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Second Trimester ABortion Induction With Misoprostol Only Versus Misoprostol Plus Isosorbide Mononitrate: A Randomized Controlled Study

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ABSTRACT

Background: Efficacy of isosorbide mononitrate to reduce the interval of induction time in second trimester missed abortion.

Aim of the work: To compare efficacy and safety of Isosorbide Mononitrate (IMN) and misoprostol for cervical ripening in second trimester abortion.

Patients and methods: A randomized controlled prospective study was conducted. 160 patients aged between 18 & 35 years presenting with missed 2nd trimester abortion 13-26 wk gestation were included in this prospective clinical study. One group received only vaginal Misoprostol and the other group received combined vaginal Misoprostol with Isosorbide5-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 to 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 such as abdominal pain.

Conclusion: Misoprostol is a good agent for cervical ripening when used alone but we can get a benefit from combining both misoprostol and isosorbide-5- mononitrate making a synergistic action with fewer side effects.

Keywords: Abortion; cervical ripening; Misoprostol; Isosorbide MonoNitrate; (IMN).

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INTRODUCTION

In all recorded induced abortions second trimester abortion accounts for 10-15% and thought to be responsible for more than 70% of all abortion recorded related complications.¹

In past, abortion surgical induction methods were often practiced for pregnancy termination. Fortunately nowadays with the availability of potent uterotonic drugs Like prostaglandins and its analogue e1 and e2 , medical termination of abortion is preferred. Misoprostol is commonly used for termination of second trimester abortion.² Drugs as mifepristone have been used with it to reduce the interval time for abortion induction and outcome improvement³. Mifepristone has shown to be effective but it is unavailable and expensive.

Ripening of cervix is a very important milestone for successful termination of abortion . Nitric oxide(N.O) donors as isosorbide mononitrate(Effox_R) have been used for ripening of cervix in first

trimester and also for induction of labour at term for a long time.⁴

Cervical ripening has been linked to an inflammatory response. During ripening there is an influx of inflammatory mediators into the cervical stroma. Pro-inflammatory cytokines (interleukin-1 and interleukin-8) are thought to play a key role on metabolism of extracellular matrix and ripening of cervix.⁵

Nitric oxide donors thought to induce matrix metalloproteinases production namely MMP-1 and MMP-9, which are essential for degradation of collagen.⁶ It also increases proinflammatory mediators as prostaglandins and cytokines . The previous agents use for second trimester termination of pregnancies can shorten the induction time of abortion . The study aims to complete evaluation of the efficacy of isosorbide mononitrate when combined with pg e1 analogue misoprostol in shortening the induction to abortion interval in termination of pregnancy in second trimester

The aim of this work is to compare the efficacy of the usage of misoprostol alone versus a combination of misoprostol and isosorbide mononitrate in cervical ripening and induction of abortion in second trimester 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 AND METHODS

This study was a randomized clinical trial on the Second trimesters (13-26 weeks) missed abortion pregnant women who 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, uterine cervix is not dilated, no bleeding from vagina .

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 any manipulation, uterine anomaly, presence of IUCD in situ, underlying medical diseases as cardiovascular diseases, history of allergy or adverse effects to vaginally administered medication e.g. isosorbide -5-mononitrate, those unwilling to participate in the trial and 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 Transvaginal 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-mononitrate using identical sealed envelopes technique. We prepared 200 identical envelopes, 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-mononitrate” group” with all instruction details. All envelopes 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 follow the New FIGO Guidelines for Misoprostol use 2017)

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 misoprostol doses needed for complete expulsion when prostaglandins used alone and when prostaglandins and a nitric oxide donor used together.

Secondary outcomes: Association between Adverse symptoms 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.

Statistical analysis of the collected data: Data were analyzed statistically in terms of mean±standard deviation (\pm SD), median and range, or frequencies (cases number) and percentages when appropriate. Numerical variables comparison between the study two groups was done using Student t test for independent samples. For categorical data comparing , Chisquare (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 el Hussein university hospital during time interval from June 2021 till December 2022 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 200 women divided into 2 groups. One group received misoprostol and isosorbide mononitrate (nitrate group) and the other group received misoprostol only (misoprostol group).

	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

Table 1: Demographic features and obstetric parameters of the studied patients

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.

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

Table 2: Success of abortion at the end of 24 hours

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).

		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 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	11.2	16	21.9	24.411	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		

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

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 trimester abortion (P value>0.001).

Group	Mean Estimate	T-tests For Equality of Means			
		SD	Std.Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Misoprostol	20.78	13.791	2.128	7.945	16.353
Nitrate	10.72	12.78			

Table 5: Mean time of induction of abortion in both groups

This table shows the mean time of induction needed.

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

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%).

	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

Table 6: Proportion of selected side effects occurring in both groups

This table shows the adverse symptoms of both drugs

DISCUSSION

This study aimed to compare the effect of isosorbide mononitrate when combined with misoprostol and misoprostol when only used in induction of second trimester missed abortion, expecting that usage of both drugs together will be more beneficial ,effective and associated with fewer recorded side effects.

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

There was no statistical difference between the two groups regarding to age, gestational age and also parity

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

The end 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 used alone with much 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 plus misoprostol compared to group treated with misoprostol only. This not agreed with the study done there were no difference in abortion rate in cases primed with isosorbide mononitrate 40 mg, given per vagina posterior fornix 12 hours before induction followed by vaginal misoprostol.

Hidar et al.⁷ also performed a trial studying misoprostol and isosorbide dinitrate for termination of second trimester pregnancy. The two groups were also given oxytocin drip infusion at 30 mU/min. the

abortion interval rate at 48 hours didn't significantly change between both groups (27/30) 90% versus (29/30) 93%.⁷

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

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

On the other hand, Mousiolis et al.¹⁰ performed a study comparing the efficacy of IMN and misoprostol compared to misoprostol alone, he found that in the group of misoprostol, 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 isosorbide mononitrate group. However, this difference was not significant statistically (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) = 16.6324.17) for patients 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 significant statistically (P value=0.001).

Eppel et al.⁹ when used IMN with gemeprost versus gemeprost alone in induction of second trimester abortion found that the mean time for induction was not significantly different among the two 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 degrees. Headache may be due to the vasodilator effect of NO.¹¹

Radulovic et al.⁶ found that misoprostol induce a more noticeable cervical ripening than IMN, but in both groups, there was a high incidence of side effects recorded.⁶

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.

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