Comparative Study Between Sublingual and Vaginal Misoprostol for Induction of Labor in Post Term Pregnant Patients with Unfavourable Cervix

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ABSTRACT
Background: Pharmacological studies suggest that sublingual route might be the optimal route of administration for PGE1 analogue misoprostol because the avoidance of the first pass hepatic circulation would yield bioavailability like that achieved with the vaginal route along with an earlier onset of action and a prolonged activity.
Objective: The aim of this study was to compare the efficacy and the safety of vaginal misoprostol with sublingual misoprostol for induction of labor in post-term pregnancy.
Subjects and Methods: This study included 50 cases, each with a singleton post-term pregnancy and a live fetus requiring induction of labor were allocated to sublingual and vaginal administration of misoprostol. Outcome measures related to labor and maternal and fetal side effects were compared between the 2 groups and evaluated using Chi square test.
Results: The sublingual route of misoprostol was associated with a reduced risk of failed induction, reduced time from initiation to induction, reduced induction to delivery interval and a higher incidence of maternal and fetal side effects. However, the differences were not statistically significant.
Conclusion: The sublingual route of administration of misoprostol is comparable in efficacy and safety to the vaginal route for induction.

Key words: Induction of labor, Misoprostol, Sublingual.

INTRODUCTION

Amongst the plethora of techniques available for induction of labor, Prostaglandins remain the single most effective means of achieving cervical ripening and inducing labor and have been administered through various routes. Pharmacological studies suggest that sublingual route might be the optimal route of administration for PGE1 analogue misoprostol because the avoidance of the first pass hepatic circulation would yield bioavailability similar to that achieved with the vaginal route along with an earlier onset of action and a prolonged activity [1].

This has generated an interest in the sublingual route for labor induction. An additional possible advantage is that avoidance of direct cervical effects might reduce the risk of uterine hyperstimulation. Sublingual dosing for labor induction is attractive also because of ease of administration, less frequent need for vaginal examination, greater freedom of position and the possibility of its convenient use despite vaginal bleeding or ruptured membranes [2].

A few studies have found that sublingual administration of misoprostol is also effective for induction of labour [3].

The aim of this study was to compare the efficacy and the safety of vaginal misoprostol with sublingual misoprostol for induction of labor in post-term pregnancy.

SUBJECTS AND METHODS

This study included a total of 100 pregnant women whose gestational ages were beyond 42 weeks attending at Department of Obstetrics and Gynecology, In Al-Azhar University Hospitals. Approval of the ethical committee and a written informed consent from all the subjects were obtained. This study was conducted between September 2017 and May 2018. Subjects were divided into two groups as follows:

I- Group I: This group included 50 pregnant women who received vaginal misoprostol in a dose of 25 µg to be repeated every 4 hours if no response was achieved with a maximum of 6 doses. This dose was placed in the posterior fornix of the vagina. (1 tablet of Vagiprost, Adwia, Egypt).

II- Group II: This group included 50 pregnant women who received sublingual misoprostol in a dose of 50 µg to be repeated every 4 hours if no response was achieved with a maximum of 6 doses. This dose was placed under the tongue till completely dissolved. (1/4 of Misotac tablet, Sigma, Egypt). In both groups gestational age was determined by reliable history of dating of the last menstrual period with regular cycles and / or sonography at first trimester. Unification of the baseline characteristics between both groups was attempted. This study was approved by Al-Azhar University hospitals and

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informed consent for participation was obtained from each study participant. The nature of the study was explained to all patients and they were willing to have their results registered in this study.

Inclusion criteria: Post term pregnant female (beyond 42 weeks gestation). Singleton pregnancies. Vertex presentation. Normal fetal heart tracing. Unfavorable cervix (a cervix that is not adequately prepared for a vaginal delivery of a newborn child "one with a Bishop's score of 6 or less")

Exclusion criteria: Twin pregnancy. Abnormal fetal presentation. Fetal macrosomia (>4 Kgms). Previous uterine scar. Placenta previa centralis and marginalis posterior. Absolute contraindication for induction of labor as (inadequate pelvis, severe oligohydramnios, placental insufficiency). High risk pregnancy (a pregnancy that threatens the health or life of the mother or her fetus e.g. elevated blood pressure or diabetes mellitus.

A detailed history, general physical examination and Obstetrical examination were carried out. Per vaginum examination was done for assessing bishop's score and pelvis. Subjects meeting the above criteria with no contraindication to vaginal delivery were allocated alternately in each group. Failure of induction was defined as unfavourable cervix after 5 doses (evaluated 4 hours after last dose). The subsequent dose was withheld in the presence of any of the following: at least three regular uterine contractions in 10 minutes, active phase of labor (defined as regular uterine contractions with cervical dilation >3 cm), cervix favorable for amniotomy (Bishop score >8).As soon as fetal head engagement and cervical dilation permitted, amniotomy was performed, followed by oxytocin augmentation if the frequency of contractions was less than three per 10 minutes or the contractions pattern was dysfunctional. Oxytocin was administered not earlier than 4 hours after the last misoprostol dose, starting at 1mU/minute and increased by 1mU/minute every 15 minute until adequate contractions persisted. If the woman went into labor or if the Bishop's score was 8 or more, an artificial rupture of membranes was performed. Induction of labor was considered to have failed when cervix was unfavorable (Bishop's score <8) after 5 doses of misoprostol (evaluated 4 hours

after last dose). If there was failure of induction, caesarean section was performed.

During entire intrapartum period strict monitoring of fetal heart rate and rhythm was done & uterine activity was monitored for tachysystole, hypertonus and hyper stimulation syndrome.

Determination of the outcomes: Primary outcomes: successful induction of labor is measured by several factors that include induction-delivery interval, mode of delivery, number of doses given, number of women given oxytocin. Secondary outcomes: Any maternal obstetric complications: such as uterine hyperstimulation, antepartum hemorrhage, postpartum hemorrhage. Any fetal complications: all neonates were subjected to Apgar scoring at 5 minutes then neonatal morbidity was considered by the following criteria: Apgar score less than 6 at 5 minutes, fetal academia, neonatal admission to the Neonatal Intensive Care Unit(NICU), neonatal birth weight(NBW). Side effects of misoprostol: such as nausea, vomiting, diarrhea or hyperthermia.

Statistical analysis: The data was analyzed with the help of computer software SPSS version 12.0 for windows. Statistically significant differences were evaluated using Chi square test. P value of <0.05 was considered as statistically significant.

RESULTS

Table (1) shows that no statistically significant difference was found between the two groups regarding their baseline characteristics which denote homogeneity of the two groups.

Table (1): Distribution of patients in both groups (50 cases in each group) by their Baseline characteristics (Age, Parity, Previous abortion, Bishop score, EFW by U/S, Body mass index-BMI-).

Item		Group I (vaginal) No = 50	Group II (sublingual) No = 50	P value	T
Age		25.27 ± 3.523	26.23 ± 2.725	0.240	-1.189
Parity (mean ± SD)	Primipara	10 cases	9 cases	0.423	-0.856
	Para 1	12 cases	13 cases	0.560	-0.586
	Para 2	13 cases	12 cases	0.356	-0.624
	Para ≥ 3	15 cases	16 cases	0.521	-0.238
Previous abortion		0.37 ± 0.765	0.50 ± 0.731	0.493	-0.690
Bishop score		4.63 ± 0.556	4.87 ± 0.681	0.152	-1.453
EFW by U/S		3.283 ± 0.126	3.277 ± 1.331	0.843	-0.199
BMI		19.864 ± 2.145	20.324 ± 1.023	0.234	-0.964

Table (2) shows that the mean of the induction to delivery interval in group I was 12.03 ± 4.004 hours while in group II was 11.68 ± 3.475 hours. No statistically significant difference between the two groups was found (T= -0.358, P= 0.722) which denotes homogenecity of the two groups.

Table (2): Distribution of patients in both groups by their induction to delivery interval.

Item	Group I (Vaginal) No = 50	Group II (Sublingual) No = 50	P value	T
Induction to delivery interval (mean ± SD)	12.03 ± 4.004	11.68 ± 3.475	0.722 (NS)	-0.358

Table (3) shows that the number of patients who needed oxytocin augmentation in the vaginal group was 32 cases (64%) and in the sublingual group was 30 cases (60.0%). No statistically significant difference between the two groups was found (P= 0.791).

Table (3): Number of cases which needed oxytocin augmentation.

Item	Group I (Vaginal) No = 50	Group II (Sublingual) No = 50	P value	T
Oxytocin augmentation (Number of cases)	32 cases (64%)	30 cases (60%)	0.791 (NS)	0.712

Table (4) shows that the number of maternal obstetric complications in the vaginal group were: a) Antepartum hemorrhage 3 cases (6%), b) Postpartum hemorrhage 5 cases (10%), c) Uterine hyperstimulation 5 cases (10%). The number of maternal complications in sublingual group were: a) Antepartum hemorrhage 2 cases (4%), b) Postpartum hemorrhage 6 cases (12%), c) Uterine hyperstimulation 7 cases (14%). No statistically significant difference between the two groups was found (P= 0.688 for antepartum hemorrhage, P=0.657 for postpartum hemorrhage, P=0.732 for uterine hyperstimulation).

Table (4): Maternal obstetric complications in both groups.

Maternal complications	Group I (Vaginal) No = 50	Group II (Sublingual) No = 50	P value	T
Antepartum hemorrhage	3 cases (6%)	2 cases (4%)	0.688	0.103
Postpartum hemorrhage	5 cases (10%)	6 cases (12%)	0.657	0.116
Uterine hyperstimulation	5 cases (10%)	7 cases (14%)	0.732	0.131

Table (5) shows that the distribution of neonatal complications in the vaginal group was: a) Low Apgar score < 7 at 5 minutes 3 cases (6%), b) NICU admission 4 cases (8%), Low neonatal birth weight < 2.5 kg. 3 cases (6%). The distribution of neonatal complications in the sublingual group was: a) Low Apgar score < 7 at 5 minutes 2 cases (4%), b) NICU admission 3 cases (6%), Low neonatal birth weight < 2.5 kg. 5 cases (10%).

No statistically significant difference between the two groups was found (P= 0.577 for low Apgar score, P=0.554 for NICU admission, P=0.286 for low neonatal birth weight).

Table (5): Neonatal complications in both groups.

Neonatal complications	Group I (Vaginal) No = 50	Group II (Sublingual) No = 50	P value	T
Low Apgar score < 7 at 5 minutes	3 cases (6%)	2 cases (4%)	0.577	0.561
NICU admission	4 cases (8%)	3 cases (6%)	0.554	0.602
Low neonatal birth weight < 2.5 kg.	3 cases (6%)	5 cases (10%)	0.286	1.078

Table (6) shows that the distribution of side effects of misoprostol in the vaginal group was: a) nausea 3 cases (6%), b) vomiting 4 cases (8%), c) diarrhea 3 cases (6%), d) hyperthermia 5 cases (10%).

The distribution of side effects of misoprostol in the sublingual group was a) nausea 2 cases (4%), b) vomiting 3 cases (6%), c) diarrhea 5 cases (10%), d) hyperthermia 6 cases (12%).

No statistically significant difference between the two groups was found (P= 0.577 for nausea, P=0.554 for vomiting, P=0.286 for diarrhea, P= 0.365 for hyperthermia)

Table (6): Side effects of misoprostol in both groups.

Side Effects	Group I (Vaginal) No = 50	Group II (Sublingual) No = 50	P value	T
Nausea	3 cases (6%)	2 cases (4%)	0.577	0.561
Vomiting	4 cases (8%)	3 cases (6%)	0.554	0.602
Diarrhea	3 cases (6%)	5 cases (10%)	0.286	1.078
Hyperthermia	5 cases (10%)	6 cases (12%)	0.365	0.985

DISCUSSION

In our study we found that 50 µg sublingually administered misoprostol is similarly effective as 25 µg vaginal misoprostol with respect to our primary outcome.

There was no significant difference in the number of pregnant women who delivered within the first 24 hours which was 41 (82%) in vaginal group and 38 (76%) in sublingual group.

Regarding induction-delivery interval the difference between vaginal and sublingual groups was non-significant 12.03 ± 4.004 vs. 11.68 ± 3.475, p≥0.05.

Regarding maternal or neonatal complications the difference between vaginal and sublingual groups was non-significant, P ≥ 0.05.

The pharmacokinetic studies that have shown that the peak plasma concentration and bioavailability after a single dose of misoprostol are higher after sublingual administration than those after vaginal administration. This may be explained by the absence of a first-pass effect by the liver after sublingual administration. The good blood supply under the tongue and the relatively neutral pH in the buccal cavity may also be contributing factors [1].

The sublingual route has been shown to produce significantly higher serum peak concentration of misoprostol than vaginal administration. In addition, the area under the curve for plasma levels over 4 and 6 hours was significantly greater following sublingual administration than for vaginal administration [4].

A recently published study evaluated the effects of misoprostol on uterine contractility following different routes of administration. The sublingual application of misoprostol has, with regard to effects on the myometrium, at least as rapid an effect on uterine contractility as oral administration and is similar to that following vaginal administration [2].

These findings may explain the shorter induction to delivery interval with sublingual misoprostol than vaginal misoprostol in our study, that is still non-significant difference (P=0.722). It must, however, be emphasized that we compared a higher sublingual dose (50 mg) with a lower dose of vaginal misoprostol (25 mg). This approach was adopted because data from two previous studies [5].

Comparing 50 mg of sublingual with 50 or 100 mg of oral misoprostol for labor induction, suggested that 50 mg of misoprostol administered sublingually might be the optimal dose that maintains the balance between efficacy and safety and a dose that might not have been effective was not acceptable.

Different routes of misoprostol administration for labor induction necessitate carefully balancing the benefit (shorter induction to delivery interval) against the risk (uterine hyperstimulation, adverse neonatal and maternal outcomes). The considerably higher rate of tachysystole with 50 mg of misoprostol given sublingually when compared with vaginal administration of 25 mg was a cause for concern, even though similar rates of hypertonus and hyperstimulation syndrome were observed. This suggests that avoidance of a direct effect on the cervix did not reduce the risk of excessive uterine activity [6].

Zahran et al. evaluated sublingual versus vaginal misoprostol for induction of labor at post-term, but in randomized prospective placebo controlled study. We found similar results like Zahran et al study as fetal distress in both group had the highest frequency, but there was no difference between groups in case of induction to delivery interval, duration of labor, neonatal outcome or maternal side effects [7]. However in comparison to their study, we found low number of attributed labors that had meconium staining in both studied groups, but less active labor in sublingual group. They found sublingual route promised to higher patient's satisfaction level. Although we didn't evaluate the patients' satisfaction level in our results.

Akare and Patel conducted a study at Department of Obstetrics and Gynecology, Medical College, Baroda, Gujarat, India. 2 groups 50 cases each with a singleton post-term pregnancy and a live fetus requiring induction of labor were allocated to sublingual and vaginal administration of misoprostol. Outcome measures related to labor and maternal and fetal side effects were compared between the 2 groups. The results revealed that the sublingual route of misoprostol was associated with a reduced risk of failed induction, reduced time from initiation to induction, reduced induction to delivery interval and a higher incidence of maternal and fetal side effects. However, the differences were not statistically significant [8]. The results of this study are consistent to our study.

Bartusevicius *et al.* designed a double-blinded, randomized controlled trial to compare the efficacy and safety of 50 mg of sublingual misoprostol with 25 mg of vaginal misoprostol administered for labor induction on a total of 140 pregnant women at post-term and concluded that a 50 mg of sublingual misoprostol 4 hourly for labor induction at post-term seems to have similar efficacy as 25 mg of vaginal misoprostol[3]. The results of this study are consistent to our study.

Moraes-Filho *et al.* performed a randomized controlled clinical trial to compare the effectiveness and safety of sublingual misoprostol (25 µg) versus vaginal misoprostol (25 µg) for labor induction with gestational age $\geq$ 37 weeks and unripe cervices. The results revealed that 25 µg of sublingual misoprostol every 6 h. presented the same effectiveness and safety as an equal vaginally administered dose of this substance [9]. The results of this study correlates with our study as there were no statistically significant differences between the vaginal and sublingual groups in the induction-delivery interval, the number of vaginal deliveries, but this study differs in the number of doses used, number of patients enrolled in the study and the gestational age of the patients.

Although the research has reached its aims, there are still some limitations. First, because of the time limit, this research was conducted only on a small size of population who attended our hospital during research period. Therefore, to generalize the results for larger groups, it would be better if it was done in a longer time. Other limitations may involve that lack of blinding in our study as the nature of the study has been explained to all participants. There is no time or place for long term follow up of all participants that if was present it would help us to determine more outcomes of the study such as post-partum hemorrhage, post-partum depression.

Further future studies should take into consideration increasing the study base through increasing the sample size and the duration of the trial to be more representative and eliminate any bias that may occur.

CONCLUSION

Induction of labor in post-term pregnant women with unfavorable cervix with either 25 µg vaginal misoprostol or 50 µg sublingual misoprostol seems to be effective, safe, low cost and worthy to induce labor without forgetting the precautions we mentioned and close observation to the mother and fetus.

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