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Original article

Intrauterine mepivacaine instillation for pain relief during intrauterine device insertion in nulliparous women: a double-blind, randomized, controlled trial☆,☆☆,★

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ABSTRACT

Objective: To evaluate whether intrauterine mepivacaine instillation before intrauterine device (IUD) insertion decreases pain compared to placebo.
Study design: We performed a double-blind, randomized, controlled trial comparing mepivacaine 1% 10 mL versus 0.9% NaCl intrauterine instillation using a hydrosonography catheter 5 min before IUD insertion in women 18 years of age or older. Participants completed a series of 10-cm visual analogue scales (VAS) to report pain during the procedure. The primary outcome was the difference in VAS scores with IUD insertion between intervention group and placebo. Secondary outcomes included VAS before and after insertion and analgesia method acceptability.
Results: We randomized 86 women in a 1:1 ratio; both groups had similar baseline characteristics. In the intention-to-treat analysis, the primary outcome, median VAS with IUD insertion, was 4.8 cm in the intervention group [n=41, interquartile range (IQR) =3.1–5.8] and 5.9 cm in the placebo group (n=40, IQR=3.3–7.5, p=.062). In the per-protocol analysis, the median VAS with IUD insertion was 4.8 cm (IQR=3.1–5.5) and 6.0 cm (IQR=3.4–7.6) for the intervention and placebo groups, respectively (p=.033). More women in the intervention group reported the procedure as easier than expected (n=26, 63.4% vs. n=15, 37.5%), and fewer reported it as worse than expected (n=3, 7.3% vs. n=14, 35%, p=.006).
Conclusion: Intrauterine mepivacaine instillation before IUD insertion modestly reduces pain, but the effect size may be clinically significant.
Implications statement: While the reduction in VAS pain scores did not meet our a priori difference of 1.3 points for clinical significance, participants' favorable subjective reaction suggests that this approach merits further study.
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1. Introduction

Underutilization or user errors are common reasons for unintended pregnancy when contraception can be easily accessed. Long-acting reversible contraceptive methods (LARCs), such as subdermal implants and intrauterine devices (IUDs), result in significantly lower rates of unintended pregnancies partly due to less user error, especially among young users [1,2]. However, the worldwide use of IUDs is estimated to be merely 14% [3].

Among barriers to using IUDs, fear of pain at insertion is commonly stated [4,5]. Though many methods for pain relief during IUD insertion have been studied, few methods apart from paracervical block (PCB) have proven to reduce pain effectively [6–8]. Access to safe PCB is limited since not all inserters are trained, and when it is not available, women cannot be provided with effective pain relief and might choose another method for contraception. Thus, more effective treatments for pain at IUD insertion may increase use of IUDs and reduce the number of unintended pregnancies in all settings.

Lidocaine has been evaluated using intrauterine instillation prior to gynecological procedures and IUD insertion [9–11]. For pain relief at IUD insertion, intrauterine infusion of lidocaine 2% 1.2 mL did not

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significantly decrease pain scores [11]. Compared to lidocaine, mepivacaine 1% has a more rapid onset and less potential toxicity [12]. We hypothesize that intrauterine mepivacaine instillation will numb the uterine and cervical lining and reduce pain with IUD insertion.

2. Material and methods

We performed a double-blind, randomized, controlled trial at a youth clinic (center 1) and a contraceptive counseling clinic (center 2), both in Stockholm County, Sweden. A single study investigator, well-experienced with IUD placement, performed all IUD insertions at each site. This trial was approved by the Swedish Medical Product Agency.

We included nulliparous women 18 years or older desiring any type of IUD for contraception. We excluded women with previous conization, known cervical stenosis, signs of ongoing genital infection, known uterine abnormality, bleeding disorder or any local anesthetic contraindication. The investigator screened and enrolled study participants at a contraceptive counseling visit or at the appointment for IUD insertion. Eligible patients received both oral and written information before the participant signed an informed consent form.

We collected participants' demographic characteristics and previous contraception. We randomly assigned women to intervention or control group by consecutive opening of opaque sealed envelopes containing the allocation code unique to each study site. We used a 1:1 allocation ratio of intervention (mepivacaine 1% 10 mL) to placebo (NaCl 09% 10 mL). The envelopes were prepared by a study coordinator not involved in any other participant-related work according to a computer-generated randomization list with random permuted blocks of 6 to 10 from www.randomization.com. A nurse midwife or nurse assistant nonmember of the research team opened the envelopes without the presence of the participant or study investigator, prepared the mepivacaine or placebo, and delivered an unmarked syringe to the

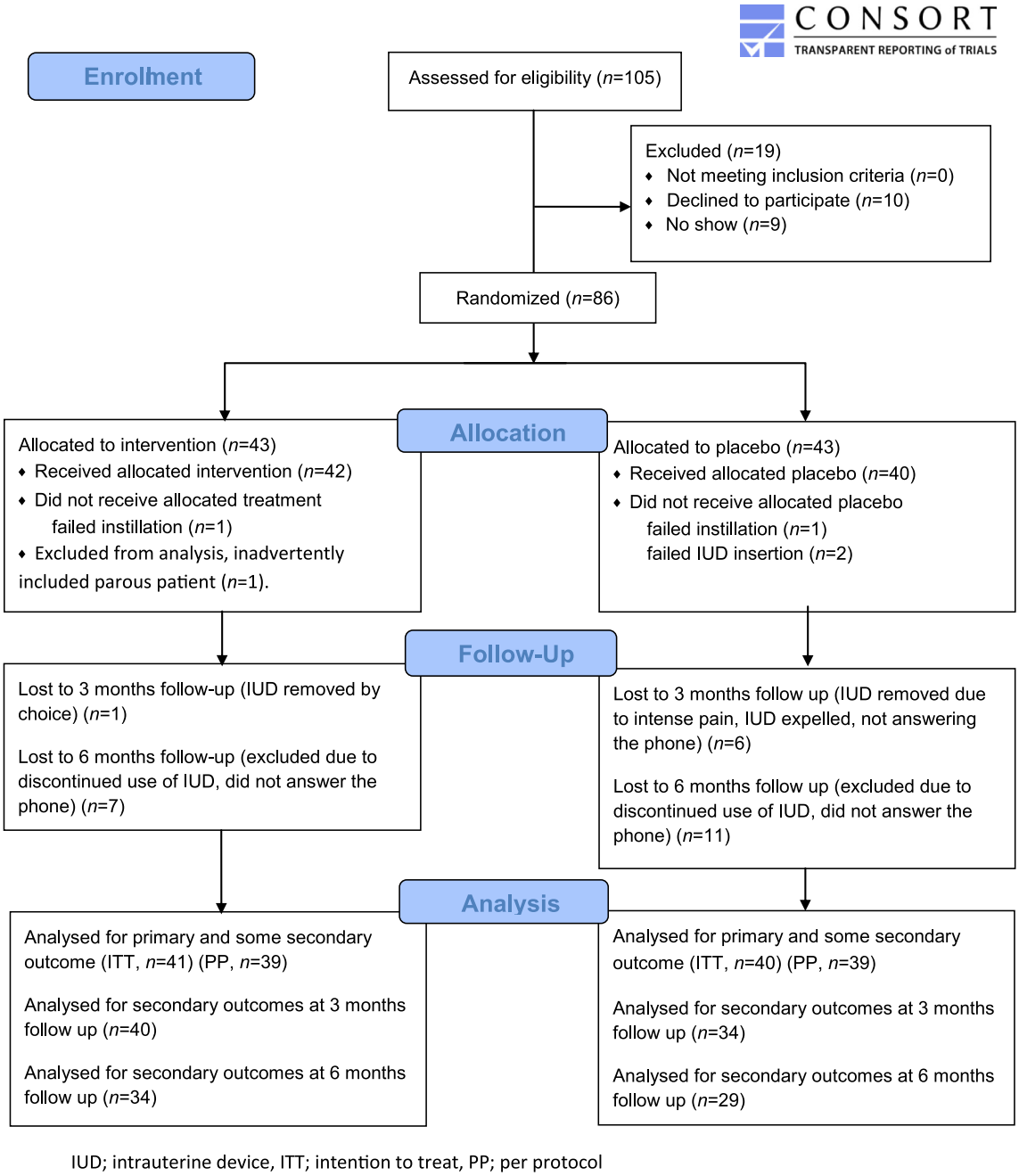

Fig. 1. Consort flow diagram of the study participants randomized to intrauterine mepivacaine instillation or placebo before IUD insertion. ITT, intention to treat; PP, per protocol.

study investigator. Both mepivacaine and the placebo (normal saline) are odorless and clear, minimizing the risk of unblinding during intrauterine instillation. Blinded research personnel outside the clinics performed the follow-up. All data remained blinded until data analysis.

We inserted all IUDs according to a standardized protocol, with use of speculum, tenaculum placement and sounding prior to IUD insertion. Participants chose their IUD which included one of four types: three levonorgestrel (LNG) intrauterine system (IUS) products containing 52 mg (Mirena®), 19.5 mg (Kyleena®) or 13.5 mg (Jaydess ®) and one copper IUD (Nova-T 380®, all produced by Bayer AG, Leverkusen, Germany). The inserter diameters are 4.4 mm, 3.8 mm, 3.8 mm and 3.6 mm, respectively.

We used a paper-printed 10-cm visual analog scale (VAS) for all pain assessments, marked with *no pain* at the 0-cm anchor point and *worst pain imaginable* at the 10-cm anchor point. Before starting the insertion routine, we collected VAS scores for usual period cramping and current baseline pain. We inserted the speculum, and the participant received the assigned study treatment instillation with a sterile hydrosonography catheter (Probimed, Neuilly-en-Thelle, France). This catheter is thin (1.6 mm) and flexible without a balloon tip. After instillation, we waited 5 min before tenaculum placement with the speculum in place. The investigator then performed IUD insertion according to the standardized protocol. During the procedure, participants completed five VAS measures: first immediately after intrauterine instillation, tenaculum placement, sounding and IUD insertion, as well as at the time of leaving the clinic which women generally did within 10 min after the insertion. In addition, participants assessed acceptability of the method (receiving intrauterine instillation and waiting 5 min in lithotomy position) by willingness to recommend the pain relief method to a friend. Participants also assessed the insertion procedure (including all insertion procedure steps) as easier than expected, as expected or worse than expected. We contacted participants by phone at 3 and 6 months after insertion to assess IUD continuation. We used the difference in VAS score between intervention and placebo at the time of IUD insertion as the primary outcome measure.

We estimated sample size based on a previous study assessing insertion pain after pretreatment with misoprostol in which the control group (no intervention) had a mean pain score of 6.5±1.8 on a 10-cm VAS with IUD insertion [13]. We hypothesized a 20% decrease in VAS pain score in our intervention group, equivalent to an absolute decrease of 1.3 cm, consistent with previous studies on clinically relevant reduction of VAS for acute pain [14,15]. To demonstrate this difference with a power of 90% at a significance level (alpha) of 0.05, each group needed 38 participants. To account for an expected loss to follow-up of 10% to 15%, we aimed to enroll 86 participants.

We used IBM® SPSS Statistics version 24.0 for the intention-to-treat analysis. Three women were inadvertently included although not being 18 years or above (two were 15 years old and one was 16 years old). We performed an additional per-protocol analysis for the primary outcome in which these participants were excluded. We compared skewed variables using a Mann–Whitney *U* test and categorical variables using χ^2 test.

3. Results

We enrolled participants from November 2013 to May 2017, with the last follow-up contact in November 2017. We assessed 105 patients for eligibility of which 86 (82%) enrolled. A total of 81 and 78 women were included in the intention-to-treat and per-protocol analysis, respectively (Fig. 1). Participant characteristics for the 41 women in the intervention group and 40 in the placebo group are detailed in Table 1. Center 1 recruited 50 participants, whereas center 2 recruited 31, with small difference in allocation proportions between centers (p=.65).

Baseline pain was low and did not differ between allocation groups (Table 2). In the intention-to-treat analysis, IUD insertion pain score was 1.1 cm smaller in the intervention group [4.8, interquartile range (IQR)=3.1–5.8] versus the placebo group (5.9, IQR=3.2–7.5, p=.062). Among pain scores for all procedure steps, the difference with sounding reached 1.5 cm between the groups (p=.048, Table 2 and Fig. 2). More women in the intervention group reported the procedure as easier than expected (*n*=26, 63.4% vs. *n*=15, 37.5%), and fewer women reported it as worse than expected (*n*=3, 7.3% vs. *n*=14, 35%) (χ^2 test, 2×3 contingency table, p=.006, Table 2). In the per-protocol analysis, the pain score with IUD insertion was 4.8 (IQR=3.1–5.5) in the mepivacaine group compared to 6.0 (IQR 3.4–7.6) in the placebo group (p=.033).

We found only small differences at the follow-up contacts between the intervention and the placebo group in acceptability of the pain relief method, continued use of IUD, opting for another IUD in the future and recommendation of IUD to a friend (Table 3). Overall, 75 (92.6%) study participants reported that they would recommend the intrauterine instillation for pain relief to a friend.

Table 1
The baseline characteristics and type of IUD of study participants by analgesia used before IUD insertion

	Mepivacaine (*n*=41)		Placebo (*n*=40)		p[a]
	Median	IQR	Median	IQR	
Age (years)	22	19.5–25.5	22	20–25.8	.835
Usual period cramping (VAS)	4	2.4–6.1	3.2	2–6.5	.674
Previous medical abortion	6 (14.6)		5 (12.5)		1
Previous surgical abortion	1 (2.4)		3 (7.5)		.36
Previous IUD insertion	7 (17.1)		6 (15)		1
Type of inserted IUD					
LNG-IUS 52 mg	20 (48.8)		18 (45)		.82
Copper-IUD	12 (29.3)		11 (27.5)		.29
LNG-IUS 13.5 mg	3 (7.3)		14 (35)		.62
LNG-IUS 19.5 mg	1 (2.4)		0 (0)		1

All data are presented as median, interquartile range and *n* (%).
[a] Two-group comparison using independent-sample *t* test and Mann–Whitney *U* test where appropriate.

4. Discussion

In this double-blind, randomized, placebo-controlled trial, we find that intrauterine mepivacaine instillation reduced the IUD insertion pain by 1.1 cm, which was less than our hypothesized effect size. In the per-protocol analysis, including only women 18 years or older, the 1.2-cm difference in the pain scores was statistically significant but still less than our hypothesized effect size of 1.3 cm. The groups were highly different in stating that the procedure was worse than expected, as expected or easier than expected.

Table 2
The primary and secondary outcomes during and after IUD insertion by analgesia used before the procedure

	Mepivacaine (*n*=41)		Placebo (*n*=40)		p[a]
	Median	IQR	Median	IQR	
VAS					
Baseline pain	0	0–0.2	0	0–.1	.734
Instillation of study drug or placebo	1.4	0.8–2.9	2.15	.3–3.5	.319
Tenaculum	2.2	0.9–3.4	2.4	.3–4.5	.487
Sounding	3.4	1.7–5.9	4.9	2.6–6.6	.048
IUD insertion	4.8	3.1–5.8	5.9	3.3–7.5	.062
Before leaving the clinic	1.3	0.5–2.5	1.3	.6–3.7	.545
Overall experience of IUD insertion					
Easier than expected	26 (63.4)		15 (37.5)		.006[b]
As expected	12 (29.3)		11 (27.5)		
Worse than expected	3 (7.3)		14 (35)		

All data are presented as median, interquartile range and *n* (%).
[a] Two-group comparison using Mann–Whitney *U* test.
[b] χ^2 test.

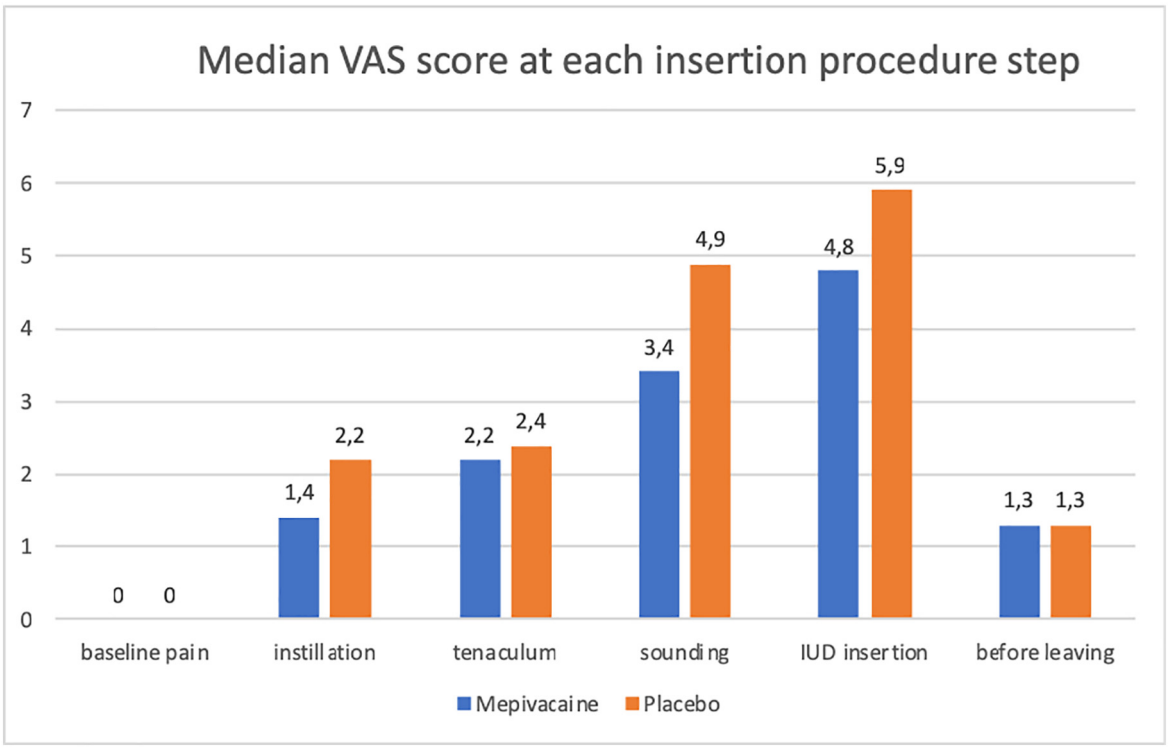

Fig. 2. The median VAS score of study participants at each different IUD insertion procedure step by analgesia used before the procedure. The use of mepivacaine did reach statistical significance (p=.048) in pain reduction at sounding but not for any other procedure step compared to placebo.

There were two outliers among the women below 18, one in the intervention group (VAS 9.3) and one in the placebo group (VAS 0.1). Their pain scores affected the median VAS in the placebo group as well as the variance in both groups, resulting in a nonsignificant difference between groups in the intention-to-treat analysis.

Sounding before IUD insertion is well known to cause discomfort and pain. We found a significant difference in the pain scores at sounding between intervention and placebo. Since pain from all procedures steps could add up and affect the experience of the insertion, this finding is relevant. However, this secondary outcome is not as relevant as the insertion pain score since sounding may be omitted in IUD insertion protocols [16].

The clinically significant pain reduction cutoff for insertion of IUD has not been established. Pain from IUD insertion is a lower pelvic pain, similarly to endometriosis-associated pain for which a reduction of 1.0 cm has been reported as the minimal clinically important difference for ongoing pain treatment [17]. However, pain from IUD insertion could be considered acute, a type of pain for which 1.3 cm has been presented as clinically relevant pain reduction when assessed in emergency departments [14,15]. Although our results only showed a difference of 1.1 cm, the intervention may have contributed to fewer participants perceiving the insertion procedure as worse than expected.

Table 3
The secondary outcomes at end of visit and at follow-up by analgesia used before IUD insertion

	Mepivacaine	Placebo	p[a]
Before leaving (*n*=81)			
Would recommend the method for pain relief	39 (95.1)	36 (90)	.43
Would choose IUD for contraception again	39 (95.1)	37 (92.5)	.68
Would recommend IUD to a friend	40 (97.6)	38 (95)	.62
7–10 days (*n*=78)			
Would choose IUD for contraception again	37 (92.5)	36 (94.7)	1.00
Would recommend IUD to a friend	37 (92.5)	37 (97.4)	.62
3 months (*n*=74)			
Are still using IUD	38 (95)	32 (94.1)	1.00
Would choose IUD for contraception again	34 (87.2)	29 (87.9)	1.00
Would recommend IUD to a friend	35 (89.7)	32 (97)	.37
6 months (*n*=63)			
Are still using IUD	31 (91.2)	28 (96.6)	.62
Would choose IUD for contraception again	29 (93.5)	28 (96.6)	1.0
Would recommend IUD to a friend	29 (93.5)	29 (100)	.49

All data are presented as *n* (%).
[a] Two-group comparison using Fisher's Exact Test.

Since this study was initiated, other studies on intrauterine instillation of a local anesthetic prior to IUD insertion have been reported. In the first trial, investigators infused lidocaine 2% 1.2 mL using an endometrial aspirator and demonstrated a difference of 0.7 cm in pain scores compared to placebo (3.0 vs. 3.7, p=.4). That study included both nulliparous and parous women, and women rated pain on a numerical rating scale from 0 to 9 [11]. The 1.2-mL volume and the potency of the lidocaine might not have been sufficient to have a clinical and statistically significant effect. We used a larger volume, 10 mL, but still did not identify a clinical or statistically significant effect. In a second trial, investigators used a new formula of lidocaine 4% gel in different volumes in three locations: around the outer cervical os, into the cervical canal and into the uterine cavity. They assessed a primary outcome of the worst pain score (using a VAS) during a 10-min period after insertion. They found a difference of 1.6 in mean VAS score for their intervention compared to placebo (2.8 vs. 4.4, p<.0001) [18]. That study also included both nulliparous and parous women which may explain the overall lower pain score. To recall worst pain within a 10-min period might introduce some bias that may have resulted in the lower pain scores in both intervention and placebo group compared to other studies on IUD insertion. Our study participants held a paper-printed VAS in front of them during the procedure and marked their VAS score immediately after each of the insertion procedure steps, which may yield more accurate measures.

One could argue that an acceptable pain relief method must not give more discomfort than the actual insertion procedure. Hence, method acceptability is an important study finding. In the topical gel study, approximately 36% and 52% of study participants receiving lidocaine

or placebo, respectively, reported the administration of the gel resulted in "strong" or "very strong" discomfort [18]. In comparison, a study on insertion of all LNG-IUS types in nulliparous women reported that only 33% of women experienced moderate or severe pain during insertion without the use of any pain relief [19]. Several studies have shown that nulliparous women tolerate insertion of intrauterine contraception well [19–21]. However, it would be valuable to find a method that is easy for clinics to provide and well accepted by the receiver. The method we used had high acceptability, with close to 93% of participants stating that they would recommend the method for pain relief to a friend.

The double-blinded randomized study design is the main strength of this study. We followed a standardized and identical insertion procedure for all patients. We used VAS score as a measure of pain, which is a validated standard instrument used for research on pain management. We also collected the VAS scores immediately after the five different insertion procedure steps. One nurse-midwife at each clinic performed all insertions, which also limits effects of interprovider variability. However, this caused slow patient enrollment as nurse-midwives often work alone with staff not trained to handle medications.

Compared to placebo, intrauterine mepivacaine instillation reduced pain with IUD insertion by 1.1 or 1.2 cm on the VAS scale, which was just less than our difference of 1.3 cm that we had specified as our outcome of interest a priori. Fewer participants in the intervention arm, however, experienced the insertion as worse than expected compared to placebo group participants. A larger sample size study could be of future interest, with the total experience of the insertion as the primary outcome, using 2% mepivacaine and a refined instillation technique that could significantly affect the pain perception.

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References

[1] Trussell J. Contraceptive failure in the United States. Contraception 2011;83:397–404.
[2] Winner B, Peipert JF, Zhao Q, Buckel C, Madden T, Allsworth JE, et al. Effectiveness of long-acting reversible contraception. N Engl J Med 2012;366:1998–2007.
[3] United Nations DoEaSA, Population Division. Trends in contraceptive use worldwide 2015; 2015.
[4] Asker C, Stokes-Lampard H, Beavan J, Wilson S. What is it about intrauterine devices that women find unacceptable? Factors that make women non-users: a qualitative study. J Fam Plann Reprod Health Care 2006;32:89–94.
[5] Envall N, Groes Kofoed N, Kopp-Kallner H. Use of effective contraception 6 months after emergency contraception with a copper intrauterine device or ulipristal acetate — a prospective observational cohort study. Acta Obstet Gynecol Scand 2016;95:887–93.
[6] Lopez LM, Bernholc A, Zeng YW, et al. Interventions for pain with intrauterine device insertion. Cochrane Database Syst Rev 2015(126).
[7] Zapata LB, Jatlaoui TC, Marchbanks PA, Curtis KM. Medications to ease intrauterine device insertion: a systematic review. Contraception 2016;94:739–59.
[8] Akers AY, Steinway C, Sonalkar S, Perriera LK, Schreiber C, Harding J, et al. Reducing pain during intrauterine device insertion: a randomized controlled trial in adolescents and young women. Obstet Gynecol 2017;130:795–802.
[9] Edelman A, Nichols MD, Leclair C, Jensen JT. Four percent intrauterine lidocaine infusion for pain management in first-trimester abortions. Obstet Gynecol 2006;107:269–75.
[10] Isley MM, Jensen JT, Nichols MD, Lehman A, Bednarek P, Edelman A. Intrauterine lidocaine infusion for pain management during outpatient transcervical tubal sterilization: a randomized controlled trial. Contraception 2012;85:275–81.
[11] Nelson AL, Fong JK. Intrauterine infusion of lidocaine does not reduce pain scores during IUD insertion. Contraception 2013;88:37–40.
[12] Kasaba T, Onizuka S, Takasaki M. Procaine and mepivacaine have less toxicity in vitro than other clinically used local anesthetics. Anesth Analg 2003;97:85–90 [table of contents].
[13] Saav I, Aronsson A, Marions L, Stephansson O, Gemzell-Danielsson K. Cervical priming with sublingual misoprostol prior to insertion of an intrauterine device in nulliparous women: a randomized controlled trial. Hum Reprod 2007;22:2647–52.
[14] Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med 1996;27:485–9.
[15] Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med 2001;38:633–8.
[16] Christenson K, Lerma K, Shaw KA, Blumenthal PD. Assessment of a simplified insertion technique for intrauterine devices. Int J Gynaecol Obstet 2016;134:29–32.
[17] Gerlinger C, Schumacher U, Faustmann T, Colligs A, Schmitz H, Seitz C. Defining a minimal clinically important difference for endometriosis-associated pelvic pain measured on a visual analog scale: analyses of two placebo-controlled, randomized trials. Health Qual Life Outcomes 2010;8:138.
[18] Tornblom-Paulander S, Tingaker BK, Werner A, Liliecreutz C, Conner P, Wessel H, et al. Novel topical formulation of lidocaine provides significant pain relief for intrauterine device insertion: pharmacokinetic evaluation and randomized placebo-controlled trial. Fertil Steril 2015;103:422–7.
[19] Gemzell-Danielsson K, Schellschmidt I, Apter D. A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena. Fertil Steril 2012;97:616–22 [e1-3].
[20] Suhonen S, Haukkamaa M, Jakobsson T, Rauramo I. Clinical performance of a levonorgestrel-releasing intrauterine system and oral contraceptives in young nulliparous women: a comparative study. Contraception 2004;69:407–12.
[21] Marions L, Lovkvist L, Taube A, Johansson M, Dalvik H, Overlie I. Use of the levonorgestrel releasing-intrauterine system in nulliparous women — a non-interventional study in Sweden. Eur J Contracept Reprod Health Care 2011;16:126–34.