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EFFICACY OF MIFEPRISTONE FOLLOWED BY MISOPROSTOL VERSUS MISOPROSTOL ALONE IN MEDICAL MANAGEMENT OF EARLY PREGNANCY FAILURE

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ABSTRACT Purpose of the study- To study the efficacy of mifepristone followed by misoprostol over misoprostol alone in early pregnancy failure in terms of complete evacuation of uterus.

METHODS: In a randomized comparative study at the Department of Obstetrics and Gynaecology of Kasturba Hospital, 100 women with early pregnancy failure and gestational age ≤12 weeks between January 2017 and December 2017 were recruited. Of these, 50 women were given a single oral dose of mifepristone (200 mg) followed by 800 mcg misoprostol vaginally (if required) after 24 hours and the other 50 women were treated with 800 mcg misoprostol vaginally alone.

RESULTS: Complete evacuation of uterus was achieved in 96% women treated with a sequential combination of mifepristone and misoprostol versus 84% women treated with misoprostol alone. The difference in the rate of complete expulsion was 12% ($p < 0.05$, 95% CI). Also, pre-treatment with mifepristone resulted in statistically significant reduction in induction to abortion interval (2.40 ± 1.774 vs 3.30 ± 1.951 hr), amount of bleeding (402.2 ± 111.84 vs 535.0 ± 114.84 ml) and duration of bleeding (10.7 ± 2.30 vs 12.4 ± 3.38 days).

CONCLUSION Medical treatment of early pregnancy failure with a sequential combination of mifepristone and misoprostol was more effective than misoprostol alone. Hence, women with early pregnancy failure may be offered mifepristone pre-treatment before misoprostol to increase the chance of successful management, while reducing the need for surgery.

KEYWORDS : Early pregnancy failure. Mifepristone. Misoprostol. Induction to abortion interval.

INTRODUCTION

Early pregnancy failure (EPF) is a common complication of pregnancy, as 10 to 20% of all clinically recognized pregnancies will end in EPF.[1]

For many years surgical evacuation was the standard treatment as it is associated with complete evacuation rates of 93–98%. However, surgical evacuation is associated with high costs and carries risk of complications such as pelvic infection, cervical injury, uterine perforation, excessive bleeding, intrauterine adhesions, cervical insufficiency and increased spontaneous preterm birth rates in subsequent pregnancies.[2] Medical management has been a welcome alternative and has high degree of patient acceptance without increasing the risk of infection. Therefore, the potential of successful medical management of EPF is of utmost importance[1] and needs to be explored. Non-operative management may also help to minimize the psychological burden for the affected woman.

Mifepristone is an anti-progesterone and anti-glucocorticoid drug that primes the myometrium before prostaglandin exposure[3] and is registered for induction of abortion in viable pregnancies up to a gestational age of 63 days.[1] Several studies examined the combination of mifepristone and misoprostol in cases of EPF finding it an effective and safe alternative to surgical treatment or even misoprostol alone with success rates ranging between 65.5% and 93%. On the other hand, some studies have shown that mifepristone does not improve the rate of successful tissue expulsion, while increasing the risk of heavy bleeding. Therefore, conflicting findings about value of mifepristone in EPF needs to be resolved by additional studies.[1]

Hence in the present study we aim to conduct a prospective study to compare expulsion rates with a combination of mifepristone and misoprostol versus misoprostol alone in women with EPF.

Methods And Materials

A randomized comparative study was conducted on 100 women in the department of obstetrics and gynaecology of Kasturba hospital from January 2017 to December 2017. The present study was approved by the institutional ethics committee.

100 women aged 18 to 45 years with EPF and gestational age ≤12 weeks were included in the study. EPF was defined by one of the following ultrasound criteria-

a. Evidence of foetal demise (no foetal cardiac activity despite recognizable embryo and dates consistent with the likelihood of visible pregnancy)
b. Empty gestational sac with a blighted ovum (an absent foetal pole within a gestation sac of >25mm diameter).[4]

Exclusion criteria included (1) Hb<8gm%; (2) inevitable miscarriage i.e. products of conception passing through the cervical os; (3) Incomplete miscarriage which is defined as retained products of conception after expulsion of an intrauterine pregnancy; (4) History of previous caesarean section; (5) Active bleeding at enrolment; (6) Contraindication to mifepristone such as chronic corticosteroid administration; (7) Contraindication to misoprostol such as glaucoma, mitral stenosis, sickle cell anaemia, poorly controlled seizure disorder; (8) Allergies to mifepristone or misoprostol; (9) Presence of trophoblastic disease; (10) Known or suspected extrauterine pregnancy or pelvic infection; (11) Known clotting defect or receiving anticoagulants; (12) Cardiovascular disease or any serious medical condition; (13) Pregnancy with an intrauterine device in situ.

Following admission, informed consent was obtained from all individual participants included in the study and women were randomly assigned into Group A and Group B. Women in Group A were given a single oral dose of 200 mg of mifepristone. They were watched for 24 hrs for expulsion of products of conception. If expulsion of products of conception did not take place with mifepristone alone, misoprostol 800 mcg was given vaginally. Women in Group B were given a single dose of misoprostol 800 mcg vaginally. If products of conception did not pass in either group, a further two doses of

400 mcg each of misoprostol was administered vaginally at 4 hourly intervals. If products of conception were expelled and appeared to be complete, the women were observed for further twenty-four hours before sending home. Patients who failed to pass products of conception were offered a choice of either repeat medical management or surgical evacuation. Surgical evacuation was carried out in women of either group who returned with retained products of conception (>20cc) on USG after 15 days.

The primary outcome parameter was complete expulsion, defined as asymptomatic women after clinical signs of a complete miscarriage, or an empty uterine cavity seen on ultrasound. Secondary outcome parameter observed was induction-expulsion interval (in hours) after first dose of misoprostol or if expelled with mifepristone alone.

Statistical analysis

Statistical analysis was performed by the SPSS program for Windows, version 17.0 (SPSS, Chicago, Illinois). Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Continuous variables were compared using the unpaired t test and categorical variables were analysed using either the chi square test or Fisher's exact test (as appropriate).

For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

RESULTS

A total of 100 women were recruited for the present randomized comparative study. While 50 women received mifepristone 200 mg orally followed by misoprostol 800 mcg vaginally (Group A), the other 50 women received misoprostol 800 mcg vaginally (Group B). There was no loss to follow-up. Analysis of the demographic characteristics of the two cohorts showed no significant difference with respect to age, parity, religion, BMI, consanguity, previous miscarriages, previous missed abortions, period of gestation and type of pregnancy (Table 1).

Table 1- Baseline Characterstics

	Mifepristone and misoprostol (Group A)	Misoprostol (Group B)	P value
Age (years), mean ± SD	26.1 ± 4.87	27.3 ±5.40	0.271
Parity			
Nulli	20 (40%)	18 (36%)	0.680
Multi	30 (60%)	32 (64%)	
Religion			
Hindu	10 (20%)	11 (22%)	0.806
Muslim	40 (80%)	39 (78%)	
BMI			
<18.50 (underweight)	6 (12%)	5 (10%)	0.442
18.50-24.99 (normal)	33 (66%)	28 (56%)	
25-29.99 (overweight)	10 (20%)	13 (26%)	
≥30 (obese)	1 (2%)	4 (8%)	
Consanguity	23 (46%)	21 (42%)	0.687
Previous miscarriages	29 (58%)	26 (52%)	0.546
Period of gestation			
≤7wk	12 (24%)	8 (16%)	0.603
7w1d-9wk	14 (28%)	16 (32%)	
9w1d-12wk	24 (48%)	26 (52%)	
Type of pregnancy			
Missed	35 (70%)	37 (74%)	0.656
Anembryonic	15 (30%)	13 (26%)	
Previous missed abortions	24 (48%)	29 (58%)	0.313

A statistically significant difference was observed in the analysis of primary outcome. Complete evacuation of uterus was observed in 48 patients in Group A and 42 patients in Group B (Table 2). The difference in the rate of expulsion was 12% (p value < 0.05). Mifepristone alone induced expulsion of products of conception in 4% (2 women) in Group A.

Table 2. Primary Outcome Of Medical Management

Outcomes	Mifepristone and misoprostol (Group A)	Misoprostol (Group B)	P value
Complete evacuation of uterus	48 (96%)	42 (84%)	0.046
Number of additional doses of misoprostol required			
0	46 (92%)	26 (52%)	<0.001
1	0 (0%)	6 (12%)	
2	4 (8%)	18 (36%)	
Surgical intervention after failed medical management	2 (4%)	8 (16%)	<0.001

Fewer additional doses of misoprostol were required in Group A (8%) as compared to 48% women in Group B (p value <0.001). All the 10 women (2 in Group A and 8 in Group B) who needed surgical intervention, had presented after 15 days with bleeding with bulky uterus clinically and ultrasound report showing significant retained products of conception (>20cc). These women chose surgical evacuation over repeat medical management.

Induction to abortion interval was calculated from the first dose of misoprostol till the expulsion of initial products of conception. Two women in Group A expelled products of conception after mifepristone, one after 8 hours and the other after 11 hours of mifepristone administration. Hence, 48 women were evaluated for calculating induction to abortion interval in Group A. Table 3 depicts the mean induction to abortion interval after first dose of misoprostol which was 2.40 ± 1.774 hr and 3.30 ± 1.951 hr in Group A (n=48) and Group B (n=50) respectively and it was found to be statistically significant (p value <0.05). Amount of bleeding was calculated by subtracting the weight of dry pads from soaked pads. Average amount of bleeding in Group A was 402.2 ± 111.84 ml which was significantly less than the amount of bleeding in Group B which was 535.0 ± 114.84 ml (p value <0.001). Also, the average duration of bleeding per vaginum in Group A was 10.7 ± 2.30 days while in Group B was 12.4 ± 3.38 days (p value=0.003).

Table 3. Secondary Outcomes Of Medical Management

Outcomes	**Mifepristone and misoprostol (Group A) n= 48**	**Misoprostol (Group B) n= 50**	**P value**
Induction to abortion interval (in hours)	2.40 ± 1.774	3.30 ± 1.951	0.018
Average amount of bleeding (ml)	402.2 ± 111.84	535.0 ± 114.84	<0.001
Duration of bleeding (days)	10.7 ± 2.30	12.4 ± 3.38	0.003

DISCUSSION

Miscarriage is common but nonetheless a very emotional experience for women. Providing women with effective choices allows them to regain a sense of control. Medical management has gained popularity progressively over the past two decades; however, much of the initial data used to develop protocols have been extrapolated from studies investigating pregnancy termination.[5] Also, unfortunately, the small number of studies available had limitations due to study design, small sample size and heterogeneous inclusion criteria. Therefore, large prospective multicentre double blinded randomized trials are the need of the hour.[1]

Complete evacuation of uterus in our study was significantly higher in women who received mifepristone followed by misoprostol compared to those who received misoprostol only. Furthermore, fewer incidences of surgical management to complete miscarriage were reported in the mifepristone plus misoprostol group compared with the misoprostol alone group. Among the 50 women in Group A (mifepristone and misoprostol), the success rate was 96%. This success rate is near the range of several studies that examined the combination of mifepristone and misoprostol in cases of EPF, with success rates ranging between 65.5% and 93%. Dunford et al (2017) found that the expulsion rate of missed miscarriage was significantly different between the two groups; 73% of women in the mifepristone and misoprostol group required no further treatment compared to only 52% of women in the misoprostol only group ($P = 0.003$).[5] Sinha et al (2018) showed that pre-treatment of misoprostol with mifepristone significantly increased the complete abortion rate compared to misoprostol alone (86.7 vs.57.8%, $p = 0.009$).[6] Chu et al in 2020 revealed that 59 (17%) of 348 women in the mifepristone plus misoprostol group did not pass the gestational sac spontaneously within 7 days, which was significantly lower than the 82 (24%) of 348 women in the placebo plus misoprostol group.[3]

Some studies however have a lower success rate. The dissimilarity of these reports may be due to differences in patient selection, treatment regimen and outcome measures used to define success. Joyce van den Berg et al in 2014 found that complete expulsion was achieved in 66.8% of the women treated with a sequential combination of mifepristone and misoprostol compared to 54.9% of the women treated with misoprostol alone.[1] The difference in rates of complete expulsion was 11.9% ($P < 0.05$). In their centre, clinicians used a maximum endometrial lining of 15 mm with absence of vaginal bleeding to diagnose complete miscarriage one week after treatment. This may have led to a lower success rate of treatment compared to other studies using less stringent criteria for complete miscarriage. Joyce van den Berg et al in 2015 reviewed the available literature on the added value of mifepristone to current non-surgical treatment regimens in women with EPF.[2] This systematic review revealed success rates of sequential treatment with mifepristone and misoprostol to be varied between 52% and 95%. The reason for large variation could be heterogeneity in treatment protocols, inclusion criteria and definition of successful treatment.

We also found that the mean induction to abortion interval in Group A was significantly lower than Group B. This is in keeping with the findings of Sinha et al (2018) who observed the induction to abortion interval to be significantly lower in the combined mifepristone and misoprostol group compared to misoprostol only group (4.74 ± 2.24 vs. 8.03 ± 2.77 h, $p=0.000$).[6]

The strengths of this study include it's randomised approach, controlled design with high adherence to treatment, enhancing internal validity and consistent use of similar mode of administration of misoprostol (vaginally) in both the groups. However, some limitations of the study should also be considered. We studied the effect of study drugs in missed miscarriage, and therefore, the results are not generalisable to patients diagnosed with incomplete miscarriage where some pregnancy tissue has already been passed.

CONCLUSION

The data from this study has shown that the combination of mifepristone and misoprostol is more successful in the management of early pregnancy failure than misoprostol alone. Also, pre-treatment with mifepristone has significantly reduced induction to abortion interval, number of additional doses of misoprostol required, average blood loss and duration of blood loss.

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