



THE EFFECTIVENESS OF MIFEPRISTONE AND MISOPROSTOL COMBINATION VS MISOPROSTOL ALONE AMONG PATIENTS WITH MISSED MISCARRIAGE IN FIRST TRIMESTER

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ABSTRACT

Background- Early pregnancy failure is a common cause for women to approach the Gynaecologist. It could be treated medical or surgically. Non-surgical option has the potential for better acceptance and lesser agony for the woman and family. This study aims to compare the clinical outcomes of 2 popular regimens of medical management and its cost-effectiveness. **Study design-** This prospective observational study enrolled 100 women with gestational age below 13 weeks from september 2023 for 7 months at SUTAMS Trivandrum, Kerala. Eligible women received either (1) mifepristone 200mcg orally followed by 4 doses of 400 mcg misoprostol 48 hours later or (2) 2 doses of 800 mcg misoprostol alone. They were followed up with ultrasonography after 2 weeks for completion. **Results-** Among the 100 women who received misoprostol alone 35(70%) and mifepristone and misoprostol 38(76%) were noted to have complete expulsion, showing that both the groups have comparable good outcome. The secondary outcomes were to look for the need of increased dose, need for surgical intervention. Among the day care subjects we could find that 26.2% in the misoprostol alone group and 5% in the mifepristone with misoprostol group needed an increase in dose, which was statistically significant. The other outcome to look for was the need for surgical intervention. Out of the total population 16% in the misoprostol group and 12 % in the mifepristone with misoprostol group required a surgical intervention. **Conclusion-** Our study showed that both regimens had comparable efficacy, acceptability and side effects. Whenever there is availability and affordability pre-treatment with mifepristone should be considered. Misoprostol alone regimen has the advantage of low cost, long shelf life, lack of need for refrigeration, easy availability, hence may be used in low- income settings and when mifepristone is contraindicated even at primary care level.

KEYWORDS : Medical abortion, Mifepristone, Misoprostol, Missed miscarriage, Early pregnancy failure.

INTRODUCTION

First trimester pregnancy failure is one of the most common complications of pregnancy with incidence as high as 50% of conceptions. Miscarriage is of different types; of which missed miscarriage is our subject of interest as it is a nonviable intrauterine pregnancy that has been retained within the uterus without any symptoms besides amenorrhoea and is found out during routine ultrasound examination when a foetal heart beat is not observed.

The treatment for missed miscarriage could be expectant management, medical or surgical management. After the diagnosis of pregnancy failure, surgical evacuation is still commonly performed worldwide.¹ In recent years, there has been wide acceptance of medical termination of pregnancy using a combination of mifepristone and misoprostol as approved by Food and Drug Administration. This drug regimen was consistently shown to be associated with high success rates of 90%-95%. However, medical treatment of pregnancy failure (missed miscarriage) has not yet gained wide acceptance².

Various drug protocols have been studied. The recent guidelines worldwide including the federation of obstetrics and gynaecology, national institute of central excellence and world health organisation recommends the use of combination regimen when available or the misoprostol only regimen. In india most clinicians follow the combination regime or surgical management.

Mifepristone is an expensive drug than misoprostol and is a large part of the cost of medical management. In this respect, this study provides an important opportunity to better

understand the real difference in efficacy of the two regimens of medical management, in addition to the costs and benefits of these regimens².

Objectives:

Primary Objective:

To compare the clinical outcomes of mifepristone and misoprostol vs misoprostol 1600mcg alone without needing additional intervention among patients with missed miscarriage.

Secondary Objective:

To assess the proportion needing surgical evacuation or increased doses among the patients with missed miscarriage.

Methodology:

The specific entry criteria were, positive pregnancy test with no fresh bleeding and ultrasound showing no embryonic cardiac activity, the gestational age determined should be less than 13 weeks of gestation by LMP/USS. If the patients fulfilled the entry criteria, she was informed about the study.

The exclusion criteria were, suspicion of ectopic, allergy or contraindications for the drugs, signs of infection. In our hospital we follow two treatment regimens for missed miscarriage.

The Two Treatment Regimens Are:

1. Medical treatment with a single dose of mifepristone 200mg orally on day one as outpatient basis. The patient returned to the gynaecology ward on day 3 and was given misoprostol 400 mcg orally to a total of 4 doses.
2. Medical treatment only with misoprostol 800 mcg orally on

day 1. If no vaginal bleeding occurred within 4 hours, additional dose of misoprostol 800mcg was given.

The patients to each group were allocated according to simple random sampling.

All patients were given pain relief tablet as and when required. Rh anti immunoglobulin was offered to all rh negative women. An USS examination was conducted to look for complete abortion before discharge, which is taken as endometrial thickness less than or equal to 15mm and advised to report if she had fever, severe abdominal pain not relieved with regular analgesics, or any discharge.

All patients were asked to return a questionnaire after 14 days. They were asked about the length of bleeding, spotting, need for analgesics, if they have received any antibiotics for pelvic inflammatory disease.

The main outcome measures were, not requiring surgical evacuation after medical management, need of surgical evacuation after medical treatment, need for stepping up of drug doses.

OBSERVATION AND RESULTS

The patients were assigned into 2 groups- Group 1: Pre-treated with mifepristone followed by misoprostol, Group 2: Misoprostol alone.

There were 10(20%) in 6 to 8 weeks, 17(34%) in 8 to 10 weeks, 23(46%) in 10 to 13 weeks among subjects who received misoprostol alone while 7(14%) in 6 to 8 weeks, 24(48%) in 8 to 10 weeks and 19(38%) in 10 to 13 weeks among subjects who received mifepristone with misoprostol and no statistically significant relation was noted (p value 0.349) between gestational age and treatment groups.

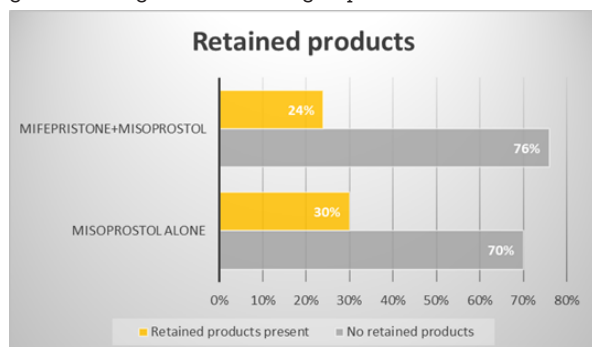


Chart 1- Comparison of retained products after initial medical management among treatment groups

Table 1- Comparison of need for increased dose to treatment groups

Factors	M n=50 n (%)	M+M n=50 n (%)	p value
Not needed increase dose	37(74%)	44(88%)	0.076
Needed increased dose	13(26%)	6(12%)	

Table 2- Comparison of surgical intervention in treatment groups.

Factors	M n=50 n (%)	M+M n=50 n (%)	p value
No surgical intervention	42(84%)	43(86%)	0.779
Needed surgical intervention	8(16%)	7(14%)	

There was no noted significant relation (p value: 0.779) between each group.

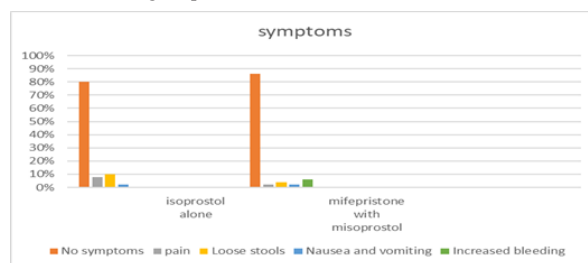


Chart 2- Comparison of symptoms in treatment groups

DISCUSSION

The study was to look for the efficacy of mifepristone with misoprostol vs misoprostol alone as medical management of missed miscarriage in the first trimester up to 13 weeks and was divided as two groups. There was no statistically significant relation noted (p value 0.349) between gestational age and treatment groups in the current study which was corroborated by Schreiber et al⁴2018.

Primary Outcome

After receiving treatment, the study population were subjected to an ultrasound scan, to confirm complete expulsion of products. 35(70%) in Group A and 38(76%) in Group B were noted to have no retained products. There was no statistically significant relation noted (p value: 0.528) among each group.

Similar success rates (74% in women treated with a combination of mifepristone and misoprostol vs. 71% after treatment with misoprostol alone) were reported by Gronlund et al.⁵ Stockheim et al¹ in his study determined success rate as no need for surgical intervention which was 65.5% in misoprostol alone group and 73.6% in mifepristone with misoprostol group. This was not statistically different in contrast to the study by Schreiber et al⁴ in 2018 which had a significant higher rate of complete expulsion of gestational sac in pre-treatment with mifepristone followed by misoprostol (83.8%) than with misoprostol alone (67.1%). Wagaarachchi et al⁶ noted that the overall success rate of medical management was 84.1%.

Mifepristone alone induced natural expulsion of products of conception in 18.1% of women. The median dose of misoprostol required was 1600 microgram.

Secondary Outcome

We analyzed the need for further increase in dose among each group and found that out of the total 19 ; 13(26%) of those in Group A and 6(12%) of Group B required a further increase in dose. There was no statistically significant relation (p value: 0.076) in both groups. Schreiber et al⁴ in his study said that with the increase in dose, complete expulsion occurred in 87.8% in Group B and 71.7% in Group A. Chan et al³ in 2012 noted that 22% had complete expulsion after increasing dose of misoprostol alone. Gronlund et al⁵ noted that additional dose was given to 24% and 59% in mifepristone with misoprostol and misoprostol alone group respectively in contrast to Zala'nyi et al⁷ who found an effect of vaginal misoprostol in doses up to 0.6mg, but no further effect of higher doses.

Analysis was done to look for the need for surgical intervention after medical management. 8(16%) in Group A and 7(14%) in the Group B required a surgical evacuation following failure of medical management. There was no noted significant relation (p value: 0.779) between each group. Schreiber et al⁴ noted that 8.8% in the mifepristone with misoprostol group and 23.5% in the misoprostol alone group needed a surgical

evacuation, in contrast to the study done by Stockheim et al¹ reported that, needed for surgical evacuation was 17.2% and 17.5% in mifepristone with misoprostol and misoprostol alone group respectively. Grounlund et al⁵ in 2012 reported 25.9% and 28.8% needing surgical evacuation in mifepristone with misoprostol and misoprostol alone groups respectively.

Considering side effects due to medical treatment, it was found that 83(83%) of them had no symptoms. The most common side effect was loose stools which is 10% in Group A and 4% in Group B. Other side effects noted were nausea-vomiting which was 2 in each group and increased bleeding among 6% in Group B. There noted to be no significant relation (p value: 0.185) among both groups. Stockheim et al¹ reported that there were no disabling side effects and most being gastrointestinal and thermoregulatory changes. Schreiber et al⁶ in his study reported fatigue, headache and gastrointestinal discomfort as common side effects. Increased bleeding was noted to be 2% and 0.7% in mifepristone with misoprostol and misoprostol alone group respectively.

Limitation Of The Study

From our study we could not find any statistically significant association between treatment groups. This could be due to our small sample size and short period of time. A larger sample size would have increased the precision of the results.

CONCLUSIONS

Our study showed that both regimes had comparable efficacy, acceptability and side effects. Whenever there is availability and affordability pre-treatment with mifepristone should be considered. The mifepristone being a costly drug, its use may not be feasible in low-income settings and thus may add to the burden on health care systems.

Misoprostol being effective in evacuation of the uterus in missed abortion, with the advantage of low cost, long shelf life, lack of need for refrigeration, easy availability and requires no surgery and hence no anaesthesia. Thus, it may be advocated to be used in outpatient setting in the treatment of early pregnancy failure even at the primary care level and in low-income settings.

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