Research Article

USE OF MIFEPRISTONE AND MISOPROSTOL COMBINATION ON ABORTION IN FIRST TRIMESTER PREGNANCY AT GOVERNMENT HOSPITAL IN CHITWAN DISTRICT IN NEPAL

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ABSTRACT

The present study is a prospective study and was aimed to identify the type and pattern of side effects during and after a medical abortion using a combination therapy of Mifepristone and Misoprostol, association between gestational age and success rate, and its efficacy. Assessment on acceptability, women's perceptions towards medical abortion, and reasons for abortion were also performed. The study was carried out in 500 bedded government hospital in Chitwan district in Nepal. The women (n=85) with a gestational history of less than 59 days were enrolled. The regimen used was oral Mifepristone 200 mg followed by sublingual Misoprostol 800 mcg after 24 hours of Mifepristone administration. The women's profile form was used as a major data collection tool. Side effect sheet (typed in Nepali language for convenience) to be filled by the women undergoing medical termination of pregnancy (MTP) was issued, which was later submitted to us at the time of their follow-up visit. On follow-up, a pre-tested questionnaire was administered to determine perception and acceptability of MTP. The success rate was found to be 97.6%. Side effects recorded were vaginal bleeding, uterine cramping, abdominal pain, nausea, vomiting, headache, loss of appetite, and sleeplessness. There was a significant association between gestational age and success rate with P value of 0.003. The women provided different reasons for abortion and had a positive attitude towards MTP. In conclusion; the combination of oral Mifepristone and sublingual Misoprostol for medical abortion was found to be efficacious and sublingual administration of Misoprostol has a number of benefits over other routes (vaginal and oral) which could be further studied over a large population in future.

Key words: Abortion, side effects, counseling, Mifepristone, Misoprostol.

INTRODUCTION

Abortion is the termination of a pregnancy before the fetus has attained viability, i.e. becomes capable of independent extra-uterine life. The term medical abortion refers to early pregnancy termination (usually before 9 weeks' gestation) performed without primary surgical intervention and resulting from the use of abortion-inducing medications.¹ Medical abortion became an alternative method of abortion with the availability of prostaglandin analogs in the early 1970s and the antiprogesterone Mifepristone in the 1980s. It is an important alternative to surgical methods. The World Health Organization (WHO) recommends this drug combination, with an initial dose of Mifepristone followed by Misoprostol 36 to 48 hours later, for early medical abortion. The World Health Organization approved both Mifepristone and Misoprostol for termination of early pregnancy by including them in the list of Essential Medicines in 2005.²

Mifepristone acts by binding to the progesterone receptor, thus inhibiting the effect of progesterone. The sensitivity of myometrium to exogenous prostaglandins is also increased by administration of

Mifepristone. Thus, in early pregnancy, administration of Mifepristone results in regular uterine contractility and increased sensitivity of prostaglandins.³ Misoprostol is a synthetic prostaglandin E₁ analogue and because of its uterotonic and cervical-repeneing actions, Misoprostol is also widely used for various gynaecological and obstetrical purposes, such as cervical ripening and induction of labour, for pretreatment of the cervix prior to surgical termination of pregnancy and, in combination with Mifepristone for medical abortion.⁴ Prostaglandin causes powerful contraction of uterus.⁵

Drug delivery via sublingual mucous membrane is considered to be a promising alternative to the oral route. This route is useful when rapid onset of action is desired. In terms of permeability, the sublingual area of the oral cavity is more permeable than cheek and palatal areas of the mouth.⁶ The drug absorbed via sublingual blood vessels bypasses the hepatic first-pass metabolic processes giving acceptable bioavailability with low doses and hence decreases the side effects.⁷

MATERIALS AND METHODS

Approvals for the study: The study was approved by Pokhara University and Mahendra Aadarsha Chikitsalaya (Bharatpur Government Hospital, Chitwan, Nepal). The hospital facilitated us to carry out the study in their MTP ward in close supervision of HOD, Gynecology Department. Written consent from all women who meet our inclusion criteria was taken. Ethical clearance number for research is: 0100-69.

Study Design: Women with a viable singleton intrauterine pregnancy (confirmed by ultrasound scan) requesting medical abortion within 59 days gestation were asked to participate.⁸ Gestational age was estimated by ultrasound scan measurement in all cases. Women received Mifepristone 200 mg administered orally under the pharmacist and nursing supervision. They were allowed home and re-visited to hospital 24 hours later for Misoprostol 800 mcg administration. Women were given Misoprostol via sublingual route. Side Effect sheets were given to the women and insisted to assess side effects experienced (nausea, vomiting, diarrhoea, shivering, lethargy, headache, hot flushes, etc) from day 1 till they return hospital for follow-up. They were also interviewed regarding the acceptability and the perception of the MTP, pharmacist interventions regarding safe abortion, and impact of counseling on follow-up visit. Follow-up of women was carried out by the Gynecologist, Pharmacist and the nursing staffs.

Study population and Sampling Procedures: Total 85 women were enrolled. The target population was all women who wished to undergo MTP in the hospital and meet the inclusion criteria (Purposive Sampling). A prospective study was carried out during the period of May 2013 to October 2013 after getting approval from the Hospital.

Study Site: Mahendra Aadarsha Chikitsalaya (Bharatpur Government Hospital, Chitwan, Nepal) is located at Bharatpur, Chitwan, established in 2020 B.S. It is the only government hospital in Chitwan District. It is a 500 bedded hospital having all medical facilities including MTP.

Inclusion criteria: Women who needed termination of pregnancy with live intrauterine pregnancy up to 59 days gestation.

Exclusion criteria: Pregnant women with more than 59 days of gestation, previous allergic reaction to the drugs involved, diseases / disorders like inherited porphyria, chronic adrenal failure, acute renal failure, hemorrhagic disorder, severe anemia, pre-existing heart disease, long-term corticosteroid therapy, known or suspected ectopic pregnancy and pregnancy with placenta previa.

Analysis of Data: Statistical analysis in this study was carried out by using IBM-SPSS version 20. All the information recorded in the patient profile form were analyzed for various parameters like socio-demographic, age group, side effect caused by these agents, and perceptions. The data was even used for formulating the outcome variables. The early work of the analysis started with the descriptive statistics. Therefore, the baseline characteristics of women undergoing MTP were generated as illustrated in table. Relevant quantitative variables were subjected to normality test. The variable did not pass the normality test and hence Mann-Whitney test was used.

Table 1: Demography

Demography	Categories	No. of patient	Percentage
Age of Women (years)	15-19	5	5.9
	20-24	19	22.4
	25-29	28	32.9
	30-34	21	24.7
	35-39	12	14.1
Age of Gestation (Days)	<20	1	1.2
	30-39	21	24.7
	40-49	59	69.4
	>=50	4	4.7

Table 2: Success rate

Abortion status	Frequency	Percentage
Complete Abortion	83	97.6
Incomplete Abortion	2	2.4
Total	85	100

Table 3: Association between gestational history and success rate

Variable	MTP Successful		
	Yes	No	P-Value
Gestational History (Days)†	42	55.5	0.003*

Note: † median

Table 4: Side effects

ADR	Days								
	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)	8 n (%)	9 n (%)
Vaginal Bleeding	85 (100)	85 (100)	85 (100)	85 (100)	64 (75.3)	31 (36.5)	12 (14.1)	8 (9.4)	2 (2.4)
Uterine Cramping	84 (98.8)	85 (100)	61 (71.8)	17 (20)	6 (7.1)	2 (2.1)	-	-	-
Abdominal Pain	84 (98.8)	82 (96.5)	39 (45.9)	23 (27.1)	7 (8.2)	5 (5.9)	2 (2.4)	-	-
Nausea	14 (16.5)	17 (20)	7 (8.2)	1 (1.2)	-	-	-	-	-
Vomiting	4 (4.7)	9 (10.6)	6 (7.1)	2 (2.4)	-	-	-	-	-
Headache	19 (22.4)	21 (24.7)	10 (11.8)	1 (1.2)	-	-	-	-	-
Backache	17 (20)	16 (18.8)	8 (9.4)	-	-	-	-	-	-
Anxiety	22 (25.9)	16 (18.2)	11 (12.9)	3 (3.5)	1 (1.2)	-	-	-	-
Sleeplessness	13 (15.3)	15 (17.6)	11 (12.9)	6 (7.1)	4 (4.7)	3 (3.5)	2 (2.4)	-	-
Loss of appetite	21 (24.7)	24 (28.2)	17 (20)	10 (11.8)	4 (4.7)	1 (1.2)	-	-	-
Diarrhoea	2 (2.4)	5 (5.9)	5 (5.9)	5 (5.9)	1 (1.2)	-	-	-	-

Table 5: Reason for Abortion

Reason For Abortion	Frequency	Percentage
Cultural Issues	3	3.6
Due to Job	1	1.2
Due to Study	10	11.8
Failure of Contraception	7	8.2
Have completed my Childbearing	3	3.5
Household Problems	13	15.3
Low Socioeconomic Condition	1	1.2
No Specific Reason	46	54.1
Not ready to have child	1	1.2
Total	85	100

Figure 1: Pattern of Vaginal Bleeding

Table 6: Perception regarding MTP

Questionnaire	Yes (%)	No (%)
MTP Stressful	14.1	85.9
MTP Contribute for better reproductive health.	100	0
MTP can reduce unsafe abortion related mortality.	100	0
Pharmacist counseling proved to be helpful for MTP.	100	0

Figure 2: Pattern of Uterine Cramping and Abdominal Pain

Figure 3: Nausea, Vomiting and Headache

Figure 4: Loss of Appetite and Sleeplessness

RESULTS

Demography

Age Distribution: Out of total pregnant women studied, maximum number of 28 (32.9%) women belonged to the age group of 25- 29, followed by 21 (24.7%) of age group of 30-34 years.

Gestational Age: There were 59 (69.7%) women with fetal gestational age of 40-49 days followed by 21 (24.7%) women with 30-39 days. Mean gestational age 41.5 days.

Success Rate

Out of 85 respondents, 83 (97.6%) had a complete abortion where as 2 (2.4%) required a surgical interventions.

Association between gestational history and success rate

Mann-Whitney Test was used to determine the association between gestational history and success rate which shows that P value is less than 0.005, which is statically significant.

Side effects of the Combination of Mifepristone and Misoprostol

The overall side effects have been presented in table below. The side effect-sheet provided to each woman enrolled in study were collected and represented as follow. None of the side effects were experienced after 9 days and hence has not been shown in the table.

Patterns of Side Effects

Vaginal bleeding: Vaginal bleeding, one of the most common and expected side effect during abortion has been experienced by all women for four days, 64 (75%) for 5 days, 31 (36.5%) for 6 days, 12 (14.1) for 7 days, 8 (9.4%) for eight days, and 2(2.4%) for 9 days.

Uterine cramping and abdominal pain: Uterine cramping and abdominal pain were also found to be common side effects. Uterine cramping was experienced by 84 (98.8%) women on the first day, 85 (100%) on the second day, 61 (71.8%) on the third day, 17 (20%) on the fourth day, 6 (7.1%) on the sixth day, and 2 (2.1%) on the seventh day. Abdominal pain was experienced by 84 (98.8%)

women on the first day, 82 (96.5%) on the second day, 39 (45.9%) on the third day, 23 (27.1%) on the fourth day, 7 (8.2%) on the fifth day, 5 (5.9%) on the sixth day, and 2 (2.4%) on the seventh day.

Nausea, Vomiting and Headache: Nausea was experienced by 14 (16.5%) of women on the first day, 17 (20%) on the second day, 7 (8.2%) on the third day, and 1 (1.2%) on the fourth day. Vomiting was experienced by 4 (4.7%) on the first day, 9 (10.6%) on the second day, 6 (7.1%) on the third day, and 2 (2.4%) on the fourth day. Headache was experienced by 19 (22.4%) on the first day, 21 (24.7%) on the second day, 10 (11.8%) on the third day, and 1 (1.2%) on the fourth day.

Loss of Appetite and Sleeplessness: Loss of appetite was experienced by 21 (24.7%) women on the first day, 24 (28.2%) on the second day, 17 (20%) on the third day, 10 (11.8%) on the fourth day, 4 (4.7%) on the fifth day, and 1 (1.2%) on the sixth day. Sleeplessness was experienced by 13 (15.3%) women on the first day, 15 (17.6%) on the second day, 11 (12.9%) on the third day, 6 (7.9%) on the fourth day, 4 (4.7%) on the fifth day, 3 (3.5%) on the sixth day, and 2 (2.4%) on the seventh day.

Reason for Abortion

Various reasons for abortion were obtained. Most of the women 46 (54.1%) did not want to disclose any reason for abortion. Among the respondents, 13 (15.3%) women had household problems, 10 (11.8%) elected not have child due to study, 7 (8.2%) reported that they got pregnant due to failure of contraception, 3 (3.6%) did not want to have child due to cultural issues, 3 (3.5%) realized that they have completed childbearing, 1 (1.2%) had a reason of low socioeconomic condition, and 1 (1.2%) reported not yet ready to have child.

Perceptions regarding MTP

To assess perception regarding MTP, close-ended questions were asked. There was a mixed response for stressful status of mind, 14.1% reported MTP to be stressful and 85.9% reported it not to be stressful. Rest of the questions were all answered 'yes' indicating MTP to contribute for better reproductive health, reduces unsafe abortion related mortality, and pharmacist counseling be helpful for MTP.

DISCUSSION

Success rate of the combination (Mifepristone and Misoprostol) in medical abortion: In our study, women with gestational age <59 days were considered. The success rate (defined as the nonsurgical evacuation of the products of conception), of oral Mifepristone and sublingual Misoprostol was found to be 97.6%. In a study done by Pirruccello et al., focused on regimen, efficacy, acceptability and future directions in 2003 and revealed 92-99% of success rates at < 49 days gestation. The authors also mentioned that newer regimens and alternative route of drug administration could improve the result, as future direction. Intravaginal administration of Misoprostol is associated with significantly more prostaglandin-related side effects.⁹ Shrivastava in 2006 performed similar research in Nepal Medical College, Nepal, and assessed the safety, and efficacy. In her prospective study, Misoprostol was used vaginally and the success rate was 92.6%.¹⁰ Kathleen et al., in 2011 performed a similar research with misoprostol administered vaginally, and the success rate was 80%.¹¹ Recently, sublingual administration of Misoprostol has been studied for medical abortion and cervical priming. The Misoprostol tablet is very soluble and can be dissolved in 20 minutes when it is put under the tongue. The peak concentration is achieved about 30 minutes after sublingual route, whereas following vaginal administration, it takes 75 minutes. Therefore, it appears that

the sublingual has the quickest onset of action. This is due to rapid absorption through the sublingual mucosa as well as avoidance of first pass metabolism via the liver. The abundant blood supply under the tongue and the relatively neutral pH in the buccal cavity may be contributing factor.⁶ Our study also showed a significant ($P=0.003$) association between gestational age and success rate. Failure of abortion was found in women with higher gestational age as compared to those with lower gestational age.⁴

Pattern of side effects: Vaginal bleeding and uterine cramping (usually heavier than with menstruation) are expected.¹⁰ In our study, women undergoing MTP experienced minimum 4 days and maximum 9 days of vaginal bleeding. None of the women reported heavy bleeding (Heavy bleeding: Two soaked maxipads in 1 hour for 2 consecutive hours¹²), and none required a transfusion. The higher incidence of vaginal bleeding is related to the dose and duration of exposure to the drug. In a research done by Schaff et al., two days after receiving Mifepristone, intravaginal administration of Misoprostol 800 mcg, with mean gestational age of 43 days, resulted in heavy bleeding in 13.3% of the women undergoing MTP.¹³ Uterine cramping and abdominal pain, in our study, were experienced for two days lasting up to 6 days for few women.

Pain related side effects like abdominal pain, backache, and headache were experienced by the participants due to uterine contraction and Misoprostol (Prostaglandin E_1) related side effects.¹⁴ NSAIDs were prescribed to few participants for the management as there is no evidence that NSAIDs reduce the efficacy of Misoprostol treatment. Mifepristone acts by binding to progesterone receptor, thus inhibiting the effect of progesterone. The endogenous prostaglandins induce uterine contractility and increase sensitivity of prostaglandins and leads to the uterine bleeding and disruption of placental function.³

The pattern of nausea, vomiting and diarrhea, experienced by the participants has been increased in day 2, (16.5% Vs 20%), (4.7% Vs 10.6), and 2.4% Vs 5.9) respectively, after administration of Misoprostol, and then significantly decreased in day 3 and 4, and none experienced nausea, vomiting, and diarrhoea after 5th day. El-Refaey et al., conducted a randomized trial to compare oral and intravaginal routes of Misoprostol administration among women at ≤ 63 days' gestation showing that oral Misoprostol group has higher rates of gastrointestinal side effects, 70% had nausea, 44 % had vomiting, and 36 % had diarrhea.¹⁵

In our study, anxiety, sleepless and loss of appetite were experienced by number of women. This could be attributed to mental health of women who have undergone abortion. Research done by Coleman et al., revealed that the women who have aborted are at higher risk for a variety of mental health problems, including anxiety (panic attacks, panic disorder, agoraphobia), mood (bipolar disorder, major depression), and substance abuse disorders when compared to women without a history of abortion after controls were instituted for a wide range of personal, situational, and demographic factors.¹⁶ Yet another research done by different universities together in 2008, reflects preexisting and co-occurring conditions in woman's life that place her at a greater or lesser risk for poor mental health in general, regardless of how she resolves her pregnancy.¹⁷

Reasons for abortion: It was an open-ended question as they were allowed to list even more than one answer. However, all women who responded to the particular question have given different reasons for abortion. Most of the women did not wish to disclose the reason for abortion. In most cases, husbands were the sole decision makers. Husbands played the major role in making decisions for abortion. Among the respondent, the most common reason was household problems. A study in Nepal reveals that unintended

pregnancies amongst married couples are common. Given the circumstances – in which young women have relatively less power than men in fertility decision making, and are often pressured by their mothers-in-law or other relatives to get pregnant immediately after marriage to secure their marital relationship or to avoid marital breakdown - this finding is not surprising. Rather, it suggests that the socio-cultural context compels Nepalese young couples to go through with childbearing, even when the conception was unintended. The researcher also emphasized on the fact that the role of friends, family members (other than husbands) was not decisive with regards to decision making regarding abortion.^{18,19}

Perception regarding MTP: Once the abortion was complete, counseling was focused on women's experiences and perception on the procedure. They were asked few close-ended questions (yes/no) regarding emotional status, pharmacist counseling, impact of MTP on reproductive health, and its role on reducing mortality due to unsafe abortion. In our study, there was a mixed response regarding the stressful mind state during and after abortion. An extensive research reveals that most women feel relieved after abortion, although some have a feeling of sadness and guilt for short time. A prospective study done on psychological responses to abortion, showed no differences in post-abortion depression, anxiety, or self-esteem among women randomly assigned to receive Mifepristone and Misoprostol or to undergo suction curettage.¹⁷ However, in other questions, they all had 'yes' response which means pharmacist counseling had helped them to understand MTP better, MTP could improve reproductive health, and can reduce mortality related to unsafe abortion. A research done in different hospitals of Karachi, Pakistan, to evaluate patient counseling, revealed that pharmacists' involvement in patient care reduced number of hospital admissions and emergency department visit and improved health status of the patient and their quality of life.²⁰

CONCLUSION

The standard protocol followed by the hospital was oral administration of 200 mg Mifepristone followed by (24 hours later) sublingual administration of Misoprostol 800 mcg. The success rate of the combination was excellent and was found to be significantly associated with gestational age. Most of the side effect patterns were expected side effects of the drugs; however, Misoprostol related gastrointestinal side effects were minimal which could be attributed to sublingual administration of Misoprostol. Women had different reasons for abortion, but most of them did not disclose it. Unwanted pregnancies due to failure of contraception were one of the noticeable reasons which was intervened and counseled properly. Only few women found MTP stressful, but all of them had positive attitude towards benefit of MTP in reproductive health and reducing unsafe abortion related mortality. On interviewing, they also answered positively and agreed that counseling done during and after abortion had good impact throughout the process of MTP and encouraged them to visit hospital for follow-up to confirm their abortion status and get necessary post-abortion counseling.

Limitations of the study

The selection of the sample was based on the inclusion criteria. The women who failed follow-up were excluded from the study. Hence, it cannot be claimed to be rigorously representative from the statistical point of view. However, since the study was basically quantitative, the effect of this could be minimal.

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