Efficacy and safety of Vaginal Misoprostol in reducing pain during Levonorgestrel Intrauterine Device insertion.

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ABSTRACT

Background: One of the reversible, efficient, globally used contraceptives is the intrauterine contraceptive device (IUCD). However, what restrict its adoption is the Lack of training, The concern about inflicting pain during the process, and complications throughout the procedure that might lead to insertion failure are the main barriers to its adoption.

Aim: Our research seeks to assess the impact of vaginal misoprostol prior to LNG-IUD (Mirena®) placement on pain reduction in women who have previously had cesarean sections.

Materials and method: we conducted randomized controlled study. 130 women were contacted to take part in the research. Of them, four IUD insertions failed. In all, one hundred twenty-six people were included in the analysis, sixty-four in the misoprostol trial group and sixty-two in the placebo control group. In order to decrease the frequency of unsuccessful insertions, insertion-related problems, and discomfort during insertion, the current research assessed the effectiveness of 400mcg vaginal misoprostol 6 hours before LNG-IUD insertion in women who had only had a cesarean section before.

Results: Our study found that there were significant differences between placebo group and misoprostol group regarding the ease of LNG-IUD insertion with the prior use of misoprostol and regarding pain which was found to be more in the placebo group, regarding side effects, no significant differences were found as regard shivering, nausea, vomiting and syncope between both groups. But there was significant difference regarding to diarrhea, more in the study misoprostol group.

Conclusion: Misoprostol could be effective in facilitating the insertion of (Mirena®) IUD and decreasing the pain at insertion.

keywords: misoprostol, Intrauterine Device (IUD), VAS

Introduction

IUDs are reversible way of contraception that are widely used because they are secure and economical. Currently, 8 to 15% of reproductive-age females over the globe utilize IUDs. Reversible contraception includes copper and levonorgestrel-releasing IUDs (LNG-IUDs) [1]. In addition, there are non-contraceptive applications for the LNG-IUD (Mirena®), including the management of menorrhagia and dysmenorrhea and the prevention and/or treatment of endometrial hyperplasia [2]. Insertion failure, uterine perforation, and expulsion are problems of IUD insertion that are connected to the insertion procedure. Syncope and other issues are related to women's experience of discomfort. Women who have never given birth vaginally tend to have more insertion failures[3]. The tiny or immature cervix, cervical stenosis, and the anteverted or retroverted location of the uterus are cervical issues that may make the cervical canal difficult to be sounded and may prevent the IUD from being inserted[1]. It is difficult to estimate the pain associated with IUD implantation since women perceive pain differently and are influenced by a variety of variables, including cultural variations and personal experiences. According to some studies, nulliparity is the best predictor of pain, along with the length of time since the previous pregnancy, for increased insertion pain[4]. Women often anticipate more pain than they actually feel, and most nulliparous women only feel mild discomfort following IUD implantation. However, a small percentage of people (about 17%) experience excruciating discomfort after IUD implantation. These ladies need efficient pain management[5].

The rate of IUD use may be somewhat connected to women's fear of experiencing pain during device insertion, which may discourage some women from adopting IUDs and cause medical professionals to advise or promote alternative, less effective treatments to these women. Therefore, reducing discomfort during IUD insertion may be very important for promoting IUD usage[5, 6].

Misoprostol is a drug that costs little to buy. that contains a prostaglandin E1 analogue that very rarely causes adverse effects such nausea, vomiting, and pains in the abdomen. Studies have demonstrated the benefits of misoprostol as a cervical ripening agent in non-pregnant women and have shown that priming with misoprostol before hysteroscopy and before dilatation and curettage (D&C) increases cervical dilatation and decreases the risk of cervical laceration in perimenopausal women1. Misoprostol promotes cervical effacement by increasing the quantity of fluid in the stroma by increasing the amount of collagen fiber at the cellular matrix where it acts.

Our research seeks to assess the impact of vaginal misoprostol prior to LNG-IUD placement on pain reduction in women who previously had cesarean sections.

Patients and method

This Randomized controlled trial set in Outpatient clinic in Department of Obstetrics and Gynecology, Faculty of Medicine, Helwan University Hospital at Badr city from March 2021 to March 2022.

Study population: 130 females with a previous cesarean section attending for Mirena LNG-IUD insertion.
The protocol and all related documents revised and approved by the faculty of medicine, Helwan University, Research Ethics Committee No harmful procedure was performed or used on any patient, A written informed consent about the study was obtained from participant before their enrollment.
The patients were simply randomized after fulfilling the following criteria:

Inclusion criteria:

We included women from 20 to 45 years old, Delivered only by one or two CS, No previous vaginal delivery, Negative pregnancy test, No history or current pelvic inflammatory disease, No contraindication to LNG-IUD insertion (Gynecological malignancy, Undiagnosed abnormal vaginal bleeding) and No allergy to misoprostol or contraindication for the use of it.

Exclusion criteria:

we excluded women < 20 or > 45 years old, delivered by more than two CS, Previous Vaginal Delivery, Positive pregnancy test, any signs of pelvic inflammatory infection, Uterine anomaly, any contraindication to LNG-IUD insertion (Gynecological malignancy, Undiagnosed abnormal vaginal bleeding) and Allergy to misoprostol or patients are contraindicated to the administration of misoprostol.

Group 1: (misoprostol group): received 400 μg misoprostol vaginally 6 hours before LNG-IUD insertion. while women are menstruating, starting from the fifth to the tenth day of the menstrual cycle. **Group 2: (A placebo control group**): we used YAZ (contraceptive tablets) white placebo tablets which are equal in shape, weight, and color to the misoprostol tablet and has placebo proven efficacy with no

active substances vaginally 6 hours before LNG-IUD insertion. while women are menstruating, starting from the fifth to the tenth day of the menstrual cycle.

Procedures:

The following was done for all participants

Complete history taking:

Full history taking included obstetric history, menstrual history, and medical history.

Complete clinical examination: General examination, Abdominal examination and pelvic examination.
All of the women have received counseling about the different kinds of IUDs, the benefits and drawbacks of LNG-IUDs, and the study's methodology.

Following a history-taking, abdominal, and pelvic examination to rule out genital infections or masses, we performed a transvaginal ultrasound on the patient to confirm the results of the physical examination and to rule out any uterine or pelvic pathology that would be contraindicated for the insertion of an IUD. to measure the size and axis of the uterus. We applied the levonorgestrel-releasing IUD (LNG-IUD) (Mirena®) using the manufacturer's recommended standard procedure when women were menstruating, beginning on the fifth to the tenth day of the menstrual cycle. On the day of LNG-IUD placement, the clinic nurse tested each participant's urine for pregnancy. The subjects were in the lithotomy posture six hours prior to the LNG-IUD implantation. Two tablets of Misotac (SIGMA Pharmaceutical Industries, Egypt) containing 400 mg of misoprostol, the study drug, or two white YAZ (Bayer HealthCare Pharmaceuticals contraceptive pills), the placebo drug, were inserted as deeply into the posterior vaginal fornix as possible. The participants have been advised they may go home and come back in six hours to have the LNG-IUD implanted.

Steps of (LNG-IUD) (Mirena®) insertion:

We inserted the speculum into the vagina and used povidone-iodine to clean the cervix. A single-toothed vulsellum was used to hold the anterior lip of the cervix, to fix the uterus. This was followed by the insertion of a uterine sound to measure the length and angle of the uterus. To maintain sterility, the LNG-IUD (Mirena®, Bayer HealthCare Pharmaceuticals) was held using a non-touch method and then

inserted. A vaginal ultrasound was performed to check the IUD's location within the uterus after the threads were cut off, leaving 3 cm. Only the proximal and distal ends of the LNG IUD's arms are echogenic.

We did note the minutes it took to implant the LNG-IUD (from insertion to removal of the speculum) and any acute difficulties, such as vasovagal response, uterine perforation, or insertion failure, straight after the insertion process. and 5 minutes after. The participant chose the point on the VAS sheet that matched the intensity of her discomfort while the research assistant held the sheet for her. Patients were asked to assess their level of discomfort throughout the operation on a VAS scale from 0 (painless) to 10 (worst pain).

VAS: Visual Analog Scales

is a line, often 10 cm long, with the words "no pain" and "the most intense pain imaginable" at each end, respectively. The patient makes a mark on the line at the location where they would rate their level of pain. Although either a horizontal or vertical orientation of the line may be used to represent it, horizontal lines are often chosen. The horizontal VAS was used.

Women received one intramuscular injection of 75 mg/3 ml diclofenac sodium (Voltaren, Novartis, Basel, Switzerland) if their pain level was 5 or higher. We evaluated the failure rate of LNG-IUD insertion and the difficulty score of LNG-IUD insertion (which was evaluated by the gynecologist performing the operation on a scale from 0 to 10 equal to pain).

Before inserting the LNG-IUD, we inquired about the patient's misoprostol adverse effects (abdominal pains, nausea, and vomiting) to be sure they were caused by the medication and not the insertion process. We documented the LNG-IUD insertion's side effects, including bleeding and uterine perforation.

Measures of study results:

The main goal: is to assess the level of discomfort experienced after the insertion of an intrauterine device following vaginal misoprostol or a placebo.

Secondary goals; included assessing the difficulty of LNG-IUD insertion, the failure rate of LNG-IUD insertion, misoprostol use-related adverse effects, and complications of LNG-IUD insertion.

The gathered information was arranged, tallied, and subjected to proper statistical tests for analysis.

Sample size: According to data from the family planning literature, a difference of 1.5 points on the scale for the main outcome of pain with LNG-IUD insertion is clinically significant. With a sample size of 130 patients (65 patients each group), we were able to identify a 1.5 difference in VAS pain levels between the two research groups with a standard deviation of 2 and a power of 90%. Utilizing the Epi-Info statistical software tool, the sample size and power analysis were computed.[8].

Statistics

With the use of SPSS software (SPSS; SPSS Inc., 28 Chicago, Illinois, USA), the gathered data were tabulated and examined. While categorical data were reported as number and percentage, continuous variables were presented as mean standard deviation (SD), mean difference (MD), and 95% confidence interval (CI), if applicable. To evaluate categorical data, we used the Chi-square (2) test or the Fisher exact test (where the predicted frequency was 5), and to compare continuous variables, we used the student t-test. Statistical significance was defined as a P value 0.05.

Results

We approached 150 women to participate in the study. We excluded 24 of them; 15 did not meet inclusion criteria, 5 declined participations, and 4 failed insertions. One hundred twenty-six were included in the final analysis.

Variable		Misoprostol (64)	Placebo (62)	P-value
Age		35.05+6.18	35.3+6.8	0.791
BMI		30.2+3.3	29.8+3.5	0.531
Residence	Urban	25(39%)	28(45.2%)	0.28
	Rural	39(61%)	34(54.8%)	
Education	Low	8(12.5%)	7(11.3%)	0.963

level	Medium	13(20.3%)	12(19.4%)	
	High	43(67.2%)	43(69.3%)	
Parity	P1	21 (32.8%)	22(35.5%)	0.752
	P2	43 (67.2%)	40(64.5%)	
Previous abortion	Yes	37(57.8%)	32(51.6%)	0.905
	No	27(42.2%)	30(48.4%)	
Duration from last pregnancy		4.23+2.96	4.06+2.97	0.747
Position of uterus	AVF	52(81.3%)	51(82.3%)	0.884
	RVF	12(18.6%)	11(17.6%)	

Table1; Demographic data of the studied groups

There was no statistical significance in age, BMI, residence, and education level; 0.791,0.531, 0.28, 0.963 respectively. There were no significant statistical in parity, previous abortion, duration from last pregnancy and the position of the uterus p-value >0.05.

Variable	Misoprostol (64)	Placebo (62)	P-value
Ease of insertion	4.48+1.2	2.66+1.3	<0.001
Anticipated pain	6.16+1.8	6.3+1.9	0.756
Pain speculum	4.61+1.4	5.26+2.01	0.041
Pain tenaculum	3+1.4	4.5+1.6	<0.001
Uterine sounding	3.6+1.7	5.2+1.4	<0.001
Pain at insertion	2.8+1.1	4+1.7	<0.001

Pain after 20 min	1.9+1.1	2+1.2	0.496
Insertion time	4.4+1	4.5+1	0.527
Satisfaction	49(76.5%)	27(43.5%)	<0.001

Table2; outcomes of the procedure

There were no statistically significant terms of anticipated pain speculum, Pain after 20 min and insertion time p-value>0.05.

On the other hand, we found a statistical difference in Ease of insertion, Pain tenaculum, Uterine sounding and Pain at insertion and satisfaction <0.001.

Variable	Misoprostol (64)	Placebo (62)	P-value
Spotting	10(16.1%)	15(23.4%)	0.304
Abdominal cramps	11(17.7%)	20(31.3%)	.078
Nausea	3(4.8%)	6(9.4%)	0.367
Vomiting	1(1.6%)	3(4.7%)	0.619
Shivering	2(7.8%)	5(7.8%)	0.440
Diarrhea	11(17.2%)	0(0%)	<0.001
Fever	2(3.2%)	4(6.3%)	0.680
Need additional analgesia	20(31.3%)	26(41.9%)	0.267

Table 3; adverse events of the participant.

There was no statistically significant spotting, abdominal cramps, nausea, vomiting, shivering, fever, and need additional analgesia p-value>0.05.

On the other hand, we find a statistical difference in diarrhea <0.001.

Our main goals were to compare the two groups' pain scores and how challenging the Mirena IUD was to install. We found that inserting the Mirena IUD was simpler in group 1 (the misoprostol groups) than in group 2 (the placebo groups).

We discovered that group 1 (the misoprostol group) had substantially less discomfort during the installation of the Mirena IUD than did group 2 (the placebo group).

Discussion

One of the most effective kinds of contraception now in use is the IUD. ACCORDING TO MANY STUDIES, the LNG-IUD is perhaps the most effective and cost-efficient form of birth control now in use since it only requires a single procedure to provide considerable contraceptive effectiveness over an extended period of time.[9,10].

Age, parity, the interval since the previous pregnancy, and the kind of IUD are all factors that affect how easily an IUD is inserted and how much pain the patient experiences. The Mirena IUD's sheath is 4.4 mm wider than those of certain other IUDs, which makes insertion a little less pleasant[11].

The purpose of the present research was to determine how using vaginal misoprostol prior to LNG-IUD implantation helped in insertion and reduced pain and discomfort. When taken vaginally, misoprostol reaches a peak concentration about an hour. In contrast to oral or sublingual treatments, it gradually declines, with levels remaining high for at least 6 hours. In order to get the optimum effect via direct local action and higher plasma concentration, we used vaginal misoprostol in our experiment. In this research, it was discovered that the primary group receiving vaginal misoprostol 400mcg had less pain during the insertion of Mirena than the placebo group. But compared to the misoprostol group, the placebo group had less side symptoms (vomiting, nausea, and uterine cramps). **Salama et al.**[13] discovered, in line with the results of the present investigation, that misoprostol administered vaginally prior to the implantation of a Mirena IUD might aid in facilitating the insertion procedure with few side effects when given in a dosage of 200mcg as opposed to greater doses. While we only utilized one 400mcg dosage in our trial, their study evaluated two doses of misoprostol to compare effectiveness to adverse effects.

El-Gawad et al.[14] research on women who delivered exclusively through elective cesarean section showed that misoprostol, given vaginally three hours before IUD installation at a dose of 400mcg, significantly improved the ease of insertion and reduced the incidence of pain during the procedure. In our study, we found that

taking 400mcg of vaginal misoprostol six hours prior to the placement of an IUD allows the insertion of the Mirena IUD with less side effects.

According to **Mansy et al.,**[15] parous women who had previously had unsuccessful IUD insertion were given 200mcg of vaginal misoprostol before the procedure. This enhanced the rate of successful insertion, particularly in those who had previously undergone a cesarean birth. But whereas we utilized the LNG-IUD in our trial, they employed the copper IUD in their investigation. Additionally, we employed a dosage of 400mcg just 6 hours before to insertion whereas they compared the time of insertion with doses of 200mcg 4 and 10 hours prior to insertion.

M El-Garhy et al.[16] studied the outcomes of 120 women who had previously had a cesarean section but had never given birth vaginally on 600mcg sublingual misoprostol administered two hours prior to the implantation of a Tcu 380A IUD. They discovered that using Misoprostol prior to IUD implantation decreased pain perception but increased the frequency of mild side effects such nausea, fever, and stomach cramps. They used more of the drug than we did, and sublingual delivery was used as opposed to our vaginal one. This is in line with the findings of **Maged et al,** who discovered that using 600 mcg of misoprostol vaginally six hours before the implantation of a copper T 380A IUD in women who had never given birth vaginally sped up the procedure and lessened discomfort.

In order to facilitate IUD insertion in women with a tight cervix, **Elgharbawy et al.**[17] and her research team found that sublingual 200mcg misoprostol did not affect pain relief or the ease of IUD insertion; however, the results with misoprostol are better than placebo, but the difference is not statistically significant. This is in line with the findings of **Ibrahim et al.**[3], who examined the effects of sublingual 400mcg misoprostol given one hour prior to intrauterine device (IUD) insertion on pain in parous women who were only delivered by elective cesarean section (CS) and found that doing so did not speed up the procedure. They took sublingual misoprostol one hour before implantation; this might be explained by differing dosage and timing strategies.

In a detailed meta-analysis that was published in 2020, **Tassi et al** [18] came to the conclusion that sublingual misoprostol did not improve insertion facilitation. Contrarily, misoprostol is commonly mentioned in connection with patient comfort. Further research has not shown an increase in insertion ease.

In a systematic review of drugs used to facilitate intrauterine device insertion, **Zapata et al**[19] found that the majority of the evidence did not support the use of 400mcg of misoprostol prior to IUD insertion, regardless of the route or timing of administration. They also found no evidence that this practice increased provider ease of insertion, decreased the need for adjunctive insertion measures, or increased insertion success among general samples of women seeking IUDs. According to **Espey et al.** [20], 400 mcg of misoprostol had no impact on alleviating pain or enhancing ease of insertion. But only nulliparous females were used in this investigation.

The RCT conducted by **Dijkhuizen et al**[1] to determine if misoprostol usage prior to IUD implantation facilitates the installation of an IUD in nulli- and multi-parous women was unsuccessful in demonstrating a difference between the misoprostol and placebo groups. However, a diverse group of individuals, including both multiparous and nulliparous women, were used in that research. This may suggest that misoprostol may only be advantageous for a certain group of patients, such as our patients who have only had one prior cesarean section[1].

In a study by **Chaves et al.**[21], it was discovered that women who had previously given birth vaginally experienced less pain at the time of levonorgestrel IUD implantation than nulligravida and women who had previously undergone an elective cesarean delivery without any prior labor. In our research, we discovered that women who got vaginal misoprostol after having an elective cesarean birth in the past had a less unpleasant time inserting a levonorgestrel IUD.

In the present research, problems related to insertion, such as hemorrhage, insertion failure, and perforation, did not significantly vary between the two groups with (P value >0.05), **Scavuzzi et al**. with the same result also. Additionally, there was no discernible difference in the analyzed groups' shivering, vomiting, or nausea in the present investigation.

Although advantages overweight side effects of misoprostol were seen in the present trial, diarrhea was substantially more common among the misoprostol group; this concurs with **Abbas et al**[22] for shivering with (P value=0.001). However, the findings did not support the findings of several research suggesting misoprostol was ineffective for making IUD insertion easier. The majority of these earlier investigations, however, were nulliparous women, while the participants in the current research were those who had elective cesarean sections [23,24].

Our research has certain drawbacks. Due to factors including the study's small sample size and exclusion of women who had previously given birth vaginally, the findings may have been affected. Therefore, in order to examine the impact of vaginal delivery on the simplicity of LNG-IUD implantation, we need more research with a large participant pool that includes both women who have previously given birth vaginally and who have previously had CS.

Conclusion

According to this study results, the usage of 400mcg of vaginal misoprostol 6 hours prior to insertion of Mirena IUD in women with only previous cesarean section with no previous vaginal bleeding, seems to be effective in facilitating the insertion of Mirena IUD and decreasing the pain at insertion, But with significantly increased side effects more than placebo.

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