Comparison of safety and efficacy of two low dose Misoprostol regimen for cervical ripening and induction of labour

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Abstract

Background: Prostaglandins are being tried in various doses for the induction of labour. Early studies showed that high doses cause rapid delivery but frequent hyperstimulation while low doses have the reverse effect. Our study aims to find out the safety, efficacy, maternal and fetal complications of vaginal Misoprostol (PGE1) 25 µgm given as a single dose versus vaginal Misoprostol 25µgm given as two doses 6 hours apart for cervical ripening and induction.

Material and methods: This was a prospective randomised study on 201 patients using block randomisation. Parity index, colour of liquor, fetal heart rate abnormalities, duration of labour, mode of delivery and fetal and maternal outcome were noted down and compared between the two groups. The statistical significance of the association of effect of different doses of Misoprostol in induction of labour along with secondary objectives was assessed using chi-square test out of "fisher's exact test" and cross tabulation.

Results: 201 pregnant women were selected for this study of which 101 patient were allocated to single dose 25 µgm vaginal Misoprostol regimen and another 100 to a regimen of two doses of 25 µgm Vaginal Misoprostol given 6 hours apart. We had a significant improvement in the Bishops score in both the arms more so after the second dose in the Group II. There was a significantly higher number of maternal complications related to PPH in group I- 0.8% ($p<0.02$). There was an 8% lower incidence of Caesarean section and 74.7% delivered in <12 hour in Group II patients.

Conclusion: Low dose regimens are safe for cervical ripening and induction of labour. A second dose of Misoprostol seems to be more effective and safe in achieving a normal delivery when initial Bishop scores are low with no major complication.

Key words: efficacy; low dose Misoprostol; cervical ripening

Introduction

Induction of labour is usually carried out for maternal as well as fetal indications after the period of viability in order to achieve a normal vaginal delivery. There are several methods to induce labour of which Prostaglandins are the commonest and most effective. Misoprostol has been used for induction of labour since 1987[1,2]. In using Misoprostol for induction, there is a critical balance to be achieved. Early studies showed that high doses cause rapid delivery but frequent hyperstimulation while low doses have the reverse effect. Much of the research conducted over the last twenty years has been an attempt to find a safe but effective induction dose. Our study aims to find out and compare the efficacy and safety of vaginal Misoprostol 25 µgm given as a single dose versus vaginal Misoprostol 25 µgm given as two doses 6 hours apart for cervical ripening and induction.

Objectives of the study

1. To compare and study the effect of two low dose regimens of Misoprostol for cervical ripening and induction of labour.
2. To study the time interval from labour induction with Misoprostol to delivery.

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3. To compare the maternal and foetal outcome.

Inclusion criteria:

1. Gestational Age(GA): 36-41 weeks
2. Bishop's score < 4
3. Normal Cardiotocography (CTG)
4. Pregnancy Induced Hypertension (PIH), Gestational Diabetes Mellitus (GDM) patients with normal fetal Doppler
5. With or without membranes
6. Fetal anomalies
7. Cephalic presentations

Exclusion criteria:

1. Grand multiparas

Materials and methods

Design of the study: This is a prospective randomised study to investigate the effects of different doses of Misoprostol in cervical ripening and induction of labour. Our study was conducted from August 2009 to July 2011 in the department of Obstetrics and Gynaecology, at a tertiary referral centre in Kerala. We screened 250 women and enrolled 201 women.

Sample size*:* Based on the results observed in an earlier publication[3] on cervical ripening using single dose and two doses 6 hours apart, with 90% power and 99% confidence, minimal sample size comes to 100 women in each group. Block randomization was done for the allocation of patients in the two groups. Blocks of 50 were taken for the purpose. Due to lack of consent and exclusion criteria, 49 patients were excluded from the study. We had 201 patients enrolled in the study with 101 in group I and 100 in group II.

Method: Patients reporting to the out-patient on their first visit to the department were registered. Allocation was done when patient visited hospital at or near term. Approval of the institutional ethics committee was obtained. Informed consent was taken from all the patients. The gestational age was confirmed and normal fetal heart rate was measured by cardiotocography (CTG). Cervical examination was done in labour room to assess the condition of cervix prior to intervention.

All patients of Group I and Group II with Bishop's score of 4 or less received a single dose of Misoprostol 25µgm vaginally in the posterior fornix at 9 pm the same night. Group II received a second dose of Misoprostol 25µgm vaginally in the posterior fornix at 3 am coming morning. CTG was taken after each administration of Misoprostol in all the patients.

Patients were reviewed at four hourly intervals after each dose. Changes in Bishop's score and uterine contractions were observed and documented. The patient was kept ambulant and simultaneously progress of labour was noted with duration and frequency of contractions. Labour was augmented wherever necessary with 2.5 units of Oxytocin for the multigravida and 5 units Oxytocin for Primigravida as a titrated intravenous drip. Care was taken not to start Oxytocin drip before a minimum 4 hours of last dose of Misoprostol.

Continuous fetal heart monitoring was done. Condition of cervix was assessed in labour room every 4th hourly and findings were noted down under- consistency, position, effacement, size of the internal os and station of fetal head. Artificial rupture of Membranes (ARM) was done when there was atleast 2 cm dilatation of cervix. Colour of liquor, fetal heart rate abnormalities, duration of labour, mode of delivery and fetal & maternal outcome were noted down and compared between the two groups. Post partum haemorrhage (PPH) was diagnosed when there was loss of more than 500ml of blood from the genital tract following child birth and was assessed by taking the pad weight and finding of intermittent uterine relaxation. It was graded as mild, moderate and severe. For statistical purpose this was taken as whether present or not and tabulated.

In our study misoprostol was the primary agent for ripening and induction. Since our study compared two low dose misoprostol regimen, labour was further augmented by either ARM or Oxytocin depending on the uterine contraction and bishop's scores. Therefore before starting oxytocin, bishop score was assessed and care was taken not to start oxytocin before 4 hours after vaginal instillation of misoprostol. Bishop score was reassessed every fourth hourly. A failed induction was considered when there was no progression of labour and no change in Bishop score for more than 8 hours after augmentation with oxytocin. Such patients were considered for Lower segment Caesarean Section (LSCS). Mode of delivery, induction to delivery interval, maternal and fetal complications were recorded in detail and managed accordingly. In the cases where neonatal complications were present, the baby was managed in neonatal ICU. All the data was recorded on a proforma and then entered to an excel sheet. Data was computed and analysed using SPSS software v.12 and Microsoft Excel. The statistical significance of the association of effect of different doses of PGE1 in induction of labour along with secondary objectives

was assessed using chi-square test out of "fisher's exact test". Crosstab or Log rank test was applied to find out other survival parameters.

Results

Our study had 201 pregnant women of which 101 patient were allocated to single dose 25µgm vaginal Misoprostol regimen and another 100 to a regimen of two doses of 25µgm vaginal Misoprostol given 6 hours apart.

There were 143 primigravida and 58 multigravida with age ranging from 18-38 (avg 25.8 +/- 3.99). The average age of primigravida was 25.1 and 28.1 for the multigravida, There were 54 (26.8%) patients with GDM, 4 (2%) had PIH and 143 (71.1%)patients had neither GDM or PIH. Table 1 shows Bishop score distribution in group I and II before induction. On comparative analysis of the two arms after induction, there was a significant increase in Bishop score after the second dose of misoprostol ($p<0.01$).

Liquor was meconium stained in only 10% of the patients in each arm (11/101 vs 11/100). There were 16 (8%) incidences of fetal complications in first stage of labour, of which 15 (92%) required caesarean. 10 of these were in group I and 6 in group II. There were no maternal complications in the first stage of labour in our study. There were 18 NICU admissions in the study and when a cross tabulation and chi-square was applied it was found that there was no statistical difference in Group I and II. Neonatal and maternal complications are shown in table 2.

We found that in our series there is a significantly higher number of maternal complications related to PPH (table 2). When crosstab was done for the patients having PPH there was a statistically significant increase in group I- 0.8% ($p<0.02$). Though group I multigravida had a slightly increased incidence of vaginal laceration (3/5) as compared to group II, it did not reach statistical significance ($p =0.5$).

Both the groups had an equal incidence of a normal vaginal delivery(NVD). Group II primigravida had increased incidence of successful induction than multigravida and the result was statistically significant ($p<0.001$). There was an 8% lower incidence of caesarean section in group II patients probably due to nearly double the incidence of instrumental delivery in this group. (Table 3)

When induction to delivery time was taken, we found this interval was decreased by nearly 50% in group II patients (14.75 hours +/- 3.19 in Group I and Group II patients 7.71 +/- 1.87 hours).Total number of patients with NVD is 138 (65 in group I & 73 in group II).

For better statistical correlation all the patients were then classified into just two groups where the induction to delivery time was taken as either less than 12 hours or more than 12 hours. The data was then again computed and the table is shown below (Table 4).

More patients in group II (74.7%) delivered in <12 hour. This result is statistically significant ($p<0.001$). Majority of the group II patients delivered within 6-12 hours of administration of misoprostol(Table 4).

Table 1. Bishop Score distribution in Group I and II

Bishop Score	Group I	Group II
2	36	54
3	45	43
4	20	3

Table 2. Maternal and neonatal complications

Maternal and Fetal complications	Group I	Group II
PPH	11/101 (10.8%)	3/100 (3%)
Vaginal laceration	5/101 (4.9%)	7 /100 (7%)
Second stage fetal complications	6/101 (5.8%)	5/100 (5%)
NICU Admissions	8/101 (7.8%)	10/100 (10%)
Meconium staining	11/101 (10.9%)	11/100 (11%)

Table 3. Type of delivery

	Group I	Group II
Normal vaginal delivery	62/101 (61.8%)	64/100 (64%)
Caesarean section	35/101 (34.3%)	27/100 (27%)
Forceps/Vaccum extraction	5/101 (4.9%)	8/100 (8%)

Table 4. Induction to delivery interval in Group I and II

	Delivery Interval	
	<12 hr	>12 hr
Group II	74.7%	25.3%
Group I	49.0%	51.0%

When Bishop score at induction were lower, chance of successful vaginal delivery was better in group II patients while it was nearly the same at higher Bishop scores in both groups. These values were found to be statistically significant ($p<0.001$). Most of the primigravida were having a lower Bishop score as compared to the multigravida who had a higher Bishop score at term. In case of a lower Bishop score, chance of successful delivery was better in group II patients while chance of delivery was nearly the same

at higher Bishop scores in both group (table 5).These values were found to be statistically significant (p<0.001). Second dose of misoprostol seems to be more effective in achieving a normal delivery when initial Bishop scores are low.

From table-6 we can see that majority (65%) of the multigravida are having a higher Bishop score (3-4) at term than the primigravida (51%). The difference between these percentages was statistically significant(p<0.001). Primigravida have a lower (1-2) Bishop score at term and may require higher doses of Misoprostol for induction of labour.

Patients in both the groups had a similar possibility of being taken up for an LSCS (Table 7) and as the Bishop score increases the possibility of patient undergoing LSCS decreases. But when Bishop score 4 was individually considered there was a statistically significant increase in the number of patient in group I who underwent LSCS (p<0.001).Indication for LSCS in both the groups is shown in Table 8.

Primigravida were more likely to have a LSCS and multigravida were more likely to have a normal delivery and this association was statistically significant (p<0.001) Table 9.

Table 5. Bishop score and normal delivery

	Bishop 1 and 2	Bishop 3	Bishop 4
Group I	19/36 (52.8%)	34/45 (73.9%)	14/20 (70%)
Group II	44/54 (81.2%)	27/43 (64.3%)	2/3 (66.7%)

Table 6. Bishop score and parity

		PARITY		Total
		Multi	Primi	
Bishop score	1-2	20 (34.5%)	70 (49.0%)	90 (44.8%)
	3	26 (44.8%)	62 (43.4%)	88 (43.8%)
	4	12 (20.7%)	11 (7.7%)	23 (11.4%)
Total		58 (100.0%	143 (100.0)	201 (100.0)

Table 7. LSCS and Bishop score

LSCS in patients	Bishop score 2	Bishop score 3	Bishop score 4
Group I	17 (48.6%)	11 (34.3%)	6 (17.2%)
Group II	10 (37%)	16 (55.6%)	1 (7.4%)

Table 8. Indications for LSCS

	Total	LSCS for failed induction	LSCS for fetal distress
Group I	35/101 (34.3%)	23/35 (65.7%)	12/35 (34.3%)
Group II	27/100 (27%)	17/27 (63%)	10/27 (37%)

Table 9. Parity and mode of delivery

		Mode of delivery		Total
		NVD	LSCS/Inst	
PARITY	Multi	45	13	58
		77%	23%	100%
	Primi	81	62	143
		57%	43%	100%
Total		126	75	201

Discussion

Labour induction is an important part of obstetric care that ensures benefit and minimizes risk to the mother or fetus. Previously oxytocin was the commonest inducing agent and has been gradually replaced by prostaglandins. When the cervix is not favourable at term, cervical ripening using prostaglandins should precede labor induction[4].

In a cash strapped society like ours the most common prostaglandin used for cervical ripening in the present day is Misoprostol[5]. In most centres either Dinoprostone (PGE2) or Misoprostol are used for cervical ripening but consensus on ideal dose has never been reached. However, judicious use of Prostaglandins guided by institutional policies that reflect the evidence-base[4] reduces maternal and fetal risks. Misoprostol has been used as cervical ripening agent and studied extensively regarding route (oral, vaginal, sublingual, iv infusion) and dose (25 µgm, 50µgm, 100µgm) of administration[6]. Studies have shown that it is an effective cervical ripening agent at higher doses[7]. Ours is a low dose regimen.

In most other studies 25µgm or 50 µgm of Misoprostol was given every 4-6 hourly for five to six doses or 100 µgm 6th hourly[7,8,9,10] and few of them were augmented with oxytocin. A Cochrane review compared the effects of different doses of vaginal Misoprostol[11]. In our study Misoprostol was given predominantly for cervical ripening and induction. Lower doses compared to higher doses were associated with more need for Oxytocin augmentation (dose <50 µgm), less uterine hyperstimulation, with and without fetal heart rate changes, and fewer admissions to neonatal intensive care unit. The lower dosage regimen did not show more failures to achieve delivery within 24 hours. Based on the analysis, the Cochrane reviewers recommend a starting dose of 25µgm every four hours[11,12]. A longer latent phase of labour (6-12 hours) results in prolonged active phase as well as higher risk of chorioamnitis (~25%) and PPH(~15%)[13]. Probability of entering the active phase of labour without increasing the adverse outcome is very low

Therefore counselling the patient is essential. If failed induction is diagnosed at an appropriate time one can decide whether to continue with induction of labour or to perform LSCS.

We had a significant improvement in the bishops score in both the arms, more so after the second dose in the group II. Both the low dose regimen are equally effective, with comparable rates of failed induction. A single dose of 25µgm Misoprostol p/v may suffice in most patients but giving a second dose of the drug after 6 hours may be beneficial in reducing the induction to delivery interval. In our series there was a higher incidence of LSCS in group I primigravida, possibly related to lower bishop score. Many authors and RCT's[10,14,15] showed decreased incidence of caesarean section in the high dosage group but Has et al[16] showed an increased incidence. In our study the most common reason for LSCS was failed induction. For the multigravida in our series there was a good improvement in Bishop score with both dosage schedules of Misoprostol.

Our study showed that Misoprostol results in short induction to delivery interval similar to other studies[17]. This was more pronounced in Group II which is still considered a low dose group. There was not a single incidence of uterine hyperstimulation or tachysystole in the study. We had a successful induction of labor in 138/201 (68.65%) patients comparing with other studies[18]. A low dose decreases incidence of hyperstimulation but prolongs induction to delivery interval. There was no difference in the incidence of meconium staining and neonatal outcome between the two groups. These results are also consistent with many RCTs[19,20].

Fetal and maternal complications were comparable to other studies[21]. There was no statistical significance between group I and group II with respect to maternal complication or meconium staining as there was nearly equal incidence of complications in both series except for PPH which was more in group I. Misoprostol is used as a treatment option of PPH[22]. Both regimens were well tolerated by the fetus. Similar findings were seen in many studies[21,23].

Since patients were randomised to Group I and II, there were a subset of patients in group II who may not have required a second dose and a subset of patient in Group I who were ideal patients for a second dose.

We find that there is adequate response of the patients with these low dosage regimen. The incidence of failed induction is also comparable with the higher dosage regimens (25µgm 4th hourly and 50µgm 4th hourly) as published by many series[7,8,9,11]. It is suggested that this low dose regimen in our study could be considered adequate for a safe induction till such time that further research brings out the exact dosage scheduling for induction of labour in patients.

***Conclusion**:* Low dose regimen is safe for cervical ripening and induction of labour. A single dose of Misoprostol may usually suffice in multigravidae but a second dose of Misoprostol seems to be more effective in achieving a normal delivery when initial Bishop scores are low especially in primigravida. The double dose regimen of misoprostol does not increase maternal or fetal complications. There is a lower incidence of PPH in the double dose regimen and hence could be considered safe in induction of labour.

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Conflict of interest: Nil

Source of funding: Nil

Date received: October 16th 2019

Date accepted: January 7th 2020