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Role of adding Isosorbide-5-Mononitrate to misoprostol in Induction of the second trimesteric abortion, a randomized controlled trial

Abstract

Objective: To compare the therapeutic efficacy of prostaglandins when they used alone versus a combination therapy of prostaglandins and a nitric oxide (NO) donor as isosorbide-5-mononitrate to induce cervical ripening and effacement for induction of the second trimester missed abortion and occurrence of complete abortion.

Methods: A Randomized clinical trial study in which 160 Second trimester (13-26weeks) missed abortion pregnant women admitted for medical induction of abortion, were randomly divided into two group (80 patients in each). One group received only vaginal Misoprostol and the other group received combined vaginal Misoprostol with Isosorbide-5-mononitrate. To determine the efficacy in form of " induction abortion interval ": the duration interval between the beginning of the induction and the complete expulsion of the abortus and also the number of the doses of misoprostol needed to complete expulsion and also the adverse events that increased or newly discovered when prostaglandins and a nitric oxide donor used together such as severe bleeding, headache, abdominal pain, pelvic pain, sever hypotension, backache, fever, nausea and vomiting.

Results:It is proved in the study that combination between misoprostol and isosorbide mononitrate gives better results regarding cervical consistency improvement, cervical dilatation, effacement, the whole induction time and the number of misoprostol doses needed to complete expulsion when compared to misoprostol alone and also fewer side effects as abdominal pain.

Conclusion: Misoprostol is a good cervical ripening agent when used alone but we can get a benefit from combining both misoprostol and NO donor (isosorbide-5- mononitrate) making a synergistic action with fewer side effects.

Keywords: misoprostol, isosorbide -5- mononitrate, cervical ripening, abortion

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Amerayehia, HalaAlansary
Obstetrics and Gynecology department, Cairo University, Egypt

Correspondence: AmeraYehia, Lecturer, Obstetrics and Gynecology department, Cairo University, Egypt, Email amira_el_sayed_yehia@hotmail.com

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Introduction

Abortion is defined as termination of pregnancy before fetal viability which is now considered to be reached at 23-24 weeks of gestations. Second trimester or mid trimester is a period ranging from 13 to 26 weeks of gestations. (Schorge et al., 2008).Cervical ripening is associated with a decrease in total collagen content; increase in collagen solubility and increased matrix metalloprotinase activity.[1]

Cervical ripening has been linked to an inflammatory response. During ripening there is an influx of inflammatory cells into the cervical stroma. Pro-inflammatory cytokines (interleukin-1 and interleukin-8) are thought to play a key role on extracellular matrix metabolism and cervical ripening.[2]

Cervical ripening is clinically diagnosed by softening, effacement, and dilatation of the uterine cervix.[3]Misoprostol could be taken either vaginally or orally , it has short half-life (10-20min).[4]Nitric oxide (NO) plays an active role in cervical remodeling since it's positively correlated with both shortening of the cervix and Bishop Score. NO and PGs are two pathways that cross activate each other, trigger the cascade of events responsible for cervical ripening.[5]

We hypothesize that the cervical ripening effects of nitric oxide donors and of prostaglandins might be additive. If this hypothesis is correct, this would allow a small dose of nitric oxide donor to be given with a small dose of prostaglandins to affect cervical ripening. Such a strategy might reduce the side effects associated with large doses of either agent used alone.

Objective

The aim of this work is to compare the efficacy of the usage of misoprostol alone versus a combination of misoprostol and isosorbide -5- mononitrate in cervical ripening and induction of abortion in second trimesteric missed abortion patients demonstrated by the change of cervical dilatation and effacement, decreased time required for complete expulsion of the abortus and to evaluate safety of both drugs and side effects.

Patients & methods

This study was a randomized clinical tri**al** at the OBGYN hospital–KasrAlainy during time interval from September 2019 till March 2020 in which 160 Second trimesters (13-26weeks) missed abortion pregnant women were admitted for medical induction of abortion.

Inclusion criteria: Maternal Age 18-35years, Gestational age: Second trimester of pregnancy (between 13-26weeks), missed abortion confirmed by ultrasound, singleton pregnancy, unscarred uterus, normal uterus and cervix on clinical examination, cervix is not dilated, no vaginal bleeding.

Exclusion criteria: The patient with the following was excluded from the study.

Evidences suggesting start of spontaneous abortion as previous trial to induce abortion, presence of uterine contraction or bleeding, multi-fetal pregnancy, septic abortion, history of Previous cervical surgery or manipulation, uterine anomaly, presence of IUD in situ , underlying medical diseases, history of allergy or adverse effects to vaginally administered medication e.g. isosorbide -5- mononitrate, those unwilling to participate in the trial.

All patients were informed about the study and will be included in the study after their approval and will be subjected to

Consent

Written consent was obtained from the pregnant women who are included in the study after explanation of the study and its aims in addition to consent for performing surgical evacuation for any remnants if needed.

Full history taking

Name, Maternal Age, obstetric history (Gravidity and parity)

First day of last menstrual period, gestational Age, medical and surgical history, previous laparotomies and their types, previous Pregnancy complications, history of smoking, pelvic pain.

Clinical examination

Height(in cm) and weight(in kg) measurements, BMI calculation

Blood pressure measurement, obstetric Examinations (PV Examination) Previous scars analysis

Laboratory investigations: Preoperative and postoperative CBC, Coagulation profile, Kidney and liver functions

Investigation: All women underwent Trans-abdominal or Trans-Vaginal Ultra-sonography during the Routine examination to confirm the inclusion criteria of the study (Gestational age and confirmation of the intrauterine fetal death).

Randomization: Participants were randomly assigned to misoprostol alone or misoprostol+isosorbide-5-mononitrite using identical sealed envelopes technique. We prepared 160 identical envelops, half of them filled with a label identifying "misoprostol" group with all instruction details, while the other half filled with a label identifying the "misoprostol+isosorbide-5-mononitrite" group" with all instruction details. All envelops was prepared by the investigator and sealed before starting enrollment. After enrollment, each participant was allowed to choose one envelop to determine to which group she will be assigned.

Group A (n=80) received combined Isosorbide-5-mononitrate 20mg (Effox 20mg) once vaginal with Misoprostol 400mcg (2 tablets Cytotec) at first then one tablet every 4-6 hours to a maximum of four doses or until reaching cervical ripening.

Group B (n=80) received only vaginal Misoprostol 400mcg (2 tablets Cytotec 200mcg) at first then one tablet every 4-6 hours to a maximum of four doses or until reaching cervical ripening.(The doses of Misoprostol will followthe New FIGO Guidelines for Misoprostol use 2017)

Success (complete abortion) means complete expulsion of the fetus, the placenta and the membranes within the first 24 hours from starting first dose. The cases who failed to abort within the first 24 hours, administration of the doses were continued till abortion occurs. Documentation of number of doses of both drugs, duration and complications were done.

Study outcomes

Primary outcomes: The Efficacy in form of "induction abortion interval": the Duration interval between the beginning of the induction and the complete expulsion of the abortus and also the number of he doses of misoprostol needed for complete expulsion when prostaglandins used alone and when prostaglandins and a nitric oxide donor used together.

Secondary outcomes: Association between Adverse events that increased or newly discovered when prostaglandins and a nitric oxide donor used together such as severe bleeding , headache, abdominal pain, pelvic pain, severe hypotension , backache, fever, nausea and vomiting.

Sample size calculation was done using the comparison of induction-abortion interval between women with 2nd trimester abortion treated with vaginal misoprostol alone and those treated with misoprostol+isosorbide-5-mononitrite, as it was the primary outcome of our study. As reported in previous publication,[6]the mean and 95%CI of induction-abortion interval in misoprostol + isosorbide-5-mononitrite group was approximately 12.4 (10.33 to 14.47, n=30) hours, while in misoprostol alone group it was approximately 20.4 (16.63 to 24.17, n=30) hours. After calculating the SD from the CI, we concluded that the minimum proper sample size was 80 participants in each group to be able to reject the null hypothesis with 80% power at α=0.05 level using Student's t test for independent samples. Sample size calculation was done using PS Power and Sample Size Calculations software, version 3.0.11 for MS Windows.[6]

Statistical analysis of the collected data

Data were statistically described in terms of mean±standard deviation (±SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. Two sided*p* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

Results

This study was a randomized clinical trial at the OBGYN hospital–KasrAlainy during time interval from September 2019 till March 2020 in which 160 Second trimester (13-26weeks) missed abortion pregnant women admitted for medical induction of abortion.

Patient characteristics

Age, Parity, Gestational age were summarized in Table 1.The above table shows the mean age, parity and gestational age of the studied patients.The study contained 160 women divided into 2 groups. One group received misoprostol and isosorbide mononitrate (nitrate group) and the other group received misoprostol only (misoprostol group).

Table 1 Demographic features and obstetric parameters of the studied patients

	Group				t-test	P-value
	Misoprostol		Nitrate			
	Mean	SD	Mean	SD		
Age(year)	25.1	3.5	23.4	3.2	3.139	0.002
Parity	1.3	1.1	1.01	1.07	1.882	0.062
Gestational age(weeks)	17.4	2.3	18.5	2.7	-3.94	0

The age of the participating female ranged from 19 to 33years. The mean age of misoprostol group was 25.1(SD=3.5) years while it was 23.4(SD=3.2) years in nitrate group. The difference was not statistically significant.

There was no significant statistical difference between both groups regarding parity and gestational age.

The above table shows the difference in success of induction of abortion in both groups within 24 hours. It was 91.3% in nitrate group and 77.5% in misoprostol group.

The difference between both group was statistically significant (P value=0.028) indicating that isosorbide mononitrate when added to misoprostol increase the chance of success of abortion. This table shows number of doses given for both groups. The statistical difference is significant indicating that the number of given doses in nitrate group was much less than in misoprostol group (P value>0.001).

This table shows number of doses needed till abortion occurs. In nitrate group 16 women received single dose, 45 women received two doses and 12 women received three or more doses. In misoprostol group only 7 women aborted by single dose, 11 women aborted by two doses and 44 women needed three or more doses for abortion to occur.

The difference between both groups was highly significant indicating that isosorbide mono nitrate decreases the number of doses of misoprostol needed for second trimesrter abortion (P value>0.001**)**.

The mean time needed for abortion in Nitrate group was 10.72 hours, while it was 20.87 hours for misoprostol group.

Table 2 Success of abortion at the end of 24 hours

		Group				Chi square	P value
		Misoprostol		Nitrate			
		No	%	No	%		
Induced abortion	Failure	18	22.5	7	8.8	5.736	0.028
	Success	62	77.5	73	91.3		

Table 3 Comparison between the two groups regarding number of received doses for the whole group

		Group				Chi square	P value
		Misoprostol		Nitrate			
		No	%	No	%		
Number of doses for the whole group	Single dose	7	8.7	16	20.05	24.411	> 0.001
	Two doses	11	13.7	45	56.2		
	Three doses	28	35.1	10	12.5		
	Four doses	34	42.5	9	11.25		

Table 4 Comparison between the two groups regarding the number of received doses for the success of abortion

		Group				Chi square	P value
		Misoprostol		Nitrate			
		No	%	No	%		
Number of doses for the whole group	Single dose	7	11.2	16	21.9	24.938	> 0.001
	Two doses	11	17.7	45	61.8		
	Three doses	28	45.3	10	13.6		
	Four doses	16	25.8	2	2.7		
Mean		3.88		2.64			

Citation: Amerayehia, Alansary H. Role of adding Isosorbide-5-Mononitrate to misoprostol in Induction of the second trimesteric abortion, a randomized controlled trial. *ObstetGynecolInt J.* 2020;11(4):202–206. DOI: 10.15406/ogij.2020.11.00510

Table 5 Mean time of induction of abortion in both groups

Group	Mean Estimate	SD	t-test for Equality of Means		
			Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Misoprostol	20.87	13.791	2.128	7.945	16.353
Nitrate	10.72	12.78			

Table 6 Proportion of selected side effects occurring in both groups

	Group				Chi square	P value
	Misoprostol		Nitrate			
	No.	%	No.	%		
Headache	7	8.80%	31	38.60%	19.81	0.001
Vomiting	19	23.70%	24	30.00%	0.075	0.476
Colic	53	66.30%	53	66.30%	0	1
Bleeding	7	8.80%	16	20.00%	4.113	0.07

There is a statistically significance difference indicating that the second trimester induction of abortion using isosorbide mononitrate with misoprostol takes much shorter time than misoprostol alone. The selected side effects were recorded positive when the patient needed medications to relieve her complaint. Among the reported side effects only headache showed significant difference with higher proportion among nitrate group (38.6%) compared to misoprostol group (8.8%).

Discussion

The study aimed to compare the effect of isosorbide mononitrate when combined with misoprostol and misoprostol when used alone in induction of second trimesteric missed abortion, expecting that both drugs when used together will be more effective and associated with fewer side effects.

In this study 160 second trimester missed abortion pregnant women were enrolled, divided into two groups. The first group (Nitrate group), 80 women received misoprostol and isosorbide -5- mononitrate. The second group (misoprostol group), 80 women received misoprostol only. The primary aim of the study was the occurrence of complete abortion in the first 24 hours.

There was no statistical difference between both groups regarding age, parity and gestational age.

The difference between both group was statistically significant regarding number of women who had abortion in the first 24 hours (P value=0.028) indicating that isosorbide mononitrate when added to misoprostol increase the chance of success of abortion.

The net result is in nitrate group the number of doses needed for successful abortion was significantly lower than in misoprostol group (P value >0.001).

There was a statistical significant difference in time needed for induction of abortion using isosorbide mononitrate with misoprostol compared to misoprostol when it used alone with a shorter time for nitrate group.Abdominal colic was the main side effect in both groups but headache occurred more frequent in nitrate group.

In the present study the rate of success of abortion was significant higher in group treated by isosorbide mononitrate added to misoprostol compared to group treated with misoprostol only. This not agreed with the study done by Li,C-F et al., 2003, who found no difference in abortion rate in cases primed with 40 mg isosorbide mononitrate, given intra vaginally 12 hours before induction followed by intravaginal misoprostol.

Hidar et al.,[7]also performed a trial studying misoprostol and isosorbide dinitrate for termination of second trimester pregnancy. Both groups were also given oxytocin infusion at 30 mU/min. the abortion rate at 48 hours didn't significantly change between the 2 groups (27/30) 90% versus (29/30) 93%.[7]

On the other hand Makhlouf et al.,[8]stated that the rate of complete abortion was 100% in nitric oxide (glyceryltrinitrate) induced group after introducing a complementary procedure. The complementary method was oxytocin drip which is not used in our study.[8]

In our study we found that the number of doses needed to fulfill abortion was much less when isosorbid mononitrate was used with misoprostol. This similar to the data taken from the study done by Eppel et al.,[9]who stated that vaginally administrated IMN given in combination with gemeprost reduces the number of doses required for successful abortion compared to the prostaglandin alone.[9]

On the other hand, Mousiolis et al.,[10]conducted a study comparing the efficacy of IMN and misoprostol compared to misoprostol alone, he found that in the group of misoprostol administration, a mean of 8.15(200 mcg) tablet were used (SD=4.211), in comparison with 6.6 tablets (SD=2.197) used in misoprostol plus IMN group. However, this difference was not statistically significant (P value= 0.05). We think that the difference is because of the number of repeated doses of IMN used (20 mg of IMN every 4 hours).[10]

In our study, we found that induction abortion interval is shorter in nitrate group, this is similar to what Mousiolis et al.,[10] stated, that

it took a mean of 20.4hrs (95% confidence interval (CI) = 16.63-24.17) for women in the misoprostol group to complete abortion compared to 12.4hrs (95% CI = 10.33-14.47) for those administrated IMN plus misoprostol. This difference was statistically significant (P value=0.001).[10]

Eppel et al.,[9] when used IMN with gemeprost versus gemeprost alone in induction of second trimester abortion found that the mean induction time was not significantly different among groups. Although this study used the same doses of IMN as we did, but it included only Primigravida women and used gemeprost instead of misoprostol.[9]

In our study the difference in development of side effects was not statistically significant between both groups except for headache (P value=0.001).

Almost all studies of NO donors used in cervical ripening documented the occurrence of headache in its population with variable degree. Headache may be due to the vasodilator effect of NO.[4,11]

Radulovic et al.,[12]found that misoprostol encouraged a more noticeable cervical ripening than IMN, but in both groups, there was a high incidence of side effects.[12]

Conclusion

Based on our results, the current study demonstrated that vaginal administration of nitric oxide donors in the form of isosorbide mononitrate combined with misoprostol could be more effective and makes a synergistic action than using misoprostol alone in second trimester abortion but with more side effects especially headache.

Limitations and recommendations

Larger and multi-centric further studies are needed in this issue to find other new adjuvant therapy like nitric oxide donors that help in cervical ripening and induction of abortion with larger sample size.

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None.

Conflicts of interest

All authors declare that they have no competing interests.

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