

COMPARISON OF MEAN DURATION REQUIRED FOR COMPLETE EXPULSION WITH ISOSORBIDE MONONITRATE VERSUS MISOPROSTOL IN FIRST TRIMESTER MISSED MISCARRIAGE

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ABSTRACT

Background: Medical management of first trimester miscarriage possess significant advantages over surgical management. Misoprostol has been previously tested in the management of miscarriage in different regimens and settings. Isosorbide mononitrate (IMN) is also an effective and safe drugs for early expulsion of conception material. But controversial results have been noticed from literature. So we conducted this study to confirm more effective drug.

Objective: To compare the mean duration required for complete expulsion with isosorbide mononitrate versus misoprostol for first trimester missed miscarriage.

Material & Methods

Study Design: Randomized Controlled Trial.

Setting: unit I, Department of Obstetrics & Gynaecology, Lahore General Hospital, PGMI, Lahore.

Duration: Six months (August, 2017 to January,2018)

Data Collection Procedure: Females were randomly divided in two groups by using lottery method. Group A was given 800 µg misoprostol in posterior fornix of vagina 3 hourly maximum 2 doses. Group B was given 40mg IMN in posterior fornix of vagina 3 hourly maximum 2 doses. Patients were reassessed if vaginal bleeding or uterine contractions were noted otherwise repeat dose was given after 3 hours. Time till complete expulsion was noted. Complete expulsion was confirmed subsequently by ultrasonography when no products of conception are found in utero. All the data was entered and analyzed through SPSS version 21.

Results: The mean age of females was 30.40 ± 5.51 years. In this study, 18 (25%) were para 1, 27 (37.5%) were para 2, 15 (20.83%) were para 3 and 12 (16.67%) were para 4. The mean gestational age of females was 9.51 ± 1.11 weeks. The mean BMI of females was 24.56 ± 3.76 kg/m². The mean duration required for complete expulsion was 91.69 ± 15.74 min in misoprostol group and 122.58 ± 16.55 min in IMN group. There was significant difference in both groups ($p < 0.05$).

Conclusion: Thus the mean expulsion time was significantly less for misoprostol than IMN. For future, we can recommend misoprostol for complete evacuation of conception material during first trimester missed miscarriage.

Key words: Complete Expulsion, Isosorbide Mononitrate, Misoprostol, First Trimester Missed Miscarriage

INTRODUCTION

Missed miscarriage in first trimester refers to spontaneous pregnancy loss before 12 weeks, that can manifest as anembryonic gestation or fetal demise with or without minimal symptoms.¹ As the women may not experience cramping or bleeding so it is usually diagnosed on routine ultrasonography during antenatal checkup where fetal heartbeat is not detected.

The incidence of clinically recognized miscarriages remains around 10-20%.² Out of these

miscarriages 80% occurs before 12 weeks of gestational.³

A complete abortion usually needs no further treatment, medically or surgically.⁴

Dilatation and curettage, typically done in an operating room, has been the standard treatment not only increases the cost but complications like uterine perforation infection, prolonged hospital stay and antibiotic prophylaxis. Moreover about 197,000 women are treated each year for complications of surgical termination of miscarriages.⁵

The medical management of miscarriage involves administering a medication to induce complete miscarriage. Misoprostol is the medication recommended for this purpose.^{6,7}

Medical management for first trimester miscarriage poses significant economical benefits and health advantages like no need of instrumentation or anesthesia over traditional surgical management.

Misoprostol, a prostaglandin E1 analogue is a uterotonic and is widely used for cervical ripening, termination of missed miscarriage and induction of labor whereas isosorbide mononitrate (IMN), a newer and well tolerated drug, is NO donor which stimulate PGE2 alpha and is a major paracrine mediator of numerous biological processes including smooth muscle relaxation, host defense and inflammation and so help to soften the cervix and expel the products of conception.

Merie-Ledingham in their study have concluded that the mean duration of complete expulsion was 169±29 minutes with misoprostol (n=21) which was significantly higher than IMN (n=22) i.e. 150±28 minutes ($P<0.05$).⁸ Another study has shown the complete expulsion was noted in 86% women with IMN and in 83% in whom misoprostol was given.⁹

Waleed El-Khayat has shown that out of 162 patients recruited for the study, mean duration of complete expulsion with misoprostol (n=81) was 49±20.1 minutes which was significantly lower than IMN (n=81) which was 73±34.2 minutes ($P<0.05$).¹⁰ Similarly another study concludes that complete evacuation was found in the misoprostol (60%) and compared with the IMN (27.7%) group ($p<0.0001$).¹¹

In literature controversial results are present regarding the effect of misoprostol and IMN for cervical ripening. So through this study we want to confirm the less time consuming drug to be implemented in future in routine procedure. Moreover, in previous studies, sample size was small. But we will take large sample size to achieve more reliable results.

OBJECTIVE

To compare the mean duration required for complete expulsion with isosorbide mononitrate versus misoprostol for first trimester missed miscarriage.

OPERATIONAL DEFINITIONS

First trimester missed miscarriage:

It was said when:

Mean gestational sac diameter is >2.5 cm with no fetal pole or fetal pole of >8 mm with no heart pulsations on transabdominal ultrasound

Mean gestational sac diameter is >2 cm with no

fetal pole or fetal pole of >7 mm with no heart pulsations on transabdominal ultrasound

Duration of expulsion:

It was calculated in minutes from time of administration of drug till complete expulsion

Complete expulsion:

It was considered as no conceptus material present in uterine cavity on ultrasonography

Hypothesis:

There is difference in mean duration required for complete expulsion with isosorbide mononitrate versus misoprostol for first trimester missed miscarriage

MATERIAL AND METHODS

Study Design: Randomized Controlled Trial.

Setting: Unit I, Department of Obstetrics & Gynecology, Lahore General Hospital, PGMI, Lahore.

Duration: Six months .

Sample Size: Sample size of 72 cases; 36 cases in each group is calculated with 95% confidence level, 80% power of test and taking magnitude of duration of cervical dilatation i.e. 169±29 minutes with misoprostol while 150±28 minutes with IMN for missed miscarriage.

Sampling Technique: Non probability, consecutive sampling.

SAMPLE SELECTION

Inclusion Criteria

- Women presenting with first trimester missed miscarriage (as per operational definition) with following criteria:
- Age 20-40years
- Gestational age <12 weeks on LMP
- Parity <5

Exclusion Criteria

1. Females with previous cervical surgery
2. Known allergy to either IMN or misoprostol
3. Females with acute liver disease (ALT >40 IU, AST >40 IU) and renal problem (creatinine >1.5 mg/dl)
4. Asthma
5. Incomplete miscarriage

Data Collection Procedure:

After approval from hospital ethical committee, 72 patients fulfilling the selection criteria were included in this study from emergency of Department of Obstetrics & Gynecology, Lahore General Hospital, Lahore. An informed consent was obtained. Demographic profile

(name, age, parity, gestational age) was also noted. Then females were randomly divided in two groups by using lottery method. Group A was given 800 µg misoprostol (Misotac; Sigma Co., Egypt), 3 hourly, maximum of two doses, into the posterior fornix of vagina. Group B was given 40mg IMN (Effox; Roche, Basel, Switzerland), 3 hourly, maximum of two doses, into the posterior fornix of vagina.

After administration of drugs, time was noted and vital monitoring was done hourly. Patients were reassessed if vaginal bleeding or uterine contractions were noted otherwise repeat dose was given after 3 hours. Time till complete expulsion (which was assessed clinically) was noted. Complete expulsion was confirmed subsequently by ultrasonography when no products of conception are found in utero (as per operational definition). All the information was collected through a specially designed proforma.

Data Analysis:

All the data was entered and analyzed through SPSS version 21. The quantitative variables like age, duration of gestation, BMI and duration of cervical dilatation was presented as mean & SD. The qualitative variable like parity was presented as frequency. Both groups were compared by using t-test. P-value ≤ 0.05 was taken as significant. Data was stratified for age, BMI and parity. Post-stratification t-test was applied taking P-value ≤ 0.05 as significant.

RESULTS

In this study, we included 72 females with first trimester missed miscarriage. The mean age of females was 30.40 ± 5.51 years. Minimum age was 21 years while maximum age was 40 years. **Table 1**

In this study, 18 (25%) were para 1, 27 (37.5%) were para 2, 15 (20.83%) were para 3 and 12 (16.67%) were para 4, **Fig1**.

In misoprostol group, 12 (33.3%) were para 1, 12 (33.3%) were para 2, 7 (19.4%) were para 3 and 5 (13.9%) were para 4. In IMN group, 6 (16.7%) were para 1, 15 (41.7%) were para 2, 8 (22.2%) were para 3 and 7 (19.4%) were para 4. **Table 2**.

The mean gestational age of females was 9.51 ± 1.11 weeks. Minimum gestational age was 8 weeks while maximum gestational age was 11 weeks. **Table 3**.

The mean BMI of females was $24.56 \pm 3.76 \text{ kg/m}^2$. Minimum BMI was 18.50 kg/m^2 while maximum BMI was 32.09 kg/m^2 .

The mean BMI of females in misoprostol group was $24.51 \pm 3.73 \text{ kg/m}^2$. The mean BMI of females in IMN group was $24.61 \pm 3.84 \text{ kg/m}^2$.

The mean duration required for complete expulsion was 91.69 ± 15.74 minutes in misoprostol group and 122.58 ± 16.55 minutes in IMN group. There was significant difference in both groups ($p < 0.05$).

Table 4.

In misoprostol group, 100% female required only one dose of misoprostol and achieved delivery within 2 hours. While in IMN group, 18 (50%) females required 2 doses of IMN to achieve complete evacuation. The difference was significant ($P < 0.05$). **Table 5**.

Data was stratified for age of females. In patients aged 21-30 years, the mean duration required for complete expulsion was 89.56 ± 14.82 minutes in misoprostol group and 125.38 ± 17.46 minutes in IMN group. There was significant difference in both groups ($p < 0.05$). In patients aged 31-40 years, the mean duration required for complete expulsion was 93.83 ± 16.76 minutes in misoprostol group and 120.35 ± 15.87 minutes in IMN group. There was significant difference in both groups ($p < 0.05$). **Table 6**.

Data was stratified for parity of females. In primigravida patients, the mean duration required for complete expulsion was 90.75 ± 11.84 minutes in misoprostol group and 135.83 ± 12.84 minutes in IMN group. There was significant difference in both groups ($p < 0.05$). In multiparous females, the mean duration required for complete expulsion was 92.17 ± 17.59 minutes in misoprostol group and 119.93 ± 16.08 minutes in IMN group. There was significant difference in both groups ($p < 0.05$). **Table 7**.

Data was stratified for BMI of females. In normal BMI females, the mean duration required for complete expulsion was 92.67 ± 15.96 minutes in misoprostol group and 126.25 ± 11.51 minutes in IMN group. There was significant difference in both groups ($p < 0.05$). In overweight females, the mean duration required for complete expulsion was 90.14 ± 15.99 minutes in misoprostol group and 120.44 ± 20.35 minutes in IMN group. There was significant difference in both groups ($p < 0.05$). In obese females, the mean duration required for complete expulsion was 89.20 ± 17.40 minutes in misoprostol group and 112.50 ± 7.78 minutes in IMN group. There was insignificant difference in both groups ($p > 0.05$). **Table 8**.

Table 1: Descriptive statistics of age of patients

Age (years)	n	72
	Mean	30.40
	SD	5.51
	Minimum	21
	Maximum	40

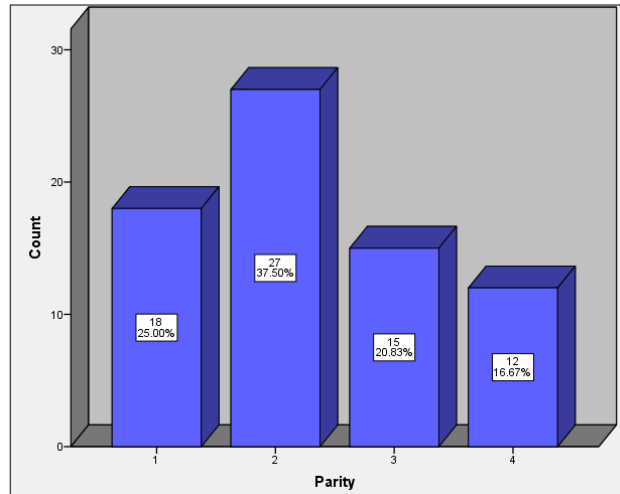


Fig 1: Distribution of parity

Table 2: Distribution of parity of females in both groups

		Group		Total
		Misoprostol	IMN	
Parity	1	12 (33.3%)	6 (16.7%)	18 (25.0%)

	2	12 (33.3%)	15 (41.7%)	27 (37.5%)
	3	7 (19.4%)	8 (22.2%)	15 (20.8%)
	4	5 (13.9%)	7 (19.4%)	12 (16.7%)
Total		36 (100%)	36 (100%)	72 (100%)

Table 3: Descriptive statistics of gestational age of patients

Gestational Age (weeks)	N		72
	Mean		9.51
	SD		1.11
	Minimum		8

Table 4: Descriptive statistics of duration for complete expulsion in both groups

Duration (min)		Group	
		Misoprostol	IMN
	N	36	36
	Mean	91.69	122.58
	SD	15.74	16.55

Independent sample t-test = 8.114

p-value = 0.000 (Significant)

Table 5: Comparison of number of doses required for complete expulsion

		Group		Total
		Misoprostol	IMN	
Number of doses required	1	36 (100%)	18 (50.0%)	54 (75%)
	2	0 (0.0%)	18 (50.0%)	18 (25%)
Total		36 (100%)	36 (100%)	72 (100%)

Chi-square test = 24.00

p-value = 0.000 (Significant)

Table 6: Comparison of duration for complete expulsion in both groups stratified for age

Age (years)	Duration	Group		p-value
		Misoprostol	IMN	
21-30	N	18	16	0.000
	Mean ± SD	89.56±14.82	125.38±17.46	
31-40	N	18	20	0.000
	Mean ± SD	93.83±16.76	120.35±15.87	

Table 7: Comparison of duration for complete expulsion in both groups stratified for parity

Parity	Duration	Group		p-value
		Misoprostol	IMN	
Primiparous	N	12	6	0.000
	Mean±SD	90.75±11.84	135.83±12.84	
Multiparous	N	24	30	0.000
	Mean±SD	92.17±17.59	119.93±16.08	

Table 8: Comparison of duration for complete expulsion in both groups stratified for BMI

BMI	Duration	Group		p-value
		Misoprostol	IMN	
Normal	N	24	16	0.000
	Mean±SD	92.67±15.96	126.25±11.51	
Overweight	N	7	18	0.002
	Mean±SD	90.14±15.99	120.44±20.35	
Obese	N	5	2	0.141
	Mean±SD	89.20±17.40	112.50±7.78	

DISCUSSION

In this study, we included 72 females with first trimester missed miscarriage with the mean age of 30±5 years. The mean gestational age of females was 9 ±1 weeks. The mean duration required for complete expulsion was 91.69±15.74minutes in misoprostol group and 122.58±16.55minutes in IMN group. There was significant difference in both groups ($p<0.05$).

Merie-Ledingham found that the mean duration of complete expulsion was 169±29 minutes with misoprostol ($n=21$) which was significantly higher than IMN ($n=22$) i.e. 150±28 minutes ($P<0.05$).⁴ Al-Saffar and Marouf also showed that mean duration of complete expulsion was 8.4±3.2 hours with misoprostol which was higher than IMN i.e. 7.6±4.2 hours, but the difference was insignificant ($P<0.05$).¹

Waleed El-Khayat has shown that out of 162 patients recruited for the study, mean duration of complete expulsion with misoprostol ($n=81$) was 49±20.1 minutes ($n=81$) which was significantly lower than IMN ($n=81$) which was 73±34.2 minutes ($P<0.05$).⁶ Another trial also showed that the mean duration of complete expulsion was 15.4±5.4 hours with misoprostol which was significantly lower than IMN i.e. 26.3±7.3 hours ($P<0.05$).⁸

One more study supported the evidence and showed that the mean duration of complete expulsion was 4.47±2.042 hours with misoprostol ($n=50$) which was significantly lower than IMN ($n=50$) i.e. 8.03±2.833 hours ($P<0.05$).⁹ In contrast, Wolfieret al. showed that vaginal application of IMN plus dinoprostone appeared to be no more effective than placebo.¹⁰

One trial showed that the mean duration of complete expulsion was 19.56±3.96 hours with combination of IMN with misoprostol which was significantly lower than misoprostol alone i.e. 23±2.62 hours ($P<0.05$). It was concluded that using a combination of IMN and misoprostol is effective than misoprostol alone in terms of fast cervical ripening.¹¹

We stratified data for age of females. In patients aged 21-30years, the mean duration required for complete expulsion was 89.56±14.82minutes in

misoprostol group and 125.38±17.46minutes in IMN group. There was significant difference in both groups ($p<0.05$). In patients aged 31-40years, the mean duration required for complete expulsion was 93.83±16.76minutes in misoprostol group and 120.35±15.87minutes in IMN group. There was significant difference in both groups ($p<0.05$). Thus the misoprostol was more effective than IMN in any age group.

We stratified data for BMI of females. In normal BMI females, the mean duration required for complete expulsion was 92.67±15.96minutes in misoprostol group and 126.25±11.51minutes in IMN group. There was significant difference in both groups ($p<0.05$). In overweight females, the mean duration required for complete expulsion was 90.14±15.99minutes in misoprostol group and 120.44±20.35minutes in IMN group. There was significant difference in both groups ($p<0.05$). In obese females, the mean duration required for complete expulsion was 89.20±17.40minutes in misoprostol group and 112.50±7.78minutes in IMN group. There was insignificant difference in both groups ($p>0.05$). Thus the misoprostol was more effective than IMN in any BMI group, except obese patients. In obese patients, both drugs were equally effective ($p>0.05$).

CONCLUSION

Thus the mean expulsion time was significantly less for misoprostol than IMN. Through this study, we found misoprostol more effective than IMN. Now in future, we can recommend misoprostol for complete evacuation of conception material during first trimester missed miscarriage.

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