



A COMPARATIVE STUDY OF SUBLINGUAL, ORAL AND VAGINAL ADMINISTRATION OF MISOPROSTOL IN THE MANAGEMENT OF MISSED ABORTION

Gynaecology

Dr. Sandip Ghosh Gangarampur SDH & SSH, WB.

Dr. Palash Kanti Kundu* Mathabhanga SDH. WB. *Corresponding Author

Dr. Debarshi Jana IPGMER and SSKM Hospital, Kolkata.

ABSTRACT

Aim: A comparison of the efficacy of Misoprostol used in sublingual, oral and vaginal routes for missed abortion. A comparison of dose and time interval of drug administration to onset of action of three different routes. **Material and methods:** The study was conducted at the Department of Obstetrics and Gynaecology in Nilratan Sircar Medical College and Hospital, Kolkata after approval by the ethical committee. The sample size was 100 women being treated for missed abortions where prospective sampling was carried out to determine the candidates to be selected for the study. Single centred, institution based, randomized controlled trial. Cases included in this study were divided into 3 groups: Sublingual Group, Oral Group and Vaginal Group. **Result:** The mean Duration of induction to delivery time in hrs (mean $\pm$ s.d.) of the patients was 14.0206 $\pm$ 1.4587 hr. In sublingual, the mean Duration of induction to delivery time in hrs (mean $\pm$ s.d.) of patients was 9.3353 $\pm$.8388 hr. In vaginal, the mean Duration of induction to delivery time in hrs (mean $\pm$ s.d.) of patients was 10.4412 $\pm$ 1.2502 hr. Difference of mean Duration of induction to delivery time in hrs vs. group was statistically significant (p<0.001). **Conclusion:** Incomplete abortion was higher in oral, followed by Vaginal and Sublingual misoprostol. Success rate was higher in Sublingual compared to Vaginal and Oral.

KEYWORDS

Misoprostol, Vaginal, Sublingual, Missed Abortion

INTRODUCTION

Abortion is defined as spontaneous or induced termination of pregnancy before age of viability. Missed abortion is defined as death of conceptus without expulsion of its conceptus with closed cervix before foetal viability. The age of viability differs in different countries. In Egypt it is 28 weeks, in U.K. 24 weeks and in USA 20 weeks¹. WHO defines 500 gram as the cut of mark for age of viability².

Management of missed abortion includes:

1. Surgical management by evacuation of uterus either by Dilatation and Evacuation method or by Suction Evacuation method which is again of two types- Electrical and Manual.
2. Medical evacuation by using prostaglandin, oxytocin and ergometrin.
3. Expectant management hoping for spontaneous expulsion product of conception.

Medical management which is considered to be safe and well accepted by common people deals with effectiveness, side effect and route of administration.

Misoprostol acts as a cervical ripening and uterotonic agent.³ It is widely used for termination of pregnancy and combined with mifepristone for medical abortion. It is inexpensive and stable at room temperature. Surgical procedure is associated with faster results, but it can lead to more complications like cervical incompetence, uterine synechiae and uterine perforations. So, nowadays medical method is the treatment of choice for medical termination of pregnancy. Different doses and routes of administration of misoprostol in both first and second trimester have been investigated and results are compared, but optimal dose and route have not been properly identified. Due to its rapid absorption, sublingual route reaches its peak concentration in a short time and has the highest bioavailability.⁴ Vaginal route causes prolonged regular uterine contractions and has fewer side effects after administration. So, the present study is done to compare the efficacy of sublingual and vaginal misoprostol for medical abortion up to 20 weeks of gestation.⁵

Misoprostol as an abortifacient is effective in all forms of its administration, although different applications have different advantages and effects too. A study among patients with missed abortions would help a lot in regard to identifying the advantages and disadvantages associated with all the modes of administration and statistically speaking they can be correlated with other parameters to effectively determine which situation would require which mode of administration and how effective would they be in that case. Initial study speculates oral mode of administration to be best suited for most conditions but that needs to be better explored and verified.

1. A comparison of the efficacy of Misoprostol used in sublingual, oral and vaginal routes for missed abortion.

SECONDARY

1. Comparison of dose and time interval of drug administration to onset of action of three different routes.
2. Comparison of complications, if any, encountered during the abortion process of three different routes.

MATERIALS & METHODS

1. Study design

Single centred, institution based, randomized controlled trial. Cases included in this study were divided into 3 groups:

Sublingual Group: 100 mcg of Tab Misoprostol (1/2 tablet) was administered to group 1 cases sublingually and will be repeated every 4 hourly for 4 doses.

Oral Group: 100 mcg of Tab Misoprostol (1/2 tablet) was administered to group 2 orally and that was repeated every 4 hourly for 4 doses.

Vaginal Group: 100 mcg of Tab Misoprostol (1/2 tablet) was administered to this group 3 in the posterior fornix of vagina and was repeated every 4 hourly for 4 doses.

Place of study

The study will be conducted at the Department of Obstetrics and Gynaecology in Nilratan Sircar Medical College and Hospital, Kolkata after approval by the ethical committee.

4. Period of study

The study would span over a year (from 01/06/2018 to 31/05/2019)

5. Study population

The study population would comprise of patients being treated for missed abortion in Nilratan Sircar Medical College and Hospital, Kolkata by administration of Misoprostol.

Sample size and design

The sample size would be 100 women being treated for missed abortions where prospective sampling would be carried out to determine the candidates to be selected for the study.

7. Inclusion and exclusion criteria

The candidates satisfying the below conditions would be included in the study group:

- Diagnosed case of pregnancy loss either by ultrasound or by subnormally rising quantitative hcg level (Serum hcg estimation)

may be deferred in patients with financial constraints who will follow up at a clinical site with ultrasound, if the initial diagnosis was confirmed by ultrasound)

- Woman want to expedite expulsion of product of conception without surgery
- Woman who have no contraindication like infection, haemorrhage, severe anaemia, bleeding diatheses, allergy to Prostaglandins
- Woman having easy accessibility to nearest health facility
- Woman willing to come for desired follow up

Medical treatment for missed abortion would not be considered in candidates without the following contraindications:

- Known allergy to Misoprostol.
- Previous caesarean section

Mitral stenosis

- Hypertension
- Glaucoma
- Bronchial asthma
- Use of non-steroidal drugs
- Remote area without hospital around
- Age less than 18 years
- Diagnosed or suspected case of ectopic pregnancy.
- Haemodynamically unstable patient.
- Signs of sepsis or active Pelvic Inflammatory Disease

RESULT AND DISCUSSION

Ayswarya Shanmugam et al ⁶ (2016) found that the maternal age distribution, parity and gestational age in the two groups were found to be comparable. Requirement of mean dose of misoprostol in sublingual and vaginal were 1300 mcg, 1253 mcg respectively.

We found that in oral, 11(32.4%) patients had ≤ 20 years of age, 18(52.9%) patients had 21-25 years of age, 4(11.8%) patients had 26-30 years of age and 1(2.9%) patient had 31-36 years of age. In sublingual, 6(17.6%) patients had ≤ 20 years of age, 16(47.1%) patients had 21-25 years of age, 8(23.5%) patients had 26-30 years of age and 4(11.8%) patients had 31-36 years of age. In vaginal, 10(29.4%) patients had ≤ 20 years of age, 14(41.2%) patients had 21-25 years of age, 7(20.6%) patients had 26-30 years of age and 3(8.8%) patients had 31-36 years of age. Association of age in years vs. group was not statistically significant ($p=0.5217$). Association of parity vs. group was not statistically significant ($p=0.6167$).

Hassan FI et al ⁷ (2007) found that the low incidence of side-effects especially vomiting diarrhoea and bleeding misoprostol whether by oral or rectal route seems to be an effective as a non invasive method for evacuation of the uterus in women with retained products of conception.

Diop A et al ⁸ (2009) found that 400 mcg sublingual misoprostol and 600mcg oral misoprostol. Mean pain scores were 2.95 and 3.04, respectively, for the oral and sublingual groups. Side effects included abdominal pain, bleeding, headaches and dizziness/weakness with no differences reported between the two groups. Acceptability and satisfaction were high for both routes and women indicated a preference for medical versus surgical treatment if ever needed in the future.

It was found that in oral, 4(11.8%) patients had fever. In sublingual, 6(17.6%) patients had fever. In vaginal, 2(5.9%) patients had fever. Association of fever vs. group was not statistically significant ($p=0.3220$). We found that in oral, 27(79.4%) patients had vaginal bleeding. In sublingual, 30(88.2%) patients had vaginal bleeding. In vaginal, 29(85.3%) patients had vaginal bleeding. Association of vaginal bleeding vs. group was not statistically significant ($p=0.5952$). Parveen S et al ⁹ (2011) found that the intra-operative pain score of the S/L group was significantly lower (1.9 ± 1.1 , $P < 0.05$) as compared to the vaginal (2.6 ± 1.7) or oral route (3.3 ± 1.7). Loose motions and nausea/vomiting were more with the S/L and oral routes while blood loss was more in the vaginal route. Administration of misoprostol by the sublingual route is better than the oral and vaginal routes for cervical ripening.

We found that in oral, 16(47.1%) patients had nausea. In sublingual, 8(23.5%) patients had nausea. In vaginal, 34(100.0%) patients had no nausea. Association of nausea vs. group was statistically significant

($p < 0.001$). In oral, 9(26.5%) patients had vomiting. In sublingual, 4(11.8%) patients had vomiting. In vaginal, 34(100.0%) patients had no vomiting. Association of vomiting vs. group was statistically significant ($p=0.0046$).

Farhadifar F et al ¹⁰ (2016) found that only two cases of oral misoprostol group experienced complications. Although the risk of complications in oral method.

It was found that in oral, 20(58.8%) patients had abdominal pain. In sublingual, 21(61.8%) patients had abdominal pain. In vaginal, 14(41.2%) patients had abdominal pain. Association of abdominal pain vs. group was not statistically significant ($p=0.1833$).

We found that oral, 7(20.6%) patients had diarrhoea. In sublingual, 6(17.6%) patients had diarrhoea. In vaginal, 2(5.9%) patients had diarrhoea. Association of diarrhoea vs. group was not statistically significant ($p=0.1937$). Association of tachycardia vs. group was not statistically significant ($p=0.5200$).

Gemzell-Danielsson K et al ¹¹ (2007) found that Bleeding may last for more than 14 days with additional days of light bleeding or spotting. The woman should be advised to contact a provider in case of heavy bleeding or signs of infection. A follow-up is recommended after 1 to 2 weeks.

Parveen S et al ⁹ (2011) found that the mean time taken for cervical ripening was less in sublingual administration (3.7 ± 1.2 hr) as compared to the vaginal and oral routes. The S/L group had significant cervical dilatation ($P < 0.001$) and the duration of SE was less as compared to the vaginal and oral routes. However, the mean intraoperative blood loss was more in sublingual as compared to the vaginal and oral groups.

We found that in oral, the mean times for uterine colic starting (mean $\pm$ s.d.) of the patients was 225.8824 ± 13.2842 min. In sublingual, the mean times for uterine colic starting (mean $\pm$ s.d.) of patients were 135.9412 ± 13.1009 min. In vaginal, the mean times for uterine colic starting (mean $\pm$ s.d.) of patients was 178.7353 ± 27.6727 min. Distribution of mean times for uterine colic starting vs. group was statistically significant ($p < 0.001$).

It was found that in oral, the mean cervical dilatation (mean $\pm$ s.d.) of the patients was 334.4118 ± 14.6041 min. In sublingual, the mean cervical dilatation (mean $\pm$ s.d.) of patients was 251.1765 ± 23.7110 min. In vaginal, the mean cervical dilatation (mean $\pm$ s.d.) of patients was 253.4412 ± 10.0670 min. Distribution of mean cervical dilatation vs. group was statistically significant ($p < 0.001$).

We found that in oral, the mean regression of symptoms of pregnancy (mean $\pm$ s.d.) of the patients was 10.8529 ± 1.5980 days. In sublingual, the mean regression of symptoms of pregnancy (mean $\pm$ s.d.) of patients was $7.0294 \pm .9996$ days. In vaginal, the mean regression of symptoms of pregnancy (mean $\pm$ s.d.) of patients was 8.8529 ± 1.2585 days. Distribution of mean regression of symptoms of pregnancy vs. group was statistically significant ($p < 0.001$).

Shah N et al ¹² (2010) found that the mean induction to delivery time was also similar for both groups (13.07 ± 6.95 hours for sublingual versus 13.29 ± 5.63 hours for vaginal group) as was the total number of doses required (4.44 ± 1.04 for sublingual versus 4.52 ± 0.96 for vaginal misoprostol). Side effects were seen in 18 women (72%) in the sublingual group compared to 5 women (20%) in the vaginal group ($p < 0.001$). The incidence of unpleasant taste was significantly higher in the sublingual group than in the vaginal group (60% versus 4%, $p < 0.001$). Sublingual misoprostol is as effective as vaginal misoprostol for medical management of missed miscarriage but is associated with an increased risk of side effects especially an unpleasant taste.

Nath J et al ¹³ (2013) found that Efficacy was assessed on the basis of time taken for ripening, dilatation achieved, duration of the procedure, intraoperative blood loss and pain. The patient's tolerability was noted on the basis of side effects. The mean time taken for cervical ripening was more in the sublingual group as compared to the vaginal ($P < 0.001$). The duration of suction and evacuation was less as compared to the vaginal route. The intraoperative pain score was comparatively lower ($P < 0.05$) as compared to the vaginal. Side effects like loose motions, nausea vomiting were more with sublingual group.

Our study showed that in oral, the mean Duration of induction to delivery time in hrs (mean $\pm$ s.d.) of the patients was 14.0206 $\pm$ 1.4587 hr. In sublingual, the mean Duration of induction to delivery time in hrs (mean $\pm$ s.d.) of patients was 9.3353 $\pm$.8388 hr. In vaginal, the mean Duration of induction to delivery time in hrs (mean $\pm$ s.d.) of patients was 10.4412 $\pm$ 1.2502 hr. Difference of mean Duration of induction to delivery time in hrs vs. group was statistically significant ($p < 0.001$).

Wu HL et al ¹⁴ (2017) found that the most effective treatment was sublingual misoprostol of 600ug and the least effective was oral misoprostol of 400ug. vaginal misoprostol of 400ug was reported with fewer side effects and sublingual misoprostol of 600ug was reported with more side effects. Misoprostol is a non-invasive, effective medical method for completion of abortion in missed abortion. Sublingual misoprostol of 600ug or vaginal misoprostol of 800ug may be a good choice for the first dose. The ideal dose and medication interval of misoprostol however needs to be further researched.

We also found that in oral, 8(23.5%) patients had incomplete abortion. In sublingual, 5(14.7%) patients had incomplete abortion. In vaginal, 6(17.6%) patients had incomplete abortion. Association of incomplete abortion vs. group was not statistically significant ($p = 0.6359$). In oral, 1(2.9%) patient had failure. In sublingual, 34(100.0%) patients had no failure. In vaginal, 34(100.0%) patients had no failure. Association of failure vs. group was not statistically significant ($p = 0.3643$).

Table: Distribution of mean Age, Gestation (wk), BMI, Times for uterine colic starting, Duration of induction to delivery time in hrs and Cervical dialatation in mins vs Group

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Age (yrs)	Oral	34	22.1471	3.4565	18.0000	32.0000	21.0000	0.0562
	Sublingual	34	24.5294	4.3291	18.0000	34.0000	24.0000	
	Vaginal	34	23.9118	4.6799	18.0000	36.0000	24.0000	
Gestation (wk)	Oral	34	10.3735	2.3527	6.0000	14.2000	10.2000	0.1704
	Sublingual	34	9.4912	1.9215	6.3000	16.0000	9.1000	
	Vaginal	34	9.6059	1.9506	6.3000	15.0000	9.1500	
BMI (Kg/m2)	Oral	34	22.1176	2.0213	18.3000	26.5000	22.0500	0.9276
	Sublingual	34	22.0324	2.4242	17.2000	28.3000	21.9500	
	Vaginal	34	21.9035	2.4070	17.7000	29.0000	21.7000	
Times for uterine colic starting (min)	Oral	34	225.8824	13.2842	200.0000	255.0000	230.0000	<0.001
	Sublingual	34	135.9412	13.1009	120.0000	160.0000	130.0000	
	Vaginal	34	178.7353	27.6727	142.0000	240.0000	175.0000	
Duration of induction to delivery time in hrs	Oral	34	14.0206	1.4587	10.5000	16.0000	14.2000	<0.001
	Sublingual	34	9.3353	.8388	8.2000	11.2000	9.2000	
	Vaginal	34	10.4412	1.2502	8.2000	12.5000	10.5000	
Cervical dialatation in mins	Oral	34	334.4118	14.6041	300.0000	360.0000	340.0000	<0.001
	Sublingual	34	251.1765	23.7110	180.0000	280.0000	255.0000	
	Vaginal	34	253.4412	10.0670	240.0000	280.0000	250.0000	

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CONCLUSION

In Sublingual misoprostol unpleasant taste was more common. Side effects, such as Fever, Abdominal Pain, Vaginal Bleeding, Diarrhoea, Tachycardia as not statistically significant in three groups but vomiting was significantly higher in oral compared to others. Incomplete abortion was higher in oral, followed by Vaginal and Sublingual misoprostol. Success rate was higher in Sublingual compared to Vaginal and Oral.

The mean times for uterine colic starting were lower Sublingual compared to vagina and oral administration.

Induction-abortion interval in sublingual (9.3353 $\pm$.8388 h) and vaginal (10.4412 $\pm$ 1.2502 h) groups was shorter than that in oral group (14.0206 $\pm$ 1.4587).

Oral and sublingual routes of administration have shown to be more acceptable compared to vaginal route of administration. But the efficacy of oral administration is less. Therefore, sublingual misoprostol has the advantage that it can avoid the uncomfortable vaginal administration. Also absorption of the drug may be affected when the patient starts bleeding.

The study demonstrates that both vaginal and sublingual misoprostol have similar and higher success rates in inducing abortion compared to oral route.