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Research Article

Intrauterine Device Insertion in Women with Pervious Cesarean Section Using Vaginal Versus Sublingual Misoprostol: A Randomized Clinical Trial

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Abstract

***Background**: The cesarean section (CS) makes the cervix stenosed and narrow, so that most of women who have previously had a CS always found it difficult and painful to insert an intrauterine device (IUD). Priming with misoprostol before hysteroscopy and dilatation and curettage in premenopausal women resulted in an increased cervical dilatation and lower rate of cervical laceration because of misoprostol utility for cervical ripening before this procedure.*

***Objective**: The aim of the study is to compare the effect of vaginal versus sublingual misoprostol prior to insertion of an intrauterine device in multiparous women delivered only by caesarean section.*

***Methods**: This randomized controlled clinical trial was conducted at tertiary care hospital at Ain Shams University Maternity Hospital (Family planning Clinic) from May 2021 till April 2022 and performed on total 290 patients who delivered only by CS seeking intra uterine device insertion with inclusion and exclusion criteria.*

***Results**: Easy insertion was statistically significantly more frequent in vaginal group, while difficult insertion statistically was significantly more frequent in sublingual group. Patients' pain perception was significantly lower among vaginal group. Vasovagal-like reactions statistically were non- significantly more frequent in vaginal group, while syncope statistically was non-significantly more frequent in sublingual group. Perforation (cervical/ uterine) and heavy bleeding not recorded in either group. There was no significant difference between vaginal and sublingual misoprostol groups regarding IUD Expulsion.*

***Conclusion**: As evident from the current study, Vaginal misoprostol is preferred than sublingual route as cervical ripening occurs more likely with vaginal administration. The use of vaginal 400 µg of misoprostol administered 2 h before IUD insertion facilitates IUD insertion and reduces the incidence of pain during the procedure.*

***Keywords**: Intrauterine Device Insertion, Vaginal Versus Sublingual Misoprostol.*

Introduction

Intrauterine contraception (IUC) is the most widely used method of reversible fertility regulation in the world. Over 100-millions of women worldwide use it for contraception. In Cuba, Egypt, and North Korea, intrauterine contraceptive device (IUCD) use accounts for more than 50% of contraceptive use. They have the highest rate of satisfaction and continuation of all reversible contraceptives (1).

Cervical stenosis, an immature or small cervix, and a significantly anteverted or retroverted position of the uterus has been described as factors associated with a difficult sounding of the cervical canal or even failure to insert the IUCD. The mechanical means to overcome anatomic cervical stenosis and scarring during IUCD insertion are through direct cervical traction with a tenaculum and the additional use of a probe or dilator. These techniques are usually associated with increased pain, anxiety, or even failure (2).

Many women may feel discomfort or pain during and immediately after insertion of an IUCD. The fear of painful insertion may make women hesitate to use an IUCD (3). Moreover, insertion failures and cervical problems seem to occur more often among women who have never delivered vaginally. Therefore, healthcare personnel may be reluctant to insert an IUCD as this procedure is perceived as risky, with potential complications including failure of insertion and perforation (4)

Misoprostol is a synthetic and inexpensive prostaglandin estrone analogue. It may be administered orally or vaginally the night before and, if needed, again in the morning before minimally invasive gynaecological procedures such as hysteroscopy, to assist cervical softening. Its use, however, is associated with side effects such as abdominal cramps, uterine bleeding, shivering, nausea, vomiting and diarrhoea (5).

Studies have yielded conflicting results about misoprostol use before IUD insertion. Some have reported easier insertion but no effect on pain, while others have reported no beneficial effects at all (6). One study reported benefits in both ease of insertion and pain (7).

Consequently, this study aimed to compare the effect of vaginal versus sublingual misoprostol prior to insertion of an intrauterine device in multiparous women delivered only by CS.

Patients and Methods

After ethical committee approval and written consents from the patients, this prospective randomized controlled clinical trial was performed on total 290 multiparous women delivered only by CS seeking intra

uterine device insertion and willing to participate in the study at Ain Shams University Maternity Hospital, (Family planning Clinic) starting from May 2021 till April 2022.

Study population: The study was conducted on multiparous women delivered only by CS seeking intra uterine device insertion with the following criteria:

Inclusion criteria: Women at reproductive age group between 20-40 years who previously delivered by cesarean section with BMI between 20- 30.

Exclusion criteria: Women with contraindications for misoprostol use (pregnancy, prostaglandin allergy), women with a contraindication for IUCD insertion (e.g., less than sex weeks post-partum, gynecologic malignancy, uterine bleeding of undetermined origin, fibroids or other uterine abnormalities, active vaginitis or cervicitis, a history of PID or puerperal sepsis), women on anticoagulant therapy or having any coagulopathy and women who refused to participate

Study Procedures: All participants were submitted to the following:

Participants were distributed randomly and equally into two groups; Group 1 which included 145 women to whom two tablets (400 mg) of misoprostol (Misotac ®, Sigma, SAE, Egypt) were administered vaginally 2 h before IUD insertion, as deep as possible, and to remain in supine position for half an hour and Group 2 which included 145 women to whom two tablets (400 mg) of misoprostol (Misotac ®, Sigma, SAE, Egypt) were administered sublingually 2 h before IUD insertion. These women were instructed to keep the tablets under the tongue for up to 20 minutes and if the tablets do not melt by that time, they were allowed to swallow them. All women had their copper IUCD (a T380A [Copper T 380A, ®, Egypt]).

Follow up: All patients were seen for a routine check-up 6 weeks after IUD insertion. During this visit, vaginal examination and/or vaginal ultrasound were performed. IUD expulsions and infections were recorded.

Sample size: Using STATA program, setting alpha error at 5% and power at 90%. Results from previous studies (3, 8) showed that the complications occurred in 60% of sublingual group compared to `21.8% in vaginal group. Based on this, the needed sample is 145 cases per group (290 total) after taking in consideration 20% drop out rate.

Outcome measures:

The primary outcome included the proportion of easy IUD insertions. Difficulty of IUD insertion was

measured by cervical dilatation that determined by two factors: (1) Degree of dilatation of cervix by using gradual Hegar 1, 2, 3. and (2) The degree of difficulty of the IUD insertion judged as the resistance of the internal cervical os experienced by the investigator and classified as 'easy', 'moderate' or 'difficult'.

Score of insertion:

Easy: Using Hegar 3 and easy of difficulty of insertion.

Moderate: Using Hegar 2 and moderate of difficulty of insertion.

Difficult: Using Hegar 1 and difficult of difficulty of insertion.

Secondary outcome included uterine or cervical perforation, heavy bleeding, vasovagal like reactions (dizziness, nausea and vomiting), syncope, partial- or total expulsion, pain during insertion. Pain was measured using a visual analog scale (VAS) pain score reported by participants during IUD insertion.

Ethical Considerations: The patient data were anonymous. Data presentation was not be by the patient's name but by diagnosis and patient confidentiality was protected. An informed consent was taken from all participants, it was in Arabic language and confirmed by date and time. confidentiality was preserved by assigning a number to patients initials and only the investigator knew it

Conflict of interest: the candidate declared that there is no conflict of interest and the cost of the study was paid by the candidate.

Statistical analysis: Analysis is to be performed using SPSS for windows v20.0, Data to be presented in terms of range, mean and standard deviation (for numeric parametric variables); range, median and inter-quartile range (for numeric non-parametric variables); or number and percentage (for categorical variables). Difference between two independent groups is to be analyzed using independent student's t-test as well as the mean difference and its 95% CI (for numeric parametric variables); or chi-squared test as well as the risk ratio and its 95% CI (for categorical variables). Binary logistic regression analysis is to be performed for estimating the association between good/poor response and the measured variables ROC curves are to be constructed for estimating the validity of measured variables as predictors of good or poor response validity is to be presented in terms of sensitivity, specificity, positive and negative predictive values and their corresponding 95% Cis significance level is set at 0.05.

Results:

During this study, 376 patients with previous caesarean section and no prior vaginal delivery were assessed for eligibility and 290 patients were included in the study (145 in each group). Of all eligible patients, 74 patients were excluded from the study based on the inclusion criteria and 12 patients refused to participate in of the study. Ultimately, the analysis was based on the data of 145 patients in Vaginal group and 145 in the Sublingual group.

Table (1): Baseline characteristics among the studied groups:

Variables		**Vaginal (N=145)**	**Sublingual (N=145)**	**p-value**
Age (years)	**Mean±SD**	32.2±3.8	31.7±4.3	^0.247
	Range	20.0–39.0	20.0–40.0	
BMI (kg/m^2)	**Mean±SD**	26.1±2.1	25.9±2.1	^0.550
	Range	20.5–30.1	20.2–29.9	
Parity	**Median (1st−3rd IQ)**	1.0 (1.0–3.0)	1.0 (1.0–3.0)	#0.911
	Range	1.0–4.0	1.0–4.0	
Time after delivery (weeks)	**Mean±SD**	11.8±2.5	12.2±2.2	^0.183
	Range	6.0–18.0	6.0–17.0	

IQ: Interquartile. BMI: Body mass index. ^Independent t-test. #Mann Whitnet test.

Table (1) reported no significant difference between vaginal and sublingual misoprostol groups regarding age, BMI, parity and time after delivery.

Table (2): Easy of insertion among the studied groups

Grade	**Vaginal (N=145)**	**Sublingual (N=145)**	**^P-value**	**Effect size Relative risk 95% CI**
Easy	59 (40.7%)	20 (13.8%)	**<0.001***	2.95 (1.88–4.64)
Moderate	66 (45.5%)	71 (49.0%)		0.93 (0.73–1.19)
Difficult	20 (13.8%)	54 (37.2%)		0.37 (0.23–0.59)

#Chi square test with post hoc Bonferroni test, homogenous groups had the same symbol "a,b". CI: Confidence interval. *Significant. Effect size: Value of vaginal over sublingual.

Table (2) showS that Easy insertion statistically was significantly more frequent in vaginal group, while difficult insertion statistically was significantly more frequent in sublingual group.

Table (3): Patients' pain perception (VAS-10) among the studied groups.

Measures	Vaginal (N=145)	Sublingual (N=145)	^P-value	Effect size Mean±SE 95% CI
Mean±SD	2.5±1.0	3.7±1.0	**<0.001***	-1.2±0.1
Range	1.0–4.0	2.0–5.0		-1.4–-1.0

^Independent t-test. CI: Confidence interval. *Significant. Effect size: Value of vaginal over sublingual

Table (3) showS that Patients' pain perception was significantly lower among vaginal group

Table (4): Insertion complications among the studied groups.

Complications	Vaginal (N=145)	Sublingual (N=145)	p-value	Effect size Relative risk 95% CI
Vasovagal- like reactions	17 (11.7%)	10 (6.9%)	#0.157	1.70 (0.81–3.59)
Syncope	1 (0.7%)	3 (2.1%)	§0.622	0.33 (0.04–3.17)
Perforation (cervical/ uterine)	0 (0.0%)	0 (0.0%)	Not applicable	
Heavy bleeding	0 (0.0%)	0 (0.0%)	Not applicable	

#Chi square test. §Fisher's Exact test. CI: Confidence interval. *Significant. Effect size: Value of vaginal over sublingual

Table (4) shows that Vasovagal-like reactions statistically were non-significantly more frequent in vaginal group, while syncope statistically was non-significantly more frequent in sublingual group. Perforation (cervical/ uterine) and heavy bleeding not recorded in either group

Table (5): IUD Expulsion among the studied groups.

Expulsion	Vaginal (N=145)	Sublingual (N=145)	§p-value	Effect size Relative risk 95% CI
Partial	2 (1.4%)	1 (0.7%)	0.999	2.00 (0.18–21.81)
No expulsion	143 (98.6%)	144 (99.3%)		

§Fisher's Exact test. CI: Confidence interval. *Significant. Effect size: Value of vaginal over sublingual

Table (5) showS that there was no significant difference between vaginal and sublingual misoprostol groups regarding IUD Expulsion.

Discussion

Since intrauterine device insertion in women with pervious caesarian section represents major conflict and often associated with stenosed and narrow cervix, comparing between vaginal and sublingual misoprostol for cervical ripening before IUD insertion was highlighted as a main point of interest (4).

In this study, we aimed to compare the effect of vaginal versus sublingual misoprostol prior to insertion of an intrauterine device in multiparous women delivered only by caesarean section.

This randomized controlled clinical trial was conducted at tertiary care hospital at Ain Shams University Maternity Hospital (Family planning Clinic) from May 2021 till April 2022 and performed on total 290 patients who delivered only by CS seeking intra uterine device insertion.

During this study, 376 patients with previous caesarean section and no prior vaginal delivery were assessed for eligibility and 290 patients were included in the study (145 in each group). Of all eligible patients, 74 patients were excluded from the study based on the inclusion criteria and 12 patients refused to participate in of the study. Ultimately, the analysis was based on the data of 145 patients in Vaginal group and 145 in the Sublingual group.

In women with previous cesarean section and no prior vaginal delivery, health care personnel may be reluctant to insert an IUD, as this procedure is perceived as risky, with potential complications including failure of insertion, pain during insertion, and perforation (9).

Different studies were done comparing vaginal and sublingual misoprostol prior to insertion of an intrauterine device in women with previous caesarean section, some of them agree and others differ from our results.

The current study revealed that there was no significant difference between vaginal and sublingual misoprostol groups regarding age, BMI, parity and time after delivery (p values = 0.247, 0.550, 0.911, 0.183) respectively.

Our results revealed that Easy insertion was statistically significantly more frequent in vaginal group, while difficult insertion was statistically significantly more frequent in sublingual group (p value<0.001).

These findings are in agreement with previous studies. Mohammed NH et al., (4) conducted a study to compare vaginal and sublingual misoprostol before insertion of an intrauterine device in women who have previously had a cesarean section and revealed that the use of misoprostol at a dose of 400 μg vaginally or

sublingual before IUD insertion was found to be associated with successful insertion on the first attempt in 94% in vaginally administrated group and 97% in sublingual group; these results were not statistically significant (P=0.498). On the contrary, Haddad et al. (10) reported that misoprostol for cervical ripening before IUD insertion does not ease the insertion process nor does it decrease pain, rather it seems to be associated with an increase in reported pain.

The present study revealed that there was no statistically significant difference in the position of the uterus between both groups and these results were in agreement with the study done by Mohammed NH et al., (4).

Our results revealed that Patients' pain perception was significantly lower among vaginal group (p value<0.001).

These findings are in agreement with previous studies done by Mohammed NH et al., (4) which revealed that there is a statistically significant difference between both groups regarding pain during IUD insertion, with P value of 0.001. Administration of misoprostol before IUD insertion was significantly associated with almost three-fold reduced pain during insertion in vaginal group (0.18%) than sublingual group (0.38%).

These results are also in agreement with results of previous studies done by Ward et al. (11) and Scavuzzi et al. (6) which revealed that the use of misoprostol at a dose of 400 μg administered vaginally 1 h before IUD insertion increased the ease of insertion and reduced the incidence of pain during the procedure.

In contrast to our results, Dijkhuizen et al., (8) and Guttmacher Institute (12) who performed a randomized controlled placebo trail on a group of nulliparous women, and assessed the difference in dose and time of administration. Dijkhuizen et al., (8) reported that the use of self-administered misoprostol for cervical ripening before insertion of an IUD does not improve ease of insertion for the provider or decrease reported pain for the patient and revealed that oral analgesics and antispasmodic in addition to misoprostol was given to overcome the adverse effects of misoprostol.

Edelman et al., (13) published a clinical trial in which 400 μg of misoprostol was used orally 90 min before IUD insertion in 35 women with previous CS and found no significant difference in the pain reported by the women.

Saav I et al., (3) reported that pain caused by vaginal administration of misoprostol was found to be mild with 18% of cases belonging to this group experiencing no pain, whereas in the sublingual route, pain would range from moderate to severe (4).

Regarding the complications that occurred during IUD insertion, our results revealed that Vasovagal-like

reactions statistically were non-significantly more frequent in vaginal group, while syncope statistically was non-significantly more frequent in sublingual group. Perforation (cervical/ uterine) and heavy bleeding not recorded in either group with no significant difference between vaginal and sublingual misoprostol groups regarding IUD Expulsion and infection.

These results are in agreement with results of previous studies done by Mohammed NH et al.,

(4) which revealed that there is no statistically significant difference between both groups (regarding perforation, heavy bleeding, difficulty of insertion, and vasovagal-like reaction).

Also, Li et al., (2), Ward et al. (11) and Scavuzzi et al. (6) reported that the use of misoprostol at a dose of 400 μg administered vaginally 1 h before IUD insertion increased the ease of insertion and reduced the complications that occurred during IUD insertion.

Mohammed NH et al., (4) revealed that no statistically significant difference between both groups regarding vaginal bleeding and menstrual changes after IUD insertion with no relation between route of misoprostol administration before IUD insertion and occurrence of infection which agreed with our results and Saav I et al., (2015).

On the contrary, Scavuzzi et al. (6) and Dijkhuizen et al., (8) reported that IUD insertion increases the rate of vaginal infection and even pelvic inflammatory diseases (PID) and may be mediated by irregular vaginal bleeding. Intermediate flora is associated with an increased incidence of vaginal infections (14).

Vaginal misoprostol is associated with slower absorption, lower peak plasma levels, and slower clearance and greater effect on the cervix and uterus (15). In contrast to the sublingual route, the plasma concentration increases gradually after vaginal administration, reaching its maximum level after 70–80 min before slowly declining with detectable drug levels still present after 6 h (4).

The strength points of this study:

The strength points of this study are that it is randomized controlled study design with standardized dosing and route of ingestion that had larger sample size sufficient to detect differences in pain and ease of insertion, related to the previous study by Mohammed NH et al., (4) which included 200 patients. It is the first study in Ain Shams University Hospitals to compare between two different routes of misoprostol affecting cervical ripening in relation to pain and easy insertion.

The limitations of the study:

The limitations of the study are worthy of mention including that the outcome for all studies assessing pain scores is subjective and can be affected by many factors. We did, however, try to overcome this limitation by a randomization plan that gave an equal balance of different participants

(with different pain perception thresholds) in the study. Another limitation is that we did not exclude women with psychological or neurological disorders associated with altered pain sensation.

Conclusion

Vaginal misoprostol is preferred than sublingual route as cervical ripening occurs more likely with vaginal administration. The use of vaginal 400 μg of misoprostol administered 2 h before IUD insertion facilitates IUD insertion and reduces the incidence of pain during the procedure.

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