A Comparative Study Between Simultaneous Administration and 24-Hour Mifepristone-Misoprostol Interval in Second Trimester Abortion

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ABSTRACT

Introduction: Various methods are used in India to perform second trimester abortions. The combination of mifepristone and misoprostol is an established and effective method of Medical Termination of Pregnancy(MTP). The present study was conducted to compare the efficacy of medical abortion, depending upon the time interval between mifepristone and misoprostol, in pregnant women seeking MTP between 13 to 20 weeks of gestation.

Material and methods: The present prospective comparative study was conducted in the Department of Gynaecology & Obstetrics, R. G. Kar Medical College and Hospital over a period of 1 year. The total sample size was 118. Detailed history was obtained from the clients. Investigation reports and data was collected. The data had been recorded in a pretested case report proforma. Based upon the treatment, received by patients in the hospital, they were classified into two groups. Group A: Simultaneous administration of Mifepristone and Misoprostol and Group B: Twenty-four hours Mifepristone and Misoprostol interval. Data was collected at the time of and during admission, pre and post abortion period. All data were collected, entered, and analyzed using R and Excel Analysis ToolPak software.

Results: The results of the study showed that women who took Misoprostol at 24-hour interval after taking Mifepristone were more likely to expel both fetus and placenta within 24-hour of first Misoprostol dose (91.53%) compared with those, who took both the drugs simultaneously (group-A) (84.75%). Out of the 15.25% participants in Group A, major percentage of the participants (10.17%) received Oxytocin to complete the process of abortion. It means only 3 participants (5.08%) required surgical means to complete the abortion process. In the 24-hr interval arm, the additional intervention rate was 8.48%. About 5.08% participants needed oxytocin and remaining 3.4% participants needed surgical intervention to complete the abortion process in this arm.

Conclusion: This study illustrates that both the regimens are effective and acceptable for termination of pregnancies in the second trimester. It is observed that administering the mifepristone and misoprostol at 24 hours interval results in better clinical outcome.

Keywords: Mifepristone, Misoprostol, Second Trimester Abortions.

INTRODUCTION

Abortion is defined as 'Termination of Pregnancy (TOP) by any means before the fetus is viable'. Viability is now considered reached at 23-24 weeks of gestation. Mid trimester or second trimester is a period ranging from 13 weeks to 28 weeks of gestation, which can be subdivided in two categories. Early second trimester period is between 13 and 20 weeks and late period is between 20 and 28 weeks.[1] According to the Guttmacher Institute, almost 10% (+/- 0.5%) of abortions occur between 13 weeks and 20 weeks of pregnancy. Women opt for the second trimester abortions for different reasons. They are namely, i) a fetus with serious congenital anomalies 2) mother's health may deteriorate so much during pregnancy or delivery so as to cause her serious harm or death.[2] Several complications including maternal death are associated with the abortion process and the incidence increases with the length of gestation. While it is relatively very low during first trimester pregnancy, it increases to 1 in 29000 if abortion is done between 16 and 20 weeks. It increases further to 1 in 11000 for abortion after 21 weeks.[3] In India, the Medical Termination of Pregnancy (MTP) Act was tabled and approved in the Parliament in 1971 and came into force from April 1972[4] except in Jammu and Kashmir, where it was extended in 1980. The Union Territory of Lakshadweep still has a restrictive abortion law.[5] The combination of mifepristone and misoprostol is an established and effective pregnancy termination method, including in the second trimester. In 2002, the Drug Controller of India approved the use of it up to 49 days of pregnancy.[6-7] Misoprostol was licensed for use in India in 2002.[8] According to WHO's guidelines,[9] the method of medical abortion for gestational age between 12 weeks and 24 weeks is 200 mg mifepristone administered

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orally followed by repeated doses of misoprostol 36 to 48 hours later. It recommends that the initial misoprostol dose, following mifepristone administration might be either 800 g vaginally or 400g orally. Subsequent misoprostol doses should be 400g vaginally or orally, in every three 3 hours up to four doses. The present study was conducted to perform a comparative study between Simultaneous Administration and 24- hour Mifepristone-Misoprostol interval in second trimester abortion.

MATERIAL AND METHODS

The present prospective comparative study was conducted in the Department of Gynaecology & Obstetrics, R. G. Kar Medical College and Hospital over a period of 1 year(1st July 2017 – 30th June 2018). The inclusion criteria were: Pregnant women of 19 years of age or above with gestational age of 13-20 weeks, based on menstrual history and clinical examination (with or without ultrasonography report), met legal criteria to obtain abortion, had a live intrauterine fetus and a closed cervical os, no vaginal bleeding, no known contraindication to the study drugs, were able to consent to a procedure and willing to participate were included in the study. Women with history of transmural uterine incision:namely post cesarean section, myomectomy, contraindications to vaginal delivery, including placenta previa, parity greater than five, active labor, known allergy to mifepristone or misoprostol or other contraindications to the use of mifepristone or misoprostol, signs of infection were excluded from the study. The total sample size was 118. Detailed history namely obstetrics, menstrual, medical, surgical, family, drugs was obtained from the client. Investigation such as complete hemogram, blood grouping and Rh typing, urine for sugar and protein done and recorded in the BHTs (bed head tickets). Data was collected from BHT, Antenatal card, Hospital MTP & record, hospital admission record, and also from regular observation of the patients. The data had been recorded in a pretested case report proforma. Blood was tested for complete hemogram, including ABO grouping & Rh typing. A lower abdomen and pelvic ultrasonography, testing the urine with dipsticks for sugar and albumin and other pathological, radiological and hematological tests were done depending upon the patient's clinical scenarios. All eligible participants, selected after thorough laboratory investigations and those who would request for second trimester abortion, were eligible for misoprostol dosing. After obtaining informed consent in form C for medical termination of pregnancy, clients were included in the study and they were admitted immediately. Based upon the treatment, received by patients in the hospital, they are classified in two groups.

Group A: Simultaneous administration of Mifepristone and Misoprostol – 200 mg Mifepristone orally followed immediately by 400 microgram Misoprostol orally at 3 hours interval up to maximum of 5 doses.

Group B: Twenty-four hours Mifepristone and Misoprostol interval – 200 mg Mifepristone orally followed 24 hours later by 400 microgram Misoprostol orally at 3 hours interval up to maximum of 5 doses.

All patients were monitored throughout abortion period by checking pulse rate, blood pressure, temperature, uterine tenderness, bleeding per vagina and expulsion of products of conception. Women who did not abort by 24 hours after taking first misoprostol dose were considered failure of the process and given the option for surgical management or repeated dosage of misoprostol. The patients were also monitored in the post expulsion period by checking pulse, blood pressure, temperature and persistence of vaginal bleeding. The patients were then discharged from hospital between 24-48 hours after the completion of the process with contraceptive advice. All the patients were advised to follow up after 2 weeks for persistent bleeding. Data was collected at the time of and during admission, pre and post abortion period. Since all the patients were admitted, they were regularly assessed for vital signs, any side effects of Mifepristone and Misoprostol, namely nausea, vomiting, diarrhea, fever, amount of bleeding and all findings were recorded in the BHTs & case proforma. The sample was segregated by gestational age categories: 13-16 weeks and 17-20 weeks. All data were collected, entered, and analyzed using R and Excel Analysis ToolPak software. Continuous variable was analyzed using Mann-Whitney, Pearson X2 test, Fisher exact test, or t test as appropriate. Relative risk with 95% confidence intervals were calculated to measure treatment effect for the primary and secondary outcome. The Kaplan-Meier method was used to generate probability estimates of time interval to complete abortion. The Venn diagram analysis was done to analyse the side effects of the procedure.

RESULTS

In this study, 118 participants out of 140 were included. These 118 participants, who met the inclusion criteria for MTOP, were divided in two groups such as group A (n=59), which received mifepristone and misoprostol simultaneously and group B (n=59), received mifepristone and misoprostol in 24 hours interval. In both the groups, majority were in the age group of 20 to 29 years {32 (54.24%) in group A and 31 (52.54%) in group B}. Test of significance for the above three groups for age distribution shows chi-square value of 1.364 and p value was 0.506. In group A, the mean age (mean ± standard deviation) of patients was 26.66 ± 5.32 years. In group B, the mean age (mean ± standard deviation) of patients was 28.15 ± 4.67 years. Difference of mean age in two groups was not statistically significant.

In Group-A, the majority of the participants in study population fell under the primigravida category. Whereas in Group-B, the majority of the study participants fell under 2nd and 3rd Gravida. Out of total participants (n=118), maximum participants (26.27%) fell under 1st Gravida. Test of significance for the above five groups for distribution of parity showed a chi- square value of 4.454. In group A, the mean gravida (mean ± standard deviation) of 59 participants was 2.63 ±1.45. In group-B, the mean gravida (mean ± standard deviation) of 59 participants was 2.75

± 1.33. Difference of mean gravida in two groups was not statistically significant.

In group-A twenty-five (42.37%) participants out of 59 were nulliparous and in group- B twenty (33.90%) participants out of 59 were nulliparous. It means remaining 57.63% and 66.10% participants were multiparous in group-A and group-B respectively.

Chi-square: 4.867	Degrees of freedom: 4	p-value: 0.3012

In group A, the mean parity (mean ± standard deviation) of 59 participants was 1.02 ± 1.04. In group-B, the mean parity (mean ± standard deviation) of 59 participants was 0.98 ± 0.88. Difference of mean parity in two groups was not statistically significant.

Almost all of the 59 participants in group-A were almost equally distributed in blood group A positive (16), B positive(14) and O positive(16). There were 2 participants each having blood group A negative and B negative. In group-B, 19 (32.20%) participants had blood group B positive and 17(28.81%) participants had A positive blood. There were 10 and 11 paricipants in the AB positive and O positive blood groups.

In group-A, seventeen participants had hemoglobin between 8 g/dL and 10 g/dL and in group-B, sixteen participants had hemoglobin between 8 g/dL and 10 g/dL.

Based on gestational week, the participants were divided in two groups. One set included participants 13 -16 weeks. The second included 17 – 20 weeks.

Chi-square: 0.137	Degree of freedom: 1	P-value: 0.711

Test of significance for the above distribution of parity showed a chi-square value of 0.137.

In group A, almost 56% participants belonged to the first set and remaining 44% participants to the second set whereas, in group B the first set had total 52.54% participants and the second set had 47.46% participants.

Women who took Misoprostol at 24-hour interval after taking Mifepristone (group-B) were more likely to expel both fetus and placenta within 24-hour of first Misoprostol dose (91.53%) compared with those, who took both the drugs simultaneously (group-A) (84.75%).

Among women who took the drugs at a 24-hr interval, there was a difference of almost 11% in the rate between 13 to 16 week and 17 to 20 - week group. At the same time, in the simultaneous arm there was a significant difference between two gestational age groups (90.91% compared with 76.92%).

Out of 15.25% participants, major percentage of the participants (10.17%) received Oxytocin to complete the complete abortion. It means only 3 participants (5.08%) required surgical need to complete the expulsion of the foetus. In 24-hr interval arm the additional intervention rate was 8.48%. Out of which 5.08% participants needed oxytocin and remaining 3.4% participants needed surgical intervention to complete the abortion process. All 14 women (considering both regimens) needed oxytocin or surgical abortion, because full expulsion of foetus did not happen within 24 hours of the first misoprostol dose

The mean time to abortion from the first Misoprostol dose was considerably shorter for women who took the mifepristone and misoprostol at a 24-hr interval (12.3 compared with 16.39 hours). This time interval was compared by Kaplan-Meier survival analysis.

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Among 118 participants, a considerable number of participants (54) had diarrhea during the procedure or post procedure. In the simultaneous regimen (Group-A), 31 (52.54%) participants and in 24-hour interval regimen, 23(38.98%) participants had diarrhea. Overall 45.76% of participants had diarrhea. A total of thirty-seven participants (31.36%) had nausea. In the simultaneous regimen (Group-A), 19 (32.20%) participants and 18 participants (30.51%) in the 24-hour interval regimen, had nausea. There was no major difference in terms of overall percentage of participants affected by

Parity	Group – A	Group – B	Total
0	25(42.37%)	20(33.90%)	45(38.14%)
1	13(22.03%)	23(38.98%)	36(30.51%)
2	17(28.81%)	13(22.03%)	30(25.42%)
3	3(5.08%)	3(5.08%)	6(5.08%)
4	1(1.69%)	0(0.00%)	1(0.85%)
Total	59(100%)	59(100%)	118(100%)

Table-1: Distribution of participants according to Parity (n=118)

Blood Group	Group – A	Group - B	Total
A-	2(3.39%)	1(1.69%)	3(2.54%)
A+	16(27.12%)	17(28.81%)	33(27.97%)
AB+	7(11.86%)	10(16.95%)	17(14.41%)
B-	2(3.39%)	1(1.69%)	3(2.54%)
B+	14(23.73%)	19(32.20%)	33(27.97%)
O+	18(30.51%)	11(18.64%)	29(24.58%)
Total	59(100%)	59(100%)	118(100%)

Table 2: Distribution of participants according to Blood Group (n=118)

Haemoglobin	Group-A	Group-B	Total
8-10	17(28.81%)	16(27.12%)	33(27.97%)
>=10	42(71.19%)	43(72.88%)	85(72.03%)
Total	59(100%)	59(100%)	118(100%)

Table-3: Distribution of participants according to Haemoglobin (n=118)

Gestational Week	Group-A	Group-B	Total
13-16	33(55.93%)	31(52.54%)	64(54.24%)
17-20	26(44.07%)	28(47.46%)	54(45.76%)
Total	59(100%)	59(100%)	118(100%)

Table-4: Distribution of participants according to Gestational Week (n=118)

	Simultaneous group (n=59)	24-h interval group (n=59)	P value
Complete vaginal evacuation at 24 h	50 (84.75%)	54 (91.53%)	0.255
13-16 weeks	30/33 (90.91%)	30/31 (96.77%)	0.333
17-20 weeks	20/26 (76.92%)	24/28 (85.71%)	0.406
Intervention rate	9/59 (15.25%)	5/59 (8.48%)	
Oxytocin	6/59 (10.17%)	3/59 (5.08%)	
Surgical evacuation	3/59 (5.08%)	2/59 (3.39%)	
Time to complete abortion from first Misoprostol dose	16.39 (+/-4.36)	12.3 (+/-2.72)	
13-16 weeks	14.56 (+/- 4.19)	10.36 (+/- 1.63)	< .00001
17-20 weeks	19.15 (+/- 2.92)	14.70 (+/- 1.68)	< .00001
Time to complete abortion from mifepristone			
13-16 weeks	14.56 (+/- 4.19)	34.36 (+/- 1.63)	< .00001
17-20 weeks	19.15 (+/- 2.92)	38.71 (+/- 1.68)	< .00001
No of Misoprostol Doses*	4.53 (+/- 0.83)(5)	3.75 (+/- 0.97)(4)	
13-16 weeks	4.18 (+/- 0.97)	3.1 (+/- 0.69)	< .00001
17-20 weeks	4.96 (+/- 0.19)	4.46 (+/- 0.68)	<.01778
Time not recorded beyond 24 hours, P value calculated using Mann-Whitney test Significant at p<0.05			

Table-5: Rates of complete vaginal evacuation and time to expulsion

	Hours								
	3	6	9	12	15	18	21	24	27
Simultaneous arm	59	59	58	57	50	40	28	17	9
24 hours Interval arm	59	59	59	52	33	17	5	5	5

Table-6: Number of women requiring ongoing management by 3 hours interval

Outcome	Simultaneous Administration (Group - A)	24-hour interval Administration (Group - B)
Acceptability	54 (91.53%)	56 (94.92%)
Pain score over time	6.68 (+/- 2)	6.25 (+/- 0.5)
Serious Adverse events	2 (3.39%)	1 (1.69%)

Table-7: Acceptability, Pain, Adverse events as reported by Women

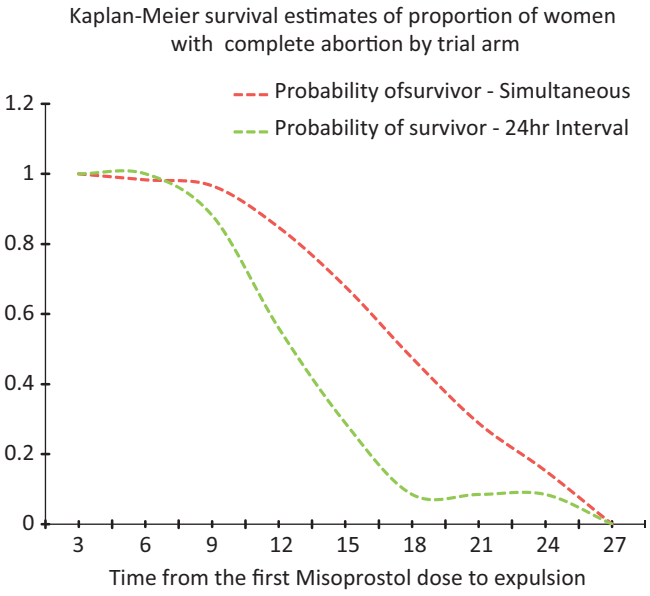

Figure-1: Kaplan-Meier analysis

vomiting and nausea. In case of nausea, the percentage was 31%, in case of vomiting while it was 25%. Affected participants in Group-A and Group-B were 27.12% and 23.73% respectively. Twenty-nine participants had suffered from mild fever. There were no symptoms of rash among the participants. No report of high fever was recorded during the study. Only 27.12% and 22.03% of participants had suffered from fever in Group-A and Group-B respectively. Overall 24.58% of participants out of the total 118 had suffered from fever. Only a few participants had chills. It was observed that most people who had fever, also experienced chills. In simultaneous regimen, 13(22.03%) and in 24-hour interval regimen, 11(18.64%) had chills. Out of 118 participants, only 20.34% had shown the same symptoms, which subsided spontaneously in most of the participants.

In both the regimens, there were reports of similar experience with pain and without any statistically significant differences in mean pain scores, severity and acceptability of pain. It was also observed that a longer time to complete abortion is associated with higher mean pain score.

DISCUSSION

This study was conducted between July 1, 2017 and June 30, 2018 and included 118 pregnant women, who consented to MMA to terminate their second trimester pregnancy. They were equally divided in the simultaneous and 24-hour interval regimen.

Women who took Mifepristone and Misoprostol simultaneously were less likely to expel both fetus and placenta within 24-hour of first Misoprostol dose (84.75%) compared with those, who took Misoprostol at 24-hour

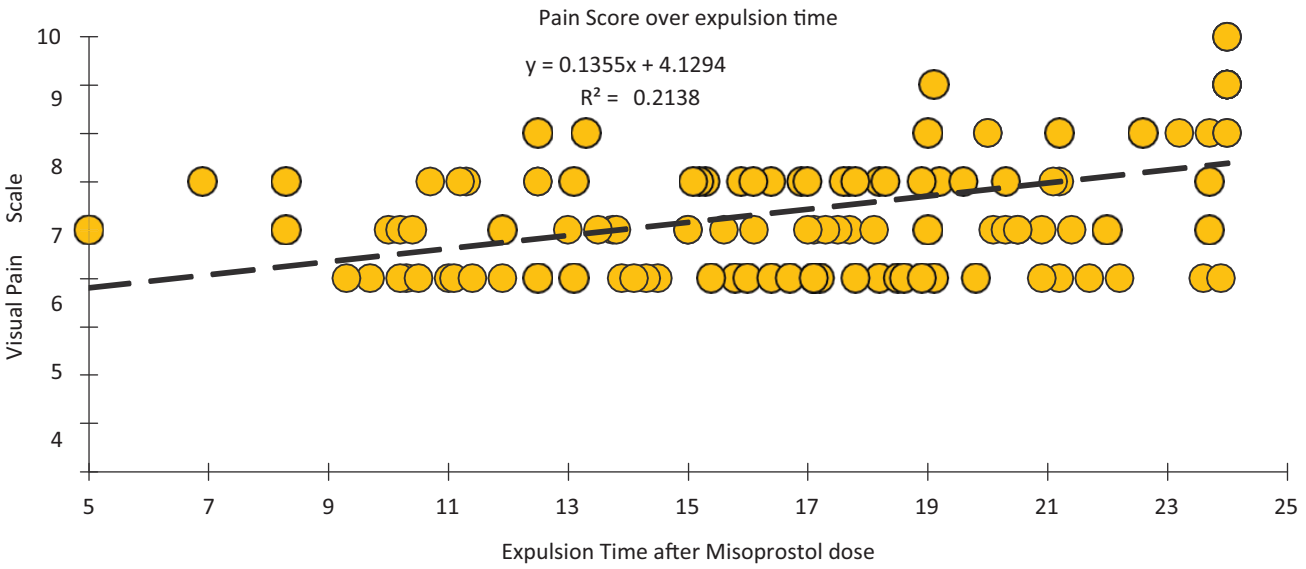

Figure-2: Pain score regression analysis

interval after taking Mifepristone.

The mean time to abortion from the first Misoprostol dose was considerably shorter for women who took the mifepristone and misoprostol at a 24-hour interval (12.3 compared with 16.39 hours).

The study also showed that the Misoprostol dose increased with increasing gestational age. For simultaneous regimen, the average Misoprostol dose was 4.18 for 13-16 weeks gestational age. But for 17-20 weeks gestational age the same Misoprostol dose increased to 4.96. When Misoprostol was taken in a 24-hour interval for 13-16 weeks gestational age, the average Misoprostol dose were 3.1. Whereas, the same Misoprostol dose increased to 4.46 for 17-20 weeks gestational age.

It was found out that the mean time to complete abortion was significantly lower in the 24-hour interval regimen when compared with simultaneous regimen. It was also observed that the neither parity nor gravida impact the rate or time of the complete uterine evacuation.

A regimen that requires Misoprostol to be given 24 hours after Mifepristone creates scheduling and additional cost barriers to women and their family.

A review article, "Evidence for shortening the time interval of prostaglandin after mifepristone for medical abortion" by Eric Schaff published in an international reproductive health journal, Contraception in July 2006 identified five randomized controlled studies that evaluated shorter intervals between mifepristone and either the prostaglandin misoprostol or gemeprost for medical abortion. Four were from the United States and three of these five studies had enrollments of >1000. The route of administration of the prostaglandin was used vaginally, except in one study where misoprostol was divided in two doses 2 hours apart. Four studies provided information about a 1-day interval and two trials provided information about an interval of 6-8 h evaluating mifepristone 200 mg and misoprostol 800 microgram vaginally. There were no significant differences noted between the 2-day interval compared with the 1-day interval. There was one study suggesting no difference with an interval of 6-8 hours. It concluded that the interval between mifepristone and misoprostol can be decreased from 48 to 6–8 h without loss of efficacy.[10]

In the year 2007, another study by Creinin et al. (2007) demonstrated that simultaneous administration of mifepristone and vaginal misoprostol is at least as effective as administration of the medications 24 hours apart in the first trimester.[11]

The first randomized study comparing two intervals of administration of Misoprostol after pretreatment with Mifepristone for second trimester abortion was done by J Chai et al. in December 2008. The results of this study showed that the success rate of medical termination of pregnancy at 24 hours with 200 mg oral Mifepristone followed by vaginal Misoprostol was significantly lower with the simultaneous regimen compared with that of the 36–38 hours regimen. The simultaneous use of Mifepristone and Misoprostol was associated with a longer induction-to-abortion interval and a higher requirement of Misoprostol. It was also associated with more side effects in terms of febrile episodes and chill, which were typical side effects of Misoprostol. The increase in incidence of these side effects was probably due to the increase in the total amount of Misoprostol required to induce abortion in the simultaneous administration group. The result of the 36-38 hours regimen showed that 98.6% participants aborted within 12 hours and 100% participants within 24 hours. Additionally, the median induction-to-abortion interval was 4.9 hours. Whereas, the result of the simultaneous regimen for the administration of Mifepristone and Misoprostol for second trimester termination of pregnancy suggested that this regimen was not as effective as the routine regimen of 36–38 hours interval with the success rate at 24 h of 91.5% only as compared with 100%.[12]

Another randomized controlled study, "simultaneous administration compared with a 24-hours Mifepristone-Misoprostol interval in second trimester abortion" done by Dina Fatima Abbas et al. in Vietnam, 2016 showed

similar results. The findings of this study demonstrated that both regimens were effective and acceptable to terminate pregnancies in the second trimester. Similar to the previous study, a 24 hours interval significantly increased the likelihood that abortion would be completed within 24 hours of the Misoprostol dose. By 48 hours, more than 95% of participants in both the regimens had expelled the foetus and placenta without any additional interventions. In this study the 24 hours interval also reduced the median Misoprostol dosing time by 5.3 hours, consequently reducing the duration of labor. However, the extra 24 hours between administration of the two drugs increased the total time of the procedures.[13] Likewise these three studies, the outcome of my study is also similar in nature. The findings of my study showed that the success rate of medical termination of pregnancy at 24 hours with 200 mg oral Mifepristone followed by vaginal Misoprostol was lower with the simultaneous regimen compared with that of the 24 hours regimen. The outcome of this study was 84.75% and 91.53% successful expulsion of fetus at 24 hours in the simultaneous and 24 hours interval regimen respectively.

CONCLUSION

This study illustrates that both the regimens are effective and acceptable for termination of pregnancies in the second trimester. It is observed that administering the mifepristone and misoprostol at 24 hours interval results in better clinical outcome.

Strength: The strength of the study was the vast range of participants, who belonged to the rural, semi urban and urban population to which our hospital supports. Many participants were also treated for the entire pregnancy period and so follow up could be done properly.

Limitation: The limitation was moderate sample size. A larger sample size and double-blind placebo-controlled design with randomized trial would have reduced the potential influence and confounding variables and health care provider bias on clinical outcomes and also would provide us better idea of the difference in efficacy of two regimens. In addition, lesser incidence of second trimester abortion was the main obstacle to get a sizable sample size.

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