

Missed Abortion-Mifepristone and Misoprostol Versus Misoprostol Management at Kempegowda Institute of Medical Sciences, Bangalore, India

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Abstract

Objective: One of the most confusing aspects of medical treatment of missed abortion is that till now there is no fixed and standard medical regimen suggested. The objective was to investigate the effectiveness of mifepristone/misoprostol regimen versus misoprostol only regimen in treatment of missed abortion at Kempegowda Institute of Medical Sciences, Bangalore, India. **Methods:** A non-interventional prospective study was conducted during a one-year study, 200 women were enrolled, each with a documented missed abortion < 13 weeks of gestation through ultrasound examination. Hundred women were administered 200 mg of oral mifepristone followed by two doses of 400 mcg of misoprostol with a four-hour gap. The rest of the subjects were administered 200 mcg of misoprostol every four hours up to four doses. **Results:** The effectiveness of treatment of missed abortion with mifepristone/misoprostol regimen was 93% while the effectiveness with misoprostol only regimen was 79% ($p=0.004$). **Conclusion:** Treatment of missed abortion with mifepristone/misoprostol regimen is more effective than treatment with misoprostol only regimen.

Keywords: Dilatation and Curettage, Mifepristone, Misoprostol, Missed abortion.

Introduction

In the past decades, the only treatment for miscarriage before 14 weeks was surgery (Neilson and Hickey M, Vazquez, 2006). Except of the anesthesia risk, surgery is associated with many complications (Danielsson et al., 2007). But in recent years, medical management has been introduced which is effective, safe, and acceptable. Hence many different regimens have been studied and used (Royal College of Obstetricians and Gynaecologists, 2004), more or less successfully and it is one of the most confusing aspects of medical treatment of abortion. In fact, more than one regimen may be used at a particular stage of pregnancy. Even World Health Organization has not recommended a standard regimen for administration of misoprostol in treatment of missed abortion (Garipey and Stanwood, 2013).

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The oral anti-progesterone RU 486 (mifepristone) has been used alone or in combination with oral prostaglandins to affect abortions in early gestation (Mohammed, 2003). Mifepristone inhibits the action of progesterone which leads to softening of cervix and shedding of uterine lining (Donaldson et al., 1993). Antiprogesterone alone is not clinically useful for terminating pregnancy because it is not sufficiently effective when being administered alone (Bygdeman et al., 1994). Misoprostol is Prostaglandin E1 analog and its off-label use is termination of pregnancy (Goldberg, Greenberg and Darney, 2001). Misoprostol would facilitate the medical abortion with mifepristone (Mohammed, 2003).

Despite of the studies that have been done there is no fixed standard medical regimen for treatment of missed abortion. Some experts believe that administration of misoprostol alone is effective and sufficient for treatment of missed abortion especially in the early stages of gestation (Adisso et al., 2014; Spitz et al., 1998; Moodliar, Bagratee and Moodley, 2005). But in other hand there are other studies that did not result in high success rate of treatment of missed abortion with misoprostol only regimen (Murchison and Duff, 2004; Betsy and Habeebullah, 2004). Some findings recommended the administration of different regimens of oral mifepristone followed by various routes of misoprostol to be more effective in treatment of missed abortion (Royal College of Obstetricians and Gynaecologists, 2004; Jain et al., 2002; Jyothi and Pallavi, 2006; Creinin, Pymer and Schwartz, 2001). This lack of agreement among the experts justifies further investigations. Mifepristone is expensive and is not available in many countries so finding out an effective regimen without mifepristone can reduce the cost of treatment.

The purpose of this study was to compare the effectiveness of mifepristone/misoprostol regimen versus misoprostol regimen in treatment of missed abortion < 13 weeks of gestation.

Methods:

The study was a non-interventional prospective trial conducted in KIMS hospital, Bangalore from June 2016 to May 2017 after obtaining ETC of the institute. Women who were eligible for the study were thoroughly counseled and informed consent was taken orally.

Patients were recruited for the study based on the Inclusion criteria:

1. Females of age group 18 to 45 years
2. Women with gestational age of < 13 weeks of gestation from last menstrual (LMP)
3. Diagnosis of missed abortion by Ultrasonography (USG)
4. Mild vaginal bleeding or spotting or no bleeding and spotting at all
5. Close cervix on pelvic examination
6. Hemoglobin ≥ 9 gm/dl
7. No history of asthma, liver disease or known allergy to misoprostol
8. Willingness to comply with follow up schedule

Patients with any degree of cervical dilation, BP $\geq 160/90$ mmHg, Signs and symptoms of infection History of any bleeding disorder, known allergy to misoprostol, Twin gestation sac, Molar pregnancy, Refusal of compliance with follow up schedule were excluded from the study.

During a one-year study, 246 patients confirmed by ultra-sonographic examination were selected based on the availability of the cases and out of 246 patients only 200 were enrolled in the trial and the rest were excluded due to not matching with the inclusion criteria. Hundred women were administered 200 mg of oral mifepristone on first day followed by 400 mcg of misoprostol orally or vaginally every four hours up to two doses after three days. If complete abortion did not happen after 12 hrs. of last dose, surgical evacuation was performed. The rest of the subjects were administered 200 mcg of misoprostol orally or vaginally every four hours up to four doses. If complete expulsion did not occur 12 hours after the last dose, surgical evacuation was done.

All patients were monitored for vaginal bleeding and expulsion of uterine content. In case of any expulsion, the products of conception (POC) were examined by the gynecologists. Also a bimanual pelvic examination was performed to determine any retained gestational material. If complete abortion occurred before the completion of all doses, the next doses were not given.

Clinical outcomes had been considered before the initiation of the trial as:

- Effectiveness of trial had been defined as the expulsion of uterine content completely confirmed by ultrasonography without the need for surgery.

- Failure was defined as the need for surgery for completing the course of treatment.

Clinical outcomes were recorded 12 hours after the last dose of misoprostol. Surgical evacuation was done in case of severe pain, infection, heavy vaginal bleeding or failure of complete expulsion of POCs after administration of the last dose of misoprostol.

Subjects were observed for 12 hours after complete abortion and then discharged. All women were then asked to return to hospital 14 days after discharge for examination with USG to make sure that there was no retention of any conception product in the uterine.

The data were presented by mean \pm SD. Statistical significance was determined by Chi-square test or Fisher exact test for complete evacuation. $P < 0.05$ was considered statistically significant. The SPSS 16.0 statistical package was used for analyzing the data.

Results

As illustrated in Table 1, baseline characteristics of both groups in terms of age, parity and period of gestation were comparable.

Table 1: Characteristics of the patients

characteristics	Mifepristone/misoprostol Group (n=100)	misoprostol group (n=100)	P value
Age (years)			
18-27	34 (34%)	29(29%)	P= 0.92
28-37	52 (52%)	51(48%)	
38-45	14 (14%)	20(23%)	
mean \pm SD	33.51 \pm 3.33	32.5 \pm 4.95	
Parity			
1	19 (19%)	25(25%)	P= 0.83
2	24 (24%)	20(20%)	
3	45 (45%)	32(32%)	
4	12 (12%)	23(23%)	
mean \pm SD	2.50 \pm 0.93	2.53 \pm 1.09	
gestation duration (weeks)			
5-6	1(1%)	0(0%)	P=0.25
7-8	32(32%)	23(23%)	
9-10	39(39%)	46(46%)	
11-12	28(28%)	31(31%)	
mean \pm SD	9.34 \pm 1.43	9.58 \pm 1.56	

Values are given as number (percentage) or mean \pm SD unless otherwise indicated

There was a significant difference between mifepristone/misoprostol and misoprostol only regimen in success of treatment ($P=0.004$). (Table 2)

Table 2: Effectiveness of mifepristone/misoprostol and misoprostol only regimen in treatment of missed abortion

	Success	Failure	χ^2 (p value)
Mifepristone/misoprostol	93 (93%)	7 (7%)	8.139 (0.004)
misoprostol	79 (79%)	21 (21%)	

Values are given as number (percentage) unless otherwise indicated

Discussion

The results of the study confirm that a regimen of mifepristone and misoprostol is more effective compared to the regimen of misoprostol alone for treatment of missed abortion less than 13 weeks of gestation. These findings support the conclusions that even a small dose of mifepristone when combined with misoprostol is more effective than administration of multiple doses of misoprostol alone (Creinin MD, Pymer HC, Schwartz, 2001). Abortifacient action of mifepristone was confirmed by a study in which the results showed four successful abortions only after the administration of mifepristone (Jain et al., 2002). Anti-progesterone like RU-486 work by binding to progesterone receptors in the women's uterus and blocking the action of progesterone which is needed for maintaining of the endometrium. The drug opens the cervix and leads to contraction that helps to expel the uterine content (RU-486 The New Abortion Pill: How Safe Is It?, 2017). Treatment with antiprogesterin results in increased uterine contractility and increased sensitivity of myometrium to prostaglandin. Except from activating of the uterus, antiprogesterin causes ripening of the cervix (Bygdeman et al., 1994).

Incomplete miscarriage can be managed with the regimen of misoprostol alone (Henshaw et al., 1993; Chung et al., 1997) but in the presence of an intact sac and closed cervix, administration of misoprostol in combination with the mifepristone makes the regimen more effective (El-Refaey et al., 1992; Hinshaw, 1997).

Although there are some studies that their results do not support our finding regarding the effectiveness of mifepristone together with misoprostol in treatment of missed abortion (Singh et al., 2005; Nielsen, Hahlin and PtetZrChristensen, 1997), the findings of some studies are in line with the results of our study (Jain et al., 2002; Creinin, Pymer and Schwartz, 2001; Henshaw et al., 1993; Ashok et al., 1998; El-Refaey and Templeton, 1994; van den Berg et al., 2014).

Use of misoprostol as a single agent for treatment of missed abortion has its own value in clinical situation (Jain et al., 2002). Because mifepristone is expensive and is not available in many countries so it would be desirable to develop a regimen without it (Grønlund et al., 2002). This reason and the fact that there is not an agreement among the researchers about the superiority of mifepristone/misoprostol regimen over misoprostol alone regimen further investigations should be done.

Many studies have been performed earlier on this, but are few in number to come to any conclusion. The present study with more clear selection criteria and study method tries to lay the platform to carry out further studies.

Limitations of the Study

This study was open label which is one of the limitations of this study. Also misoprostol was prescribed in two different routes (oral and vaginal) which may have effect on the result of the study. Further double-blind studies are needed to be done by considering the route of administration of misoprostol.

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