

SUBLINGUAL MISOPROSTOL VS SUBLINGUAL MISOPROSTOL WITH VAGINAL ESTRADIOL FOR LABOR INDUCTION

By

Eslam N. A. A. Abd El-Razek, Abdullah K. Ahmed and Al-Refaai A. Marai

Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University (Cairo) Egypt

E-mail: es.nabl01@gmail.com

ABSTRACT

Background: Induction of labor is usually performed when the risks of continuing pregnancy are higher than the benefits of delivery. Uterine cervical tissue ripening or its softening has a close relationship with success rate of delivery.

Objective: To compare the safety and effectiveness of sublingual misoprostol with combined sublingual misoprostol and vaginal estradiol for induction of labor in unfavorable cervix.

Subjects and methods: This was a prospective single blinded study conducted in Obstetrics and Gynecology Departments, El-Hussein University Hospital ELAlamin Standard Hospital, Matrouh including 160 women with unfavorable cervix and gestation ≥ 40 till 42 weeks with clinical indication for induction of labor. They would be randomly assigned to either the misoprostol+ placebo or misoprostol+ estradiol. The duration of the study was 12 months from 01 May 2019 till 01 May 2020.

Results: Women's Time to active labor in women with misoprostol+ placebo ranged between 5-9 hours with mean \pm S.D. 6.99 ± 1.419 hours while in women with misoprostol+ estradiol was ranged between 5-9 hours with mean \pm S.D. 6.96 ± 1.400 hours. There were no statistically significant differences between groups.

Conclusion: Sublingual misoprostol alone was as effective as sublingual misoprostol and vaginal Estradiol for induction of labor at term.

Keywords: Induction, unfavorable, sublingual, misoprostol, Estradiol.

INTRODUCTION

The success of induction of labor is influenced by a combination of events existing prior to initiation of labor, such as Braxton Hicks contractions, ratio of estrogen to progesterone, prostaglandin synthesis, and the state of cervical collagen matrix. Labor induction in presence of unfavorable cervix is often prolonged, tedious, and may lead to induction failure. The failure rate with an

unfavorable cervix range from 25 to 50%. Hence cervical ripening is required before induction of labor to achieve more successful outcome (*Iliodromiti et al., 2012*).

Prostaglandins play a critical role in cervical ripening by increasing inflammatory mediators in the cervix and inducing cervical remodeling. Prostaglandin E1 (PGE1) and prostaglandin E2 (PGE2) exert different

effects on these processes and on myometrial contractility. These mechanistic differences may affect outcomes in women treated with dinoprostone, a formulation identical to endogenous PGE₂, compared with misoprostol, a PGE₁ analog. The objective of this review is to evaluate existing evidence regarding mechanistic differences between PGE₁ and PGE₂, and considers the clinical implications of these differences in patients requiring cervical ripening for labor induction (*Bakker et al., 2017*).

The present study aimed to compare between using misoprostol alone sublingually VS misoprostol sublingually and estradiol vaginally as regard to safety and efficacy in induction of labor.

PATIENTS AND METHODS

A prospective single blinded study was conducted at the Obstetrics and Gynecology Departments at El-Hussain University and Hospitals and EL- Alamin Standard Hospital, Matrouh from 2019 to 2020.

The study had been carried out on total of 160 women with unfavorable cervix and gestation ≥ 40 till 42 weeks with clinical indication for induction of labor. They had been randomly assigned to either the misoprostol placebo or misoprostol estradiol.

All patients had been subjected to complete history taking personal history, obstetric history, present history, past history and surgical history of operation, laparoscopic interference.

Examination:

A. General examination.

B. Abdominal and local clinical examination.

C. Bimanual pelvic examination.

D. Investigations: Complete blood count a coagulation profile.

E. Ultrasound Estimated fetal weight, gestational age, AFI and umbilical Doppler.

Outcome measures of the study as following:

Primary Outcome: Measure the time to cervical ripening.

Secondary Outcome: Measure the time to active labor, Number of misoprostol doses, Induction delivery time and fetal outcome (APGAR score).

Ethical Consideration: This Study had been submitted for approval by Institution Research Board (IRB) of Faculty of Medicine Al-Azhar University. An Informed verbal consent had been obtained from each participant sharing in the study. Confidentiality and personal privacy had been respected in all levels of the study.

Data management and Statistical Analysis:

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0).

Tests used were Fisher's exact test and Mann-Whitney test, and P value <0.05 was considered significant.

RESULTS

Women’s Gestational age in women with misoprostol + placebo was ranged between 40-42 weeks with mean±S.D. 40.94±0.852 weeks while in women with misoprostol estradiol was ranged between

40-42 weeks with mean±S.D. 40.88±0.857 weeks. There were no statistically significant differences between groups where P=0.658 (Table 1).

Table (1): Comparison between two groups as regard to patient’s Gestational age

Gestational age	Groups	Misoprostol + placebo (n=79)	Misoprostol + estradiol (n=81)	MW P Value
	Min.-Max.		40-42	
Mean± S.D		40.94±0.852	40.88±0.857	0.658

MW: Mann-Whitney test of significance

Women’s mode of delivery in women with misoprostol + placebo show that 41(51.9%) mode of delivery were NVD and 38(48.1%) had Caesarean delivered while in women with misoprostol

estradiol 40(49.4%) mode of delivery were NVD and 41(50.6%) had Caesarean. There were no statistically significant differences between groups where P=0.750 (Table 2).

Table (2): Comparison between two groups as regard to patient’s mode of delivery

Mode of delivery	Misoprostol + placebo (n=79)		Misoprostol + estradiol (n=81)		FEP Value
	No.	%	No.	%	
NVD	41	51.9	40	49.4	0.750
Caesarean	38	48.1	41	50.6	

FE: Fisher’s Exact test of significance

Women’s Time to active labor in women with misoprostol + placebo was ranged between 6-9 hours with mean±S.D. 7.53±1.107 hours while in women with misoprostol estradiol was

ranged between 5-12 hours with mean±S.D. 7.90±2.221 hours. There were no statistically significant differences between groups where P=0.920 (Table 3).

Table (3): Comparison between two groups as regard to patient’s Time to active labor

Time to active labor	Misoprostol + placebo (n=79)	Misoprostol + estradiol (n=81)	MW P Value
Min.-Max.	6-9	5-12	0.188
Mean± S.D	7.53±1.107	7.90±2.221	

MW: Mann-Whitney test of significance

Women's Number of misoprostol doses in women with misoprostol + placebo was ranged between 1-3 with mean±S.D. 1.96±0.629 while in women with misoprostol estradiol was ranged

between 1-3 with mean±S.D. 2.02±0.612. There were no statistically significant differences between groups where P=0.522 (Table 4).

Table (4): Comparison between two groups as regard to patient's Number of misoprostol doses

Number of misoprostol doses	Misoprostol + placebo (n=79)	Misoprostol + estradiol (n=81)	MW P Value
Min.-Max.	1-3	1-3	0.522
Mean± S.D	1.96±0.617	2.02±0.618	

MW: Mann-Whitney test of significance

Women's Gestational age in women with misoprostol + placebo was ranged between 5-10 with mean±S.D. 7.56±1.542 while in women with misoprostol estradiol was ranged between 5-10 with mean±S.D. 7.69±1.729. There were no

statistically significant differences between groups where P=0.593. Relation between APGAR score and each of mode of delivery and cause of CS show no statistically significant differences between groups (Table 5).

Table (5): Comparison between two groups as regard to patient's Fetal Outcome (APGAR score)

Fetal Outcome (APGAR score)	Misoprostol + placebo (n=79)	Misoprostol + estradiol (n=81)	MW P Value
Min.-Max.	5-10	5-10	0.593
Mean± S.D	7.56±1.542	7.69±1.729	
NVD	7.39±1.547	7.90±1.676	0.684
CS	7.74±1.537	7.49±1.777	

MW: Mann-Whitney test of significance

DISCUSSION

Several methods have been used for the induction of labor and termination of pregnancy with different degrees of safety and success, and many investigations have been performed on this topic. Nonetheless, a consensus has yet to emerge about the most appropriate method for all women (*Jahromi et al., 2016*).

Vaginal and sublingual misoprostol have a rapid onset action, due to their

prolonged activity and bioavailability. A sublingual dose of 50 mg every 4 h in most of cases, induce vaginal delivery within 24 hours and compared to an equivalent oral dose, less oxytocin augmentation is required. However, the previous studies found few significant differences among the effectiveness of different doses of the Misoprostol, oral, vaginal or sublingual (*Fakoor et al., 2013*).

The main objective of our study was to compare the safety and effectiveness of sublingual misoprostol with combined sublingual misoprostol and vaginal estradiol for induction of labor in unfavorable cervix.

Women's gravity in women with misoprostol + placebo was ranged between 1 – 3, while in women with misoprostol estradiol was ranged between 1 – 3. There were no statistically significant differences between groups. There were no statistically significant differences between groups regarding women's parity.

Our results supported by study of *Dasgupta and Singh. (2012)*, as they conducted study to assess the effect of Vaginal Misoprostol vs Vaginal Misoprostol with Estradiol for Labor Induction and they found that there were no statistically significant differences between groups regarding the age and parity.

Furthermore, *Tanha et al. (2013)*, reported that there was no statistically significant difference in women's age, gestational age, number of previous pregnancies, miscarriages and termination of pregnancies between the two groups. 40.2% patients were primiparous and 59.2 % were multiparous. In the vaginal group, 38.8 % patients were nulliparous and 61.1 % were multiparous. In sublingual group, 41.7 % were nulliparous and 58.2 % were multiparous.

According to *Ayati et al. (2014)*, there was no significant difference in the demographic characteristics between two studied groups of women.

Regarding *Dickinson et al. (2014)* there were no significant differences between the groups regarding maternal age or gestational age.

Induction of labor is usually performed when the risks of continuing pregnancy are higher than the benefits of delivery. Undoubtedly, uterine cervical tissue ripening or its softening has a close relationship with success rate of delivery (*Mirteimouri et al., 2012*).

Around 20 % of all deliveries were preceded by labor induction. Prolonged pregnancy and maternal hypertensive disorders being the major indications for the last 50–60 years. The 'other' indications are ante partum hemorrhage, diabetes mellitus, red-cell alloimmunization, demonstrable placental failure and previous unexplained still birth at term (*Hofmeyr et al., 2010*).

In the present study, women's indications for inductions in women with misoprostol + placebo showed 51.9% with postdatism, 48.1% with PROM, 44.3% with PIH and 53.2% with IUGR, while in women with misoprostol estradiol 50.6% with postdatism, 49.4% with PROM, 48.1% with PIH and 58% with IUGR. There were no statistically significant differences between groups.

Women's time to active labor in women with misoprostol + placebo ranged between 5-9 hours while in women with misoprostol estradiol was ranged between 5-9 hours. There were no statistically significant differences between groups.

Our results were in line with study of *MacIntyre et al. (2012)* as they reported that there were no differences among the

three groups as to the distribution of these medical obstetric complications.

According to *Tanha et al. (2013)* induction to termination period does not differ significantly between the two groups.

Dodd and Crowther (2010) evaluated sublingual versus vaginal misoprostol for induction of labor at term, found that there was no difference between groups in case of induction to delivery interval and duration of labor.

In contrary with our results, study of *Dasgupta and Singh (2012)* as they found that time required for cervical ripening, time required for starting of active and time required for delivery in vaginal delivery cases were found significantly less in combined estradiol and misoprostol group. In misoprostol group, induction initiation to cervical ripening interval, induction initiation to active labor initiation and induction initiation to delivery. Other studies have also shown intervals of similar duration (*Khadem and Khadivzadeh., 2015*).

The current study shows that women's Number of misoprostol doses in women with misoprostol + placebo ranged between 1-3 with while in women with misoprostol estradiol ranged between 1-33. There were no statistically significant differences between groups.

Our results are supported by study of *Ayati et al. (2014)* as they found that findings showed that there weren't any statistically significant differences between the numbers of administered doses of misoprostol every four hours. Although the frequency of two doses were significantly higher than the other group.

Regarding *Jahromi et al. (2016)* reported that there were no statistically significant differences between the numbers of administered doses. None of the women needed to receive the sixth dose of misoprostol because they all reached a Bishop score >8. Only 4 women in the sublingual and 7 in the vaginal group needed to take the fifth dose of misoprostol.

According to *Tanha et al. (2013)* there were no statistically significant differences between the vaginal and sublingual groups in the number of tablets administered or endometrial thickness after termination of pregnancy.

Dickinson et al. (2014) observed that all women included in the study received at least one dose of misoprostol. A total of 17.2% women required a second course of treatment, 20.2% in the sublingual group and 14.1% in the vaginal group.

Different routes of misoprostol have been administrated for cervical priming. Both oral and vaginal forms seem to be equally effective (*Dodd and Crowther., 2010*). However, some women found the vaginal forms inconvenient and unacceptable *Parveen et al. (2011)* compared sublingual and vaginal misoprostol for preoperative cervical priming, prior to surgical termination and found similar preoperative side-effects within groups. However, sublingual misoprostol has the advantages like being more convenient to administer.

Pharmacokinetic studies on the different routes of the administration of misoprostol have demonstrated that sublingual misoprostol acid reaches a higher serum peak concentration with a shorter time-to-peak concentration than

does vaginal misoprostol acid (*Siwach et al., 2012*).

In contrary with our results, study of *Dasgupta and Singh. (2012)* found that doses of misoprostol required for cervical ripening was found significantly less in combined estradiol and misoprostol group. Various studies have found induction delivery interval with vaginal misoprostol 16–20 h, which is in agreement with their study (*Khadem and Khadivzadeh, 2015*). On an average, 4–5 doses of misoprostol were required in their study for cervical ripening or initiation of active labor which is similar to other studies; however dose required in combined group was significantly less.

The present study showed that fetal outcome (Apgar score) in women with misoprostol + placebo ranged between 5-10 while in women with misoprostol estradiol was ranged between 5-10. There were no statistically significant differences between groups.

Our results were in agreement with study of *MacIntyre et al. (2012)* as they reported that there were no differences among the three groups as to the Apgar score.

According to *Dasgupta and Singh. (2012)* there were no significant difference was found in pre induction Bishop's score, fetal outcome and maternal complications.

Furthermore, *Jahromi et al. (2016)* observed that there was no significant difference was found fetal outcome and complications.

Regarding *Tanha et al. (2013)* there was no significant difference with regards to complications between the two groups.

First and foremost, among the limitations of the present study is its small sample size, which precludes exact conclusions. Also, we did not compare fever and hyperthermia, as a common complication of misoprostol, between the 2 groups. Another drawback of note is that we could not evaluate patient satisfaction due to the special design of the study and the simultaneous administration of both routes of the medication and the placebo.

CONCLUSION

Estradiol acts synergistically with misoprostol sublingually and significantly hastens the process of cervical ripening, initiation of active labor and vaginal delivery; we concluded that sublingual misoprostol seems as effective as sublingual misoprostol and Vaginal Estradiol for induction of labor at term.

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الميزوبروستول تحت اللسان مقابل الميزوبروستول تحت اللسان مع إستراديول المهبلي لتحريض المخاض

إسلام نابل عبدالحسيب، عبد الله خليل احمد، الرفاعي عبد الفتاح مرعي

أمراض النساء والتوليد، كلية الطب، جامعة الأزهر، مصر

خلفية البحث: يتم تحريض المخاض عادة عندما تكون مخاطر استمرار الحمل أعلى من فوائد الولادة. ونضج أنسجة عنق الرحم أو تليينه له علاقة وثيقة مع معدل نجاح الولادة.

الهدف من البحث: مقارنة سلامة وفعالية الميزوبروستول تحت اللسان مع الميزوبروستول المشترك تحت اللسان والاستراديول المهبلي لتحريض المخاض في عنق الرحم غير المواتي.

المرضى وطرق البحث: كانت هذه دراسة عمياء مستقبلية و أجريت في أقسام التوليد وأمراض النساء، مستشفى الحسين الجامعي، مستشفى العلمين النموذجي بمحافظة مطروح، وكان عدد المربضات 160 امرأة مع نتائج لفحص عنق الرحم تدل علي انها غير مواتية للولادة الطبيعية وكذلك العمر الرحمي من 40 إلى 42 أسبوعًا مع مؤشرات سريرية لتحريض المخاض. تم تعيينهم بشكل عشوائي إما للميزوبروستول + وهمي أو الميزوبروستول + استراديول. كانت مدة الدراسة 12 شهرًا من 1 مايو 2019 حتى 01 مايو 2020.

نتائج البحث: تراوح وقت المرأة في المخاض النشط لدى النساء اللواتي يعانين من الميزوبروستول + الدواء وهمي بين 5-9 ساعات بمتوسط S. ± تراوحت 6.99 ± 1.419 ساعة أثناء النساء مع الميزوبروستول + استراديول بين 5-9 ساعات بمتوسط S.D. 6.96 ± 1.400 ساعة, لم تكن هناك فروق ذات دلالة إحصائية بين المجموعات.

الاستنتاج: كان الميزوبروستول تحت اللسان و الدواء الوهمي له نفس فاعلية الميزوبروستول تحت اللسان والاستراديول المهبلي في نتائج التحريض علي المخاض عند إكمال العمر الرحمي للجنين.