Original Article

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Evaluation of Low-dose and High-dose Intravaginal Misoprostol for Induction of Labour: A Randomised, Double-blinded, Single Centre Study

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: Misoprostol is a synthetic prostaglandin E1 analogue widely used for cervical ripening and labour induction. However, optimal dose of misoprostol required to induce labour is still controversial.

Aim: To determine the efficacy and safety of 25 µg and 50 µg of intravaginal misoprostol for induction of labour at term and to evaluate maternal and neonatal complications.

Materials and Methods: The present study was a prospective, randomised, double blind, single centre study carried out during March 2019 to December 2020. The present study was conducted at Department of Obstetrics and Gynaecology, Maharaja Institute of Medical Sciences, Vijayanagaram, Andhra Pradesh, India. All the selected participants were randomised (1:1) to group 1 which received 25 µg of intravaginal misoprostol (n=70) and group 2 received 50 µg of intravaginal misoprostol (n=70). Based on the Bishop's score, misoprostol was chosen as labour inducing agent. Number of misoprostol doses, mode of delivery, vaginal delivery duration, maternal and neonatal complications was recorded. Statistical significance among study groups were analysed by using Chi-square test.

Results: Postdatism was most frequently reported indication in both the study groups (57.1% and 52.9%). A total of 14 and 4 participants in group 2 and group 1 received only single dose of misoprostol (p<0.01). Participants who received misoprostol 50 µg (n=60, 85.7%) had showed slightly higher vaginal deliveries compared to misoprostol 25 µg (n=57, 81.4%). The mean duration of induction time in group 2 was 10.12 hours and group 1 women showed 13.56 hours (p<0.0001). Maternal and neonatal complications were slightly higher in 50 µg misoprostol group. Maternal complications such as uterine tachysystole (n=4), Postpartum Haemorrhage (PPH) (n=3) and uterine hyperstimulation syndrome (n=2). Neonatal complications with 50 µg misoprostol were APGAR <7 at 1 min (n=4), APGAR <7 at 5 min (n=3), Special Care Baby Unit (SCBU) admissions (n=2) and severe birth asphyxia (n=1). Misoprostol with 25 µg has showed APGAR <7 at 1 min (n=2), APGAR <7 at 5 min (n=2), SCBU admissions (n=1).

Conclusion: The efficacy and safety results of 25 µg intravaginal misoprostol were comparable with 50 µg of intravaginal misoprostol for labour induction. The advantages of 50 µg misoprostol were it favours the vaginal deliveries, lesser active induction time and decrease number of misoprostol doses required to induce labour. However, higher dose of misoprostol showed higher frequencies of both maternal and neonatal complications.

Keywords: Duration of vaginal deliveries, Maternal complications, Neonatal complications, Number of doses

INTRODUCTION

In day-to-day obstetric practice, induction of labour is one of the most frequent intervention. This intervention is performed by a qualified gynaecologist by using different class of drugs which artificially induce same physiological uterine contractions and dilatation of cervix which results in cervical effacement [1]. In developed countries, the prevalence of this intervention carried out is 1 in 5 pregnancies and 1 in 10 pregnancies in developing countries like India [2]. This procedure is preferred when benefit favour over risks in benefit-risk analysis, conditions where continuing of pregnancy is not suitable or advisable such as gestational hypertension, gestational diabetes mellitus, and intrauterine growth retardation, premature rupture of membranes, post-dates, and infections which cause foetal death. Unfavourable cervix is one of the drawbacks which accounts nearly 50% of women who are undergoing labour induction intervention [3-5].

Improper dilatation of cervix may lead to increased risk of instrumental deliveries, prolonged labour, prolonged postpartum time, and increased prevalence of neonatal Intensive Care Unit (ICU) admissions [6]. Asynthetic prostaglandin E1 analogue, Misoprostol (chemically15-deoxy-16-hydroxy-16-methyl prostaglandin E1) is widely used pharmacological drug for induction of labour other than oxytocin [7,8]. Originally misoprostol was prescribed for the treatment of peptic ulcers other than labour inducing agent because it can reduce Hydrochloric acid (HCL) secretion and gastric mucosal protection action [9]. As compared to oral and sub-lingual routes, vaginal administration of misoprostol has quick onset of action with long duration of action. It has both cervical softening and priming and utero-tonic effects [10,11]. As of now, there are no clear cut evidence for labour induction with regard to dose and frequency of misoprostol administration [12]. Along with misoprostol, gynaecologist may use inducing agents such as oxytocin, Prostaglandin E2 (PGE2) and mechanical methods. A shorter interval of labour induction time and failed induction has been seen with misoprostol over oxytocin. Higher dose can stimulate uterus more vigorously which can lead to uterine hyper-stimulation [13].

Hence, the present study was aimed to determine the misoprostol safe dose for inducing labour. The primary objective of the present study was to determine the efficacy and safety of different doses of

intravaginal misoprostol i.e 25 µg and 50 µg for induction of labour at term in a tertiary care teaching hospital. The secondary objective was to evaluate the maternal and neonatal complications after misoprostol administration.

MATERIALS AND METHODS

A prospective, randomised (1:1), double-blind, parallel study was conducted at Department of Obstetrics and Gynaecology, Maharaja Institute of Medical Sciences, Vijayanagaram, Andhra Pradesh, India during the period from March 2019 to December 2020. The present study was approved by scientific committee as well as Institutional Ethics Committee (IEC) (MIMS/IEC/26 Dated on 13.02.2019) and informed consent was obtained from all of the study participants. Study was conducted according to the Declaration of Helsinki.

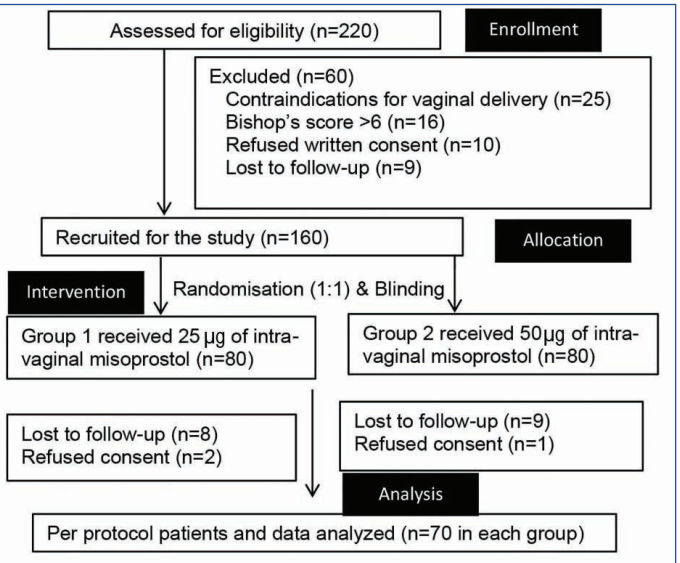
Inclusion criteria: Women with ≥37 weeks of gestation, vertex presentation, singleton pregnancy with intact membranes were included.

Exclusion criteria: Women with Bishop's score >6 parity >4 and contraindications of prostaglandins usage and vaginal mode of delivery were excluded from the study.

Sample size calculation: Sample size was calculated by taking mean difference of number of misoprostol doses required to induce labour after administration of 25 µg and 50 µg of intravaginal misoprostol as done in a study by Srilaxmi et al., [14] setting power at 80% and α value at 0.05 and considering a dropout rate of 10% by using power and sample size software (Version 3.1.6, 2018, Vanderbilt university, Nashville, Tennessee, USA). Hence, the sample size required to test the hypothesis was 70 subjects in each group.

Randomisation was carried out by using Random Number Generator (RNG) Software. Both investigator and patients did not knew the treatment intervention of what drug they are giving and taking. Blinding was carefully followed by masking the brand and genetic names with white colour adhesive patch with unique codes and decoding was done at the time of analysis. Randomisation, random allocation sequence, participants assignment to interventions and blinding were performed by Social and Preventive Medicine faculty who was not involved in the study.

All the study participants were randomly (1:1) divided into two groups, one group received 25 µg of misoprostol intravaginally as a labour inducing agent as Group 1 and another group received the 50 µg of misoprostol intravaginally to induce labour as Group 2. Flowchart of patient recruitment is shown in [Table/Fig-1].



[Table/Fig-1]: Flowchart showing patient recruitment.

Data sheet was prepared and verified for the groups. If, the Bishop's score was <6, misoprostol of chosen dose was injected in the posterior fornix with proper aseptic environment. The duration of each misoprostol dose was kept as six hours with a minimum of five doses in one day in order to get sufficient enough uterine contractions (three contractions in every 10 minutes or >3 cms of cervical dilatation). All the study participants were moved to labour ward at onset and labour was monitored by using partogram. Misoprostol administration time and onset of labour after administration of drug was recorded. A minimum of 4 cms of cervical dilatation achieved and no further contraindications was observed, manual foetal membrane rupture was performed. If uterine contractions are not sufficient enough, 10U of oxytocin in 1 L of normal saline was used as i.v infusion to augment the uterine contractions. The following parameters were checked and documented carefully during the course of study which includes total doses needed for induction, maternal side effects due to caesarean section, mode of labour, foetal outcome measures like APGAR score, neonatal ICU admissions.

STATISTICAL ANALYSIS

All the collected data was entered into Microsoft Excel spread sheet. A software of Statistical Package for the Social Sciences (SPSS) version 20.0 was used to perform the statistical analysis. Baseline demographic details were presented as percentages, mean and standard deviation. Statistical difference of discrete data among study groups (number of misoprostol doses, mode of delivery, vaginal delivery duration and maternal, foetal complications) was carried out by using Chi-square test.

RESULTS

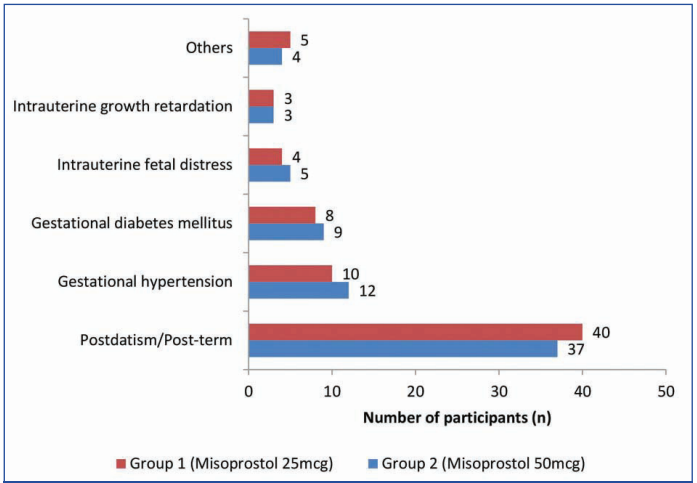
The mean age of the study subjects of group 1 and group 2 was 26.56 years and 27.12 years respectively. A total of 60% women in the group 1 and 64.3% in group 2 were pregnant for the first time. There was no statistical difference between the groups at baseline parameters like age, Body mass Index (BMI), and parity [Table/Fig-2].

Characteristic	Group 1 (N=70)	Group 2 (N=70)	p-value
Age in years			
Mean±SD	26.56±3.23	27.12±3.93	0.358
Range	21-35	21-35	
Age in years, n (%)			
21-24	15 (21.4)	17 (24.3)	0.869*
25-29	46 (65.7)	43 (61.4)	
30-35	09 (12.9)	10 (14.3)	
Weight (kg), mean±SD	58.54±9.34	60.18±9.62	0.307
Height (cm), mean±SD	168.43±14.29	169.04±14.30	0.801
BMI (kg/m^2), mean±SD	20.5±2.3	21.0±2.4	0.210
Gravida, n (%)			
Primigravida	42 (60.0)	45 (64.3)	0.601
Multigravida	28 (40.0)	25 (35.7)	

[Table/Fig-2]: Baseline characteristics of study groups.
Unpaired t-test was performed to calculate p-values; *Chi-square test

Postdatism was most frequently reported indication in both the study groups. A total of 40 (57.1%) and 37 (52.9%), participants received intravaginal 25 µg and 50 µg misoprostol for post-term labour respectively. Other indications being gestational hypertension (group 1, 10 (14.3%), group 2, 12 (17.1%), gestational diabetes mellitus (group 1, 8 (11.4%), group 2, 9 (12.9%), intrauterine foetal distress (group 1, 4 (5.7%), group 2, 5 (7.1%), intrauterine growth retardation (group 3 (4.3%), group 4, (4.3%). There was no

statistically significant difference between the study groups with respect to indications (p=0.643) [Table/Fig-3].



[Table/Fig-3]: Indications for labour induction among study groups.

A total of 14 and 4 participants in group 2 and group 1 received only single dose of misoprostol for their labour induction and showed statistical significance in the difference (p<0.01). Same way, only 1 subject in group 2 and 6 subjects in group 1 has received total of 5 doses of 50 µg and 25 µg misoprostol respectively which again showed the statistical significance (p<0.04) [Table/Fig-4].

There was no statistically significant difference between study groups among vaginal, caesarean and instrumental deliveries [Table/Fig-5].

Number of doses	Group 1 (Misoprostol 25 µg) N=70, n (%)	Group 2 (Misoprostol 50 µg) N=70, n (%)	p-value
1	4 (5.7)	14 (20.0)	0.011
2	21 (30.0)	25 (35.7)	0.471
3	27 (38.6)	22 (31.4)	0.375
4	12 (17.1)	8 (11.4)	0.333
5	6 (8.6)	1 (1.4)	0.048

[Table/Fig-4]: Number of misoprostol doses received among study groups.
Chi-square test was used to calculate the p-values

Mode of delivery	Group 1 (Misoprostol 25 µg) N=70, n (%)	Group 2 (Misoprostol 50 µg) N=70, n (%)	p-value
Vaginal	57 (81.4)	60 (85.7)	0.493
Caesarean	8 (11.4)	6 (8.6)	0.573
Instrumental	5 (7.1)	4 (5.7)	0.730

[Table/Fig-5]: Mode of delivery after administration of misoprostol among study groups.
Chi-square test was used to calculate the p-values

A total of 24 (40.0%) and 11 (19.3%) of study participants in group 2 and group 1 showed less than 12 hours of vaginal delivery duration after misoprostol administration, this difference has showed statistical significance (p<0.014). Hence, misoprostol 50 µg has showed less duration of delivery time as compared to 25 µg of misoprostol. The mean duration of induction time in group 2 was 10.12 hours and group 1 women showed 13.56 hours which showed statistically significant (p<0.0001) [Table/Fig-6].

Misoprostol 50 µg has showed following maternal complications such as uterine tachysystole (n=4), PPH (n=3) and uterine hyperstimulation syndrome (n=2). Misoprostol 25 µg group showed only PPH and uterine tachysystole (n=2 each). Neonatal complications with 50 µg misoprostol were APGAR <7 at 1 min (n=4), APGAR <7 at 5 min (n=3), SCBU admissions (n=2) and severe birth asphyxia (n=1). Misoprostol with 25 µg has showed APGAR <7 at 1 min (n=2), APGAR <7 at 5 min (n=2), SCBU admissions (n=1) [Table/Fig-7].

Duration (hrs)	Group 1 (Misoprostol 25 µg) N=57, n (%)	Group 2 (Misoprostol 50 µg) N=60, n (%)	p-value
<12	11 (19.3)	24 (40.0)	0.014
12-24	32 (56.1)	28 (46.7)	0.305
>24	14 (24.6)	8 (13.3)	0.120
Mean±SD	13.56±4.68	10.12±3.23	0.0001#

[Table/Fig-6]: Duration of vaginal deliveries among study groups.
Chi-square test was used to calculate the p-values; #Un-paired t-test was used

Category	Group 1 (Misoprostol 25 µg) N=70, n (%)	Group 2 (Misoprostol 50 µg) N=70, n (%)	p-value
Maternal complications			
Post-partum hemorrhage	2 (2.9)	3 (4.3)	0.648
Uterine tachysystole	2 (2.9)	4 (5.7)	0.403
Uterine hypertonus	0	1 (1.4)	0.221
Uterine hyperstimulation syndrome	0	2 (2.9)	0.421
Neonatal complications			
APGAR <7 (1 min)	2 (2.9)	4 (5.7)	0.403
APGAR <7 (5 min)	2 (2.9)	3 (4.3)	0.648
SCBU admissions	1 (1.4)	2 (2.9)	0.559
Severe birth asphyxia	0	1 (1.4)	0.221

[Table/Fig-7]: Frequency of maternal and neonatal complications among study groups.
SCBU: Special care baby unit; Chi-square test was used to calculate the p-values

DISCUSSION

Labour induction is advisable when the Bishop's score is <6. Misoprostol, a prostaglandin E1 analogue is widely used in recent times as a labour inducing agent, if oxytocin is contraindicated or not preferred at the time of delivery [15,16]. Postdatism or post-term pregnancy (57.1% in group 1 and 52.9% in group 2) was the main indication for the use of intravaginal misoprostol as labour inducing agent in the present study. After postdatism, gestational hypertension (14.3% and 17.1%), (p=0.788) was second most indication followed by gestational diabetes mellitus (11.4% and 12.9%) in group 1 and group 2 respectively. Vidyashree MM [17] and Bharathi A et al., [18] conducted a separate studies and reported that postdatism was the foremost common indication to initiate labour with misoprostol. The present study findings were in agreement with their findings. The reasons for postdated pregnancies are not clear, perhaps, ultrasound scans availability at remote places and prior booking might be the reasons for postponement.

In the present study, number of misoprostol doses required for induction of labour was comparatively less in group 2 than group 1. A total of 20% women required only single dose of 50 µg misoprostol and single dose of 25 µg misoprostol received by 5.7% women which showed the statistically significant difference. Hence, misoprostol 50 µg has limited the number of doses required for labour. A total of 68.6% and 67.1% in group 1 and group 2 has received 2 and 3 doses respectively. Only one woman received the maximum number of 5 doses of 50 µg misoprostol and six women received the 25 µg of misoprostol. Meydanli MM et al., [19] conducted a study and reported that mean number of misoprostol doses was less in 50 µg group compared to 25 µg misoprostol group. These study findings were similar to present study.

In the present study, 24/60 (40%) vaginal deliveries in women received 50 µg of misoprostol showed within 12 hours of labour induction whereas 25 µg received women reported

11/57 (19.3%), these values showed statistically significant difference. The findings of the present study was in agreement with studies published by El-Sherbiny MT et al., [20] and Meydanli MM et al., [19] who reported labour induction was within 12 hours in 50 µg received group. Other similar findings have been observed in these studies with same clinical setting [21-23].

The mean time for induction of active labour was 10.12 hours in group 2 and 13.56 hours in group 1. Similar observations was reported by Elhassan EM et al., which observed that women who received 25 µg of misoprostol has significantly longer duration of induction time compared to 50 µg misoprostol treated women [24]. Meydanli MM et al., reported that women received 50 µg of misoprostol has showed 5 hours less duration of active labour compared to 25 µg misoprostol group [19].

The incidence of maternal complications with different doses of misoprostol was observed. PPH was most frequently reported maternal complication in both the groups. Group 1 showed 2.9% and group 2 showed 4.3% of PPH cases. These findings are in accordance with studies published by Girija S and Manjunath AP [25] and Azubuike IJ et al., [26]. Uterine tachysystole was observed 5.7% of women with 50 µg misoprostol and 2.9% with 25 µg misoprostol. Similarly, uterine hyper-stimulation was observed only with 50 µg misoprostol received group (2.9%). If uterine rupture seen either due to tachysystole or hyper-stimulation, it become a serious maternal complication. However, such events were not observed in the present study.

Neonatal complications with 25 and 50 µg misoprostol were observed. APGAR <7 @ 1 min was reported by 5.7% and 2.9% in group 2 and group 1 respectively. These findings were not statistically significant. Gupta HP et al., [27]. reported that women received 50 µg of misoprostol has showed higher incidence of APGAR scores <7 @ 1 min as well as ICU admissions. SCBU/NICU admissions were reported by 2.9% and 1.4% neonates in group 2 and group 1 respectively. One neonate born from 50 µg misoprostol as inducing agent reported severe birth asphyxia. These findings are in agreement with studies published by Srilaxmi; Meydanli MM et al., and Nigam A et al., [14,19,28].

Study design and relatively high sample size were major strengths of the present study. In addition, maternal and neonatal complication were measured. Clinical trial with larger sample size studies may be warranted in future to generate more reliable conclusions. The clinical implications of the present study were that 25 µg misoprostol can be used as routinely preferred drug for inducing labour and 50 µg misoprostol may be preserved its use in women with lower Bishop's scores.

Limitation(s)

The present study was conducted at single centre and subject's recruitment was restricted to the specific geographical region were the major limitations of the study.

CONCLUSION(S)

The efficacy and safety results of 25 µg intravaginal misoprostol were comparable with 50 µg of intravaginal misoprostol for labour induction. The only added advantage of using 50 µg misoprostol was as it favours the vaginal deliveries, lesser active induction time and decrease number of misoprostol doses required to induce labour. Perhaps, some of these variables are not statistically significant but favour towards higher misoprostol dose. However, higher dose of misoprostol reported higher frequencies of both maternal and neonatal complications. Therefore, the results of the present study concludes that 25 µg misoprostol can be used as routinely preferred drug for inducing labour and 50 µg misoprostol may be preserved its use in women with lower Bishop's scores.

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