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Original Article

Inserting intrauterine devices in nulliparous women: is misoprostol beneficial? A registered clinical trial

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Abstract: Background: To determine if misoprostol use prior to intrauterine device (IUD) insertion decreases pain and eases insertion in nulliparous women. Study Design: Nulliparous women requesting IUDs for contraception were randomized to 400 micrograms of misoprostol or placebo prior to IUD insertion. The primary outcome was pain at the time of insertion using a 100 mm visual analog scale. Additional outcomes included medication side effects, patient satisfaction, and provider rated ease of insertion. Results: The 2 groups were similar, with 31 subjects in the placebo group and 30 receiving misoprostol. There was no difference in baseline pain, and no difference in pain immediately after IUD insertion (57.2 ± 22.5 mm for placebo, 56.7 ± 22.1 mm for misoprostol, P=0.92). Patients receiving misoprostol experienced more cramps (16.7% placebo, 60% misoprostol, P=0.002) and fevers and chills, though this did not reach significance (7% placebo, 27% misoprostol, P=0.081). Providers reported easier insertions following misoprostol (24.1 ± 14.2 mm misoprostol vs 33.4 ± 20.3 mm placebo, P=0.04). All patients had successful IUD placement and none had complications. Overall satisfaction with the IUDs was high, with 84% of the women in the placebo group and 77% of women in the misoprostol group reporting they were satisfied or very satisfied (P=0.94). Conclusions: Routine use of misoprostol prior to intrauterine device insertion is not warranted in nulliparous women.

Keywords: Intrauterine device, nulliparous, misoprostol, pain, cervical priming

Introduction

Intrauterine devices (IUDs) can provide women with safe and effective contraception. The benefit to long acting reversible contraception (LARC) over other forms of contraception is that there is virtually no difference between perfect use and typical use in terms of failure rates. Once inserted, these are "forgettable" contraceptive methods [1]. Use of IUDs is increasing in the United States; despite the trends, only 5% of contraceptors are using this method [2]. There are many reasons for the slow uptake of this form of contraception, including old myths and provider comfort levels. Two groups in particular that may have limited access to IUDs are adolescents and nulliparous women. Backed by evidence, the American College of Obstetrics and Gynecology (ACOG) and the World Health Organization (WHO) have issued documents endorsing the use of IUDs in these women [3, 4].

Some providers have been hesitant to insert IUDs in nulliparous patients for fear of pain or difficulty with insertion. Misoprostol is an agent which has been used successfully to help dilate the cervix prior to abortions and hysteroscopic procedures [5-7]. One study in Sweden showed successful insertion in 218 out of 224 consecutive nulliparous women [8]. Despite success, a Chilean study showed that while ibuprofen didn't alter perceptions of pain, women of lower parity experienced more pain [9]. A few European trials have examined the use of misoprostol prior to IUD insertion, with one showing easier insertion after misoprostol but no differences in side effects or pain [10], while another showed no difference in the ease of insertion, but more side effects with misoprostol, and more pain in nulliparous women than multipara [11]. Some small trials in the US have also shown misoprostol was not helpful to either decrease pain or increase ease of insertion for

providers, but was associated with more adverse effects [12, 13].

Our goal is to give women and providers more information regarding the best practices to help nulliparous women get the contraception they desire. This study was undertaken as part of a larger, prospective meta-analysis [14], to help determine if misoprostol has any benefit to IUD insertion. The specific questions regarding IUD insertion were: 1) is there less pain during IUD insertion in nulliparous women after receiving misoprostol; 2) is IUD insertion easier for the provider after the patient received misoprostol; 3) is patient satisfaction of the IUD insertion improved after receiving misoprostol.

Materials and methods

We conducted a single center, randomized, double blind, placebo controlled trial. This trial was approved by the Human Subjects Protection Program at the University of Arizona. Participants were recruited in the University Physicians gynecology clinics and with flyers posted around the University of Arizona. The subjects were enrolled in the study and given a medication to take prior to their visit for IUD insertion. The medication was prepared and randomized in blocks of 8 by the clinical pharmacy at the University of Utah Medical Center. Troches (lozenges) of placebo were made to look, taste, smell, and feel identical to those troches containing 400 mcg of misoprostol. The pills were sequentially numbered in identical pill vials, each containing a single troche. Randomization was performed at the University of Utah, and the study was not unblinded until all participants had completed the study.

From January of 2009 through January of 2011, women were recruited into this study. Nulliparous women 18 years of age and over who were interested in IUDs were invited to participate. Exclusion criteria were previous pregnancy beyond 14 weeks gestation, active pelvic infection or cervicitis, uterine anomaly, fibroid uterus, copper allergy/Wilson's disease (for Paragard® only), undiagnosed abnormal uterine bleeding, cervical or uterine cancer. All participants were counseled on all contraceptive methods, including the IUD, and were able to choose which type of IUD they wanted. Enrollment was stopped after recruiting an adequate number of participants for the predetermined study size. Using data from a study on pain during other procedures involving uterine manipulation, the authors cited a 15 mm difference in the visual analogue scale as being clinically relevant, with a standard deviation of 23 mm [15]. Using a one sided test, a power of 80%, and an alpha of 0.05, this would require a sample size of 30 subjects in each group.

The primary objective of the study was pain during IUD insertion. This was determined by using a 100 mm visual analog scale, immediately following the procedure. Additional objectives included provider perception of ease of insertion, use of adjuvant measures, medication side effects, complications, and patient satisfaction with the insertion procedure. Participants filled out pre-insertion questionnaires regarding demographics, prior contraceptive use, and obstetric and gynecologic history. All women were given instructions on how to take the medication, either vaginally or buccally, two hours prior to the IUD insertion. The women were allowed to choose how they wanted to take the medication. All participants had pregnancy tests before taking the study medication, to ensure they were not pregnant. They could choose to wait the 2 hours and have IUD insertion on the same day as enrollment, or return on a different day. If they returned another day, they were given pregnancy tests to use at home prior to taking the study medication. Women were assessed for side effects of the medication prior to the IUD insertion.

A Paragard® or Mirena® IUD was inserted according to patient preference. Both resident physicians in 2nd, 3rd, or 4th year of training and attending physicians were performing the actual IUD insertions in one of three university clinic locations. The IUD insertion technique was standardized, and included cervical preparation with betadine, use of a tenaculum, placed without any anesthetic, and sounding prior to IUD placement. All women were asked to rate the pain of insertion on a 100 mm visual analog scale, (VAS, anchors 0 mm no pain to 100 mm worst pain imaginable) immediately following the procedure. One week after IUD insertion, patients were contacted by phone for a follow up questionnaire, to assess pain levels, medication usage, satisfaction, and complications. Their satisfaction was measured using a 5 point Likert scale, with 1 being very unsatisfied and 5 being very satisfied. Additionally, patients returned to the clinic one month after IUD insertion for a follow up visit. IUD placement was confirmed, either by strings check alone or with

Table 1. Participant Characteristics

	Placebo N (%)	Misoprostol N (%)	*P*-value
Group assignment	31	30	
Age	M=26.32, SD=4.41	M=24.86, SD=4.26	0.19
BMI	M=24.78, SD=4.4	M=24.82, SD=7.0	0.98
Race/Ethnicity			0.70
Hispanic/Latina	21 (68)	17 (59)	
White	7 (23)	10 (34)	
Asian American	1 (3)	-	
Mixed race	2 (6)	2 (7)	
Relationship Status			0.48
Single	19 (61)	20 (67)	
Single, living with partner	8 (26)	3 (10)	
Married	3 (10)	4 (13)	
Other	1 (3)	3 (10)	
Education			0.50
High school diploma/GED	-	1 (3)	
In college or some college	7 (23)	10 (33)	
Graduated college	15 (48)	13 (43)	
Graduated graduate school	9 (29)	6 (20)	
Sexual partners in last 6 mo.	M=1.19, SD=0.60	M=1.2, SD=0.66	0.95
Prior first trimester SAB/TAB			0.51
Yes	4 (13)	1 (3)	
No	27 (87)	29 (97)	

ultrasound if indicated, and another questionnaire was given to assess satisfaction. Providers filled out a form immediately after IUD insertion in which they were asked to rate the degree of difficulty of the placement, on a 100 mm VAS scale (anchors 0 mm easiest insertion to 100 mm most difficult insertion). They were to note use of any adjuvant measures such as ultrasound guidance, dilation, or anesthesia. In addition, the providers were asked if they thought that the patient had received medication, placebo, or they couldn't tell.

An intent-to-treat analysis was performed using Stata software version 11. Categorical variables are presented in frequencies and relative frequencies while continuous data is presented with means and standard deviations. Chi square tests and Fisher's Exact tests have been utilized for categorical variable comparison between groups. T-tests and the Wilcoxon rank-sum test have been used for comparisons between groups. Level of statistical significance is 5%. *P*-values are presented with accompanying test.

Results

There were 62 women who enrolled in this study and 61 underwent IUD insertion. Randomization provided two groups that were similar at baseline. (**Table 1**) They were predominately in their 20's, Latina, single, and well educated. The majority of women had used oral contraceptive pills in the past, 94% of those receiving placebo and 83% of those receiving misoprostol (P=0.25). Similar numbers in each group had tried the patch, the ring, the 3 month injection, and condoms for contraception. Additionally, more than a third (39% placebo, 33% misoprostol) of women had used emergency contraception in the past (P=0.66). In the placebo group, 19 (37%) of women took the study medication vaginally and 11 (63%) took it buccally, while in the misoprostol group, 17 (57%) took it vaginally, and 13 (43%) took it buccally (P=0.79). The mean time from taking the medication to IUD insertion was 160 minutes in the placebo group and 161 minutes in the misoprostol group (P=0.92). Most subjects in each group (22 in placebo and 25 in misoprostol) chose to have a Mirena® IUD placed (P=0.68).

The primary objective in the study was pain at the time of insertion. Prior to IUD placement, there was no difference in baseline pain. After IUD insertion, the pain levels were also similar, 57.2 ± 22.5 mm for placebo vs. 56.7 ± 22.1 mm for misoprostol (P=0.92). (**Table 2**) One week later, there were no differences reported in pain levels. The worst pain described over the week since the IUD insertion was 38.2 ± 34.1 mm for the placebo group and 31.3 ± 29.7 mm for the misoprostol group (P=0.43). Most women in each group reported taking ibuprofen for the discomfort, ranging equally from

Table 2. Primary outcome measures: Pain with IUD insertion and Ease of Insertion

	Placebo	Misoprostol	*P*-value
Pain prior to IUD insertion	3.4 mm ± 9.6 mm	5.0 mm ± 8.3 mm	0.52
Pain immediately after IUD insertion	57.2 mm ± 22.5 mm	56.7 mm ± 22.1 mm	0.92
Ease of Insertion (millimeters)	M = 33.4 ± 20.3	M = 24.1 ± 14.2	0.04
Provider assessment of medication: *Do you think the patient received the drug or the placebo?*			0.03
Misoprostol	7 (23%)	17 (57%)	
Placebo	10 (33%)	5 (17%)	
Don't know	13 (43%)	8 (27%)	

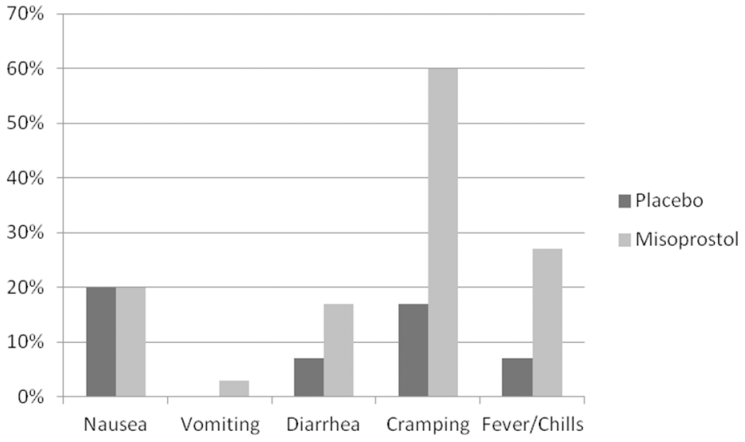

Figure 1. Medication Side Effects. Placebo black, misoprostol gray; Cramping P=0.002, Fevers/Chills P=0.081.

once to daily. When asked how they would describe the discomfort of IUD insertion to a friend, 56% of those who received placebo, and 52% of those who received misoprostol stated severe or very severe (P=0.76).

More patients in the misoprostol group reported side effects. Only 16.7% of participants receiving placebo complained of cramps, all mild, while 60% of participants receiving 400 mcg misoprostol complained of cramps, 33.3% of which were described as more severe (P=0.002). More women in the misoprostol group also described fevers and chills, though this did not reach statistical significance (7% placebo vs 27% misoprostol, P=0.081). Other side effects did not differ and are presented in **Figure 1**.

Additionally, this study examined the ease of IUD insertion for providers. Providers, who were blinded to the treatment group, found it easier to insert IUD's after receiving misoprostol, 24.1 ± 14.2 mm vs. 33.4 ± 20.3 mm (P=0.04). Since our providers have used misoprostol to help in cases of difficult dilation prior to gynecologic procedures, they presumably have a bias that misoprostol will aid in cervical preparation. Thus, as an additional way to determine provider assessed ease of insertion, they were asked which medication they believed the subject had received. When patients received misoprostol, only 17% of the time did the provider guess it was placebo, or the perception of a more difficult insertion. Conversely, when the subject received placebo, only 23% of the time did the provider guess it was misoprostol, or the perception that it was a very easy insertion. There were also large numbers of women in each group in whom the provider was unable to guess whether she had received misoprostol or placebo. (**Table 2**) Despite these perceptions, there was only one patient that required any additional measures to insert her IUD. She received placebo, and required dilation prior to insertion. There were no complications or perforations in either group, and all 61 subjects had successful IUD insertion.

At one week, 25/30 (83%) of the participants receiving placebo were available for follow up, and 26/31 (84%) of those who received misoprostol. Overall satisfaction with IUDs was high, with 84% of women in the placebo group reporting they were satisfied or very satisfied with their IUD vs 77% in the misoprostol group (P=0.94). (**Figure 2**) One patient in the misoprostol group experienced expulsion prior to the 1 week follow-up. A majority of patients in each group felt that the wait time to take medication

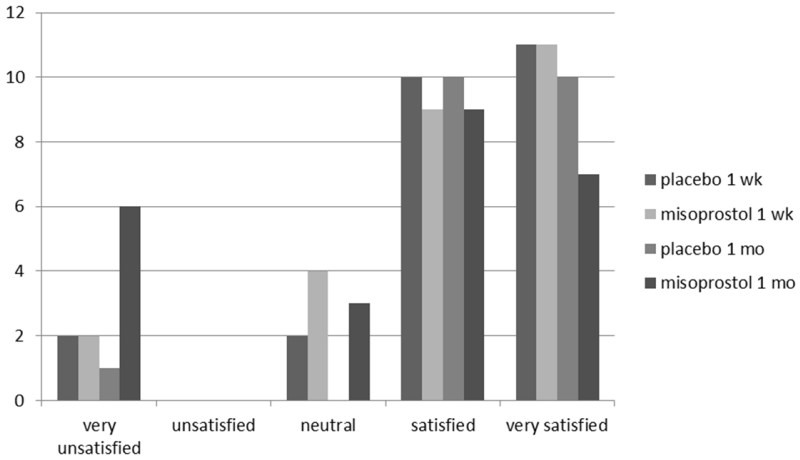

Figure 2. Satisfaction at 1 week and 1 month. Placebo 1 wk gray, Misoprostol 1 wk light gray, Placebo 1 mo gray, Misoprostol 1 mo black. P=0.940 at 1 week, P=0.153 at 1 month.

prior to IUD insertion was no problem at all, 84% vs 89%, P=0.50, for placebo and misoprostol, respectively.

After one month, 23/30 (76.7%) and 25/31 (81%) returned for follow up visit. While more women in the placebo group, 87% placebo vs. 64% misoprostol, expressed satisfaction with their IUD's, this was not significant (P=0.15) (**Figure 2**), and an identical number, 87% of each group would definitely recommend an IUD for birth control to a friend (P=0.61). None of the participants reported complications or needed to see other providers for IUD related problems.

Discussion

In our study we had a 100% successful IUD insertion rate in nulliparous women, with or without the use of misoprostol. Pain levels were unaffected by study medication and the overall impression of providers was that of relatively easy insertions. Satisfaction rates of the subjects were high.

IUDs are a popular form of contraception in many parts of the world. As highly reliable forms of contraception, they have the ability to decrease the unplanned pregnancy rate. As seen in our study, more than a third of the subjects had used emergency contraception in the past, indicating prior lapses in adequate contraception. The very large contraceptive CHOICE project, in the United States, has shown high rates of patient satisfaction and continuation with IUDs [16] and improved efficacy over shorter acting contraceptive methods [17].

This study shows that use of misoprostol prior to IUD insertion in nulliparous women did not lessen pain, did not alter satisfaction with the IUD, but did make the insertion slightly easier for the provider. We also noted more side effects in women receiving misoprostol. Our data seems relatively consistent with other studies regarding pain and side effects [10-13]. Some of the studies showed easier insertions for the providers, but others did not. In our study, misoprostol did lead to easier insertions for the clinician, but since all of the insertion scores were estimated to be easy (24 mm vs 33 mm with 100 mm being the hardest), and all patients had successful insertion of their IUDs, the side effects may not be justified. Despite the level of pain at the time of IUD placement, most women were satisfied with their IUDs and would recommend them to a friend for contraception.

There were multiple strengths with this study. First, it was a randomized, double blind and placebo controlled study. Second, providers of varying experience level in IUD insertion participated in the study and they were all able to successfully insert them with no complications. This is in contrast to several other studies, in which only family planning experts were inserting IUDs and may not be as generalizable to all clinicians who place IUDs. We also had a large Latina population, which includes a patient population that has not been well represented in many of the other studies. In addition, we had high levels of follow up through one month post insertion, which allowed us to obtain more information regarding symptoms of pain and discomfort post IUD insertion. While this study itself was relatively small, it was performed in the context of a prospective meta-analysis, which will contribute to the body of knowledge addressing optimal IUD insertion methods.

One of the weaknesses of the study is that the patient population was highly educated and

may not reflect the general population. It is unclear if educational level impacts perception of pain, but it should not have any effect on the ease or success of insertion. In addition, the timing during the patient's menstrual cycle was not taken into consideration. The presence or absence of the woman's menses may have an impact on perception of pain, side effects, and ease of IUD insertion. We did not gather information regarding dysmenorrhea or pelvic pain, which may alter the experience of pain. Also, the women were not asked if they had premedicated with analgesics prior to their IUD insertion. As a rule, they were not instructed to do so, but nor were they expressly forbidden to use it. No woman was given a prescription for any medication prior to or after the IUD placement. Theorectically, the randomization process helped to alleviate differences in these last few points.

In conclusion, it appears that routine use of misoprostol prior to IUD insertion in nulliparous patients is not justified. The potential benefit seen in this study, though not in some of the other trials, is an easier insertion. However, all women had successful IUD placement and none had complications, so misoprostol does not make the insertion safer for the patient. Many patients or providers may be discouraged from IUD placement if they believe an additional visit is necessary to provide the misoprostol prior to insertion. They should be encouraged that same day IUD insertion is possible. Providers can be assured that IUD insertion is quite feasible in nulliparous patients, and they should routinely offer this option as a contraceptive method for nulliparous women.

Acknowledgements

The trial is registered at ClinicalTrials.gov number NCT01001897.

Disclosure of conflict of interest

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