ORIGINAL ARTICLE

A Comparative Study between Mifepristone Vs. Placebo as an Uterine Sensitizer for Second Trimester Abortions

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ABSTRACT

Introduction: Mifepristone can be used prior to prostaglandins as an uterine sensitizer in second trimester abortion. This accelerates the expulsion of fetus. This study was done to compare the efficacy and side effects of using oral mifepristone tablet vs placebo 24 hours prior to induction of second trimester abortion.

Methods: This was a randomized control study conducted in the dept of obsand gynae, RIMS. Women for termination of pregnancy between 13 to 20 weeks were selected according toMTP Act. Group A: Women in this group (n=50) received 200mg of oral Tablet Mifepristone 24 hours prior to induction of abortion. Group B: Women in this group (n=50) received tablets of placebo 24 hours prior to induction of abortion. Induction was done in both groups by intracervical application of dinoprostone (PGE2)gel followed by vaginal misoprostol. Data was compared using chi square test.

Result:: In group A, 36 patients and in group B, only 3 patients expelled within 12-24 hours whereas 47 patients in group B took more than 24 hours to complete the expulsion process (p value is <0.00001). In group A, 30 patients had vaginal bleeding upto 100 ml during the entire process of MTP whereas 38 patients had bleeding >200 ml in group B (p value is < 0.00001). In group A, 42 patients had complete abortion, whereas in group B, only 24patients had expelled completely.

Conclusion: Pretreatment with mifepristone in second trimester abortionis an effective uterine sensitizer with safety and good tolerability.

Keywords : second trimester abortion, mifepristone, misoprostol, induction delivery interval

INTRODUCTION

Abortion is defined as 'termination of pregnancy (TOP) by any means before the fetus is viable.' Viability is now considered to be reached at 23–24 weeks of gestation. TOP by induced abortion is practiced worldwide. Induced abortion, either elective or therapeutic termination of a viable pregnancy, is one of the most ancient procedures. Although the majority of abortions are performed in the first trimester, there is still a gradual increase in second-trimester abortion because of the wide scale introduction of prenatal screening programs detecting women whose pregnancies are complicated by serious fetal abnormalities such as cardiovascular and skeletal malformation.[1]MTP Act came into force on April 1, 1972, and revised again in 1975 and 2002.In India under MTP Act, termination of pregnancy can be performed up to 20 weeks of gestation. In second trimester upto20 weeks, the opinion of two registered medical practitioners is required to terminate the pregnancy. Various surgical and medical methods have been tried for the second trimester MTP with varying success and induction abortion interval.[2]

Prostaglandins are associated with not only a high success rate but also with a short induction abortion interval. Misoprostol, a newer synthetic prostaglandin E1 has proven its efficacy as an abortifacient for second trimester MTP since 1987. It is superior to all other available prostaglandins as it is stable at room temperature, requires no refrigeration, is cost effective, has fewer side effects, is a potent uterotonic and cervical ripening agent, free from bronchoconstrictive effect. It can be used by both the oral as well as vaginal route and in concurrence with other drugs as well. PGE2 is effective for induction of abortion causing cervical effacement and dilatation.

It reduces the dose of misoprostol or oxytocin used for augmentation of expulsion process. PGE2 gel (dinoprostone) is readily available in India but are expensive and require refrigeration, otherwise it becomes unstable at room temperature. Mifepristone, (RU 486, a substitute 19-norethisterone derivative) by blocking the progesterone receptors causes estrogen dominance resulting in necrosis and detachment of placenta and ultimately leading to intrauterine fetal death. It also softens the cervix and causes mild uterine contractions. It sensitizes the uterus to the action of prostaglandin which is given 1–2 days later, like synthetic prostaglandin E1 analogue, misoprostol, which binds to myometrial cells causing strong myometrial contractions and causes cervical softening and dilatation. This leads to expulsion of fetus from the uterus.[3]

AIMS & OBJECTIVES

The aim of the study was to compare the induction abortion interval of mifepristone over placebo when used as an uterine sensitizer 24 hours prior to induction and to assess the tolerability and safety of using oral mifepristone tablet.

MATERIAL & METHODS

This was a randomized control study conducted in the department of obstetrics & gynaecology, RIMS, Ranchi, Jharkhand, India between March 2017 to February 2019.Healthy women requesting for termination of pregnancy between 13 to 20 weeks(according to MTP Act) were included in this study after detailed history, clinical examination, ultrasonography and complete blood count.

Women presenting with bleeding disorders, inherited porphyrias, women with anemia (Hb < 10g/dl),any history of heart disease, uterine or vaginal infection, any known allergy to the study medication, women with congenital malformations of the uterus, women with cardiac or bronchial asthma and women not giving voluntary informed consent, were excluded from the study. The women were randomized and allocated to group A and group B on the basis of odd or even entry into the study. 50 Odd entries were allocated into group A and 50 even entries were allocated in group B.

Group A: Women in this group (n=50) received 200mg of oral Tablet Mifepristone 24 hours prior to induction of abortion.

Group B: Women in this group (n=50) received tablets of placebo24 hours prior to induction of abortion.

Induction was done in both groups by intracervical application of dinoprostone (PGE2) gel. Augmentation of the expulsion process was done after 6 hours by intravaginal tablet misoprost 400μg upto maximum of 6 doses. Misoprost tablets were repeated at an interval of 4 hours. The side effects including nausea, vomiting, diarrhoea and fever were recorded. The blood pressure, pulse, temperature and frequency of uterine contractions were monitored every 4 hourly. After abortion, the products of gestation (fetus and placenta) were examined to see whether the abortion was complete. In case of incomplete abortion, further management was done according to guidelines. Rh antibody was given to Rh negative mothers.

Complete abortion was defined as the expulsion of both the fetus and the placenta without operative intervention. The induction abortion interval was measured from the time of administration of dinoprostone (PGE2) gel to the time of completion of abortion. The volume of blood loss during abortion was estimated clinically by measuring the difference in weight of blood soaked gauze and the dry weight of the gauze. The side effects such as nausea, vomiting, fever was recorded. Data were spread on Microsoft excel sheet and statistically described in terms of frequencies (number of cases), percentages when appropriate. Data was compared using chi square test.

OBSERVATION & RESULT

Table 1 shows the distribution of cases on the basis of induction abortion interval. In group A, in which oral tablet mifepristone 200 mg was given 24 hours prior to starting induction, 36 patients (72 %) expelled within 12-24 hours, 6 patients within 12 hours and 8 patients (16 %) >24 hours. In group B, in which placebo was used 24 hours prior to starting induction, only 3 patients (6%) expelled within 24 hours of starting induction whereas 47 (94%) patients took more than 24 hours to complete the expulsion process. The chi squarestatistics is 61.8 (p value is <0.00001).The result is significant at $p< 0.05$.

Table 2 shows the distribution of cases on the basis of time taken for uterine contractions to start. Mifepristone acts as auterine sensitizer. Hence, uterine contractions started within 12 hours in group A. In only 2 patients (4%) of group B, uterine contractions started within 12 hours where as in 96%, uterine contractions started after 12hours.The chi square is 81.1 (p value is <0.00001). The result is significant at $p < 0.05$.

Table 3 shows the distribution of cases on the basis of blood loss during the process. In group A, 30 patients (60%) patients had vaginal bleeding upto 100 ml during the entire process of MTP,12 (24%) patients around 100-150 ml, 7(14%) around 150-200 ml

and only 1 patient(2%) had bleeding >200 ml. To the contrary, 38 patients (76%) had bleeding >200 ml, only 12 (24%) patients had less than 200 ml blood loss. The chi square in this case is 59.5 (p value is < 0.00001). The result is significant at $p < 0.05$.

Table 1: Distribution of cases on the basis of Induction Abortion Interval (IAI)

I.A.I.	Group A (n=50)	Group B (n=50)
<12 hrs	06 (12)	1 (2)
12-24 hrs	36 (72)	2 (4)
24-36hrs	5 (10)	28 (56)
36-48hrs	2 (4)	15 (30)
>48hrs	1 (2)	4 (8)

Chi square =61.8; p value =<0.00001

Table 2: Distribution of cases on the basis of start of uterine contractions

Time taken to start uterine contractions	Group A (n=50)	Group B (n=50)
<6 hrs	27 (54)	1 (2)
6-12 hrs	20 (40)	1 (2)
12hrs -18 hrs	2 (4)	26 (52)
>18 hrs	1 (2)	22 (44)

Chi square =81.1;p value= <0.00001

Table 3: Distribution of cases on the basis of blood loss

Volume of blood loss	Group A (n=50)	Group B (n=50)
<100ml	30 (60)	7 (14)
100-150ml	12 (24)	1 (2)
150-200ml	7 (14)	4 (8)
>200ml	1 (2)	38 (76)

Chi square = 59.5 ;p value= <0.00001

Table 4: Distribution of cases on the basis of side effects

Side effects	Group A (n=50)	Group B (n=50)
Nausea	3 (6)	22 (44)
Vomiting	2 (4)	6 (12)
Diarrhoea	5 (10)	9 (18)
Fever	2 (45)	10 (20)

Table 5: Distribution on the basis of incomplete abortion

Incomplete abortion	Group A (n=50)	Group B (n=50)
Yes	08 (16)	26 (52)
No	42 (84)	24 (48)

Chi square = 14.4 ;p value=0.000145

Table 4 shows the distribution of cases on the basis of side effects of both regimens. In group A, most of the cases expelled within 24 hours, so the dose of misoprost was less in these cases. Hence the side effects related to misoprost was less. 3 patients had nausea, 2 patients had vomiting, 5 complained of loose motion and 2 had fever. In group B, 22 patients complained of nausea, 6 had vomiting, 9 had loose motions and 10(20%) had fever.

Table 5 shows the distribution of cases on the basis of incomplete abortion where some or part of placenta or fetus was retained inside the uterus. In group A, 42 patients (84%) had complete abortion, no product of conception was retained whereas in group B, only 24patients (48%) had expelled completely. 16 % of group A and 52% of group B had to undergo check curettage. The chi square is 14.4 (p value = 0.000145). The result is significant at $p < 0.05$.

DISCUSSION

In our study, induction abortion interval was <24 hours in 36 patients (72 %) whereas same duration was only in3 patients (6%), whereas 47 (94%) patients took more than 24 hours to complete the expulsion process. Rodger et al in a double blind study using 600 mg mifepristone 36 hours prior to gemeprost found that the induction abortion interval was significantly reduced to 6.8 hrs as compared to 15.8 hrs in the placebo group.[4] Similar results have been shown by Hinshaw K, [5]Refaey HE et al, [6]HO P C et al, [7]Premila WA et al [8],Nga SW[9] and Nagaria Tet al [3]. In the study by Khairnar MM[10], the mean induction abortion interval was 6.2±2.1(range 3 to 10 hrs) and in group B was 10.8±2.5 (range 4 to 15.5 hrs).

Mifepristone combined with misoprostolis a widely used method for early first trimester MTP. Primimg of the uterus with mifepristone makes it more sensitive to prostaglandins. It binds with the progesterone receptors and antagonizes the actions of progesteroneon prostaglandin synthesis and metabolism resulting in increase in production and decreased deactivation of prostaglandins. It also induces cervical softening, thus enhancing the efficacy of the prostaglandins as an abortifacient. In 94% of the cases, uterine contraction started within 12 hrs. Similarly, the time interval between the insertion of the first tablet of misoprostol and start of contraction was significantly shorter in the mifepristone group in the study by Nagaria T.[3]

The mean blood loss (52.55ml) was less in the mifepristone group in the study by Akkenapally PL [11] and Nagaria T [3].The present study also had the similar result.

In group A, most of the cases expelled within 24 hours, so the dose of misoprost was less in these cases. Hence the side effects related to misoprost was less. 3 patients had nausea, 2 patients had vomiting, 5 complained of loose motion and 2 had fever. In group B, 22 patients complained of nausea, 6 had

vomiting, 9 had loose motions and 10(20%) had fever. In the study by Akkenapally PL et al, there was no difference in the prevalence of gastrointestinal side effects between the two groups.[11].In the study by Bijeta et al, there was no significant difference in adverse effects observed in both groups.[12]In the study by Nagaria T, the side effects observed were mainly nausea, vomiting 10 and 14%, fever 18 and 23%,abdominal cramps 10 and 13%,flushing and diarrhea in 2%each in the study and control group, respectively.[3]

In group A, the success rate was 84% whereas it was 48% in group B (Chi square = 14.4; p value=0.000145). P value was statistically significant. Nagaria T[3] observed a success rate of 100%. Khairnar MM observed a success rate of 98.6% in group A.[10]

CONCLUSION

Pretreatment with mifepristone in second trimester abortion significantly reduces the induction abortion interval, blood loss, incomplete abortion, dose of misoprostol required, duration of hospital stay and adverse side effects. It is cost effective, safe, non invasive with a high success rate. It other ways, Mifepristoneis well tolerated and efficacious in cases of second trimester abortions when used as an uterine sensitizer prior to use of prostaglandins. It should be routinely practiced in all tertiary care centres.

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