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Use of Misoprostol versus Combined Misoprostol and Isosorbide Mononitrate for Cervical Ripening before Surgical Evacuation of Early Missed Abortion

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ABSTRACT

Background: Prior to a first-trimester abortion, a vaginal misoprostol administration has been shown to have less adverse effects than either an oral or sublingual dose.

Objective: The aim of the current work was to determine whether a combined therapy with isosorbide mononitrate and misoprostol for preoperative cervical ripening in the first trimester would result in improved clinical effectiveness and fewer side effects compared with misoprostol used alone.

Patients and methods: This randomized clinical trial study included a total of 54 women with first trimester missed abortion between 7-12 weeks, attending at Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University Hospitals. They were divided into two equal groups: Group I: included 27 cases received 400 µg misoprostol inserted in the posterior fornix 4 hours prior to the surgical evacuation. Group II: included 27 cases received 20 mg isosorbide mononitrate and 200 µg misoprostol inserted in the posterior fornix 4 hours prior to the surgical evacuation.

Results: Both groups were effective in achieving cervical ripening in terms of effacement, dilatation and softening but combination group was more effective than misoprostol group. The operative duration was statistically significantly shorter in combination group than in misoprostol group. Colicky lower abdominal pain was statistically significant and more prominent in group I (Misoprostol group) while headache was more significant in group II.

Conclusion: It could be concluded that combination of both misoprostol and NO donors makes a synergism in action with fewer side effects. It softens the cervix and decreases its length with less operative time. It has less abdominal pain than misoprostol alone

Keywords: Misoprostol, Isosorbide Mononitrate, Missed Abortion**.**

INTRODUCTION

A missed abortion occurs when the demise of the embryo occurs inside the uterus but is not noticed by the mother and her medical provider. About 15% of all pregnancies with a clinical diagnosis fall into this category. The absence of a fetal heartbeat during a prenatal ultrasound is the most common cause of this diagnosis before 20 weeks of pregnancy **(1).**

As a simple surgical technique with a high success rate (about 99 percent), uterine evacuation is an option for treating early missed abortions between the ages of five and thirteen weeks. However, if cervical ripening has not occurred beforehand, there is a higher risk of problems such cervical rupture, uterine perforation, and endometritis **(2).**

The clinical signs of cervical ripening are the cervix becoming softer, effaced, and dilated **(3).** Disintegration and dissolution of collagen in the cervical stroma is a hallmark of cervical ripening, and prostaglandins are a popular treatment option **(4).** Misoprostol, a homologue of prostaglandin E1, is a particularly effective medication in the cervical priming process **(5).**

In order to achieve the best possible balance between efficacy and adverse effects, research has indicated that administering 400 µg g of misoprostol vaginally 3-4 hours prior to a surgical abortion in the first trimester is the optimal dose and regimen. The most common unwanted effects of vaginal misoprostol include nausea, vomiting, diarrhea, abdominal cramps, chills, fever, and vaginal bleeding; however, these effects are less severe than those associated with oral or sublingual treatment **(6)**.

Nitric oxide donor isosorbide mononitrate may be helpful for cervical ripening due to its effect on prostaglandin E2 release and vasodilation in the cervix. If used cautiously, it is safe, does not stimulate the myometrium, and causes few non-life-threatening side effects **(7).**

We aimed at this work to determine whether a combined therapy with isosorbide mononitrate and misoprostol for preoperative cervical ripening in the first trimester would result in improved clinical effectiveness and fewer side effects compared with misoprostol used alone.

PATIENTS AND METHODS

This randomized clinical trial study included a total of 54 women with first trimester missed abortion between 7-12 weeks, attending at Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University Hospitals.

The included subjects were randomly divided into two groups; **Group I (Misoprostol Group):** included 27 cases received misoprostol 400 µg (2

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tablets of **Cytotec, Pfizer** each 200 µg) in the posterior fornix 4 hours prior to the surgical evacuation.

Group II (Combination Group): included 27 cases received combination of half the dose of each drug (misoprostol 200 µg and isosorbide mononitrate 20 mg **MonoMAK, October Pharma S.A.E**) **i.e.,** one tablet of each in the posterior fornix 4 hours prior to the surgical evacuation.

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Inclusion criteria

Any women who underwent tumor debulking surgery for gynecological cancer (ovarian, uterine, cervical, or endometrial):

1. Age 18-40 years.
2. Missed abortion with gestational age ≤ 12 weeks.
3. Uterus and cervix apparently normal on clinical examination.
4. cervix is not dilated with absence of effacement.
5. Absence of uterine activity and vaginal bleeding**.**

Exclusion criteria

1. Evidence suggesting onset of spontaneous abortion.
2. Previous trial to induce abortion or the use of pre-induction agent during the current pregnancy.
3. History of any cervical surgery or manipulation.
4. Inability to insert vaginal medications high in vagina.
5. Mental condition rendering the patients unable to understand the nature, scope and possible consequences of the study.

Cases were confirmed to have first trimester missed abortion by **careful history taking** and by **trans-vaginal ultrasound examination** which also had been used to assess cervical length.

After medications, the following parameters had been noted:

1. The subjects had been kept under close observation for vital data and development of vaginal bleeding during the 4 hours period.
2. Possible adverse events had been recorded: (a) Headache. (b) Abdominal pain. (c) Vaginal bleeding. (d) Fever, chills. (e) Gastro-intestinal upsets. (f) Severe allergic reaction (anaphylaxis).
3. Occurrence of active vaginal bleeding or expulsion of the sac had been noted.
4. Measurement of cervical length by trans-vaginal ultrasonography before operation.
5. After 4 hours, the patients had been admitted to the operation theater for dilatation and evacuation under general anesthesia.
6. Under general anesthesia, assessment and recording of the following: (a) Cervical consistency either soft or hard. (b) Cervical dilatation had been tested by passage of 1st Hegar dilator and the last Hegar size.10 *mm* without resistance.
7. Duration of operation in minutes.
8. Occurrence of complications.

***Ethical Consideration*:**

This study was ethically approved by Zagazig University's Ethical Institutional Review Board (ZU-IRB #9560/20-5-2022). Written informed consent of all the participants was obtained after being informed of the research's goals. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis

Data was analyzed using SPSS 20 (Statistical Package for the Social Services) (SPSS). The findings were displayed using both tabular and graphical formats. Results were displayed using standard statistical measures such as means, medians, standard deviations, and confidence intervals. The accuracy of the data was demonstrated with the help of statistics. Kolmogorov–Smirnovwas used.

When assessing data involving quantitative independent variables, the student's t test (T) is utilized. Pearson Chi-Square and Chi-Square for Linear Trend were used to analyse the quantitatively diverse data (X^2). In this example, a P value of 0.05 or less was judged statistically significant.

RESULTS

Table (1) shows that the two groups had no significant differences regarding age, gestational age, parity, and previous abortions.

Table (1): Comparison between the two groups as regard clinical characteristics of the patients participating in the study on admission:

Variables / Group	Age	GA by weeks	Parity	Prev. abortion
Misoprostol (N=27)	25.7 ± 3.1	8.8 ± 1.2	1.5 ± 0.9	0.3 ± 0.5
Combination (N=27)	24.7 ± 3.6	8.3 ± 1	2 ± 1.1	0.4 ± 0.5
P-value	0.254	0.085	0.059	0.442
	(NS)	(NS)	(NS)	(NS)

Table (2) shows that the difference was greater in the combination group (More decrease in the blood pressure occurs with the combination group).

Table (2): Comparison between the two groups as regard the difference between baseline mean BP and after cervical ripening (pre-operative) mean BP

Variable / Group	MBP change
Misoprostol (N=27)	2.2 ± 3.9
Combination (N=27)	6.1 ± 6
P-value	0.004 (S)

Table (3) shows that there was a significant changes in temperature between the two groups 4 hours after drug insertion which is higher in group I (misoprostol group) than combination group.

Table (3): Comparison between the two groups as regard baseline temperature and after cervical ripening (preoperative) temperature in C°

Variables / Group	Temp-Baseline	Temp-4hrs after ttt
Misoprostol (N=27)	37 ± 0.3	38.1 ± 0.5
Combination (N=27)	36.9 ± 0.7	37.9 ± 0.5
P-value	0.475 (NS)	0.001 (S)

Table (4) shows that in both groups, there was a significant decrease in the length of the cervix but more significant decrease in group II than group I.

Table (4): Comparison between the two groups as regard the difference between baseline cervical length and after cervical ripening (pre-operative) cervical length by transvaginal ultrasound:

Variables / Group	Cx. Length difference
Misoprostol (N=27)	0.95 ± 1.47
Combination (N=27)	1.05 ± 1.1
P-value	0.001 (S)

Table (5) shows that there was no significant difference between two groups as regard 1st Hegar passed without resistance but as regard last Hegar passed without resistance, the difference is significantly higher in group II than group I.

Table (5): Comparison between the two groups as regard the first and last Hegar passed without resistance during surgical evacuation:

Variables / Group	1st Hegar passed without resistance	Last Hegar passed without resistance
Misoprostol (N=27)	2.8 ± 2.2	8.1 ± 2.02
Combination (N=27)	3.35 ± 2.22	9.9 ± 2.19
P-value	0.339 (NS)	0.001 (S)

Table (6) shows that there was significant change of the cervical consistency from harder to softer in both group, more softening occurred in combination group (19 cases with soft cervix preoperatively) than Misoprostol group (12 cases with soft cervix preoperatively) from the total cases which is (27).

Table (6): Comparison between pre-operative (4 hrs after TTT) cervical consistency in the two groups:

Variables / Group	Cervical character	Frequency	%	P-value
Group I Misoprostol (N=27)	Hard	15	55.5	0.001 (S)
	Soft	12	44.5	
Group II Combination (N=27)	Hard	8	29.6	
	soft	19	70.4	

Table (7) shows that there was significant difference in operative time between the two groups. Longer operative time in Misoprostol group.

Table (7): Comparison between the two groups as regard the operative duration in minutes:

Variables / Group	Operative duration in mins
Misoprostol (N=27)	13.00 ± 1.39
Combination (N=27)	9.07 ± 1.31
P-value	0.001 (S)

Table (8) shows that there was no significant difference between the two groups in term of the amount of intra-operative blood loss.

Table (8): Comparison between the two groups as regard amount of intra-operative blood loss in ml:

Variables / Group	Intraoperative blood loss in ml
Misoprostol (N=27)	175 ± 48.05
Combination (N=27)	200 ± 73.41
P-value	0.125 (NS)

Table (9) shows that Group I had more frequent abdominal pain than group II. Group II had more headache than group I. All other variables were not significantly different.

Table (9): Comparison between the two groups as regard pre-operative complications and protrusion or expulsion of the gestational sac:

Factors	Group (N of each=27)	Frequency	Percentage %	P-value
Abdominal pain	Misoprostol	16	59.2	0.004 (S)
	Combination	10	37	
Vaginal bleeding	Misoprostol	6	22.2	0.381 (NS)
	Combination	9	33.3	
Headache	Misoprostol	2	7.4	0.001 (S)
	Combination	12	44.4	
Nausea and vomiting	Misoprostol	3	11	0.130 (NS)
	Combination	1	3.7	
Expulsion of the sac	Misoprostol	0	0	
	Combination	0	0	—

DISCUSSION

There is a wide variation in reported success rates for expectant management, from 25% to 76%.

Waiting for the fetus to be expelled on its own is a waste of time and can cause stress and anxiety for pregnant women. Medical or surgical intervention is preferable because failure may need surgical evacuation. Miscarriages that occur in the first three months of pregnancy are typically ended by having the uterus surgically removed **(8).**

The nitric oxide donor and vasodilator isosorbide mononitrate is prescribed to treat chest pain caused by angina. The finding that inducible nitric oxide synthase isoforms are more highly expressed in the human cervix late in pregnancy suggested a therapeutic role for nitric oxide donors in cervical softening **(9)**.

In the present study, there were no statistically significant differences regarding age, gestational age, parity and previous abortions (p-value > 0.05). The difference between the baseline mean blood pressure and 4-hours after drug administration was greater in the combination group than Misoprostol group *i.e.*: More decrease in the blood pressure occurs with the combination group (p-value <0.004) which may be due to the vasodilator effect of IMN. However, this lowering in blood pressure had n't affected the hemodynamic of cases to degree of occurrence of dizziness or other symptoms of hypotension. **Mirteimouri *et al.* (10)** stated that after receiving ISMN for cervical ripening at term, maternal blood pressure was shown to drop significantly. **Abu-Zaid *et al.* (11)** stated that isosorbide dinitrate (ISDN) was proven to reduce both systolic and diastolic blood pressure more effectively than PG equivalents.

In the present study, the body temperature 4 hours after drug administration increased significantly (P<0.05) in group I compared with group II. **Lui and Ho (12)** reported a rise in temperature after using misoprostol. This could be because misoprostol oral solution leads to larger peak plasma concentrations of misoprostol acid. High plasma concentrations of misoprostol acid likely operate on receptors elsewhere that are primed by the pregnant state to result in altered thermoregulation, in addition to working on uterine receptors to cause contractions.

In the present study, comparing cervical length that was measured by transvaginal ultrasound indicated that there was a significant decrease in cervical length with time in both groups (p-value < 0.006), but cervical length difference between baseline length and pre-operative length (4hrs after ttt) was more significant in group II than group I. it meant that cervical length became shorter in group II (combination group). **Souizi *et al.* (13)** reported that utilizing IMN in addition to misoprostol for cervical priming before surgical evacuation of a first trimester abortion was more effective than using misoprostol alone in producing a more effaced uterine cervix, and our current study's findings corroborate these findings.

In the present study, there was a significant change in Hegar size passed without resistance as an indicator of cervical dilatation in both groups. But by comparing both groups, there was no significant difference between them as regard 1st Hegar passed without resistance during cervical dilatation and evacuation while regarding last Hegar passed without resistance, it was significantly higher in combination group.

Allen and Goldberg (6) and Moustafa *et al.* (14) found that the cervical dilatation prior to treatment with misoprostol was considerably higher in the misoprostol group than in the NO donor group. On the other hand, **Dave *et al.* (7)** in a study similar to the present study founded that neither gender showed any significant variations in cervical dilatation at baseline. This could be because of the smaller sample size in our study.

In the present study, there was a significant change of the cervical consistency from harder to softer in both Misoprostol and Combination groups. More softening occurred in Combination group (19 case with soft cervix preoperatively) than Misoprostol group (12 case with soft cervix preoperatively).

In both human and animal research, nitric oxide donors have been demonstrated to successfully relax the cervix of the pregnant uterus [7].

Zullino *et al.* [15] found that PGF2 α. production in the cervix could be increased by administering the NO donor isosorbide mononitrate during the first trimester. Therefore, PGF2 synthesis appeared to be a mediator of ISMN-induced cervical ripening.

In the present study, by comparing both groups as regard duration of surgical evacuation. there was significant difference between them ($p < 0.001$) and combination group showed shorter operative time than misoprostol group which may be explained by the more softening and shortening and dilatation of the cervices in combination group.

Dave *et al.* [7] observed that the misoprostol group had a shorter median time to surgical evacuation than the nitric oxide donor group.

On the other hand, **Ledingham *et al.*** [16] said that compared to isosorbide mononitrate alone, combination therapy with isosorbide mononitrate and misoprostol considerably decreased cervical resistance and, hence, operation time. However, as compared to misoprostol alone, the combination of these two medications did not improve upon its ability to reduce cervical resistance and operating time. Potential explanations for the statistical discrepancy between our study and others include variations in drug dosage and/or study population size.

In the present study, by comparing both groups as regard the amount of blood loss during evacuation there was no significant difference between them which agrees with results obtained by **Dave *et al.*** [7].

On the other hand, **Laban *et al.*** [17] stated that intraoperative blood loss in the IMN group was larger than lost in the Misoprostol group, and this difference was statistically significant, according to a study comparing the two drugs for softening the cervical mucosa in cases of early missed abortion (p-value 0.0004). This is because to IMN's vasodilator effect and the high dose of IMN (80mg) employed in this study.

In the present study, Occurrence of abdominal pain was more frequent in group I (p-value < 0.004). It was the most common side effect in misoprostol group while Headache was more frequent in combination group (p-value <0.001).

Headaches were reported in a noticeable proportion of study participants who used NO donors for cervical ripening, however their frequency and severity varied [7]. Possible link between NO's vasodilator effect and headache.

In the present study, none of the both groups had severe preoperative vaginal bleeding. But 6 cases of misoprostol group had mild vaginal bleeding in the form of bloody vaginal discharge and 9 case of the combination group had the same presentation. But that was statistically insignificant (p-value > 0.05).

Dave *et al.* [7] found that 21% of women in the misoprostol group and 1% of women in the control (placebo) group experienced vaginal bleeding prior to suction evacuation ($p<0.001$). Also **Dülger *et al.*** [18] recorded 33% preoperative hemorrhage in the PGE1 group and 3% in the isosorbide mononitrate group. Misoprostol's uterotonic action could be to blame for this.

In the present study, expulsion of the gestational sac had not occurred in both groups during the 4 hours' period and no statistical significance was realized in other side effects e.g. nausea and vomiting which agrees with results obtained by **Dave *et al.*** [7].

Allen and Goldberg [6] stated that cervical ripening was induced more strongly by misoprostol than by isosorbide mononitrate, but both treatments were accompanied with a high rate of adverse events.

Dülger *et al.* [18] compared to gemeprost, pretreatment with isosorbide mononitrate to ripen the cervix prior to first-trimester termination of pregnancy is linked with fewer side effects and adequately diminishes cervical resistance. Gemeprost may be replaced by isosorbide mononitrate in this application.

CONCLUSION

Misoprostol is a good cervical ripening agent and was effective in changing the character of the cervix from harder to softer, and effective in decreasing the length of the cervix (effacement). But with a prominent side effect including colicky abdominal pain and hyperthermia. Combination of both misoprostol and NO donors makes a synergism in action with fewer side effects. It softens the cervix and decreases its length with less operative time. It has less abdominal pain than misoprostol alone.

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