A STUDY ON THE USE OF A COMBINATION OF MIFEPRIN AND MISOPROSTOL FOR SECOND TRIMESTER TERMINATION OF PREGNANCY

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ABSTRACT

The significant need to conduct second trimester abortions safely is being addressed by the use of a combination of mifepristone and misoprostol, though their dosage regimen continue to be debated. The present study was conducted on 50 selected women in the Department of Gynecology and Obstetrics, Andhra Medical College, Visakhapatnam, from April 2014 to October 2015 to determine the safety and efficacy of 200mg of mifepristone orally followed 24hrs. later by 400mcg of misoprostol administered vaginally every 6hrs. upto a maximum of 5 doses, which is the regimen recommended by FOGSI and the results were analysed. The mean induction abortion interval (IAI) was 10.08±2.9hrs. and 76% of cases had IAI of ≤12hrs. The side effects were few and manageable. Hence, the above regimen should be used for safe and effective termination of a second trimester pregnancy.

KEYWORDS

Abortion, Mifepristone, Misoprostol, Second trimester.

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INTRODUCTION

Abortion is the single most common procedure performed for women worldwide. Second trimester abortions constitute 10-15% of all induced abortions worldwide, but are responsible for two-thirds of all major abortion-related complications. Medical abortion, the termination of pregnancy through the use of a drug or a combination of drugs has the potential to reduce complications. Though the medical abortions upto nine weeks of gestation were approved in some countries by 1992, the approval for the use of the above drugs for second trimester abortion was obtained in these countries only in 1999-2000. The optimal method of second trimester abortion continues to be debated.

Advantage of medical abortion in second trimester includes the scope for examination of the fetus in abortions done for fetal anomalies to further evaluate the subsequent risk of recurrence and provide information to help in counseling of these patients, which is not possible if dilatation and evacuation is the method chosen.[1] The most commonly used combination is mifepristone taken first and misoprostol administered 24-48 hours later. Mifepristone an antiprogesterone leads to cervical softening, increased uterine sensitivity to prostaglandins and conversion of the quiet pregnant uterus into an organ of spontaneous activity with maximal effect at 36-48 hours.[2] Misoprostol a synthetic PGE-1 analogue induces cervical ripening as well as strong uterine contractions and leads to expulsion of a pregnancy.

The oral tablet is effective in different routes of administration and the dose of prostaglandin can be easily adjusted according to need.

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It is stable at room temperature, is cost effective and has limited effect on the bronchi and blood vessels.

Side effects are dose-dependent, usually mild and self-limiting.[3] Mifepristone and Misoprostol act synergistically in combination and where both are available both should be used. Misoprostol alone should be used in countries where Mifepristone is not available. Pre-treatment with Mifepristone increases success rate, shortens the Induction Abortion Interval (IAI) and reduces the amount of prostaglandins required for second trimester abortion.

During the second trimester due to increased sensitivity of the uterine muscles to prostaglandins, lower doses of misoprostol are sufficient as compared to first trimester. Uterine rupture has been reported in association with medical abortion at late gestation. The risk is less than 1 in 1000. FOGSI ICOG good clinical practice recommendation for second trimester abortion suggests 200mg mifepristone followed after 36-48hrs. by 400mcg of misoprostol administered at 3-6hrs. interval upto 5 doses. This study was undertaken to assess the safety and efficacy of the combination of Mifepristone and Misoprostol for second trimester medical abortion following the above guidelines.

MATERIALS AND METHODS

The present study was conducted in the Department of Gynecology and Obstetrics, Andhra Medical College, Visakhapatnam from April 2014 to October 2015. Women requesting a mid-trimester termination of pregnancy (Between 13 and 20 weeks of pregnancy) were screened for eligibility by interview, clinical examination, and laboratory investigations including determination of the hemoglobin concentration and liver and renal function tests. Duration of pregnancy and viability of the fetus were confirmed by ultrasound scan.

Fifty healthy women who fulfilled the legal criteria for a termination of pregnancy and had a singleton viable pregnancy of 13-20 weeks' duration were included. Exclusion criteria were hypersensitivity to mifepristone and misoprostol, contraindications for the use of the 2 drugs, previous scarred uterus (Cesarean delivery, myomectomy), hemoglobin level below 8gm/dl and serious medical diseases such as severe hypertension, uncontrolled diabetes or renal and liver disease. All participants provided a written and

informed consent. The indications for termination of pregnancy were as per the medical termination of pregnancy rules in India and included fetal anomalies, social and economic factors and pregnancy resulting from contraceptive failure.

All participants received 200mg of mifepristone orally followed 24hrs. later by 400mcg of misoprostol every 6hrs., administered vaginally upto a maximum of 5 doses. With the onset of vaginal bleeding misoprostol was administered by the oral route. The cases were closely monitored for side effects if any, the onset of contraction, bleeding, cervical dilatation each time before insertion of each misoprostol. IAI since the insertion of the first intravaginal tablet of misoprostol was noted. The products of conception were examined for completeness.

The process was considered failed if abortion failed to occur within 24 hours of insertion of the first tablet of misoprostol without any additional intervention, incomplete if part or whole of the placenta was retained. If placenta was retained for more than 2 hours, surgical evacuation was done. In case of failure, another method medical or surgical was tried. Rh antibody was given to all Rh negative cases at the beginning of the procedure. Adverse effects were recorded from the time of mifepristone administration until 24 hours after the abortion.

A successful abortion was defined as complete expulsion without additional intervention within 24hrs. of the first dose of misoprostol. IAI and rates of adverse effects and complications were noted. An ultra-sonogram was performed 24hrs. after the abortion to check for retained products of conception. Unless the patient requested sterilization procedure or had any complications, she was discharged 24 hours after the abortion and advised to come for followup after 6 weeks.

OBSERVATIONS

Majority of cases were between 21 and 30 years of age (Figure 1). The mean gravidity of the cases was 2.16±1.04. The mean parity was 0.96±0.95 (Figure 2). The mean gestational age was 17.52±2.02 (Figure 3). The number of women having pregnancy with gestational age less than 16 weeks was 8 (16%) and between 16 to 20 weeks was 42 (84%) (Table 1). The reasons for requesting a termination of pregnancy included social causes 30 (60%), economic constraints 12 (24%), women having medical disorders 4 (8%), and failed vasectomy 4 (8%).

The mean IAI was 10.08 ± 2.9hrs.; 38 (76%) women had a complete abortion within ≤12hrs.; 48 (96%) women had a successful complete abortion within 24hrs. without additional intervention; 2 (4%) women required surgical evacuation following the detection of retained products on the ultrasonogram; 96 % of the fetuses were aborted dead and ensac. The mean dose of misoprostol required was 1.96±0.77. No case required more than 3 doses of misoprostol (Table 4). The side effects observed were mainly nausea (10%), vomiting (12%), fever (15%), abdominal cramps (12%), diarrhea (2%).

DISCUSSION

Labor induction abortion is effective throughout the second trimester. Compared with misoprostol alone, the combination of mifepristone and misoprostol results in a clinically significant reduction of 40% to 50% in time to abortion and can be used at all gestational ages. Misoprostol can be absorbed by many routes and has different pharmacokinetic properties in each route. It is absorbed the fastest via sublingual route. Orally absorption is slower than sublingual, but faster than vaginal/rectal routes. The vaginal or rectal route leads to a lower peak level of misoprostol, but has a much slower elimination curve.

Oral or sublingual administration leads to higher levels and faster onset of action, but will be associated with greater side effects (Predominantly fever and chills)[3] There have been a number of randomized studies investigating the optimal dosage of misoprostol for second trimester abortion. Dickinson et al. found that 1) IUFD inductions complete much quicker than live abortions and 2) 400mcg of misoprostol administered vaginally every 6 hours was the optimal dose, providing nearly the best delivery characteristics but avoiding the side effects associated with higher dosing.[4] Tang et al. did a randomized trial which showed vaginal misoprostol to be more effective than sublingual in second trimester abortion.[5] Based on these data, the most evidence based dose of misoprostol for second trimester induction is 400mcg administered vaginally every 6hrs.

In the present study, the IAI was 10.08±2.9hrs. as compared to 6.72±2.26hrs. in the study by Tripti et al. This may be because no initial loading dose was given and the dosage schedule was different[6]. Kapp et al. randomized women at 18 to 23 weeks gestation to mifepristone 24hrs. before buccal misoprostol or misoprostol alone. The median abortion time with mifepristone was 10hrs., a 45% reduction in time compared to the group without mifepristone.[7] Nilas et al. compared cohorts of women using a 1- or 2-day interval between mifepristone and vaginal misoprostol at 17-22 weeks.

The women in the 1 day group had longer induction times, 9.8 versus 7.5hrs. ($p<0.1$); 98% of the women in each group delivered within 24hrs. of receiving misoprostol.[8] Increasing gestational age is also correlated with increased induction time when using mifepristone and misoprostol from 12 to 20 weeks. In our study too women with gestational age <16 weeks had a lower (8.5±.8hrs.) IAI as compared to women with gestational age ≥16 weeks (10.52 ±2.87hrs). Nullipara had a longer IAI of 10.6±2.8hrs. as compared to parous women who had an IAI of 9.3±2.6hrs. (Table 2).

Low rates of intervention for placental delivery are also reported for regimens using mifepristone and misoprostol. In a small study that noted the time to placental delivery after mifepristone abortion and buccal misoprostol, only 1(3%) of 32 women required placental removal.[7]

CONCLUSION

Mifepristone followed by repeated doses of misoprostol is an effective regimen available for second trimester abortion and has added advantage of being low cost, easily administrable, easily stored and has minimal side effects. Abortion of intact fetus and placenta is of help for fetal evaluation in case of fetal malformations. Further large randomized studies are needed on the need to evaluate the treatment of women with failed medical abortion after 24hrs. and the use of the above 2 effective drugs in women with a scarred uterus.

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Variable	Mifepristone+Misoprostol [N=50]
Age: Mean in Years	25.88±6.5 years
Minimum	13 years
Maximum	37 years
Gravidity: Mean	2.16±1.04
Minimum	1
Maximum	4
Parity: Mean	0.96±0.95
Minimum	0
Maximum	3
Gestational Age: Mean	17.52±2.02
Minimum	14
Maximum	20

Table 1: Demographic variables of the study population

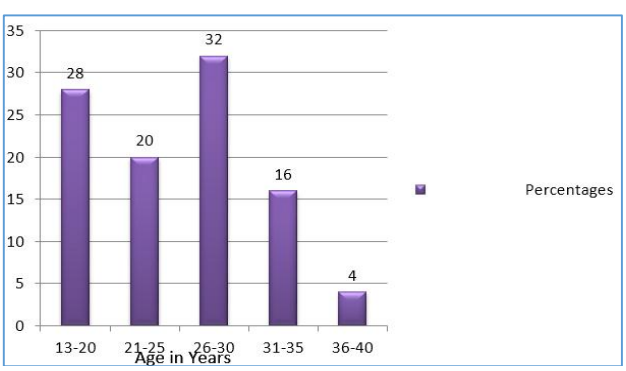

Fig. 1: Age of Clients Requesting Abortion

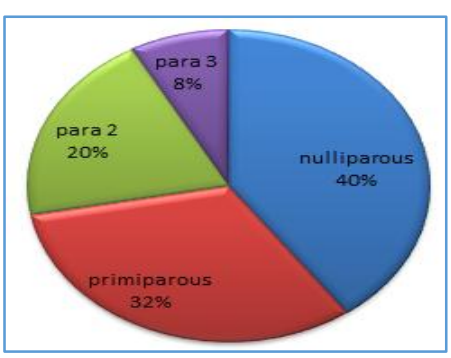

Fig. 2: Parity Status of Clients requesting Abortion

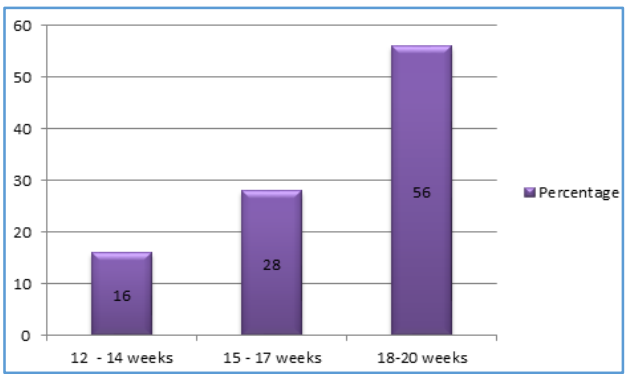

Fig. 3: Gestational Age at which Clients Requested Abortion

Variable	Induction to abortion interval
Parity Nullipara	10.6±2.8 hrs
Parous	9.3±2.6 hrs
Pregnancy Duration < 16 weeks	8.5±1.8 hrs
≥16 weeks	10.52±2.87 hrs

Table 2: Induction to abortion interval by parity and pregnancy duration

Sl. No	I.A.I duration in hours	N = 50
1.	0-5 hrs	0
2.	6-10 hrs	28 (56%)
3.	11-15 hrs	22 (44%)
Minimum	6 hrs	
Maximum	15 hrs	

Table 3: Distribution of cases according to the induction abortion interval

Variable	N = 50
Successful complete abortions within 24 hrs without additional intervention.	48(96%)
Surgical evacuation(incomplete abortion)	2 (4%)
Induction to abortion interval (in hrs)	10.08 ± 2.9 hrs
Complete abortion within ≤ 12 hrs	38 (76%)
No of Misoprostol doses Mean	1.96 ± 0.77
1-2 doses	36
3-5 doses	14

Table 4: Outcome Measures