Use of vaginal misoprostol in women demanded copper intrauterine device insertion after the end of bleeding days of their menses: a randomized clinical trial

Running title: Misoprostol before IUD insertion in non-menstruating women

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Abstract

Objective: To assess the effectiveness and safety of misoprostol before IUD insertion in women after the end of bleeding days of their menses.

Materials and methods: The study was a randomized clinical trial conducted at Assiut Woman's Health Hospital; Egypt from October 2021 to March 2023 including women who requested copper T380A IUD insertion after the stoppage of bleeding days of the menses. The women were randomized to either group I: misoprostol (400 µg misoprostol tablets vaginally 3 hours before IUD insertion) and group II: no intervention group. The primary outcome was the degree of pain during IUD insertion measured using the visual analogue scale (VAS). The data was analyzed by an unpaired t-test, Mann-Whitney test, and chi-square test.

Results: Sixty women consented to participate and were divided into two equal groups. There was a significantly lower VAS score for pain during and 5 minutes after IUD insertion. Also; a significantly lower easiness and higher woman's satisfaction was noted in the misoprostol group. However; the successful device placement, duration of insertion, and complications were comparable in both groups.

Conclusion: The vaginal misoprostol use before copper T380A IUD insertion during the bleeding-free days of the menstrual cycle is safe and reduces IUD insertion pain, increases easiness of insertion, and women's satisfaction.

Key words: Intrauterine device; insertion pain; satisfaction; misoprostol.

Implications

Most of care providers as well as clients will be reluctant to insert IUD in non-bleeding days. The easiness and less pain associated with misoprostol use before insertion will increase acceptance of IUD use in non-bleeding days.

Introduction

The intrauterine device (IUD) is a reliable, safe, long-acting reversible, and effective contraceptive method [1]. Despite that, the associated pain with IUD insertion can be a cause of client's refusal of use [2]. Many researches have been done directing to decrease the pain during IUD insertion [3, 4].

The physicians usually prefer the insertion of the IUD during women's menses as the women are mostly not pregnant, the insertion is easier (opened cervix) and the pain is much lower [5, 6]. The easiness of IUD insertion is a very important issue that can increase both women's and physician's satisfaction [7, 8].

However; in practice; some women ask for IUD insertion on bleeding-free days of their menses. Those women may have lactational amenorrhea, want to switch from any birth control method to an IUD, or refuse to introduce an IUD into the uterus at a time of menses. Finally; some women want a rabid and reliable contraception because their husbands will come unscheduled within a few days. So; we think that those women may face some difficulty during insertion and subsequent more pain.

Misoprostol is a prostaglandin E1 analog that used successfully for cervical priming before IUD insertion [9]. It also was used in women with previous failed trials of IUD insertion with promising results [10].

A systematic review suggested that the timing of Cu-IUD insertion has little effect on pain at insertion but it recommended further randomized trials look at the IUD insertion effect during later days of the menstrual cycle [11].

So, this work aimed to evaluate the effectiveness and safety of misoprostol before IUD insertion in women not during the bleeding days of their menses. To our knowledge, this is the first trial that addressed this subject.

Material and methods

At Assiut Woman's Health Hospital; an open randomized registered clinical trial (Clinical trial.gov- NCT04932382) was conducted from 1st of October 2021 to March 2023. Women who came after the end of their menses and requested copper IUD insertion were invited to participate. The study protocol was approved by Assiut University Medical Ethical Review Board (IRB17101568).

Eligible participants

Non-pregnant women aged 18-45 years who want to use an IUD after the end of bleeding days of their menses were included. The exclusion criteria included women who received any analgesics or misoprostol in the 24 hours before insertion, any contraindications to IUD insertion [12] or misoprostol [13]. Women who refused to participate were also excluded.

Randomization

Blocked randomization was done using https://www.sealedenvelope.com. A table of random numbers and codes was generated. Eligible women were randomly assigned to either group I: misoprostol and group II: no intervention group. Allocation concealment was done using serially-numbered closed opaque envelopes. Once allocation has been done, it can't be changed.

Study intervention

All participant women signed a written consent before participation after discussing the details of the study. The participants received pre-insertion instructions, and then demographic and obstetrics-gynecology data were collected. BMI was measured. Transvaginal ultrasound (TVS) was done

using Medison X8, Digital Ultrasonic Diagnostic, Imaging System, USA machine to assess the uterine position and size before insertion.

Following that; women in group I received 400 µg misoprostol tablets vaginally (Misotac®; Sigma Pharma, SAE, Egypt); these tablets were introduced by the principal investigator 3 hours before IUD insertion into the posterior vaginal fornix in the lithotomy position [14]. While women in group II did not receive any pre-insertion medications.

The consistency of the cervix was assessed immediately before IUD insertion. It was divided into soft (like mouth lips), firm (tip of the nose), or hard. Then; women in the 2 study groups received a copper T380A IUD (PREGNA T380A; Pregna International Ltd, Chakan, India).

The principal investigator inserted the IUD in all participants. A Cusco speculum and single-toothed tenaculum were used, while uterine sound was not used [2, 3]. After insertion; the accurate place of the IUD was evaluated by TVS.

Study outcomes

The primary outcome was the degree of pain during IUD insertion measured by VAS from 0-10 (0 means no pain and 10 means maximum pain) [15]. While secondary outcomes included the degree of pain 5 minutes after IUD insertion, need for analgesics, easeness of IUD insertion as measured by VAS (0 means very difficult and 10 means very easy), the women's satisfaction (0 means maximum dissatisfaction and 10 means maximum satisfaction.) [3].The successful IUD placement, the duration of insertion, the rate of complications and side effects of misoprostol as well as the ideal device placement after 1 month were also assessed.

Sample size

To calculate the required sample size; the principal investigator recorded the degree of pain during IUD insertion in 15 non-menstruating women, after obtaining written consent; we did not include them in the study. The mean degree of pain during IUD insertion in those women by VAS was about 6.5 ±1.5. So, using 95% power with an error of 0.05, a sample size of about 60 women (30 in each group) to detect a 1.5 difference in the pain score between both groups assuming the rate of lost follow-up 10% (OpenEpi, Version 3, open source calculator-SS Mean).

Statistical Analysis

The data was collected and entered into the Microsoft access database to be analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, version 21). Comparisons between means of the groups were done using an unpaired t- in the scale variables. Non- parametric variables were shown as median and range and analyzed by Mann-Whitney test. Categorical data were shown by number or percentage. For dichotomous variables, chi-square was used to estimate the significance value. For analysis, $p<0.05$ considered to be significant.

Results

Seventy-four women were counseled for participation, however; 14 women were not included in the study. The remaining sixty women were allocated into two equal groups; group I (misoprostol group) and group II (no-intervention group). Forty-eight participant women were finally analyzed while 12 women were lost from follow-up (Fig.1 the study flow chart).

Both groups were comparable in baseline socio-demographic data without statistically significant differences (Table 1). The consistency of the cervix was softer in group I (Misoprostol group) (70%) than in group II (No- intervention group) (33.3%) with a statistically significant difference (P=0.006) (Table 2).The study outcomes were presented in table 3. The median of pain during IUD insertion (4.5 vs. 7) and 5 minutes after insertion (2.5 vs. 5) was lower in group I than

group II with statistically significant difference (P=0.000).

The insertion is easier in group I than in group II with a statistically significant difference (7.77 ± 0.68 vs. 5.57 ± 0.90; P=0.000). Also, the mean of women's satisfaction is higher in group I (8.30 ± 0.53) than in group II (7.33 ± 0.96) with a statistically significant difference (P=0.003). The need for analgesics was more in group II (51.7%) than in group I (20.0%) with a statistically significant difference (P=0.011). Duration for application, successful IUD placement, and ideal placement after 1 month were comparable in both groups (p>0.05) (Table 3).

No statistically significant difference was noted between groups regards the rate of early and late complications. Most of the women (76.7%) had no side effects from misoprostol. Other side effects included headache (3 cases), nausea/vomiting (2 cases), and shivering (2 cases) (Table 4).

Discussion

To our knowledge; this is the first randomized study compassing the efficacy and safety of using misoprostol before copper IUD device insertion in in women after the end of bleeding days of their menses. Our results showed that misoprostol was associated with lower pain and easier IUD insertion with higher women's satisfaction with a little bit of side effects and complications.

In practice; many providers recommend the IUD be inserted during the last few days of menstruation when the cervical opening is wide, the insertion's bleeding mixes with menstrual bleeding, and the woman is not pregnant. Although these advantages; there is no strong reason to delay insertion if the woman requests an IUD at any other time during her menstrual cycle [16].

The idea of this study came from that some women, not during the menses; choose an IUD as contraception during their first visit to the family planning clinic. Some women are very anxious and refuse, at all, to be touched during their menses and it is easier to examine for signs of genital tract infections when a woman is not menstruating.

Assuming the challenges presented by unprepared cervix in those women, it might seem that misoprostol may be helpful in the IUD insertion process. Multiple studies have elucidated that prophylactic misoprostol increased the ease of IUD insertion and decreased the insertion pain [1, 17-19]. The misoprostol is also beneficial in patients who have already experienced failure of IUD insertion [6].

In this study; we found that the VAS for IUD insertion pain and 5 minutes after insertion were significantly lower and the easiness score was significantly higher in the misoprostol group. Also, the need for analgesia after IUD insertion was also few in his group. Reduced cervical tone and improved cervical consistency after using misoprostol may be behind these results. So; we are on the same track as all studies that proved the beneficial use of misoprostol before insertion of IUD [1, 17-19].

Although, many studies reported no significant differences among women receiving misoprostol to ease IUD insertion [20-25]; we think there is still a non-negligible role for misoprostol with IUD insertion. Priming with misoprostol before hysteroscopy, dilatation and curettage, and the sounding of the uterus in premenopausal women yielded an increased cervical dilatation and a lower rate of laceration of the cervix[7].

Increasing women's satisfaction during IUD insertion may improve IUD acceptance [3]. It is unsurprisingly, in this study, the women with misoprostol were more satisfied than women in no intervention group because they had little pain. Evaluation of women's satisfaction with the IUD is a very important issue because it increases the desire toward using this method [27].

Finally, both groups in this study had comparable either early or late side effects. Expulsion or displacement was reported in one woman in the no-intervention group (4.34%). Also, about 22% of women developed misoprostol side effects in the form of headache, nausea/vomiting, and shivering.

Nausea and abdominal cramps most common side effects reported as side effects for misoprostol [13, 27]. However; these side effects are dose and route dependent [27].

A major strength of this work was the novelty of the idea and the randomized type of this study. In spite of small sample size (60 women); we used 95% power to calculate the sample size was another good point in this research. Additionally, we standardized the insertion protocol for all participants by only one provider. However, the present work had some limitations. The study did not include other types of IUDs like multiload or LNG-IUS. The heterogenous characteristics of the studied women (some delivered vaginally and another women delivered by CS). The long-term outcomes were not studied. The subjective evaluation of the pain, easiness, and satisfaction is another limitation of this study.

Conclusion

The vaginal misoprostol's use before IUD insertion in women in the bleeding-free days of their menses is relatively safe and reduces IUD insertion pain and need for analgesics as well as increases women's satisfaction. In addition, clinicians will find the insertion procedure easier with misoprostol use.

Disclosure statement: The authors report no conflicts of interest

Authors' contributions

MA and MY designed the study and prepared the proposal. NM and AA did the intervention and collected data. AN and II did the analysis of data and prepared first manuscript. All authors contributed in the preparation and revision of the final manuscript.

Table 1: Socio-demographic and obstetrics data of the women sharing in the study
BMI body mass index, **CS** cesarean section, **IUD** intrauterine device, **kg/m²** kilogram

Personal data	Misoprostol group (n= 30)	No intervention group (n= 30)	P-value
Residence, n (%)			
Rural	15(50.0)	14(46.7)	0.796
Urban	15(50.0)	16(53.3)	
Level of education, n (%)			
Illiterate	5(16.7)	4(13.3)	0.714
Basic education	16(53.3)	14(46.7)	
Secondary or more	9(30.0)	12(40.0)	
BMI (kg/m²), mean ± SD	26.12 ± 3.30	25.77 ± 4.00	0.711
Parity, median (Range)	4.0 (1.0-6.0)	3.0 (1.0-7.0)	0.774
History of previous abortion, n (%)	8(26.7)	5(16.7)	0.347
Mode of previous delivery, n (%)			
Vaginal only	13(43.3)	14(46.7)	
Cesarean section only	14(46.7)	12(40.0)	0.846
Vaginal and Cesarean section	3(10.0)	4(13.3)	
Number of living children, median (Range)	3.0 (1.0-6.0)	3.0 (1.0-7.0)	0.970

Duration from last pregnancy (years), median (Range)	4.0 (1.0-120.0)	6.0 (1.0-168.0)	0.519
Previous IUD insertion, n (%)	12(40.0)	14(46.7)	0.286
Indications of IUD insertion, n (%)			
Switch from birth control method	16(53.3)	11(36.7)	0.291
LAM	11(36.7)	15(50.0)	
Refused IUD insertion during menses	0(0.0)	2(6.7)	
Unscheduled coming of the husband	3(10.0)	2(6.7)	

per square meter, **n (%)** number and percentage, **LAM** lactational amenorrhea, **SD** standard deviation, **VD** vaginal delivery

Table 2: Ultrasonographic and per-vaginal examinations in the studied women

	Misoprostol group (n= 30)	No intervention group (n= 30)	P-value
Uterine length (mm), mean ± SD	76.10 ± 5.79	75.47 ± 5.72	0.672
Uterine position, n (%)			
Anteverted	20 (66.7)	24 (80.0)	0.501
Midway	7 (23.3)	4 (13.3)	
Retroverted	3 (10.0)	2 (6.7)	
Consistency of cervix, n (%)			
Soft	21(70.0)	10(33.3)	0.006*
Firm	9(30.0)	15(50.0)	
Hard	0(0.0)	5(16.7)	

* Statistical significant difference (P < 0.05)

mm millimeter, **n (%)** number and percentage, **SD** standard deviation

Table 3: The study outcomes

Study outcome	Misoprostol group (n= 30)	No intervention group (n= 30)	P-value
Pain during IUD insertion, median (Range)	4.5 (3.0-6.0)	7 (4.0-8.0)	0.000*
Pain 5 minutes after IUD insertion, median (Range)	2.5 (1.0-5.0)	5 (2.0-7.0)	0.000*
Easiness of the insertion, mean ± SD	7.77 ± 0.68	5.57 ± 0.90	0.000*
Woman's satisfaction, mean ± SD	8.30 ± 0.53	7.33 ± 0.96	0.003*
Need of analgesia, n (%)	6 (20.0%)	15 (50.0%)	0.011*
Duration of insertion (minutes), mean ± SD	6.53 ± 1.20	6.76 ± 1.43	0.514
Successful IUD insertion, n (%)	30 (100%)	29 (96.7%)	1.000
Ideal IUD placement after 1 month, n (%)	1(4.0)	2(8.7)	0.601

* Statistical significant difference (P < 0.05)

IUD intrauterine device, **n (%)** number and percentage, **SD** standard deviation

Table 4: The reported complications and side effects in women shared in this RCT

	Misoprostol group (n= 30)	No intervention group (n= 30)	P-value
Early complications, n (%)			
Cramps	2 (6.7)	5 (16.7)	
Vaginal bleeding	3(10.0)	1 (3.3)	
Failure of insertion	0 (0.0)	0 (0.0)	0.316
Vasovagal	0 (0.0)	0 (0.0)	
No	25 (83.3)	24 (80.0)	
Side effects of misoprostol, n (%)			
Headache	3 (10.0)	0(0.0)	
Nausea/ vomiting	2 (6.7)	0(0.0)	0.053
Shivering	2 (6.7)	0(0.0)	
No	23 (76.7)	0(0.0)	
Late complications at 1 month, n (%)			
Perforation	0 (0.0)	0 (0.0)	
Expulsion/ displacement	0 (0.0)	1 (4.34)	0.132
PID	0 (0.0)	0 (0.0)	
No	25 (100.0)	22 (95.66)	

IUD intrauterine device, **n (%)** number and percentage, **PID** pelvic inflammatory disease

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