Misoprostol With or Without Letrozole for Treatment of Missed Miscarriage: A randomized controlled trial

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Abstract
Presentation Misoprostol is utilized for the clinical administration of unnatural birth cycle as it is more compelling in the beginning phases of pregnancy. Letrozole has an enemy of estrogen impact and is utilized for the pretreatment of premature delivery with misoprostol. Intend To look at the viability and wellbeing of letrozole with fake treatment pretreatment in the clinical administration of first trimester missed unsuccessful labor. Plan an imminent randomized twofold visually impaired case-control study. Patients and Methods Patients with missed unsuccessful labor of pregnancy as long as 63 days. 320 ladies were arbitrarily isolated into two gatherings of 160; the fake treatment bunch got fake treatment tablets once day by day for 3 days, trailed by 800 micrograms of misoprostol vaginally on the Third day of enrolment, while the letrozole bunch got letrozole 7.5 mg once every day for three days followed by same portion of vaginal misoprostol. The total fetus removal rate and Hb shortage of the two gatherings were looked at. The essential result measure was the finished fetus removal rate. Results A sum of 320 ladies were enrolled. The total premature birth pace of the letrozole bunch was fundamentally higher than that of the fake treatment gathering (82.6% contrasted and 68.2% (p < 0.001). There were noteworthy Hb shortage in letrozole gathering (p= 0.011) with non-huge factual distinction deprived for blood bonding. End Adding letrozole to misoprostol is related with a higher complete fetus removal rate.

1. Introduction
Misoprostol is a prostaglandin that causes myometrial constrictions, cervical relaxing and dilatation. It is utilized to prompt fetus removal and other ecobic impact [1]. It has the benefit of being financially savvy and stable with a low pace of results, which has prompted it being remembered for the World Health Organization rundown of fundamental meds [11]. Misoprostol is authorized for use to incite unsuccessful labor in Egypt. It is utilized off-mark to initiate work in the UK [6] and in Germany. Misoprostol without anyone else is utilized for the clinical administration of unnatural birth cycle as an option in contrast to medical procedure, with a triumph pace of somewhere in the range of 65 and 93%. It is more powerful in the beginning phases of pregnancy, where it additionally has the benefit of being less expensive, less obtrusive and staying away from careful intricacies [7].
Mifepristone utilized in blend with misoprostol accomplished higher paces of finished premature births of up to 95% [10] and is suggested for pretreatment in fetus removal and clinical unsuccessful labor, yet a less expensive and broadly accessible option is required, particularly in agricultural nations.
Letrozole is an oral aromatase inhibitor, which has been affirmed by the FDA [5]. Its enemy of estrogen impact has been demonstrated to be helpful in the pretreatment of pregnancy terminations when joined with misoprostol. It can accordingly supplant mifepristone, which is costly and not accessible in numerous nations [4].

The utilization of letrozole in mix with misoprostol to get higher paces of finished fetus removal was assessed by Lee and colleagues [3]. In their examination, letrozole was directed for 3 days followed by misoprostol and made a progress pace of 86.9%. In a pilot concentrate by Yeung and associates, a letrozole convention was utilized for 7 days and made a 95% progress rate [12].
In another pilot study [2] by Chai and Ho, mifepristone and letrozole were controlled preceding misoprostol and accomplished a 98% pace of complete fetus removal. In any case, bigger preliminaries are expected to build up the clinical adequacy of pretreatment with letrozole to accomplish total unsuccessful labor.
This randomized case control study intended to think about viability of misoprostol alone or in blend with letrozole in the clinical administration of first trimester missed unnatural birth cycle.

2. Patients and methods
This imminent randomized examination was completed in Zagazig General Hospital, Sharquia governorate.

Moral endorsement
The Ethical Committee of Benha University affirmed this investigation on March 2019. All ladies selected to the investigation gave their educated assent (Age over 18 years) preceding enrolment in the examination.
All ladies (n = 434) who were determined to have missed unnatural birth cycle (gestational age as long as 63 days) between January 2019 and March 2020 were drawn nearer for enrolment into the investigation.
Missed unsuccessful labor was analyzed by the ultrasound finding of no fetal cardiovascular movement in the fetal shaft. Rejection models incorporated a past endeavor to end the pregnancy, molar pregnancy, anomalous uterine injuries, for example, fibroids or innate distortions, clinical issues, for example, cardiovasular or hemorrhagic sickness, paleness (hemoglobin under 10 gm/dl), irregular BMI (Less than 25 Kg/m2 Or in excess of 35 Kg/m2) and realized extreme touchiness to any of the drugs utilized. 114 ladies were prohibited from the examination.
An itemized clinical history was taken of all ladies remembered for the examination (n = 320) and incorporated the date of the principal day of the last feminine time frame to ascertain gestational age. All ladies went through physical assessment including nearby assessment to survey the cervix. Examinations performed...
included blood gathering, Rh composing, CBC for hemoglobin worth and Trans-vaginal ultrasound to affirm missed fetus removal and to avoid molar pregnancy, fibroid, or uterine abnormalities.

Ladies were partitioned into 2 gatherings with 160 in each gathering. Gathering A (Letrozole gathering) got letrozole 7.5 mg once every day for 3 days followed by 800 micrograms of misoprostol controlled vaginally on the third day of enrolment. While bunch B (fake treatment gathering) got a fake treatment of reasonable inactive material once day by day for 3 days, trailed by 800 micrograms of misoprostol directed vaginally on the third day of enrolment.

Members remained in the clinic for in any event 4 hours after organization of misoprostol. Essential signs were recorded hourly. Results, presence of vaginal draining and the hour of removal of tissue mass were recorded as well. Careful clearing was done quickly under broad sedation in the event of vaginal draining influencing general condition.

Upon release from medical clinic, members were given journal cards to record the presence of vaginal draining and results. Patients were given severe guidelines to return to medical clinic once they create afflictions, significant vaginal dying, hostile vaginal release, or fever more than 38°C.

Subsequent visit on day seven, during which a transvaginal ultrasound was performed to screen result. Blood test was taken for hemoglobin level. Careful clearing was performed if there was missed or deficient unsuccessful labor.

An essential result measure was the pace of complete fetus removal accomplished inside multi week from the main portion of misoprostol. Optional result measures were careful departure (held results of origination or extensive dying) and decrease in hemoglobin esteem.

Randomization and blinding

Patients distributed into the investigation were randomized into both of two gatherings utilizing a PC produced list at a 1: 1 proportion. Disguise was accomplished utilizing shut envelopes as per the PC created list and an envelope was apportioned to every patient in like manner.

Test size figuring

The example size was determined with 160 ladies in each arm of the investigation, utilizing the recipe for examination of extent dependent on 95% certainty span and intensity of the investigation 80% with Alpha (α) blunder 5%. The point was to analyze the viability and security of misoprostol with letrozole versus misoprostol alone in treatment of missed premature delivery.

2.1 Statistical analysis

Information were broke down utilizing IBM® SPSS© Statistics variant 21 (IBM® Corp., Armonk, NY). Quantitative information were communicated as mean ± standard deviation (SD). Subjective information were communicated as recurrence and rate.

Autonomous t-trial of importance was utilized to look at 2 methods. Chi-square (χ2) test was utilized to think about extents of 2 subjective boundaries. Likelihood (p-esteem): p > 0.05 was viewed as immaterial, p ≤ 0.05 was viewed as noteworthy, and p < 0.001 was considered exceptionally critical.

3. Results

During the study period between January 2019, and March 2020, 434 women with missed miscarriage were approached and 114 patients were excluded or declined to participate in the study. Thus, 320 participants were recruited.

Individuals were randomized into the letrozole and placebo groups with 160 participants in each group (Fig. 1). 155 patients in letrozole group were analyzed, as five patients dropped out (two patients did not come back, and three patients were non-compliant). While 157 patients in placebo group were analyzed, as three patients dropped out (two patients did not come back, and one patient was non-compliant).
This study compared two treatment modalities for the medical management of missed miscarriage. The first group was received pretreatment with letrozole followed by misoprostol, while the second group was given placebo and misoprostol. There were no significant differences in age, body mass index and gestational age between the two groups Table (1).

Table (1) Demographic data in both groups.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Misoprostol (n=157)</th>
<th>Misoprostol-Letrozole (n=155)</th>
<th>t-Test</th>
<th>p-Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>Mean: 24.019; SD: 3.82822</td>
<td>Mean: 24.4903; SD: 3.97291</td>
<td>-1.067</td>
<td>0.287</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>8.382</td>
<td>1.5129</td>
<td>8.245</td>
<td>1.5887</td>
<td>0.78</td>
</tr>
<tr>
<td>BMI</td>
<td>23.223</td>
<td>4.1934</td>
<td>23.103</td>
<td>4.9467</td>
<td>0.23</td>
</tr>
</tbody>
</table>

The complete abortion rate in the letrozole group was significantly higher than that in the placebo group (82.6% compared with 68.2%, p-Value < 0.001), with a difference in complete abortion rates of 14.4% as shown in Table (2).

Table (2) Rate of complete miscarriage in both groups.

<table>
<thead>
<tr>
<th>Trans-vaginal US</th>
<th>Misoprostol (n=157)</th>
<th>Misoprostol-Letrozole (n=155)</th>
<th>Z</th>
<th>p-Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete miscarriage without surgical intervention (1ry outcome)</td>
<td>107</td>
<td>68.2</td>
<td>128</td>
<td>82.6</td>
<td>3.3165</td>
</tr>
</tbody>
</table>

The rate of incomplete abortion requiring surgical treatment was significantly lower in the letrozole group when compared with the placebo group. Eleven participants (7.07%) in the letrozole group who required surgical treatment versus 29 individuals (18.47%) in the placebo group needed surgical treatment as shown in Table (3). Moreover, both the missed miscarriage rate and inevitable miscarriage rate were lower in the letrozole group but the difference was not statistically significant Fig (2).

Table (3) Outcome after 7 days.

<table>
<thead>
<tr>
<th>Trans-vaginal US</th>
<th>Misoprostol (n=157)</th>
<th>Misoprostol-Letrozole (n=155)</th>
<th>Z</th>
<th>p-Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete miscarriage</td>
<td>29</td>
<td>18.47</td>
<td>11</td>
<td>7.07</td>
<td>3.0099</td>
</tr>
<tr>
<td>Missed miscarriage (no change in TVUS picture 7 days after Misoprostol)</td>
<td>7</td>
<td>4.43</td>
<td>3</td>
<td>1.94</td>
<td>1.303</td>
</tr>
<tr>
<td>Inevitable miscarriage</td>
<td>14</td>
<td>8.9</td>
<td>13</td>
<td>8.39</td>
<td>0.1571</td>
</tr>
</tbody>
</table>

Fig (2) outcome after 7 days.
Table (4) demonstrates mean hemoglobin before and after treatment between both groups. In the placebo group, mean hemoglobin before treatment was 11.78 g/dl (SD: 1.37 g/dl), while, in the letrozole group it was 11.69 g/dl (SD: 1.37 g/dl). There was no significant difference between both groups (p = 0.597). After treatment, mean hemoglobin was 11.19 g/dl in the placebo group (SD: 1.26 g/dl) and 10.91 g/dl (SD: 1.16 g/dl) in the letrozole group, with significant difference between groups (p = 0.042).

Table (4) hemoglobin changes in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Misoprostol (n= 157)</th>
<th>Misoprostol-Letrozole (n= 155)</th>
<th>t- Test</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ±SD</td>
<td>Mean ±SD</td>
<td>t</td>
<td>p-Value</td>
</tr>
<tr>
<td>Hb % before treatment</td>
<td>11.776 ± 1.3718</td>
<td>11.694 ± 1.3764</td>
<td>0.529</td>
<td>0.597</td>
</tr>
<tr>
<td>Hb % after treatment</td>
<td>11.186 ± 1.2588</td>
<td>10.906 ± 1.1587</td>
<td>2.046</td>
<td>0.042</td>
</tr>
<tr>
<td>Hb deficit</td>
<td>0.5898 ± 0.67198</td>
<td>0.7877 ± 0.70096</td>
<td>-2.546</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Blood transfusion commenced for patients with hemoglobin level less than 7 gm/dl. Table (5) clears that six patients in letrozole group received blood transfusion (3.9%). Seven patients in placebo group received it (4.5%). No statistically significant difference between the two groups as regards blood transfusion (p= 0.795).

Table (5) Comparison as regards blood transfusion.

<table>
<thead>
<tr>
<th></th>
<th>Misoprostol (n= 157)</th>
<th>Misoprostol-Letrozole (n= 155)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>150</td>
<td>149</td>
<td>299</td>
</tr>
<tr>
<td>%</td>
<td>95.5%</td>
<td>96.1%</td>
<td>95.8%</td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>%</td>
<td>4.5%</td>
<td>3.9%</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

4. Discussion

The current investigation is planned to evaluate letrozole as another synergistic operator in blend with vaginal misoprostol contrasted and misoprostol alone for clinical premature birth. Our outcomes exhibited a total fetus removal pace of 82.6% in ladies with missed premature delivery of gestational age as long as 63 days with routine of letrozole and vaginal misoprostol with lower contrasted with 68.2% in ladies with the routine of fake treatment and vaginal misoprostol.

In one randomized controlled investigation [3], the total premature birth rate in the letrozole bunch was essentially higher than that in the fake treatment gathering (86.9% contrasted and 72.6%). A higher pace of complete unsuccessful labor without careful mediation was found in that review than in our own (86.9% contrasted with 82.6%) in Letrozole gathering. In fake treatment gathering, it is additionally higher (72.6% contrasted with 68.2%). Nonetheless, the past examination utilized diverse routine of letrozole with the portion of 10 milligram every day for three days (in our investigation we utilized 7.5 milligram of letrozole for three days) which may clarify the higher complete unsuccessful labor rate which may likewise be alluded to the number of cases in that review (168 all out member in Lee investigation).

The pace of fragmented unnatural birth cycle requiring careful treatment was fundamentally lower in the Letrozole bunch when contrasted with the fake treatment gathering, which concurred with our examination. Both missed premature delivery rate and continuous pregnancy rate were lower in the letrozole gathering however the thing that mattered was not measurably huge, thus, Lee and his partners [3] concurred with our examination as well.

In another investigation done by Tang and his associates, 40 patients who mentioned end of pregnancies as long as 63 days, clinical unsuccessful labor was performed with Letrozole 7.5 milligram day by day for two days followed by 800 microgram vaginal misoprostol in 20 ladies and Letrozole 7.5 milligram joined with 200 mg mifepristone in another 20 ladies [9]. In that review, the routine of Letrozole and misoprostol shows a total
unnatural birth cycle pace of 80%, which is near our investigation results (82.6%).

Yeung et al. directed a preliminary on 20 ladies that were applicants of fetus removal acceptance. The subjects were allowed Letrozole 7 days before accepting vaginal Misoprostol, which was unique in relation to the current examination since our patients began getting Letrozole 3 days preceding taking vaginal Misoprostol. The referenced examination announced a general total premature birth pace of 95%, which is higher than our finding and might be clarified by longer length of pretreatment with Letrozole. Modest number of members might be a potential clarification [12].

Moreover, Chai et al. in 2013 played out a preliminary on 50 ladies and gave them a solitary portion of 200mg Mifepristone and 10mg Letrozole day by day 3 days preceding giving them 800μg vaginal Misoprostol. They inferred that Letrozole builds the pace of complete premature birth to 98% [2]. In spite of the fact that it is higher pace of complete fetus removal than in our examination (82.6%), yet, it clears the improving impact of letrozole over the standard routine which known to be 95%.

At last, various new examinations express that, executing powerful medication regimens for actuating fetus removal is more reasonable and danger free than techniques, for example, vacuum yearning [8], which ought to be focused by doctors.

5. Advantages and Limitation

The current examination has the upside of being an all around planned RCT (Randomized Controlled Trial), effectively material selecting patients from general clinic, with investigation expressed to be ITT (Intention To Treat). The most significant constraint of this investigation was absence of exact assessment of cost examination. We propose more examinations as respects cost adequacy in private clinics in which D&C may cost significantly more.

6. Conclusions

Along these lines, consolidating Letrozole with misoprostol is viable in end of first trimesteric pregnancy. The wellbeing profile of letrozole was consoling. There was no genuine unfriendly function. Further examinations are expected to refine the routine to improve its adequacy.

References


