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Outpatient versus Inpatient Vaginal Misoprostol Administration for the First-trimester Abortion: A Randomized Clinical Trial

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ABSTRACT

Background & aim: Misoprostol is widely used for the first-trimester abortion. This study aimed to assess the success rate and side effects of outpatient versus inpatient vaginal misoprostol administration for the first-trimester abortion.

Methods: A prospective randomized clinical trial included 280 women with first-trimester abortion (≤14 week's gestation) referred to three educational hospitals of Mashhad University of Medical Sciences, Mashhad, Iran in 2019-2020 .Patients were randomly assigned to receive vaginal misoprostol either in an inpatient or outpatients setting Intra-vaginal misoprostol 800-mcg was administered every twenty-four hours up to two doses. Treatment success, the primary outcome, was defined as complete evacuation after one or two doses. Elective curettage was performed if complete evacuation failed after one week, while emergent curettage was considered in cases of heavy vaginal bleeding. To analyse data, SPSS software (version 19.0) and Independent t-test, Chi-square test, and Logistic regression model was used.

Results: Success rates for outpatient and inpatient treatments were 96.6% (114 out of 118) and 91.5%, (119 out of 130), respectively, showing no significant difference (P = 0.167). Additionally, side effects did not significantly differ between inpatient and outpatient groups (P = 0.698).

Conclusion: Vaginal misoprostol (800-mcg every twenty-four hours for a maximum of two doses) in an outpatient setting is as effective as in an inpatient condition with similar side effects. Outpatient medical abortion can be a viable alternative to hospitalization.

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Introduction

Abortion is defined as a clinically recognized pregnancy loss before the 20th week of gestation (1). The World Health Organization (WHO) defines it as expulsion of an embryo or fetus weighing 500 gram or less (2).

Surgery, medication, and expectant management have comparable efficacy for

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uterine evacuation in women with a first trimester abortion. This has been demonstrated in systematic reviews of randomized trials involving women with all types of first-trimester abortion.(3-6). Since misoprostol is easily administered in a variety of routes, cheaper than surgical methods and has fewer side effects, as it is widely used (7). Its safety and efficacy have been established by many studies (8-10). Misoprostol administration can be safely performed by trained non-clinician providers (11). In many countries, outpatient setting is used for treatment of abortion with medication. More satisfaction of patients is reported in outpatient setting due to easier application and lower cost (12).

Diarrhea is the major side effect that has been reported consistently, but it is usually mild and self-limiting. Nausea and vomiting may also occur (13-15). Some side effects of misoprostol include uterine cramping and bleeding during expulsion of the remaining products of conception; however, these side effects are transient and tolerable (16). To manage this, the majority of cases can be treated expectantly or with anti-emetic or anti-diarrheal medication.

In the study by Ng et al., they concluded that medical evacuation using intra-vaginal misoprostol 800 mcg every eight hours for a maximum of three doses in an outpatient group is as effective as in inpatient setting with tolerable side effects (17). However, there are limited researches in this field; therefore, the present study was performed aimed to evaluate the success rate and complications of outpatient versus inpatient vaginal misoprostol prescription for the treatment of first trimester abortion.

Materials and Methods

This prospective randomized clinical trial was performed at three educational hospitals related to Mashhad University of Medical Sciences ،Mashhad, Iran from February 2019 to March 2020. The trial was registered in Iranian Registry of Clinical Trials with code of IRCT20190128042522N1.

Written informed consent was obtained from the patients in our study. The purpose of this research was completely explained to the patient and they were assured that their information will be kept confidential by the researcher.

There was no age limitation in this study. All women with first trimester abortion (≤14 weeks' gestation) were participated in this study. The missed abortion and blighted ovum was previously confirmed by two ultrasounds. Women who fulfilled the inclusion criteria were included in this study. Therapeutic abortion was not included in this study

The inclusion criteria were as follows: Hemodynamically stable, No suspicion of septic abortion (no fever or foul-smelling discharge), No concurrent medical disorders (e.g., cardiovascular, respiratory, renal, hepatic disorders, uncontrolled seizure, coagulopathy), No heavy vaginal bleeding, Hemoglobin ≥10 gr/dl, Absence of Intrauterine device (IUD), No allergy to misoprostol, Easy access to hospital—e.g. transport available, Living with someone not alone. The exclusion criteria were as follows: Patient's decision to discontinue participation in the trial. Refusal to receive a second dose of misoprostol in an outpatient setting. Desire to be discharged from the hospital with informed consent before the end of the treatment period in hospitalized patients Computer generated randomization with 'Research Randomizer' was used to randomize patients to either group A or B. Patients in group A received misoprostol in outpatient setting and patients in group B treated in inpatient setting. Due to the type of the study design and the fact that the patients were placed in two groups of inpatient and outpatient, and the patient was aware that whether she was hospitalized or not, so it was not possible to blind the study.

The sample size was calculated according to the previous study (17) and the confidence of 95% and power of 80%, therefore, 111 was determined in each group. Considering to the possibility of sample loss, the sample size of 140 cases was considered in each group and a total of 280 women entered the study.

Gestational age was determined based on the patients' accurate date of last menstrual period or previous ultrasonography report. All patients received 800-mcg misoprostol every twenty-four hours up to two doses. Acetaminophen was administered as either an analgesic or antipyretic. The aborted product would be

collected in a bottle and sent to the pathology laboratory. The duration of passing out products of conception, side effects, and complications were recorded.

The first dose of misoprostol 800 mcg was vaginally administered at the hospital. The patient was observed for 1 hour for any immediate side effects. Then the patient was sent home and asked to record the time of their expulsion. They were instructed to collect the product of conception to send it over for further pathology analysis. If not repelled, patients were asked to return twenty-four hours later for administration of their second dose of misoprostol. Acetaminophen was prescribed 1 g every eight hours to subside any pain or/fever. A twenty- four-hour contact number of the main researcher was given to patients for any questions regarding their experience.

Both doses of misoprostol 800 mcg were prescribed in the ward twenty- four hours apart. The timing of administration was documented. If the patient did not repel after two doses of intravaginal misoprostol, they were discharged and sent home.

The definition of a successful medical treatment as primary outcome was defined if complete evacuation had occurred within one or two doses of misoprostol. Treatment failure was defined if no product of conception had been passed out and/or an endometrial line ≥20 mm in trans-vaginal ultrasonography on 7 days apart from the second dose of misoprostol, or development of heavy vaginal bleeding before day seven requiring urgent surgical evacuation. It should be noted that a single radiologist performed the patients' ultrasound. Successful expulsion, elective curettage, emergent curettage, nausea, diarrhea and fever as secondary outcomes were assessed. The secondary outcomes were recorded in a checklist by the researcher.

Data were analyzed by SPSS software (version 19.0). Descriptive and demographic data were presented in the form of frequency distribution tables. Independent t-test was used to evaluate the relationship between the quantitative variables in the two groups. In addition, Chi-square test was used to evaluate the relationship between the qualitative variables in the two groups. Logistic regression model was used to control the confounding variables. $P<0.05$ was considered statistically significant.

Results

A total of 280 women were recruited into this trial. Twenty-two patients from the outpatient group and ten patients from the inpatient group had no willingness to complete the trial, so 118 patients from the outpatient group (group A) and 130 patients from the inpatient group (group B) were included in this analysis (Figure 1).

The baseline characteristics of the patients in two study groups were shown in Table 1.

Table 1. Baseline Characteristics of the Study Groups

Variable	Outpatient group N=118	Inpatient group N=130	P-Value
Age (year, M±SD)	28.92±7.09	28.74±5.51	0.826
Gestational age (week, M±SD)	8.14±1.63	8.87±1.87	0.317
Parity (M±SD)	1.50±1.08	1.25±0.87	0.045
	55(46.6)	58(44.6)	0.867
Previous cesarean section, N (%)	43(36.4)	43(33.1)	0.854
Primigravidity N (%)	22(18.6)	26(20.0)	
Smoking N (%)	12(10.2)	22(16.9)	0.123
Blighted Ovum N (%)	58(49.2)	71(54.6)	0.390
Missed Abortion N (%)	60(50.8)	59(45.4)	

Baseline characteristics of the patients were not significantly different between the two outpatient and inpatient groups ($P>0.05$) (Table 1).

The parity difference between the two groups was significant, so the parity effect was modified using logistic regression (Table 2).

The results of logistic regression showed that by adjusting the effect of parity, the chances of spontaneous abortion in the two groups are not significantly different.

Dose number and time to expulsion was compared in two study groups of patients and the results were presented in Table 3.

Side effects of vaginal misoprostol were mostly fever, nausea, vomiting, and diarrhea. There were no statistical significant differences in side effects between the outpatient and inpatient groups (Table 5). In our investigation, there was no documented serious complication like blood transfusion or uterine rupture.

The overall success rate for medical abortion using misoprostol was 93.5 % (Table 4). The success rate for the outpatient group was 96.6% vs 91.5% in an inpatient group. It was not statistically significant (p value=0.167).

Table 2. Comparison of Spontaneous Abortion Rates between Two Groups with Adjustment of the Effect of Parity Using Logistic Regression

Variable	Odds ratio	%95 CI	P-Value
Group 1	2.48	0.764 , 8.54	0.130
Group 2	1Ref	-	-
Number of parity	1.384	0.759 , 2.525	0.289

Table 3. Dose Number and Time to Expulsion in the Study Groups

Variable	Outpatient group N=118	Inpatient group N=130	P-Value*
Interval of drug to expulsion,(hour, M±SD)	22.69±9.88	21.20±11.01	0.26
Dose number, One Dose, N (%)	79(66.9)	90(69.2)	0.70
Dose number, Two Doses, N (%)	39(33.1)	40(30.8)	

*Chi-square test

Table 4. Comparison of Expulsion Outcomes and Curettage Rates in the Study Groups

Variable	Outpatient N=118	Inpatient N=130	P-Value
Successful Expulsion, N (%)	114(96.6)	119(91.5)	0.167
Elective curettage, N (%) (pregnancy residue)	1(0.8)	5(3.8)	
Elective curettage, N (%) (No expulsion)	0(0)	3(2.3)	
Emergent curettage, N (%)	3(2.5)	3(2.3)	
Total, N (%)	118(100)	130(100)	

Table 5. Comparison of Side Effects and Clinical Outcomes Between Two Groups

Variable	Outpatient N=118	Inpatient N=130	P-Value
No side effect, N (%)	5(4.2)	3(2.3)	0.845
Nausea, N (%)	20(16.9)	21(16.2)	
*Diarrhea, N (%)	21(17.8)	23(17.7)	
**Fever, N (%)	72(61.0)	83(63.8)	

* Loose, watery and possible more frequent bowel movements
** Having a temperature above 37.8 sublingually by thermometer

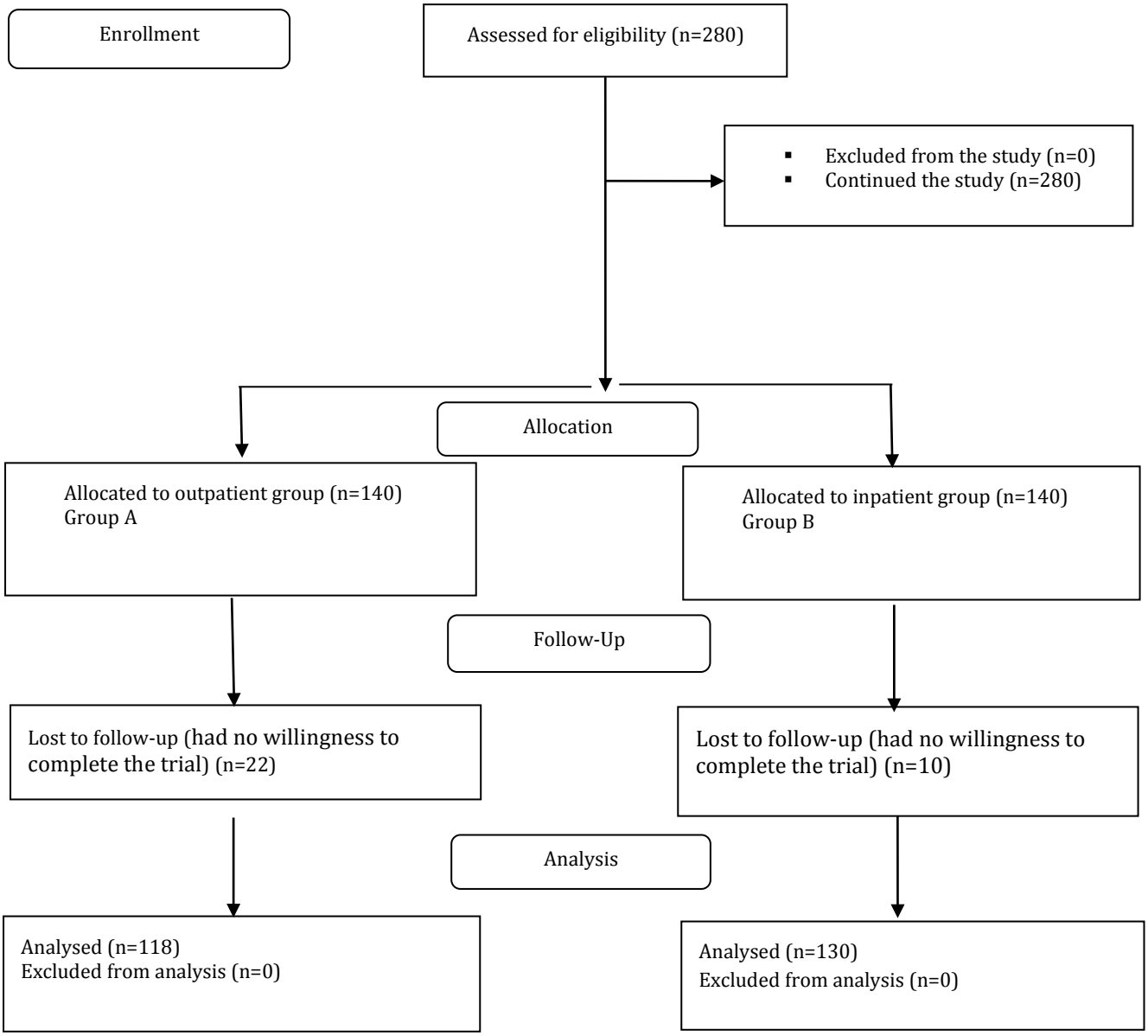

Figure 1. Flow diagram of the study process

Discussion

This study demonstrates that outpatient treatment did not differ significantly from hospitalization in terms of drug side effects, curettage requirements, and treatment success with a success rate of 96.6% vs 91.5%, respectively.

A previous study by Abdullah and Al-Jassim (2016) in Iraq evaluated the efficacy and safety of vaginal misoprostol in an outpatient setting. The protocol used 800 mcg of vaginal misoprostol on day 1 at the clinic, followed by another dose of 800 mcg of vaginal misoprostol on day 2 if expulsion was not complete. Complete expulsion, method failure, patient's tendency to elective curettage, incomplete

abortion, and need for emergency curettage occurred in 90.7%, 3.3%, 4.7%, 1.3% and 1.3% respectively. The success rate in that study was lower than in our study (93.95%). This difference may be due to the smaller sample size. Neither in our study nor in their study did any patients require transfusions. In the Iraq study, 4.6% of the subjects underwent curettage due to patient preference, but in our study, these individuals were excluded from the study and were not considered as final statistics (18).

In the study by Ng et al. (2015) on 154 patients with a first trimester abortion, patients were divided into outpatient and inpatient groups, 800 mcg of vaginal misoprostol was given at 8-hour intervals up to a maximum of three doses. The success rate in the outpatient method was 89.2% and in the inpatient method was 85.7%, which was not significantly different between the two groups and it was less successful than our study (91.5% in the inpatient group and 96.6% in the outpatient group) which can be due to the different sample size and the different dose and drug intervals.

Fever was the common side effect seen in our study, similar to that of the study by Ng. In our study, there was no significant difference between the outpatient and inpatient groups. However, in the study by Ng et al (2015)-, there was a statistically significant higher incidence of fever in the inpatient group. It was mentioned that a higher documented fever rate in the inpatient group was probably due to the regular temperature monitoring during hospitalization, which was not being practiced in the outpatient patients (17).

Previous study have demonstrated that home self-administration of vaginal misoprostol for medical abortion is as effective as hospital administration (19). In our study, the administration of misoprostol was performed as an outpatient basis by a researcher. Subsequent studies may examine the administration of misoprostol at home and by the patient herself.

The limitations of the present study are lack of evaluation of patient's satisfaction, self-reporting of fever by outpatients (fever was more frequently not measured by a thermometer), and the long interval between prescribing the two doses of the drug, which could have led to low satisfaction in patients. Also, another limitation is that blinding was not performed in the present study.

One of the strength of the present study is the appropriate sample size compared to the similar previous studies.

Conclusion

Our study confirmed efficacy and safety of outpatient treatment of the first trimester abortion. Outpatient treatment can be a good alternative to hospitalization and has less burden on hospitals and medical systems.

Further studies can be performed on the outpatient administration of misoprostol at home and by the patients themselves without the need of a caregiver, as well as further evaluation of patient satisfaction and - cost-effectiveness.

Declarations

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Conflicts of interest

Authors declared no conflicts of interest.

Ethical considerations

Written informed consent was obtained from the patients in the study.

Ethical approval

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences with ethical code of IR.MUMS.MEDICAL.REC.1397.639.

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Authors' contribution

AV, LP and SA contributed substantially in the conception and design of the study and supervised the project and writing the article. AS performed data collection and writing the article. SA performed data analysis. All authors read and approved the final manuscript and

agreed to be accountable for all aspects of the work.

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