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**Original Research Article**

# Randomized, double-blind, three-arm, parallel-group study to compare the efficacy and safety of a single dose of 100 and 200 mg of mifepristone for cervical ripening in term pregnancies

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## ABSTRACT

**Background:** Mifepristone is an antiprogestin developed to antagonize the action of progesterone by inhibiting its receptors. It has had a recognized role in the medical termination of early pregnancy, reduction in the volume of uterine fibroids and endometriosis symptoms. A new indication for labor induction and cervical ripening in has been proposed. The objective was to compare the efficacy and safety of mifepristone 100 and 200 mg with placebo for cervical ripening in term pregnancies.
**Methods:** Double-blind, placebo-controlled trial of 90 term pregnancy women randomly assigned to receive orally tablet of 100 mg and 200 mg mifepristone or placebo. Efficacy was assessed by measuring changes in cervical ripening according to Bishop 72 hours after treatment. Statistical analysis was using the t-student test and the chi-square test. The relative risk (RR) was determined with a 95% confidence interval.
**Results:** The bishop score and the number of contractions at 48 hours in the group of 200mg of mifepristone presented a significantly higher mean value in relation to the placebo ($p=0.04$). At 72 hours, cervical length showed a significant difference ($p<0.01$) in both mifepristone groups compared to the placebo group. Also, at 72 hours a significant increase in the mean duration of contractions was demonstrated in the 100 mg mifepristone group.
**Conclusions:** There was a significant increase in Bishop's score for the 200 mg mifepristone group probably due to a significant increase in contractions at 24 hours. No differences were observed between groups in adverse events.

**Keywords:** Cervical ripening, Labor induction, Mifepristone

## INTRODUCTION

Mifepristone is a 19-nor steroid with high affinity for the progesterone receptor to which it strongly binds and inhibits its activity at the cellular level with a powerful antiprogestin, anti-glucocorticoid and weak antiandrogenic effects.[1,2] It has been used as an abortifacient in high doses of 600 mg and in Cushing's syndrome at 200 mg/day.[3] At present it has been proposed for other pathologies such as fibroids and endometriosis in long-term low doses and due to its effects on uterine contractility and the maturation of the cervix without apparent serious adverse effects on the mother and fetus, it has been considered as a good option for cervical ripening and induction of labor in term pregnancies.[4-11]

Studies carried out in the induction of labor indicate that mifepristone is effective in a wide range of doses of 50-600 mg.[6-8] However, the appropriate dose of mifepristone for cervical ripening has not yet been established. It is currently believed that lower doses may be just as

effective and have a better safety profile; some studies have showed that doses of 200 mg are effective, and it is not ruled out that lower doses may also be effective.[9,12,13]

In a systematic review, mifepristone was found to be better than placebo in ripening the cervix. In addition to a possible reduction in the incidence of caesarean sections without adverse effects related to its use.[14]

The objective of this study was to evaluate the effectiveness and safety of doses of 100 and 200 mg mifepristone versus placebo for cervical ripening in term pregnancies.

## METHODS

Study type: A randomized double-blind, three-arm, parallel-group study to compare the efficacy and safety of a single dose of 100 and 200 mg mifepristone for cervical ripening in term pregnancies was performed in a private setting Hospital in Managua, Nicaragua between October 2016 to November 2017.

Randomization was performed using a generating computer random table and a numbered opaque enveloped were used to conceal the list of generated numbers. Blinding was performed with pills that were identical in size and color, they were stored in the hospital pharmacy and dispensed according to the assigned number. Patients and investigators were blinded. The pills were provided by Litaphar laboratories. 20730 Azpeitia, SS, España.

Selection Criteria: Women between 18 and 40 years of age at the time of signing the consent; with a single cephalic pregnancy of 37-41 weeks duration confirmed by early ultrasound or reliable FUR, who were not in labor and that labor induction could be postponed for 72 h. Exclusion criteria were multiparous women (parity >5), with previous cesarean delivery or history of uterine surgery, fetal weight estimated by ultrasound less than 2000 g or greater than 4000 g with suspicion of cephalopelvic disproportion. Non-reactive non-stress test, antepartum hemorrhage, chorioamnionitis, severe oligohydramnios, known hypersensitivity to mifepristone or prostaglandins or any condition that, in the judgment of the investigator, may interfere with compliance with patient safety procedures or study assessments. Procedure: The patients were randomized in a ratio of 1: 1: 1 to Group 1 (100 mg of mifepristone), Group 2 (200 mg of mifepristone) or Group 3 (placebo). All recruited patients were included in the statistical analysis.

The study comprised 3 periods: 1. Selection period: inclusion, exclusion, and informed consent. 2. Delivery period, which included visit 1 (baseline), visit 2 at 24 hours, visit 3 at 48 hours. 3. Postpartum period, within 24 hours of delivery. The estimated maximum study duration per patient was approximately 96 hours.

Ethical approval: Monte España Hospital Ethic Board approved the protocol.

Statistical analysis: The sample size necessary was 90 pregnant women to test with 80% power a p value of .05 and 95% confidence interval. The relative risk (RR) was determined, with respect to the 95% confidence interval (95% CI) and the determination of the chi-square test as a measure of association between the two doses of mifepristone evaluated in relation to placebo. for primary and secondary end points (Bishop's index ≥7, changes in uterine dynamics and use of oxytocin). All analyzes were developed using Stata 10.1 (Stata Corp, 2009. Tx, USA) and a statistically significant value of 0.05 was defined.

## RESULTS

A total of 90 patients were recruited into the study with 30 participants allocated to 200mg mifepristone, 29 with 100mg of mifepristone and 31 women to the placebo group. No significant differences were found in the baseline characteristics (Table 1).

**Table 1: Baseline characteristics of the population according to group.**

| Baseline characteristics | Placebo (M±SD) (n=31) | Mifepristo 100 mg (n=29) | P value | Mifepristo 200 mg (n=30) | P value** |
|---|---|---|---|---|---|
| **Years** | 26.82±4.35 | 25.89±4.37 | 0.42 | 25.23±4.52 | 0.17 |
| **Week gestation** | 38.20±0.68 | 38.21±0.57 | 0.96 | 38.23±0.77 | 0.89 |
| **previous vaginal delivery N (%*)** | 17 (100.00) | 15 (100.00) | 1.00 | 14 (100.00) | 1.00 |
| **Vital signs at first assessment** | | | | | |
| **SAP** | 108.7±5.62 | 108.3±5.62 | 0.77 | 108.3±5.83 | 0.35 |
| **PAD** | 70.32±4.06 | 70.68±3.71 | 0.72 | 70.57±5.69 | 0.84 |
| **Pulse** | 75.06±3.98 | 75.10±3.35 | 0.97 | 75.48±3.65 | 0.67 |
| **Temperature (°C)** | 36.38±0.24 | 36.26±0.27 | 0.08 | 36.42±0.29 | 0.59 |

* Denominator: Number of patients with previous delivery, ** Comparison according to placebo group.

**Table 2: Comparative baseline characteristics between groups.**

| | Placebo (M±SD) (n=31) | Mifeprist 100 mg (n=29) | P value | Mifeprist 200 mg (n=30) | P value |
|---|---|---|---|---|---|
| **Uterine contraction time (s)** | 2.06±8.41 | 15.40±19.0 | <0.01 | 8.57±15.89 | 0.23 |
| **Number of contractions in 10 min** | 0.22±0.50 | 0.62±0.78 | 0.02 | 0.48±0.78 | 0.21 |
| **Tachysystole N (%)** | 0 (0.00) | 0 (0.00) | 1.00 | 1 (3.33) | 0.30 |
| **Bishop index** | 1.82±1.37 | 1.77±1.45 | 0.88 | 1.56±1.50 | 0.51 |
| **IOC dilation - cm** | 1.29±2.34 | 2.96±3.54 | 0.06 | 2.50±3.60 | 0.23 |
| **Cervical length –mm** | 33.8±8.32 | 36.6±8.31 | 0.20 | 32.9±7.64 | 0.67 |

**Table 3: Evaluation of quantitative secondary endpoints according to dose of Mifepristone vs placebo and evaluation visit.**

| | Placebo | | | Mifepristone 100 mg | | | | Mifepristone 200 mg | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Secondary endpoints** | **N** | **Media** | **SD** | **N** | **Media** | **SD** | **p*** | **N** | **Media** | **SD** | **p**** |
| **Visit 2** | | | | | | | | | | | |
| Duration of contraction (sec) | 31 | 2.6 | 14.33 | 29 | 3.96 | 21.33 | 0.38 | 30 | 1.46 | 17.19 | 0.9 |
| Number of contractions | 31 | 0.1 | 0.76 | 29 | 0.48 | 1.18 | 0.23 | 30 | 0.76 | 1.35 | 0.02 |
| Bishop punctuation | 31 | 1.41 | 2.13 | 29 | 2.37 | 2.12 | 0.09 | 30 | 2.86 | 3.02 | 0.04 |
| ICO Dilatation (cm) | 31 | 4.26 | 3.9 | 29 | 4.57 | 5.23 | 0.87 | 30 | 6.25 | 8.29 | 0.51 |
| Cervical length difference-(mm) | 31 | 4.4 | 5.77 | 29 | 5.41 | 7.19 | 0.55 | 30 | 6.33 | 9.57 | 0.35 |
| **Visit 3** | | | | | | | | | | | |
| Number of contractions | 24 | 0.58 | 0.83 | 23 | 0.7 | 1.43 | 0.74 | 20 | 0.85 | 1.46 | 0.45 |
| Bishop punctuation | 24 | 2.41 | 2.9 | 23 | 3.08 | 1.99 | 0.36 | 21 | 3.85 | 2.93 | 0.1 |
| ICO Dilatation (cm) | 24 | 5.01 | 4.04 | 23 | 7.78 | 8.17 | 0.24 | 21 | 6.15 | 6.98 | 0.72 |
| Cervical length (mm) | 24 | 4.62 | 4.51 | 23 | 8.61 | 7.17 | 0.02 | 21 | 10 | 8.46 | <0.01 |

* Comparison of Mifepristone 100 mg vs. placebo; ** Comparison of Mifepristone 200 mg vs. placebo.

**Table 4: Comparison of mean time to labor or birth according to comparison group.**

| | Placebo | | | Mifepristone 100 mg | | | | Mifepristone 200 mg | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Secondary endpoints** | **N** | **Media** | **SD** | **N** | **Media** | **SD** | **P*** | **N** | **Media** | **SD** | **P**** |
| **Average time to delivery (hours) ǂ** | 22 | 191.5 | 187.44 | 20 | 124.90 | 76.35 | 0.52 | 22 | 71.45 | 22.41 | <0.01 |
| **Route of pregnancy termination** | **Placebo (n=31)** | **Mifepriston 100 mg (n=29)** | **P*** | **Mifepriston 200mg (N=30)** | | | **P**** | | | | |
| **Caesarean, N (%)** | 9 (29.03) | 9 (31.03) | 0.87 | 18 (60.00) | | | 0.02 | | | | |

* Comparison of Mifepristone 100 mg vs. placebo; ** Comparison of Mifepristone 200 mg vs. placebo. ǂ Based on the balanced mean of time from recruitment to pregnancy conclusion, excluding 5% of cases with longer times and 5% of cases with shorter times.

Comparing the baseline characteristics of the cardiotocography and Bishop's index, a significantly greater number of contractions were observed in the 100 mg group compared to the placebo group ($p<0.01$), but no differences were demonstrated between the placebo group and the 200 mg group of mifepristone (Table 2). When evaluating the effect in both groups of mifepristone to achieve the Bishop index ≥7, no significant association was observed at any visit. However, the change in the bishop score and the number of contractions during the second visit of the group with 200mg mifepristone presented a significantly higher mean value in relation to placebo. Furthermore, during visit 3 the mean difference in cervical length showed a significant difference ($p<0.01$) in both mifepristone groups (Table 3). The evaluation of the subgroup of women with a gestational age ≥39 weeks (excluding 37 and 38 weeks) showed that, at 72 hours the only parameter that evidenced a significant difference was the difference in cervical length for the 200 mg dose of mifepristone ($p<0.05$). Mean time for delivery showed a significant difference for the 200 mg mifepristone, however it showed a significantly higher percentage of cesarean (Table 4).

The indication of oxytocin for each of the doses of mifepristone did not show a significant difference with placebo. Also, in the comparison of adverse events no significant differences were observed between groups.

## DISCUSSION

There was a significant increase in Bishop's score for the 200 mg mifepristone group at 24 hours, probably due to a significant increase in the number of contractions at 24 hours, and a significant shortening in the length of the cervix at 48 hours. Similar results were observed with the same doses of mifepristone in a recent study.[15] Also, as a previous observed by other authors, a significant shortening of the mean times to delivery (in hours) was evidenced in the group of 200 mg.[16]

The results did not show a significant mifepristone efficacy at any doses to improve a Bishop index, as well as Berkane et al did not find efficacy at different doses of mifepristone.[17]

However, a statistical tendency was shown not reaching a significant change may be due to the small sample size of the study. More research may be needed with more participants. Regarding the use of oxytocin, no differences were found in any of the groups evaluated. However, unlike other studies, there was an increase in the percentage of caesarean sections in the 200 mg mifepristone group.[14]

The study did not show a significant increase in the presence of adverse events in any of the doses evaluated. The principal limitation of the study was the small sample size of the study, also there were some limitation in the medical decision to perform a caesarean considering local legal aspects.

## CONCLUSION

Mifepristone (200 mg) was efficient on shortening cervical length in full-term pregnancy. There was no significant difference in Bishop Index between mifepristone use and placebo. It should be observed that the average gestational age was 38 weeks for the three groups, considering the result of the significant difference in the length of the cervix, clinical trials with higher statistical power could be performed testing the 200 mg dose in pregnancies from 39 weeks to 41 weeks. There were no serious adverse side effects of mifepristone, but there were a major number of caesarean sections that might be not directly related to the mifepristone action.

Our results confirm the potential use that mifepristone may have in the clinical obstetrics rooms.

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## REFERENCES

1. Mahajan DK, London SN. Mifepristone (RU486): a review. Fertil Steril. 1997;68(6):967-76.
2. Frydman R, Lelaidier C, Mleux C, Fernandez H, Vial M, Bourget P. Labor induction in women at term with mifepristone (RU 486): a double-blind, randomized, placebo-controlled study. Obstet Gynecol. 1992;80(6):972-5.
3. Newhall EP, Winikoff B. Abortion with mifepristone and misoprostol: regimens, efficacy, acceptability and future directions. Am J Obstet Gynecol. 2000;183(2):44-53.
4. Tristan M, Orozco LJ, Steed A, Morera A, Stone P. Mifepristone for uterine fibroids. Cochrane Database Systematic Rev. 2012;8:CD007687.
5. Fu J, Song H, Zhou M, Zhu H, Wang Y, Chen H, Huang W. Progesterone receptor modulators for endometriosis. Cochrane Database Systematic Reviews. 2017;7:CD009881.
6. Berkane N, Verstraete L, Uzan S, Boog G, Maria B. Use of mifepristone to ripen the cervix and induce labor in term pregnancies. Am J Obstet Gynecol. 2005;192(1):114-20.
7. Clark K, Ji H, Feltovich H, Janowski J, Carroll C, Chien EK. Mifepristone-induced cervical ripening: structural, biomechanical, and molecular events. Am J Obstet Gynecol. 2006;194(5):1391-8.
8. Elliott CL, Brennand JE, Calder AA. The effects of mifepristone on cervical ripening and labor induction in primigravidae. Obstet Gynecol. 1998;92(5):804-9.
9. Fassett MJ, Wing DA. Uterine activity after oral mifepristone administration in human pregnancies beyond 41 weeks' gestation. Gynecol Obstet Invest. 2008;65(2):112-5.
10. Fathima S, Nayak SR, Rao B, Praveena G, Shameem VPA. Mifepristone in the induction of labour at term. Int J Pharm Biomed Res. 2013;4(3):164-6.
11. Frydman R, Lelaidier C, Mleux C, Fernandez H, Vial M, Bourget P. Labor induction in women at term with mifepristone (RU 486): a double-blind, randomized, placebo-controlled study. Obstet Gynecol. 1992;80(6):972-5.
12. Wing DA, Fassett MJ, Mishell DR. Mifepristone for preinduction cervical ripening beyond 41 weeks' gestation: a randomized controlled trial. Obstet Gynecol. 2000;96(4):543-8.
13. Wing DA, Guberman C, Fassett M. A randomized comparison of oral mifepristone to intravenous oxytocin for labor induction in women with prelabor

rupture of membranes beyond 36 weeks' gestation. Am J Obstet Gynecol. 2005;192(2):445-51.
14. Hapangama D, Neilson JP. Mifepristone for induction of labour. Cochrane Database Systematic Rev. 2009;3:CD002865.
15. Baev OR, Rumyantseva VP, Tysyachnyu OV, Kozlova OA, Sukhikh GT. Outcomes of mifepristone usage for cervical ripening and induction of labour in full-term pregnancy. Randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2017;217:144-9.
16. Wing DA, Fassett MJ, Mishell DR. Mifepristone for preinduction cervical ripening beyond 41 weeks' gestation: a randomized controlled trial. Obstet Gynecol. 2000;96(4):543-8.
17. Berkane N, Verstraete L, Uzan S, Boog G, Maria B. Use of mifepristone to ripen the cervix and induce labor in term pregnancies. Am J Obstet Gynecol. 2005;192(1):114-20.

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