
Letrozole And Misoprostol Vs. Misoprostol Alone In Management of First Trimester Missed Abortion; A Randomized Controlled Trial At Benha University Hospitals

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Abstract

Foundation: Miscarriage is the end of pregnancy before 20 weeks of development or an embryo conceived weighting under 500 grams. Inciting early termination by drugs is an option for medical procedure mediation, which has financial advantages with lower results and its pace of achievement is 60 to 95 percent. The point of this investigation was to analyze the adequacy and security of letrozole pretreatment with misoprostol and misoprostol alone in the management of first trimester missed Abortion. **Strategies:** This investigation was directed at outpatient clinic and emergency division of obstetrics and gynecology department at Banha univeristy hospitals. Itemized history was taken and cautious assessment was accomplished for all patients. Likewise fundamental examinations as hemoglobin, blood gathering, RH and trans-vaginal ultrasound were done for patients before the investigation. **First gathering:** The patients got 600 mcg of misoprostol (three tablets, every tablet 200 mcg) orally as a solitary portion. **Second gathering:** The patients got letrozole 10 mg (4 tablets, every one 2.5 mg) as a solitary portion for 3 days followed by 600 mcg misoprostol orally. **Results and end:** The utilization of letrozole pretreatment followed by misoprostol for termination of missed abortion in the first trimester is related with higher complete fetus removal rate than misoprostol alone. Along these lines, it is prescribed to utilize letrozole followed by misoprostol routine for enlistment of early termination in cases with first trimesteric missed abortion rather than misoprostol alone.

Keywords: Letrozole; Misoprostol; Missed abortion

1. Introduction

Inducing abortion by drugs is vastly used in worldwide level and its utilization has expanded since 1950. Chosen technique for ending pregnancy in 1960s was vacuum yearning a medical procedure, and afterward by assembling mifepristone in 1980s, utilization of pregnancy end strategies by drugs expanded [1].

Prompting fetus removal by drugs is an option for medical procedure mediation, which has monetary advantages with lower results and its pace of progress is 60 to 95 percent. In clinical treatment strategy different medications could be utilized to actuate fetus removal. Considering constraint in admittance to mifepristone medications and its significant expense, it isn't open in the vast majority of the nations and elective medications are utilized to actuate early termination [2].

One of these medications which utilized both vaginally and orally is prostaglandin E1 simple, misoprostol, which is known as Cytotec exchange mark. Misoprostol is a modest medication which could be kept in room temperature and typically utilized as vaginally and orally. Other than being moderate and proficient, misoprostol has lower results and needn't bother with uncommon consideration during use. This medication is all around endured by patients and lessens treatment costs essentially and furthermore altogether decreases curettage and need for careful mediation [3].

Letrozole is likewise one of aromatase inhibitors, which is utilized to invigorate ovulation in fruitless ladies enduring ovulatory brokenness. This medication is one of the primary medications for hindering aromatase, with a moderately short 45-hour half-life, which is dynamic orally and represses aromatase compound reversibly. By this medication, estrogen blend block prompts increment

endogenous gonadotropin lastly invigorates development of ovarian follicles, and furthermore this medication could assume a part in fetus removal treatment through hindering estrogen amalgamation. This medication is likewise used to bosom malignancy identified with estrogen. [4].

Misoprostol is a prostaglandin that causes myometrial withdrawals, cervical relaxing and dilatation. It is utilized to incite early termination and work and to treat atonic baby blues drain and peptic ulcers. It has the benefit of being practical and stable with a low pace of results, which has prompted it being remembered for the World Health Organization rundown of fundamental prescriptions. Misoprostol is authorized for use to actuate unsuccessful labor in Egypt. It has not been authorized to initiate work or premature delivery in specific nations, for example, Germany, however it is utilized off-name to actuate work in the UK and in Germany. Misoprostol without help from anyone else is utilized for the clinical administration of unsuccessful labor as an option in contrast to a medical procedure, with a triumph pace of somewhere in the range of 65 and 93%. It is more compelling in the beginning phases of pregnancy, where it additionally has the benefit of being less expensive, less obtrusive and evading careful complexities. Misoprostol is additionally utilized in mix with different prescriptions, for example, mifepristone and methotrexate to build the achievement rate [5].

Mifepristone utilized in blend with misoprostol accomplished higher paces of finished fetus removals of up to 95% and is suggested for pretreatment in early termination and clinical unnatural birth cycle, yet a less expensive and broadly accessible option is required, particularly in creating countries[6].

The utilization of letrozole in blend with misoprostol to acquire higher paces of finished early termination was assessed by lee et al. [7]. In their investigation letrozole was regulated for 3 days followed by misoprostol and made a progress pace of 86.9%. In a pilot concentrate by Yeung et al., [8] a letrozole convention was utilized for 7 days and made a 95% progress rate.

This investigation analyzes the wellbeing and viability of misoprostol alone or in mix with letrozole in clinical administration of first trimester Abortion.

The point of this investigation was to look at the viability and security of letrozole pretreatment with misoprostol and misoprostol alone in the clinical administration of first trimester missed Abortion.

2. Patients and methods

This study is a prospective randomized interventional controlled study that included 50 patients with missed abortion from those attended the outpatient clinic and emergency unit of Obstetrics and Gynecology department at Banha university hospitals during the period between May 2020 to December 2020 , The participants were randomly divided into two equal groups: an intervention group and a control or placebo group. All Patients was subjected to complete history taking and thorough clinical examination.

- Intervention group: to induce drug abortion, patients first daily received 10 mg oral letrozole for 3 days, then they received 600 microgram single dose oral misoprostol.
- Control group: patients first daily received placebo of letrozole like intervention group and then 600 microgram single dose oral misoprostol was used.

Patients in both groups, who had spontaneous abortion before taking misoprostol in the first three days of study, will be excluded from the study. For patients in both groups' hemoglobin levels was measured at the beginning and end of the study. Through the study single blinding was applied and patients are not aware of studied groups. Both groups was monitored for 4 hours after receiving single dose of misoprostol and was examined for possible side effects such as abdominal cramp or possible bleeding, and in terms of lack of abdominal cramp or severe bleeding, was released after explaining risk and warning signs such as bleeding more than normal menstruation.

In case of failure in full disposal of the remnants of pregnancy or failure in termination of pregnancy, repeated doses of misoprostol or curettage candidates underwent surgery and patients in both groups of control and intervention was put in two categories of response to treatment and failure in response to treatment

2.1 Sample size:

50 patients were divided into two groups 25 in the intervention group and 25 in the control or placebo group.

2.2 Inclusion criteria:

- Mothers more than 18 years old
- First trimester of pregnancy (less than 13 weeks based on LMP),
- Non-living fetus
- Absence of any maternal diseases such as: heart disease, asthma, history of thromboembolism, cancer, renal failure, and liver diseases, and consent of patient and her spouse to participate in the study.

2.3 Exclusion Criteria:

Any medical problem in patient which need to interfere and emergency treatment, or history of allergy to misoprostol or letrozole drugs.

2.4 Study Outcome:

Primary outcome: success of complete evacuation of uterine contents without need of evacuation under anesthesia.

Secondary outcomes: Hemoglobin and hematocrit values pre and post evacuation, Side effects of drug use, Complications of surgical evacuation, Dose needed to achieve full evacuation, and Hospital stay.

2.5 Statistical methods

Data management and statistical analysis were done using SPSS vs.25. (IBM, Armonk, New York, United states). Numerical data was summarized as means and standard deviations. Categorical data was summarized as numbers and percentages. Correlation analysis was done between age & time before surgery with other parameters. "r" is the correlation coefficient. It ranges from -1 to +1. -1 indicates strong negative correlation, +1 indicates strong positive correlation and 0 indicates no correlation. Adductor pollicis motor gradings were compared as regard compliance to physical therapy using Chi-square test. All P values were two sided. P values less than 0.05 were considered significant.

2. Results

This study was conducted at outpatient clinic and emergency department of obstetrics and gynecology department at Banha university hospitals, demographic data in table 1.

Table (1): Comparison between groups as regard demographic data.

	Group		t-test	p- value	Difference (95% CI)
	Misoprostol (N=25)	Misoprostol -Letrozole (N=25)			
	Mean ± SD	Mean ± SD			
Age (years)	28.36 ± 5.35	28.44 ± 5.54	0.072	0.943	-0.08 (-2.44 -2.27)
Weight (kg)	70.88 ± 8.76	70.63 ± 9.48	0.128	0.899	0.25 (-3.69 -4.19)
Height (cm)	163.33 ± 5.54	164.77 ± 5.42	1.206	0.231	-1.43 (-3.8 - 0.93)
BMI (kg/m²)	26.57 ± 3.08	26.04 ± 3.48	0.753	0.453	0.54 (-0.88 -1.95)
Gestationa l age (weeks)	8.9 ± 1.97	8.95 ± 2.01	0.113	0.911	-0.05 (-0.91 -0.81)

Onset of bleeding was faster and duration of bleeding was shorter in misoprostol-letrozole, table 2
Table (2): Comparison between groups as regard onset and duration of vaginal bleeding.

	Group		t-test	p-value	Difference (95% CI)
	Misoprostol (N=25)	Misoprostol -Letrozole (N=25)			
	Mean± SD	Mean ± SD			
Onset of bleeding (hours)	6.4 ± 0.7	5.7 ± 0.95	3.828	<0.001	0.7 (0.34 - 1.07)
Duration of vaginal bleeding (days)	4.85 ± 1.79	3.79 ± 1.85	2.641	0.010	1.06 (0.26 - 1.87)

Figure 1 shows no statistically significant difference between groups as regard US examination at day 3 but shows statistically significant difference between groups as regard US examination at day 7 after first misoprostol dose. This means that combined therapy was associated with higher rate of complete evacuation than single therapy at the end of study.

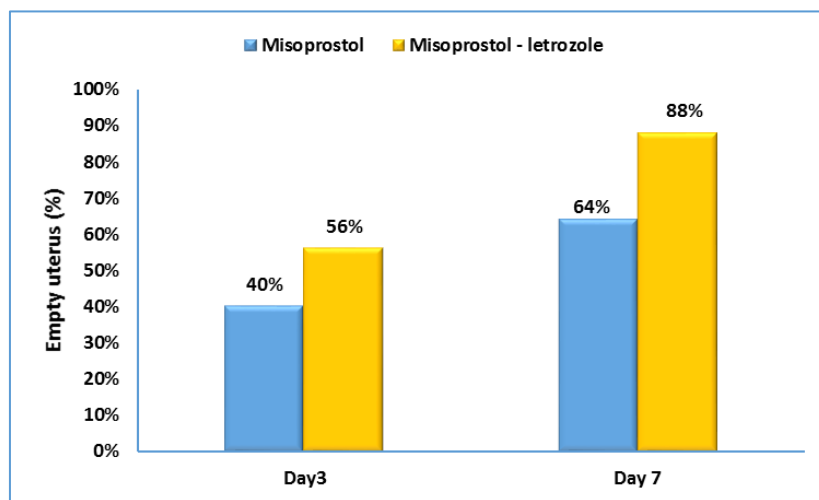


Fig (1): Results of US examination at day 3 and 7 day in both study groups.

There was no statistically significant difference between groups as regard hemoglobin level before study. There was statistically significant drop in Hb level of participants in both groups, but the drop was more in the misoprostol group and the difference in the drop was statistically significant, table 3.

Table (3): Hemoglobin level in both study groups before and after study.

	Group		t-test	p-value	Difference (95% CI)
	Misoprostol	Misoprostol -Letrozole			
	Mean ± SD	Mean ± SD			
Hb before	10.96 ± 0.45	10.98 ± 0.54	-0.180	0.858	-0.02 (-0.24 - 0.2)
Hb after	10.03 ± 0.47	10.27 ± 0.54	-2.235	0.028	-0.25 (-0.46 - -0.03)
Hb Before - Hb after	0.93 ± 0.440	0.70 ± 0.4037	2.468	0.016	0.226 (0.049-0.409)

The combined therapy was associated with higher rate of complete evacuation than single therapy at the end of study. Two patients in misoprostol group and one patient in misoprostol-letrozole group needed emergency D&C for inevitable abortion. Figure 2

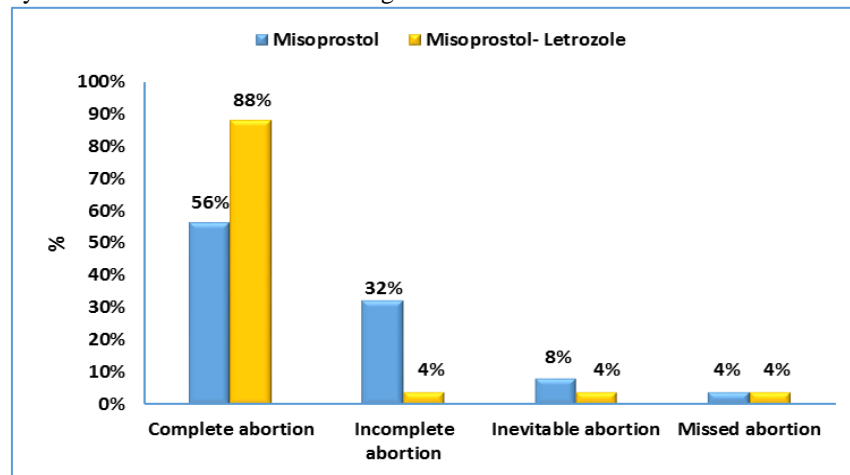


Fig (2): Outcome of abortion in both study groups.

There was no statistically significant difference between groups as regard Incidence of side effects. figure 3

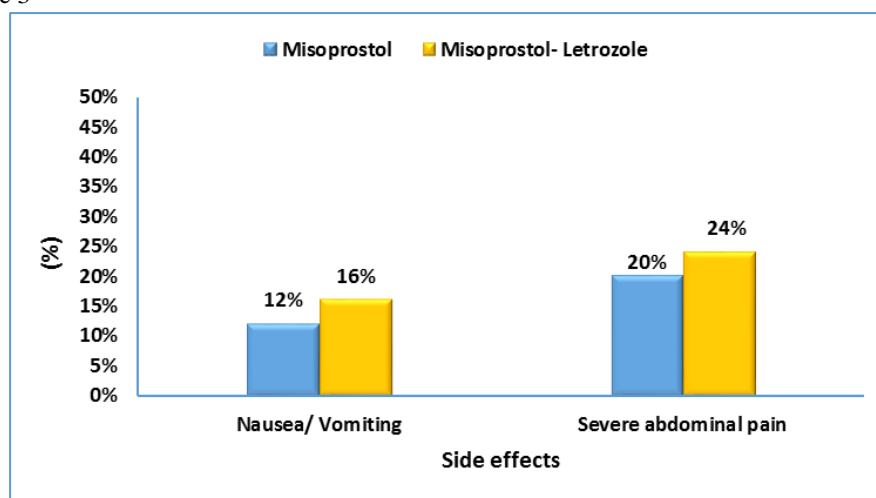


Fig (3): Incidence of side effects in both study group

3. Discussion

Our investigation was carried on 50 patients. The main gathering got 600 mcg of misoprostol without a moment's delay of finding orally. The subsequent gathering got letrozole 10

mg orally once every day for 3 days as pretreatment then 600 mcg of misoprostol orally.

Our outcomes showed that no measurably huge contrasts between bunches as respect the segment information.

In the main gathering (misoprostol just), 25 patients were broke down of which 14 patients brought about complete unnatural birth cycle (56%), 8 patients brought about inadequate premature delivery (32 %), 2 patients brought about unavoidable early termination (8 %) in which pressing clearing and curettage was required, and 1 patients demonstrated no distinction in the ultrasound examine (4%)

In the subsequent gathering (letrozole pretreatment followed by misoprostol), 25 patients were examined of which 22 patients brought about complete unnatural birth cycle (88 %), 1 patients brought about deficient premature delivery (4 %), 1patients brought about unavoidable early termination (4%) in which earnest clearing and curettage was required, and 1 patients demonstrated no distinction in the ultrasound check (4%).

The essential result of our examination which is finished premature delivery rate without careful intercession in pregnancies as long as 90 days (12 weeks incubation + 6 days) was 56% in the principal gathering (misoprostol just) contrasted with 88 % in the subsequent gathering (letrozole pretreatment followed by misoprostol), Therefore, the investigation shows measurably critical distinction between bunches as respect the pace of complete unsuccessful labor.

The pace of inadequate, unavoidable and missed premature delivery requiring further careful mediation was higher in the misoprostol gathering.

In one randomized fake treatment controlled clinical preliminary done by Naghshineh and her associates in 2014, on 130 ladies who were applicant of clinical fetus removal and qualified for legitimate early termination with gestational age <17 weeks, ladies were arbitrarily separated into two gatherings, each gathering 65 subjects, Case gathering; incorporate ladies who got pretreatment day by day oral portion of 10 mg letrozole for three days. Control gathering; incorporate ladies who got every day oral fake treatment for three days. Followed by sublingual misoprostol for cases and controls, as per ACOG rules dependent on patients' gestational age. The total premature delivery rate was seen in 76.7% in the letrozole gathering and in 42.6% of subjects of the control group[9].

This past examination shows genuinely huge contrast between the gatherings of the investigation which was concurred by our investigation, yet the pace of complete unnatural birth cycle as an essential result in our investigation was higher which might be clarified by the distinction in the gestational period of populace of the investigation and the

distinction in the course of organization of misoprostol.

In our examination the, the most widely recognized results were queasiness or potentially heaving, stomach torment or colic.

As respect stomach torment after organization of misoprostol, it was somewhat lower in the first (misoprostol just) bunch as it happened in 5 patients (20%) while in the second (letrozole) bunch it happened in 6 patients (24%) yet shows no measurably huge contrast.

As respect queasiness as well as spewing, it happened in 3 patients (12%) of the misoprostol gathering and in 4 patients (16%) of the misoprostol-letrozole gathering yet in addition shows no genuinely huge distinction.

Shuddering or hyperpyrexia didn't happen in any patient in our investigation and this might be because of utilizing the vaginal course for organization of misoprostol.

Nobody of our examination populace required blood bonding for extreme draining or sickliness influencing the overall condition in the two gatherings.

As respect the cost, it was a lot higher in the second gathering as the expense of 12 tablets of letrozole 2.5 mg, which was utilized as a pretreatment before misoprostol, was around 222 L.E. furthermore, this was covered by the scientist.

When looking at both examination bunches as respect beginning and span of vaginal seeping after first misoprostol portion it shows genuinely huge contrast.

The beginning of vaginal draining was altogether more slow in the first (misoprostol just) bunch than the second (letrozole) gathering, which imply that patients of the letrozole bunch start vaginal draining sooner than patients of the misoprostol gathering.

The span of vaginal draining was altogether more in the first (misoprostol just) bunch than the second (letrozole) gathering.

Likewise the shortage in hemoglobin level was fundamentally higher in the first (misoprostol just) bunch than that of the second (letrozole) gathering, which implies that vaginal draining was more in the principal gathering.

Our examination has demonstrated that letrozole with misoprostol routine is more powerful than misoprostol just in enlistment of first trimester missed unnatural birth cycle.

4. Conclusion

The utilization of letrozole pretreatment followed by misoprostol for enlistment of early termination in the first trimester is related with higher complete fetus removal rate than misoprostol as it were. Thus, it is prescribed to utilize letrozole followed by misoprostol routine for acceptance of fetus removal in cases with

first trimesteric missed abortion rather than misoprostol alone.

5. References

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