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Comparison of the efficacy and safety of titrated oral misoprostol solution and conventional oral misoprostol tablet regimen for Induction of labor

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Abstract

Objective: *To compare the efficacy and safety of titrated oral misoprostol solution (OMS) and conventional oral misoprostol tablet (OMT) regimen for induction of labor.*

Material and Methods: *A cohort of two hundred pregnant women with term, singleton pregnancies with an indication for induction were included in the study. The study group(OMS) included hundred women who were allocated to receive 20 ml of oral misoprostol solution(1µg/ml) hourly maximum of 4 doses , then titrated to 40 ml (40µg) hourly maximum of 8 doses. In the control group (OMT) hundred women were induced with 50 µg of misoprostol tablet orally, 4 hourly maximum of 6 doses. The induction to delivery interval, requirement of oxytocin, dose of misoprostol used, mode of delivery, maternal and neonatal outcome were analyzed statistically.*

Results: *The number of patients who delivered vaginally were more in study group i.e 81(81%) patients as compared to control group i.e 73(73%) patients and the difference was statistically significant(p value=0.03). The number of patients who had meconium stained liquor with non reassuring fetal heart rate were significantly higher in control group (OMT) as compared with study group(OMS)[26 {96%} versus 12{63%} p value =0.01].Whereas induction to delivery interval, proportion of patient delivered vaginally in 24 hours, need for oxytocin augmentation, maternal adverse reaction and neonatal outcome were not significantly different (p>0.05).*

Conclusion: *Titrated oral solution is as effective as conventional oral tablet of misoprostol for labor induction in term pregnant women and small doses at frequent intervals seem to be safer in terms of risk of meconium stained liquor with abnormal fetal heart rate and caesarean section.*

Keywords: *Titrated misoprostol, Induction of labor, Cesarean section, Efficacy and safety*.

Introduction

Misoprostol, is a synthetic 15 –deoxy-16-hydroxyl-16 methyl analogue of prostaglandin E1. In 2002, the US food and drug administration approved vaginal misoprostol for cervical ripening and labor induction, safety doses and dose intervals were not included[1]. Misoprostol is also recommended by American college of obstetrics and gynecologists for cervical ripening and labor induction at a dose of 25 microgram.[2] WHO

recommends a fixed oral misoprostol dose of 25 microgram every 2hr for labor induction based on moderate quality evidence and strong recommendations.[3] A Cochrane review (2014) which was based on 76 trials (14,412 women), recommends administering oral misoprostol solution as 20-25ug every 2 hours.[4]

Misoprostol is frequently used for IOL worldwide, mainly because it is stable at room temperature, effective if taken orally and is also considerably cheaper than the alternative prostaglandin.[5] Oral administration of misoprostol has been shown to have similar safety and efficacy to vaginally administered misoprostol for induction of labor, but oral misoprostol performs better in terms of treatment interval and number of doses required.

Titration refers to process of adjusting the dose, frequency or both of a medication on the basis of frequent review to achieve optimal outcomes. Titrated regimens have the advantages of avoiding adverse outcomes, by using smaller doses, and dosing only as required. Titration of oral misoprostol for labor induction using a misoprostol solution was pioneered by Hofmeyr and colleagues[1]. Hofmeyr et al showed that a titrated oral misoprostol solution given in a dose of 25µg at 2 hourly intervals had a comparable efficacy to PGE2 gel with similar hyperstimulation rates.[1] It's half-life is 20- 40 min following oral administration, followed by a rapid decline to low levels during the period of 120 min, thereafter a more gradual decline, and no drug accumulation phenomenon.[1] Several studies have reported on a range of misoprostol titrated regimen for labor induction.[1,6,7,8]In these studies dose starting from 20µg oral solution upto max of 60µg oral misoprostol solution in different dosing schedule has been successfully used for induction of labor. The study was planned to evaluate the safety and efficacy of titrated misoprostol compared with conventional oral misoprostol tablet, for IOL.

Material and Methods

This prospective study was conducted in the Department of Obstetrics and Gynecology at Dr. Rajendra Prasad Government Medical College at Tanda District Kangra, H.P. from January 2021 to December 2021.The study was approved from College Ethical Committee and Clinical trial registry India (CTRI/2021/12/038541).

The inclusion criteria were singleton pregnancy with vertex presentation at a gestational age ≥37 to 42 weeks, parity ≤ 3, bishop score ≤ 5 and intact membranes. The exclusion criteria were non-Reactive NST, antepartum hemorrhage, cephalo-pelvic disproportion, previous uterine surgery, patient with history of glaucoma, bronchial asthma, epilepsy known allergy to misoprostol and all contraindications to vaginal delivery. Patients with known heart disease, renal and hepatic failure and clinically suspected chorioamnionitis were also excluded. The patients meeting the above criteria were evenly divided into study group(*OMS*) and control group(*OMT)* after obtaining informed consent. The entire procedure of giving oral misoprostol solution / oral misoprostol tablet (50 µg) was explained in detail to patients.

1. Study group (*OMS*): Included 100 patients who were given titrated misoprostol,20 ml(1µg/ml) hourly maximum of 4 doses, then titrated to 40 ml (40µg) hourly maximum of 8 doses. Patients received maximum of 12 doses.

2. Control group (*OMT*): Included 100 patients, who were induced with 50 µg of misoprostol tablet orally, 4 hourly maximum of 6 doses.

On admission detailed history was taken and thorough general physical and systemic examination was done. Evaluation of baseline fetal heart rate pattern by auscultation /electronic fetal monitoring and NST was done. Per vaginal examination was done for pelvic assessment and assessment of cervical status. Cervical status was assessed using bishop's scoring system.

Preparation of misoprostol solution

Tablet misoprostol is water soluble. Misoprostol tablet of 200 µg was dissolved in 200 ml of portable drinking water in a sterile graduated bottle, thus 1ml = 1µg.

Study group *(OMS)*: Women allocated to this group received 20 ml of misoprostol solution. Starting with 20 ml (20 µg) 1 hourly, before giving next dose patient was assessed for temperature, pulse, respiratory rate, blood pressure, uterine activity and fetal heart rate pattern. The frequency, intensity and duration of uterine contractions was assessed before and after every dose of misoprostol. If adequate uterine contractions did not occur after 4 doses of 20 ml (20 µg) of misoprostol solution the dose was doubled to 40 ml (40 µg) hourly for maximum of 8 doses. Cervical status was assessed after 4 hours of first dose, or earlier, if patient complained of leakage, in situation of non-reassuring fetal heart rate pattern to rule out the presence of meconium or a cord accident.

The subsequent dose of drug was withheld if any/ all of the following was achieved:

1. Cervical dilatation ≥ to 4cm and 50% effacement, bishop's score ≥ 6
2. Good regular uterine contractions each lasting for 40-45 sec duration and minimum of 3 contractions in 10 minutes are achieved.
3. Spontaneous rupture of membrane.

Fetal heart rate was monitored before administration of drug and 30 minutes after administration of misoprostol. Close watch was kept for clinical features of uterine tachysystole, hypertonus and hyperstimulation syndrome.

With evidence of hypertonus, tachysystole and hyperstimulation, the following measures were to be taken,

- Further dose of misoprostol was stopped
- Patient was made to lie in left lateral position
- Oxygen infusion of 8 liters/min
- Adequate hydration was done

If any of the above untoward adverse drug reaction occurred, further dose of misoprostol was withheld and was monitored and recorded.

Control group (*OMT):* Women allotted to this group was given oral misoprostol 50 µg tablet 4 hourly maximum of 6 dose. Monitoring and cervical assessment followed similar pattern as in case of study group.

Once the patients in both the groups reached in active phase of labor, she was managed partographically in the labor room as per the departmental protocols. In case if progress of labor was found to be slow on partograph, artificial rupture of membranes was done and oxytocin infusion was started. Oxytocin was given at a dose of 4 mIU/min (2U of oxytocin dissolved in 500ml of RL @16 drops per min) escalated to a maximum dose of 64 mIU (8 U of oxytocin dissolved in 500ml of RL @ 60 drops per min) or till pains were established.

Primary parameter to measure efficacy was taken to be the number of women delivering vaginally within 24 hours of first dose of misoprostol in the two groups. Other measures of efficacy included the induction to delivery interval, mean total dose of misoprostol, the number of patients given oxytocin for augmentation of labor.

The measures of safety included the uterine hyperstimulation rates, the incidence of meconium and neonatal outcome. Baseline data included maternal parity, gestational age indication for induction and pre- induction bishop's score.

Statistical analysis: Data were entered into SPSS-19 and was analysed using Pearson's chi-square test as test of significance**.**

Results

One hundred women received titrated misoprostol and another 100 received misoprostol tablet.

Maternal demographic characteristics and indication of induction were similar in both the groups(Table1).

Mean total dose of titrated misoprostol used in study group was 201.7± 80.15µg which was more

than required by control group i.e 184.4±61.73µg but this did not reach statistical significance(Table 2). There were more women in control group who received oxytocin for augmentation of labor than study group(40% vs 31% patients), although this was not statistically significant (Table 2).

Induction to delivery interval was slightly longer in study group than in the control group(18.36± 4.16 hours versus 16.55 ±5.15 hours respectively).The difference was not statistically significant, p =0.31(Table 2).

Of the 81 patients in the study group and 73 patients in control group who delivered vaginally, 98% and 100% respectively did so within 24 hours of administration of first dose of misoprostol(Table 2).

The indication for cesarean delivery were similar in the two groups but the number of cesarean section done for meconium stained liquor with non reassuring fetal heart were significantly more in the control group, p value =0.01(Table 3). The total incidence of abnormal fetal heart rate was 19% patients in the study group and 33% patients in control group. In our study only one patient had failed induction i.e in study group for which cesarean was done (Table 3).

In the present study(Table 4) we observed that (38/200) patients had meconium stained liquor out of which 12(12%) patients were in study group and 26(26%) patients were in control group and the difference was statistically significant (p=0.02). It was found that 3(3%) patient in study group had tachysystole and 2(2%) patients in control group developed tachysystole. Further hyperstimulation was seen in 1(1%) patient in study group and 2(2%) patients in control group(Table 4). The patients with abnormal uterine contractions were put in left lateral position, were given oxygen inhalation and hydration, they responded to the above treatment. None of the patients needed terbutaline injections.

The occurrence of these intrapartum complications were comparable in both the groups except for meconium stained liquor where the difference was found to be statistically significant(p=0.02).

Observations regarding neonatal outcome were comparable between the two groups.

There was no significant difference in neonatal outcome in terms of neonatal resuscitation (p=0.46), NICU admissions (p=0.75) and neonatal hyperbilirubinemia (p=0.75)[Table 5]

Table 1: Maternal demographic data. Values are given as mean ±SD

	STUDY GROUP *(OMS)*	**CONTROL GROUP** *(OMT)*	p-value
Mean maternal age(years)	27.72±3.25	27.51±3.43	0.85(NS)
Nulliparous(%)	74	60	0.9(NS)
Mean gestationl age(weeks)	39.1±1.6	39.4±0.96	0.44(NS)
Mean pre-induction bishop's score	3.67±0.84	3.72±0.88	0.79(NS)
Indication for IOL			
Post date pregnancy	37	40	
Intrahepatic cholestasis of pregnancy	20	17	
Hypertensive disorders	16	14	
Oligohydramnios	14	15	
Gestational diabetes mellitus	5	8	
IUGR	6	4	
Decreased fetal movement	2	2	

NS: Not statistically significant, OMS: Oral misoprostol solution, OMT: Oral misoprostol tablet, IOL: Induction of labor

Table 2: Primary induction outcome

	STUDY GROUP (*OMS*)	**CONTROL GROUP** *(OMT)*	p- value
Mean total dose of misoprostol(µg)	201.7±80.15	184±61.73	0.6
Oxytocin augmentation (% of patients)	31	40	0.18(NS)
Induction to delivery interval (hours)	18.36±4.16	16.55±5.15	0.3(NS)
Delibvered within ≤24 hours of IOL(% of patients)	98	100	

NS:Not statistically significant,OMS: Oral misoprostol solution,OMT: Oral misoprostol tablet

Table 3: Mode of delivery and indication of operative vaginal delivery

Mode of delivery	**STUDY GROUP** (*OMS)* N=100	**CONTROL GROUP** *(OMT)* N=100	p -value
Spontaneous vaginal delivery	80	67	0.03
Operative vaginal delivery	1	6	0.123
Cesarean section	19	27	0.56
Indication for cesarean section			
MSL+NRFHR	12	26	0.01
NRFHR	6	1	0.02
Failed induction	1	0	0.4
Indication for instrumental delivery			
MSL+NRFHR	0	4	0.12
Acute fetal distress	1	2	0.56
Total incidence of abnormal FHR	19	33	

OMS: Oral misoprostol, OMT: Oral misoprostol tablet

Table 4: Intrapartum complication

Intrapartum complications	**STUDY GROUP** *(OMS) N=16*	**CONTROL GROUP** *(OMT) N=35*	p -value
Meconium stained liquor	12	31	0.21
Tachysystole	3	2	0.146
Hyperstimulation	1	2	0.939

OMS: Oral misoprostol solution, OMT: Oral misoprostol tablet

Table 5: Neonatal outcome

Neonatal outcome	**STUDY GROUP** (*OMS)*	**STUDY GROUP** (*OMT)*	p- value
Mean birth weight	2.85±0.27	2.74±0.33	0.5
Apgar score <7 at 5 minutes	3	3	0.9
Neonatal resuscitation	8	11	0.469
NICU admissions	6	5	0.75
Neonatal mortality	0	0	-
Neonatal hyperbilirubinemia	5	6	0.75

OMS: Oral misoprostol solution , OMT: Oral misoprostol tablet

Discussion

The results in our cohort of patients did not show any significant difference in the number of patients delivering vaginally within 24 hours of first dose of misoprostol, neonatal outcome and uterine hyperactivity between titrated misoprostol and conventional misoprostol tablet.

In our study, Intrahepatic cholestasis has emerged as second most common indication for IOL in both the groups (Table 1)but none of the studies reported it as a common indication for IOL. The reason for the same needs to be further evaluated in more trials with larger sample size.

Patients induced with titrated misoprostol required higher mean total dose of misoprostol for IOL(201.7±80.15µg) and slightly longer mean induction to delivery interval(18.36± 4.16hours). *Thaisomboon A et al*[8] also used titrated misoprostol solution (20µg to 40µg /hour) and 50 µg of misoprostol orally 4 hourly. Their results also suggested higher dose of titrated misoprostol(236±110.1µg) in comparison to 50 µg misoprostol (103.1±35.7µg) which was statistically significant(p=0.01). Induction to delivery interval was more in OMS group (21.2±8.1 hours) as compared to 50µg misoprostol(18.8±9.2 hours).

In the present study patients induced with titrated misoprostol solution 81% patients delivered vaginally and induction to delivery interval was 18.36±4.16 hours. Similar outcome was observed in the study by *Wallstrom T el*[9], on inducing patients with titrated misoprostol (82% delivered vaginally and induction to delivery interval was 19 hours).

Wang X et al[7] used titrated dose of misoprostol for IOL, in their study the incidence of meconium stained liquor was 21.7% and tachysystole in 9.5% patients, hyperstimulation and hypertonus in 2.4% patients each which is higher than the present study. In our study we titrated the dose of misoprostol by gradually increasing from 20 µg to 40 µg over a period of 4 hours (initial 4 doses of 20µg) in contrast to *Wang X et al* [7]who used different doses by hourly administration(20µg, 40µg,50µg,60µg were initial 4 doses).

While using titrated misoprostol gradual and smaller increase in dose of misoprostol is safer and effective for IOL but more trials in larger number of patients needs to be done to have a standard dosing regimen.

Komala K et al[10] observed meconium stained liquor in 20% patients and hyperstimulation in 1% patient in OMT group which is consistent with the findings in the present study. It is observed in the above and our present study that the incidence of meconium stained liquor is more when 50µg oral misoprostol tablet is used 4 hourly. It shows that the chances of meconium stained liquor is higher with higher dose of oral misoprostol tablet.

At the expense of slightly higher mean dose of misoprostol and longer induction delivery interval higher spontaneous birth and lower cesarean section rates were observed in titrated misoprostol group along with less incidence of meconium stained liquor with non reassuring fetal heart rate.

Conclusion

Titrated oral solution is as effective as conventional oral tablet of misoprostol in labor induction for term pregnant women and small doses at frequent intervals seem to be safer in terms of risk of caesarean section and meconium stained liquor with abnormal fetal heart rate**.**

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