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Original Research Article

Outpatient-based misoprostol to prevent prolonged pregnancy

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ABSTRACT

Background: Prolonged pregnancy is defined as the one that persist at or beyond 42 weeks of gestation. Incidence of prolonged pregnancy is around 10%. Aim of the study was to evaluate the efficacy and safety of single dose vaginal misoprostol (25 µg) in preventing prolonged pregnancy when given on outpatient basis at 40 completed weeks of gestation. Objective was to compare number of women entering spontaneous labor between 40 to 41 weeks of gestation, time from enrolment in study till delivery, need for cesarean section and neonatal outcome in early neonatal age in study vs control group.
Methods: Total no. of 130 subjects of uncomplicated singleton pregnancy with vertex presentation with bishop score ≤5 were recruited for the study. Patients were randomly allocated into two equal study and control groups. Women allocated to study group received intra-vaginal 25µg misoprostol and control group did not receive any intervention.
Results: 92.3% (60/65) of women in the study group had onset of spontaneous labor in one week in comparison to only 72.3% (47/65) in the control group. Mean duration from enrolment to delivery was 1.33±2.03 days in study group and 4.98±2.74 days in control group, which is nearly four times less in women in study group. Women in study group did not have any side effects from single dose of misoprostol given. Mean birth weight, meconium stained liquor rate, NICU admission rate and neonatal morbidity were found to be comparable in both the groups. No neonatal or perinatal mortality was observed in either group.
Conclusions: The present study supports the use of 25µg single dose vaginal misoprostol at 40 weeks of gestation to prevent prolonged pregnancy.

Keywords: Misoprostol, Prolonged pregnancy, Prevention

INTRODUCTION

Prolonged pregnancy is defined as the one that persist at or beyond 42 weeks of gestation. Incidence of prolonged pregnancy is around 10%.[1] Prolonged pregnancy is associated with adverse fetal, neonatal and maternal outcomes.

According to WHO guidelines for induction of labor (IOL), 2011, it has to be done at 41 weeks to decrease fetal, neonatal and maternal morbidity.[2] It also states that sweeping of membranes done at 40 weeks of gestation is one of the interventions which reduces the frequency of pregnancy continuing beyond 41 weeks. However, it is associated with discomfort, bleeding and irregular contractions and can only be done when cervix admits at least one finger which is not present always.[3]

So, there is a need of a method, which can reduce the number of inductions routinely done at 41 weeks, not associated with discomfort and can be used in unfavourable cervices. One such option is misoprostol which is a prostaglandin E1 analogue as it is very cheap, safe, effective drug and is stable at room temperature.

In our study, vaginal route is chosen because of its greater bioavailability, direct ripening effect on cervix and induces regular uterine contractions in contrast to oral route.[4] The use of misoprostol on outpatient basis can help in reducing health care cost by avoiding inductions needed at 41 weeks and at the same time can be more comfortable for the patients as it will reduce the duration of stay in the labor room which is otherwise more if the women is admitted for induction of labor.

Aim of the study was to evaluate the efficacy and safety of single dose vaginal misoprostol (25 µg) in preventing prolonged pregnancy when given on outpatient basis at 40 completed weeks of gestation.

Objectives was To compare number of women entering spontaneous labor between 40 to 41 weeks of gestation in study versus control group, to compare time from enrolment in study till delivery in both the groups, to compare need for cesarean section in both the groups, to compare neonatal outcome in early neonatal age (Apgar score at 1 and 5 minutes, meconium stained liquor, neonatal morbidity and mortality) in both the groups, to observe side effects of misoprostol in mother, if any.

METHODS

This study was an open randomized controlled trial carried out from November 2011 to April 2013. Total number of 130 subjects of uncomplicated singleton pregnancy at 40 completed weeks (gestational age based on LMP or scan before 20 weeks of gestation) of gestation with vertex presentation with Bishop score ≤5.

Sixty-five subjects per group were needed to detect 2 days difference in mean interval to delivery in two groups based on earlier studies, which includes 10% loss to follow-up subjects when significance level is set at 5% and power of study at 80%. Ethical clearance was taken from the institutional ethical committee. A written informed consent was taken from all the subjects. Clinical trial registration number – CTRI/2014/09/005006 (Clinical Trial Registry of India).

Inclusion criteria

- Intact membranes or no leaking per-vaginum
- No contraindication for vaginal delivery
- Normal biophysical profile

Exclusion criteria

- Grand multiparity (≥5)
- Any maternal systemic disease
- Previous LSCS / uterine scar
- Unexplained vaginal bleeding
- EFW >3.5 kg
- Fetal growth restriction, oligohydramnios (AFI ≤5)
- Fetal anomalies
- Contraindications for misoprostol (allergy, cardiovascular diseases, renal impairment etc.)

Each patient was assigned a serial number from 1, 2, 3 till 130. Subjects were then randomly allocated into two groups, study and control, using computer generated random number table.

Methodology

After written informed consent and randomization, women who were allocated to the study group received 25 µg tablet misoprostol moistened in saline in the posterior fornix and were then closely monitored in labor room for any maternal side effects (nausea, vomiting, diarrhea, tachysystole and hyperstimulation), vitals, uterine contractions, fetal heart sound and leaking or bleeding per-vaginum for a period of 6 hours. If they went into labor in these 6 hours, they were admitted for further management of labor. If there were no signs of labor in this observation period of 6 hours and FHS was good, then the subject were sent home with the advice that she has to report if there is pain abdomen, leaking or bleeding per vaginum, decreased fetal movements or at 41 weeks of gestation whichever is earlier. Controls did not receive any intervention at 40 weeks and were sent home with the same advice. Women in either group at 41 completed weeks of gestation were admitted for IOL as per departmental protocol.

Outcomes measures

Primary: Number of women entering spontaneous labor between 40 to 41 weeks of gestation

Secondary: Time from enrolment in study till delivery, Need for cesarean section, Neonatal outcome in early neonatal age (Apgar score at 1 and 5 minutes, meconium stained liquor, neonatal morbidity and mortality), Side effects of misoprostol in mother (nausea, vomiting, diarrhea, fever and abnormal uterine activity, etc.)

Statistical analysis

Chi-square test, Fisher's exact test and Mann-Whitney tests were used for categorical variables. Unpaired student t-test was used for continuous variables. P-value <0.05 was considered significant.

RESULTS

Nearly 92.3% of subjects (study and control group; 120/130) were in the age group of 20-30 years (Figure 1). Almost 47.6% of subjects (study and control group; 62/135) were primigravida (Figure 2). Nearly 88.4% of subjects (study and control group; 115/130) were recruited at 40 weeks of gestation (figure 3). Age, parity status, period of gestation and bishop score at the time of enrolment were comparable in study and control groups as shown in Table 1 and Figure 1-3 above. 92.3% (60/65)

of women in the study group went into spontaneous labor within one week in comparison to only 72.3% (47/65) in the control group, the difference being highly significant with P value = 0.003 (Table 2 and Figure 4).

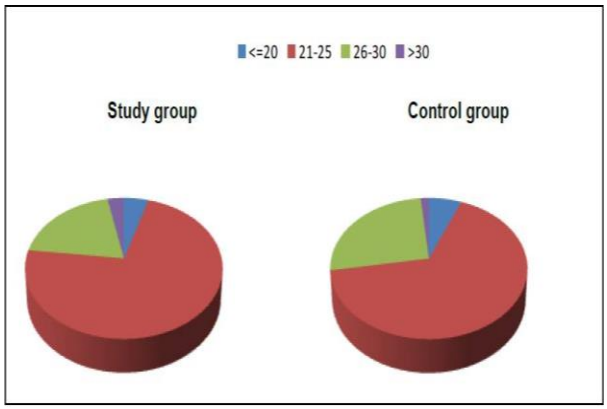

Figure 1: Comparison of age distribution in study versus control group.

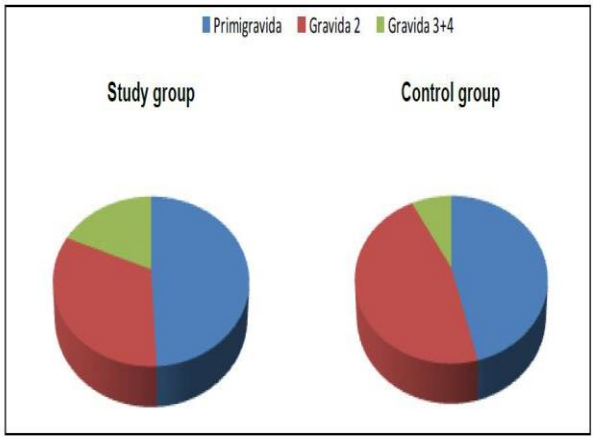

Figure 2: Parity distribution in study versus control group.

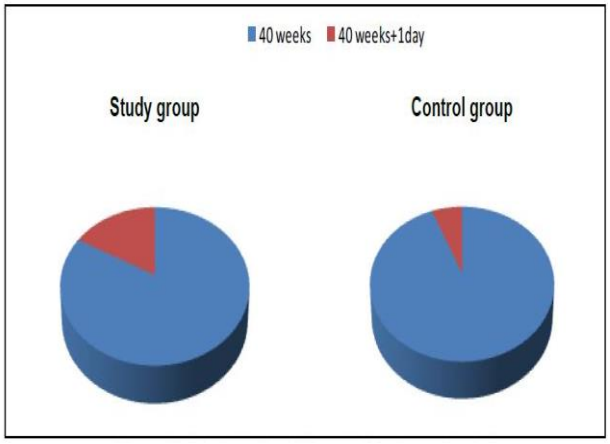

Figure 3: Period of gestation in study versus control group.

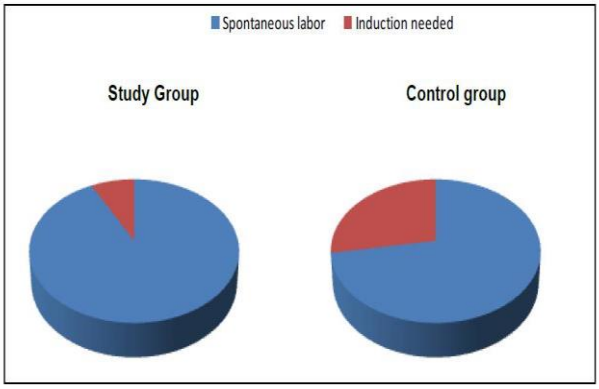

Figure 4: Onset of spontaneous labour within one week in study versus control group.

Induction was needed in only 7.7% (5/65) of women in the study group, whereas in the control group, induction was required in 27.7% (18/65) of women. Induction was successful in all the cases of both the groups. 86.1% (56/65) of women in the study group went into spontaneous labor within 24 hours after enrolment, in comparison to only 9.2% (6/65) in the control group, P value < 0.001 (Table 3).

Mean dose of misoprostol needed for induction was comparable in both study and control group (P value = 0.4543) (Table 4).

Table 1: Characteristics of study vs control group.

Characteristics	Study group (n=65)	Control group (n=65)	P value
Age (Mean±S.D.)	23.95±2.83	24.17±2.930.	664
Parity			
Primigravida	32	30	0.104
Gravida 2	21	30	
Gravida 3+4	12	05	
Period of gestation			
40 weeks	54	61	0.055
40 weeks+1day	11	04	
Bishop score (Mean ± S.D.)	3.38±0.55	3.34±0.54	0.676

Table 5 shows 73.8% (48/65) of women in intervention group delivered within 24 hours in contrast to only 1.5% (1/65) of women in the non-intervention group. Duration from enrolment to delivery was significantly lesser in the study group in comparison to control group with P value < 0.001.

Mean duration from enrolment to delivery was nearly four times less in the study group in comparison to control group (1.33±2.03 days vs 4.98±2.74 days).

Table 2: Onset of spontaneous labor within one week in study vs control group.

	Study group (n=65)	Control group (n=65)	P value
Spontaneous labor	60 (92.3%)	47 (72.3%)	**0.003**
Induction needed	05 (7.7%)	18 (27.7%)	

There was no difference in the mode of delivery between the study and the control groups (P value = 0.555). Cesarean section was required in 13.9% (9/65) and 15.4% (10/65) in study and control groups respectively. The commonest indication for cesarean section was meconium stained liquor with fetal bradycardia in both the groups. Women in study group did not have any side effects (nausea, vomiting, diarrhoea, hypertonus or tachysystole) from single dose of misoprostol given. Mean Apgar score both at 1 and 5 minutes was found to be significantly better in study group as compared to control group P value 0.0117 and 0.0001 respectively. Mean birth weight, Meconium stained liquor rate, NICU admission rate and neonatal morbidity were found to be comparable in both the groups. No neonatal or perinatal mortality was observed in either group as shown in Table 6.

Table 3: Onset of spontaneous labor within one week in study vs control group.

Duration	Study group (n=65)	Control group (n=65)	P value
≤6 hrs	30 (46.1%)	0	< 0.001
6-12 hrs	12 (18.5%)	0	
12-24 hrs	14 (21.6%)	06 (9.2%)	
1-3 days	03 (4.6%)	15 (23.1%)	0.002
3-7 days	01 (1.5%)	26 (40.0%)	< 0.001
> 7 days (needed induction)	05 (7.7%)	18 (27.7%)	0.003

Table 4: Mean dose of misoprostol needed for induction in study vs control group.

Misoprostol	Study group	Control group	P value
Mean dose±S.D.	35±13.7 µg	37.5±23.1 µg	0.4543

Table 5: Duration from enrolment to delivery in study vs control group.

Duration	Study group (n=65)	Control group (n=65)	P value
Less than 1 day	48 (73.8%)	01 (1.5%)	
1 - 3 days	11 (16.9%)	18 (27.7%)	
3 - 5 days	01 (1.5%)	12 (18.5%)	
5 - 7 days	0	16 (24.6%)	
7 - 9 days	05 (7.7%)	18 (27.6%)	
Mean±S.D.	1.33±2.03 days	4.98±2.74 days	
Median	14 hours 59 minutes	5 days 4 hours	
Mean rank	39.9	91.65	<0.001

Table 6: Early neonatal outcome parameters in study vs control group.

Neonatal parameters	Study group (n=65)	Control group (n=65)	P value
Apgar at 1 minute (Mean±S.D.)	9.43±0.53	8.97±1.35	0.0117
Apgar at 5 minutes (Mean±S.D.)	9.78±0.41	9.32±0.83	0.0001
Birth weight (Mean ± S.D.)	2.83±0.34	2.74±0.34	0.1337
Meconium stained liquor	10 (15.4%)	16 (24.6%)	0.1880
NICU admission	10 (15.4%)	17 (26.2%)	0.1300
Morbidity	1 (1.5%)	4 (6.2%)	0.1710
Mortality	0	0	NA

DISCUSSION

The present study, outpatient based misoprostol to prevent prolonged pregnancy, is an open randomized controlled trial carried out in the Department of Obstetrics and Gynaecology and Department of Pediatrics, UCMS and GTB Hospital, Delhi, India from November 2011 to April 2013. Total number of 130 subjects of uncomplicated singleton pregnancy at 40 completed weeks of gestation with vertex presentation with Bishop score ≤5 were recruited from gynaecology OPD. Subjects were randomly allocated into two groups, study and control, each group containing 65 patients. A comparison of similar studies on outpatient based vaginal misoprostol is shown in Table 7. In all of the previous studies, sample size was small so the authors could not generalize the results. Hence in the present study larger sample size was taken. Dose of misoprostol chosen was 25 µg, like other previous studies as this dose did not have any significant side effects. Observation period in the present study was taken as 6 hrs as detectable levels of drug remain in blood for as long as 6 hrs. So any possible immediate side effects of the drug are expected to occur within these 6 hours. Characteristics like age, parity, period of gestation and bishop score were comparable in study and control groups.

Table 7: Comparison of methodology with other studies.

Study	Stitley et al[5], (USA)	Mc Kenna et al[6], (USA)	Mostaghel et al[7] (Iran)	Present study, (India)
Study design	Randomised double blind placebo controlled trial	Randomised double blind placebo controlled trial	Open randomised controlled trial	Open randomised controlled trial
Sample size	62	68	44	130
Gestational age at enrolment	41 weeks to 41 weeks + 6 days	≥40 weeks	40 weeks	40 weeks to 40 weeks + 1 day
Bishop score at enrolment	≤4	<9	≤6	≤5
Dose of misoprostol	25 µg	25 µg	25 µg	25 µg
Observation period	4 hours	1 hour	2 hours	6 hours
Repeat dose	After 24 hours	-	-	-
Followed up till	48 hours	42 weeks	41 weeks + 3 days	41 weeks

The study and control groups showed significant difference in number of women entering labor within 1 week of enrolment. 92.3% (60/65) of women in the study group had onset of spontaneous labor within one week in comparison to only 72.3% (47/65) in the control group. This difference was found to be significant with P = 0.003. On further break up, 86.1% (56/65) women in study group entered spontaneous labor within 24 hours of enrolment in comparison to only 7.7% (5/65) women in the control group. This difference was also found to be highly significant with P <0.001. These findings are comparable to findings of Stitely et al, who observed that 44.4% of women in study group entered in spontaneous labor within 24 hours of initial dose as compared to 9.1% of control group with P <0.001.[5] Also, it was observed that around half (46.1%) of women in study group had onset of labor within 6 hours of enrolment whereas there was no woman in control group who had onset of labor within 6 hours. This explains the need of 6 hours out-patient based observation period after misoprostol administration and can be picked up while the patient is still in the hospital.

Induction of labor was required in as high as one fourth (27.7%) of the women in non-intervention group as compared to only 7.7% of women in the study group, the difference being highly significant with P value = 0.003. These observations are not consistent with findings of McKenna et al who observed induction of labor in 36% (12/33) of women in study group and 54% (19/34) of women in control group, these results were comparable with P value=0.15.[6] The reason for this disparity could be that they did not exclude high risk pregnancies like hypertension, oligohydramnios etc., which also formed indication for induction of labor in their study as against our study where all inductions were done for prolonged pregnancy only.

On comparing duration from enrolment to delivery in study vs control group, it was found to be significantly lesser in study group in comparison to control group with P = <0.001. In our study mean duration from enrolment to delivery was nearly four times less in the study group in comparison to control group (1.33±2.03 days vs 4.98±2.74 days). These findings are comparable to findings of Stitely et al, who have found initial dose to delivery time was 36.9±3.8 hours in study group as compared to 61.3±3.8 hours in control group.[6] Similar results have also been observed by other authors as well. McKenna et al, have found mean interval to delivery was

4.2±4.1 days in study group in comparison to 6.1±3.6 days in control group with p-value <0.04. Mostaghel et al found the interval between intervention and delivery which was 68.30±68.263 hours in misoprostol group and 125.81±72.744 hours in placebo group.[7] Mode of delivery was observed to be comparable in study vs control group (P value = 0.555). Cesarean section rate was 13.9% (9/65) in study group and 15.4% (10/65) in control group. Similar results were observed in study done by Stitely et al, McKenna et al and Mostaghel et al.[5-7] This finding is against the popular belief that out-patient misoprostol can increase cesarean section rate by increasing incidence of meconium stained liquor, fetal distress, maternal hypertonus and tachysystole.

In our study, the commonest indication for which cesarean sections was done was meconium stained liquor with fetal bradycardia in both the groups (7/9 in study group vs 7/10 in control group). In the study group, women in whom single dose of outpatient 25µg misoprostol was given vaginally, there were no cases of fetal distress, tachysystole, hypertonus, nausea, vomiting and diarrhea during 6 hrs of observation period. McKenna et al and Stitely et al have advocated larger sample size to draw conclusion on drug safety. Our study with sufficient sample size has established the safety of single dose (25µg) intravaginal misoprostol for use in prevention of prolonged pregnancy.[5,6]

In our study, Apgar score at 1 and 5 mins was significantly better in study group as compared to control group with P value=0.0117 and 0.0001 respectively. But, all our babies had normal score of >8. Therefore this statistically observed difference was not clinically significant. Mean birth weight, Meconium stained liquor rate, NICU admission rate and neonatal morbidity were found to be comparable in both the groups. No neonatal and perinatal mortality was observed in either group. So single dose of 25µg misoprostol in mother is safe for neonates. Similar results were observed in study done by Stitely et al, McKenna et al and Mostaghel et al.[5-7] To summarise, after receiving single dose of 25 µg misoprostol intravaginally at 40 weeks of gestation, half of the women had onset of labor within six hours, two third of the women delivered within 24 hours, 92.3% of women delivered within a week and as low as 7.7% required induction of labor. There was no change in cesarean section rate, no maternal side effects and no neonatal morbidity and mortality.

Based on these findings, it is believed that outpatient cervical ripening with intravaginal misoprostol is a reasonable safe alternate to the customary management of prolonged pregnancy. It is very effective and safe for both mother and neonate, convenient for the patient by decreasing duration of hospital stay and has considerable cost implications by decreasing the need of fetal monitoring.

CONCLUSION

To conclude, present study supports the use of 25µg single dose vaginal misoprostol at 40 weeks of gestation to prevent prolonged pregnancy. In resource limited countries outpatient misoprostol can have immense benefit in reducing health care cost by preventing prolonged labor, hence decreasing duration of hospital stay also reducing the need of ante-partum fetal monitoring. Further studies with sublingual route of administration can be done and if found to be effective and safe it would have the ease of self-administration of drug at home and patient can come to hospital when labor starts.

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REFERENCES

1. Norwitz ER, Snegovskikh VV, Caughey AB. Prolonged pregnancy: when should we intervene? Clin Obstet Gynecol. 2007;50(2):547-57.
2. WHO recommendations for induction of labour. Geneva: World Health Organization, 2011 (available at: http:// whqlibdoc. who.int/ publications/2011/9789241501156_eng.pdf). Accessed on 12 May 2016.
3. Boulvein M, Sten CM, Irion O. Membrane sweeping for induction of labor. Cochrane Database Systematic Reviews. 2005;1:CD000451.
4. Danielsson K, Marions L, Rodriquez A, Spur BW, Won PYK, Bygdeman M. Comparison between oral and vaginal administration of misoprostol on uterine contractility. Obstet Gynecol. 1999;93:275-80.
5. Stitely ML, Browning J, Fowler M, Gendron RT, Gherman RB. Outpatient cervical ripening with intravaginal misoprostol. Obstet Gynecol. 2000;96:684-8.
6. McKenna DS, Ester JB, Proffitt M, Waddell KR. Misoprostol outpatient cervical ripening without subsequent induction of labour: a randomized trial. Obstet Gynecol. 2004;104:579-84.
7. Mostaghel N, Nakhaee F, Amiri Z. Outpatient vaginal misoprostol and its effect on post term pregnancy. Middle East J Fam Med. 2009;7(4):33-9.

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