Original Article

Use of Misoprostol before Copper T380A Intrauterine Device Removal in Women Delivered Only by Elective Caesarean Section: A Randomized Clinical Trial

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ABSTRACT

Objective: To evaluate the effect of misoprostol on the removal of pain of copper T380A intrauterine device (IUD) among women who had delivered by elective cesarean delivery (CS).

Study Design: The study was a randomized clinical trial.

Patients and methods: The study was conducted from the 1st of July 2019 to the 1st of July 2020 at Assiut Woman's Health Hospital, Egypt. Women who requested copper T380A IUD removal and delivered only by elective CS were included. The participants were assigned to the misoprostol group or no intervention group. The primary outcome was the difference in the intensity of immediate pain after IUD removal. Identification of potential predictors associated with high VAS immediately after IUD removal was explored. The data was analyzed using an unpaired t-test, chi-square test, Mann–Whitney U test, and multiple logistic regression.

Results: Eighty women were finally analyzed. The median of immediate VAS after IUD removal in the misoprostol group (4.0) was lower than the no-intervention group (6.0) with a statistically significant difference (p=0.000). A higher satisfaction score and lower ease score were also determined among the women in the misoprostol group. The longer time from IUD insertion, removal of IUD in non-menstruating women, women who did not use misoprostol before IUD removal, and women who did not use IUD before were significant clinical predictors associated with higher VAS immediately after IUD removal.

Conclusions: The use of vaginal misoprostol before copper T380A IUD removal reduces the removal pain and improves the ease and satisfaction among women who had delivered only by elective CS.

Key Words: Intrauterine device, misoprostol; VAS.

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INTRODUCTION

Intrauterine device is the most commonly used method of contraception in the world, mostly in developing countries, because it offers long-term, reversible, and relatively safe contraception[1]. At present, 50% of IUD users are women of reproductive age and most of them are requesting IUD removal to regain their fertility[2]. In general, an IUD should be removed during menses or preferably immediate after menses because IUD removal becomes easy due to soft cervix[3].

The IUD is usually removed by firmly grasping the threads at the external os; the traction should be applied away from the cervix[4]. Uncommonly, IUD removal may be challenging. The primary indicator of a problem is the inability to visualize IUD strings extending from the cervical os[5]. Some deeply embedded IUD may need to be removed by hysteroscopy[6].

In practice, some women may have an intolerable pain during IUD removal, and requesting strong analgesia to allow the physician to remove it. Cervical hardening and adhesions are the major factors making IUD removal difficult[7,8]. Insertion and removal of IUD in nulliparous women are possible but it may carry more pain and more difficulty than in parous women[9].

Many medical agents for cervical ripening before the IUD removal have emerged like misoprostol and mifepristone[10]. Misoprostol is commonly used for cervical ripening before IUD insertion[11]. The use of vaginal misoprostol before IUD insertion in women who had delivered by elective CS may increase the ease and success of insertion with less pain felt during the procedure[12].

So from the above evidence; we think that women who delivered by elective CS may face some difficulty during the IUD removal and misoprostol may facilitate this difficulty paving the way to painless, easy IUD removal.

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Up to our knowledge; no studies had been conducted or registered to show the effect of misoprostol on IUD removal pain in women who were delivered by elective CS.

PATIENTS AND METHODS

The study was a single-center, open randomized, parallel, and registered clinical trial (Clinical trial. gov:NCT03600064). It was conducted between the 1st of July 2019 and the 1st of July 2020 including women who attended the Family Planning Clinic at Assiut Woman's Health Hospital, Egypt requesting Copper T380A IUD removal and delivered only by elective CS. The protocol of the study was approved by The Assiut University Medical Ethical Review Board (IRB17101568).

Eligible participants

We included in this study non-pregnant women aged 18-45 years who were delivered only by elective CS. Elective CS means CS before the onset of labor[13]. Those women did not receive any analgesics or misoprostol in the 24 hours before IUD removal and were using a copper T380A IUD for contraception only. All included women were non-menstruating or at the last day of her menses. Finally, all of them requested IUD removal for returning fertility.

Women with an allergy to misoprostol or any medical disease that contraindicates its use, women with ultrasonographic evidence of displaced IUD, women who had received any other type of IUD, inability to visualize IUD strings extending from the cervical os, and women who refused to participate in the study were excluded.

Randomization

Eligible women who gave their written consent were randomized in two equal groups. Randomization was conducted using a computer-generated random table with allocation concealment. Serially-numbered closed opaque envelopes were used. Once the allocation has been done, it could not be changed.

Study intervention

The principal investigator (HKA) approached all included women and collected the demographic data. Then, the standard 10-cm VAS for pain scoring was discussed to the participants[14].

In group I (Misoprostol group); the women had received two tablets of misoprostol 200 mcg vaginally 3 hours before IUD removal (Misotac®; Sigma Pharma, SAE, Egypt)[15,16]. The tablets were introduced digitally by HKA into the posterior vaginal fornix while the woman leys in the lithotomy position. In group II (no intervention group); the women did not receive any cervical ripping agent.

Before the IUD removal; the position of the uterus was determined by the PV examination. Then the Cusco speculum was inserted to separate the walls of the vagina. The IUD strings were checked then by using forceps the IUD strings were securely grasped. Finally; the IUD strings were slowly pulled and the flexible arms of the IUD folded up as the IUD come out through the cervix.

After the IUD removal; the women were asked to rate the intensity of pain immediately and 5 minutes after IUD removal. A score of more than four points in VAS considered a significant pain[17]. The ease of IUD removal and the woman's satisfaction were reported using the graduated VAS-like scale from 0 to 10[18,19].

Study outcomes

The primary outcome was the difference in the intensity of immediate pain after IUD removal. Secondary outcomes included the difference in the intensity of pain 5 minutes after IUD removal, the ease of IUD removal, the women's satisfaction, and the needed analgesics, and the rate of removal complications.

Sample size calculation

To our knowledge; no previous studies addressed the immediate pain after IUD removal in women delivered by elective CS. So we conducted a pilot study on 20 women, after obtaining written consents, delivered only by elective CS who were requesting IUD removal and fulfilled out the recruitment criteria (they did not include in the study). They were asked to report their pain degree immediately after IUD removal. The mean of VAS immediately after IUD removal in those women was about ± 5. So, using 95% power with an error of 0.05, a sample size of about 80 women (40 in each group) to detect a 1.5 difference in the VAS score between the misoprostol group and no intervention group after IUD removal (OpenEpi, Version 3, open-source calculator-SS Mean).

Statistical Analysis

The data was collected and entered into the Microsoft Excel database to be analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, version 21). Comparisons between the groups were done using a Student t-test and Mann–Whitney U test to compare the mean values in scale variables. Categorical data were shown by number or percentage. For dichotomous variables, chi-square was used to estimate the significance value. The median and range were used for non-parametric variables. The multiple logistic regression model was

utilized to explore the potential clinical predictors for high VAS immediately after IUD removal. The odds ratio (OR) with a 95% confidence interval (CI) was calculated. The *p-value* <0.05 was considered statistically significant.

RESULTS

Ninety-eight women were counseled for participation, however; 18 women were excluded from the study. So; eighty women consented to participate (Figure 1). Both groups were similar in baseline data without statistically significant differences (Table 1). The median of immediate VAS after IUD removal in the misoprostol group (4.0) was lower than the no intervention group (6.0) with a statistically significant difference (p=0.000). Again; the median of the VAS after 5 minutes of IUD removal was significantly lower in the misoprostol group (4.0 vs. 6.0; p=0.000). A significantly higher median satisfaction score and lower median ease of insertion were also reported in women in the misoprostol group (7.0 vs. 5.0; p=0.000, 3.0 vs. 5.0; p=0.000; respectively). Moreover; the need for analgesia was lower in the misoprostol group (p=0.019) (Table 2). No statistically significant differences were found between both groups regards the side effects (p> 0.05) (Table 3).

The participated women were divided into two subgroups; women reported a VAS ≤ 4, and women had a VAS > 4. The baseline data between both subgroups were compared and the women who used misoprostol before IUD removal, women who used IUD before, shorter time from IUD insertion, removal of IUD at time of menses, and women with anteverted flexed or mid-position uterus were significant factors associated with low VAS (< 4) immediate after IUD removal (P<0.05) (Table 4).

We tried to find the significant predictors associated with high VAS (>4) immediately after IUD removal. The multiple logistic regression model was used and the significant factors revealed in the table 4 plus other factors that seemed to affect our outcome were entered in the regression model. The multiple logistic regression model found that the longer time from IUD insertion (p=0.007), removal of IUD in non-menstruating women (p=0.049), women who did not use misoprostol before IUD removal (p=0.007) and women who did not use IUD before (p=0.021) were significant clinical predictors for high VAS immediate after IUD removal (Table 5).

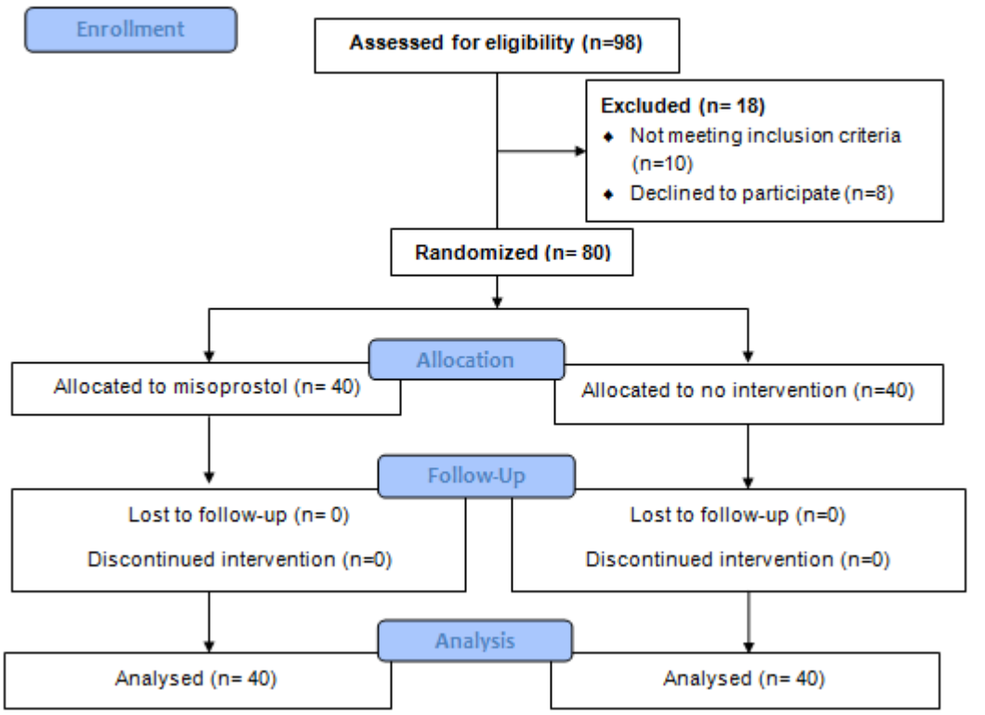

Fig. 1: Flowchart of our participants

Table 1: The baseline characteristics of the study participants

	Misoprostol group (n= 40)	No intervention group (n= 40)	*P- value*
Age, mean ± SD	28.40 ± 6.22	29.75 ± 6.32	0.339
Residence, n (%)			
Rural	21(52.5%)	18(45.0%)	0.502
Urban	19(47.5%)	22(55.0%)	
Level of education, n (%)			
Illiterate	17(42.5%)	17(42.5%)	0.657
Basic education	13(32.5%)	16(40.0%)	
Secondary or more	10(25.0%)	7(17.5%)	
Employment, n (%)	23(57.5%)	20(50.0%)	0.501
Parity, median (range)	3.0 (1.0-6.0)	2.0 (1.0-6.0)	0.084
Number of living children, median (range)	2.0 (1.0-6.0)	3.0 (1.0-4.0)	0.667
Duration from last delivery (months), median (range)	25.0 (10.0-40.0)	25.0 (15.0-60.0)	0.568
Number of CS, n (%)			
1 CS	8 (20.0%)	9 (22.5%)	0.347
2-3 CS	16 (40.0%)	21(52.5%)	
>3 CS	16 (40.0%)	10(25.0%)	
History of previous abortion, n (%)	13 (32.5%)	10 (25.0%)	0.459
Lactation, n (%)	12 (30.0%)	9 (22.5%)	0.446
Previous IUD Insertion, n (%)	21(52.5%)	27(67.5%)	0.171
Duration from IUD insertion, median (range)	24.0 (10.0-40.0)	24.0 (10.0-60.0)	0.604
Time of removal, n (%)			
Menstruating	23(57.5%)	22(55.0%)	0.822
Not menstruating	17(42.5%)	18(45.0%)	
Uterine position, n (%)			
AVF	19(47.5%)	16(40.0%)	0.780
Mid-position	12(30.0%)	13(32.5%)	
RVF	9(22.5%)	11(27.5%)	
BMI (kg/m^2), mean ± SD	26.47 ± 2.53	25.92 ± 2.51	0.333

AVF anteverted, BMI body mass index, CS caesarian section, IUD intrauterine device, kg/m^{2}kilogram per square meter, n (%) number and percentage, RVF retroverted, SD standard deviation

Table 2: The study outcomes

Outcomes	Misoprostol group (n= 40)	No intervention group (n= 40)	*P-value*
VAS immediate after IUD removal, median (range)	4.0 (2.0-7.0)	6.0 (4.0-8.0)	0.000*
VAS 5 minutes after IUD removal, median (range)	4.0 (2.0-7.0)	6.0 (4.0-8.0)	0.000*
Women satisfaction, median (range)	7.0 (2.0-9.0)	5.0 (3.0-9.0)	0.000*
Easiness of the technique, median (range)	3.0 (2.0-5.0)	5.0 (3.0-7.0)	0.000*
Need of analgesia, n (%)	3 (7.5%)	11 (27.5%)	0.019*

IUD intrauterine device, n (%) number and percentage, SD standard deviation, VAS visual analogue scale. * Statistical significant difference ($P < 0.05$)

Table 3: Reported adverse effects among the study groups

Side effects, n (%)	Misoprostol group (n= 40)	No intervention group (n= 40)	*P-value*
Vaginal bleeding	5 (12.5%)	3 (7.5%)	0.712
Vaso-vagal attack	0	0	--
Cervical tear	0	0	--
Headache	4 (10%)	0	0.116
Lower abdominal cramps	6 (15%)	0	0.055
Shivering	4 (10%)	0	0.116
Nausea/ vomiting	2 (5%)	0	0.494
Diarrhea	2 (5%)	0	1.000

Table 4: Comparison between women with VAS ≤ 4 and women with VAS > 4 in both groups

	VAS immediate		*P-value*
	≤ 4	> 4	
Intervention groups, n (%)			
Misoprostol	25 (62.5%)	15(37.5%)	0.025*
No intervention	15 (37.5%)	25(62.5%)	
Previous IUD Insertion, n (%)	31(77.5%)	17(42.5%)	0.001*
Duration from IUD insertion, median (range)	20.0 (10.0-40.0)	28.5 (10.0-60.0)	0.000*
Time of removal, n (%)			
Menstruating	28 (70.0%)	17 (42.5%)	
Not menstruating	12 (30.0%)	23 (57.5%)	0.013*
Uterine position, n (%)			
AVF	17 (42.5%)	18 (45.0%)	0.039*
Mid-position	17 (42.5%)	8(20.0%)	
RVF	6(15.0%)	14(35.0%)	

AVF anteverted, IUD intrauterine device, n (%) number and percentage, RVF retroverted, SD standard deviation, VAS visual analogue scale. * Statistical significant difference ($P < 0.05$)

Table 5: Multiple logistic regression analysis for high VAS (>4) immediate after IUD removal

Variables	*P-value*	OR	95% CI	
			Lower	Upper
Duration from IUD insertion	0.007*	1.131	1.034	1.236
Time of removal (not menstruating)	0.049*	3.260	1.008	10.547
Uterine position: (r= AVF)	0.092			
Mid-position	0.166	0.382	0.098	1.489
RVF	0.252	2.536	0.517	12.444
No intervention group	0.007*	6.003	1.616	22.301
Duration from last delivery (months)	0.280	0.962	0.896	1.032
No previous IUD Insertion	0.021*	5.008	1.276	19.647

AVF: anteverted, CI: confidence interval, IUD: intrauterine device, OR: odds ratio, R: reference, RVF: retroverted. * Statistical significant difference ($P <0.05$)

DISCUSSION

To our knowledge; this is the first randomized study addressing the effect of misoprostol on the removal pain of copper T380A in women who were delivered before by elective CS. The present work proved that misoprostol was effective in reducing the IUD removal. Also, higher satisfaction and more easiness of removal were reported with the misoprostol use. Moreover; some significant clinical predictors associated with higher VAS immediately after IUD removal were revealed from the subgroup analysis.

Under normal conditions, removal of an IUD is a simple practice; However, some difficulty at the time of removal may be noted which needs additional techniques to remove the device[20]. Many studies in the literature cared about IUD insertion pain especially in women in the childbearing period[12,14], however; the studies talked about IUD removal pain are scarce in the literature.

Misoprostol is a synthetic prostaglandin E1 analogue that was widely used as uterotonic and cervical ripening effects[21]. The misoprostol administration routes included oral, vaginal, sublingual, buccal, or rectal routes, but its effect is dependent upon the route of administration[22,23]. We preferred the vaginal route of misoprostol because it seems that it is more effective than other routes in cervical ripping[24].

In our study; misoprostol succeeded to decrease the IUD removal pain in women delivered by elective CS. This effect was secondary to the cervical ripping effect of the misoprostol. Before randomization; we noticed that the IUD removal pain without using any cervical ripping agent was about ±5 (VAS) which considers a significant pain[17]. This was a unique point in this study because most of the studies talked about the misoprostol and IUD removal addressed the easiness of removal, not the removal pain[25].

Lower ease of insertion score was also determined among the women in the misoprostol group. Wahle *et al*. and his colleagues found that the use of vaginal misoprostol was associated with increased ease of IUD removal[25]. Moreover; Cowman *et al*. reported three cases of nonvisible IUD strings and following the use of vaginal misoprostol, the IUD strings became visualized, and the IUDs were easily removed[20]. So, we are on the same track

with these mentioned results. This indicates the beneficial effect of misoprostol on cervical ripping which leads to easy removal. The higher satisfaction in the misoprostol group may be attributed to the lower pain in this group.

We found that the longer time from IUD insertion, removal of IUD in non-menstruating women, women who did not use misoprostol before IUD removal, and women who did not use IUD before were significant clinical predictors for higher VAS immediate after IUD removal.

IUD removal after a long period of insertion is more difficult and may associate with unbearable pain which increased the risk of complications like cervical injury or uterine perforation[26]. The cervical adhesions or cervical hardness were the major factors making IUD removal difficult[27].

The practitioners recommend scheduling the insertion during a menses because the cervix is likely to be dilated, making insertion easier and more comfortable[28]. We also think that the IUD removal is easier and less painful when removed during the menses.

Another factor associated with significant IUD removal pain was women who did not use IUD before (first-time users). Thus, given this finding, it is not surprising because some research has shown that nulliparity and first-time IUD users are associated with more insertion pain[29]. Similarly; women who had been subjected to IUD removal before may experience less pain. Psychological and anatomic factors may be behind this finding.

This study has both strengths and weaknesses. A major strength of this study was its design as a randomized study. The hypothesis of our study that misoprostol may be effective in reducing the IUD removal was approved in our study. To our knowledge; this is the first study that addressed this topic. The interesting issue in our study was the trial to find the significant predictors associated with high VAS immediately after IUD removal. Also, the removal of IUD was performed by only one investigator; this may be eliminated the removal bias. We were able to recruit our calculated sample size for achieving sufficient power to detect a clinically significant difference according to our primary outcome.

However, the present work had some limitations. Blinding of the patients in our RCT was not done. The study included only the removal of Copper T380A and did not include other IUD types. Subjective assessment rather than objective evaluation was used for pain, satisfaction and easiness was another issue. The study did not include women who delivered vaginally.

CONCLUSION

Using vaginal misoprostol 3 hours before Copper T380A IUD removal can reduce the removal pain, increase the ease of removal and woman's satisfaction, and decrease the need for analgesia in women who had delivered only by elective CS. Moreover; the revealed predictors should be put into our consideration before IUD removal.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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