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ORIGINAL ARTICLE

Prospective Comparative Study of Misoprostol Alone Versus Mifepristone Plus Misoprostol for Second-Trimester Pregnancy Termination

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Abstract

Introduction MTP has been legalized in India through the Medical Termination of Pregnancy Act, of 1971, which allows pregnancy termination up to 20 weeks. The present study included second-trimester pregnancy terminations and the main aim of the study is to compare the efficacy and safety of tablet mifepristone 24 h before vaginal tablet misoprostol in group-I with vaginal tablet misoprostol alone in group-II as a method of second-trimester pregnancy termination.

Methodology It was a prospective randomized comparative study conducted at the Department of Obstetrics and Gynaecology, R.N.T. Medical College, Udaipur, Rajasthan, by selecting 100 patients, with equal no, i.e., 50 in each group who attended the inpatient department for second-trimester pregnancy termination (who were fulfilling the criteria as per MTP Act).

Results From the data analysis of 100 subjects in this study, we observed that the most common indication for second-trimester pregnancy termination was indication (III), which accounts for a total of 60%. Majority of the patients in either group were in the age group between 20 and 30 years, and there was more multigravida as compared to primigravida. The induction termination interval in the Mife-Miso group (group-I) was shorter, i.e., 10.21 h as compared to the Miso group (group-II), i.e.,18 h, and the difference between them was found to be statistically significant (*P*-value 0.004). The complete expulsion rate within 24 h in group-I was 92% as compared to 72% in group-II.

Conclusion The pretreatment with oral mifepristone, provides a more safe, non-invasive, and effective regimen for second-trimester termination of pregnancy, which significantly reduces induction termination interval with more success rate.

Keywords Abortion induced · Misoprostol · Mifepristone · Second-trimester pregnancy

Introduction

MTP has been legalized in India through the Medical Termination of Pregnancy Act of 1971. The main aim of this act was to provide better health care and reduce the rate of repeated unsafe abortions. The law was passed in parliament in 1971 and enforced from April 1972. The law provides a framework for safe and legal pregnancy termination services in the country. Even though women in India do not have the right to terminate on demand, the act allows a woman to undergo termination of pregnancy by a registered medical practitioner only up to 20 weeks under a certain range of circumstances. Second-trimester MTP is associated with higher morbidity and mortality like excessive hemorrhage, perforation of the uterus, and sepsis. Although the majority of terminations are performed in first trimester, there is still a higher rate of second-trimester terminations mainly because of advancements in prenatal screening programs for the detection of complications in pregnancy like serious fetal malformations (cardiovascular, central nervous system, and skeletal), logistic and financial difficulties in obtaining termination services, and failure to recognize an undesired pregnancy in the First-trimester, which all contribute to the

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continuing need for late termination. The MTP ACT offers protection to the practitioner if she /he adheres to and fulfills all the requirements under the act [1].

Recently, the union cabinet has approved the medical termination of pregnancy (MTP) (Amendment) Bill [2]. The Bill seeks to extend the termination of pregnancy period from 20 to 24 weeks, making it easier for women to safely and legally terminate pregnancy under certain circumstances.

Second-trimester abortions are a small percentage of all abortions worldwide; only 9–11% of all induced abortions occur in the second trimester [3]. However, these abortions are responsible for two-third of all major complications. To avoid these complications, second-trimester abortion must be performed as per criteria laid down in the MTP Act and Rules, following the appropriate method and taking all necessary precautions [3]. It can also be carried out by both surgical and medical methods [3]. Surgical methods include dilatation and evacuation (D&E up to 15 weeks) and hysterotomy. Medical methods are comparatively safer and preferred over surgical methods because of associated risks in surgical methods like hemorrhage, pelvic infections, and iatrogenic injuries. Advantages of medical methods include less chance of damage to the cervix and sequelae such as cervical incompetence because of gradual dilatation of the cervix. Commonly used medical methods includes.

Misoprostol Alone Regimen

The prostaglandin analog misoprostol (gemeprost) (prostaglandin E1 analog) was introduced in the late 1970s. It binds to myometrial cells, causing strong uterine contractions, cervical softening, and dilatation. This leads to the expulsion of products of conception from the uterus. Misoprostol has an advantage over other prostaglandins also as it is well absorbed from different routes of administration; is economical; and stable at room temperatures in comparison to PGF2-alfa derivatives.

Mifepristone and Misoprostol Regimen

The subsequent introduction of anti-progestin, mifepristone in the 1980s, which binds to progesterone receptors but does not activate the receptors and thereby acting as anti-progesterone before prostaglandin (PG) administration. The known actions of mifepristone on the uterus include decidual necrosis, which leads to detachment of implanted embryo, cervical softening, increased uterine contractility, and prostaglandin sensitivity. It accentuates the sensitivity of myometrium to the stimulatory effects of exogenous PG. The combination of mifepristone f/b misoprostol has been found safe and effective for second-trimester termination of pregnancy. Among the various routes of misoprostol, vaginal route has better systemic bioavailability, sustained effect, and has lower side effects than the oral route. According to the WHO and Royal College of Obstetrics and Gynaecology, mifepristone f/b misoprostol is considered an effective and safe method for second-trimester pregnancy termination.

We divided the patients into two groups in our study. Group 1–Tablet mifepristone 24 h before tablet misoprostol (in repeated dose–max 5 dose) group. Group 2–tablet misoprostol alone (in a repeated dose–max 5 dose) group.

Misoprostol

Misoprostol exerts a protective effect on the gastrointestinal mucosa by increasing mucus and bicarbonate ions secretion and by increasing mucosal blood flow. In addition, it inhibits acid secretion, thus protecting against the erosive effects of NSAIDs. Misoprostol is also a myometrial stimulant, which binds to both E2 and E3 prostaglandin receptors and causes calcium influx and cAMP modulation. The uterine contraction in turn promotes placental separation and release of endogenous prostaglandins [4]. After absorption, misoprostol converts to misoprostol acid and its bioavailability decreases by concomitant intake of diet or antacids [5]. Constriction of spiral arterioles leads to ischemic necrosis of decidua and embryonic detachment which in turn results in a fall in HCG and progesterone from trophoblast. Cervical changes by increasing collagenase activity and altering glycosaminoglycans. It was studied that systemic bioavailability was found higher vaginally than orally. It is faster absorbed orally than vaginally with higher peak serum levels, but vaginally absorbed misoprostol levels are more prolonged.

A recent study showed that buccal administration of misoprostol promotes cervical ripening in labor induction but associated with in a higher incidence of tachysystole compared to intravaginal administration [5]. Dose-dependent adverse effects of misoprostol are nausea, vomiting, diarrhea, abdominal cramps, shivering, and fever [6].

Incidence of Mobius syndrome and limb defect noted as a result of an unsuccessful attempt to induce abortion after taking misoprostol in first trimester [5].

Mifepristone

Mifepristone binds to progesterone receptors having anti-progesterone activity. Mifepristone has a high affinity for the human uterine progesterone receptor compared to progesterone, mifepristone has two to ten times higher affinity to the receptors. Mifepristone binds to progesterone receptors and fails to induce the change in receptor shape required for chromatin binding and prevents transcription. Following oral administration mifepristone is rapidly absorbed and the time to peak serum concentration (t-max)

is approximately 1–2 h. The t-max has been similar within the dose range of 2–600 mg (Kekkonen et al., 1996). It reaches a maximum plasma concentration of 2.5 mg/L at 1.35 h irrespective of the dose of 100–800 mg.

Materials and Methods

This prospective randomized study comparing the efficacy and safety of tablet mifepristone 24 h before vaginal tablet misoprostol in repeated doses in group-I with vaginal tablet misoprostol alone in repeated doses in group-II as a method of second-trimester pregnancy termination conducted at the Department of Obstetrics and Gynaecology, RNT Medical college, Udaipur, Rajasthan, by selecting 100 cases, with equal no, i.e., 50 in each group attending inpatient department after first October 2019 until we completed our sample size.

Inclusion Criteria

Patients admitted for second-trimester termination with duration of pregnancy > 12–20 weeks (satisfying criteria of MTP Act, 1971). Only live pregnancy is included. After explaining various methods for termination to the patient and those who opt for the medical methods are included in the study.

Exclusion Criteria

Known allergy or contraindication to the drugs (mifepristone and misoprostol). Intrauterine fetal demise. Already an indication of laparotomy and previously done uterine surgery. If the patient is in a state of inevitable abortion/incomplete abortion. Anemia (hemoglobin < 8 gm%). Confirmed or suspected ectopic pregnancy, undiagnosed adnexal mass. Uncontrolled hypertension or bp > 160/100. Heart problems such as angina, valvular heart disease, and arrhythmias, can lead to sudden cardiovascular collapse, current anticoagulant therapy, and current long-term systemic corticosteroid therapy.

Methodology

For second-trimester MTP, patients are randomly allocated in equal numbers into two groups which include group-I (tablet mifepristone 24 h before tablet misoprostol in repeated doses (max 5 dose) and group-II (tablet misoprostol alone in repeated doses (max 5 dose including loading dose).

At the time of admission, a detailed history regarding the age, occupation, education, address, and obstetrics history was taken regarding parity, time since last delivery, and number of previous MTP. General condition at the time of admission was noted specifically recording of pulse, blood pressure, and respiratory rate.

Routine blood investigations and USG was done to confirm pregnancy and period of gestation and to confirm congenital anomalies. A thorough general physical and systemic examination was done. Per abdomen, per speculum, and per vaginal were also done to note uterine size and cervical status. All patients once admitted, remain in the hospital throughout the procedure till complete termination. After admission injection tetanus toxoid IM was given to all patients. Prophylactic injection ceftriaxone 1gm IV single dose and tablet metronidazole 400 mg thrice a day for 3 days given to all patients. Injection Anti-D 300 mcg IM is given in Rh-negative cases.

Group-I: Mifepristone—Misoprostol Group

Dosage schedule: Day I: tablet mifepristone 200 mg was given orally, and the patient was observed, after 24 h. Tablet misoprostol 800 mcg administered vaginally, after 4 h. misoprostol 400 mcg administered vaginally every 4 h until delivery (or a total of 5 doses, including the loading dose). If undelivered 4 h after the 4th dose, additional measures were used including instrumental evacuation, oxytocin infusion, or mannitol induction.

Group-II: Misoprostol Group

Eight hundred mcg misoprostol inserted vaginally, 4 h later misoprostol 400 mcg repeated every 4 h until delivery or total of 5 doses (including loading dose).

Check USG also done next day to check for incomplete abortion (retained products). If retained products are present further management was done. During the study, following side effects were noted and treated symptomatically. We used a maximum of five doses of misoprostol, because side effects are likely to occur more frequently with repeated and higher total doses of misoprostol. Although a concern, side effects are known and manageable [6].

Outcome

Parameters that were studied included induction-abortion interval, success rate, side effect profile (vomiting, diarrhea, fever, headache, rigor, hemorrhage, and infection), and indication for MTP as per MTP act, need for additional measures like evacuation, mannitol, or oxytocin.

Statistical Analysis

Data were analyzed using SPSS software using ANOVA, independent sample test, and Chi-square test, and the significant *P*-value being less than 0.05.

Results

The present study was targeted to compare the efficacy of oral tablet mifepristone 24 h before vaginal tablet misoprostol (group-I) and tablet vaginal misoprostol alone (group-II) regimen in second-trimester pregnancy termination. For this purpose, a total of 100 patients were enrolled in the study.

In this study, primi were 36% in group-I compared to 42% in group-II, while the majority, i.e., 64 and 58% were the multigravida in group-I and group-II, respectively.

In our study, the majority of patients in each group were in the age group between 20 and 30 years, i.e., 66% in the Mife-Miso group (group-I) and 76% in the Miso group (group-II).

In our study, most of the patients terminated between 16 and 20 weeks of gestational age, i.e., 60 and 80% in group-I and group-II, respectively.

indication for termination (I) to (V):

(I) To save the life of pregnant women.
(II) To prevent grave injury to the physical and mental health of the pregnant women.
(III) In view of the substantial risk that the child would suffer from abnormalities.
(IV) As the pregnancy caused by rape.
(V) As the pregnancy has occurred as a result of failure of any contraceptive device or method used by married woman or her husband for the purpose of limiting the number of children.

Indication (III) as per the MTP act accounts for most of the termination, i.e., 60% in our study, which may be due to the development of advanced technologies that detect the congenital anomalies antenatally, followed by indication (I) and (V), i.e., 24 and 8%, respectively.

Table 1 Mean induction-abortion interval in hours

Induction abortion	Mife-Miso (group-I) $N=50$	Miso (group-II) $N=50$	*P*-value
Mean	10.21	18.00	0.004
Std. deviation	8.95	16.54	
Std. error mean	1.26	2.33	

From the above Table 1, it can be inferred that the induction termination interval was more in group-II as compared to group-I, and on applying the independent t-test it was found to be statistically significant with *P*-value less than 0.05.

On applying ANOVA for various categories of gestational age groups, the *P*-value which was calculated and mentioned in the above Table 2. The *P*-value for the gestational age group came out to be 0.883 which means that the gestational age had no significant effect on the induction time. The *P*-value for the two-intervention group-I and group-II came out to be 0.04 which is less than 0.05 which points to the fact that the induction termination interval is dependent upon the type of treatment with group-II having a longer induction termination interval and this is statistically significant. The *P*-value for the combine effect of gestation age categories and treatment group was 0.579 and thus was not found to be statistically significant.

On applying ANOVA for the categories, the *P*-value was obtained (Table 3). For the treatment group, the *P*-value which was calculated was 0.004 which means that the difference between the induction termination of the two treatment groups is significant. For gravidity, the *P*-value was found to be 0.262 which means that it had no significant impact on the mean induction termination time. Similarly, the combined effect of gravidity and treatment group has no significant impact on the induction time.

The successful termination included those patients who were expelled completely or incompletely (who required the help of additional intervention for the complete expulsion) within forty-eight hours. The number of patients who had successful termination in group-I (Mife-Miso) was 96% while in group-II (Miso) was 94%. Ninety-two

Table 2 Induction-abortion interval according to gestational age

Gestational age (in weeks)	Induction-abortion interval		*P*-value
	Mife-Miso (group-I)	Miso (group-II)	
> 12–15	11.84	13.9	GA-0.883
> 15–18	9.34	20.55	Group-0.044
> 18–20	10.28	18.00	GA and group-0.579

Table 3 Induction-abortion interval according to gravidity

Gravidity	Induction-abortion interval (hours)		*P*-value
	Mife-Miso (group-I)	Miso (group-II)	
Primigravida	10.55	21.27	For group 0.004
Multigravida	10.02	15.63	For parity 0.262

percentage of patients in group-I were expelled completely within 24 h as compared to 72% of patients in group-II. In failure, we included the patients who failed to expel at the end of 48 h either completely or incompletely and we opted for the other methods for termination other than medical methods. 4% of patients in group-I while 6% of patients in group-II are those who failed to expel within 48 h so we opted for another method other than the medical method.

The percentage of complete termination in the Mife-Miso group (group-I) was 90%, while that in the Miso group (group-II) was 70% (Fig. 1). The incomplete termination was 6% in the Mife-Miso group, while 24%in the Miso group. The number of patients who were in the failure category (those in which we needed an alternative method to intervene) is 4% in Mife-Miso group and 6% in the Miso group (*P*-value 0.018).

On applying the Chi-square value to find out whether the outcome was significantly different in the two groups, it was observed that the complete termination was more in group-I as compared to group-II with more incomplete abortion, this was found to be statistically significant.

Overall, 10% of patients in group-I (Mife-Miso) and 30% of patients in Group -II (Miso) required some form of intervention for the completion of the abortion process. The group-II required more intervention as compared to group-I, but it was not statistically significant on applying the Chi-square test, with a *P*-value of 0.07. The commonest intervention in each group was instrumental evacuation. Eighty-four percentage of patients in the Mife-Miso group

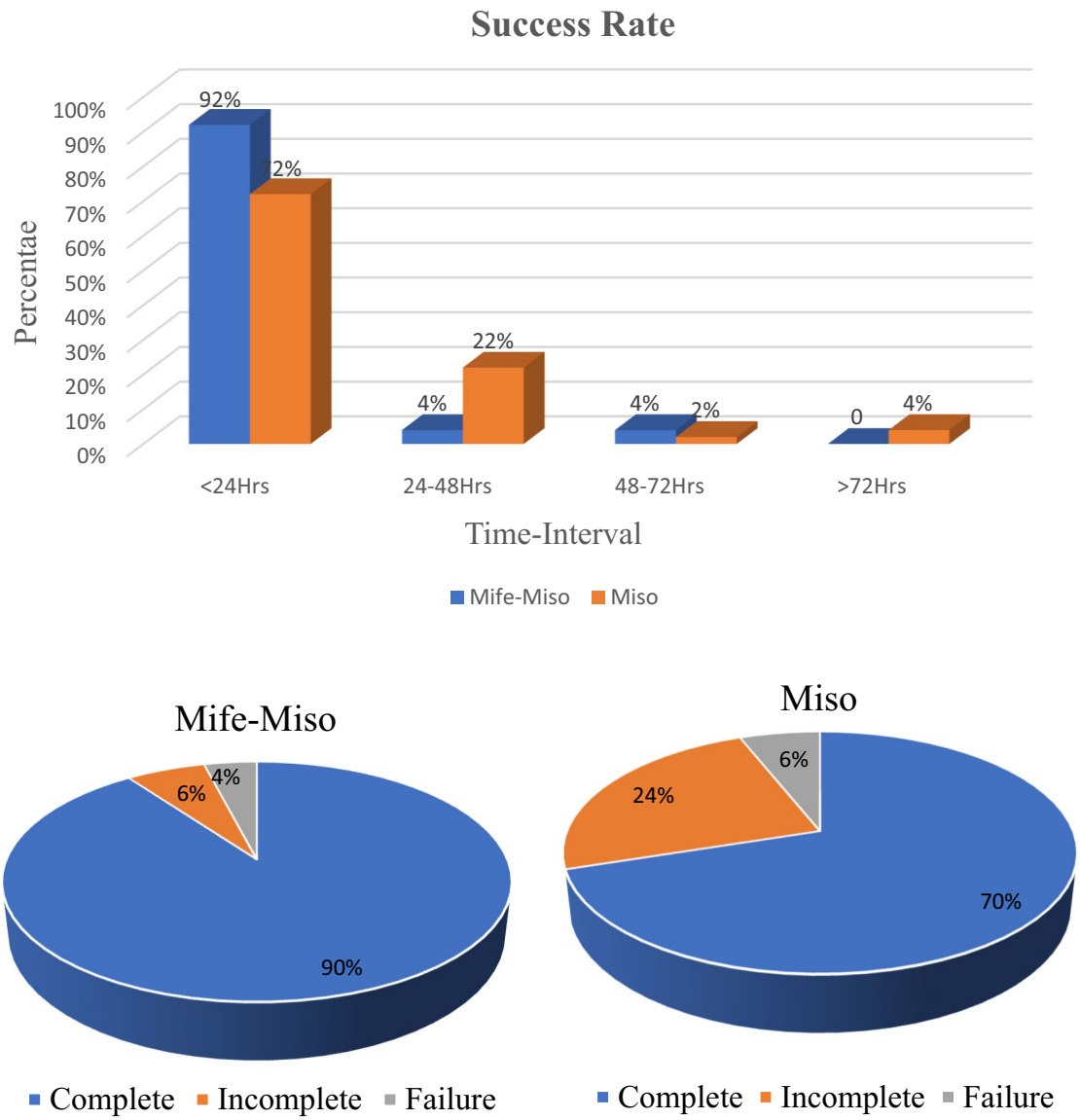

Fig. 1 Outcome among patients in both groups

experienced side effects and the most common side effects were GI side effects (66%) including nausea, vomiting, diarrhea, and abdominal cramps followed by headache and rigor, respectively.

Eighty-six percentage of patients in the Miso group experienced side effects, and the most common side effect experienced was also GI side effects (48%) same as in the -Miso group, followed by rigor headache and fever, respectively.

The difference between the side effects was not statistically significant between the two groups. Side effects were treated symptomatically and no major complications were found in both groups. The most common indication for termination was indication (III) as per the MTP act, which includes the total number of 60 patients (i.e., 60%) out of 100.

The most commonly affected system in the affected fetus was CNS (i.e., in 75% of patients) followed by CVS, respiratory, renal, and GIT in 9, 6, 6, and 4% of patients, respectively. Also, in CNS the most common anomaly that was detected was Anencephaly followed by Chiari-II malformation, occipital meningomyelocele, cystic hygroma, and ventriculomegaly in decreasing order, respectively. Anomalies that were detected on antenatal ultrasound were also confirmed with repeat scans at our center before starting the procedure.

Discussion

The present study evaluated the efficacy of medical methods including vaginal misoprostol with prior use of mifepristone (group-I) versus vaginal misoprostol alone (group-II) in second-trimester pregnancy termination. For this purpose, a total of 100 pregnant women who wants second-trimester pregnancy termination were enrolled in the study.

In the study of Hammond [7], recent advances in second-trimester abortion the recommended regimen of Royal College of Obstetricians and Gynaecologists was given—day one: mifepristone 200 mg orally 36–48 h later: misoprostol 800mcg vaginally 3 h later: misoprostol 400mcg orally or vaginally every 3 h until delivery or total of 4 doses. If undelivered 3 h after 4th dose: repeat mifepristone 200 mg and resume induction next day or consider surgical abortion.

In the study of Jan E Dickinson [8], the median duration of abortion was noted as 15.5 h in the misoprostol group and 8.6 h in the mifepristone primed group ($P < 0.001$). Abortion interval was prolonged in patients with nulliparity and advancing gestation. They noticed a shorter hospital stay in the combination group (27.2 h) than in the misoprostol alone group (31.5).

In the study of Kulkarni [9], the age of the patients in both groups ranged between 20 and 38 years, the average being 29.5 years, and the mean period of gestation age between both groups was between 16 and 17 weeks. They observed significantly shorter induction–abortion interval in the study group, thereby decreasing the side effects of the drug as well as the duration of hospital stay. They concluded that combining mifepristone before misoprostol offers a reliable, safe, and cost-effective option by decreasing the induction–abortion interval.

In a study by Dabash, et al. [10], "A double-blind randomized controlled trial of mifepristone or placebo before buccal misoprostol for abortion at 14–21 weeks of pregnancy" complete abortion duration was recorded 48 h in 55 (91.7%) women in the combined group versus 43 (71.7%) in the misoprostol alone group. The mean time to complete abortion was 10.4 h. in the group who received mifepristone versus 20.6 h. in the misoprostol alone group ($P < 0.001$). they concluded that adding mifepristone before misoprostol can improve the quality of second-trimester abortion care by making the process faster.

In a comparative study of misoprostol only and mifepristone plus misoprostol in second-trimester MTP done by Akkenapally [11], the success rate in only the misoprostol group was 89%, whereas in combination mifepristone misoprostol group it was 96%. They also concluded that pretreatment with mifepristone significantly reduces the induction-abortion interval and the misoprostol dose along with minimal blood loss.

Our results are comparable with a study done by Jan E Dickinson [8] and Kulkarni [9] in which the multipara was 57.8 and 60% in the Mife-Miso group, while 60.3 and 66% in the Miso group, respectively.

Conclusion

The need for second-trimester pregnancy termination is increasing worldwide mainly because of the wide-scale introduction of more advanced prenatal screening programs for the detection of various abnormalities. Various surgical and medical methods have been tried for the second-trimester MTP with varying success and induction-abortion intervals.

In our study, comparing tablet mifepristone before vaginal tablet misoprostol (group-I) with vaginal tablet misoprostol alone (group-II) for second-trimester pregnancy termination, it was observed that the pre-treatment with oral mifepristone provides a more safe, non-invasive, and effective regimen for second-trimester termination of pregnancy, which significantly reduces the induction termination interval with more success rate and minimum side effects.

Declarations

Conflict of interest There are no conflict of interest in this study.

Ethical approval Institutional ethical committee clearance was obtained for study.

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