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Original Research Article

Prophylactic vaginal dinoprostone administration six hours prior to copper-T380A intrauterine device insertion in nulliparous women: A randomized controlled trial ☆,☆☆

Ahmed Samy [a], Mohamed Fikry Yosif Kasem [a], Ahmed El Lithy [a], Ahmed M Ibrahim [a], Mohamed El Mahy [a], Amr Hassan Hussein [a], Hala A-Wahab [a], Amal Hanafy Hussien [a], Ahmed A. Mageed A. Allah [a], Ahmed Alaa El Din Wali [a], Hossam H. Soliman [b], Ahmed Taher Masoud [c,*], Hossam Abdou [d], Mohamed Hussein [a], Rana M. Abdella [a], Mona Mostafa [a], Sherif Sameh Zaki [a]

[a] Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Cairo, Egypt
[b] Al Gala Maternity Teaching Hospital, Cairo, Egypt
[c] Faculty of Medicine, Fayoum University, Egypt
[d] Helwan University, Cairo, Egypt

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ABSTRACT

Objective: To determine the effectiveness of 3 mg vaginal dinoprostone administered six hours prior to copper intrauterine device (IUD) insertion compared to placebo in increasing ease of insertion and reducing insertion pain among nulliparous women. Study design. This was a single-center double-blinded randomized controlled trial (RCT). We randomly divided the two hundred nulliparous women requesting a copper T380A IUD to receive 3 mg vaginal dinoprostone or placebo six hours before IUD insertion. The primary outcome was provider ease of insertion. Patients reported their perceived insertion pain using a 10 cm visual analog scale (VAS). We also reported number of failed IUD insertions.

Results: Baseline characteristics were similar between groups. Ease of insertion score was lower in dinoprostone group than placebo group (3.6 ± 2.5 vs. 5.4 ± 2.8; $p < 0.01$) denoting easier insertion for clinicians in dinoprostone group. Mean pain score during copper IUD insertion was lower in dinoprostone group (3.7 ± 2.3 vs. 5.0 ± 2.8; $p < 0.01$). Failed IUD insertion occurred in two cases of dinoprostone group (2%) versus four cases in control group (4%) (p-value; 0.68).

Conclusions: Although vaginal dinoprostone administration six hours prior to copper IUD insertion in nulliparous women leads to an easy IUD insertion, we do not routinely advise it as the reduction in IUD insertion pain scores with vaginal dinoprostone lacked clinical significance.

Implications: In settings where it is feasible to provide dinoprostone vaginally six hours before copper IUD insertion, clinicians will find insertion easier, and nulliparous women may experience somewhat less pain during the procedure. Where waiting six hours is practical, this may prove to be useful.

1. Introduction

Intrauterine device (IUD) is a highly safe, effective, and reversible method of contraception for women, including adolescents and nulliparous women with comparable efficacy to sterilization [1]. Nevertheless, the use of IUDs remains low in nulliparous women, and adolescents [2,3] and this could be attributed to a lack of information, common misconceptions among patients and physicians, and procedural Pain [4].

Besides, many health care providers continue to limit IUD access in nulliparous women due to concerns of potential insertion difficulties [5]. However, IUD can be successively inserted in both nulliparous and parous women [6]. Intrauterine contraception with copper or levonorgestrel-releasing IUD is an attractive option for adolescents who desire long-term, uninterrupted contraception

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* Corresponding author.
E-mail address: at1263@fayoum.edu.eg (A.T. Masoud).

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and fertility returns quickly after removal [7]. Additionally, IUDs are recommended as first-line options for adolescents by the American Academy of Pediatrics [8] and the American College of Obstetricians and Gynecologists [9].

Wildemeersch et al. reported that nulliparous women have narrow uterine cavities, and conventional-framed IUDs do not fit properly in them [10], and this could result in higher pain during insertion, thus limiting utilization of IUDs in nulliparas [10,11].

Several medications were used to ease IUD insertion and increase rates of successful insertions such as misoprostol, 2% intracervical lidocaine as a topical gel or injection, diclofenac plus 2% intracervical lidocaine as a topical gel, nitric oxide donors, specifically nitroprusside or nitroglycerin gel. The effectiveness of those medications was evaluated in a recent systematic review and meta-analysis by Zapata et al. [12]. They concluded that there were no significant differences between women receiving interventions to ease IUD insertion versus controls. Women with a recently failed insertion who underwent a second insertion attempt may benefit from misoprostol administration as it increased their chance for successful IUD insertion; however, this evidence is reported from a single RCT [12].

Dinoprostone, a natural PGE2, is used in obstetrics for cervical ripening and labor induction. Studies have reported that dinoprostone is comparable to or better than misoprostol for cervical ripening in labor induction [13]. Also, dinoprostone was used for cervical ripening and priming in nulliparous women before diagnostic and operative hysteroscopic procedures and proved its efficacy and safety regarding ease of hysteroscope entry, procedure pain, or side effects [14,15].

No prior study has explored the effect of vaginal dinoprostone administration six hours prior to copper IUD insertion in nulliparous women; therefore, we aimed to investigate its effect mainly on provider ease of insertion and copper IUD insertion pain.

2. Materials and methods

We conducted a double-blind, randomized, placebo-controlled study at Gynecology Clinic of Obstetrics and Gynecology Hospital, Faculty of Medicine, Cairo University, Cairo, Egypt, from September 2018 to March 2019. We prospectively registered the study in clinicaltrials.gov (NCT03686085), and we obtained ethical approval from the scientific departmental committee. All women who were willing to participate signed written informed consent, after having a detailed explanation of the procedure, possible side effects, and complications. All providers participating in the study were obstetrician-gynecologists with advanced training in family planning.

Nulliparous women requesting copper T 380A intrauterine contraception were offered to share in the trial if they were 18 years of age or older, had a negative pregnancy test, had no previous pregnancies beyond 13 6/7 weeks of gestation. We excluded women with the following conditions: pelvic inflammatory disease diagnosed within the last three months, active vaginitis or cervicitis, currently pregnant or were pregnant within six weeks of study entry, had a history of cervical surgery. Also, we excluded women with undiagnosed abnormal uterine bleeding, World Health Organization Medical Eligibility Criteria category 3 or 4 precautions to a copper IUD, had a previous attempted or successful IUD insertion, fibroids or other uterine abnormalities distorting uterine cavity, a known allergy or contraindication to dinoprostone.

We performed preprocedural counseling and evaluation according to the standard clinic protocols; we adequately took medical history, carried out abdominal and vaginal examinations to exclude genital infections or masses. Participants completed a demographics form, and the study nurse performed a urine pregnancy test to all participants on the day of copper IUD insertion.

We randomized women into two groups using a 1:1 allocation ratio and a computer-generated random numbers table. A statistician, not directly involved in the study, generated the computerized randomization list and kept the key for group allocation concealed from investigators until completion of the study. The first group received 3 mg vaginal dinoprostone six hours before the procedure. The second group received a placebo created by department of pharmaceutical chemistry in Faculty of Pharmacy, Cairo University to be identical in shape, size, and color to dinoprostone tablets. Dinoprostone and placebo tablets were put into opaque, sealed envelopes with sequential serial numbers. We used them consecutively according to order of attendance of women. Participants, research staff, and providers were blinded to allocation.

The study nurse introduced dinoprostone or placebo tablets digitally without speculum into the posterior vaginal fornix of women six hours before copper IUD insertion. We gave participants the choice to sit in the waiting room and watch TV or read magazines or to go home and return after six hours for IUD placement

The physicians inserted intrauterine contraceptive devices from the third to the fifth day of menstrual cycle. The IUD used was copper T380A (Pregna Copper T 380A, Pregna, Egypt), and all the providers used the standard technique for IUD insertion prescribed by the manufacturer [16]. The inserting physicians placed a speculum, cleaned the cervix with antiseptic, applied a single-toothed tenaculum and sounded the uterus to measure its length, followed by IUD insertion without ultrasound guidance. We determined degree of cervical dilatation prior to copper IUD insertion by whether or not Hegar dilators with a diameter of four mm or smaller could pass through internal cervical os without resistance. The providers inserted Hegar dilators gently without force so as not to induce pain or discomfort for patients.

The primary endpoint was the difference in ease of IUD insertion score between study groups (as reported by physicians responsible for IUD insertion). This score is graduated as a 10-cm VAS scale from 0 to 10 where 0 denotes very easy insertion while 10 represents extremely difficult insertion.

Secondary endpoints were the frequency of women with cervical dilation $\leq$ four mm, and intensity of patient-perceived pain at time of IUD insertion, using a visual analog scale. The VAS scale is graded from 0 to 10 on a 10 cm horizontal straight line, where 'zero' corresponds to no pain at all, and '10' to the worst possible pain imaginable. Research assistants held VAS sheet for the participant to select the point that corresponded to level of pain she had experienced. At the end of procedure, the providers reported ease of insertion using ease of insertion score (ES).

Before IUD insertion, we asked for fever (oral temperature $\geq$38 °C) which was measured immediately before the procedure, nausea, vomiting, shivering, diarrhea, and cramps and recorded them immediately before IUD insertion to make sure that they were related to the drug and not to the insertion procedure itself. We also recorded patient-reported postprocedural bleeding five minutes after procedure, vasovagal reaction, uterine perforation, failed insertions and insertion time from speculum in until speculum out.

We set the minimal clinically important difference in ease of insertion scores at o.76 (i.e., ease of insertion score in dinoprostone group should be lower than that of placebo group by at least 0.76) [17]. A minimum of 90 participants was needed in each study group to detect this difference with 90% power and an alpha level of 0.05. We accounted for attrition or disqualification of participants by nearly 10% increase in calculated sample size. Final sample size reached 200 subjects (100 patients in each group) [18].

We analyzed data using IBM SPSS software, version 20 (IBM). We used Chi-square or Fisher exact tests to evaluate categorical

variables and Student t-test to compare means for continuous variables. Categorical variables were expressed as number and percentage.

Clinical trial registration number: NCT03686085.

3. Results

We offered study participation to 240 nulligravid women and excluded 40 women: 30 were ineligible, and 10 declined to participate (Fig. 1). Table 1 shows baseline characteristics of study population.

Differences were found between the two groups with provider reported less difficulty in inserting IUD in dinoprostone group ($P < 0.01$) and less risk of cervical dilatation ≤ four mm ($P < 0.01$) when dinoprostone was used prior to insertion (Table 2). Insertion

Table 2
Principal RCT measurements during insertion of the IUD in Egyptian nulligravidas according to whether vaginal dinoprostone or placebo was administered six hours prior to the procedure.

End points	Dinoprostone group ($n = 100$)	Placebo group ($n = 100$)	p-value
Provider ease of insertion (VAS score)[a]	3.6 ± 2.5	5.4 ± 2.8	<0.01
Cervical dilatation			
≤4 mm	28 (28%)	58 (58%)	<0.01
>4 mm	72 (72%)	42 (42%)	
Insertion time (minutes)	4.1 ± 1.1	4.3 ± 1.0	0.35
Failed insertion	2 (2)	4 (4)	0.68

All data are presented as n (%) or mean ± SD.
Statistically significant difference.
VAS, visual analog scale RCT: randomized controlled trial.
[a] Ease of insertion score was rated on a scale from 0 to 10.

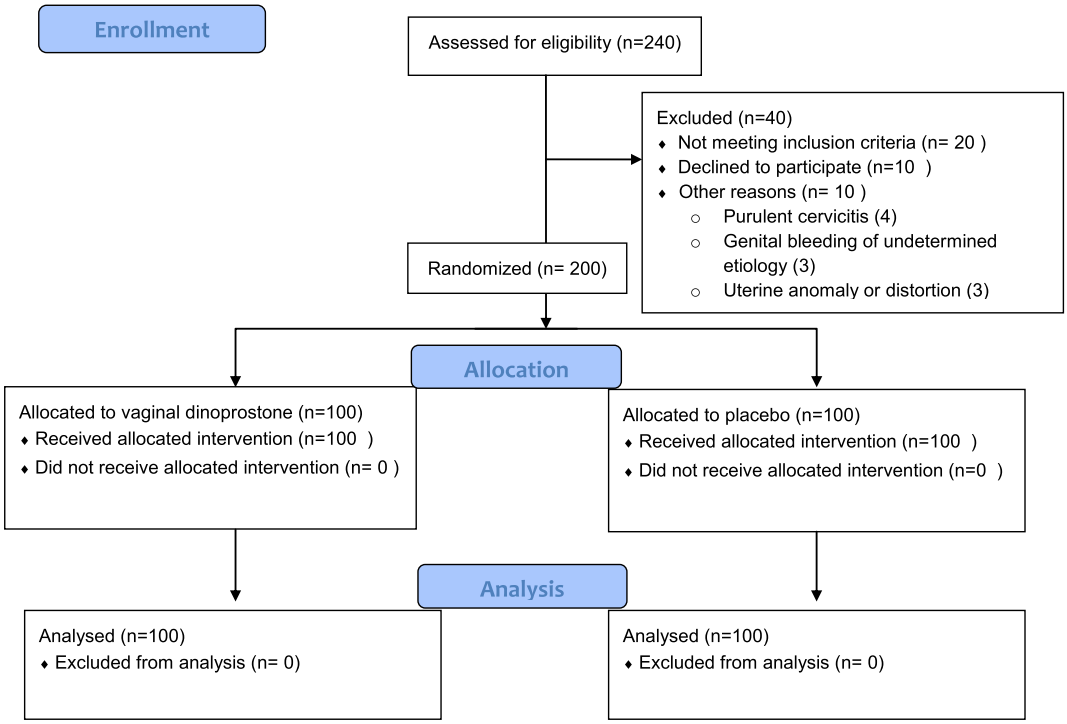

Fig. 1. Consort flowchart showing enrollment of participants in vaginal dinoprostone and placebo groups given six hours before copper IUD insertion.

Table 1
The baseline RCT characteristics of the Egyptian women according to the medication used prior to IUD insertion.

Characteristics		Dinoprostone group ($n = 100$)	Placebo group ($n = 100$)	p-value
Age (years)		26.6 ± 6.3	26.9 ± 6.9	0.75
Education level (years of schooling)		10.4 ± 3.5	10.5 ± 3.6	0.92
Position of the body of the uterus				
Anteverted/anteflexed		82 (82%)	78 (78%)	0.35
Midposition		7 (7%)	13 (13%)	
Retroverted/retroflexed		11 (11%)	9 (9%)	
BMI, kg/m^2		21.9 ± 2.2	22.1 ± 3.9	0.66
Gravidity	Nulligravida	83 (83%)	86 (86%)	
	1	14 (14%)	12 (12%)	
	2	2 (2%)	1 (1%)	0.54
	≥3	1 (1%)	1 (1%)	
History of	Spontaneous abortion	15/21 (72%)	12/17 (71%)	0.47
	Induced abortion	6/21 (28%)	5/17 (29%)	

All data are presented as n (%) or mean ± SD.
BMI: body mass index RCT: randomized controlled trial.

Table 3
RCT Side effects during insertion of an IUD in Egyptian nulligravidas according to whether vaginal dinoprostone or placebo was administered six hours prior to the procedure.

Variable	Dinoprostone group (n = 100)	Placebo group (n = 100)	p-value
Nausea	21 (21)	30 (30)	0.14
Vomiting	5 (5)	3 (3)	0.72
Shivering	5 (5)	0 (0)	0.05
Diarrhea	4 (4)	0 (0)	0.12
Fever	5 (5)	0 (0)	0.05
Vagovagal reaction	7 (7)	8 (8)	0.78
Cramps	95 (95)	93 (93)	0.55
Pain at insertion (VAS score)[a]	3.7 ± 2.3	5.0 ± 2.8	<0.01
Post-procedural bleeding			
None	7 (7)	9 (9)	0.60
Minimal bleeding/spotting	93 (93)	91 (91)	

Dara are presented as number (percentage).
RCT: randomized controlled trial.
[a] Pain was rated on a scale from 0 to 10.

failures were similar in both groups (Table 3). There were six IUD insertion failures; Two of them occurred in dinoprostone group. No cases of uterine perforation occurred in either group.

Moreover, the women randomized to dinoprostone reported lower pain scores than women in the placebo group (3.7 ± 2.3 vs. 5.0 ± 2.8, $p < 0.01$; Table 2).

Frequencies of post-procedural bleeding, vasovagal reaction, cramps, nausea, and vomiting, were similar in both groups (Table 3).

4. Discussion

Dinoprostone has been utilized for non-obstetric indications as in hysteroscopy to ease insertion and decrease pain associated with the procedure.

We conducted this study to assess whether or not vaginal dinoprostone administered six hours before IUD facilitates IUD insertion and decreases IUD insertion pain. We found that easier copper IUD insertion with less resistance at the level of internal cervical os and less insertion pain occurred in vaginal dinoprostone users. However, the reduction in pain scores was not clinically significant.

Todd et al. [19] defined minimum clinically significant difference (MCSD) in VAS pain score as the numeric change in VAS pain score that is associated with patient's subjective assessment of a little less pain or a little more pain. Changes less than 13 mm in VAS pain score may have no clinical importance [19] as MCSD in acute pain ranged between 13 and 20 mm [20,21].

Dinoprostone also increased cervical dilatation, 72% of our patients had a cervical dilatation of more than four mm. In our study, Postprocedural bleeding, vasovagal reaction, cramps, nausea, vomiting, and insertion failures did not differ significantly between dinoprostone and placebo groups which were also found in a recent RCT of vaginal dinoprostone in outpatient hysteroscopy [22]. Few non-significant side effects in our study may be due to the small 3 mg dose of dinoprostone used as severity of prostaglandin side effects is dose-dependent. Also, nature of the procedure and population type may affect the frequency of side effects as observed in our study compared to other studies with different procedures and different study populations; however, this needs further multicenter studies with subgroup analysis according to the race and ethnicity. We also did not find a statistically significant difference in insertion time between both groups.

Our findings are consistent with other studies in the literature. In Tan et al., [23] and Ferraiolo et al. [24] studies, dinoprostone given as pessaries or intravaginal gel proved effectiveness in inducing cervical ripening in labor.

Many medications are routinely used to ease intrauterine device insertions. About 10 trials have investigated the effect of misoprostol in facilitating IUD insertion, and only two trials reported that misoprostol is associated with significant easier insertion [12]. Additionally, lidocaine alone did not have a significant impact on facilitating IUD insertion [12]. However, 2% lidocaine combined with oral diclofenac facilitated IUD insertion and decreased IUD insertion pain [25].

In Samy et al. [26] network meta-analysis, lidocaine plus prilocaine (genital mucosal application) significantly improved ease of IUD insertion compared with placebo. Moreover, misoprostol 400 mg orally and lidocaine plus prilocaine (genital mucosal application) ranked the highest for improving ease of insertion; however, misoprostol was associated with more side effects [26].

Three trials reported different results when misoprostol was compared with dinoprostone during hysteroscopy [14,15,27]. In nulliparous women undergoing diagnostic hysteroscopy, Abulnour et al. found no significant difference between 3 mg vaginal dinoprostone versus 400 μg vaginal misoprostol regarding cervical ripening, hysteroscope entry, and associated pain. Misoprostol was associated with more side effects [14]. However, Inal et al. found that 10 mg vaginal dinoprostone induced more cervical ripening than 400 μg misoprostol ($p < 0.001$) with fewer clinical side effects and complications [15].

On the other side, Preutthipan and Herabutya [27] found that dinoprostone is less effective than vaginal misoprostol for cervical priming in nulliparous women before hysteroscopic surgery. High doses of misoprostol used in those trials (400 μg in two trials [14,15] and 200 μg in one study [27]) may be the cause of higher side effects in misoprostol treated groups compared to other groups

A recent randomized study reported a two-fold increase in side effects (nausea, vomiting, and cramps) with 400 μg of oral misoprostol before hysteroscopy compared to 200 dose [28] with no additional efficacy benefit which proved the correlation between dose and rate of side effects [29].

Van der Griendt and Goldstuck [30] were the first to use dinoprostone (PGE_2) gel in IUD insertion in 1990 on two nulliparous patients and proved its efficacy in cervical dilatation. The study, however, had many limitations and lacked statistical significance tests, in addition to absence of a control group.

We aimed to provide a clear, reliable, and evidence-based source of information about the use of dinoprostone before IUD insertion. This gives our study some strength, In addition to good sample size (200 patients) and proper randomization, and adherence to CONSORT guidelines for clinical trials.

Our main study limitation is the subjective assessment of pain scores that could be affected by confounding variables. However, proper study design and randomization could overcome this limitation. Another limitation is that we did not assess pain at different time points after the procedure. Also, the six hours time interval between study drug administration and IUD insertion was relatively long. All participants were given the choice to wait in a waiting room with lots of entertainment or to go home and come back after six hours for IUD placement. However, waiting six hours to have a 5 minute IUD insertion might be impractical in most clinics and inconvenient for many patients particularly with the limited clinically relevant reduction of pain scores. Nevertheless, shortening time interval between medication intake and IUD placement is recommended in future studies.

In addition, dinoprostone has two main disadvantages; first, it is costly. However, in Egypt, most healthcare facilities provide this medication for free in outpatient clinics. Second, it is an unstable compound that must be refrigerated to preserve its potency. The

presence of refrigerators in our hospitals encouraged the use of dinoprostone. Finally, unavailability of other drugs, as misoprostol, urges the need for finding a substitute for facilitating IUD insertion.

We suggest comparing dinoprostone with other commonly used drugs in IUD insertion, such as lidocaine, misoprostol, and non-steroidal anti-inflammatory drugs and other study populations as multiparous patients and patients delivered only by cesarean section. Objective Assessment of patient satisfaction using a validated tool as the 10 cm VAS and shortening the interval between drug administration and IUD insertion are recommended.

In conclusion, although vaginal dinoprostone administration six hours prior to IUD insertion in nulliparous women facilitates the ease of insertion and increases the cervical dilatation, its usage is not routinely advised because the pain-relieving effect of dinoprostone is not clinically relevant. We did not find any statistically significant side effects between dinoprostone compared to placebo.

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