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Original Article

A randomized double-blind controlled trial of two different doses of self-administered vaginal misoprostol for successful copper intrauterine device insertion

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ABSTRACT

Objective: The current study aims to compare the efficacy and safety of 200 mcg versus 400 mcg vaginal misoprostol administered 3 h prior to intrauterine device (IUD) insertion in parous women.
Study design: A randomized double-blind controlled trial.
Setting: Women's Health Hospital, Assiut, Egypt.
Materials and methods: Two-hundred twelve women were randomized into two groups; group I received 2 misoprostol 400 mcg tablets and group II received one misoprostol 200 mcg and one placebo tablet vaginally three hours before a copper IUD insertion. The primary outcome was the rate of successful IUD insertion in both groups. The secondary outcomes include the rate of adverse effects.
Results: There was no statistical difference between both groups as regard successful IUD insertion ($p = 0.17$). Additionally, the satisfaction score reported by the women was not statistically different ($p = 0.11$). Failure of IUD insertion was present in three cases in the misoprostol 400 mcg group versus four cases in the misoprostol 200 mcg group ($p = 0.45$). Both groups were similar regarding the duration of insertion ($p = 0.85$). Abdominal cramping and shivering were the main side effects in both groups, however the rate of their occurrence was significantly higher in the misoprostol 400 mcg group than the other group (30.2% versus 10.4% and 7.5% versus 1.9%, respectively; $p = 0.0001$).
Conclusion: Vaginal misoprostol 200 mcg prior to IUD insertion appears to be similar to 400 mcg as regard the success of IUD insertion and procedure duration with significantly lower side effects.

1. Introduction

The intrauterine device (IUD) is one of the most effective contraceptive methods available in addition to one of the safest Long-acting reversible contraception (LARC) [1]. Its effectiveness is related to its low rate of unintended pregnancy that is expected due to independent use by women [2]. In spite of that, the incidence of its use is only 7.6% of women in developed countries and 14.5% in developing countries [3]. This can be attributed to worry for difficulty of insertion, pain for the woman during insertion, and an increased risk of infection [4,5].

Misoprostol is an inexpensive, prostaglandin E1 analogue used successfully for cervical ripening and dilatation prior to minimally invasive gynecological procedures; as evacuation and hysteroscopy [6,7] or for therapeutic termination of miscarriages [8]. Despite limited data to support its use, misoprostol is used frequently by clinicians before IUD insertion.

Previous reports in the literature about its use before IUD insertion are contradictory. While some of them found an easier insertion after its use but no difference in pain [9–11], others report neither easier insertion nor pain relief [12,13]. The most striking finding in all studies that women used misoprostol experienced more unwanted adverse effects reaching up to 61% of study participants as abdominal cramps, nausea, vomiting, shivering and diarrhea [9–13].

As there is no consensus has yet been reached in the literature as regard the administration of misoprostol prior to IUD placement, the current study aims to evaluate and compare the efficacy and safety of misoprostol 200 mcg versus 400 mcg administered vaginally prior to IUD insertion in regard to the success and ease of insertion procedure among parous women beside the rate of occurrence of adverse effects.

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2. Materials and methods

2.1. Study settings and duration

The current study was a randomized, double-blind, controlled trial, conducted in Assiut Women's Health Hospital, Egypt between the 1st of September and the 31st of December 2016. The Assiut Medical Ethical Review Board approved the study. The study was registered on ClinicalTrial.gov under the number NCT02901561.

2.2. Study participants

All women attended the Family Planning Clinic during the study period requested for an IUD insertion were clinically evaluated and invited to participate in the study if they have no contraindications for IUD insertion in accordance with WHO eligibility criteria [14]. All included women were non-pregnant, aged 18–45 years old, and did not receive any analgesics in the 24 h prior to IUD insertion.

We excluded women with any uterine abnormalities as congenital anomalies, endometrial lesions, adenomyosis, fibroids and intrauterine adhesions. In addition, women with chronic pelvic pain, abnormal uterine bleeding and history of cervical surgery were excluded. Moreover, women with allergy to misoprostol or any medical disease contraindicate its use and those who refused to participate in the study were also excluded.

2.3. Enrollment

Informed consent was obtained from all eligible participants included in the study before participation after explaining the nature of the study. Before insertion, one of the study investigators collected the baseline data. Each woman received a copper T380A IUD (Paragard®T380A; Teva Pharmaceuticals USA, Inc. North Wales) for insertion. IUD insertion was performed while women were menstruating. The day of the menstrual cycle ranged from the first to the fifth.

2.4. Intervention

Eligible participants were randomly allocated into one of two groups: **Group I** (**misoprostol 400 mcg):** Women received 2 tablets (400 mcg) of misoprostol vaginally (Misotac®; Sigma Pharma, SAE, Egypt), and **Group II** (**misoprostol 200 mcg):** women received I tablet (200 mcg) of misoprostol and 1 placebo tablet created by a pharmacist in the Department of Pharmaceuticals, Faculty of Pharmacy, to be identical in size, shape, weight and color to the misoprostol tablets. A single pharmacist was responsible for the packaging of both preparations, so neither the physician nor the patient knew the type of the preparation (double-blind study). Women were instructed to self insert the tablets deep in the vagina three hours before IUD insertion.

IUD insertion was done by one of the study investigators who was experienced in IUD insertion using the standard technique of application prescribed by the manufacturer. Firstly, the speculum was placed into the vagina and the cervix was cleansed with Povidone iodine. After placement of single toothed volsellum on the anterior lip of the cervix for traction and fixation of the uterus, the uterine sound was inserted for measurement of uterine length and evaluation of the uterine position followed by IUD insertion. Immediate complications of IUD insertion such as uterine perforation, failure of insertion, and vasovagal reaction and the duration of IUD insertion were recorded.

After the end of insertion, the clinician reported the ease of IUD insertion using the ease of insertion score (ES). The ES was calculated at a graduated VAS-like scale from zero to 10; in which 10 means terribly difficult insertion and zero means very easy insertion. The ES was validated for use in previous similar studies about IUD insertion [11,15]. Also, all women expressed their level of satisfaction with IUD insertion by completing a 10-cm VAS (with 0 = no satisfaction and 10 = maximum satisfaction). Finally, the clinician asked all women about the need for any additional analgesics at 15 min after completing the procedure.

After insertions, all women were subjected to TV/US to assess the IUD place and to ensure that the IUD was located in the uterine cavity correctly. Side effects of the medications were also reported by the participants. The side effects queried were headache, nausea/vomiting, abdominal cramping, shivering, fever and diarrhea.

2.5. Randomization

Randomization was done by a statistician using computer-generated random table. After acceptance of eligible women to participate in the study, they were assigned randomly to either one of the two groups. Allocation concealment was done using serially-numbered closed opaque envelope. Each envelope was labeled with a serial number and had a card noting the intervention type inside. Once allocation had been done, it could not be changed. Randomization was carried out (1:1) in accordance with a list created using the block randomization method and containing sequential numbers from 1 to 212 (the number of women to be randomized). Once allocation had been done, it could not be changed.

2.6. Study outcomes

The primary outcome was the successful IUD insertion as defined by a distance from the IUD to the endometrial end of less than 25 mm [16]. The secondary outcomes included the ease of IUD insertion; the duration of insertion; the women's level of satisfaction at the end of insertion, the number of women who need analgesics after the insertion and the side effects of the study medication.

2.7. Sample size

Sample size was calculated using G∗ power 3 software program. As our hypothesis assumed a similar rate of success of IUD insertion with lower side effects when misoprostol 200 mcg used, we calculated the sample size based on the rate of side effects reported with misoprostol 400 mcg in previous studies. Dijkhuizen et al., 2011 reported that the rate of side effects with vaginal misoprostol 400 mcg was 56.6% [12]. Using two sided chi-square (χ^2) test with α of 0.05, a total sample size of at least 202 women in both groups (101 in each arm) using 80% power to detect 30% reduction in the rate of side effects with the use of misoprostol 200 mcg [Odds Ratio = 0.45]. We assumed a drop-out rate 5%, so 212 women were included in the study.

2.8. Statistical analysis

All data were analyzed using SPSS software Chicago, IL, USA, version 21. Qualitative data were expressed as frequency and percentage. Comparison between dichotomous variables in both groups was done by Chi-square test. Quantitative data were presented in terms of mean and standard deviation. For quantitative data, Student T-test was used for comparison between two groups. Level of significance "P" value was evaluated, where P value < 0.05 is considered of significant value.

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