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Titrated Oral Misoprostol Solution and Intravenous Oxytocin for Labor Augmentation: A Randomized Controlled Trial

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Abstract: *INTRODUCTION: Labor dystocia is a common problem, especially among nulliparous women resulting in increased maternal and perinatal mortality and morbidity. This study was conducted to compare the safety and efficacy of titrated oral misoprostol solution to titrated intravenous oxytocin for labor augmentation*
MATERIALS AND METHODS: Women at 36 and 42 weeks of gestation bearing a live singleton fetus in cephalic presentation with spontaneous onset of active labor having regular but inadequate contractions reassuring fetal heart rate with effaced cervix dilated between 4 cm and 8 cm with or without ruptured amniotic membrane and were randomized to titrated intravenous oxytocin group or titrated oral misoprostol group. Primary parameters to evaluate the efficacy were interval from the initiation of augmentation to vaginal delivery and percentage of women delivering vaginally within 12 or 24 hours after initiation of augmentation. Primary parameters to evaluate adverse effects were the occurrences of tachysystole, hypertonus and hyperstimulation.
RESULT: A total of 175 consenting women were randomly assigned,87(49.71%) to titrated oral misoprostol group and 88(50.29%) to titrated intravenous oxytocin group. The titrated intravenous oxytocin was more effective than titrated oral misoprostol in terms of the median interval of augmentation to vaginal delivery in our study: median 286.5 minutes vs 313 minutes (p <0.0001). Eighty(91.95%) women in misoprostol group and 82(93.18%) in oxytocin group delivered vaginally within 12 hours (p 0.757;RR =0.9868;95% CI; 0.90 to 1.07).The occurrence of tachysystole was significantly higher in oxytocin group (p 0.028). Hyperstimulation and hypertonus were insignificant. Difference of maternal side effects and neonatal outcomes between the two groups also was not significant.
CONCLUSION: Titrated oral misoprostol solution was as efficacious as intravenous oxytocin infusion in labor augmentation, exhibiting similar rates of vaginal delivery within 12 and 24 hours and was even safer as we found less uterine contractile abnormalities than titrated intravenous oxytocin.
Keywords: *Labor augmentation, Oral misoprostol solution, Oxytocin*

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I. Introduction

Labor dystocia is a common concern affecting labor outcomes both maternal and neonatal resulting in negative birth experience [1,2] leading to fetal distress requiring operative birth, either by emergency cesarean section or vaginal instrumental birth [3,4] Based on the hypothesis that the most frequent cause of dystocia is inadequate uterine contraction, early diagnosis of prolonged labor and appropriate augmentation may avoid the adverse labor outcomes as well as reduce the rate of cesarean delivery [5]. Oxytocin augmentation is widely used in the modern obstetric practice to treat a slow labor[6].

Misoprostol, a synthetic prostaglandin E1 analogue, has both uterotropic and uterotonic properties [7],is an effective agent for cervical ripening and labor induction in term pregnancy[8]. Oral regimens are recommended over vaginal regimens because of the more frequent occurrence of fetal heart rate abnormalities in vaginal route [9]. It is a logical alternative to oxytocin for labor augmentation. Fixed dose oral misoprostol(75µg 4 hourly) for augmentation was effective but caused more uterine tachysystole, hypertonus and fetal heart rate abnormality questioning its safety in one study [10] where as other study shows [11] less tachysystole. Low dose titration regimen (starting with a 20µg hourly for 4 hours and increasing 20µg/hour thereafter depending on uterine response) resulted in similar rates of vaginal delivery within 12 and 24 hours, comparable neonatal outcomes with less incidence of uterine hyperstimulation, tachysystole and hypertonus than oxytocin [12].Effectiveness of low dose titration regimens in induction of labor has been established [13-17]. Because of this limited evidence regarding use of misoprostol as augmentation agent and disparity between the results,this randomized clinical trial was

conducted to compare safety and efficacy of titrated oral misoprostol solution and titrated intravenous oxytocin in terms of labor outcomes of patients treated for labor dystocia.

II. Materials And Methods

This randomized controlled trial was conducted in the Department of Obstetrics &Gynaecology of R. G. Kar Medical College & Hospital, Kolkata from July 2012 to June 2013. This study was approved by the Ethical Committee and written informed consent was obtained from each participant admitted to the Labor and Delivery Unit.

Inclusion criteria were pregnancy between 36 and 42 weeks of gestation with no history of uterine surgery, bearing a live singleton fetus (with no known fetal anomaly) in cephalic presentation with spontaneous onset of active labor having regular contractions, cervix dilated between 4 cm and 8 cm (Bishop Score > 6) with or without ruptured amniotic membrane and a reassuring fetal heart rate (FHR) pattern. Exclusion criteria were nonreassuring FHR pattern at the time of enrollment, meconium stained amniotic fluid, parity greater than five, estimated fetal weight of 4,500 grams or more, any contraindication to labor or vaginal delivery or both, epidural analgesia, significant maternal cardiac, renal or hepatic disease, and hypersensitivity to misoprostol or prostaglandin analogues.

Pregnant women admitted in the labour room and meeting the inclusion criteria were selected after informed consent. During the study period 324 women fulfilling the inclusion criteria consented for the study. Out of them 175 (54.01%) women in the first stage of activelabor developed inadequate uterine contractions (two or fewer contractions per 10 minutes in 30 minute window)within one hour after admission. After determination of Bishop Score they were enrolled andrandomized into the two study treatment groups: Titrated Oral Misoprostol Solution and Titrated Intravenous Oxytocin for augmentation of labor (Fig.1).Randomization was done by computer-generated table of random numbers**.**The randomization assignments were placed into consecutively numbered opaque, sealed envelopes. When inadequate uterine contractions occurred, the envelope given to woman was opened by the patient's obstetrician to determine the treatment allocation. Blinding of the obstetrician and patient couldn't be done from knowledge of which intervention a participant received.

In the titrated oxytocin group oxytocin was given via the intravenous route by infusion pump initially at the rate of 1 mU/min for 20 minutes, and then increased by 1 mU/min every 20 minutes until adequate uterine contractions were achieved.

In the titrated oral misoprostol group one 200µg tablet of misoprostol was completely dissolved in 200 ml of water and used completely within 24 hours after preparation. The misoprostol solution was administered according to the following rules (Fig.2):

- Misoprostol was initially given at a dose of 20µg/hour. If adequate uterine contractions were not achieved after 4 hours (four doses), the dosage were increased to 40µg and repeated every hour until adequate uterine contractions occurred. Nothing by mouth, except medication, were allowed during the period.
- Once uterine activity was adequate over 1 hour, no further misoprostol was given.
- If contractions subsequently became inadequate, hourly doses of misoprostol solution were started at 10µg/hour and increased to 20µg/hour and to a maximum of 40µg/hour based on uterine responsiveness. This process was repeated until adequate uterine contractions wereachieved.

Intravenous oxytocin and oral misoprostol solution were administered keeping the following in mind:

- Both fetal heart rate and uterine activity were continuously monitored throughout labour with only external technique by means of cardiotocography.
- The maximum allowed dosing rate of oxytocin was 20 mU/min and the maximum cumulative dosage of misoprostol was 1,600µg.
- Injection Terbutaline (250µg) subcutaneously could be considered at the discretion of the obstetrician in case of uterine hyperstimulation.
- Caesarean delivery was offered to all patients in case of failure of labour to progress or when non-reassuring FHR occurred.

The active phase was defined as achieving regular uterine contractions with cervical dilatation greater than 4cm. Labor was considered failed to progress when there was no progress of cervical dilatation or fetal descent for at least 3 hours after entering the active phase of labor and initiation of augmentation. Adequate uterine contraction was defined as occurring at least 3 contractions in 10 minutes, each lasting for 40-90 seconds with relaxation in between. Tachysystole was defined as presence of more than 5 contractions in 10 minutes for at least two 10 min windows in 30 min period. Hypertonus was defined as single uterine contraction lasting for more than 2 minutes. Hyperstimulation was defined as Tachysystole or Hypertonus with nonreassuring FHR changes. Non-reassuring FHR pattern included late deceleration, severe variable deceleration, prolonged deceleration, tachycardia and reduced FHR variability.

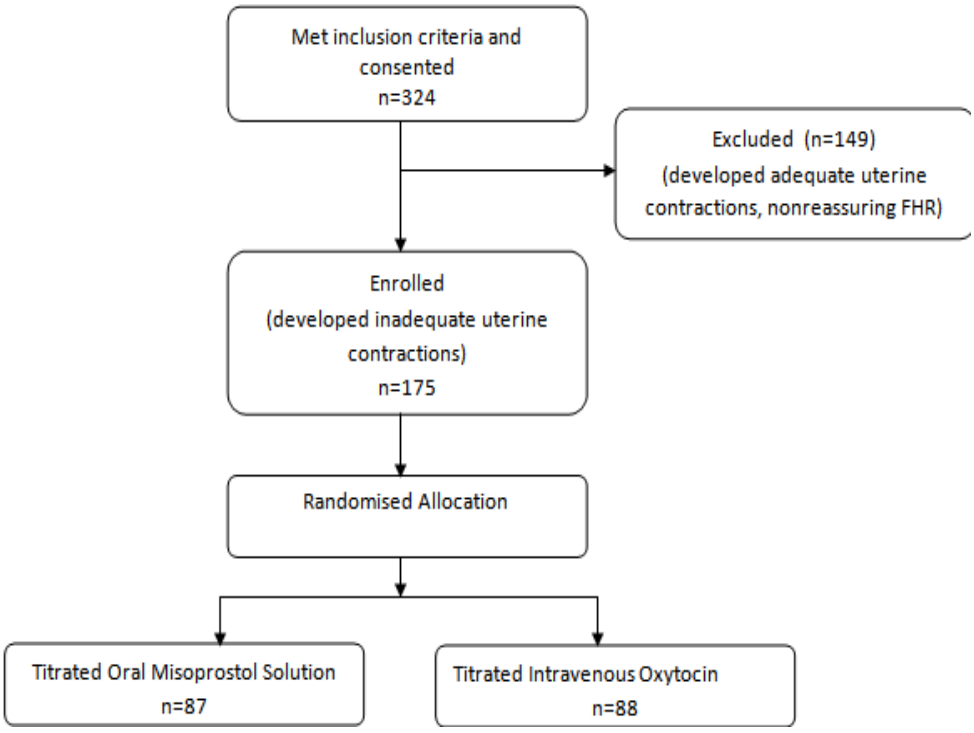
Primary parameters to evaluate the efficacy were interval from the initiation of augmentation to vaginal delivery and percentage of women delivering vaginally within 12 or 24 hours after initiation of augmentation. Primary parameters to evaluate adverse effects were the occurrences oftachysystole, hypertonus and hyperstimulation. Secondary parameters to evaluate the efficacy or adverse effects also included total dosage of oxytocin or misoprostol, rates of caesarean births, percentage of women whose labor failed to progress, occurrences of maternal side effects- nausea, vomiting, diarrhea, shivering, and pyrexia. Neonatal outcomes were evaluated by determining APGAR score less than 7 at 1 minute and 5 minutes after birth and admission to neonatal intensive care unit (NICU).

Sample size calculation was based on the augmentation-delivery interval as the primary outcome measure. It was determined that 79 women would be required per group in order to detect a 0.7 hours (42 min) difference in this interval with 80% power and 5% probability of Type I error. This calculation assumed a standard deviation of 2 hours (120 min) for the augmentation-delivery interval. Allowing for a potential 10% dropout rate, this translated to a recruitment target of 87 women per group and in total 175 women was included in the study.

Statistical analysis was done using MedCalc version 12.7.4 [MedCalc Software 2013, Acacialaan 22, B-8400 Ostend, Belgium].Analysis data were summarized by descriptive statistical measures such as mean and standard deviation for numerical variables that were normally distributed and median and interquartile range for those that were skewed. Key variables were expressed with their 95% confidence intervals. Numerical variables were compared between groups by Student's unpaired t test if normally distributed, or by Mann-Whitney U test if otherwise. The Chi-square test or Fisher's exact test (when the assumptions of the Chi-square test were violated) was employed to compare unpaired proportions. The data were analyzed by intention to treat. All analyses were two-tailed and P value of< 0.05 was considered statistically significant**.** Relative risks (RRs) and their 95% confidence intervals (CIs) were used to estimate the strength of association between the two groups. Kaplan-Meier survival analysis was done to compare augmentation to vaginal delivery interval in two groups of vaginally delivered women. Cesarean deliveries were censored.

III. Results:

Fig. 1: Participation Flow Chart



A total of 175 women who met the inclusion criteria were randomized into the two study groups; 87 (49.71%) to titrated oral misoprostol solution, and 88 (50.29%) to titrated intravenous oxytocin. Outcome data were available for analysis.

The baseline characteristics for the two groups are compared in Table 1. The two groups were similar with respect to maternal age, gestational age, maternal body height and weight, BMI, maternal parity, Bishop Score, and rupture of membranes at start of augmentation.

Labor outcomes are shown in Table 2. The median duration of labor from initiation of augmentation to vaginal delivery, augmentation to full dilatation& 2nd stage were 313 minutes (298-342 min, 25th-75th percentile), 239.5 minutes (228-268 min), 76 minutes (63-91 min) in Misoprostol group and 286.5 minutes (240-320 min, 25th-75th percentile), 225 minutes (190-247min), 55 minutes (45-75 min) in oxytocin group respectively. All intervals were significantly shorter in oxytocin group ($P < 0.0001$). Fig.2 shows Kaplan-Meier survival analysis of vaginally delivered women from initiation of augmentation to vaginal delivery. End point was determined by vaginal delivery. It demonstrated the proportion of women undelivered at any point of time in two study groups. As seen in the graph the subjects treated with titrated intravenous oxytocin for augmentation completed labor faster than those treated with titrated oral misoprostol Solution.

In misoprostol group, out of total 87 women, 80 (91.95%) women delivered vaginally and 7(8.05%) women were delivered by cesarean section whereas in oxytocin group out of 88 women 82 (93.18%) delivered vaginally and six (6.82%) by cesarean section. The rate of vaginal delivery did not differ significantly between the two groups (P 0.757; RR 0.9868; 95% CI; 0.91 to 1.07). Cesarean delivery was done due to failure of labor to progress and fetal distress or nonreassuring fetal heart rate. Women in both groups who delivered vaginally completed their labor within 12 hours. Seven(8.05%) women in misoprostol group and 6(6.82%) women in oxytocin group underwent cesarean section but the difference was not statistically significant. Furthermore, difference in the ratesof vaginal instrumental birth was also not statistically significant (6.9% in titrated oral misoprostol group vs 5.7% in titrated intravenous oxytocin group).

Tachysystole occurred significantly more in oxytocin group ($P<0.027$) but the occurrence of hyperstimulation were not significantly different between the two groups. Hypertonus did not occur in any of the groups. Tachysystole developed in five (5.75%) women in misoprostol group and in 15 (17.05%) women in oxytocin group.In our study we observed that the occurrence of tachysystole in titrated intravenous oxytocin group was dose related and was associated with dosing rate more than 6mU/min. Hyperstimulation occurred in two women in misoprostol group and in four women in oxytocin group.When tachysystole and hyperstimulation occurred oxytocin and oral misoprostol were stopped, ringer lactate solution started and moist oxygen inhalation was given. All tachysystole resolved after resuscitation. Tocolytics were not needed, only resuscitative measures were sufficient to ensure uterine relaxation. This suggests that administering misoprostol in small, frequent doses with continuous adjustment according to response can avoid uterine hyperstimulation and adverse outcomes and is analogous to the conventional titrated use of oxytocin. After resuscitation fetal heart rate returned to normal in two women in oxytocin group and in one woman in misoprostol group. Out of 20 women who developed tachysystole, 17 women delivered vaginally and three were delivered by cesarean section due to nonreassuring fetal heart rate.

The median total dosage was 60µg (40–80µg) in the misoprostol group and 1250mU (1010-1482 mU) in the oxytocin group. The maximal cumulative dosage of misoprostol was 160 µg and that of oxytocin was 2030mU and maximum dosing rate of oxytocin was 7mU/min.

The common side effects of misoprostol included nausea, vomiting, diarrhea, pyrexia, and shivering. Nausea occurred in five and vomiting in two women in the misoprostol group, none of these side effects occurred among the women in the oxytocin group. These all were statistically insignificant.

There were no statistically significant differences in neonatal outcomes between the two groups. Birth weight distributions were similar in both groups (P 0.496). APGAR score less than 7 was observed in three newborns at 1 min and one newborn at 5 min in misoprostol group and in one newborn in oxytocin group at 1 min. Seven (8.05%) newborns in oral misoprostol group compared to four (4.54%) newborns in intravenous oxytocin group were admitted in NICU which was statistically insignificant (P 0.348).All seven newborns admitted in NICU in misoprostol group were delivered vaginally (five by instrumental vaginal delivery and two by vaginal delivery). All of them underwent augmentation to vaginal delivery interval more than 6 hours.In oxytocin group, out of four newborns admitted in NICU, three newborns were delivered vaginally and one newborn was born by cesarean section. None of the findings were statistically significant and women in titrated misoprostol group were no more likely to experience adverse neonatal outcome than titrated oxytocin group.

IV. Discussion

Titrated oral misoprostol solution was as efficacious as intravenous oxytocin infusion in labor augmentation, exhibiting similar rates of vaginal delivery within 12 and 24 hours and was even safer as we found less uterine contractile abnormalities than titrated intravenous oxytocin. We also found that there were no

significant differences in cesarean delivery rates and neonatal outcomes between the two groups although the augmentation to vaginal delivery interval was longer for misoprostol.

There is already evidence about pharmacological and nonpharmacological methods of augmenting labour. Methods vary in effectiveness, and some methods may be more appropriate for use in high or low resource settings, either because of cost, availability or resources. As an inexpensive drug that does not need refrigeration and can be administered orally, misoprostol may offer an alternative to other commonly used augmentation agents. Titration regimens using oral misoprostol have now been examined in trials to fills a gap in the evidence[18]. The aim of this study was to compare the labour outcomes of patients treated for labour augmentation with titrated oral misoprostol solution or titrated intravenous oxytocin.

Primary parameters to evaluate the efficacy were interval from the initiation of augmentation to vaginal delivery and percentage of women delivering vaginally within 12 or 24 hours after initiation of augmentation.

The titrated intravenous oxytocin was more effective than titrated oral misoprostol in terms of the median interval of augmentation to vaginal delivery in our study: median 286.5minutes vs 313 minutes (p <0.0001).Ho and colleagues[12] also found similar result. Augmentation to vaginal delivery for misoprostol was 5.22hours vs oxytocin 5.20 hours (p =.019). However,Bleich et al[10] found that there was no difference in the time interval between initiation of augmentation and delivery: median 306 minutes in the misoprostol group compared with 276 minutes in the oxytocin group (P=0.29).

Vaginal delivery within 12 or 24 hours was the other clinical parameter evaluated. We found that there were no significant differences between the groups in the percentages of women who delivered vaginally within 12 or 24 hours of augmentation (91.95% in misoprostol group versus 93.18% in oxytocin group;P= 0.757). Ho et al[12] also found that there were no significant differences between the two groups who delivered vaginally within 12 and 24 hours.

According to the pharmacokinetics, the onset time of oxytocin is quicker than that of misoprostol. In this study, it was therefore not unexpected that the titrated intravenous oxytocin would be more effective than titrated oral misoprostol in terms of the interval of augmentation to vaginal delivery. However, the difference of these intervals (median 313 minutes vs 286.5 minutes) is not significant in actual clinical practice. Vaginal delivery within 12 or 24 hours is the more important clinical factor. The rates of caesarean delivery and failure of labour to progress were low and comparable in the two groups.

Parameters to evaluate adverse effects were the occurrences of tachysystole, hypertonus and hyperstimulation. Tachysystole occurred significantly more in oxytocin group (p=.027) but the occurrence of hyperstimulation were not significantly different between the two groups. Hypertonus did not occur in any of the groups. Our findings are found to be similar to study conducted by Ho and colleagues[12.] In contrast to these studies, Bleich et al[10] observed that women in misoprostol group were more likely to experienceuterine tachysystole, hypertonus, or both tachysystole andhypertonus compared with those in the oxytocin group(76% compared with 64%, respectively; P 0.02). Reason behind this increased uterine contractile abnormality may be use of higher dose of misoprostol orally in fixed dosage (75µg 4 hourly).

Neonatal parameters showed that women in titrated misoprostol group were no more likely to experience adverse neonatal outcome than titrated oxytocin group. APGAR score less than 7 was observed in one newborn in oxytocin group and in three newborns in misoprostol group at 1 min(P 0.3322) and only one newborn at 5 min (P 0.4949) in misoprostol group. Seven (8.05%) newborns in oral misoprostol group compared to four (4.54%) newborns in intravenous oxytocin group were admitted in NICU which was statistically insignificant (P 0.348). Similar observations were demonstrated by Ho et al[12]. This suggests that administering misoprostol in small, frequent doses with continuous adjustment according to response is a better way to avoid uterine hyperstimulation and is analogous to the conventional titrated use of oxytocin.

Our study had limitations. First the study was inevitably an open study. It was not possible to blind treatment allocation. Secondly, although our sample size was powered for an assessment of efficacy of labour augmentation, it was not powered to account for the infrequent neonatal adverse outcomes or adverse maternal outcomes such as postpartum haemorrhage, uterine atony, and need for caesarean hysterectomy. Thus, this study could not establish the safety of misoprostol in so far as uncommon adverse outcomes both maternal or fetal are considered.

In conclusion, titrated oral misoprostol solution is an effective agent for augmentation of labour. It is as effective as intravenous oxytocin infusion. Given that misoprostol offers several advantages over oxytocin such as longer shelf life, stability at room temperature, and easier administration, it may be an alternative to the traditional oxytocin for labour augmentation.

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RESULTS

TABLE 1: BASELINE CHARACTERISTICS OF THE WOMEN IN STUDY

CHARACTERISTICS	TITRATED ORAL MISOPROSTOL (n=87)	TITRATED INTRAVENOUS OXYTOCIN (n=88)	P VALUE
Maternal age (yrs)*	23.195 ± 3.854	23.091 ± 4.030	0.8617
Gestational age (wks)*	38.299 ± 0.820	38.407 ± 0.803	0.3799
Height (cms)*	153.451 ± 4.908	153.641 ± 4.669	0.7933
Weight (kgs)*	59.356 ± 5.069	59.136 ± 6.288	0.7993
BMI*	25.204 ± 1.776	25.029 ± 2.117	0.5546
Parity†			
a. Nulliparous	71 (81.61%)	69 (78.41%)	0.7337
b. Multiparous (≥1)	16 (18.39%)	19 (21.59%)	0.7337
Bishop score*	9.184 ± 1.451	8.875 ± 1.492	0.1667
Rupture of membrane†	31 (35.63%)	24 (27.27%)	0.3038

Data presented as mean ± SD or n (%).
*Student's unpaired t-test
†Chi square test 2-tailed
Statistical significance, $P<0.05$

TABLE 2: LABOUR OUTCOMES

VARIABLE	TITRATED ORAL MISOPROSTOL (n=87)	TITRATED INTRAVENOUS OXYTOCIN (n=88)	P VALUE	RELATIVE RISK (95% CI)
PRIMARY OUTCOMES				
Augmentation to vaginal delivery interval (min)*	313 (298-342)	286.5 (240-320)	<0.0001	
Augmentation to full dilatation interval (min)*	239.5 (228-268)	225 (190-247)	0.0001	
Duration of 2nd stage (min)*	76 (63-91)	55 (45-75)	<0.0001	
Vaginal delivery in 12 hrs†	80 (91.95%)	82 (93.18%)	0.7570	0.9868 (0.9073-1.0733)
Vaginal delivery in 24 hrs†	80 (91.95%)	82 (93.18%)	0.7570	0.9868 (0.9073-1.0733)
Tachysystole†	5 (5.75%)	15 (17.05%)	0.0277	0.3372 (0.1281-0.8875)
Hypertonus	0 (0.0%)	0 (0.0%)	-	-
Hyperstimulation¥	2 (2.3%)	4 (4.55%)	0.4240	0.5057 (0.0951-2.6902)
SECONDARY OUTCOMES				
Total dosage	60 (40-80) micrograms	1250 (1010-1482) milliunits	NA	
Mode of delivery†				
Vaginal	80 (91.95%)	82 (93.18%)	0.7570	0.9868 (0.9073-1.0733)
Caesarean section	7 (8.05%)	6 (6.82%)	0.7571	1.1801 (0.4132-3.3702)
Failure to progress¥	5 (5.75%)	4 (4.55%)	0.7197	1.2644 (0.3512-4.5519)
Long blade forceps delivery¥	6 (6.90%)	5 (5.68%)	0.7411	1.2138 (0.3846-3.8305)
Maternal side effects				
Nausea¥	5 (5.75%)	0 (0.0%)	0.1011	11.1250 (0.6245-198.1994)
Vomiting¥	2 (2.30%)	0 (0.0%)	0.2932	5.0568 (0.2463-103.8374)
Diarrhea	0 (0.0%)	0 (0.0%)	-	-
Shivering	0 (0.0%)	0 (0.0%)	-	-
Pyrexia	0 (0.0%)	0 (0.0%)	-	-

CI, confidense interval; NA, test not applicable because of different units.
Data presented as median (25^{th} – 75^{th} percentile) or n (%)
*Mann-Whitney U test
†Chi square test 2-tailed
¥Fisher's exact test 2-tailed
Statistical significance, P<0.05

TABLE 3: NEONATAL OUTCOMES

VARIABLE	TITRATED ORAL MISOPROSTOL (n=87)	TITRATED INTRAVENOUS OXYTOCIN (n=88)	P VALUE	RELATIVE RISK (95% CI)
Birth weight*	2.872 ± 0.197	2.849 ± 0.246	0.4960	-
APGAR score <7				
1 min¥	3 (3.45%)	1 (1.14%)	0.3322	3.0345 (0.3218-28.6104)
5 min¥	1 (1.15%)	0 (0.0%)	0.4949	3.0341 (0.1253-73.4781)
Admission in NICU¥	7 (8.05%)	4 (4.54%)	0.3478	1.7701 (0.5373-5.8314)

Data presented as mean ± SD or n (%).
*Student's unpaired t-test
¥Fisher's exact test 2-tailed
Statistical significance, P<0.05

FIGURE-2

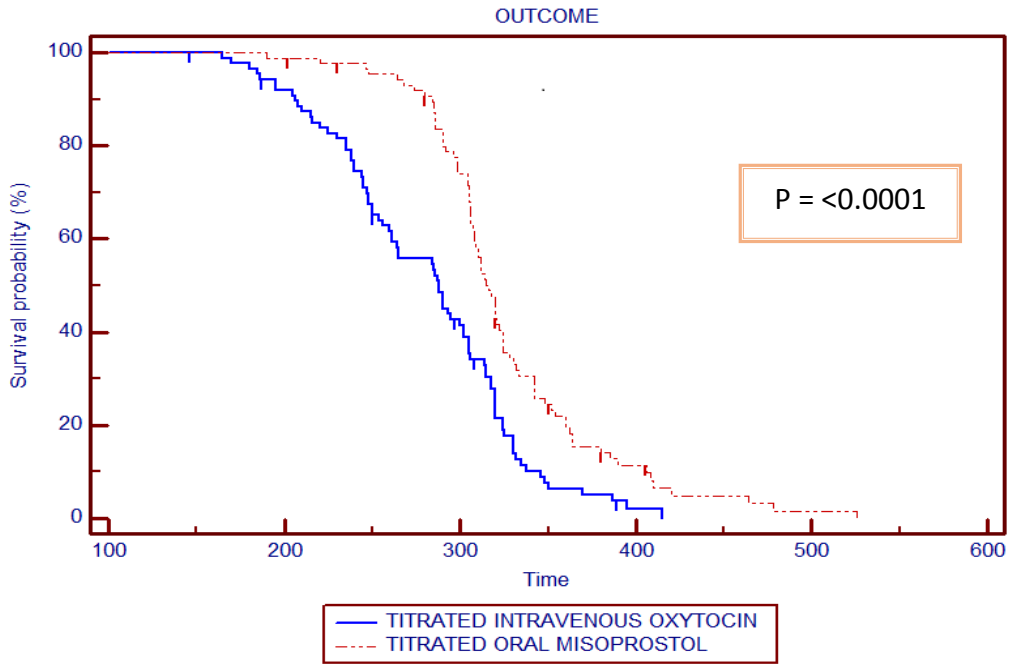

FIG. 2 : KAPLAN-MEIER SURVIVAL ANALYSIS OF TIME FROM INITIATION OF AUGMENTATION TO VAGINAL DELIVERY(Time in minutes)

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