Original Article

Randomized controlled trial between sublingual and vaginal misoprostol for induction of labour at term

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ABSTRACT

Background: Induction of labor is an obstetrical intervention that implies stimulation of uterine contractions before the spontaneous onset of labor, with or without rupture of membranes. When the cervix is unfavorable, cervical ripening with prostaglandins to soften and open the cervix will often commenced to induce labor.

Objective: To compare 50 µg of sublingual misoprostol to 50 µg of vaginal misoprostol for induction of labour at term regarding efficacy and safety.

Patients and Methods: This prospective randomized controlled trial included 104 pregnant women who were recruited from Department of Obstetrics and Gynecology, Faculty of Medicine Ain-Shams University and Al-Glaa Teaching Hospital, Delivery Unit.

Results: Regarding induction-delivery interval (time from given drug for both groups to vaginal delivery), there was no significant statistical difference between both groups regarding the mean time from initial dose to the delivery. Mean 15.04 ± 4.67 for sublingual group versus 14.16 ± 4.45 for vaginal group (*P= 0.331*). As regarding fetal and maternal complications in our study, there was significant statistical difference between the vaginal and sublingual groups according to secondary outcome (hyperstimulation). The risk of hyperstimulation was higher in vaginal group (5 cases) compared to the sublingual group (No cases) *P= 0.046*.

Conclusion: Sublingual misoprostol 50 µg administered at 6 hourly intervals is as effective in promoting cervical ripening and inducing labor as vaginal misoprostol 50 µg administered 6 hourly intervals as regarding induction to delivery interval, number of doses, shorter hospitalization and neonatal outcome. Sublingual misoprostol 50 µg has a higher maternal and perinatal safety profile than the vaginal 50 µg misoprostol including cesarean rates due to fetal distress, adverse maternal outcomes as hyperstimulation.

Recommendations: We recommend sublingual 50 µg misoprostol administered at 6 hourly intervals as an efficacious and safe option for labor induction, low cost and availability is its added benefits.

Key Words: Induction to delivery interval, induction of labor, misoprostol

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INTRODUCTION

Induction of labour implies artificial initiation of regular uterine contraction before their spontaneous onset, resulting in progressive effacement and dilatation of cervix, with an aim to secure safe vaginal delivery (Kreft *et al.*, 2014).

The indication for induction has been widened in recent years and could be simplified in "labour is induced when risk of continuing pregnancy outweighs the risk of delivery." (Sheela *et al.*, 2014).

Studies on induction of labour using different inducing agents as misoprostol, dinoprostone (PGE2) and oxytocin raised a debate on the method of induction with least side effects and high success rate (Kehl *et al.*, 2015). Different doses, routes of administration and doses time interval had been used. In this study, we choose misoprostol (PGE2) as the inducing agent in 50 µg dose every 6 hours comparing the route of administration sublingual versus vaginal (Zahran *et al.*, 2009, Nassar *et al.*, 2007, Caliskan *et al.*, 2005).

Misoprostol, a synthetic prostaglandin E1 (PGE1) analogue has been studied and widely accepted as an inducing agent in different doses and routes (Chow *et al.*, 2004). Originally, misoprostol was licensed as an oral treatment for gastric ulcers while it is used off label worldwide in obstetrics (Bartusevicius *et al.*, 2006). Misoprostol binds

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selectively to prostanoid receptors, increases intracellular calcium and contracts myometrium while also softening the cervix by collagen disintegration and dissolution. As a result, it shortens the induction-to-delivery interval compared to placebo, oxytocin or other induction agents in women with an unfavourable cervix (Kreft *et al.*, 2014).

AIM OF THE WORK

To compare 50 µg of sublingual misoprostol to 50 µg of vaginal misoprostol for induction of labour at term regarding efficacy and safety.

PATIENTS AND METHODS

This prospective randomized controlled trial included 104 pregnant women who were recruited from Department of Obstetrics and Gynecology, Faculty of Medicine Ain Shams University and Al-Glaa Teaching Hospital, Delivery Unit.

Study population: The current study included pregnant women who were presented for induction of labor with singleton pregnancy and cephalic presentation with reassuring fetal heart rate pattern and medical or obstetric indication for induction of labor.

The methods had been explained to them and only those who agreed to the procedure had been selected for the study. Patients who met the selection criteria had been informed about the advantages and disadvantages of the procedures.

Inclusion criteria:

• Primigravida, para1 or para2.
• Singleton pregnancy.
• Pregnancy duration ≥ 37 weeks.
• Oligohydramnios (AFI < 5).
• P.R.O.M (pre-labor rupture of membranes).
• Past-date pregnancy (GA ≥ 41 weeks).
• Clinically adequate pelvis.
• Bishop score of 5 or less.
• A reactive cardiotocographics trace.

The exclusion criteria:

• Grand mutliPara
• Multiple gestations
• Malpresentation
• Non- reassuring fetal heart rate pattern.
•All patients with severe systemic illnesses like uncontrolled diabetes mellitus, severe pre-eclampsia, cardiac disease.
• Known hypersensitivity to prostaglandins.
• Any uterine anomaly or history of surgical intervention To the uterus, including cesarean delivery
•Any other maternal or fetal factors contraindicating induction of labor.

These criteria were assessed during the initial evaluation in the delivery suite as the follows:

History taking: Personal, menstrual, obstetric, past and family history was taken carefully. History of present pregnancy was taken including the first day of last menstrual period, duration of pregnancy, any warning symptoms was asked about headache, visual symptoms, edema of the face and fingers, excessive vomiting, heart burn, epigastric pain, pain in the loin, vaginal bleeding, reduced fetal movements, edema of the lower limbs ; we asked about any medication and its nature.

Examination was done as:

• ***General examination including:*** vital signs, chest, heart, and lower limb examination.

• ***Abdominal examination:*** for assessment of fundal level, presentation and position, expected fetal weight, fetal heart rate by sonicade or pinard and presence of scars of previous operation as cesarean section or myomectomy.

• ***Vaginal examination:*** and assessment of cervical position, dilatation, consistency, length and head station (Bishop's score) also condition of membranes, pelvic capacity, and to ensure presentation and position.

Investigations:

• ***Laboratory:*** blood grouping and Rh typing, complete blood count and complete urine analysis.
• ***Abdominal ultrasound:*** was done to confirm the gestational age, fetal number, viability, presentation, position and to estimate fetal weight.
• **CTG:** evaluation of fetal heart rate tracing for average 20 minutes.

Methods of administrations:

Demographic profile including the age, parity, gestational age, obstetric history, indication for induction and amniotic fluid volume at induction were noted. Bishop's score was assessed and non-stress test (NST) was performed before induction. Those with a Bishop's score of ≤5 and with reassuring NST were included in the study. Written informed consent was taken from each patient agreed to participate in the study.

Method of randomization:

A randomization sheet developed by the computer contains 104 patients randomly assigned into 2 groups (group A and group B) each group of 52 patients. The

randomization was concealed using the sequentially numbered opaque sealed envelop (SNOSE). One hundred and four opaque easy opening envelopes had been numbered serially, in each envelope the corresponding letter in randomization sheet was placed in one box. Pregnant women were allocated to each group according to the letter inside the envelope.

Misoprostol tablets are available as 200mg per tablet (trade name: cytotec, manufacturer: Pfizer, stored at room temperature). Each tablet was divided into 4 quadrants using a pill splitter (Apex ultra pill splitter 70068, USA), each quadrant should contain about 50mg.

Group V : Vaginal misoprostol:

One quadrant was placed into the posterior vaginal fornix and dose was repeated every six hours for a maximum of four doses or until active labor started.

Group S : Sublingual misoprostol:

One quadrant was taken sublingually. The dose was repeated every six hours for a maximum of four doses or until active labor started.

The doses were repeated till effective uterine contractions (more than 3 contractions in 10 minutes), cervical dilatations of 3 cm and Bishop's score of ≥ 8 achieved. Patients were monitored for uterine contractions and fetal heart rate during this period.

PV examination was done at 6 hours and 12 hours following drug administration or earlier if the patient complained of labor pain or gush of water per vagina. Amniotomy was done when cervix is effaced with a cervical dilatation of ≥ 4cms.

Outcomes:

The primary outcome measure was the induction to delivery interval IDI (time from inserting the drug to delivery).

Secondary outcomes included maternal and fetal outcomes:

Mode of delivery: Whether vaginal delivery or cesarean sections (the incidence of Cesarean sections for fetal distress).

Failed induction: defined as no onset of labor by the end of the induction protocol.

Uterine hyperstimulation or tachysystole.

Apgar score at 15- minutes.

Other side effects as nausea, vomiting, maternal pyrexia (maternal temperature ≥ 38 or NICU admissions.

Sample size justification:

The required sample size has been calculated using IBM© sample power© software (IBM© Corp., Armonk, NY, USA).

The primary outcome measure is the induction to vaginal delivery interval (IDI). The secondary outcome measure is the total number of misoprostol doses required.

A previous study reported that the mean ± SD IDI in patients receiving sublingual or vaginal misoprostol was 13.1 ± 4.1 h or 17.9 ± 5.4 h, respectively (Sheela *et al.*, 2014). The mean ± SD total number of misoprostol doses required was 1.87 ± 0.81 doses or 2.57 ± 0.99 doses in association with the sublingual or vaginal route, respectively.

So, it is estimated that a sample size of 104 patients equally randomized into either study group (52 per group) would achieve a power of 90% (beta-error, 0.1) to detect a statistically significant difference between the two groups as regards the total number of misoprostol doses using a two-sided student-t test with a confidence level of 99% (type I error, 0.01).

The mean ± SD total number of misoprostol doses is assumed to be identical and equals 2.57 ± 0.99 doses in both groups under the null hypothesis. Under the alternative hypothesis, the mean ± SD total number of misoprostol doses is assumed to equal 1.87 ± 0.81 doses or 2.57 ± 0.99 doses in patients receiving sublingual or vaginal misoprostol, respectively (Sheela ***et al.***, 2014). These differences are equivalent to an effect size (Cohen d) of 0.36.

On the other hand, a sample size of 52 patients per group would achieve a higher power of 99% (beta-error, 0.01) to detect a statistically significant difference between the two groups as regards the IDI using a two-sided student t test with the same confidence level of 99% (type I error, 0.01).

The mean ± SD IDI is assumed to be identical and equal 17.9 ± 5.4 in both groups under the null hypothesis. Under the alternative hypothesis, the mean ± SD IDI is assumed to equal 13.1 ± 4.1 h or 17.9 ± 5.4 h in patients receiving sublingual or vaginal misoprostol, respectively (Sheela ***et al.***, 2014). These differences are equivalent to an effect size (Cohen d) of 0.44.

The effect size (d) is calculated as follows: d = (m1- m2) / sd where m1 and m2 are the means of group I and group II, respectively, and sd is the common standard deviation (Chow *et al.*, 2004).

STATISTICAL ANALYSIS

Data will be collected, tabulated then analyzed using IBM© SPPS© Statistics version 22 (IBM© Corp., Armonk, NY, USA).

Normally distributed numerical data will be presented as mean and SD and skewed data as median and interquartile range. Qualitative data will be presented as number and percentage. Comparison of normally distributed numerical data will be done using unpaired t test. Skewed data will be compared using the Mann-Whitney test. Categorical data will be compared using the chi-squared test. A two-sided *p-value <0.05* will be considered statistically significant.

RESULTS

Table 1 shows no statistically significant difference between sublingual and vaginal according to age (years).

Table 2 shows no statistically significant difference between sublingual and vaginal according to parity.

Table 3 shows no statistically significant difference between sublingual and vaginal according to gravidity.

Table 4 shows no statistically significant difference between sublingual and vaginal according to GA (wks).

Table 5 shows no statistically significant difference between sublingual and vaginal according to indications.

Table 6 shows no statistically significant difference between sublingual and vaginal according to bishop score.

Table 7 shows no statistically significant difference between sublingual and vaginal according to no. of doses.

Table 8 shows no statistically significant difference between sublingual and vaginal with mean 15.04 ± 4.67 versus 14.16 ± 4.45, respectively according to induction to delivery interval, *p-value >0.05* NS.

Table 9 shows no statistically significant difference between sublingual and vaginal according to mode of delivery.

Table 10 shows statistically significant difference between sublingual and vaginal according to secondary outcome fetal/ maternal complications (hyperstimulation).

Table 11 shows no statistically significant difference between sublingual and vaginal according to Apgar score.

Table 1: Comparison between sublingual and vaginal according to age (years).

Age (years)	Sublingual (N=52)	Vaginal (N=52)	t-test	*p-value*
Mean±SD	25.85±4.27	25.21±3.86	0.631	0.429
Range	18-36	19-38		

t-independent sample t-test
p-value >0.05 NS

Table 2: Comparison between sublingual and vaginal according to parity.

Parity	Sublingual (N=52)		Vaginal (N=52)		Chi-square test	
	No.	%	No.	%	x2	*p-value*
P1	16	30.8%	15	28.8%	1.175	0.759
P2	17	32.7%	13	25.0%		
PG	19	36.5%	24	46.2%		
Total	52	100.0%	52	100.0%		

x2: Chi-square test
p-value >0.05 NS

Table 3 : Comparison between sublingual and vaginal according to gravidity

Gravidity	Sublingual (N=34)		Vaginal (N=29)		Chi-square test	
	No.	%	No.	%	x2	*p-value*
G2	16	47.06%	15	51.7%	5.213	0.266
G3	16	47.06%	12	41.4%		
G4	2	5.90%	0	0.0%		
G5	0	0.0%	2	6.9%		

x2: Chi-square test
p-value >0.05 NS

Table 4: Comparison between sublingual and vaginal according to GA (wks)

GA (wks)	Sublingual (N=52)	Vaginal (N=52)	t-test	*p-value*
Mean±SD	39.20±1.71	39.66±1.83	1.745	0.189
Range	37-43	37-43		

t-Independent Sample t-test
p-value >0.05 NS

Table 5: Comparison between sublingual and vaginal according to indication

Indication	Sublingual (N=52)		Vaginal (N=52)		Chi-square test	
	No.	%	No.	%	x2	*p-value*
GDM	1	1.9%	1	1.9%	0.000	1.000
Oligohydramnios	6	11.5%	3	5.8%	0.469	0.493
Pastdate	10	19.2%	16	30.8%	1.299	0.255
PET(+)	1	1.9%	1	1.9%	0.000	1.000
PIH	1	1.9%	5	9.6%	1.601	0.206
PROM	34	65.4%	28	53.8%	1.011	0.315

x2: Chi-square test
p-value >0.05 NS

Table 6 : Comparison between sublingual and vaginal according to bishop score

Bishop score	Sublingual (N=52)	Vaginal (N=52)	t-test	*p-value*
Mean±SD	3.00 ± 1.08	2.83 ± 0.79	0.869	0.353
Range	1-5	1-4		

t-Independent Sample t-test
p-value >0.05 NS

Table 7: Comparison between sublingual and vaginal according to no. of doses

No. of doses	Sublingual (N=52)		Vaginal (N=52)		Chi-square test	
	No.	%	No.	%	x2	*p-value*
1.00	30	57.7%	27	51.9%	2.391	0.495
2.00	16	30.8%	22	42.3%		
3.00	5	9.6%	2	3.8%		
4.00	1	1.9%	1	1.9%		
Total	52	100.0%	52	100.0%		

x2: Chi-square test
**p-value <0.05* S

Table 8: Comparison between sublingual and vaginal according to induction to delivery interval

Induction to delivery interval	Sublingual (N=52)	Vaginal (N=52)	t-test	*p-value*
Mean±SD	15.04±4.67	14.16±4.45	0.954	0.331
Range	6-27	7.5-28		

t-Independent Sample t-test
P value >0.331

Table 9: Comparison between sublingual and vaginal according to mode of delivery

Mode of delivery	Sublingual (N=52)		Vaginal (N=52)		Chi-square test	
	No.	%	No.	%	x2	*p-value*
CS	1	1.9%	2	3.8%		
NVD	51	98.1%	50	96.2%	0.343	0.558
Total	52	100.0%	52	100.0%		

x2: Chi-square test
p-value >0.05 NS

Table 10 : Comparison between sublingual and vaginal according to secondary outcome fetal/ maternal complications

Secondary outcome: Fetal / Maternal complications	Sublingual (N=52)		Vaginal (N=52)		Chi-square test	
	No.	%	No.	%	x2	*p-value*
None	48	92.3%	45	86.5%	0.412	0.521
Fever	2	3.8%	0	0.0%	0.491	0.483
Tachysystole	1	1.9%	3	5.8%	0.275	0.600
Blood Transfusion	1	1.9%	0	0.0%	0.011	0.990
Hyperstimulation	0	0.0%	5	9.6%	4.362	0.046*
Fetal Distress	0	0.0%	1	1.9%	0.011	0.990

x2: Chi-square test
p-value >0.05 NS

Table 11: Comparison between sublingual and vaginal according to Apgar score

Apgar score	Sublingual (N=52)	Vaginal (N=52)	z-test	*p-value*
Apgar score at 1min. Mean±SD Range	8 (1) 7-9	8 (1) 6-9	1.095	0.298
Apgar score at 5min. Mean±SD Range	9 (0) 8-9	9 (0) 8-9	0.624	0.431

z-Man-Whitney test
p-value >0.05 NS

DISCUSSION

Multiple clinical trials have compared the different routes and doses of misoprostol for induction of labor due to different indications, in order to show the optimal dose, the dosing regimen, the route of administration and the effectiveness of misoprostol as a wide used agent for induction of labor in current clinical practice (Nassar *et al.*, 2007, Caliskan *et al.*, 2005, Sheela *et al.*, 2014, Kreft *et al.*, 2014, Komala *et al.*, 2013).

Other prostaglandins analogues as PGE2 (dinoprostone) used for induction of labor were not included in this study due to poor availability in the market and high cost for daily clinical practice side by

side, several studies comparing the efficacy and safety of intravaginal misoprostol and PGE2 (dinoprostone) vaginal inserts for labor induction found no statistically significant difference between the two groups with respect to mode of delivery, indication for caesarean delivery and fetal adverse outcome (Khoury *et al.*, 2001). Studies have been conducted comparing vaginal misoprostol with PGE2 (dinoprostone) for induction of labor in women without PROM and have found misoprostol to be equally effective (Prager *et al.*, 2008 and Calder *et al.*, 2008) or more effective than PGE2 with similar maternal and neonatal outcomes (Nanda *et al.*, 2007).

Different clinical trials compared and studied different routes of administration of misoprostol to clarify both effectiveness and safety for induction of labor, most of them concluded that both sublingual and vaginal administration of misoprostol is more effective, safer, more suitable and had better maternal and fetal outcomes (Komala *et al.*, 2013, Hofmeyr *et al*., 2005, Bartusevicius *et al.*, 2005, Nassar *et al.*, 2007).

The optimum dose of misoprostol to be used for induction of labor was studied in many clinical trials comparing 50 µg and 25 µg in both sublingual and vaginal routes. Most of the results of these studies showed that 50 µg dose was more effective than 25 µg dose (vaginal route more than sublingual); although there was less side effects in the 25 µg dose (sublingual route had less side effects) and some trials compared 50 µg sublingual misoprostol to 25 µg vaginally upon the previously mentioned results (Caliskan *et al.*, 2005, Souza *et al.*, 2008, Nassar *et al.*, 2007, Sheela *et al.*, 2014, Kreft *et al.*, 2014).

In our study, both groups were demographically similar regarding maternal age, parity, gravidity, gestational age and Bishop Score; there was no significant statistical difference. (maternal age *P =0.429*, parity *P = 0.759*, gravidity *P= 0.266*, gestational age *P = 0.189*, bishop score *P= 0.353*).

In the present study, regarding indication for induction of labor, there was no significant statistical difference in both groups. PROM was the most common indication in both groups then past date followed by oligohydramnios (PROM *P=0.315*, pastdate *P= 0.255*, oligohydramnios *P= 0.493*).

In our study regarding induction-delivery interval (time from given drug for both groups to active phase of labor and to vaginal delivery), there was no significant statistical difference between both groups regarding the mean time from initial dose to the delivery. Mean 15.04 ± 4.67 for sublingual group versus 14.16 ± 4.45 for vaginal group (*P= 0.331*).

These results agreed by Zahran *et al.*, in the study of 480 women divided in 2 groups of 240 each (sublingual and vaginal) The mean duration from start of induction to delivery was 17.2 - 3.9 h and 17.8- 3.5 h for the sublingual and vaginal groups, respectively (*P = 0.76*) (Zahran *et al.*, 2009).

These results also agreed by Caliskan et al., they suggested that induction to delivery intervals were not significantly different in their randomized controlled trial which conducted among 160 women who received 50 µg of misoprostol by sublingual and vaginal routes given every 4 hours. The mean induction to delivery interval was 748 +/- 379 min in the vaginal group and 711 +/- 425 in the sublingual group (p = 0.56). The number of women delivering within 24 h was 73 (91.3%) in the vaginal group and 74 (92.5%) in the sublingual group (p = 0.78) (Caliskan et al., 2005).

In the study conducted by Sheela *et al.*, comparing 50 µg of sublingual misoprostol with 25 µg vaginally in 200 women (100 for each group) with dose interval of 6 hours, the induction to vaginal delivery interval was significantly lesser in the sublingual group, being 13.1 ± 4.1 as compared with 17.9 ± 5.4, in the vaginal group (Sheela *et al.*, 2014).

As regarding number of doses needed in both groups, in our study, there was no significant statistical difference between both groups in the number of doses. With maximum number of doses 4 and time interval 6 hours, almost 88.5% of cases needed 2 doses in sublingual group; while about 94.2% needed 2 doses in the vaginal group (*P = 0.495*). Both groups had the same incidence of failed induction one case in each group and both of them were a primigravida for different indications of induction of labor.

These results are not that much different from the Caliskan *et al.*, study which conducted that the mean number of misoprostol doses required was higher in the sublingual group (1.9 ± 1.2) compared with the vaginal group (1.1 ± 0.4; $p < 0.001$) with dose time interval 4 hours (Caliskan *et al.*, 2005).

While it was found by Sheela *et al.*, that a statistically significant difference was seen in the total number of doses required, with the sublingual group (50 µg) requiring lesser dose compared

with the vaginal group (25 µg). (1.87 ± 0.81 vs 2.57 ± 0.99 with $p < 0.001$), a higher incidence of failed induction was observed in the vaginal group (25 µg) (Sheela *et al.*, 2014).

As regarding the mode of the delivery in our study, although there was increased risk of cesarean delivery in the vaginal group 2 cases (1 due to failed induction and the other due persistent fetal distress) compared to 1 case in the sublingual group (due to failed induction), there was no significant statistical difference between the two groups (*P=0.558*).

These results are agreed by Zahran *et al.*, the sublingual group had lower CS rate compared to vaginal group (*P = 0.52*), relative risk (RR) was 0.98, 95% confidence limits 0.94-1.12). The main indications for CS in both groups were fetal distress and failure to progress. However, rate of failed induction was higher in sublingual group compared to vaginal group. Seven patients in the sublingual and four in the vaginal group did not respond to the four doses of misoprostol and for each of them, CS was carried out 24 hours after starting induction (Zahran *et al*., 2009).

The study conducted by Caliskan *et al.*, found the rate of CS due to fetal distress was higher in the sublingual group compared to the vaginal group. Seven cases (8.8%) in the vaginal group and 12 cases in the sublingual group (15%) required cesarean delivery for persistent fetal distress (*P = 0.220*) (Caliskan *et al.*, 2005).

As regarding fetal and maternal complications in our study, there was significant statistical difference between the vaginal and sublingual groups according to secondary outcome (hyperstimulation). The risk of hyperstimulation was higher in vaginal group (5 cases) compared to the sublingual group (No cases) *P= 0.046*. Regarding other maternal and fetal complications, there was no significant statistical difference between both groups. Though the increased incidence of tachysystole in vaginal group (2 cases) compared to (1 case) the sublingual group (*P= 0.600*) and the only case of CS due to persistent fetal distress was in the vaginal group.

These results agreed by Zahran *et al.* The rates of contractility disturbances, such as tachysystole were similar in the two groups, while the rate of hyperstimulation was more common in the vaginal than in the sublingual group (25 [10.4%] vs 16 [6.7%]), respectively, (Zahran *et al.*, 2009).

While Nassar *et al.*, study conducted on 170 women divided into two groups (sublingual and vaginal) using 50 µg in each of them, the mean number of tachysystole and hyperstimulation was the same in both groups with no significant statistical difference. Despite a similar proportion reporting the labour induction as more painful than expected in both groups, a significantly lower proportion mentioned that the pelvic examinations were very painful in the sublingual group (19.7 versus 36.1%, relative risk [RR] 0.5, 95%). Request for analgesia was similar in both groups. More women in the sublingual group thought that the labour experience was better than expected (RR 2.0, 95%), had a positive attitude towards induction in subsequent pregnancies (RR 1.6, 95% CI 1.) and preferred the same route in subsequent pregnancies (Nassar *et al.*, 2007).

In the present study, as regards Apgar score at 1 and 5 minutes, there was no significant statistical different between the sublingual and vaginal groups (*P= 0.298* and 0.431, respectively).

These findings agreed by Nassar *et al.,* Caliskan *et al.*, Zahran *et al.*, Sheela *et al.*, (Zahran *et al.*, 2009, Nassar *et al.*, 2007, Caliskan *et al.*, 2005).

CONCLUSION AND RECOMMENDATION

Sublingual misoprostol 50 µg administered at 6 hourly intervals is as effective in promoting cervical ripening and inducing labor as vaginal misoprostol 50 µg administered 6 hourly intervals as regarding induction to delivery interval, number of doses, shorter hospitalization and neonatal outcome. Sublingual misoprostol 50 µg has a higher maternal and perinatal safety profile than the vaginal 50 µg misoprostol including cesarean rates due to fetal distress, adverse maternal outcomes as hyperstimulation. We recommend sublingual 50 µg misoprostol administered at 6 hourly intervals as an efficacious and safe option for labor induction with low cost and availability as its added benefits.

CONFLICT OF INTEREST

There are no conflicts of interest

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