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Original Research Article

Sequential use of oral and vaginal misoprostol versus oral or vaginal misoprostol alone for induction of labor and the caesarean delivery risk: a retrospective study

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ABSTRACT

Background: Induction of labor is now a common practice and every institute faces the task of developing a safe and cost-effective protocol. We aimed to study the effects of sequential use of oral and vaginal misoprostol when compared to oral or vaginal misoprostol alone. Our primary objective was to determine the caesarean delivery rates and secondarily the maternal and neonatal complications between the different induction regimes.
Methods: A single-center retrospective observational study was conducted, with patient records divided into three groups based on their methods of induction: those who were administered vaginal misoprostol only, those who had oral misoprostol only, and those who had oral misoprostol followed by vaginal misoprostol. We extracted all the necessary data from the records and analyzed it using SPSS.
Results: 768 records with comparable demographic characteristics were reviewed. The majority of women were induced at 39 completed weeks. There was no significant difference in the proportion of caesarean deliveries when comparing the three groups but the number of caesarean sections was lower among women who had been administered vaginal misoprostol alone. Among the patients included in the study, the women who developed postpartum hemorrhage received a higher mean dose of misoprostol (130±70 mcg) compared to those who did not (104±57 mcg).
Conclusions: Sequentially administering misoprostol may not decrease the caesarean section rate compared to using only one route of administration. However, it is important to monitor the amount of misoprostol given to each patient to prevent the incidence of PPH.

Keywords: Misoprostol, Induction of labor, Caesarean sections, PPH

INTRODUCTION

Labor induction is performed worldwide for several maternal and fetal indications, to improve pregnancy outcomes. This requires careful planning and individualized induction methods to achieve a low primary caesarean section rate while promoting the health of both the mother and child. Misoprostol, a synthetic analog of Prostaglandin E1, is extensively used off-label for cervical ripening in those women who require induction of labor. It is a cheap and heat-stable drug that can be stored at room temperature and administered by an unskilled attendant which makes it especially appealing for developing countries. However, the drug has many maternal and fetal risks, including uterine hyperstimulation with changes in fetal heart rate, and meconium staining of the amniotic fluid, thereby increasing the need for emergency cesareans.[1] And among women who have had a vaginal delivery, the risk of post-partum hemorrhage (PPH) was found to be higher in those with induced versus spontaneous labor, regardless of the induction method.[2] The effectiveness of misoprostol depends on how it is

administered. When taken orally, misoprostol reaches its peak serum levels within 30 minutes and the duration of action is approximately 2 hours. However, when inserted vaginally, plasma concentrations gradually increase, reaching their peak after 70-80 minutes before being slowly eliminated. Through this route plasma levels are still detectable 6 hours after administration.[3] In a Cochrane review that involved 61 trials and 20,026 participants, it was found that the use of low-dose oral misoprostol (25 mcg) was associated with a lower risk of hyperstimulation and caesarean sections due to fetal distress compared to administering misoprostol vaginally. In contrast, another systematic review has shown that the risk of meconium-stained amniotic fluid (MSAF) and caesarean sections were higher in women who took oral misoprostol in comparison to those who received the drug vaginally.[4,5] Moreover, a study conducted by Handal-Orefice et al has concluded that women who received 50 mcg oral misoprostol every 4-6 hours up to a maximum of 6 doses had a higher risk of caesarean delivery compared to those who received 25 mcg vaginal misoprostol in the same dosing interval.[6] Therefore, standardization of misoprostol dose schedules and routes of administration is necessary to reduce primary caesarean section rates during labor induction. In 2017, FIGO introduced the oral misoprostol regimes for inducing labor at term which has been reaffirmed in 2023. Starting in 2018, our institution began prescribing oral misoprostol to induce labor. However, we observed that many women did not experience labor pains. Later, there was a gradual shift towards using vaginal misoprostol after administering oral misoprostol if adequate cervical ripening was not achieved and uterine contractions had not started. Although no major complications have been observed, there is insufficient evidence to justify the continued use of this combination. Therefore, we proposed this study to explore the pros and cons of sequential use of misoprostol through different routes and to compare its effectiveness to previous regimes. Ultimately, we hope to develop an optimal protocol for using misoprostol that ensures the best obstetric care while reducing the primary caesarean section rate.

METHODS

This historical cohort was conducted in the department of obstetrics and gynecology at Malankara Orthodox Syrian Church Medical College Hospital, Kerala India. From 2017, through 2020 patient records of women who were admitted for induction of labor were reviewed and assessed for eligibility. Gestational age was determined from the first-trimester ultrasound scan when available or from the date of the last menstrual period for women with regular cycles. Regardless of parity, records of women who had completed 36 weeks of gestation with a modified Bishop's score <4 and a normal fetal heart tracing before induction of labor were included in the study. Major exclusions were multiple pregnancies, malpresentation, prior caesarean delivery/ previous scarring on the uterus, fetal demise or known major fetal anomaly, antepartum hemorrhage, cerclage in current pregnancy, and mothers with chronic medical disorders i.e., chronic hypertension, pregestational diabetes mellitus, renal diseases. The data from a previous study was used to estimate a sample size of 252 for each group.[6] Convenient sampling was used to distribute the records into the three groups depending on the method that was used by the attending obstetrician. The regime adopted for induction of labor was chosen by the obstetrician after individualized consults.

Table 1: Description of various groups.

Groups	Description
Group 1-VM	Vaginal Misoprostol 25 mcg kept vaginally and repeated every 4 hours up to a maximum of 3 doses
Group 2-OM	Oral misoprostol 25 mcg taken orally repeated every 2 hours up to a maximum of 5 doses
Group 3-OM-VM	Oral Misoprostol 25 mcg repeated every 2 hours up to a maximum 5 doses and followed by vaginal misoprostol 25 mcg kept the next day (when Modified bishop score less than 6), repeated every 4 hours up to maximum 3 doses.

*OM, oral misoprostol; VM, vaginal misoprostol, OM-VM-oral misoprostol followed by vaginal misoprostol.

As per protocol, women who had undergone any of the mentioned regimes (Table 1) were monitored closely. If a patient had more than four uterine contractions in 10 minutes and a favorable Bishop's score, artificial rupture of membranes was performed and oxytocin augmentation was implemented if there was no progress of labor. If the women did not develop uterine contractions by the next day, oxytocin infusion (5 units in 500 ml RL) was started at a rate of 4 drops per minute. Upon reviewing the labor progress notes and operative records, the indication for caesarean section was determined. Furthermore, we also gathered information regarding any intrapartum clinical measures taken and any postpartum complications that occurred.

The primary outcome measure was the proportion of caesarean sections in each group. Additionally, the patient records were specifically searched for presence of any abnormal cardiotocograph (CTG), MSAF, uterine hyperstimulation, PPH, and any neonatal complications.

All the data collected from these records were completely anonymized, hence informed consent was not obtained. Data were expressed as mean±SD or counts and percentages. Qualitative data were analyzed using Chi-square or Fisher's exact test.

The normality assumption of the quantitative measures was verified by the Shapiro-Wilk test and the significance of between-group differences was assessed using the Kruskal-Wallis rank test or the one way ANOVA. All the

tests were two-tailed with a significance level set at 5%. All data was analyzed using the SPSS software.

RESULTS

Of all the patient records assessed for eligibility over four years (2017-2020), a total of 768 cases were included in the study and was divided into the three groups (Figure 1). Demographic characteristics were comparable (Table 2). All women had a pre-induction Bishop's score less than 4. The mean gestational age at induction was 39 completed weeks and among the indications for induction 66% of the patients were electively induced (VM-62.4%, OM-68.6%, OM-VM-66.7%) after 39 completed weeks. The other indications for induction were gestational diabetes mellitus (11.2%), hypertensive disorders of pregnancy (12%) fetal growth restriction (3%), premature rupture of membranes (5.5%), and decreased fetal movements (2%) (Figure 2).

Table 2: Baseline demographic and pregnancy characteristics

Characteristics, N (%)	VM (n=258)	OM (n=255)	OM-VM (n=255)	P value*
Maternal age (years)	26.6 (3.8)	26.9 (3.8)	26.7 (4.2)	0.67
BMI	24.0 (4.2)	23.9 (4.3)	24.0 (4.2)	0.95
Parity	1 (1-4)	1 (1-4)	1 (1-4)	0.87
Gestational age (days)	273 (7)	273 (6)	273 (6)	0.48
Bishop's Score	2 (0-3)	2 (0-3)	2 (0-3)	1.0

*Quantitative data are presented by median (range) or mean with standard deviation. For qualitative factors, absolute and relative frequencies are given, p<0.05 was considered significant. OM, oral misoprostol; VM, vaginal misoprostol, OM-VM-oral misoprostol followed by vaginal misoprostol.

Table 3: Outcome parameters among all women.

Characteristics, N (%)	VM (n=258)	OM (n=255)	OM-VM (n=255)	P value*
Normal vaginal delivery	185 (71.7)	176 (69)	172 (67.5)	0.57
Operative vaginal delivery	18 (7)	11 (4.3)	13 (5.1)	0.39
Caesarean section	55 (21.3)	68 (26.7)	70 (27.5)	0.21
Failed induction	23(41.8)	21 (30.9)	24 (34.3)	0.44
Misoprostol tablets given (each 25 mcg)	2 (1-2)	4 (1-5)	7 (3-9)	<0.05
Epidural analgesia received	72 (27.9)	46 (18)	61 (23.9)	<0.05
Abnormal CTG	23 (8.9)	19 (7.5)	13 (5.1)	0.25
Post-partum hemorrhage	10 (3.9)	10 (3.9)	20 (7.8)	0.16
Arterial umbilical pH <7.10 at birth	10 (3.9)	14 (5.4)	17 (6.7)	0.37
APGAR<7 at 5 min	4 (1.6)	1 (0.4)	5 (2)	0.26
Meconium-stained amniotic fluid	22(8.5)	19 (7.5)	17 (6.7)	0.73
Unplanned admission to NICU	39 (15.1)	48 (18.8)	47 (18.4)	0.47

*Quantitative data are presented by median (range). For qualitative factors, absolute and relative frequencies are given, p<0.05 was considered statistically significant, CTG-cardiotocograph.

Table 4: Outcome parameters among nulliparous women.

Mode of delivery, N (%)	VM (n=179)	OM (n=176)	OM-VM (n=185)	P value*
Normal vaginal delivery	109 (60.9)	102 (58)	108 (58.4)	0.83
Operative vaginal delivery	18 (10.1)	11 (6.3)	13 (7)	0.36
Caesarean section	52 (29.1)	63 (35.8)	64 (34.6)	0.35
Failed induction	22 (42.3)	20 (31.7)	21 (32.8)	0.44
Misoprostol tablets given (each 25 mcg)	2 (1-4)	4 (1-5)	7 (3-9)	<0.05
Epidural analgesia received	68 (38)	41 (23.3)	52 (28.1)	<0.05
Abnormal CTG	23 (12.8)	17 (9.7)	10 (5.4)	<0.05
Post-partum hemorrhage	7 (3.9)	7 (4)	14 (7.6)	0.3
Arterial Umbilical pH <7.10 at birth	9 (5)	12 (6.8)	15 (8.1)	0.5
APGAR<7 at 5 min	4 (2.2)	1 (0.6)	4 (2.2)	0.38
Meconium-stained amniotic fluid	17 (9.5)	16 (9.1)	16 (8.6)	0.96
Unplanned admission to NICU	33 (18.4)	41 (23.3)	40 (21.6)	0.52

*Quantitative data are presented by median (range). For qualitative factors, absolute and relative frequencies are given, p<0.05 was considered statistically significant.

The proportions of each indication among the different groups were comparable (p>0.05). The number of vaginal examinations performed was also not significantly reduced even when the oral misoprostol regime was used. Twenty-five percent of the women underwent caesarean section and there was a higher number in the OM-VM group and OM group compared to the VM group but it was not statistically different. The most common indication for caesarean section was the arrest of descent (VM-33%, OM-43%, OM-VM-41%), followed by failed induction and abnormal CTG. Forty-two percent of the patients in the VM group had failed induction resulting in an emergency caesarean section while it was lower in the other groups (OM 31%, OM-VM 34%) but this was not significantly different.

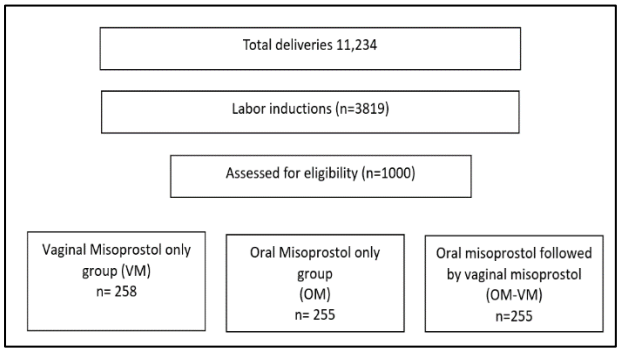

Figure 1: Study flow chart.

In total, 179 women received epidural analgesia during labor. There was a significantly lower number of women who chose epidural analgesia in the OM group. Incidence of PPH was not significantly different among the groups though there was a rise in the absolute number in the OM-VM group. The total dose of misoprostol in each group was compared and the least dose of misoprostol was administered in the vaginal group (49±20 mcg) followed by the oral group (94±31 mcg) and the sequential group (172±30 mcg). The dose administered was significantly higher in the OM-VM group. On comparing the women who developed PPH to those who did not irrespective of the route of administration, we observed that the mean dose of misoprostol administered to women who developed PPH (N=40) in the whole sample was 130±70 mcg compared to mothers who did not develop PPH (N=728) who received 104±57 mcg. Unplanned admissions to the NICU were lowest in the VM group and the most common indication for NICU admission was MSAF and others included hypoglycemia, respiratory distress, low birth weight and arterial umbilical pH <7.1. None of the patients in any of the groups had uterine hyperstimulation or any other maternal complications (Table 3). On sub-group analysis, there were 540 nulliparous women with a mean age of 25.8±3.4 years included in the study and their mean gestational age of induction was 39 completed weeks (±6 days). The proportion of caesarean section was higher in the OM and OM-VM groups compared to the VM group but this difference was not significant. The incidence of abnormal CTG was significantly higher among women who were in the VM group. Ninety percent of the nulliparous women opted for epidural analgesia and the numbers were significantly higher in women in the VM and the OM-VM group compared to the OM group (Table 4).

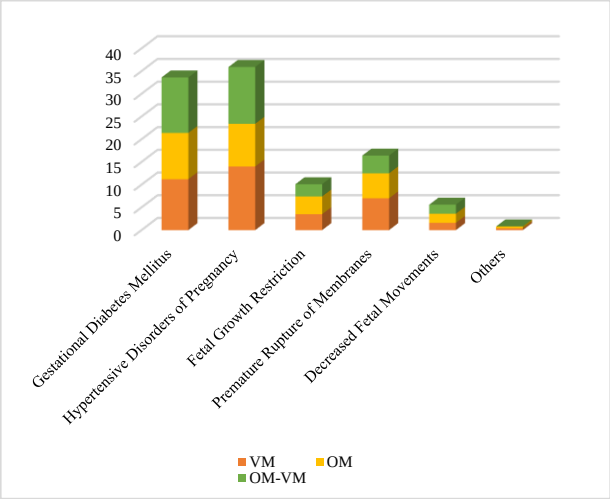

Figure 2: Proportion of women with each indicated indication for induction of labor in each group.

DISCUSSION

Inducing labor before 40 weeks has been linked to an increase in caesarean section rates compared to spontaneous labor. Although many studies suggest that inducing labor can improve pregnancy outcomes, a rise in caesarean section rates is not desirable. According to the National Health Survey (NFHS-5), our state (Kerala) has a primary caesarean section rate of 42.4%.[7] This high rate could be due to the advanced obstetric techniques that enable early detection of antenatal complications. Therefore, it is crucial to ensure that labor induction does not contribute to this high caesarean section rate. Our study focused on women who underwent induction of labor with misoprostol-only regimens. The majority of the participants were low-risk nulliparous women who were electively induced at 39 completed weeks. We found no statistically significant difference in the primary caesarean section rates among the different groups, regardless of the route of misoprostol administration. This contrasts with studies that have found a higher frequency of caesarean sections in women who received oral misoprostol compared to vaginal misoprostol.[5,6] Fortunately, none of the women in any of the groups had developed uterine hyperstimulation. However, there was an increase in the number of women who developed PPH in the sequential group (OM-VM) but we could not compute a statistical difference. This could be due to the higher dose of misoprostol that was used in the sequential group (172±30 mcg) which was statistically higher. In a study conducted by Brun et al revealed that inducing labor using vaginal misoprostol up to a maximum dose of 150 mcg did not increase blood loss after delivery and therefore high doses of vaginal misoprostol cannot be considered a risk factor

for PPH but sequential use did result in a higher mean dose of misoprostol which could have caused the higher number of PPH cases.[8] There has also been a study that inferred that the risk of PPH is higher in those with induced versus spontaneous labor, regardless of induction method, due to an increase in the total quantity of oxytocin received during labor.[2] Seventy-three percent of the women in our study had received oxytocin as it was commenced if uterine contraction was absent after receiving the maximum dose of misoprostol assigned to each group and also for labor augmentation. In this context, though we had not quantified the amount of oxytocin received by the patients, it is not plausible that women who received higher doses of misoprostol had prolonged exposure to oxytocin.

An interesting observation was that nulliparous women who received vaginal misoprostol insertion were more likely than others to choose epidural analgesia, despite it being offered to all women. There was a statistically significant decrease in the number of women who opted for epidural analgesia in the group that had taken oral misoprostol alone compared to the other groups. This could be similar to findings in study by Redling et al who found that women who received a vaginal insert with misoprostol for labor induction more often required intrapartum analgesia with opioids.[9] However, there was no standardized pain scale used to assess the level of pain, which could be a potential reason for the variation in the numbers. The evaluation of pain was largely dependent on the individual's pain threshold and predisposition, making it a subjective process. Consequently, patients were given epidural analgesia based on subjective assessments.

We also observed that among the neonatal outcomes, there was no significant difference in the incidence of abnormal CTG or MSAF depending on the mode of induction.

A recent review described a lesser incidence of MSAF while administering vaginal misoprostol when compared to oral route but in contrast, our study showed a higher number of MSAF cases while administering misoprostol vaginally though the difference was not significant.[5] Lesser number of abnormal umbilical artery pH at birth and unplanned NICU admissions were seen in the vaginal misoprostol group but this was also not statistically different. Among the nulliparous women, there was a significantly higher incidence of abnormal CTG in the vaginal misoprostol-only group but it did not translate to an increase in neonatal morbidity.

Limitations

The major limitation of our study was its retrospective and observational nature, which failed to provide more precise information regarding the indications for induction and caesarean section. Furthermore, incomplete and unclear documentation might have resulted in a reduced amount of data that could be retrieved. We have not assessed the induction delivery interval as the sequential group always lagged by a day and the amount of oxytocin required to achieve a vaginal delivery was also not documented. Further clinical trials are needed to determine the optimal dose and route of misoprostol and also the amount of oxytocin that can be given without compromising the mother or the fetus

CONCLUSION

Our study has shown that there is no significant difference in the rate of caesarean sections among women who underwent induction of labor through oral, vaginal, or sequential administration of misoprostol. However, there was a decrease in the absolute number of caesarean sections in the group that received vaginal misoprostol alone. Furthermore, there was an increase in the incidence of PPH in the group that received sequential misoprostol which could be attributed to the higher mean dose of misoprostol used in this group. Since safety is our top priority, further research is necessary to determine the highest safe dose of misoprostol that can be administered without increasing the incidence of postpartum hemorrhage irrespective of the route of administration.

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Ethical approval: The study was approved by the Institutional Ethics Committee. The trial was registered prospectively under the Clinical Trial Registry of India. (CTRI/2021/09/036652).

REFERENCES

1. Allen R, O'Brien BM. Uses of misoprostol in obstetrics and gynecology. Rev Obstet Gynecol. 2009;2(3):159-68.
2. Braund S, Deneux-Tharaux C, Sentilhes L, Seco A, Rozenberg P, Goffinet F. Induction of labor and risk of postpartum hemorrhage in women with vaginal delivery: A propensity score analysis. Int J Gynecol Obstet. 2023.
3. Lapuente-Ocamica O, Ugarte L, Lopez-Picado A, Sanchez-Refoyo F, Lasa IL, Echevarria O, et al. Efficacy and safety of administering oral misoprostol by titration compared to vaginal misoprostol and dinoprostone for cervical ripening and induction of labour: study protocol for a randomised clinical trial. BMC Preg Childbirth. 2019;19:14.
4. Kerr RS, Kumar N, Williams MJ, Cuthbert A, Aflaifel N, Haas DM, et al. Low-dose oral misoprostol for induction of labour. Cochrane Database Syst Rev. 2021;6(6):14484.
5. Rahimi M, Haghighi L, Baradaran HR, Azami M, Larijani SS, Kazemzadeh P, et al. Comparison of the effect of oral and vaginal misoprostol on labor induction: updating a systematic review and meta-analysis of interventional studies. Eur J Med Res. 2023;28(1):51.
6. Handal-Orefice RC, Friedman AM, Chouinard SM, Eke AC, Feinberg B, Politch J, et al. Oral or Vaginal

Misoprostol for Labor Induction and Cesarean Delivery Risk. Obstet Gynecol. 2019;134(1):10-6.
7. Roy N, Mishra PK, Mishra VK, Chattu VK, Varandani S, Batham SK. Changing scenario of C-section delivery in India: Understanding the maternal health concern and its associated predictors. J Fam Med Prim Care. 2021;10(11):4182-8.
8. Brun R, Spoerri E, Schäffer L, Zimmermann R, Haslinger C. Induction of labor and postpartum blood loss. BMC Preg Childbirth. 2019;19(1):265.
9. Redling K, Schaedelin S, Huhn EA, Hoesli I. Efficacy and safety of misoprostol vaginal insert vs. oral misoprostol for induction of labor. J Perinat Med. 2019;47(2):176-82.

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