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Original Research Article

The results of using the combination of letrozole and misoprostol in comparison with laminaria and misoprostol in preparing the cervix for miscarriages under the second trimester of pregnancy

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ABSTRACT

Background: Therapeutic abortion in the second trimester pregnancy is the choice treatment in cases with severe anomalies or intrauterine fetal death. It can be done by a number of medical (e.g. misoprostol and letrozole) or mechanical methods (e.g. laminaria). The aim of this study was to compare the efficacy of vaginal misoprostol with and without letrozole and combination of misoprostol and laminaria for preoperative cervical ripening among women with under second trimester abortion.

Methods: In this interventional study, 80 pregnant women in the second trimester pregnancy (Gestational age under 20 weeks) were randomly divided in two groups (n=40). One group received vaginal misoprostol in combination with laminaria and oral placebo and other group received vaginal misoprostol in combination with letrozole. Patients regularly examined every 4 hours and in the absence of abortion, vaginal misoprostol repeated after 4 hours. No report of products of conception abortion considered as complete abortion and the patient discharged. Data collected in a checklist and then analyzed by statistical methods in SPSS version 21.

Results: Complete abortion was reported in 70 (87.5%) of all patients which in group letrozole+misoprostol in 34 (85%) and in laminaria+misoprostol was reported in 36 (90%). 6 (15%) Curettage was reported in group letrozole+misoprostol and 4 (10%) in laminaria+misoprostol and the difference were not statistically significant.

Conclusions: Results showed that both of combination are effective in the abortion but misoprostol in combination with laminaria is recommended for the induction of second trimester therapeutic abortion.

Keywords: Laminaria, Misoprostol, Letrozole, Second trimester

INTRODUCTION

Abortion is the termination of a pregnancy under 20 weeks or the birth of a fetus under 500 grams, which is the treatment of choice in some diseases during childbirth, such as advanced heart diseases of the mother, hypertensive vascular diseases, invasive carcinoma of the cervix, loss of the fetus in the mother's womb, and severe

deformity. It is anatomical or mental of the fetus. Ejecting the fetus from the uterus can be done without a special intervention called spontaneous abortion or with an intervention called induced abortion, which includes about 15% of pregnancies.¹ In the first trimester of pregnancy, 15 to 20 percent of pregnancies lead to miscarriage. According to the definition of the National Health Center, abortion refers to the termination of a pregnancy under 20

weeks or the birth of a fetus under 500 grams, and these conditions include about 15% of pregnancies. New research has shown that the high annual incidence rate of 39 per 1,000 women aged 14-59 can impose a heavy financial burden on families and the health care system, and is associated with serious complications such as uterine rupture, sepsis and maternal death.²⁻⁴

Since 1930, the standard treatment for first-trimester abortion has been dilatation and curettage, which can be associated with complications such as uterine perforation, severe bleeding, cervical laceration, and infection, and preparation of the cervix before surgical interventions is effective in reducing these complications. This operation is also divided into 2 mechanical and medicinal methods. In the last decade, medical methods have become a suitable alternative to terminate pregnancy in the first trimester.⁵⁻⁶ The studies conducted with misoprostol show that this type of prostaglandin is a suitable alternative for dilatation and curettage and relieves patients from the risks of surgery and anesthesia, and in the second trimester of pregnancy, it can soften the cervix and induce labor pains.⁷

To improve the effectiveness of misoprostol, some studies have tried to combine misoprostol with other agents such as letrozole because it has been reported that the combined use of letrozole with misoprostol may be more effective in terminating pregnancy than misoprostol alone.⁸ Pharmacological techniques mainly include the use of prostaglandin products.⁹⁻¹¹ Mechanical techniques are hygroscopic dilators of the cervix. One of the types of hygroscopic dilators is prepared from the stem of *Laminaria digitata* or *Laminaria japonica* (brown seaweed), which is placed inside the cervix to induce labor.^{1,12} Some studies have shown that laminaria increases the time of induction to delivery and the time of placental discharge. Other studies show that the time of induction of labor until delivery in laminaria group was shorter than misoprostol, without having more side effects.¹³⁻¹⁴ Common methods of abortion treatment in the second trimester of pregnancy include medical and mechanical treatments. Among the medicinal methods, one of the methods is the use of misoprostol, which softens the cervix and induces labor pains in the second trimester of pregnancy.¹⁵ One of the mechanical methods is to use devices that slowly dilate the cervix. Ghung et al concluded that the low price, easy insertion method and the ability to remove it quickly are the benefits of laminaria, and this method can be used in abortion treatment in the second trimester.¹⁶ Slow and gradual dilatation of the cervix by laminaria before the beginning of the medical induction of labor reduces the risk of wound and trauma to the cervix.^{15,17} Due to the different results in different studies and emphasizing the point that laminaria is a cheap medicine, it has few complications for the patient and also reduces the possibility of trauma to the cervix in patients who are candidates for abortion treatment, we decided to investigate the effects of the medicinal combination of laminaria and Let's compare

vaginal misoprostol with letrozole + misoprostol in preparation of cervix in second trimester abortion.

METHODS

Study design and participants

In this interventional study, 80 pregnant women referred to Alavi Hospital in Ardabil, who were less than 20 weeks pregnant and had to undergo abortion treatment due to fetal death confirmed by ultrasound, were studied. These 80 people were randomly divided into two groups of 40 people, and the first group was prescribed vaginal misoprostol together with letrozole for abortion treatment, and the second group, in addition to vaginal misoprostol, was prescribed Laminaria drug at the same time. week, the candidate for abortion treatment was due to the proven death of the fetus, which was confirmed by sonography, or a severe abnormality in which the fetus was not able to survive. Patients with a history of caesarean section, adrenal diseases, steroid-related cancers, asthma, history of thromboembolism, and cardio-pulmonary diseases were excluded from the study. In this study, the patients were given sufficient explanations about the treatment methods and the benefits and side effects of their drugs before the medication was prescribed, and if written consent was obtained from these people, the mentioned drugs were prescribed. If the patient did not agree, the patient was excluded from the study and another sample was replaced. In the first group, laminaria was inserted into the cervix according to its size, and at the same time misoprostol suppositories with the aforementioned doses were placed in the posterior fornix of the vagina (oral placebo was also used in this group), and in the second group, in addition to the placebo, letrozole tablets were given on the first and second day. 10 mg per day was prescribed on an outpatient basis and on the third day the patient was hospitalized and together with the third dose of letrozole, misoprostol suppository was used according to the week of pregnancy and the patient was examined regularly every 4 hours and if the fetus was not expelled after 4 Vaginal misoprostol hours were repeated. The patients who experienced severe vaginal bleeding during their stay in the hospital underwent emergency curettage and the patients who had tissue discharge underwent transvaginal ultrasound. In case of reporting pregnancy remnants or failure to expel tissue, they were subjected to curettage. The patients were under complete and strict supervision until the end of the abortion treatment, and in terms of the amount of drugs needed, the number of days of hospitalization, the need for curettage (in case of remaining placenta and remnants of pregnancy based on ultrasound the day after the expulsion of the fetus), the need for painkillers, symptoms And the side effects of the drugs (nausea, vomiting, rash, diarrhea, Waller's fever) and the time interval from the start of the treatment to the expulsion of the fetus based on the hour and pain intensity based on the Visual Analogue Score (VAS) were investigated. Gestational age based on ultrasound or date of last menstrual period, allergy history and reason for termination of pregnancy, amount of

bleeding, fever, nausea, and diarrhea were completed in a checklist for patients.

Statistical analysis

The collected data were analyzed in SPSS software version 21 using descriptive statistics methods and ANOVA and independent t test.

RESULTS

The women of the two groups did not have a significant difference in terms of age. The average gestational age based on the first day of the last menstruation in the group receiving misoprostol and laminaria was 19.11 ± 1.18 weeks and in the group receiving misoprostol and letrozole was 18.85 ± 1.23 . There was a complete miscarriage in the group receiving Laminaria and misoprostol in 36 (0.90%) people and in the group receiving letrozol and misoprostol in 34 (0.85%) people. 4 people (10%) in the first group and 6 (0.15%) people in the second group needed curettage. There was no significant difference between the two groups in terms of treatment response. Side effects such as nausea, vomiting, diarrhea were more common in the misoprostol+letrozole group than in the misoprostol+laminaria group, but there were no significant differences between the two groups in terms of the prevalence of side effects (Figure 1).

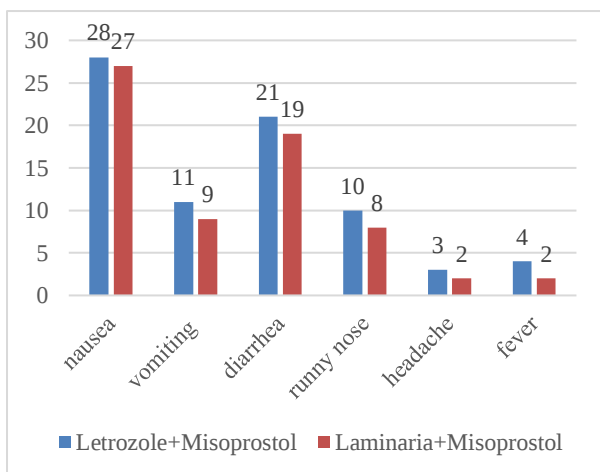


Figure 1: Frequency of side effects after receiving the drug in two groups.

Table 1: The level of cervical dilatation changes between the two study groups.

Group cervical dilatation changes	Misoprostol and laminaria		Misoprostol and letrozole		P value
	N	%	N	%	
No change	4	10	8	20	0.034
One cm	18	45	19	47.5	0.046
Two cm	13	32.5	11	27.5	0.12
Three cm	5	12.5	2	5	0.026

The average amount of cervical dilatation in the group receiving misoprostol and laminaria at the time of abortion was lower than the other group (Table 1).

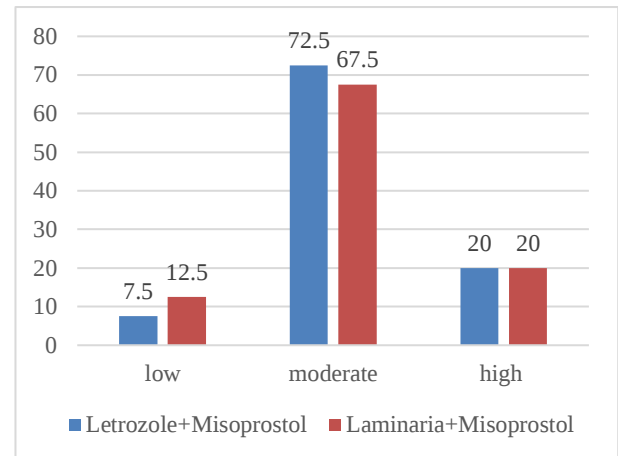


Figure 2: Bleeding level in two studied groups.

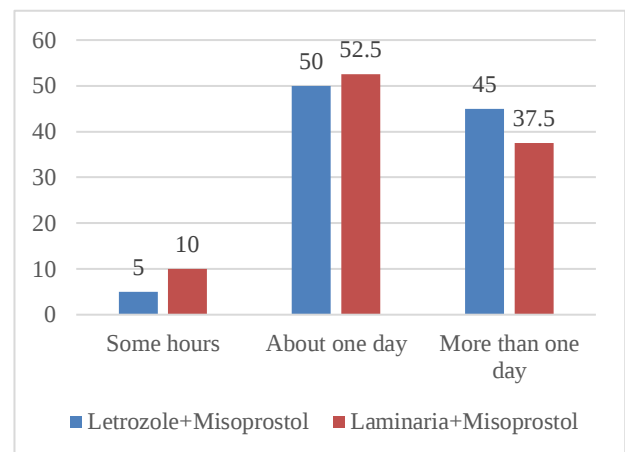


Figure 3: Duration of bleeding in the studied groups.

Table 2: Average VAS score of patients by treatment groups.

Group time	Misoprostol+ letrozole	Misoprostol+ letrozole	P value
	Mean±SD	Mean±SD	
4 hours after intervention	4.45±2.1	5.89±2.1	0.15
During abortion	0.039	8.2±1.8	0.039

The time interval from the start of treatment to the expulsion of the fetus was significantly longer in the misoprosterol+laminaria group with 5.4 hours than in the other group with 6.3 hours ($p=0.045$). In terms of the amount and duration of bleeding in the group receiving Laminaria+misoprostol, 27 people (67.5%) experienced moderate bleeding (Figure 2) and 52.5% experienced bleeding for one day (Figure 3). There was no statistically

significant difference between the two groups in terms of the amount of bleeding. The average numerical scale of pain intensity in the group receiving misoprostol+Laminaria at the time of abortion was significantly lower than the other group, but this difference was not significant in 4 hours after the start of the drug (Table 2).

DISCUSSION

Abortion treatment by drugs is an alternative to surgical curettage in cases of abnormal or non-viable fetuses, as well as in cases of missed abortions. Using this method is less expensive and reduces surgical complications such as bleeding and infection rate, as well as reduces the stress of patients. In this study, the response rate to treatment in the group receiving laminaria and misoprostol was 90% and, in the group, receiving letrozole and misoprostol was 85%. These results were consistent with the study of Salari et al. and the study of Jain et al.¹⁸⁻¹⁹ In the study of Rezaei et al in relation to the comparison of the effectiveness of the combination of letrozole with misoprostol and misoprostol alone, the induction rate of complete abortion was 84.1% in the combined group and 78.5% in the misoprostol group alone, but this difference It was not statistically significant and finally they concluded that the effect of using misoprostol+letrozole is equal to the effect of using misoprostol alone.²⁰ In a clinical trial study by Lee et al on 168 women with gestational age of less than 63 days, the complete abortion rate in the letrozole+misoprostol group was 86.9% significantly higher than the misoprostol group with 72.6%. No significant difference was observed in the incidence of side effects between the two groups.⁸ The highest amount of cervical dilatation at the time of measurement was in the laminaria and misoprostol group and the letrozole and misoprostol group, respectively. These results are consistent with the results of Bahrashi et al who concluded in their study that the amount of cervical dilatation in the group receiving laminaria is 4.4 times higher than the group receiving misoprostol in labor induction.²¹ The interval of abortion was also shorter in the group receiving laminaria and misoprostol than in other groups. These results are consistent with the results of Salari et al and Prasad et al in 2009, who stated that the interval between the start of treatment and the expulsion of the fetus in the group receiving laminaria and misoprostol was less than the group receiving misoprostol, but they are not consistent with the results of Borgata et al.^{18,22-23} In this study, there was no statistically significant difference between drug side effects and symptoms among the studied groups, which is similar to the studies of Jain et al and Salari et al.¹⁸⁻¹⁹ In terms of the duration and amount of bleeding, the lowest duration and intensity of bleeding was observed in the group receiving laminaria and misoprostol, but this difference was not statistically significant. The amount of hemoglobin in the two groups was not significantly different at the beginning, but at the end of the study, the amount of hemoglobin in the group receiving misoprostol was lower than the other groups, but this difference was not statistically significant. In the studied groups, the side effects did not have a statistically

significant difference, which is in line with the results of Lee et al.⁸ In the study of Gagné et al the average pain score in the group that used only laminaria was higher than the misoprostol group.²⁴ In this study, the average pain score in the group receiving laminaria and misoprostol was lower than the other groups, which is in line with the results of Khooshideh et al.²⁵ Among the limitations of this study, we can mention the non-cooperation of patients for the implementation of the plan, including the use of letrozole, and the limitation of patients to the second trimester of pregnancy. Rezaei et al concluded in a study that misoprostol alone is as effective as letrozole and misoprostol. They also stated that the combination of letrozole with misoprostol is an effective, safe and cheap method. The rate of curettage in the study by Rezaei et al. was higher in both groups than in the present study. Also, the percentage of complete abortion in both groups was lower than in the present study.²⁰ In our study, the most common side effects in both groups were first nausea and then diarrhea, which was consistent with the study of Rezaei et al. Also, this study is consistent with the results of Lee et al study.^{8,20}

CONCLUSION

Adding laminaria to the misoprostol drug regimen, in contrast to adding letrozole to induce abortion, leads to an increase in the percentage of successful abortion and a decrease in the use of curettage, although there was no statistically significant difference between the two drug treatment regimens. In order to reach more definitive results, it is recommended to conduct similar studies in this field in a larger sample size and taking into account other factors such as fetal age, maternal age, and fetal gender (due to hormonal effects).

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Ethical approval: The study was approved by the Institutional Ethics Committee

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