Original article

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A Comparative Study of Oral, Buccal and Vaginal Administration of Misoprostol Following Oral Mifepristone in the Termination of Early Pregnancy

Sushmitha B.*, Gayatri Devi J.**

Abstract

Objectives: To compare oral, buccal and vaginal administration of Misoprostol following oral Mifepristone, in terms of Safety, Efficacy (completion of abortion) and Patient acceptability of route of administration(Acceptance may be defined as whether the patient was satisfied with the route of administration of misoprostol after termination of pregnancy). *Study Design*: A prospective open label randomized study. *Materials and Methods:* All pregnant women with less than 9 weeks who presented to R. L. Jalappa Hospital for Medical Termination of Pregnancy between March 2014 and June 2015 were included in this study. Total number of 90 patients included in this study. Patients were divided into 3 groups by computerized randomization plan 17213 and each group comprised 30 patients. *Results*: Majority of the women were multi gravida(71.1%). Age distribution was similar in all 3 groups, majority of whom belonged to the age group between 21 and 25 years. Most common indication for termination of pregnancy was unplanned pregnancy. Patients in oral (4.3 ± 2.88 hours) and buccal (4.325 ± 2.17 hours) group had shorter induction to expulsion duration compared to vaginal group (5.79 ± 2.42 hours) which was statistically significant. Induction to expulsion duration was reduced with lesser gestational age in all the three groups. Success of complete expulsion was more with buccal route (93.3%). However, this was not significant statistically (P value-0.69). Side effects were similar in all the groups except diarrhoea which was significantly more in oral group (P value <0.001). However vaginal group had comparatively least side effects, but not significant statistically. Patient acceptance was similar in all the groups. However in oral and buccal groups, they are able to self administer the drug avoiding the vaginal route of administration. *Conclusion*: The induction to expulsion interval was similar in oral and buccal routes but vaginal route had significantly prolonged duration. Vaginal route had comparatively least side effects while oral route had highest. Buccal route had shorter induction to expulsion interval, minimal side effects and better acceptance of the route of administration.

Keywords: Mifepristone; Misoprostol; Abortion.

*Post Graduate **Professor
Department of Obstetrics and Gynaecology, Sri Devaraj URS Medical College, Kolar, Karnataka.

Sushmitha B.
Post Graduation in MS OBG, Department of Obstetrics and Gynaecology, Sri Devraj URS Medical College, Kolar,
Karnataka 563101.
E-mail
drsushmithareddy09@gmail.com

Introduction

Abortion is the termination of pregnancy before the fetus becomes viable.[1]The unmet need of safe abortion among women with unwanted pregnancy continues to be a major challenge in the efforts to provide better health care [2].

Throughout history, women have sought to terminate unwanted pregnancies in spite of the legal standing of abortion wherever they may be. Abortions have been procured without regard to culture, economic status and religion. Although safe methods for prevention are available, unsafe abortion rates are high, particularly in developing countries. Lack of access and inadequate

knowledge of effective contraceptive methods are factors which account for high incidence of unwanted pregnancies.

Maternal mortality is a key indicator of women's health and social status, the levels of which are unacceptably high in India. According to the latest government report on causes of death from 2010, 9% of maternal deaths were attributed to complications of unsafe abortion [3]. Abortion techniques have varied greatly over time and across cultures. They include a wide variety of abortifacients, mechanical devices, strenuous physical activity, excessive abdominal massage and starvation.

To overcome the complications associated with surgical abortion, FDA in 2000 approved mifepristone and misoprostol for medical abortion in first trimester abortion. India approved this combination for clinical usage in 2001 [4]. For medical abortion up to 63 days gestation, there are various regimens available as per WHO guidelines. This study was conducted with an aim to study and document the efficacy of various routes of administration of misoprostol following mifepristone in termination of early pregnancy.

Aims and Objectives

In patients undergoing Medical Termination of Pregnancy in first trimester (≤ 63 days or <9 weeks of gestation) this study is to compare oral, buccal and vaginal administration of Misoprostol following oral Mifepristone, in terms of Safety , Efficacy (completion of abortion) and Patient acceptability of route of administration (Acceptance may be defined as whether the patient was satisfied with the route of administration of misoprostol after termination of pregnancy)

Materials and Methods

Source of Data

All pregnant women with less than 9 weeks or d" 63 days of gestation (estimated by either last menstrual period or early obstetric scan, if available) who came to R.L. Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar, for Medical Termination of Pregnancy were taken for the study from March 2014 to June 2015. The study was conducted on an outpatient basis.

Study Design

Prospective open label randomized study.

90 pregnant women fulfilling the inclusion criteria in first trimester ≤ 63 days of gestation (estimated by either last menstrual period or early obstetric scan if available) were included in the study. The patients were divided into 3 groups by computerized randomization plan 17213. Each group comprised of 30 patients.

Group 1(N=30) was administered oral Mifepristone followed by oral Misoprostol.

Group 2(N=30) was administered oral Mifepristone followed by *buccal Misoprostol.*

Group 3(N=30) was administered oral Mifepristone followed by *vaginal Misoprostol.*

Inclusion Criteria

- Women more than 18years of age
- Duration of pregnancy <9weeks or d"63 days of amenorrhea
- Requesting legal termination of pregnancy according to MTP Act
- Single intrauterine pregnancy irrespective of their parity
- Hemoglobin >10g%

Exclusion Criteria

- Medical conditions contraindicating the use of Mifepristone (eg. adrenal disease)
- Medical conditions contraindicating the use of Misoprostol (eg. hypertension, cardiac diseases, bronchial asthma, glaucoma, sickle cell anemia, hypotension)
- Allergy to Mifepristone or Misoprostol
- Presence of intra uterine device
- Suspected or proven ectopic pregnancy
- Patient on anticoagulant therapy

Methodology

The institution ethics and research review board approved the present study. All the selected patients were explained the purpose of the study and their written informed consent was taken for the same. The procedure and complications were explained in detail.

Protocol

- Counseling for procedure and possible complications was done, consent taken.

- A detailed history was collected from all the patients fulfilling the inclusion criteria regarding age, parity, duration of gestation, need for termination of pregnancy, menstrual history, obstetric history and any other complications in the present pregnancy were noted.
- General clinical examination was done. Pulse rate, blood pressure and temperature were noted. Per abdominal, per speculum and per vaginal examination was done in detail
- Investigations done prior to termination are complete blood count, bleeding time, clotting time, blood group and Rh typing, urine analysis, random blood sugar, HIV, HBsAg and VDRL, Abdominal and Pelvic Ultrasonography.
- Pregnant women who met the inclusion criteria were randomized into three groups by computerized randomization plan of 17213.

Group I (Oral)	Group II (Buccal)	Group III (Vaginal)
Administered 200 mg Mifepristone orally	Administered 200 mg Mifepristone orally	Administered 200 mg Mifepristone orally
↓	↓	↓
After 24 Hours	After 24 Hours	After 24 Hours
↓	↓	↓
800 µg Misoprostol was given orally	**800 µg Misoprostol was placed in the buccal cavity (400µg between the teeth and cheek on each side) for 30minutes**	**800 µg Misoprostol was placed per vaginally in the posterior fornix**

- Patient was explained to note the time of onset and cessation of bleeding. The period between misoprostol administration and cessation of bleeding is taken as induction to expulsion interval.
- During this period side effects such as abdominal pain, fever, chills, nausea, vomiting, diarrhoea and others were noted and documented by the patient and treated symptomatically.
- Patient was explained to contact the doctor at any time if they notice excessive bleeding.
- If there was no bleeding even after 24 hours after the administration of misoprostol by any of the routes, it was considered as failed induction and was treated with suction and evacuation.
- Rh negative patients were administered Rh immunoglobulin prior to induction of abortion.

Post Procedure

At the end of the procedure the following were noted

1. Induction to abortion interval in hours.
2. Complete expulsion of products of conception.
3. Failed induction.
4. Side effects (fever, chills, nausea, vomiting and diarrhoea) were noted.
5. Estimation of blood loss(as per the change in Hemoglobin before and after the termination of pregnancy)
6. Acceptance of the patient to the route of administration

(Acceptance may be defined as whether the patient was satisfied with the route of administration of misoprostol after termination of pregnancy)

Follow Up

Follow up was done after 1 week of misoprostol induction. Abdominal and pelvic ultrasonography was repeated after 1 week of induction. Repeat haemoglobin was measured after 1week of induction.

Sample Size

Sample size of 90 was considered in the present study as there were only around 80 to 100 patients requesting medical termination of pregnancy during the period of 1 year as per the previous records of hospital. Hence all patients requesting medical termination of pregnancy, fulfilling the inclusion criteria and consenting for the study were included.

Statistical Analysis

Data was entered into Microsoft excel data sheet and analysis was done using EPI INFO 7 VERSION software. Descriptive statistics like frequency, proportion, mean, standard deviation were computed depending upon qualitative and quantitative data. Chi-square test was the test of significance for qualitative data. Incidence of adverse events was calculated and ANOVA test was used to find the difference in the mean values between and within the groups. $P \leq 0.05$ was considered as statistically significant.

Results

A prospective open label randomized study was conducted at R L Jalappa Hospital from March 2014 to June 2015, which was a comparative study of oral, buccal and vaginal administration of misoprostol following oral mifepristone in the termination of early pregnancy(less than 9 weeks or ≤ 63 days of gestational age). 90 women who met the inclusion criteria were included in the study. 30 women in each group. The following results were obtained.

Table 1: Comparison of different parameters among the three groups

Different parameters	Oral	Buccal	vaginal
Mean age(years)	24.8 ± 3.4	24.6±4.8	24.5 ± 4.0
Gravidity			
Primi	9(30%)	10(33.3%)	7(23.3%)
Multi	21(70%)	20(66.6%)	23(76.6%)
Period of gestation(weeks)			
≤7	18(60%)	22(73.2%)	13(43.2%)
7.1-8	11(36.6%)	5(16.6%)	7(23.3%)
8.1-9	1(3.3%)	3(10%)	10(33.3%)
Indication for termination			
Failed contraception	6(20%)	5(16.6%)	4(13.3%)
Unplanned pregnancy	13 (43.3%)	14 (46.6%)	14 (46.6%)
Medical disease indicating termination	3(10%)	8(26.6%)	6(20%)
Missed abortion	8(26.6%)	3(10%)	6(20%)
Induction to expulsion interval			
<12hours	23(76.6%)	26(86.6%)	26(86.6%)
12-24hours	4(13.3%)	2(6.6%)	-
>24hours	3(10%)	2(6.6%)	4(13.3%)

In this study population, the youngest patient was 18 years while the oldest patient was 37 years. Majority of the patients were between 21 and 25 years of age (55.5%). Multi gravida were more than primi gravida in all the three groups.In this study, the gestational age of less than 7 weeks was 60%, 73.2% and 43.2% in oral, buccal and vaginal groups respectively. The gestational age between 7.1 and 8 weeks was 36.6%, 16.6% and 23.3% in oral, buccal and vaginal groups respectively. The gestational age between 8.1 and 9 weeks was 3.3%, 10% and 33.3% in oral, buccal and vaginal groups respectively.

The most common indication for termination was for unplanned pregnancy 41(45.5%) followed by medical disease indicating termination and missed abortion accounting each for 17(18.8%) and failed contraception 15(16.6%).

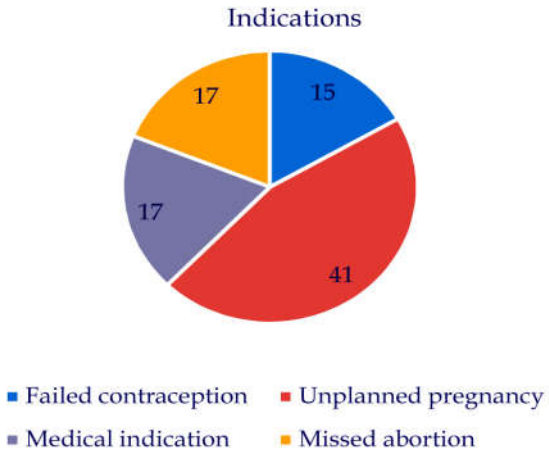

Fig. 1: Flowchart showing the successful expulsion of products of conception

Amongst 15 women with failed contraception, 13 (86.6%) women had failure of barrier methods and 2(13.3%) women had failed sterilization. In oral group, 4 women (66.6%) had failure of barrier methods and 2 women (33.3%) had failed sterilization. In buccal and vaginal groups, there were 5 and 4 women respectively who had failure of barrier methods.

In each group, 76.6%, 86.6% and 86.6% in oral, buccal and vaginal groups respectively were with induction to expulsion interval less than 12 hours.

Women with duration between 12 and 24 hours were 13.3% and 6.6% in oral and buccal group respectively. Women with duration of more than 24 hours were 10%, 6.6% and 13.3% in oral, buccal and vaginal groups respectively.

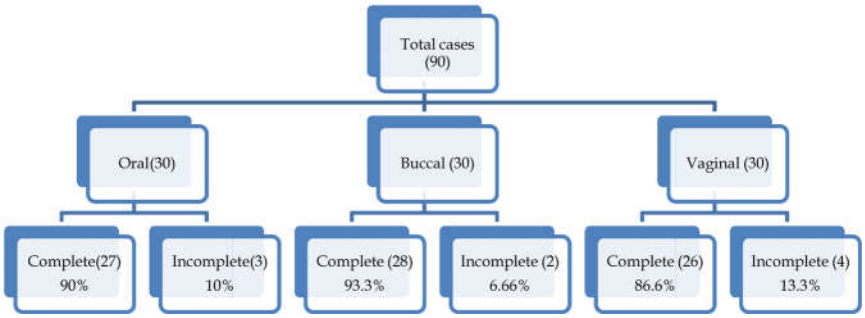

Fig. 2: Flowchart showing the successful expulsion of products of conception

There were 10%, 6.6% and 13.3% of women in oral, buccal and vaginal groups respectively, who did not expel the products of conception within 24 hours. They were further managed by suction evacuation.

Fever was noticed in 16.6%, 6.6% and 23.3% in oral, buccal and vaginal groups respectively. Chills were seen in 33.3%, 36.6% and 23.3%, nausea was in 53.3%, 50% and 36.6%, vomiting was in 23.3%, 36.6% and 10% of women in oral, buccal and vaginal groups respectively. Diarrhea was seen in 33% women in oral group alone.

Table 2: Comparison of different parameters in patients administered 800 μg of misoprostol by different routes

Different parameters		Oral	Buccal	vaginal	P_{OB} value	P_{BV} value	P_{OV} value
Mean Induction to expulsion interval (in hours)		4.3 ± 2.88	4.325± 2.17	5.79± 2.42	0.971	0.021	0.044
Acceptance of the route of administration		27 (90%)	28 (93.3%)	28 (93.3%)	0.64	1	0.64
Amount of blood loss	< 1g%	20(66.6%)	27(90%)	26(86.6%)	0.601	0.601	0.39
	1-2g%	5(16.6%)	3(10%)	3(10%)			
	>2g%	5(16.6%)	0	1(3%)			
Complete expulsion		27(90%)	28(93.3%)	26(86.6%)	0.389	0.389	0.688
Fever		5(16.6%)	2(6.6%)	7(23.3%)	0.228	0.071	0.519
Chills		10(33.3%)	11(36.6%)	7(23.3%)	0.787	0.26	0.39
Nausea		16(53.3%)	15(50%)	11(36.6%)	0.796	0.297	0.194
Diarrhea		10(33.3%)	0	0	0.001	-	0.001
Vomiting		7(23.3%)	11(36.6%)	3(10%)	0.774	0.197	0.117

The mean induction to expulsion interval was 4.3 ± 2.88 hours in oral group, 4.325 ± 2.17 hours in buccal group and 5.796 ± 2.42 hours in vaginal group. The mean induction to expulsion interval was prolonged in vaginal group. Rate of complete expulsion of products of conception was highest in buccal group (93.3%).

When we compared the vaginal route with oral route we found a significant difference ($P<0.05$) in the induction to expulsion interval as well as the occurrence of diarrhea. The oral group had a lesser induction to expulsion interval as compared to vaginal route. The rates of patients complaining of diarrhea were more in the oral group. There was no significant difference when comparing both the groups with respect to rest of the above mentioned parameters.

The induction expulsion interval of buccal route when compared with the vaginal route was found to have a significant difference with the buccal route having a lesser duration. There was no significant difference when comparing both the groups with respect to rest of the above mentioned parameters.

There was no significant difference when comparing both the groups (oral vs buccal) with respect to the above mentioned parameters except the incidence of diarrhea, which was significantly higher in the oral group.

Discussion

The present study is done to compare the efficacy of oral, buccal and vaginal misoprostol following oral mifepristone in early termination of pregnancy. Misoprostol, a prostaglandin E1 analogue, has been

extensively studied in reproductive health, and is widely recommended for the treatment of missed abortion, the induction of abortion, and cervical preparation before uterine instrumentation. The FDA recommended misoprostol as the choice of prostaglandin for termination of pregnancy. Since 1995, investigations are on to find the optimum regimen for the use of misoprostol in first and second trimester termination of pregnancy. There are number of advantages of using misoprostol instead of other prostaglandins for termination of pregnancy because of its substantially less cost and storage facilities. This drug can be given vaginally, orally, sublingually or buccally or in combinations with different dosages.

In the present study, most of the patients were in between 21 and 25 years of age (oral-53.3%, buccal-60% and vaginal-53.3%). In the present study, majority of the patients were multi gravida (70%, 66.6% and 76.6% in oral, buccal and vaginal respectively). There were almost equal number of primi gravida and multi gravida in all the three groups.

The most common indication for termination of pregnancy was unplanned pregnancy (45.5%) followed by 18.8% for medical disease indicating termination, 18.8% for missed abortion and 16.6% for failed sterilization. Observations showed no difference in indications among the three groups.

In the present study mean induction to expulsion interval was significantly less in buccal group, 4.325 ± 2.17 hours when compared to that of vaginal group, 5.79 ± 2.42 hours. In the study conducted by Tang et al, mean interval was less in buccal group but was not statistically significant [5]. In study conducted by Wiebe and Trouton exact duration was not noted but was described as no significant difference in the induction to expulsion interval [6].

In our study while comparing oral and vaginal routes of administration, the mean induction to expulsion interval was prolonged in vaginal group, 5.79 ± 2.42 hours and was significant statistically. This was not in concordance with the results of the trial conducted by Nautiyal et al, where vaginal group had shorter duration of expulsion [7]. The difference may be to due to more number of women in the advanced gestational age category in vaginal group when compared to that of oral group.

The mean induction to expulsion interval was 4.3 ± 2.8 hours in oral group, which was lower than the values obtained by Nautiyal et al, 2015, in their study (14.3± 3.3 hours) [7]. The mean induction to expulsion interval was 4.325 ± 2.17 hours in buccal group. Women in Buccal group had induction to expulsion interval almost similar to oral group. The induction to expulsion interval in the two groups was significantly different in the study by Nautiyal et al, with buccal administration having a lesser duration [7]. Our study shows no significant difference between the two groups.

The complete expulsion of products of conception within 24 hours of induction was more in buccal route (93.3%) when compared to that of vaginal route (86.6%). But there was no statistical significance between the groups (P value- 0.389) and this was comparable with the trial conducted by Garg G et al [8]. The success rate was more in oral route (90%) when compared to that of vaginal route (86.6%). But there was no statistical significance between the groups (P value- 0.688). Studies conducted by Nautiyal D et al and Refaey HE et al showed higher success rates with vaginal route [7,9]. This may be attributed to the increased number of women with gestational age between 8.1-9 weeks in vaginal group in the present study. Buccal route had higher success rate of expulsion within 24 hours of induction (93.3%) when compared to that oral route of administration (90%) which was comparable with Nautiyal D study, but this was not statistically significant (P value-0.389) [7].

Women who failed to expel the products within 24 hours after induction of misoprostol were considered under failed induction group and were treated with surgical evacuation. Total number of women who underwent surgical evacuation was similar in all the three groups.

In the present study vaginal group had comparatively lesser side effects than that of buccal group but not statistically significant. Our results were comparable with a randomized trial conducted by Wiebe and Trouton, which showed buccal route had higher incidence of side effects [6]. Except diarrhea, the occurrence of other side effects was not statistically different. The oral group had an overall higher incidence of side effects. This was comparable with the trials conducted by Nautiyal D et al and Refaey HE et al. There was significant difference (P value-0.001) [7,9].

The acceptance to the route of administration was similar in all the routes of administration without any statistical significant difference between any of the two routes of administration. This may be due to limitation in the sample size. However oral and buccal group women were more comfortable because of self administration of the drug and avoiding vaginal route of administration of the drug.

Limitations of the Study

Due to small sample size and limited time duration

in the present study, significant conclusions were not made. Further studies with long duration and larger sample size are required for significant conclusions regarding the safety, efficacy and acceptability of the route of administration.

Conclusion

The induction to expulsion interval was significantly better in the oral and buccal route when compared to vaginal group. There was no significant difference with respect to success of complete expulsion within 24 hours among the three groups. However, buccal route had the highest complete expulsion rate (93.3%). There was no significant difference with respect to side effects when comparing the three groups, except diarrhea which was significantly more in oral group (P= 0.001). The least side effects were seen when the drug was administered vaginally. Acceptability of the route of administration(may be defined as whether the patient was satisfied with the route of administration of misoprostol after termination of pregnancy) was similar in all the three groups. However, with oral and buccal routes patients can self administer the drug avoiding vaginal administration. Considering all the objectives of the study, Buccal route had shorter induction to expulsion interval, minimal side effects, highest complete expulsion rate and better acceptance of the route of administration.

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