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ORIGINAL ARTICLE

Oral Misoprostol Solution for Induction of Labour

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About the Author

Varsha L. Deshmukh is UG as well as PG examiner since last 15 years. She has about thirty (30) publications in national and international journals. She is reviewer for two national journals. She is interested in high-risk pregnancy and infertility.

Abstract

Objective To determine the effects of oral misoprostol solution for induction of labour.

Study Design This is a prospective observational study.

Setting This study was conducted in Government Medical College, Aurangabad.

Method Patients undergoing induction of labour after 36 weeks of pregnancy were allocated by randomization to induction of labour with oral misoprostol solution administered 2 h apart. Delivery within 24 h after induction with oral misoprostol solution was the primary outcome on which the sample size was based. The data were analysed by Statistical Software for Social Sciences software.

Result Two hundred patients were randomly selected for induction with oral misoprostol solution. There were no significant differences in substantive outcomes. Vaginal delivery within 24 h was achieved in 80.5 % of patients. The caesarean section rate was 19.5 %. Uterine hyperactivity occurred in 4 % of patients. The response to induction of labour in women with unfavourable cervices (modified Bishop's score <2) was somewhat slower with misoprostol, induction to delivery interval was more, oxytocin requirement was more, and vaginal delivery rate was less.

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Conclusion This new approach to oral misoprostol solution administration was successful in achieving vaginal delivery rate in 24 h in 80.5 % of patients; rate of LSCS was less 19.5 %.

Keywords Induction of labour · Oral misoprostol solution · Induction-delivery interval

Introduction

Induction of labour at term is a common obstetric intervention [1]. Induction of labour is the artificial initiation of labour before its spontaneous onset for the purpose of delivery of the fetoplacental unit using mechanical or pharmacological methods [2]. The goal of labour induction is to stimulate uterine contractions before spontaneous onset of labour, resulting in vaginal delivery [3].

Cheaper alternatives, stable at room temperature, have the potential to produce substantial cost savings in developing countries and allow safe induction of labour in those countries which cannot provide pharmacological induction of labour [1]. Misoprostol, a synthetic prostaglandin E1 analogue, presents low cost, storage at room temperature, and widespread availability [4].

Misoprostol is a unique prostaglandin E1 analogue. Tablets, marketed for anti-inflammatory drug-induced gastric ulceration, are stable and inexpensive [5–7]. The use of misoprostol in pregnancy has been reviewed since long [8]. Introduction of misoprostol was done by Sanchez-Ramos et al. [9] in 1993. Several randomized trials of labour with misoprostol have been undertaken [10–16].

Certain disadvantages are associated with oxytocin use like need to administer it by intravenous route, lack of stability at room temperature, shorter shelf life, and being relatively expensive. Misoprostol has advantages of being easy to use, convenient administration by various routes like the vaginal, sublingual and oral, being stable at room temperature, having a longer shelf life, and being relatively inexpensive [17].

Taking the advantage of short half life of misoprostol, we planned to use small doses at frequent intervals of misoprostol to find out the induction-delivery interval, rate of vaginal delivery, and the neonatal outcome.

Overall, misoprostol may be the best prostaglandin for labour induction, as titrated low-dose oral solution seems to be the safest in terms of caesarean section risk, while vaginal misoprostol tablets ($\geq$50 μg) are the most effective in achieving vaginal delivery within 24 h of induction [18].

Materials and Methods

A prospective observational study of oral misoprostol solution for induction of labour was conducted at Department of Obstetrics and Gynaecology, Government Medical College, Aurangabad, from October 2013 to October 2015. The permission was obtained from college ethical committee.

Patients recruited in the study were primigravida at term with obstetric or medical indication for labour induction. These patients were either booked attending antenatal clinic regularly (had at least 3 antenatal visits) or emergency admissions in labour room.

A total of 200 patients were randomly selected for the study.

The method of induction of labour was explained to patients, and only those who gave consent were finally selected for the study.

Inclusion Criteria

1. Primigravida.
2. Pregnancy between 36 and 42 weeks of gestation.
3. A live singleton foetus in cephalic presentation.
4. No history of uterine surgery.
5. Clinically adequate pelvis.
6. Modified Bishop's score $\leq$5.
7. Reactive NST.

Exclusion Criteria

1. Known hypersensitivity or contraindications to oral misoprostol (uterine surgery).
2. Patient's refusal to give consent.
3. Any antenatal medical complications.
4. A situation requiring LSCS.
5. Non-reacting NST.

Procedure

Each patient was questioned in detail and examined thoroughly. Last menstrual period was ascertained and correlated clinically. Patients who met the inclusion criteria were selected, and a well informed written consent was obtained for every participant.

Residential belonging rural or urban was noted.

Obstetric history—gravida, para, period of menstrual life noted.

General examination, systemic examination, per abdomen examination, and per vaginal examination were done.

Modified Bishop's score was calculated.

Blood and urine investigations were done. Ultrasonography findings noted to know the gestational age, amount of liquor, severity of IUGR, and placental localization.

Non-stress test performed in each woman and those with reactive NST was selected.

Method

Women were given 20 ml (20 μg) of misoprostol solution orally every 2 hourly until adequate uterine contractions occurred (3 contractions per 10 min lasting 30–40 s).

To overcome the problem of breaking the 200 μg tablet of misoprostol into small fragments, we dissolved the tablet in 200 ml of water (1 μg per ml) shaking the solution well before each administration. Thus, exact 20 μg of misoprostol solution could be administered. Storage of solution was done at room temperature for max 24 h in a glass bottle.

Equipment

- Measuring jug
- Spoon
- Clean drinking water (200 ml)
- 1 Misoprostol tablet (200 micrograms)
- Clean bottle

The timing and strength of uterine contractions were assessed by regular abdominal palpation.

Foetal heart rate and uterine activity were continuously monitored by electronic foetal heart rate monitor. Temperature, pulse, blood pressure, and occurrence of any side effects of the drug monitored.

Patients reassessed every 2 hourly for adequate uterine contractions (3 contractions for every 10 min lasting for 30–40 s). Repeat 20 μg oral misoprostol solution was given.

Modified Bishop's score was assessed at 6 h after the first dose, and whether it remained unchanged or increased to 5 or more than 5 was noted. In case of Bishop's score, less than 5 repeat misoprostol solution dose was given.

In case of adequate uterine contractions, per vaginal examination was done. The cervix was defined as favourable if cervical dilatation was $\geq$4 cm with 30 % effacement. In patients with favourable cervix, amniotomy was done, colour of liquor was observed, and WHO partograph was plotted. Further doses of misoprostol were not administered to these patients and progress of labour was observed as they entered the active phase of labour. If subsequent contractions become inadequate (<3 contraction in 10 min lasting for <20 s.) or no progress of labour for 2 h on partograph, those patients started with oxytocin administration. Timing of oxytocin administration was noted.

Oxytocin administration was started as 2.5 U oxytocin in 500 ml of ringer lactate at the rate of 15 drops per minute. Dose of oxytocin escalated by increasing the drop rate by 15 drops/minute at half hourly interval till maximum 60 drops per minute. If still patient had inadequate contractions, next 5 units of oxytocin were dissolved in 500 ml normal saline at the rate of 30 drops per minute. FHR and uterine contractions were monitored continuously on CTG machine.

Progress of labour was monitored. Any drug reaction or side effect was noted.

Failed Induction

If a woman was not in active phase of labour after receiving 10 doses of misoprostol solution or failed to deliver within 24 h after initial administration of misoprostol, patients who required LSCS for failure to progress were categorized as failed induction.

Successful Induction

Women who delivered vaginally within 24 h from initial administration of misoprostol were considered as successful induction.

Outcome Criteria

Primary Outcome

1. Induction-delivery interval.
2. Rate of LSCS.

Secondary Outcome

1. Need of oxytocin augmentation
2. Mode of delivery
3. Incidence of uterine hyperstimulation
4. Foetal heart rate abnormality
5. Incidence of meconium-stained liquor
6. Adverse effects of drug
7. Neonatal outcome-birth weight, NICU admission, morbidity/mortality.

Data entry, data checking, and analysis were done.

Statistical Analysis

To test outcome, qualitative data were analysed, and Pearson's Chi-square test was used as a test of significance.

Observations and Results

The number of patients randomized was 200.

Result

The number of patients randomized was 200. Data were not kept on patients excluded from participation. The characteristics of patients at trial entry are listed in Table 1. Postdated pregnancy (37.5 %), premature rupture of membranes (20 %), and hypertensive disorders of pregnancy (29 %) were the most common indications for induction of labour. Most patients had an unfavourable cervix. The mean pre-induction modified Bishop's score was 3.23 ± 0.67. Ten percentage of patients had pre-induction modified Bishop's score of 0–2, 86.5 % of patients had pre-induction modified Bishop's score of 3–4, and 3.5 % of patients had pre-induction modified Bishop's score of 5. The mean modified Bishop's score at 6 h after induction was 5.18 ± 0.87. 24.5 % of patients had modified Bishop's score of 5–8 at 6 h after induction.

Table 1 Characteristics of patients at trial entry expressed as *n* (%), mean (SD)

Sr. No.		
1.	No. of randomized trails	200
2.	Age (years)	**22.91 ± 2.97 years**
3.	Gestational age (weeks)	**39.24 ± 1.58 weeks**
4.	Indication for IOL	
	Postdatism	*n* = 75 (37.5 %)
	HDP	
	Non-severe pre-eclampsia	*n* = 32 (16 %)
	Severe pre-eclampsia	*n* = 18 (9 %)
	Gestational hypertension	*n* = 5 (2.5 %)
	Eminent eclampsia	*n* = 3 (1.5 %)
	PROM	*n* = 40 (20 %)
	Oligohydramnios	*n* = 43 (21.5 %)
	IUGR	*n* = 16 (8 %)
5.	Pre-induction modified Bishop's score	**3.23 ± 0.67**
6.	Modified Bishop's score at 6 h after induction	**5.18 ± 0.87**

Bold values indicate the main points

IOL induction of labour, *PROM* premature rupture of membranes, *IUGR* intrauterine growth retardation

Of the patients (Table 2), vaginal delivery within 24 h was achieved in 80.5 %. There were 19.5 % of caesarean section, mean induction to delivery interval was 14.16 ± 3.45 h, and 31 % of patients required oxytocin augmentation.

In particular, there were no serious side effects with misoprostol solution (Table 3). Ten percentage of patients had nausea, and 5.5 % of patients had vomiting. The incidence of tachysystole was only 3 %.

The neonatal outcome is listed in Table 4. 6.5 % of patients had meconium-stained amniotic fluid, 3 % of babies were admitted of which 33.33 % were admitted for meconium aspiration syndrome, 3 % of babies had APGAR score of ≤7 at 1 min, and 1.5 % of babies had APGAR score of ≤7 at 5 min. Take-home baby rate was 100 %.

Table 5 shows that less the pre-induction modified Bishop's score, more the induction-delivery interval is, less the vaginal delivery rate is, and more the oxytocin

Table 2 Outcomes expressed as *n* (%), mean (SD)

No. of randomized trails		200
Primary outcome		
1.	Induction to delivery interval	14.16 ± 3.45 h
2.	Rate of LSCS	*n* = 39 (19.5 %)
Secondary outcome		
1.	Mean no. of doses required for successful outcome	0.4
2.	Mode of delivery	
	Vaginal	*n* = 161 (80.5 %)
	LSCS	*n* = 39 (19.5 %)
3.	Oxytocin augmentation	
	Required	*n* = 62 (31 %)
	Not required	*n* = 138 (69 %)

LSCS lower-segment Caesarean section

Table 3 Maternal side effects and complications expressed as *n* (%), mean (SD)

Sr. No.	Side effects No. of randomized trails	Values 200
1.	Nausea	*n* = 20 (10 %)
2.	Vomiting	*n* = 11 (5.5 %)
3.	Fever	*n* = 4 (2 %)
4.	Diarrhoea	*n* = 9 (4.5 %)
5.	Uterine hyperactivity	
	Tachysystole	*n* = 6 (3 %)
	Hypertonus	*n* = 2 (1 %)
	Uterine hyperstimulation syndrome	*n* = 0

Table 4 Neonatal outcome expressed as *n* (%), mean (SD)

Sr. No.	Variables	Values
1.	MSAF	$n = 13$ (6.5 %)
2.	MAS	$n = 2$ (33.33 %)
3.	APGAR score	
	≤7 at 1 min	$n = 6$ (3 %)
	≤7 at 5 min	$n = 3$ (1.5 %)
4.	NICU admission	$n = 6$ (3 %)
5.	NICU stay duration ≤5 days	$n = 5$ (83.33 %)
6.	Mean birth weight	**2.54 ± 0.46**
7.	Neonatal death	$n = 0$

Bold value indicates the main points

augmentation required after induction with oral misoprostol solution.

Discussion

Low-dose oral misoprostol solution for induction of labour is effective in achieving vaginal delivery within 24 h, less LSCS rate, lower uterine hyper stimulation syndrome, lower foetal distress, effective as far as safety of mother and baby is concerned.

Our results are consistent with the study done by Doddet al. [19] in 2006, Cheng et al. [20] in 2008, and Aalami-Harandi et al. [21] in 2012.

Lowering the dose of misoprostol does not seem to result in lower rates of vaginal delivery; indeed, the converse seems to have been the case with significant lower LSCS rates as compared to other methods of induction of labour.

This can be explained on the basis of frequency and strength of contractions that determine the outcome of labour. High-frequency contractions may reduce the efficiency of myometrial acidemia. This provides a mechanism by which lower-frequency doses of misoprostol can be more efficient than higher doses.

Apart from clinical advantages of oral misoprostol, the solution also offers the advantage in terms of dose accuracy and patient satisfaction. This leads to the curtailing of problems such as failure to progress, or hyper stimulation syndrome.

As misoprostol solution retains its efficacy for at least 24 h and solution remains at room temperature, it can be made only once in 24 h. This adds to the convenience also. It is not surprising that oral route is more acceptable to the patients because of ease of administration and avoidance of vaginal examination. Only 31 % of patients required oxytocin augmentation, whereas 69 % of patients did not require oxytocin augmentation after induction with oral misoprostol solution.

Conclusion

The FDA has approved a new label for the use of misoprostol during pregnancy. It is thus a new promising agent for labour induction. It has excellent cervical ripening and uterotonic properties.

It is cost-effective, cheap, easily available and can be safely used in low-resourced countries.

The most important finding was lower caesarean section rate. This finding suggests that repeated small doses of misoprostol ripened the cervix and overcame the cervical barrier, resulting in a high rate of vaginal delivery. It has shorter induction-delivery interval, less incidence of failed induction, lesser need of oxytocin augmentation, less maternal side effects, and lesser NICU admissions.

The less the pre-induction modified Bishop's score, the more the oxytocin requirement is, the more the rate of LSCS is, the more the induction to delivery interval is, after induction with oral misoprostol solution.

Table 5 Association of pre-induction modified Bishop's score with oxytocin augmentation, mode of delivery and induction to delivery interval

Pre-induction modified Bishop's score	Oxytocin augmentation		Mode of delivery		Induction to delivery interval		
	Required	Not required	Vaginal	LSCS	6–12 h	12–18 h	18–24 h
0–2	$n = 13$ (65.0 %)	$n = 07$ (35.0 %)	$n = 15$ (75.0 %)	$n = 05$ (25.0 %)	$n = 02$ (10.0 %)	$n = 09$ (45.0 %)	$n = 09$ (45.0 %)
3–4	$n = 49$ (28.3 %)	$n = 124$ (71.7 %)	$n = 139$ (80.3 %)	$n = 34$ (19.7 %)	$n = 39$ (22.5 %)	$n = 108$ (62.4 %)	$n = 26$ (15.1 %)
5	$n = 00$	$n = 07$ (100 %)	$n = 07$ (100 %)	$n = 00$	$n = 07$ (100 %)	$n = 00$	$n = 00$
Total	$n = 62$ (100 %)	$n = 138$	$n = 161$	$n = 39$	$n = 48$	$n = 117$	$n = 35$
Chi-square test	14.5	15.9	34.4				
P value	$P < 0.001$ S	$P < 0.001$ S	$P < 0.001$ S				

Oral misoprostol solution is thus a new and upcoming method for induction of labour, which can be used by all obstetricians as a method of choice.

Unanswered Questions and Future Research

While the use of misoprostol as an inducing agent is associated with cost savings, this is unlikely to propel manufacturers towards seeking appropriate product licensing, and its use in pregnancy has medico-legal implications for individual practitioners and institutions. Agencies funding health care, however, may be willing, to provide indemnity for its use.

While the extent of rare but potentially serious adverse complications such as uterine rupture, maternal or perinatal death, and neonatal acidemia remains uncertain, regular audit of clinical practice and reporting of such adverse outcomes should be a requirement of clinicians and institutions adopting the use of misoprostol for the induction of labour. Efforts should be directed to ensure the availability of a licensed low-dose (20 μg) formulation for use in pregnancy, which is easy to administer orally, while retaining its low cost to enable widespread use, particularly in under-resourced countries.

Compliance with Ethical Standards

Conflict of interest None.

Ethical Approval Approval of ethical committee has been taken from Government Medical College, Aurangabad.

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