Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.234154.2873 Volume 30, Issue 1.6, September 2024, Supplement Issue
Manuscript ID ZUMJ-2311-2996 (R1) DOI 10.21608/ZUMJ.2023.246671.2996
ORIGINAL ARTICLE

Comparison between Letrozole Treatment before Misoprostol and Misoprostol Alone for Medical Management of Missed Abortion

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Submit Date 06-11-2023
Revise Date 10-11-2023
Accept Date 12-11-2023

ABSTRACT

Background: It is essential to ascertain and diagnose the optimal treatment protocol for medical abortion. Consequently, it is necessary to evaluate the efficacy of combining letrozole with misoprostol compared to the administration of misoprostol alone in the termination of missed abortions occurring in the first trimester. **Methods:** The study was done on a total of 88 patients; group A consisted of a total of 44 individuals who were administered a combination of letrozole and misoprostol. A pre-treatment regimen consisting of 5 mg of letrozole administered every 12 hours for three consecutive days was administered. This was followed by the administration of four tablets of vaginal misoprostol, each containing 200 mcg of the active ingredient. An additional dose of misoprostol was administered after three hours, if deemed necessary. Group B consisted of 44 patients who were administered "Misoprostol." A single tablet of folic acid was administered as a placebo every 12 hours for three consecutive days in a home setting, followed by the administration of four tablets of vaginal misoprostol (200 mcg). **Results:** The results indicate that 70.4% of the studied women in group A experienced complete abortion, whereas 63.6% of the studied women in group B achieved the same outcome. Group A had a reduced length from induction to abortion in contrast to group B, as well as a lower requirement for curettage when compared to group B (6.8% against 9.1%, respectively). **Conclusions:** Letrozole pretreatment with misoprostol increase the effectiveness of misoprostol without increasing side effects.

Keywords: Letrozole; Misoprostol; Missed abortion

INTRODUCTION

Missed abortion refers to the presence of a gestational sac that contains a nonviable embryo or fetus, occurring prior to 24 weeks of gestation and lacking any observable clinical signs of ejection [1]. Missed abortion, a condition characterized by the retention of pregnancy materials in the uterus for an extended period following fetal demise, is observed in approximately 15% to 20% of clinically confirmed pregnancies [2].A range of medicinal and surgical interventions have been employed in the management of missed abortions. Surgical techniques commonly employed in medical practice encompass dilatation and curettage, as well as vacuum aspiration. Medical techniques are often favored over surgical abortion methods due to their costliness and the requirement for anesthesia [3].A variety of pharmaceutical substances can be employed to initiate the termination of pregnancies. One of the pharmaceutical substances in question is misoprostol, which functions as an equivalent

of prostaglandin E1. This pharmaceutical agent is classified as a prostaglandin, which acts by inducing myometrial cervical softening, contractions, and dilatations. It is commonly employed for the purpose of inducing abortions and facilitating labor, as well as for managing cases of atonic postpartum hemorrhage and peptic ulcers.This pharmaceutical substance has the potential for administration via both vaginal and oral routes [4]. Misoprostol is a prostaglandin that induces softening of the myometrial cervical tissue, resulting in contractions and dilatation. It is commonly used for the purpose of inducing abortions and labor, as well as managing cases of atonic postpartum hemorrhage and peptic ulcers [5]. Letrozole is classified as an aromatase inhibitor and is commonly prescribed to induce ovulation in infertile women who experience ovulatory dysfunction. The administration of letrozole results in the inhibition of estrogen synthesis, which subsequently leads to an increase in endogenous gonadotropin levels. This rise in gonadotropins encourages the formation of ovarian follicles. Additionally, letrozole has been found to have potential applications in abortion therapy due to its ability to suppress estrogen synthesis. The user's text is not clear and does not provide any information. According to a study, it has been suggested that administering aromatase inhibitors prior to the administration of primary drugs like misoprostol or mifepristone for the purpose of inducing medical abortion can enhance the effectiveness of the treatment regimen and reduce the necessity for surgical procedures. A further study demonstrated that the administration of letrozole for a duration of 7 days preceding the use of misoprostol resulted in a success rate of 95% in the treatment of missed miscarriage [6].According to a recent study, the administration of letrozole prior to the use of misoprostol for early termination of pregnancy in the first trimester has been found to be correlated with a greater likelihood of complete fetal expulsion compared to the use of misoprostol alone [7]. This work aims to compare the efficacy and safety of letrozole treatment before misoprostol versus misoprostol alone in the clinical management of the first trimester missed abortions.

METHODS

The current research project was a randomized comparative clinical study that was conducted on a cohort of patients diagnosed with first-trimester missed abortions. These patients sought medical care either at outpatient clinics or the maternity (emergency) hospital affiliated with the Faculty of Medicine at Zagazig University Hospital.The study was carried out during a period spanning from March 2023 to September 2023. The study was done according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. The study encompassed a total of 88 patients.

Inclusion criteria: Pregnant individuals who have been diagnosed with first trimester missed abortion based on the last menstrual period (LMP) and further confirmed through ultrasound scan in accordance with the recommendations set forth by the Royal College for Obstetrics and Gynaecology (RCOG) in 2011. If the measurement of the crown-rump length exceeds 7mm and there is an absence of embryonic cardiac activity. In cases where the mean gestational sac diameter exceeds 25mm and no yolk sac is present, some observations can be made. Written informed consents were obtained from all participants.

Exclusion criteria: Preceding medical or surgical attempts for termination of this

current pregnancy. Various medical conditions, including cardiovascular diseases, renal disorders, liver diseases, diabetes mellitus, anemia, and hematological disorders, multiple pregnancy, uterine neoplasms, such as fibroids or congenital abnormalities, or any contraindications associated with the use of misoprostol or letrozole.

Randomization: Following the acquisition of informed consent, participants were assigned randomly to the two groups in a 1:1 ratio. This random assignment was accomplished using a computer-generated table of random numbers, ensuring allocation concealment. The study consisted of two groups: group A, referred to as the "Letrozole + Misoprostol group," and group B, referred to as the "Misoprostol group". The aforementioned operations were performed on each patient.

Every patient was subjected to: A comprehensive and precise patient history was obtained, followed by a thorough general examination. Examination: The cervical assessment involves the evaluation of many parameters, such as cervical dilatation, consistency, effacement, position, and bleeding. The usual laboratory assessments were done. According to the guidelines set forth by the Royal College for Obstetrics and Gynaecology (RCOG) in 2011, an ultrasound assessment was performed to confirm the diagnosis of missed miscarriage.

Intervention: The induction of abortion was conducted in accordance with the FIGO protocol of induction 2017. Specifically, for cases of missed abortion, a dosage of 800ug of misoprostol was administered per vagina every 3 hours, with a maximum of 2 doses. In Group A, female participants were administered a dosage of 5mg of letrozole every 12 hours for three consecutive days in their own homes. They were instructed to return the empty medication packages on the fourth day and thereafter got a dose of 4 tablets of vaginal misoprostol soaked with saline in the posterior fornix. An additional dose was administered after a 3-hour interval, if deemed necessary. In Group (B), female participants were administered two tablets of folic acid, each containing 400 micrograms, as a placebo every 12 hours for three consecutive days in their own homes. On the fourth day, they were given four tablets of vaginal misoprostol soaked with saline, which were inserted into the posterior fornix. An additional dose was administered after a three-hour interval if thought necessary. On the third day following the administration of misoprostol, an ultrasound examination was performed in order to ascertain the absence of incomplete abortion. In the instance that incomplete abortion was detected, an extra dose of misoprostol was administered, and the patients were reevaluated and managed accordingly. It was postulated that a lack of response is evident in cases where the cervix remains closed or there is no ejection of any contents. The patient's condition was diagnosed as an incomplete abortion, as per the criteria of a remnant inside the uterus measuring 2 cm or more.

Outcome:The complete abortion rate within three days of misoprostol and the induction to abortion interval were assessed.

The study protocol underwent the approval process by the Institutional Review Board (IRB) of Zagazig University, with the assigned number 10675.

STATISTICAL ANALYSIS

The data was collected, coded, tabulated, and imported into the statistical software for social science (SPSS v 20.0).

RESULTS

Our research revealed that there were no statistically significant differences between

the two groups in terms of mother age, gestational age, and body mass index **(Table 1)**. We reported no significant difference exists between the 2 groups regarding HB level before and after receiving treatment, hemoglobin level decrease after receiving treatment in the 2 studied groups, with no significant difference between the 2 groups **(Table 2).** There were no significant differences between the studied groups regarding onset of bleeding: after few hours of receiving (letrozole + misoprostol), within a day and bleeding more than a day, however, there was no bleeding in 4 (9.2%) and 6 (13.8%) patients in group A and group B respectively **(Table 3).** Within group A (letrozole + misoprostol), 70.4% of the studied participants were aborted completely compared with 63.6% of participants in group B (misoprostol). No response was detected in 6.8% of participants among group A in comparison to 9.1% of participants among group B, which is statistically significant **(Table 4).**Group A (letrozole + misoprostol) experienced less need for an additional dose of misoprostol after the third day of treatment and curettage in comparison to Group B (misoprostol) (6.8% versus 9.1%) respectively **(Table 5).** The studied participants in group A (misoprostol + letrozole) had a shorter duration from induction to abortion in comparison with participants in group B (misoprostol), which was statistically significant **(Table 6).** The side effects in the studied groups; abdominal pain, nausea, vomiting, diarrhea, dizziness, and fever show no statistically significant difference ($p>0.05$) between the two groups except fever with a statistical difference between the two groups as (4.5%) of patients among group A and (20.5%) of patients among group B had fever **(Table 7).**

Table 1: Demographic data and personal characteristic of the studied groups

Studied groups / Variables	Group A (n=44)	Group B (n=44)	P-value*
Age (years) mean±SD	25.86±7.5	26.65±7.6	0.8
Parity mean±SD	3.02 ± 1.09	4.45 ± 1.0	0.075
BMI($kg/m^{2)}$ mean±SD	26.9±2.5	27.8±2.4	0.2
Previous abortion (N. %)	15(34.09%)	18 (40.9%)	0.035
Gestational age(weeks) mean±SD	9.4±1.5	9.3±1.1	0.8

*Mann-whitney test

Table 2: Hemoglobin levels before and after treatment

Studied groups / Variables	Group A (n=44)	Group B (n=44)	P-value*
HB level before ttt mean±SD	10.3±0.9	10.7±0.3	0.9
HB level after ttt mean±SD	9.7±1.09	9.9±1.06	0.5

*Mann-Whitney test

Table 3: Onset of bleeding after receiving treatment

Studied groups / Variables	Group A (n=44)	Group B (n=44)	P-value*
Bleeding after few hours (N. %)	1 (2.3%)	1 (2.3%)	1
Bleeding within a day (N. %)	20 (45.5%)	19 (43.2%)	0.8
Bleeding more than a day (N. %)	19 (43.2%)	18 (40.9%)	0.8
No bleeding (N. %)	4 (9.2%)	6 (13.8%)	0.8

*Chi-square test

Table 4: Outcomes of the cases of missed abortion after additional doses of misoprostol and within 3 days of treatment.

Studied groups / Variables	Group A (n=44)	Group B (n=44)	P-value*
Complete abortion (N. %)	31 (70.4%)	28 (63.6%)	0.05(s)
Incomplete abortion (N. %)	10 (22.7%)	12 (27.3%)	
No response(N. %)	3 (6.8%)	4 (9.1%)	

*Chi-square test S: significant

Table 5: Need for curettage among the studied groups

Studied groups / Variables	Group A (n=44)	Group B (n=44)	P-value*
Need for additional dose of misoprostol after the third day of treatment (N. %)	4 (9.2%)	6 (13.8%)	**0.02**
Need for curettage (N. %)	3 (6.8%)	4 (9.1%)	

*Chi-square test

Table 6: Induction - abortion interval among the studied groups

Variables \ Studied groups	Group A (n=44)	Group B (n=44)	P-value*
Induction - abortion period (hours) mean±SD	28±2.16	36.6±2.3	**0.04**

*student's t-test

Table 7: Side effects among the studied groups

Variables \ Studied groups	Group A (n=44)	Group B (n=44)	P-value*
Abdominal pain (N. %)	32 (77.3%)	28 (63.6%)	0.2
Nausea(N. %)	28 (63.6%)	29 (65.9%)	0.8
Vomiting(N. %)	14 (31.8%)	12 (27.3%)	0.6
Diarrhea (N. %)	12 (27.3%)	16 (36.4%)	0.3
Dizziness (N. %)	8 (18.2%)	14 (31.8%)	0.1
Fever (N. %)	2 (4.5%)	9 (20.5%)	**0.02(s)**

*Chi-square test

DISCUSSION

Missed abortion refers to the cessation of embryonic or fetal growth, characterized by a closed cervix, absence of bleeding, and ultrasound evidence of a fetus lacking heart activity [8]. Several methods of management have been employed for the purpose of pregnancy termination. The methods employed in terminating pregnancies encompass surgical techniques, specifically dilation and evacuation (D&E), as well as medical treatments. Medical abortion has been found to reduce negative consequences such as infection and hemorrhage, as well as alleviate patient distress, in comparison to surgical procedures [9]. Several drugs have been employed for the medical management of missing abortions, with misoprostol and letrozole being among the notable pharmaceutical options [10]. Misoprostol is employed as a standalone intervention for the medical handling of miscarriage, serving as a surgical alternative, and exhibiting a success rate of up to 65%. The use of this intervention is particularly efficacious during the initial phases of gestation, offering the additional benefits of cost-effectiveness, reduced invasiveness, and the avoidance of surgical problems [11]. Letrozole is classified as a third-generation aromatase inhibitor. The postulated mechanism of action is a reduction in blood estrogen levels, which then leads to changes in the concentration of progesterone receptors. This ultimately results in the termination of pregnancy [12]. The objective of this randomized comparative clinical trial was to assess and compare the effectiveness and adverse effects of two treatment approaches: the use of misoprostol alone versus the combination of misoprostol and letrozole.

The current study focused on the medical

termination of first trimester missed abortion cases with a gestational age of less than 13 weeks. The research was conducted on a sample of 88 patients who experienced first trimester missed abortions. The results of our study indicate that there was no statistically significant difference seen between the two groups in terms of mother age, gestational age, and body mass index .

The study conducted by Bahaa et al. and Afifi et al. aimed to assess and compare the synergistic impact of methotrexate monotherapy against letrozole in conjunction with misoprostol for the induction of missed miscarriage in the first trimester. A comparison was conducted between the two groups under study with respect to their baseline data. There were no statistically significant differences seen between the two groups under study in terms of women's age, parity, BMI, gestational age, history of past abortions, and previous cesarean section, as shown by previous studies [8, 13]. In terms of bleeding, there was no significant difference observed between the two groups (group A and misoprostol group) in relation to hemoglobin (HB) levels before and after treatment. However, both groups experienced a decrease in hemoglobin levels after receiving treatment, with the misoprostol group showing a lower decrease. Nonetheless, this difference was not statistically significant between the two groups.

Consistent with the findings of our study, Bahaa et al. observed a decreased incidence of blood loss in the letrozole with misoprostol group compared to the misoprostol groups (10.20% vs. 18%, p=0.486) [8]. In the present investigation, the rate of complete abortion was found to be greater in the group receiving both letrozole and misoprostol compared to the group receiving misoprostol alone (70.4% vs. 63.6%), and this difference was statistically significant.

Consistent with our findings, Javanmanesh et al. and Afifi et al. observed that the rate of successful complete abortion was 78% in the experimental group (administered misoprostol + letrozole) and 71% in the control group (administered misoprostol), with a statistically significant difference between the two groups. Furthermore, it was shown that the group administered with only misoprostol exhibited a notably elevated rate of incomplete abortion and emergency dilation and curettage [1, 13]. The findings of our study indicate that group A, which received a combination of letrozole and misoprostol, exhibited a lower incidence of requiring curettage compared to group B, which received only misoprostol (p=0.03). Consistent with the results of our study, Abbasalizadeh et al., Afifi et al. and Bojd et al. conducted comparative analyses on the efficacy of misoprostol alone versus misoprostol combined with letrozole for the induction of abortions. The study findings indicate that the proportion of cases requiring surgical curettage was 18.8% in the misoprostol alone group, compared to 6.3% in the letrozole + misoprostol group [5, 13, 14].

In the current investigation, group A which consisting of participants who received a combination of misoprostol and letrozole, exhibited a significantly reduced duration from induction to abortion as compared to participants among group B, which solely received misoprostol. In addition, the studies conducted by Bahaa et al. and Bojd et al. revealed that the duration of induction abortion was considerably reduced in the letrozole groups compared to the misoprostol groups (2.04±1.38 vs. 2.85±1.75 days, p=0.023) respectively [8, 14]. The findings of our study indicate that there were no statistically significant differences (p>0.05) in the occurrence of abdominal pain, nausea, vomiting, diarrhea, dizziness, and fever between the two groups under investigation. However, it is worth noting that the incidence of fever was higher among participants of group A compared to participants of group B (4.5% vs. 20.5%) with a statistically significant difference (p=0.02). Therefore, the administration of letrozole before misoprostol demonstrated efficacy and enhanced safety in the induction of complete abortion for non-viable fetuses during the first trimester of pregnancy. Notably, this treatment approach did not result in any adverse effects among patients, potentially attributed to a reduced interval between induction and abortion.

This finding is similar to the studies conducted by Afifi et al. and Bojd et al., which indicated that there was no statistically

significant difference in adverse effects between letrozole and misoprostol groups [13, 14]. The observed variations in study outcomes may arise from variations in demographic characteristics of the subjects, variations in medication dosages, variations in administration methods, and variations in the gestational ages of the populations being treated.

CONCLUSIONS

The current study reported no significant difference in the success rates of abortion among the various cases examined. However, research has indicated that individuals who underwent combined therapy with misoprostol and letrozole exhibited a reduced duration between induction and abortion, as well as a decreased requirement for curettage. Hence, the administration of letrozole prior to misoprostol has been shown to enhance the efficacy of misoprostol monotherapy while minimizing the occurrence of adverse effects.

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Citation:

Elian, T., Abd Elhameid, A., Abo Hashim, M., Basha, A. Comparison between letrozole treatment before Misoprostol and Misoprostol alone for medical management of missed Abortion . ***Zagazig University Medical Journal*****, 2024; (3063-3070): -. doi: 10.21608/zumj.2023.246671.2996**