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Comparative study of mifepristone plus misoprostol and misoprostol alone for second trimester termination of pregnancy

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Abstract
Background: With the introduction of newer prostaglandins, prostaglandin analogues and anti-progesterone agent Mifepristone the outcome of early 1st trimester terminations has become more safe and effective. The objective of this study was to compare between mifepristone plus misoprostol regimen and misoprostol alone regimen for second trimester termination of pregnancy.
Methods: A tertiary hospital based prospective clinical trial of 110 pregnant women between 18-45 years of age in their second trimester (13 – 20 weeks) was included in the study. After informed written consent patient enrolled was randomly allocated into two groups of 55 each. Group I where mifepristone 200 mg oral given to 55 patients on admission and after 24 hours in these cases 600mcg of misoprostol inserted vaginally and thereafter 400 mcg every 3 hr until the abortion will occur or upto a maximum 5 doses. Group II – where misoprostol only in the same schedule will be given to 55 patients.
Results: Mean maternal age ± SD was 25.85 ± 4.32 years. Commonest indication for second trimester termination was intrauterine death (50.9%) followed by gross congenital malformation incompatible with life (37.3%): anencephaly was commonest anomaly accounted for 24.45%. Mean induction-abortion (IAI) interval in group I and II was 8.81±5.75 hours & 10.81±3.42 hours respectively, which is statistically significant (p=0.02).
Conclusion: Combination of Mifepristone with Misoprostol for second trimester termination of pregnancy decreases induction-abortion interval significantly as compared to Misoprostol given alone.

Keywords: Mifepristone, misoprostol, second trimester pregnancy, termination of pregnancy

Introduction

Abortion is defined as termination of pregnancy before fetal viability. National Centre for Health Statistics, the Centres for Disease Control and Prevention (CDC) and World Health Organization (WHO) all define abortion as pregnancy termination before 20 weeks' gestation or with a fetus born weighing less than 500gm [1]. Around 25 million unsafe abortions were estimated to have taken place worldwide each almost all in developing countries [2]. In most developing countries complication related to unsafe abortion cause the majority of maternal death & WHO estimates that each year between 4.7% - 13.2% of maternal deaths can be attributed to unsafe abortion [3]. The Medical Termination of Pregnancy (MTP) act of 1971 was introduced to counter the high incidence of illegal abortions taking place in India [4]. According to the Family Welfare Statistics, in 2009 India recorded 7.25 lacs MTPs in 2005, 7.2 lacs in 2006 and 6.82 lacs in 2007 [5]. The majority of the terminations take place in the first trimester. Worldwide second trimester abortion constitute 10-15% of all induced abortion but is responsible for two third of all major complications [6]. The prevalence of second trimester termination of pregnancy is increasing 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 and determination of the sex linked genetic, metabolic disorders [7]. Being more time taking, difficult & related with high complication rate, various surgical and medical methods have been tried for the second trimester MTP with varying success and induction abortion interval. With the introduction of newer prostaglandins and later prostaglandin analogues, the efficacy of medical abortion is improved and risk for complications and side effects has much reduced. Introduction of ant progesterone agent Mifepristone in 1980, further improved the outcome of early 1st trimester terminations safer, effective without admission and instrumentation [8].

Misoprostol, a newer synthetic prostaglandin E_1 has proven its efficacy as an abortifacient for second trimester MTP since 1987 [9]. Treatment with mifepristone softens the cervix, increases the sensitivity to prostaglandins and convert the quiet pregnant uterus into an organ of spontaneous activity. Therefore, if mifepristone is given prior to induction with misoprostol, then there is disruption of pregnancy causing decidual necrosis, myometrial contractions, and cervical softening resulting in earlier and complete second trimester abortion.

This study was planned to compare the efficacy of Misoprostol alone with combination of Mifepristone and Misoprostol in second trimester termination of pregnancy, to observe the course and outcome of abortion using the above protocol and to study any side effects of the above regimen.

So the aim of our study was to assess the efficacy and safety of Misoprostol alone and combination of Mifepristone with Misoprostol regimen for second trimester termination of pregnancy individually and to evaluate mean induction - abortion interval with Mifepristone plus Misoprostol regimen & Misoprostol alone and to assess of side effects of the dosage of drugs used in two regimens for second trimester abortion.

Method

The present study was conducted in the Department of Obstetrics & Gynaecology, U.P. University of Medical Sciences, Saifai, Etawah, over the period of 18 months from January 2016 – July 2017. The criteria for 2nd trimester MTP was considered as per the Medical Termination of Pregnancy Act, 1971 amendment 2002. The opinion of two consulting gynaecologists regarding reasons for MTP between 12-20 weeks was taken and necessary documentation was followed.

This was hospital based prospective clinical trial.110 pregnant women between 18-45 years of age in their second trimester (13 – 20 weeks) admitted to labour ward of U.P. University of Medical Sciences, Saifai, Etawah or referred from the other peripheral centres requiring termination of pregnancy for medical and obstetrical reasons was included in the study.

Inclusion Criteria

1. Cases with gestational age between 13-20 weeks of pregnancy diagnosed with fetal structural anomalies, chromosomal anomalies, genetic syndromes incompatible with life.
2. Conditions in which fetus upto 20 weeks has high risk of acquiring birth defects as radiation exposure, congenital viral infection, hydrops, severe growth restriction detected between 13-20 weeks.
3. Women with cardiac disease (NYHA class - 3 or class - 4) with history of decompensation in previous pregnancy or in between the pregnancies, cervical or breast malignancy, chronic glomerulonephritis, diabetes mellitus with progressive retinopathy or any other severe and morbid maternal conditions which may be life threatening with advancing pregnancy were included.

Exclusion Criteria

1. Women with placenta previa, chorioamnionitis, multiple gestation, Coagulation disorder
2. Women with inevitable or incomplete abortion cases.
3. Contraindication to prostaglandins as bronchial asthma, severe cardiac & renal disease, liver disease.
4. Known congenital reproductive tract malformations as unicornuate, bicornuate or uterine didelphys etc.
5. Previously failed MTP with drugs.
6. Previously scarred uterus (previous LSCS, Myomectomy, Hysterotomy)

All the enrolled women were informed of their situations, its consequences and reason to require termination of pregnancy. Women enrolled were randomly allocated into two groups by alternate method. Every alternate cases kept in Group1 & remainder in Group2. Both groups included 55 cases each.

Group 1: Mifepristone plus misoprostol-Single tablet Mifepristone of 200 mg per orally given to group 1 allocated cases which was followed by 600 mcg of Misoprostol inserted intravaginally in posterior fornix after making it wet after 24 hours of Mifepristone. Misoprostol 400 mcg was repeated every 3 hourly till abortion or maximum 5 doses whichever occur earlier.

Group 2: Misoprostol alone-Women allocated to this group received tablet Misoprostol alone intravaginally in posterior fornix 600 mcg (3 tablets of 200 mcg each available to market) followed by 400 mcg (2 tablets) every 3 hourly to maximum of 5 doses or full expulsion, whichever earlier.

Statistical analysis – Chi square test was used to compare the categorical variables between the groups. The unpaired t-test was used to compare the continuous variables between the groups.

Results and Observations

Table 1: Distribution of cases according to their Age in two study groups

Age in years	Group-1(n=55)		Group-2 (n=55)		Total		p-value
	No.	%	No.	%	No.	%	
18-25	21	38.2	23	41.8	44	40	0.49
25-30	29	52.7	30	54.5	59	53.63	
>30	5	9.1	2	3.6	7	6.36	
Mean ± SD	22.20 ± 1.56		27.20 ± 1.94		25.85 ± 4.32		

Chi-square test =1.39

The mean age of patients of Group-1 and Group-2 was 22.20 ± 1.56 and 27.20 ± 1.94 years respectively. There was no significant (p>0.05) difference in the age between the groups showing the comparability of the groups in terms of age. Maximum cases enrolled in both groups were between 25-30 years of age. Mean age of overall study is 25.85 ± 4.32 years.

Table 2: Comparison of indications for abortion between the groups

Indications for abortion	Group-1 (n=55)		Group-2 (n=55)		Total cases	
	No.	%	No.	%	No.	%
Anencephaly	15	27.27	13	23.63	19	25.45
Arnold chiari malformation	1	1.8	0	0.0	1	0.9
Encephalocele	0	0.0	1	1.8	1	0.9
Glioma	0	0.0	1	1.8	1	0.9
Holoprosencephaly	1	1.8	0	0.0	1	0.9
Hydrocephalus	2	3.6	5	9.09	7	6.36
IUD (In utero death)	26	47.3	30	54.5	56	50.9
Nil Liqor	4	7.3	4	7.3	8	7.3
Severe oligohydramnios	4	7.3	1	1.8	5	4.5
Spina bifida	2	3.6	0	0.0	2	1.8

IUD was the most common indication for abortion (54.5%) followed by anencephaly(24.45%), nil liqor (7.3%), severe oligo (4.5%), hydrocephalus(6.36%), spina bifida (1.8%), Arnold chiari malformation (0.9%), encephalocele (0.9%), glioma (0.9%), holoprosencephay (0.9%).

Table 3: Comparison of Induction-abortion interval between the groups

Induction abortion interval in hours	Group-1 (n=55)		Group-2 (n=55)		p-value
	No.	%	No.	%	
≤6	23	41.81	4	7.27	0.0001
7-12	24	43.63	43	78.18	
13-18	4	7.27	7	12.7	
19-24	3	5.45	0	0.0	
>24	1	1.8	1	1.8	

Chi-square = 22.6

In less than 6 hours expulsion occurred in 41.8% of patients of Group-1, while only in 7.27% in Group-2. In 7-12 hours, 43.6% expelled in Group-1, while 78.18% in Group-2. The difference was found to be significant in Group-1 & Group-2 regarding induction - abortion interval (p<0.05), means if mifepristone is given with misoprostol then there is significant decrease in induction – abortion interval.

Table 4: Comparison of mean induction- abortion interval

Groups	Time in hours (Mean ± SD)
Group-1	8.81 ± 5.75
Group-2	10.81 ± 3.42
p-value	0.02

[1]Unpaired t-test (t = 2.31)

The abortion interval was found to be significantly (p=0.02) short in Group-1 (8.81 ± 5.75) compared to Group-2 (10.81 ± 3.42), means addition of Mifepristone to Misoprostol for termination of second trimester pregnancy significantly decreases induction - abortion interval which is calculated from 1st dose of Misoprostol.

Table 5: Comparison of average dose of Misoprostol required between two groups

Groups	Dose in mcg (Mean ± SD)
Group-1	1238.46 ± 382.02
Group-2	1644.44 ± 383.95
p-value[1]	0.0001

Unpaired t-test (t = 8.36)

The average dose of Misoprostol required was found to be significantly (p=0.0001) lower in Group-1 (1238.46 ± 382.02 mcg) compared to Group-2 (1644.44 ± 383.95 mcg).

Table 6: Comparison of different side effects between the groups

Side effects	Group-1 (n=55)		Group-2 (n=55)		p-value
	No.	%	No.	%	
Diarrohea	3	5.5	3	5.5	0.32
Fever	7	12.7	14	25.5	
Nausea	1	1.8	0	0.0	
Vomiting	1	1.8	0	0.0	
None	43	78.2	38	69.1	

Chi-square = 1.26

Fever was the most common side effect in both Group-1 (12.7%) and Group-2 (25.5%). There was no statistically significant difference (p>0.05) found in frequency & severity of side effect between two study groups.

Discussion

In this study efficacy & safety of mifepristone plus misoprostol was compared with misoprostol aolne for second trimester termination of pregnanacy. Maximum cases in both groups were in between 25-30 years. Most common indication for second trimester termination was IUD and it accounted for 50.9% of total cases. Second most common indication was gross congenital malformation incompatible with life (37.3%), like anencephaly, hydrocephalus, spina bifida, encephalocele, Arnold chiari malformation, holoprosencephaly, glioma, most common of which was anencephaly which accounted for 24.45%. Other indications was severe oligohydramnios & absent liquor. In a study done by Kaur *et al.* [10] between January 2012- June 2015 indications for midtrimester MTP was 47.9% neural tube defects, 14.5% renal malformation, 18.7% IUD & 12.5% unwanted pregnancy. Incidence of termination of pregnancy in early second trimester was higher than late second trimester. Period of gestation in maximum patients was between 13-20 weeks. In a recent study done by Hoopman *et al.* [11] in 2014, mean gestational age was 18.7 weeks of pregnancy. In a similar study done by Kulkarni [12] 2014, mean period of gestation was between 16 and 17 weeks of pregnancy. Mean induction-abortion (IAI) interval group1 and 2 was 8.81 ± 5.75 hours & 10.81 ± 3.42 hours respectively, which is statistically significant (p=0.02). This is suggestive of that when Mifepristone is given with Misoprostol for second trimester termination of Misoprostol is given alone. In a comparative study done by Akkenapally [13] in 2016, mean induction abortion interval in mifepristone plus misoprostol group was 6.19 hours compared to misoprostol only group which was 10.67 hours (p<0.01). in a randomized double blind trial done by Dabash *et al.* [14] in 2015, mean time to complete abortion was 10.4 hours in group who received mifepristone versus 20.6 hours in misoprostol alone group (p<0.001). Mean dose of Misoprostol required was 1238.46 ± 382.02 mcg & 1644.44 ± 383.95 mcg in Group-1& Group-2 respectively, which is highly significant (p=0.0001), means addition of Mifepristone decreases total required dose of Misoprostol for second trimester termination significantly. In a comparative study done by Akkenapally in 2016, mean dose of misoprostol required was 1046mcg when given with mifepristone, & 1610 mcg when given all alone. In a prospective study done by Kulkarni in 2014, average dose of misoprostol in study group was 600 mcg, whereas in control group it was 1600 mcg of misoprostol. Side effects were absent in 78.2% and 69.1% of patients in Group-1and Group-2 respectively which is not statistically significant (p = 0.27), means both regimens are safe. Fever was the most common side effect in both groups (12.7% in Group-1 & 25.5% in Group-2). Others were diarrhoea, nausea and vomiting.

Conclusion

In our study we conclude that for second trimester termination of pregnancy, addition of mifepristone 24 hrs prior to misoprostol increased the efficacy of this regimen & it decreases Induction-abortion interval as well as total dose of misoprostol required also decreases. Both regimens had minimal side effects, in which fever was the most common. So we prefer to give mifepristone prior to misoprostol for second trimester termination of pregnancy.

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