



## A comparison between induction of labor with 3 methods of titrated oral misoprostol, constant dose of oral misoprostol and Foley catheter with extra amniotic saline infusion (EASI), in women with unfavorable cervix

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### Abstract

**Background:** Different methods of cervical ripening and induction of labor have been used in the cases of unfavorable cervix with different levels of success, but no method has been found to be the best option. The purpose of the present study was to find the effects and side effects of three different methods of cervical ripening and induction of labor. These three methods were oral titrated misoprostol, constant dose of oral misoprostol and Foley catheter with extra-amniotic saline infusion.

**Methods:** This clinical trial was performed on women with unfavorable cervix who had been admitted in Akbarabadi Teaching Hospital for induction of labor and had bishop score of less than six; between March 2014- March 2015. The eligible women were assigned into three groups. In titrated oral misoprostol group (n=33), titrated solution of misoprostol, and in oral misoprostol group (n=33), 50µg oral misoprostol every four hours and in Foley catheter group (n=50), Foley catheter with extra-amniotic saline infusion were administered. The main outcome was the number of vaginal deliveries during the first 24 hours. In addition, number of cesarean deliveries and adverse effects were compared between the three groups. The obtained data were analyzed using SPSS 18 software. Data analysis was performed according to the intention to treat principle. Chi-square test, Fisher Exact test, Student t-test, and Mann-Whitney U test, were used for comparing data. P-value≤0.05 was considered statistically significant.

**Results:** The three groups did not have any significant difference according to maternal age, gestational age at the time of admission, gravidity, parity, and primary Bishop Score. There was no significant difference between the three groups for the main outcome, which was vaginal delivery during the first 24 hours (p=0.887). There was no significant difference between the three groups according to hypertonicity, uterine hyperstimulation, meconium passage, non-reassuring fetal heart rate, neonatal Apgar score in minutes one and 5, and mean duration of beginning the intervention up to delivery. However, uterine tachysystole and NICU admission were more in the group to whom the titrated solution of misoprostol was administered (p=0.002 and p=0.037 respectively). The number of cesarean deliveries due to failure to progress was higher in the EASI group. However, EASI group showed the least number of none-reassuring fetal heart rate between the three groups. Meconium passage was more in the titrated misoprostol group, but the difference was not significant.

**Conclusion:** All three methods are appropriate methods for induction of labor in the cases of unfavorable cervix; and choosing each method depends on the expertise of labor staff, accessibility to the medications, cost, and taking care for monitoring the patients and adverse effects.

**Keywords:** Cervical ripening; extra-amniotic saline infusion (EASI), Foley catheter, Induction of labor, Misoprostol, Prostaglandin E1, Meconium, Tachysystol

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#### ↑What is “already known” in this topic:

Different methods of cervical ripening and induction of labor have been used in the cases of unfavorable cervix with different levels of success, but no method has been found to be the best option.

#### →What this article adds:

All three methods are appropriate methods for induction of labor in the cases of unfavorable cervix; and choosing each method depends on the expertise of labor staff, accessibility to the medications, cost, and taking care for monitoring the patients and adverse effects.

## Introduction

More than 20 percent of pregnant women need induction of labor (1), which can be performed with different methods. Oxytocin is the most common medication that is used for this purpose (2). However, in the cases with unfavorable cervix; there are various methods of cervical ripening which will be used before starting the labor induction process. Mechanical methods were the oldest methods used for cervical ripening (3), which have been substituted by pharmaceutical agents in recent years. However, mechanical methods are simpler, safer, and cheaper, with less adverse effects, and they do not need any specific temperature preservation (3).

Among various pharmaceutical methods, a commonly studied medication which has regularly been introduced as the best option for cervical ripening is misoprostol (Cytotec Searle), which is a prostaglandin E<sub>1</sub> analogue (4-10), and it is used off-label for induction of abortion and labor. Misoprostol can be used in different ways, including oral, vaginal, sublingual, buccal, titrated solution and rectal (4-11). Prostaglandin E<sub>2</sub> (12-16), prostaglandin F<sub>2α</sub> (12), mifepristone (17), nitric oxide donors (18, 19), corticosteroids (20-22), propranolol (23), estrogen (24), hyaluronidase (25), and relaxin (26) are among the pharmaceutical agents which have been used for cervical ripening and induction of labor.

Mechanical methods which have been used for this purpose, include balloon catheter with and without traction on the cervix (5, 21, 27), with different capacities for the bulb of foley catheter (28), and with adding extra-amniotic saline infusion (3, 21, 27). The other mechanical methods are intracervical dilators, including both natural (laminaria) and synthetic (Dilapan) (3). Sweeping of the membranes (29), breast stimulation (30), sexual intercourse (31, 32), using castor oil, bath and/ or enema (33), traditional methods like acupressure and acupuncture (34), are amongst the methods used for cervical ripening and labor induction assistance which all have some levels of success rate. There are many studies, which compare these different methods with each other, with different results. It would be beneficial for further studies to be performed in order to compare these methods to reach a definitive conclusion and finding the best method.

The purpose of the present study was to compare mechanical methods of extra amniotic saline infusion, and misoprostol with two different forms (oral misoprostol and titrated solution of misoprostol) for induction of labor in the cases of unfavorable cervix with low bishop score.

## Methods

The study was performed as a non-randomized prospective clinical trial on pregnant women who were admitted to the labor ward of Akbarabadi Teaching Hospital for induction of labor and had bishop score of less than six; between March 2014- March 2015. Written informed consent was obtained from all participants. They were fully informed about the study, and institutional review board approval and also institutional ethics committee approval was given to the study which was also registered in Iran

Registry of Clinical Trial (IRCT).(Trial registration number IRCT201702282624N22).

Inclusion criteria included maternal age between 18-40 years old; gestational age of more than 37 weeks (according to certain LMP and ultrasound confirmation of the first trimester of pregnancy); singleton; cephalic presentation; intact membrane and Bishop Score of less than 6. Exclusion criteria were any sign of fetal distress; placenta previa and any vaginal bleeding of more than bloody show; history of any surgery on uterus including cesarean section; and known uterine anomaly; intra-uterine fetal death; and known hypersensitivity to misoprostol. Firstly, all women were examined by an investigator for determination of Bishop Score and eligibility. Eligible women were assigned according to the choice of obstetrician into three groups.

In the oral misoprostol group, 50µg misoprostol was administered, and women were followed up to 4 hours. FHR and uterine contractions were checked hourly. In the cases of not having suitable contractions after 4 hours, another 50 µg of misoprostol was administered every 4 hours until obtaining suitable contractions or up to maximum 6 doses (300 µg totals). Then the women were followed up to delivery. Suitable contractions were defined as forceful contractions with duration of 40-50 seconds and intervals of 2 minutes.

In the group of titrated solution of misoprostol, 200µg misoprostol tablet was solved in 200 mL of water (this solution is stable in the room temperature and contains 1µg misoprostol in 1 mL of solution). First, 20 mL (20µg) of misoprostol was administered hourly for 4 hours. Then in spite of not having suitable contractions, 40 mL (40µg) of misoprostol solution was administered every 1 hour for 4 doses and was repeated after 4 hours with 60 mL (60µg) of misoprostol solution for a maximum of 4 doses (in total 480µg). With appropriate contractions, misoprostol was discontinued during the labor process. Whenever appropriate contractions were ceased, 10 mL of solution was prescribed and was increased to 20 mL one hour later in case of not having favorable contractions in the incremental manner of 10-20-30-up to 40 mL per hour.

In the EASI group, Foley catheter of number 18 was introduced through the cervical canal and was filled with 30 mL distilled water and was fixed above the internal cervical ostium, and was connected to normal saline solution. The normal saline was entered into the uterus with the rate of 30 drops per minute. After the expulsion of the Foley catheter, oxytocin was started in the amount of 2.5 mUI/min and was increased every 15 minutes up to 40 mUI/min.

The main outcome was defined as the number of vaginal deliveries during the first 24 hours. In addition, number of cesarean deliveries and adverse effects were compared between the three groups. In all women careful monitoring of fetal heart rate (FHR) and maternal condition was performed.

Uterine tachysystole was defined as more than five contractions per 10 minute for at least two repeated ten-minute periods. Uterine hyperstimulation was defined as uterine

tachysystole plus non-reassuring FHR. Uterine hypertonicity was defined as contractions with a duration of more than 2 minutes plus non-reassuring FHR. FHR and uterine contractions were checked every 1 hour in the latent phase of labor and every 30 minutes in the active phase of labor. Blood pressure and pulse rate were monitored every 2 hours.

In both misoprostol groups, in the case of not having delivery during the first 24 hours, oxytocin was started 4 hours after the last administered misoprostol. To obtain a power of 80% ( $\alpha=0.05$ ), we planned to include 30 participants in each group as we assumed that it would be possible to detect a difference of 10 percentage points in the main outcome (according to previously published data) between the three groups. Sampling was performed as consecutive sampling. The obtained data were analyzed using SPSS 18 software. Data analysis was performed according to the intention to treat principle. Chi-square test, Fisher Exact test, Student t-test, and Mann-Whitney U test, were used for comparing data. The statistician was not aware of

the groups of the study. P-value $\leq 0.05$  was considered statistically significant.

**Results**

One hundred forty-five women were assessed for eligibility, and finally 116 women finished the study (33 women in the titrated group, 33 women in the oral group and 50 women in the EASI group) (Fig. 1).

The three groups did not have significant difference according to maternal age, gestational age at the time of admission; gravidity, parity, and primary Bishop Score (Table 1). The mean Bishop was  $2.3\pm 1.2$ . There was no significant difference between the three groups for the main outcome, which was vaginal delivery during the first 24 hours. There was no significant difference between the three groups according to uterine hypertonicity, uterine hyperstimulation, meconium passage, non-reassuring FHR, neonatal Apgar score in minutes one and five, and mean duration of beginning of intervention up to delivery (Table 2), however, uterine tachysystole and NICU admission were higher in the titrated group. ( $p=0.002$  and  $p=0.037$  respectively) (Table

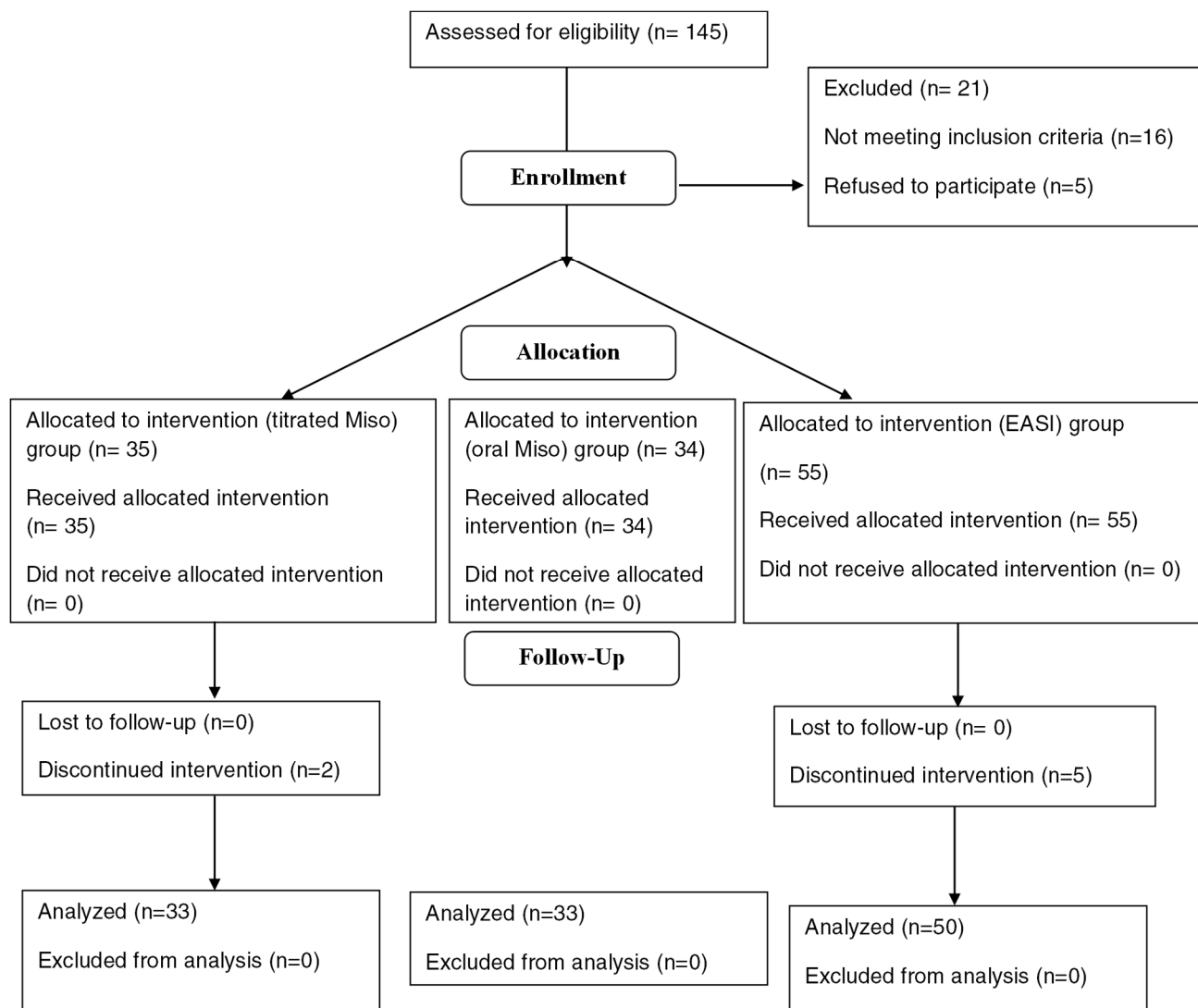


Fig. 1. The Consort E-Flowchart

Table 1. The characteristics of the women of the three groups

Characteristics	Titrated misoprostol n=33	Oral misoprostol n=33	EASI n=50	p
Age (year) M±SD	25.58±4.78	25.48±5.49	27.88±5.49	0.555
Gestational age (weeks) M±SD	39.81±0.91	39.87±1.21	39.3±1.5	0.091
Gravidity: N (%)				
1	18(54.5%)	21(63.6%)	31(62%)	
2	10(30.3%)	6(18.2%)	7(14%)	
3	4 (12.1%)	4(12.1%)	7(14%)	0.889
4	1(3%)	2(6.1%)	2(4%)	
5	0(0%)	0(0%)	3(6%)	
Parity: N (%)				
0	22(66.7%)	23(69.7%)	34(68%)	
1	8(24.2%)	6(18.2%)	9(18%)	
2	2(6.1%)	4(12.1%)	4(8%)	
3	1(3%)	0(0%)	2(4%)	0.966
4	0(0%)	0(0%)	1(2%)	
0	1(3%)	1(3%)	4(8%)	
Primary Bishop Score				
1	14(42.4%)	11(33.3%)	20(40%)	
2	16(48.5%)	18(54.5%)	26(52%)	0.311
3	1(3%)	2(6.1%)	0(0%)	
4-6	1(3%)	1(3%)	0(0%)	

Table 2. Outcome of labor in the three groups

Characteristics	Titrated misoprostol n=33	Oral misoprostol n=33	EASI n=50	p
NVD during the first 24 hours: N (%)	15(45.3%)	19(57.5%)	25(50%)	0.887
Time from intervention to delivery (h) M±SD	12.54±8.19	14.42±8.29	14.83±7.9	0.487
Total delivery NVD	17(51.5%)	21(63.6%)	27(54%)	0.568
ery c/s	16(48.5%)	12(36.4%)	23(46%)	
N (%)				
Apgar Score: min 5 M±SD	8.6±0.52	8.75±0.50	8.84±0.37	0.798
Apgar Score : min 10 M±SD	9.90±0.29	9.84±0.44	9.92±0.27	0.437
NICU admission: N (%)	15(45.5%)	6(18.2%)	21(42%)	0.037*
None-reassuring FHR: N (%)	9(27.3%)	10(30.3%)	8(16.5%)	0.261
Meconium: N (%)	9(27.3%)	3(9.1%)	6(12%)	0.082
Hypertonicity: N (%)	1(3%)	0(0%)	1(2%)	0.627
Hyperstimulation: N (%)	2(6.1%)	4(12.1%)	4(8%)	0.666
Tachysystole: N (%)	6(18.2%)	1(3%)	0(0%)	0.002*

\* Significant

Table 3. The indications of cesarean delivery in the 3 groups

The reasons for cesarean	Titrated misoprostol n=16	Oral misoprostol n=12	EASI n=23	p
Non- reassuring FHR	10(62.5%)	8(66.7%)	9(39.1%)	0.532
Meconium	2(12.5%)	1(8.3%)	2(8.7%)	0.846
Failure to progress	4(25%)	3(25%)	12(52.17%)	0.547

2). The number of cesarean deliveries due to failure to progress was higher in the EASI group. However, EASI group showed the least none-reassuring FHR between the three groups. Meconium passage was more in the titrated misoprostol group, but the difference was not significant. Occurrences of NICU admission were more in the group with titrated solution of misoprostol, because meconium passage was more and unfortunately in our hospital, this is the only reason for admitting the neonate in the NICU.

The causes for cesarean section in the three groups are shown in Table 3. In the titrated group, 29 women had appropriate contractions after 4 hours (80µg misoprostol), and the remaining four women had appropriate contractions after 6 hours (160µg) who all delivered vaginally.

In the oral misoprostol group, 31 women had appropriate contractions with four doses (200µg) of misoprostol and in two cases received six doses (250µg) for obtaining appropriate contractions, and these two cases had vaginal delivery. The minimum time from intervention to delivery was

3 hours in the titrated group, and maximum duration of intervention was 31 hours. These time periods for the other 2 groups were 4 hours and 41 hours for the oral misoprostol group and 5 hours and 35 hours for EASI group respectively, which did not show a significant difference.

### Discussion

In the present study, the number of vaginal deliveries during the first 24 hours were not different between the three groups. In addition, number of cesarean deliveries, mean interval between the beginning of intervention up to delivery, and neonatal Apgar scores, were not different between groups. However, uterine tachysystole and neonatal NICU admissions were higher in the titrated misoprostol group. Meconium passage was more in the titrated solution group, but the difference was not significant. Fetal distress, uterine hyperstimulation, and uterine hypertonicity were not different between the three groups. Cesarean section due to failure to progress was more in the EASI group. Cesarean delivery due to non-reassuring FHR was less in this group;

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however, the difference was not significant. These results are comparable with other studies.

The main limitation of this study was that it was not a randomized trial. It can cause a major selection bias. The sample size was small, especially in groups with misoprostol, and it lowers the power of the study.

Various methods of labor induction have been used throughout the world and have been compared for safety, efficiency, cost-effectiveness and patient friendliness. Several studies have been performed on different methods of cervical ripening and induction of labor in the cases of unripe cervix with semi-comparable results.

PGS was used for labor induction from 1960s (12), and several studies have been performed for their efficacy and safety. Using titrated solution of misoprostol has been suggested as an alternative to oxytocin in the hospitals without enough facilities for electronic infusion and careful monitoring of oxytocin; because the probability of uterine hyperstimulation with oxytocin is more common, (11). Oral misoprostol solution has been proposed as a safe and effective method in comparison with standard methods of induction of labor with oxytocin (8, 9).

Oral misoprostol is preferable to vaginal misoprostol especially in the cases in which the risk of ascending infection is higher while using the vaginal route (4, 10).

A comparison between the vaginal and sublingual usage of misoprostol showed similar efficacy, but meconium liquor was higher in the sublingual route (6). Also, vaginal and oral misoprostol, were compared for induction of labor. However, the best routes and dosages of misoprostol are still debatable and deserve more research (7).

Many obstetricians prefer to use dinoprostone (PGE<sub>2</sub>), instead of misoprostol, which has the legal license for induction of labor (10). In comparison between misoprostol and dinoprostone for induction of labor (13, 35), misoprostol led to more vaginal deliveries during the first 24 hours. However, uterine tachysystole and hyperstimulation were more in the misoprostol group. Using single doses of 50µg vaginal misoprostol was more cost-effective and efficient than vaginal insert of dinoprostone 10mg (15). In addition, oral titrated solution of misoprostol has been reported as effective as vaginal dinoprostone for labor induction in term pregnancies with less adverse effects (14). Comparison between 25µg and 50µg vaginal misoprostol, have proved more efficacy for higher dosages, but higher rates of uterine tachysystole and hyperstimulation, cesarean delivery due to non-reassuring FHR, NICU admission and meconium passages were reported (36). This study supported that 25µg dosages are generally safer options. Different responses to various routes and dosages of PGS might be attributable to different ethnical backgrounds (37).

Mechanical methods have been compared with PGS in different studies, and acceptable and similar results have been reported for two methods (5, 16, 38-39). Even in the cases of ruptured membrane for more than 18 hours, Foley catheter has been used for induction of labor and was effective and safe in comparison with misoprostol (38). Comparison between mechanical methods and misoprostol has shown more cases of uterine hyperstimulation in using

misoprostol. However the rate of vaginal deliveries during the first 24 hours has been the same, although, mechanical methods had lower rates of cesarean deliveries in comparison with oxytocin (3).

A comparison between Foley catheter and vaginal dinoprostone for induction of labor did not show significant difference according to cost-effectiveness because Foley catheter group had a longer duration of labor and were in the labor ward for a longer duration (16); however, efficacy on delivery rate was the same for the two groups.

A meta-analysis (39) which compared the effectiveness of Foley catheter and misoprostol, did not find a significant difference for the cesarean section rate between the two groups, while the rate of hyperstimulation and FHR changes and instrumental vaginal delivery were less reported in the Foley catheter group (39). This study has supported Foley catheter as a safe and effective method for cervical ripening with more benefits. The other study has also proposed comparable results (40).

The combination of these different methods has also been compared (5, 41, 42). Using combination of misoprostol and Foley catheter for cervical ripening in comparison with misoprostol alone (41), showed shorter duration intervals to delivery and less uterine tachysystole in the combination group, however, the rate of chorioamnionitis was higher, and the rate of cesarean did not differ. This study is in accordance with the other study concerning efficacy and safety (42).

The main limitation of the present study was to assign the women based on the choice of an obstetrician that can introduce large bias to the study, however, in the end, there were no significant differences between the groups for confounding factors.

Regarding the above-mentioned studies and the present study, all three methods are appropriate methods for induction of labor in the cases of unfavorable cervix; and choosing each method depends on the expertise of labor staff, accessibility to the medications, cost, and taking care for monitoring the patients and adverse effects.

### Conflict of Interests

The authors declare that they have no competing interests.

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