ibuprofen, had used an IUD before
Interventions	Ibuprofen 400 mg versus placebo at least 45 minutes before insertion
Outcomes	Pain score during IUD insertion (10 cm visual analog scale)
Notes	Loss to follow up: One ibuprofen participant did not have pain score data and was not analyzed IUD used: TCu380A 7 subjects also received paracervical block 94% of insertions were done within 5 days of the start of the menstrual cycle

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A-Adequate

Jensen 1998

Methods	Location: Herlev, Denmark Recruitment: May 1994 to May 1995 Randomization sequence generation: computer generated, stratified by IUD type Allocation concealment: central pharmacy packaging of drug in opaque sealed envelopes Blinding: participants and investigators were unaware of the assignment, tablets were of same size and shape, but taste may have differed Sample size calculation: formal a priori sample size calculation performed
Participants	N: 55 women, 3 nulliparous Source: one family planning clinic Inclusion criteria: Danish-speaking women in good health desiring IUD insertion Exclusion criteria: age <18 years, serious illness, allergy to NSAID or aspirin, dyspepsia or peptic ulcer

Jensen 1998 (Continued)

	disease, medication of any kind except for oral contraceptives	
Interventions	Ibuprofen 600 mg versus placebo 1 to 4 hours before insertion, 4 to 6 hours after insertion, and the morning after insertion.	
Outcomes	Primary: Pain score during IUD insertion (numerical rating scale 1 to 10, least pain to most intense) Secondary: Pain score in the first 4 to 6 hours after insertion and over the following 3 days	
Notes	Loss to follow up: None IUDs used: Nova-T and TCu380S	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A-Adequate

Massey 1974

Methods	Location: Palo Alto, CA Recruitment: Not reported Randomization sequence generation: Random permuted blocks of 10, source not specified Allocation concealment: unclear Blinding: participants and investigators were unaware of the assignment, identical appearing placebo and naproxen tablets Sample size calculation: not reported	
Participants	N: 50 women, 48 nulliparous Source: one student health center Inclusion criteria: IUD use deemed appropriate, normal physical examination and laboratory tests Exclusion criteria: severe, painful menses, or premenstrual tension	
Interventions	300 mg naproxen with paracervical block (8 mL 1% lidocaine) versus placebo with paracervical block; oral medications administered both at 10:00 PM on the night before IUD insertion and 1.5 hours before IUD insertion. Participants also ingested scheduled oral medications at 2 and 6 hours after IUD insertion.	
Outcomes	Primary: Pain score during IUD insertion (numerical rating scale 1 to 5: 1 - no discomfort, 2 - mild, 3 - moderate, 4 - severe, 5 - very severe discomfort) Secondary: requirement for additional analgesia, abdominal cramping, backache, headache, cold sweats, nausea, and vomiting recorded before and after taking the first two oral medications, before and immediately after the IUD insertion, at hourly intervals thereafter for a total of 10 hours, and at 24 hours.	
Notes	Loss to follow up: No loss to follow up at point of IUD insertion pain measurement, thereafter, all patients requiring additional medications were withdrawn from the study. IUD used: Dalkon Shield, dilated to 4 mm	
Risk of bias		

Massey 1974 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B-Unclear

Sääv 2007

Methods	<p>Location: Stockholm, Sweden</p> <p>Recruitment: September 2004 to July 2006</p> <p>Randomization sequence: Computer-generated number table by study nurse not directly involved in study</p> <p>Allocation concealment: Sealed opaque envelopes numbered and used consecutively</p> <p>Blinding: Investigators, but not participants, were unaware of the assignment; nurse administered study medication</p> <p>Sample size calculation: based on other published research</p>
Participants	<p>N: 80 women</p> <p>Source: Karolinska University Hospital</p> <p>Inclusion criteria: nulliparous, general good health, age 18 years and older</p> <p>Exclusion criteria: signs of genital infection, contraindication to misoprostol, positive pregnancy test</p>
Interventions	Sublingual misoprostol 400 µg and diclofenac 100 mg versus diclofenac 100 mg alone 1 hour before insertion
Outcomes	<p>Primary: degree of difficulty of insertion rated by provider (easy, moderate, difficult)</p> <p>Secondary: baseline cervical dilation, pain score with IUD insertion (10 cm visual analog scale), general experience of the insertion rated by woman (very unpleasant, unpleasant, or 'very little unpleasant'), side effects (shivering, diarrhea, nausea, vomiting), pain and bleeding after insertion up to 1 month.</p>
Notes	<p>Losses to follow up: 2 participants in the diclofenac-only arm had failed insertions but were included in the analysis. One participant in the misoprostol arm withdrew consent prior to insertion and was not analyzed. One participant in the misoprostol arm was lost follow up after insertion and 1 month data were not analyzed.</p> <p>Protocol violations: 2 women in the misoprostol group and 3 women in the diclofenac-only group received 2 tablets of acetaminophen/codeine (strength not reported) instead of diclofenac due to a history of asthma.</p> <p>IUD used: Nova-T</p>

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A-Adequate

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

Goldstuck 1983	Examined pain in the first 7 days after IUD insertion, not during or after IUD insertion up to 6 hours
Goldstuck 1987	Review article
Hepburn 1980	Not a randomized controlled trial
Hollingworth 1995	Review article
Kurz 1983	Not a randomized controlled trial
Newton 1977	Not a randomized controlled trial
Olot 1996	Randomized by birthdates
Thiery 1985	Not a randomized controlled trial

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

Bednarek 2008

Trial name or title	Prophylactic ibuprofen 800 mg for pain control with IUD insertion
Methods	Double-blind randomized controlled trial
Participants	266 women
Interventions	Ibuprofen 800 mg versus placebo 30 to 45 minutes before insertion
Outcomes	Pain during IUD insertion
Starting date	May 2007
Contact information	NCT00562276
Notes	

Edelman 2008

Trial name or title	Effect of prophylactic buccal misoprostol prior to IUD insertion
Methods	Double blind randomized controlled trial ⁴
Participants	40 nulliparous women
Interventions	Buccal misoprostol 400 µg versus placebo 90 minutes before insertion
Outcomes	Ease of insertion, IUD expulsion, pain during IUD insertion
Starting date	June 2007
Contact information	NCT00613366
Notes	

Helmerhorst 2008

Trial name or title	Vaginal misoprostol prior to insertion of an intrauterine device
Methods	Double blind randomized controlled trial
Participants	280 women
Interventions	Vaginal misoprostol 400 mcg versus placebo 3 hours before insertion
Outcomes	Failed insertions, insertion-related complications, pain during insertion.

Helmerhorst 2008 (Continued)

Starting date	May 2007
Contact information	Frans M. Helmerhorst, F.M.Helmerhorst@lumc.nl
Notes	

DATA AND ANALYSES

Comparison 1. Naproxen 300 mg plus paracervical block versus placebo plus paracervical block

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean pain score during IUD insertion	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.72, 0.56]
2 Mean pain score 1 hour after IUD insertion	1	50	Mean Difference (IV, Fixed, 95% CI)	-1.04 [-1.67, -0.41]
3 Mean pain score 2 hours after IUD insertion	1	41	Mean Difference (IV, Fixed, 95% CI)	-0.98 [-1.64, -0.32]
4 Mean pain score 3 hours after IUD insertion	1	35	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-1.14, 0.08]
5 Mean pain score 4 hours after IUD insertion	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.98, 0.28]
6 Mean pain score 5 hours after IUD insertion	1	33	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.69, 0.63]
7 Mean pain score 6 hours after IUD insertion	1	31	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.56, 0.64]

Comparison 2. Ibuprofen 600 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients reporting moderate to severe pain during IUD insertion (3 or greater on the 1 to 10 scale)	1	55	Odds Ratio (Peto, Fixed, 95% CI)	2.0 [0.67, 5.95]
2 Median pain score 4-6 hours after IUD insertion			Other data	No numeric data

Comparison 3. Ibuprofen 400 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean pain score during IUD insertion	1	2018	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.39, -0.01]

Comparison 4. Misoprostol 400 µg and diclofenac 100 mg versus diclofenac 100 mg alone

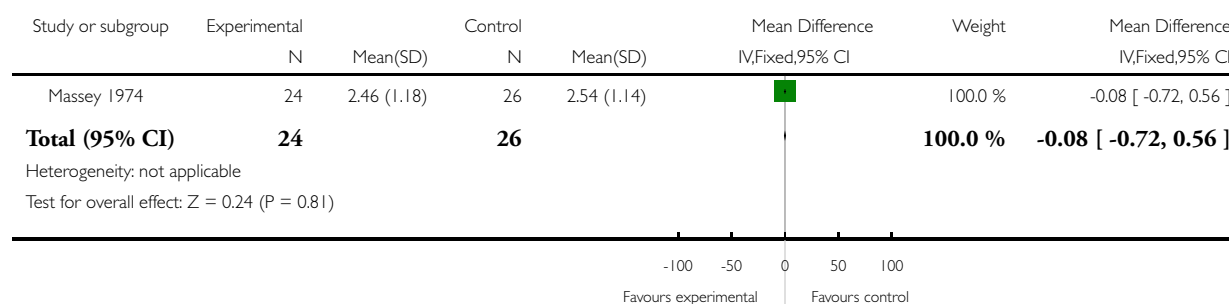
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients rating insertion experience as very unpleasant or unpleasant	1	79	Odds Ratio (Peto, Fixed, 95% CI)	2.19 [0.60, 7.97]
2 Number of patients with any side effect	1	79	Odds Ratio (Peto, Fixed, 95% CI)	1.76 [0.72, 4.29]

Analysis 1.1. Comparison 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, Outcome 1 Mean pain score during IUD insertion.

Review: Interventions for pain with intrauterine device insertion

Comparison: 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block

Outcome: 1 Mean pain score during IUD insertion



Analysis 1.2. Comparison 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, Outcome 2 Mean pain score 1 hour after IUD insertion.

Review: Interventions for pain with intrauterine device insertion

Comparison: 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block

Outcome: 2 Mean pain score 1 hour after IUD insertion

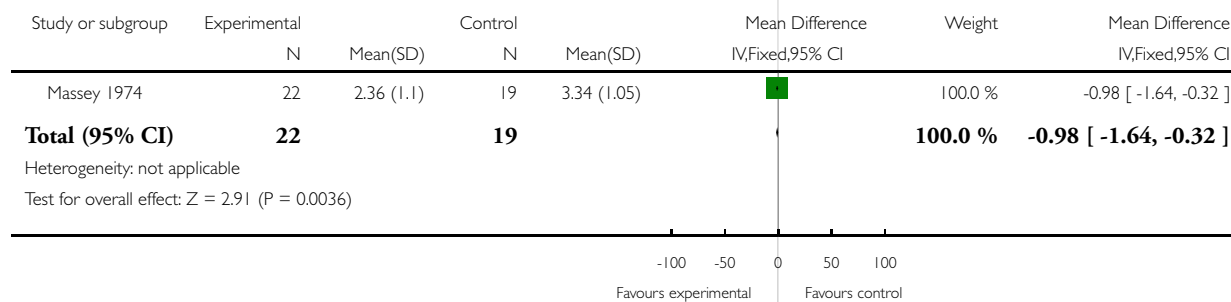


Analysis 1.3. Comparison 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, Outcome 3 Mean pain score 2 hours after IUD insertion.

Review: Interventions for pain with intrauterine device insertion

Comparison: 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block

Outcome: 3 Mean pain score 2 hours after IUD insertion

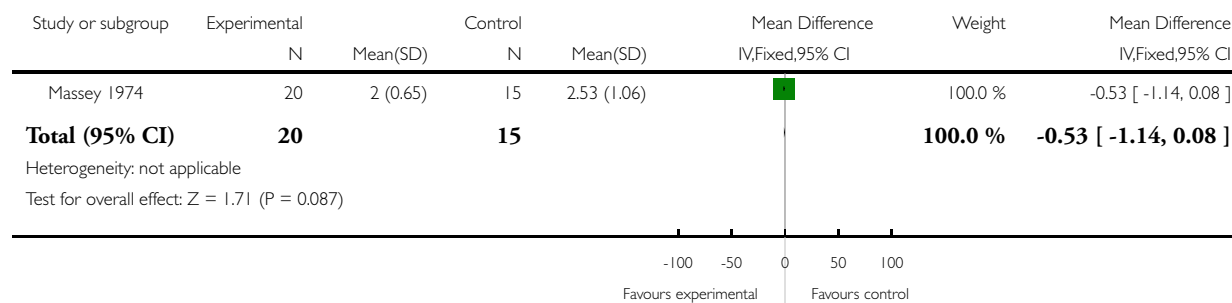


Analysis 1.4. Comparison 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, Outcome 4 Mean pain score 3 hours after IUD insertion.

Review: Interventions for pain with intrauterine device insertion

Comparison: 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block

Outcome: 4 Mean pain score 3 hours after IUD insertion

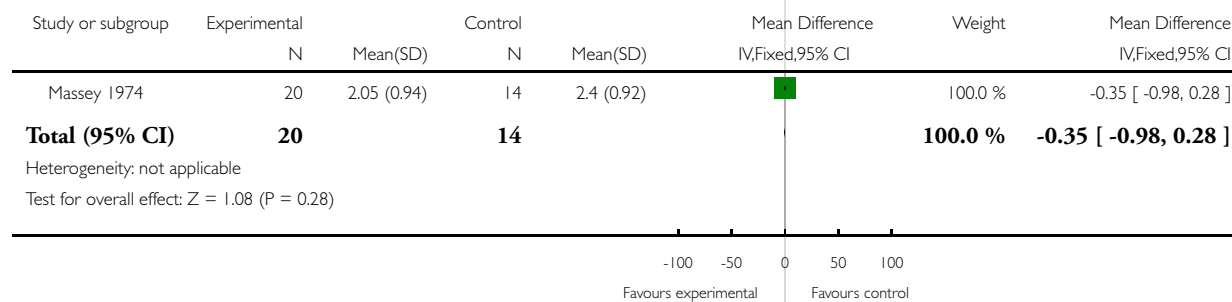


Analysis 1.5. Comparison 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, Outcome 5 Mean pain score 4 hours after IUD insertion.

Review: Interventions for pain with intrauterine device insertion

Comparison: 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block

Outcome: 5 Mean pain score 4 hours after IUD insertion

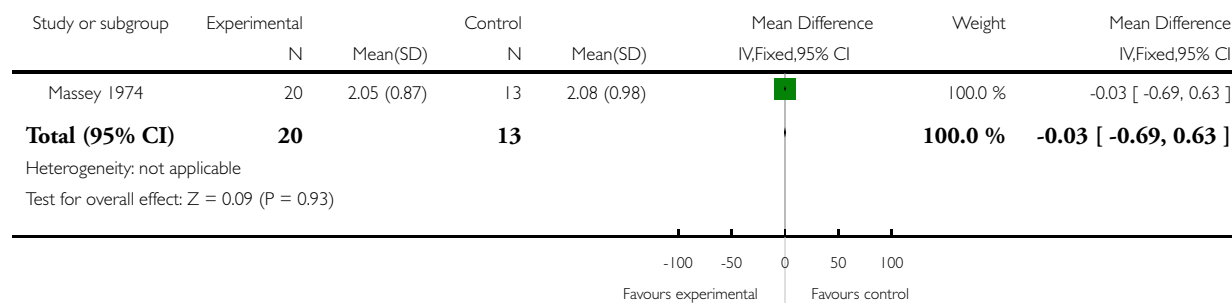


Analysis 1.6. Comparison 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, Outcome 6 Mean pain score 5 hours after IUD insertion.

Review: Interventions for pain with intrauterine device insertion

Comparison: 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block

Outcome: 6 Mean pain score 5 hours after IUD insertion

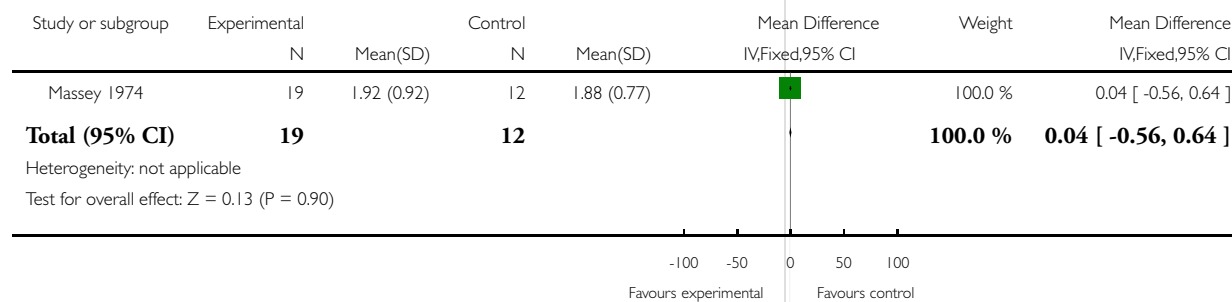


Analysis 1.7. Comparison 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block, Outcome 7 Mean pain score 6 hours after IUD insertion.

Review: Interventions for pain with intrauterine device insertion

Comparison: 1 Naproxen 300 mg plus paracervical block versus placebo plus paracervical block

Outcome: 7 Mean pain score 6 hours after IUD insertion

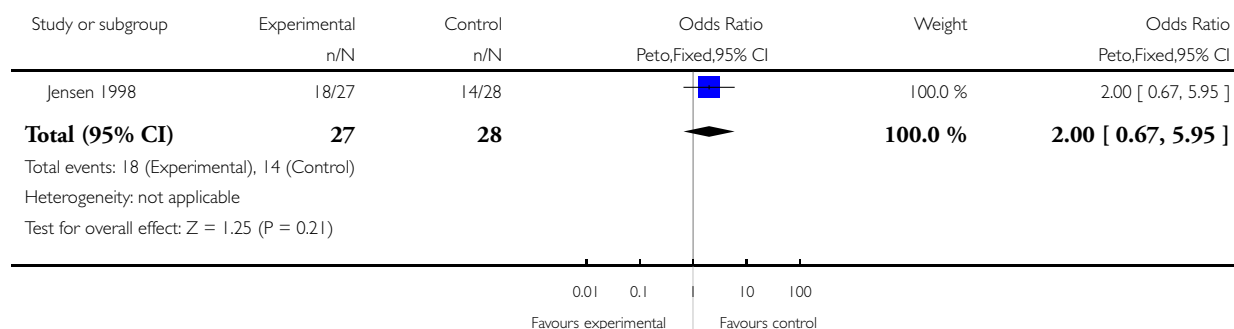


Analysis 2.1. Comparison 2 Ibuprofen 600 mg versus placebo, Outcome 1 Number of patients reporting moderate to severe pain during IUD insertion (3 or greater on the 1 to 10 scale).

Review: Interventions for pain with intrauterine device insertion

Comparison: 2 Ibuprofen 600 mg versus placebo

Outcome: 1 Number of patients reporting moderate to severe pain during IUD insertion (3 or greater on the 1 to 10 scale)



Analysis 2.2. Comparison 2 Ibuprofen 600 mg versus placebo, Outcome 2 Median pain score 4-6 hours after IUD insertion.

Median pain score 4-6 hours after IUD insertion

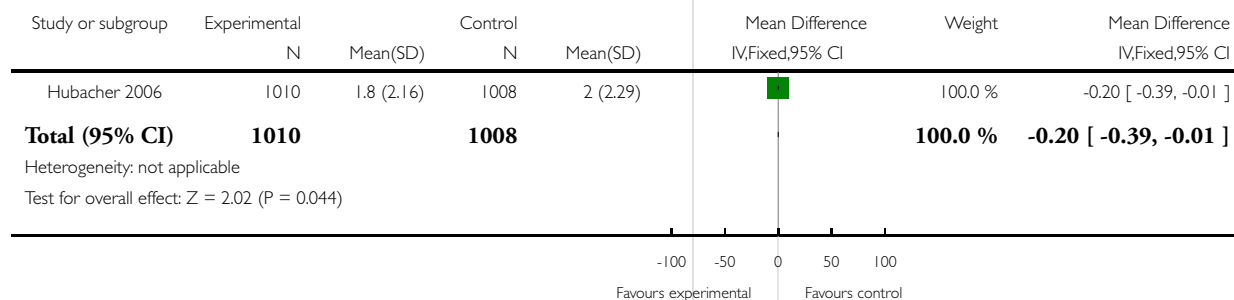
Jensen 1998	1.7	1.8
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Analysis 3.1. Comparison 3 Ibuprofen 400 mg versus placebo, Outcome 1 Mean pain score during IUD insertion.

Review: Interventions for pain with intrauterine device insertion

Comparison: 3 Ibuprofen 400 mg versus placebo

Outcome: 1 Mean pain score during IUD insertion

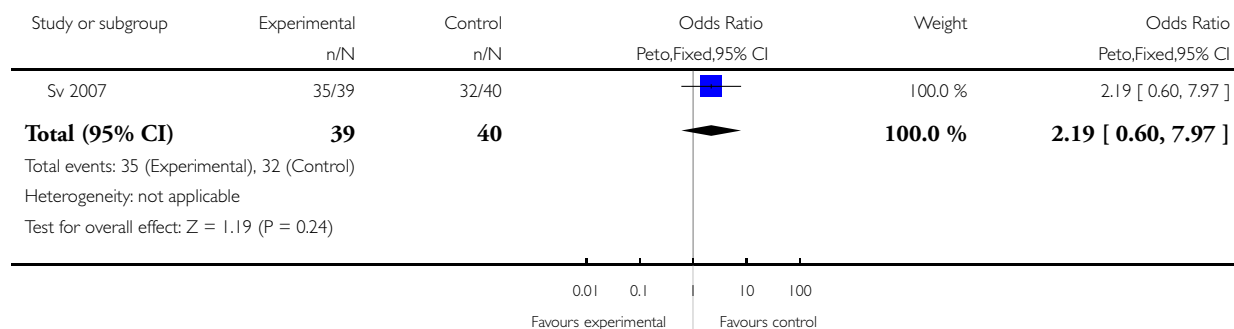


Analysis 4.1. Comparison 4 Misoprostol 400 µg and diclofenac 100 mg versus diclofenac 100 mg alone, Outcome 1 Number of patients rating insertion experience as very unpleasant or unpleasant.

Review: Interventions for pain with intrauterine device insertion

Comparison: 4 Misoprostol 400 g and diclofenac 100 mg versus diclofenac 100 mg alone

Outcome: 1 Number of patients rating insertion experience as very unpleasant or unpleasant

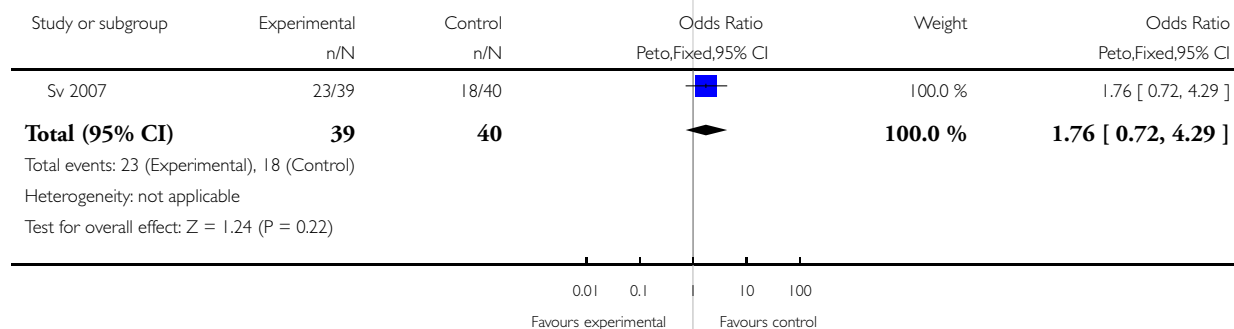


Analysis 4.2. Comparison 4 Misoprostol 400 µg and diclofenac 100 mg versus diclofenac 100 mg alone, Outcome 2 Number of patients with any side effect.

Review: Interventions for pain with intrauterine device insertion

Comparison: 4 Misoprostol 400 g and diclofenac 100 mg versus diclofenac 100 mg alone

Outcome: 2 Number of patients with any side effect



HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 3, 2009

12 December 2007	New citation required and major changes	Substantive amendment
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CONTRIBUTIONS OF AUTHORS

Rebecca Allen and Deborah Bartz developed the protocol, abstracted the data, and drafted the review.

David Grimes, David Hubacher and Paul O'Brien provided editorial assistance.

DECLARATIONS OF INTEREST

Dr. Allen has served as a speaker and clinical trainer for Organon, part of Schering-Plough.

Dr. Bartz has served as a clinical trainer for Organon, part of Schering-Plough.

Dr. Grimes has served as a consultant for or on the speakers' bureau of Duramed, Bayer, and Schering-Plough, which distribute IUDs.

Dr. Hubacher has received research funds from Duramed and authored one of the trials included in this review.

Dr. O'Brien has no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institutes of Child Health and Human Development, USA.
- US Agency for International Development, USA.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [therapeutic use]; Ibuprofen [therapeutic use]; Intrauterine Devices [*adverse effects]; Miso-prostol [therapeutic use]; Naproxen [therapeutic use]; Oxytocics [therapeutic use]; Pain [*drug therapy; prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans