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Simplifying induction of labour

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Abstract
Introduction: Labour induction is one of the most common procedure in obstetrics .Oxytocin is one of the time tested drug , but certain disadvantages associated with oxytocin can be countered by using misoprostol as labour inducing agent.
Objectives: 1. To know the efficacy of oral Misoprostol solution in inducing labour 2. To calculate the induction delivery interval 3.To know the maternal and fetal outcome in the study population.
Methodology: A prospective observational hospital based study involving 200 term pregnant patients getting admitted to the labour ward. All of them were induced with oral misoprostol in solution form at a static dose regimen, second hourly (20 ug) for a total of five doses. Labour monitored as per the labour room protocol, reassessed after five doses or earlier as per clinical progress.
Results: 200 patients were included, the efficacy of its use was excellent, mean number of doses required was 5, with the average induction delivery interval of 13.65 hrs, with 77.5% of vaginal delivery rate and 22.5% of caesarean rate, 30% needed oxytocin augmentation and 6.5% of the babies had meconium staining of liquor, of them 23.08% showed signs of meconium aspiration syndrome and one perinatal death was noted in the study.
Conclusion: Oral misoprostol solution in static dosage is a simple, safe and effective method for induction of labour at term.

Keywords: Misoprostol solution, induction of labour

Introduction

Induction of labour is the artificial initiation of labour before its spontaneous onset for the purpose of delivering the baby. The goal is to initiate uterine contractions accompanying cervical effacement, dilatation and decent of the presenting part. It is carried out for various maternal and fetal indications so as to improve pregnancy outcome. Induction of labour in the presence of an unfavourable cervix is associated with an increased risk of failed induction and higher rates of caesarean section. Caesarean section has its own risks of higher morbidity, mortality and higher cost of surgery [1].

Various methods have been tried like pharmacological and mechanical methods. Pharmacological drugs used are oxytocin and prostaglandins (dinoprostone and misoprostol). Oxytocin use as an inducing agent has certain disadvantages like its intravenous route of administration, restricted ambulation of the patient, lack of stability at room temperature make its use cumbersome [2]. Prostaglandins are still the single most effective means and are widely recognized as standard methods of induction of labour [3].

Misoprostol (PGE1) is a synthetic analogue (15 deoxy 16 hydroxy 16 methyl PGE1) causes uterine contractions and ripening of the cervix. As compared to dinoprostone it has shorter duration of action, oral activity and good safety profile. It can be administered through vaginal, oral, sublingual, buccal and rectal routes [4, 5].

Peak concentration, time to peak concentration and area under the serum concentration versus time curve dictate the pharmacotherapeutic profile of various routes of administration. Plasma concentration increases gradually after vaginal administration reaching a maximum levels after 70 – 80 mins, before slowly declining with detectable drug levels still present after 6 hours. Bioavailability of vaginal misoprostol is higher than oral route and coefficient of variation of area under curve after vaginal administration is greater than that of oral administration [5-8].

After oral administration misoprostol is rapidly absorbed almost completely from the gastrointestinal tract. The drug then undergoes extensive metabolic pathways to form misoprostoic acid. Maximum peak plasma levels are reached at about 30 mins and declines rapidly by 120 mins and remains low thereafter [5, 9].

It mainly acts on the cervical connective tissue stroma leading to disintegration and dissolution of collagen [6, 8, 9]. Certain features of misoprostol like- lower cost, stability at room temperature, wide spread availability, ease of usage, longer shelf life, short half life, excellent cervical ripening and uterotonic properties and fewer adverse effects has made it a choice of drug for induction of labour [10]

Oral misoprostol is a recommended method of labour induction by the WHO and FIGO [11]. Oxytocin has more chances of hyperstimulation, causing organizational and safety benefits of using misoprostol especially in a busy labour wards with less staff, unsupervised, low resource settings like lack of cardiotocograph machine could prove beneficial. The peculiar pharmacokinetic properties of the oral misoprostol solution gives it an advantage over vaginal route and oral tablet form.

Misoprostol could be used in solution form with static dosage schedules or titrated low dose solutions. In 2012, the international federation of gynaecology and obstetrics recommended an oral dos of 25 ug misoprostol solution to induce labour [12]. More frequent dosing addresses the short half life of 20 – 40 minutes.

Obtaining a safe dose ranging below 50 ug by breaking the available 200 ug misoprostol tablet is inaccurate and not reliable. This could lead to insufficient dose and hence failed induction or excessive dose and hyperstimulation. Hence to improve the accuracy of dosage, we can use misoprostol in solution form.

In titrated dosing schedules misoprostol tablet is dissolved and solution is made and then incremental doses of the solution is used to induce labour accordingly while in static dosing schedules a fixed dose is used at regular intervals irrespective of the requirement. Static doses appear to be safe as slow and steady induction is set.

Aqueous solution starts acting faster than oral tablet/vaginal route and more so it is noted that uterine activity is higher in the first 15 minutes of administration and then declines gradually. This could be of advantage with respect to possible risk of hyperstimulation [4, 5] Oral solution is proved to be comparatively more effective in terms of successful induction of labour leading on to better vaginal delivery rate, low incidence of caesarean delivery rate, side effects being similar, cost being same and is patient acceptable. It is best suited for patients with premature rupture of membranes [10].

Based on this feature, present study was conducted to assess the efficacy of oral Misoprostol solution in inducing labour. Repeated small doses of misoprostol ripens the cervix effectively resulting in a higher rate of vaginal delivery rates with acceptable induction delivery time.

Multigravidas would be best favoured as compared to primigravidas. Success rates have been shown to be around 80% of vaginal deliveries and around 20% of caesarean section rate with acceptable induction delivery interval although a small percentage of women may require augmentation of labour with oxytocin [10].

Objectives

1. To know the efficacy of oral Misoprostol solution in inducing labour
2. To calculate the induction delivery interval
3. To know the maternal and fetal outcome in the study population

Materials and Methods

A prospective observational hospital based study conducted at the labour ward in the department of obstetrics, at SSIMS & RC. A total of 200 consecutive women fulfilling the inclusion criteria were enrolled in the study. At admission detailed history was taken then general and physical examination followed by obstetric examination was done to confirm the gestational age, obstetric findings and pelvic examination to know the modified Bishop score and assess pelvic adequacy. After a final diagnosis was made and eligibility criteria are met, admission test was done, relevant investigations were requested depending on the associated medical illness if any.

Informed consent for induction of labour was taken and induction of labour was done using static dosage oral misoprostol solution. Women received 20ml of oral misoprostol solution every 2nd hourly for a total of 5 doses.

The basal solution was prepared by dissolving one 200 mcg misoprostol tablet in 200 ml of distilled water (1mcg / ml) in a glass container and covered with a lid after use. It is stored at room temperature and can be used within 24 hours of preparation. At the start 20 ml of the prepared solution (20 ug misoprostol) is taken in a 20 ml syringe and given orally. It has no color or taste. It can be given on empty stomach also. It is acceptable by most patients. Time was noted and the patient was asked to ambulate and the next dose would be due two hours later. Intermittent monitoring of uterine contractions and fetal heart rate were done by the postgraduates and recorded on a partograph as per the existing labour room protocol. After 5 doses, women were assessed for further augmentation with oxytocin if required.

Oxytocin augmentation was with 5 u in 500 ml of ringer lactate solution for primigravidas and 2.5 u for multigravidas at a titrating dose to achieve good uterine contractions.

Primary outcome measures were the induction - delivery interval, mode of delivery, maternal and perinatal outcome while the secondary outcome measures were to note induction failures, further augmentation with oxytocin, adverse effects of inducing drug were noted. The data was analyzed by statistical software

Hypertonus was defined as a single contraction lasting more than 2 minutes. Tachysystole is the presence of at least 6 contractions in 10 minutes, over at least two 10 mins windows. Hyperstimulation was defined as tachysystole or hypertonus with non reassuring fetal heart rate patterns like late decelerations, prolonged decelerations, tachycardia or reduced fetal heart rate variability needing intervention [3].

Induction failure was defined as not entering into the active phase after 24 hours of misoprostol treatment. Non progress of labour was defined as no progress in decent of the fetal head or cervical dilatation for three hours after entering active phase of labour.

Inclusion criteria

1. Primigravida and multigravida
2. Singleton pregnancy
3. Period of gestation of 37 – 41 weeks.
4. Cephalic presentation
5. Adequate pelvis
6. Birth weight <3.5 kg

Exclusion criteria

1. Previous scarred uterus
2. Uncontrolled medical disease in pregnancy
3. Known allergy to misoprostol
4. Any clinical evidence of fetal distress at the time of admission.

Results

Among the study group, a vaginal delivery rate of 77.2% within 24 hours of induction was achieved and caesarean delivery rate of 22.8% was noted. 8% of the vaginal delivery group had instrumental delivery by vacuum for poor maternal efforts or fetal distress in second stage of labour. The induction delivery interval ranged from 6 to 16 hours.

30% of them did need oxytocin infusion to accelerate labour process. Preinduction Bishop score of ≥ 4 and multigravidas had more favourable outcomes No serious maternal side effects noted. Meconium stained liquor was seen in 6.5% of the neonates and 4% of them needed NICU admission.

Table 1: Characteristics of patients at admission expressed as n (%), mean SD.

Sl No.	Patient characteristics	Mean SD
1.	Total number of patients	200
2.	Parity – Primigravida	120 (60.0%)
	Multigravida	80 (40.0%)
3.	Gestational age (weeks)	39.65±1.45 weeks
4.	Indication for induction of labour	
	Postdatism	25 (12.5%)
	Mild pregnancy induced hypertension	29 (14.5%)
	Severe pregnancy induced hypertension	30 (15.0%)
	Gestational hypertension	5 (2.5%)
	Imminent eclampsia	3 (1.5%)
	PROM	43 (21.5%)
	Oligoamnios	45 (22.5%)
	IUGR	20 (10.0%)
5.	Preinduction modified Bishop score	4.23±0.59
6.	Modified Bishop score after six hours of induction	8.18±0.96

Premature rupture of membranes and oligoamnios were the most common indications for induction of labour in our study.

Table 2: Outcome of induction of labour expressed as n (%), mean SD.

Sl No.	Outcome of induction of labour	Mean SD
1.	**Primary outcome**	
	1. Induction to delivery interval	13.65±3.67 hours
	2. Rate of LSCS	n=45(22.5%)
2.	**Secondary Outcome**	
	1. Mean number of doses required for successful outcome	0.5
	2. Mode of delivery	
	Vaginal	n=155(77.5%)
	LSCS	n=45(22.5%)
	3. Oxytocin augmentation	
	Required	n=60(30%)
	Not required	n=140(70%)

77.5% of vaginal delivery rate noted though 30% of them oxytocin augmentation.5 u in primigravidas and 2.5 u in multigravidas was the oxytocin dosage used.

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

Sl No.	Side effects	Values n = 200
1.	Nausea	n=30 (15.0%)
2.	Vomiting	n=10 (5.0%)
3.	Fever	n=4 (2.0%)
4.	Diarrhea	n=4 (2.0%)
5.	Uterine hyperactivity Tachysystole Hypertonus Uterine hyperstimulation syndrome	 n=4 (2.0%) n=4 (2.0%) n=0 (0.0%)

Nausea was the most common side effect noted. Though 4%patients had features of uterine hyperactivity, none of them had uterine hyperstimulation syndrome.

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

Sl No.	Outcome	Values
1.	Meconium stained amniotic fluid	n=13(6.5%)
2.	Meconium aspiration syndrome	n=3 /13 (23.08%)
3.	Apgar scores	
	< 7 at 1 min	n=6 (3.0%)
	< 7 at 5 min	n=3 (1.5%)
4.	NICU admission > 3days	n=3 (1.5%)
5.	NICU stay duration < 3 days	n=5 (2.5%)
6.	Mean birth weight	2.63±0.39 kg
7.	Neonatal death	n=1 (0.5%)

6.5% of the babies had meconium staining of liquor and 23.08% of them showed signs of meconium aspiration.

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	6-12h	12-18h	18-24h
0-2	n=10 (58.82%)	n=07(41.18%)	n=10(66.67%)	n=5(33.33%)	n=02 (11.76%)	n=07(41.18%)	n=08(47.06%)
3-4	n=48(28.92%)	n=118(71.08%)	n=115 (74.19%)	n=40(25.81%)	n=16 (9.64%)	n=118 (71.08%)	n=32 (19.28%)
5	n=2 (11.76%)	n=15 (88.24%)	n=30 (100.0%)	n=0(0.0%)	n=10 (58.82%)	n=07 (41.18%)	n=00 (0.0%)
Total	n=60 (30.0%)	n=140(70.0%)	n=155(77.5%)	n=45 (22.5%)	n=28 (14.0%)	n=132 (66.0%)	n=40 (20.0%)
Chi square test	9.51		10.69		40.20		

P value	P<0.001 S	P<0.001 S	P<0.001 S

Preinduction score of >5 at the time of induction showed a more favourable chance of vaginal delivery with shorter induction delivery interval and less oxytocin requirement and it was statistically significant.

Discussion

Induction with misoprostol solution is more safe, with good patient acceptability. Monitoring of maternal and fetal parameters during labour requires less staff, more organizational and safety benefits and can run in unsupervised settings as compared to oxytocin infusion.

It is best suited for low resource settings. In our study 60% of parturients were primigravidas, oligoamnios and premature rupture of membranes were the most common indications for induction of labour. The preinduction Bishop score of > 5 had a good favourable outcome for vaginal delivery with the average induction delivery interval in the acceptable range of 13.65 hrs and lesser need for oxytocin augmentation, results being statistically significant.

77.5% vaginal delivery rate with 22.5% caesarean rate was noted similar to Deshmukh *et al*. [10] who reported low dose oral solution is effective in achieving vaginal delivery within 24 hours with low caesarean rates, low hyperstimulation, lower fetal distress, with good safety profile. 80.5% had successful vaginal delivery,19.5% had caesarean delivery and mean induction delivery interval was 14.6 hours and 31% needed augmentation of labour with oxytocin and no serious side effects were noted in the study.

On analysing the neonatal outcome in the present study 6.5% had meconium stained amniotic fluid and 23.05% of which showed signs of meconium aspiration. As our study included women with medical disorders the rate of meconium staining appears to be more. 4% of the babies needed NICU admission for various reasons. There was one perinatal death in a woman, past dates with oligoamnios and IUGR, had a vacuum delivery for non reassuring fetal heart rate but the baby had intrapartum hypoxia and died 20 minutes after birth.

Saleh suggests that oral misoprostol in small, repeated doses in the form of titration has more efficacy and safety and associated with a low incidence of uterine hyperstimulation, low caesarean section delivery rate than vaginal misoprostol for induction of labour at term with unripe cervix [13].

Antil has commented that low dose oral misoprostol solution in titrated doses can be used as a safe and effective alternative in induction of labour as it has lower uterine hyperactivity with good neonatal outcome. Oxytocin has its own disadvantages in terms of intravenous use, expensive, shorter shelf life, misoprostol takes the upper hand in these aspects and misoprostol is as effective as oxytocin for induction of labour [3]

The BJOG review article suggests that titrated low dose oral misoprostol solution was identified to be the most cost effective method with a favourable safety profile [11].

Ashokan has used increment doses of misoprostol solution was used for induction of labour and compared with oxytocin infusion for induction of labour. Maternal and fetal complications were equal in both groups. Misoprostol solution in titrated doses appears to be safe in induction of labour with shorter induction delivery intervals, reduction in caesarean section rates [14].

Abdul Rahim conducted a randomised control trial between hourly titrated and second hourly static oral misoprostol solution for induction of labour showed similar maternal and fetal outcome in both the groups except that meconium staining was more in the titrated group as compared to the static dose group. Static dose appears to be more safer [12].

L.A Velasco compared outcomes of misoprostol in the form of oral solution or vaginal route for induction of labour .Oral solution was comparatively more effective and patient acceptable [15].

Hofmeyr in their study used titrated oral misoprostol solution in comparison with vaginal dinoprostone gel for induction of labour. Oral solution was effective at achieving vaginal birth and had lesser risk of hyperstimulation [16].

Dodd *et al*. reported that misoprostol solution is best suitable for induction of labour in women with premature rupture of membranes [17].

Chang conducted a pilot study of labour induction with titrated oral misoprostol to evaluate the safety and efficacy for induction of labour. Both multipara and primigravida were included in the study, they had a higher vaginal rate of 96.1% ,10.4% requiring oxytocin augmentation but had a higher rate of uterine tachysystole [18, 19].

In the present study, misoprostol solution use resulted in good vaginal delivery rates, more in multigravidas who received lesser than five doses schedule, shorter induction delivery interval, cervical ripening was very good, fewer patients needed for oxytocin in augmentation of labour, hyper stimulation rates were low, meconium staining was seen in some patients, no intensive monitoring was required and a small number of patients ended up with failed induction irrespective of alternative induction methods.

Slow induction with small and frequent doses of misoprostol in solution form gives excellent results in the form of vaginal delivery rates and reduction in caesarean section rates, fewer side effects in terms of hyperstimulation, fetal heart variations, meconium staining of liquor.

By titrating the dose the induction delivery interval can be shortened to a certain extent but the risk of hyperstimulation or tachysystole and associated fetal heart rate variations coexist.

Conclusion

Oral misoprostol solution in static dose aqueous solution form has simplified induction of labour. It can be used effectively as a new upcoming and promising method of choice for induction of labour with good maternal, perinatal safety profile and favourable labour outcome.

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